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Oral manifestations of systemic diseases and malignancies located elsewhere in the body R.I.F. van der Waal

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Oral manifestations of systemic diseases and malignancies located elsewhere in the body

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door

Rutger Isaäc Frederik van der Waal

geboren te Rotterdam

promotores: prof.dr. Th.M. Starink
prof.dr. I. van der Waal

Aan mijn ouders
Aan Liselotte, Frédérique en Boudewijn

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Chapter I

Introduction and aim of the study

Introduction

The mouth is an integral part of the body and, therefore, may become involved in a variety of systemic diseases. A number of diseases, including mucocutaneous disorders, may primarily manifest itself in the oral cavity (Table I). However, the oral manifestations can be rather unspecific of an underlying disease, e.g. oral candidiasis, which may delay the proper diagnosis.

Aim of the study

In **Chapter II** a brief overview will be presented of the diseases mentioned in Table I. A selected number of these diseases has been the subject of further study, the selection mainly being based on the availability of well-documented patients from the Department of Oral and Maxillofacial Surgery/Oral Pathology and the Department of Dermatology of the Vrije Universiteit Medical Centre, Amsterdam, The Netherlands. These diseases will not be presented in this chapter since these will be outlined as from chapter 3 onwards.
In **Chapter III** a study of patients with amyloidosis of the oral cavity is described. Retrospectively, we have analysed a group of 11 patients with oral manifestations of amyloidosis with emphasis on the possible presence of an underlying or associated systemic disease.
In **Chapter IV** an overview of the clinical features, histopathology, differential diagnosis, management strategies, and prognosis of cheilitis granulomatosa is presented and discussed with regard to the literature. Furthermore, a report on long-term follow-up and management experiences of 13 patients is presented, also looking into the possible association of cheilitis granulomatosa with sarcoidodis and Crohn's disease.
In **Chapter V** an overview of the oral manifestations of non-Hodgkin's lymphoma is presented. The classification of the subtypes of lymphomas, such as the revised European-American classification of lymphoid neoplasms that has recently been incorporated with minimal change into the World Health Organization (WHO) classification of haematopoietic and lymphoid neoplasms, is aimed at combining clinical aspects, histomorphologic features, immunologic phenotype, and genetic features. In this chapter a number of patients has been discussed against the background of the new WHO classification.
In **Chapter VI** two reports are presented of patients with a squamous cell carcinoma of the oral cavity as second primary malignancy following treatment for cancer in their past medical history. With substantially increased survival after most paediatric cancers over the past decades have come the late sequelae of treatment, second malignancies generally considered to be the most serious ones.
In **Chapter VII** an overview is given of 24 patients with a metastatic tumour of the oral cavity. In this retrospective case study an analysis has been made of the distribution of gender, age, the oral subsite and histopathologic type of the metastasis, the primary tumour site, and follow-up.

Table I. Some systemic diseases that may present with oral manifestations and oral lesions that may have a systemic background (e.g., amyloidosis, malignant melanoma)

Diseases of the immune system
Giant cell arteritis
HIV infection
Pyostomatitis
Behçet's disease
Blood disorders
Anaemia
Leukaemia
Thalassaemia
Granulomatous diseases
Crohn's disease
Cheilitis granulomatosa
Sarcoidosis
Wegener's granulomatosis
Hormonal disturbances
Addison's disease
Hyperparathyroidism
Lymphoreticular diseases
Multiple myeloma
Non-Hodgkin lymphoma
Miscellaneous diseases
Amyloidosis
Langerhans' cell histocytosis
Metastases
Salivary gland involvement in systemic diseases
Mucocutaneous disorders
Acanthosis nigricans
Malignant melanoma
Paraneoplastic pemphigus
Syndromes
Cowden syndrome
Gardner's syndrome
Neurofibromatosis
Peutz-Jeghers syndrome
Naevoid basal cell carcinoma syndrome

In **Chapter VIII** a series of eight patients with a primary malignant melanoma of the oral cavity is described and reviewed with regard to the literature.
In **Chapter IX** two reports are presented of patients with paraneoplastic pemphigus. Whereas approximately two-thirds of reported paraneoplastic pemphigus cases arise in the context of a known neoplasm - most frequently of a malignant nature - this chapter consists of two reports of patients with an initially occult underlying neoplasm.
In **Chapter X** a summary of the results reported in this thesis is presented.

Chapter II

Some systemic diseases that may present with oral manifestations and oral lesions that may have a systemic background; a brief overview

Some systemic diseases that may present with oral manifestations and oral lesions that may have a systemic background; a brief overview

As indicated in chapter I, a brief overview will be presented of the diseases mentioned in Table I. A selected number of these diseases has been the subject of further study, the selection mainly being based on the availability of well-documented patients from the Department of Oral and Maxillofacial Surgery/Oral Pathology and the Department of Dermatology of the VU Medical Centre, Amsterdam, The Netherlands. These diseases include amyloidosis, cheilitis granulomatosa, non-Hodgkin lymphoma, squamous cell carcinoma as second primary malignancy, metastases, malignant melanoma, and paraneoplastic pemphigus and will not be presented in this chapter since these will be outlined as from Chapter III onwards.

2 Diseases of the immune system

2.1 Giant cell arteritis

Giant cell temporal or cranial arteritis, the most common form of systemic vasculitis in adults, is a granulomatous inflammation that involves median and larger arteries, particularly the extracranial branches of the carotid artery, although other vessels including the aorta, the subclavian and axillary arteries may be involved.

Giant cell arteritis occurs almost exclusively above age 50 and is mainly found in women. Incidence in the United States is as low as 2 per 100,000 population per year, but is higher in Europe with incidences up to 75 per 100,000 population per year in the Nordic countries. The cause is unknown, but thought to be auto-immune. It may present with a variety of symptoms, including fever, malaise, and weight loss.

Manifestations in the head and neck region are not uncommon and include unilateral temporal pain, tenderness of the scalp, and unilateral headache. Neuro-opthalmic features include diplopia, ptsosis, and sudden blindness. Jaw claudication or masseteric pain, particularly during chewing, or pain in the tongue, may occur [1]. Tongue necrosis due to lingual arteritis has been described in about 50 patients with giant cell arteritis [2-4]. In these cases, the history of the acute appearance of necrosis is pathognomonic of the arterial nature of the oral lesion.

An arterial biopsy is required to confirm the diagnosis of temporal arteritis. There may be partial destruction of vessel walls by an inflammatory infiltrate that contains multinucleate giant cells. Unfortunately, skip lesions are characteristic and as a result sample error of biopsy may pose a problem.

Reported abnormal laboratory findings include an elevated erythrocyte sedimentation rate (more than 100 mm/h), normochromic normocytic anaemia, elevated plasma fibrinogen and alpha-2 globulin levels, and often raised liver enzymes as well.

Treatment consists of an initial dosage of 40-90 mg prednisolone daily. The medication should be continued for a minimum of two years [2]. The untreated patient is at risk of developing blindness within months after disease onset.

Table I. Some systemic diseases that may present with oral manifestations and oral lesions that may have a systemic background (e.g., amyloidosis, malignant melanoma)

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Syndromes
Cowden syndrome
Gardner's syndrome
Neurofibromatosis
Peutz-Jeghers syndrome
Naevoid basal cell carcinoma syndrome

2.2 HIV infection

In 1981, after reports of Pneumocystis carinii pneumonia, Kaposi's sarcoma, and other opportunistic infections in young homosexual men in Los Angeles, New York, and San Francisco, the newly recognized constellation of diseases was termed the acquired immunodeficiency syndrome (AIDS) and was later shown to be caused by the human immunodeficiency virus (HIV), a retrovirus that selectively deteriorates cell-mediated immunity. Consequently, fatal opportunistic infections and/or neoplasms may occur [5,6]. The Atlanta Centers for Disease Control and Prevention's definition of AIDS -for surveillance purposes- includes all HIV-infected persons with $\leq$ 200 CD4-positive T-cells per cubic millimeter of blood. In addition, the definition includes 26 clinical conditions that affect people with advanced HIV disease. Most of these conditions are opportunistic infections that generally do not affect healthy people. Worldwide an estimated 42 million people are HIV-infected, nearly three-quarters of them living in southern Africa [7].

Oral lesions are important in the clinical spectrum of HIV and AIDS, arousing clinical suspicion of acute seroconversion illness when aphthous ulceration and candidiasis are found, or suggesting HIV infection in the undiagnosed when hairy leukoplakia, Kaposi's sarcoma, candidiasis, or necrotizing ulcerative gingivitis are noted. A range of oral mucosal and periodontal lesions is associated with HIV infection and HIV disease progression [8]. Overall, the prevalence and severity of these oral lesions inversely correlate with the level of immunosuppression [8]. The oral lesions can be symptomatic and require treatment, but may also implicate a diagnostic as well as a prognostic role in the management of the underlying HIV infection.

In recent years, significant improvements in the treatment of HIV infection have emerged. Administration of highly active antiretroviral therapy (HAART), comprising a triple-drug combination of a protease inhibitor and two nucleoside analogue reverse transcriptase inhibitors, has resulted in sustained suppression of plasma HIV-1 RNA levels to below the limits of quantification, resulting in a reconstitution of the compromised immune system and leading to a dramatic improvement in survival of HIV patients [9,10]. HAART may reduce existing HIV-associated oral lesions or prevent occurrence of these in most patients in populations where such treatment is available [5,6,8,11,12].

A brief outline on some well-known oral lesions in this respect is presented: hairy leukoplakia and Kaposi's sarcoma.

2.2.1 Hairy leukoplakia

Hairy leukoplakia refers to white changes that may arise bilaterally on the borders of the tongue in patients with an underlying immunodeficiency, most often being the result of infection by the human immunodeficiency virus (HIV). It is unknown why the lesion is commonly limited to the borders of the tongue.

Unfortunately, the term 'hairy leukoplakia' is a misnomer for two reasons. First, hairy leukoplakia is a definable lesion [13,14], for which it is inappropriate to use the term leukoplakia,

being defined as a white lesion that cannot be classified as any other diagnosable lesion. Secondly, hairy leukoplakia is not a premalignant lesion.
Clinically, hairy leukoplakia presents as whitish, non-removable changes on the borders of the tongue. The surface may either be flat or somewhat corrugated. Symptoms are usually absent. The clinical differential diagnosis of bilateral white lesions of the tongue includes candidiasis, lichen planus, tongue chewing, white sponge naevus, and pachyonychia congenita. Oral hairy leukoplakia can be a clinical marker of a previously undetected HIV infection. Therefore, in a patient not known to suffer from HIV infection or another cause of immune deficiency, a biopsy is required to establish a firm diagnosis.
The histopathological features of hairy leukoplakia consist of hyperparakeratosis, sometimes in an irregular, 'hairy' texture. Immediately below the parakeratotic layer a band of koilocytic cells may be seen. Furthermore, there may be acanthosis and acantholysis in an otherwise non-dysplastic epithelium. For a final histopathological diagnosis the demonstration of Epstein-Barr virus in the koilocytic cells is required.
Although hairy leukoplakia does not require treatment, temporary improvement may be achieved by the use of topical alitretinoin or systemic antiviral medication.

2.2.2 Kaposi's sarcoma

Kaposi's sarcoma is a vascular neoplastic disorder, hardly ever seen before the AIDS-pandemic but nowadays the most frequently noted neoplasm in patients with AIDS. The 'classic' Kaposi's sarcoma, mainly occurring in the Mediterranean region, predominantly affects men. Kaposi's sarcomas have also been described in renal allograft recipients or other patients using long term immunosuppressive drugs. In 1981, an outbreak of Kaposi's sarcoma, in young homosexual men, haemophiliacs, and Haitians was reported [15]. Today, it is well-known that Kaposi's sarcoma is a rather common manifestation of AIDS, occurring in 15% of HIV-positive patients, most of them homosexual men [16]. The pathogenesis is not yet elucidated, but multifactorial and the sexually transmitted human herpes virus type 8 definitely participating in this process [17].
The condition is characterized by multiple skin tumours and occasionally visceral involvement. Oral involvement is not uncommon, the palate being the site of predilection. Clinical presentation varies from asymptomatic to a bleeding tumour. Oral lesions are commonly associated with involvement of other areas of the gastrointestinal tract. Furthermore, pulmonary involvement is relatively common. The diagnosis is based on the histopathological findings.
Although the 'classic' Kaposi's sarcoma may behave in a benign fashion, in HIV-positive persons the clinical course may be less favourable, especially when there is lymph node involvement. Gastrointestinal haemorrhages may be the cause of death in these patients. In AIDS-related Kaposi's sarcoma the prognosis is moreover influenced by opportunistic infections.
Treatment is largely determined by symptoms. As with many HIV infection associated diseases, treatment with protease inhibitors may stabilise or reduce size and symptoms of the lesions as CD4 counts increase and the viral load is reduced. Furthermore, a wide range of

therapeutic options has been described for individual lesions, such as surgical excision or cryotherapy. For oral lesions, radiotherapy is not the treatment of choice in view of these patients being prone to develop severe radiation-associated mucositis and ulcers.

2.3 Pyostomatitis vegetans

Pyostomatitis vegetans is a rare condition of the oral mucosa with unknown aetiology. Pyostomatitis may occur at any age and shows a predilection for males. It is characterized by multiple small pustules. These pustules develop across the oral mucosa and rupture, which leads to widespread ulceration.
The condition is the oral equivalent of pyodermatitis vegetans, in which papules, pustules, and red-brown annular vegetating plaques develop, most frequently in the intertriginous areas. The diagnosis is largely based on excluding the differential diagnoses of pemphigus vegetans, acne conglobata, atypical drug reactions, Behçet's disease, late stage syphilis, tuberculosis, and deep fungal infections [18]. The oral lesions may precede, coincide, or follow pyodermatitis, although they can also occur as the sole manifestation. Pyostomatitis, or for that matter pyodermatitis, is a highly specific marker for inflammatory bowel disease [19-21].
Pyostomatitis can often be managed with topical or systemic corticosteroids.

2.4 Behçet's disease

Behçet's disease is a rare, chronic disorder that involves inflammation of blood vessels of every type and size throughout the body, hence manifesting as a multi-system disease, of which the aetiology remains unknown [22]. Behçet's disease usually develops in the third and fourth decades of life and is more common in Middle Eastern and Asian populations, in which the male:female ratio is approximately 2:1 [23].
To date, there is no specific 'Behçet's test'. The diagnostic criteria currently used include oral aphthous ulceration or herpetiform lesions that test negative for herpesvirus and recur at least three times in one year. In addition, a patient must also meet at least two of the following four criteria:

(i) Recurrent genital aphthous ulcerations or remnant scars.
(ii) Eye lesions, including uveitis, cells in vitrous fluid, and retinal vasculitis.
(iii) Cutaneous lesions, including erythema nodosum, pseudofolliculitis, papulopustular lesions, and acneiform lesions in adults not on steroid medication.
(iv) A positive pathergy test [24-26].

The latter test consists of skin needle pricks or intradermal saline injection read after 24-48 hours and evaluated as positive when indurated erythema or a pustule is noted at the site of needle insertion. Although a positive pathergy test may be helpful in the diagnosis of Behçet's disease, only a minority of patients demonstrates the pathergy phenomenon and the test is not fully specific either.

Apart from the above-listed features, affected organs and tissues may include the central nervous system, the gastrointestinal tract, and the musculoskeletal system. Clinically, recurrent aphthous oral ulcers are nearly always present, often as the first feature of the disease, and may precede other Behçet lesions by years. The painful, round ulcers may affect any part of the oral mucosa. These lesions usually heal spontaneously and without scarring within several days to weeks.

The diagnosis of Behçet's disease may pose a challenge since there are no specific clinical, histological, or serological features and aphthous ulcers occur in about 20% of the normal population. Furthermore, the diagnosis can easily be overlooked because its clinical features are episodic and rarely occur at the same time. Moreover, symptoms occur over several years' time. Concerning the oral lesions, Behçet's disease must be differentiated from herpes simplex, the erythema multiforme spectrum, cicatricial pemphigoid, and erosive lichen planus [27].

Corticosteroids are generally effective when applied topically to mucosal ulcers or when administered systemically for more extensive and/or severe disease [28]. However, it only offers palliation since the disease usually flares when steroid treatment is tapered. Alternatively, tetracycline mouth wash may be effective palliation for oral mucosal ulcers [27,29].

Behçet's disease is characterized as a chronic, indolent disease. Over time, morbidity, e.g. ocular lesions causing blindness, and mortality, due to central nervous system involvement, bowel perforation, or vascular complications, may be significant [27,30].

3 Blood disorders

3.1 Anaemia

In case of anaemia due to iron deficiency, abnormalities of the oral mucosa may appear, such as atrophic changes [31]. These changes particularly affect the dorsal surface of the tongue. In general, the clinical aspects of atrophic epithelium of the dorsal aspect of the tongue is a common finding in the elderly population and, therefore, is not suggestive of an underlying iron deficiency anaemia. Furthermore, iron-deficiency anaemia may manifest with angular cheilitis and atrophy of the epithelium of the buccal mucosa [32].

Pernicious anaemia is a disorder characterized by megaloblastic haemopoiesis and/or neuropathy due to vitamin B12 deficiency as a result of severe atrophic gastritis. It is considered an autoimmune condition occurring frequently in elderly females. The diagnosis pernicious anaemia requires the demonstration of megaloblastic haemopoiesis, the presence of vitamin B12 deficiency, and the absence of gastric intrinsic factor. No specific pattern of oral signs and symptoms associated with vitamin B12 deficiency have been identified [33].

Sickle cell anaemia is an inherited multisystem disease caused by a defect in a chromosome. If only one of the pair of chromosomes is affected, the sickle-cell trait develops while sickle cell anaemia reflects the involvement of both chromosomes [34]. The defect results in an

amino acid substitution in the ß-haemoglobin chain of the red blood cells. Oral manifestations consist of mandibular osteomyelitis, anaesthesia of the mandibular nerve, and asymptomatic pulpal necrosis [35,36].

3.2 Leukaemia

Leukaemia, both acute and chronic types, may present either with ulcerations of the gingiva and the oral mucosa or with a firm elastic swelling of the gingival [37]. Furthermore, osseous changes in the jaws have been reported in up to 60% of cases. Radiographic findings may consist of loss or thinning of the crypts of developing teeth and of the lamina dura of erupted teeth, and displacement of teeth. Also bone destruction may be observed. Mental neuropathy, also called 'numb chin syndrome', may be the first symptom [38].

3.3 Thalassaemia

The thalassaemias are a group of inherited pathologic haemoglobin disorders resulting from a quantitative reduction of a specific globin chain. Normal adult haemoglobin consists of two alpha (α) and two beta (β) chains. The thalassaemias exhibit an imbalance in the production of either α- or β-chains. The imbalance is due to disturbances in the control mechanism of protein synthesis and results in altered function of the haemoglobin molecule and altered structure of erythrocytes; haemolysis is the most important consequence. The thalassaemias are classified according to the chain that is produced at the reduced rate. A homozygous, heterozygous, or double heterozygous form may be distinguished.

In the heterozygous α- or β-thalassaemia, also called thalassaemia minor, the disease tends to be mild, with minimal clinical expression. Homozygous and double heterozygous forms may become severe and are called thalassaemia major, also referred to as Cooley's anaemia or Mediterranean anaemia. Within the thalassaemia major group there are many genetic defects that produce various clinical and haematological findings.

Persons suffering from thalassaemia major are significantly growth-retarded. Also, extreme hypertrophy of the erythroid marrow in medullary and sometimes extramedullary sites is a well-known feature in thalassaemia major. Involvement of the facial skeleton resulting in severe disfigurement has been described in several reports [39]. Under the influence of the disorder, the typical facial appearance develops: high and bulging cheek bones, retraction of the upper lip, protrusion of the anterior teeth and spacing of other teeth, overbite or open bite, and varying degrees of malocclusion. The facial changes are the result of proliferation of the bone marrow in the facial skeleton, thus being extensively used as an ancillary haematopoietic organ to compensate for the chronic haemolysis. The bony changes may occur early in life and tend to persist, surgical correction sometimes providing a cosmetic solution.

4 Granulomatous diseases

4.1 Sarcoidosis

Sarcoidosis is an idiopathic, multisystem granulomatous disease, characterized by the presence of non-caseating giant cell granulomas [40]. Sarcoidosis affects people of all races, both sexes, and all ages. Considerable geographic differences in incidences exist, from as low as 1.4 per 100,000 population in Spain and Japan to as high as 35-64 per 100,000 population per year in the United States, the latter numbers reflecting the incidences in African Americans, whereas incidences of 10-14 per 100,000 population per year have been reported for white Americans [41].

The presenting features of sarcoidosis range from asymptomatic, but abnormal, findings on chest radiography in many patients to progressive multi-organ failure in a minority of patients [40]. The illness can be self-limited or chronic, often with exacerbations and remissions [40]. Lung involvement occurs in nearly all cases of sarcoidosis [42]. Furthermore, sarcoid lesions may occur in the skin, the liver, the spleen, the joints, the heart, the central nervous system, the eyes, the kidneys, the salivary glands, the oral mucosa and gingiva, and in the jaws

[43-46]. Oral mucosal lesions may become manifest as a solitary or multifocal nodule of a few millimeters up to more than one centimeter. These should not be confused with Fordyce's spots. Also, parotid involvement may occur, either alone or as part of the sarcoid manifestations in Heerfordt's syndrome, also called uveoparotitis, an extremely rare syndrome characterized by anterior uveitis, parotid enlargement, and paralysis of the facial nerve.

The differential diagnosis for systemic sarcoidosis includes foreign body granuloma, neoplasia, infectious and auto-immune diseases. Sarcoidosis is a diagnosis of exclusion since there is no diagnostic test [41]. The diagnosis of sarcoidosis can be confirmed by the histological demonstration of a granulomatous process without necrosis and after excluding other granulomatous disorders when feasible, e.g. tuberculosis.

Patients with oral sarcoidosis may develop systemic disease. Depending on additional history, screening for systemic involvement may include chest radiography -the presence of bilateral enlarged hilar lymph nodes supporting the diagnosis-, pulmonary function tests, a tuberculin skin test, erythrocyte sedimentation rate, hepatic and renal function tests, serum calcium, neurological evaluation, an electrocardiogram, and ophthalmic evaluation. Because elevated angiotensin converting enzyme levels at times may correlate with radiological and clinical abnormalities, these may serve as an adjunct but at the same time lack specificity for diagnosing sarcoidosis [41,47].

The indication for treatment of systemic sarcoidosis depends on disabling symptoms, organ dysfunction, and results of additional investigations [41]. Treatment of oral lesions is often not required, but corticosteroids may be administered in more extensive cases, either topical, intralesional, or systemic. Oral lesions as part of more extensive sarcoidosis activity generally respond with resolution when treatment of systemic disease is installed. However, these lesions often recur once therapy is discontinued. Hence, in chronic disease, often non-steroidal immunosuppressive drugs are used to avoid the side effects of steroids.

The prognosis of sarcoidosis is rather favourable with up to 60 % alone of patients experiencing spontaneous resolution. However, in 10-20% the disease is chronic and progressive, but only 1-5% of patients will eventually die of sarcoidosis, mostly due to failure of vital organs, especially the lungs and the heart [40].

4.2 Wegener's granulomatosis

Wegener's granulomatosis is a rare disease, first described in 1939 by Wegener [48], in which granulomatous destruction of the respiratory tract is associated with a generalized, necrotizing arteritis and glomerulonephritis.

In a recent British study, an incidence of 8 per million population per year was noted. Disease onset is usually between ages 25 to 55 years, with a male:female ratio of approximately 2:1. Since Wegener's description, clinical experience has promoted the concept of the idiopathic vascular disease progressing from involvement of the ears, the nose, the throat, and the sinus to involvement of the lungs and the kidneys. There may also be oral lesions, for instance of the gingival mucosa, so-called 'strawberry gums', the tongue or the palate, but they are seldom the first signs of the disease [49-51]. Salivary gland involvement also has been reported [52].

According to international criteria, a diagnosis of Wegener's granulomatosis is met with an 88% sensitivity and 92% specificity, if at least two of any of the following criteria are present:

(i) Nasal or oral inflammation, including the development of oral ulcers and purulent or bloody nasal discharge.
(ii) Abnormal chest radiograph, showing the presence of nodules, fixed infiltrates, or cavities.
(iii) Urinary sediment abnormalities, consisting of haematuria or red blood cell casts.
(iv) Histological examination showing granulomatous inflammation within the wall of an artery or in the perivascular area [52,53].

The differential diagnosis includes all disorders featuring a widespread vasculitis and/or granulomatous reaction. Although the aetiopathogenesis of Wegener's disease is not yet fully elucidated, anti-neutrophilic cytoplasmic antibodies (ANCA) are detected in 80-95% of patients [52,54], especially cytoplasmic (c) ANCA being rather specific and giving strong support to the diagnosis.

Untreated, Wegener's disease may be fatal in a fifth of patients within weeks to months, death commonly due to renal failure. The dismal prognosis of Wegener's granulomatosis already substantially improved with the introduction of corticosteroid drugs, but nowadays treatment usually consists of corticosteroids combined with cyclophosphamide [55]. With this regimen five-year survival of $\geq$ 90% and median survival of over 20 years have been reported [56].

However, disease- and treatment related morbidity is often profound. Follow-up of C-reactive protein and factor VIII levels together with the c-ANCA titers are of value in monitoring activity of Wegener's granulomatosis.

5 Hormonal disturbances

5.1 Addison's disease

Of the diseases of the adrenal glands, chronic insufficiency of the cortex, also called Addison's disease, is the most important one that may be accompanied by oral manifestations [57]. In most patients, Addison's disease is idiopathic, but it is commonly regarded as an autoimmune process. In the Western hemisphere, Addison's disease has an incidence of about 100 per million population per year [58].
In patients with Addison's disease, the skin and also the mucosa acquire a diffuse brownish discoloration, mimicking to some extent racial pigmentation [59]. The hyperpigmentation is caused by increased levels of beta-lipotropin or adrenocorticotrophic hormone (ACTH), each of which can stimulate melanocytes. Other symptoms in Addison's disease may consist of weakness, fatigue, weight loss, nausea, diarrhoea, and anaemia.
Apart from deranged plasma cortisol and ACTH levels, changes may be noted in the serum electrolyte levels. ACTH stimulation tests are often used as a diagnostic tool. These diagnostics often lead to establishing the diagnosis. A biopsy of a pigmented lesion of the oral mucosa would show acanthosis with silver-positive granules in the cells of the basal layer.
After treatment of the disease, i.e. in most cases by replacement of corticosteroids, the pigmentation will gradually disappear spontaneously. Since the introduction of corticosteroids, patients have a normal life span, although they should remain aware of using increased dosages of corticosteroids to compensate for stressful events.

5.2 Hyperparathyroidism

Normally, parathyroid hormone (PTH) is produced by the parathyroid glands in response to a decrease in serum calcium. A disease of one or more of the four parathyroids, usually a parathyroid adenoma but sometimes parathyroid hyperplasia -both so-called primary hyperparathyroidism-, may cause uncontrolled production of PTH. This abnormality is quite rare and appears more often in women than in men, usually at middle age. Hyperparathyroidism may also result from other disease: in patients with renal insufficiency, active vitamin D is not produced, leading to lower calcium absorption from the gastrointestinal tract and a decreased serum calcium with so-termed secondary hyperparathyroidism in response. [60].
Most patients are detected through raised plasma calcium on routine biochemistry. However, the mnemonic 'bones, stone, abdominal groans, and psychic moans' summarizes the range of

symptoms in symptomatic hyperparathyroidism: a variety of osseous changes, including fractures, renal stones, constipation, abdominal pain, duodenal ulcer, pancreatitis, and depression may occur. The two biochemical hallmarks of primary hyperparathyroidism are hypercalcaemia and hypophosphataemia - unless renal failure. Furthermore, a raised alkaline phosphatase level may represent evidence of increased bone turnover.
Through loss of phosphorus and calcium a generalized osteoporosis of the skeleton, including the jaw bones, may result. Due time, cyst-like defects in the bone develop. In a large series of hyperparathyroidism such a giant cell tumour or 'brown tumour' in the jaws has been found in just over 4% of cases. The 'brown tumour' is named after the colour of the tissue specimen, which is usually dark reddish-brown due to haemorrhage and consequent haemosiderin deposition within the osseous lesion. Occasionally, the jaw bone lesion is the first sign and leads to the detection of hyperparathyroidism. In a dentate jaw, a loss of structure of the alveolar bone may arise, resulting in an absence of the lamina dura or in severe chronic periodontitis. Resorption of the roots may take place as well. Histopathological examination of a 'brown tumour' often reveals vascular granulation tissue intermingled with numerous multinucleated osteoclast-type giant cells. Because of the possible histological resemblance with a central giant cell granuloma, in case of jaw bone lesions, it is important to look for the presence of hyperparathyroidism in these patients. Determination of the serum calcium may be considered a provisional biochemical screening. In addition, further examination by an endocrinologist should be considered.
In primary hyperparathyroidism, for a definitive treatment, the adenoma or hyperplastic parathyroid tissue must be removed surgically to reduce PTH levels to normal. In secondary hyperparathyroidism due to renal failure, treatment with an active vitamin D metabolite may temporarily control the problem of renal stones until renal transplantation provides a more permanent solution.

6 Lymphoreticular diseases

6.1 Multiple myeloma

Multiple myeloma (MM), also referred to as myeloma, myelomatosis, or Kahler's disease, is a B-cell malignancy of neoplastic plasma cells that generally produce a monoclonal immunoglobulin protein. MM belongs to a spectrum of disorders referred to as plasma cell dyscrasias. In the United States, each year 13,000 MM patients are diagnosed each year, with a male:female ratio of 2:1 and a median age of 65 years [61]. A multistep process is probably involved in the malignant transformation leading to myeloma. It is yet unclear whether all cases of MM evolve from a pre-existent essential monoclonal gammopathy or monoclonal gammopathy of unknown significance [61]. MM accounts for about one per cent of all malignancies and ten per cent of haematological tumours.
MM disease manifestations are heterogeneous and include tumour formation, monoclonal immunoglobulin production decreased immunoglobulin secretion by normal plasma cells

leading to hypogammaglobulinaemia, impaired haematopoiesis, osteolytic bone disease, hypercalcaemia, and renal dysfunction. Symptoms are caused by tumour mass effects and cytokines released by tumour cells or by host cells, i.e. marrow stroma and bone cells, in response to adhesion of tumour cells [61]. Furthermore, the abnormal MM protein may give rise to deposition diseases, such as amyloid light chain amyloidosis as presented in the following chapter, or autoimmune disorders, e.g. coagulopathies.

The first symptoms commonly consist of symptoms of anaemia, bone pain, or a pathologic fracture [61]. Usually several bones are involved at the same time. The skeletal lesions are usually confined to areas of red marrow and are located in the ribs, vertebrae, pelvis, skull, clavicles, sternum, femur and humerus.

Concerning the mouth, five per cent of patients with MM have involvement of the mandible [62,63]. This may result in anaesthesia or paraesthesia of the mental nerve. Lesions are rarely found in the maxilla. The radiographic aspect of the involved bone may show either a well-demarcated or a diffuse, destructive lytic lesion. Occasionally, external root resorption has been reported.

On histopathological examination of a biopsy specimen, aggregates of plasmacytoid cells are observed. These are usually monoclonal plasmacellular proliferations, which can further be determined with immunoperoxidase techniques. In most cases Russell's bodies, conglomerates of globulins, are present.

The diagnostic work-up scheme includes a full blood count, erythrocyte sedimentation rate, urea, creatinin, uric acid, calcium, albumin, alkaline phosphatase, and immunoelectrophoretic examination of plasma and urine. Further investigations comprise radiological imaging series of the skeleton and a bone marrow biopsy. Major criteria for the diagnosis of MM include the demonstration of marked marrow plasmacytosis, lytic bone lesions, and monoclonal protein in serum and/or in urine [64].

Treatment for MM depends on patient characteristics and tumour stage. Over the past decades, 'standard therapy' for MM has consisted of oral melphalan and predisolone, resulting in control of symptoms and/or tumour mass reduction by no more than 50% in one-half of patients and providing complete remission in only five per cent of patients. Recent studies with treatment comprising high-dose melphalan with autologous stem cell transplantation have demonstrated an induction of complete remissions up to 50% of patients as well as improved event-free and overall survival durations [65].

7 Miscellaneous diseases

7.1 Langerhans' cell histocytosis

Langerhans' cell histocytosis (LCH) is characterized by proliferation of histiocytes, either tissue macrophages or bone-marrow derived Langerhans' cells. Although the LCH cells within the lesions are clonal, LCH is generally not regarded as a neoplasm [66]. LCH has a prevalence of 1 in 50,000 population and an incidence of 1 per 200,000 population per

year for children under the age of 15 years. The disease is predominantly seen in children and young adults, twice as often in males as in females [67]. The aetiology and pathogenesis of Langerhans' cell histiocytosis (LCH) remain unknown.

Based on the clinical findings, three subgroups of LCH can be distinguished:

(i) Acute disseminated LCH (previously referred to as Letterer-Siwe disease).
(ii) Chronic disseminated LCH (previously referred to as Hand-Schüller-Christian disease).
(iii) Chronic focal LCH (previously referred to as eosinophilic granuloma) [68].

Langerhans' cell histocytosis is a disease that in most cases appears in a disseminated form in the bone and is characterized by proliferation of histiocytes and a varying number of eosinophilic leucocytes. The differential diagnosis between focal and disseminated presentations is determined by an initial bone scan and by the presence or absence of new lesions over an arbitrarily chosen period of 12 months. Common sites of involvement are the skull, the mandible, the ribs, the femur, and the vertebrae [69].

In some cases the oral lesions are the initial manifestation of the disease [70]. Involvement of the jaw bones occurs in approximately ten per cent of all cases [67,71]. Also the mandibular condyles may be involved [72]. Furthermore, the soft tissues, particularly the gingiva, may be affected [73], resulting in the clinical appearance of gingivostomatitis [74,75]. Symptoms such as pain or a slow-growing swelling may be present.

Sometimes LCH is an incidental finding on the orthopantogram radiograph. The bone lesions are often solitary, radiolucent and often ill-defined [76-78]. However, the lesions in the jaws -nearly always limited to the mandible-, may also be well-circumscribed and may even mimic the features of a cyst or granuloma and, in some cases, periodontal disease. On the other hand, lesions may occur in a multifocal fashion [79].

Light microscopic examination shows an accumulation of histiocytes in the presence, particularly in the early stage, of many eosinophils. The nuclei of Langerhans cells are indented and often kidney bean-shaped. The use of S-100 monoclonal antibody either on fresh tissue or on paraffin-embedded sections can be of additional help, together with the anti-T antibody reaction to CD1A. Ultrastructural examination may be helpful as well, since the observation of Langerhans' granules, also referred to as Birbeck granules, in histiocytic cells is considered diagnostic.

In general, the prognosis for single-system disease is favourable. Surgical curettage is usually sufficient. Occasionally, irradiation in a limited dosage of 300-600 rads has been applied successfully. Also effective treatment with intralesional injection of corticosteroids has been reported [80]. However, in the disseminated form, Langerhans' cell histiocytosis is an unpredictable disease for which treatment is not always effective. Recurrences have been observed up to 10 years after first treatment. Young age at diagnosis, hepatosplenomegaly, thrombocytopenia, and polyostotic ($\geq$ 3 bones involved) disease are associated with a poor prognosis [66,67].

7.2 Salivary gland involvement in systemic diseases

A labial or a palatal biopsy may be helpful in establishing the diagnosis of a systemic disease such as amyloidosis [81], sarcoidosis [82], Wegener's granulomatosis [83], Crohn's disease, or Sjögren's syndrome. Also a biopsy of the sublingual salivary gland has been used for this purpose. The sialographic features in these diseases are usually not typical.
In patients with rheumatoid arthritis or systemic lupus erythematosus a significant increase in the density of IgG cells within the salivary glands is found. The altered salivary composition in systemic lupus erythematosus might indicate a subclinical involvement of salivary glands in these patients [84].
A rare case of submandibular salivary gland involvement in haemochromatosis has been published [85].
Apart from increased salivary gland adiposity in alcoholic cirrhosis, there is no general salivary structural abnormality associated with chronic alcohol abuse [86].
Heerfordt's syndrome, also called uveoparotitis, is an extremely rare syndrome characterized by anterior uveitis, parotitis, and paralysis of the facial nerve. At present the syndrome is considered to be a subacute type of sarcoidosis.
Bilateral or unilateral enlargement of the parotid gland has been noted in HIV-infected patients [87] and in these cases is termed HIV-associated salivary gland disease (HIV-SGD). The swelling may be painful and is often associated with decreased salivary flow. HIV-SGD is a relatively common phenomenon in HIV-infected children.
A characteristic cystic appearance has been noted in these lesions on clinical and radiographic examination. While clinical symptoms are similar to Sjögren's syndrome, patients with HIV-SGD lack circulating anti-SS-A/Ro and anti-SS-B/La.
Histologically, a benign lymphoepithelial infiltrate with cystic degeneration is found in parotid specimens from these patients, being more or less similar to lymphoepithelial cysts in HIV-negative patients [88]. Presence of a non- Hodgkin lymphoma has also been reported [89,90].
Low-dose radiation therapy (8-10 Gy) provides reliable but temporary cosmetic palliation for HIV-SGD; higher initial doses of irradiation may be required to prolong relief and eliminate recurrences [91].

8 Mucocutaneous disorders

8.1 Acanthosis nigricans

Acanthosis nigricans (AN) is a mucocutaneous disorder, characterized by hyperpigmentation and hyperkeratosis of the epidermis. The typical appearance is of hyperpigmented, roughened papillomatous plaques giving a velvety consistency, and, infrequently, of verrucous papillomatosis [92]. In the United States, AN has a prevalence of approximately seven per cent in a general adolescent population, the prevalence varies from as low as about one per cent in Caucasians up to 13% in African Americans [93].

Acanthosis nigricans can be classified into various types, each being associated with insulin resistance. It has been put forward, that tissue resistance to insulin results in the pancreatic isle B-cells producing increased quantities of insulin. At low concentrations, insulin preferentially binds to the insulin receptor, but at higher concentrations insulin would have a greater affinity for insulin-like growth factor receptors. In turn, the latter are thought to induce proliferation, clinically seen as acanthosis. This unifying hypothesis could explain all types of AN [94].
Apart from the cosmetic aspect, AN is generally asymptomatic. It may serve as a mucocutaneous marker for a variety of systemic disorders including endocrinopathies, such as elevated plasma insulin levels, autoimmune disease, especially systemic lupus erythematosus, and malignant tumours of internal organs. The distinction between the two main groups, i.e. the benign form, including pseudo-acanthosis nigricans, and the malignant type is important for the latter is associated with malignant neoplasms.
In the group of benign AN, cutaneous lesions are usually mild as compared to the malignant form. Involvement of the oral mucosa is rare in benign AN but may be noted as small furrows. Unlike the benign forms, malignant AN is usually of sudden onset, rapidly progressive, and pruritic. Diffuse keratoderma on the palms and soles is commonly noted in malignant AN. Furthermore, also in contrast to the benign types of AN, about one-half of patients with the malignant type has lesions in the oral cavity, especially on the tongue and the lips, consisting of papillomatous proliferations [95]. Unlike the skin lesions, the oral lesions seldom show hyperpigmentation [95].
The malignant type may be preceded by, associated with, or followed by the detection of cancer elsewhere in the body, commonly an adenocarcinoma of the digestive tract, especially of the stomach [95-97]. In these cases AN may behave as a paraneoplastic mucocutaneous manifestation, remitting with reduction of tumour load [98-100]. However, in many cases, the tumour is very aggressive, preventing disappearance of lesions to be observed due to short survival time.
Although only in a minority of all patients with AN systemic disease may be found, the presence of oral AN lesions may stimulate further evaluation for the presence of associated systemic disease or an underlying malignancy, if not known already [101].

9 Syndromes

9.1 Cowden syndrome

Cowden's syndrome is named after the first described affected family [102]. It is a rare disorder predominantly characterized by the occurrence of multiple hamartomas of ectodermal, mesodermal, and endodermal tissues associated with a predisposition to development of malignant tumours, especially breast cancer [103].
Cowden's syndrome is autosomal dominantly inherited with variable expression [104]. The gene for Cowden's syndrome has been mapped to chromosome 10. Subsequently, germline

mutations in phosphatase and tensin homolog (PTEN), a tumour suppressor gene, have been identified in affected patients [104-106].
Hamartomatous lesions may arise in the skin, oral mucosa, breast, thyroid, central nervous system, the gastro-intestinal and genito-urinary tract [103]. Mucocutaneous lesions are invariably present in all reported cases by the age of twenty years and are diagnostically the most important [107]. The cutaneous lesions consist of peri-oroficial facial papules, acral warty keratoses, and palmar-plantar small translucent keratoses. The lesions have a hyperkeratotic, flat-topped appearance. Histopathologically, these are mostly identified as trichilemmomas -pathognomonic in combination with the clinical findings- or related benign tumours of the follicular infundibulum [103,107]. Cosmetic surgical excision of cutaneous lesions may be performed. Oral lesions usually present as papillomatosis of the lips, tongue, palate, and buccal mucosa [108,109]. Apart form the mucocutaneous findings, craniomegaly is most frequently encountered, affecting about 70 % of patients, often already at young age [107].
A range of other abnormalities has been reported in Cowden's syndrome, most frequently involving the thyroid and breasts. Thyroid disease -usually goitre or an adenoma, but few carcinomas have also been described- is the most common internal abnormality in these patients. Polyps of the gastro-intestinal tract and cysts and polyps of the female genito-urinary tract also frequently occur. Fortunately, seldom malignant changes of these abnormalities has been described. However, the most important association of Cowden's syndrome is with pathology of the breasts. The majority of women have severe fibrocystic disease of the breasts and in approximately 30 % malignant transformation into an adenocarcinoma may occur [107]. Since these changes may have an early onset, early recognition and diagnosis of Cowden's syndrome has been stressed and screening of at-risk family members or even prophylactic mastectomy has been recommended [110-112].

9.2 Gardner's syndrome

Multiple osteomas of the jaws are a characteristic feature of Gardner's syndrome, which consists of multiple polyps in the colon and rectum, multiple cutaneous and subcutaneous fibrous tumours, thyroid carcinoma, characteristic retinal pigmentation, osteomas of the long bones, the skull, and the jaws, and multiple impacted, supernumerary teeth [113,114]. The disorder is of an autosomal dominant trait with nearly 100% penetrance, but variable expression. The genetic defect is a mutation of the adenomatous polyposis coli gene, which has been mapped to chromosome 5. A few cases have been reported in which no hereditary pattern could be recognized.
It has been observed that familial polyposis coli is often accompanied by gastric polyps and occult osteomatous changes of the mandible. Therefore, it has been considered/ stipulated that familial polyposis coli and Gardner's syndrome are substantially the same entity [115].
By age 40, malignant transformations often occur in the intestinal polyps. Because of the inherent risk of malignant change, prophylactic colectomy is recommended as intervention as soon as the diagnosis has been established. If rectal mucosa is remaining, continued endoscopic surveillance is mandatory in view of the still increased risk of developing rectal carcinoma [116].
A single osteoma of the mandible can be the first manifestation of Gardner's syndrome. In a study of fifty patients with familial adenomatosis coli, osteomatous jaw changes were seen in 82% as compared with 10% in matched controls; supernumerary teeth, compound odontomas and/or impacted teeth were observed in 30% of the patients compared with 4% of the controls [117].
The radiograph of an osteoma of the jaws shows a rather circumscribed, opaque structure. Microscopic examination shows well-differentiated mature bone tissue, with a predominantly lamellar structure, without the presence of a true capsule. Apparently, there are no histologic differences between isolated osteomas and osteomas in patients suffering from Gardner's syndrome.
reatment of the osteomas consists of surgical removal. Recurrences are uncommon. Malignant transformation has never been reported.

9.3 Neurofibromatosis

Oral neurofibromas can be a manifestation of neurofibromatosis (NF). Diagnostic criteria for neurofibromatosis have been outlined [118]. In general, two distinct forms are recognized. NF type I constitutes about 90 % of all NF cases and is characterized by an abnormal proliferation of neural crest-derived cells, via abnormal growth of melanocytes manifesting as the so-called 'café-au-lait spots'. Furthermore, NF type I may induce neurofibromas, hamartomas of the iris, and other defects of the nervous and skeletal systems. This NF type I is the classic form of Von Recklinghausen's disease. NF type I is an autosomal dominant disease, the responsible gene being located at chromosome 17. The estimated incidence is approximately 1 per 4,000 population per year. NF type II, the responsible gene located at chromosome 22, is characterized by the development of bilateral acoustic neuromas, sometimes in association with other central nervous system tumours, such as meningiomas [119,120].
In a series of 38 patients with NF, usually type I, the majority had at least one intraoral clinical or radiographic sign of the disease [121]. Mandibular deformities and enlargement of the mandibular foramen are rather common. Oral neurofibromas cannot easily be removed because of often multiple or widespread presentation and lack of encapsulation [122,123].
One of the most feared complications of NF type I is the development of malignancy, which is estimated to occur in about five per cent of cases [124]. The most common associated malignancy is neurofibrosarcoma. Hence, follow-up may be indicated.

9.4 Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is a hereditary, autosomal dominant disorder, characterized by polyposis of the intestines, hyperpigmented maculae on the skin, especially in the face around the eyes and the mouth, and pigmentation of the oral mucosa. The gene is probably related to chromosome 19 [125]. The syndrome occurs once in 8,300-29,000 births [126] and appears as often in men as is in women.

This syndrome is associated with hamartomatous polyps. These polyps can occur anywhere in the small and large intestines and may occasionally also be located in the stomach. Only a few cases have been reported of malignant transformation of such polyps into a gastro-intestinal carcinoma. It is generally recommended that gastro-intestinal polyps larger than 1.5 cm be surgically removed. Furthermore, patients with Peutz-Jeghers syndrome are reported to be at a risk to develop malignant neoplasms in various other organs [127].

Although the cutaneous lesions may disappear with in adolescence, the mucosal pigmented lesions do not show spontaneous regression. Concerning the oral mucosa, the hyperpigmentations of the labial and oral mucosa is usually present at birth and appears as small brown maculae, measuring 1-5 mm. The buccal mucosa is the site of preference. The pigmented lesions in themselves do not require treatment or follow-up.

9.5 Naevoid basal cell carcinoma syndrome

The naevoid basal cell carcinoma syndrome (NBCS), also called Gorlin syndrome [128], is a rare hereditary entity, consisting of multiple basal cell carcinomas developing at young age, palmar and plantar pits, odontogenic keratocysts, calcification of the falx cerebri, and skeletal abnormalities, including anomalies of the spine and ribs. Mutations in the human homologue of a Drosophila gene, patched, underlie the development of basal cell carcinomas [129]. Human patched is mutated in sporadic as well as in hereditary basal cell carcinomas, and inactivation of this gene is probably a necessary step for tumour formation [129]. NBCS is an autosomal dominant disorder with variable expression in which homozygous allelic loss of patched gene, a human tumour suppressor gene located on chromosome 9, has recently been detected [130]. Supposedly due to the same patched gene mutation, patients with NBCS are more prone to developing cutaneous tumours on exposure to solar radiation and irradiation. Furthermore, the most commonly associated malignancy is a medulloblastoma. Other reported malignancies include astrocytomas, meningiomas, and craniopharyngiomas, and, to an even lesser extent, Hodgkin lymphomas and fibrosarcomas.

Apart from the aforementioned features, physical findings in NBCS may include 'coarse face', relative macroceophaly, hypertelorism, 'frontal bossing', and pectus deformity.

Oral lesions in NBCS usually comprise keratocysts of the jaw bone, sometimes solitary but often multiple [131], more commonly involving the mandible, sometimes at young age. Keratocysts are found in 90% of NBCS patients. Enucleation of odontogenic cysts in this group of patients is associated with a higher recurrence rate and does not prevent the development

of additional jaw cysts. Other associated oral abnormalities include clefts of the lips and/or palate.

Although most of the anomalies in NBCS are minor and usually not life-threatening, once the diagnosis of NBCS is established in a patient, genetic counselling and examination of family members may be recommended.

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Chapter III

Amyloidosis of the tongue as a paraneoplastic marker of plasma cell dyscrasias

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Abstract

Objective

To study the results of the medical work-up in patients presenting with amyloidosis of the oral cavity.

Study design

Patients diagnosed with amyloidosis of the oral cavity in the period January 1971 - January 2001 at the departments of Oral and Maxillofacial Surgery/Oral Pathology and Dermatology of the VU Medical Center, Amsterdam, The Netherlands, were included in this retrospective case study. In total, this series comprises 11 patients, nine female and two male. The patients' medical work-up and final diagnoses were traced via the medical records.

Results

All but one patient presented with amyloidosis of the tongue, most of them manifesting as macroglossia. In seven out of the 11 included patients a diagnosis of myeloma could be established shortly after their referral to the above-stated departments. Three of the four remaining patients appeared to suffer from a monoclonal gammopathy of undetermined significance and one patient was diagnosed with a lymphoplasmacytoid non-Hodgkin lymphoma (immunocytoma).

Conclusions

Amyloidosis of the oral cavity predominantly involves the tongue, mainly manifesting as macroglossia. Amyloidosis of the tongue is associated with an occult underlying plasma cell dyscrasia, in particular myeloma, and, therefore, should be regarded as a paraneoplastic phenomenon of these hematologic diseases.

Introduction

Amyloidosis refers to the extracellular deposition of any of a group of unrelated proteins [1,2]. With light microscopy, amyloid appears as an eosinophilic amorphous substance, which on Congo red staining demonstrates green birefringence when polarized light is used [1,2]. Amyloidosis has an incidence of about eight per one million persons per year [3].

The clinical type of amyloidosis varies with the biochemical composition of the amyloid fibril protein and its pathogenesis [2]. Amyloid deposits may be systemic, i.e. distributed throughout many organs of the body, or localized, i.e. being restricted to single organs such as the lungs, brain, or skin [1]. For the past decades, three types of systemic amyloidosis were recognized. The familial type was based on inheritance. The secondary type was characterized by long-standing inflammation, such as chronic infection (e.g. tuberculosis) or rheumatoid arthritis. All other types of systemic amyloidosis were classified as primary, i.e. meaning idiopathic in that era, but later shown to be associated with lymphoid or plasmacellular dyscrasia, with or without overt lymphoid malignancy.

The current classification of amyloidosis is based on the biochemical composition of the amyloid subunit protein (Table I) [4]. Only the AL (amyloid light chain) type amyloidosis is associated with plasma cell dyscrasias [4]. The amyloid deposits in case having been shown to be intact immunoglobulin light chains, fragments of these or fragments of immunoglobulin heavy chains [4]. In these conditions amyloid deposition occurs as a result of lymphoid or plasma cell dyscrasia and abnormal light chains of identical structure are almost always present in the serum or urine (so-called Bence Jones proteins) [1]. Most immunoglobulin amyloid fibril proteins are of lambda type, as are the serum monoclonal immunoglobulin proteins from which they are derived [1]. Typically, in AL amyloidosis the amyloid involves the tongue, heart, gastrointestinal tract, skeletal and smooth muscle, carpal ligaments, nerves, and skin [1,2]. This type of amyloidosis has high mortality rates, predominantly caused by cardiac arrhytmias and renal insufficiency.

Table I: Classification of amyloidosis by the composition of amyloid subunit protein

Amyloid subunit protein	*Precursor*	*Clinical manifestation or associated diseases*
AL or AH	Ig light chain or Ig heavy chain	Monoclonal B-cell proliferation
Amyloid A	Serum amyloid A	Chronic inflammatory diseases
		Connective tissue diseases
		Hodgkin's disease
		Renal cell carcinoma
Transthyretin amyloid	Transthyretin	Familial
		Senile
β_2-microglobulin amyloid	β_2-microglobulin	Dialysis
		Carpal tunnel syndrome
β protein amyloid	ABPP	Alzheimer's disease

AL / AH = immunoglobulin light/heavy chain amyloid;Ig = immunoglobulin;
ABPP = amyloid β protein precursor

Retrospectively, we have analyzed a group of patients with oral manifestations of amyloidosis with emphasis on a search for possibly underlying or associated systemic diseases.

Patients and methods

Patients diagnosed with amyloidosis of the oral cavity in the period January 1971 - January 2001 at the departments of Oral and Maxillofacial Surgery/Oral Pathology and Dermatology of the VU University Medical Center, Amsterdam, The Netherlands, were included in this retrospective case study (Fig. 1). The diagnosis of amyloidosis was established on histological examination, including Congo red staining (Fig. 2). The medical records were reviewed in order to be informed about a possible underlying or associated systemic disease, the amyloid type, other proven sites of amyloid involvement, treatment, and outcome. Follow-up time was measured from first visit to the above departments until the last visit to one of the participating departments, or until date of death.

The included group of patients consisted of nine females and two males (female to male ratio of 4.5). The mean age at first presentation to our departments was 68.5 years (range 50 to 82 years). Apart from the tongue and other oral lesions, other sites of proved amyloid involvement included the carpal ligaments, heart, gastrointestinal tract, skin, proximal muscles, kidney, and eyes. All patients were treated with chemotherapy. In only one patient (patient #7) also surgical correction of the nodular amyloid lesions was performed. A summary of the patients' data is presented in Table II.

Results

Diagnostic work-up was performed at the department of Hematology, VU University Medical Center, Amsterdam, The Netherlands, and included immunoelectrophoretic examination of plasma and urine protein, and bone marrow biopsy. If appropriate, CT scanning of thorax and abdomen, or radiological skeletal survey were performed. In all eleven patients an underlying hematologic disorder of the B-cell lineage was discovered. Only one patient (patient # 5) had been diagnosed as such before the macroglossia became manifest. Seven patients (patients # 2-4,6,8,9,11) were diagnosed to suffer from myeloma. In two patients (patients # 1 and #10) a monoclonal gammopathy of undetermined significance was detected and in one patient (patient # 7) a lymphoplasmacytoid non-Hodgkin lymphoma (immunocytoma) was found. All amyloid depositions were found to be AL type amyloid.

Discussion

In a review of 229 AL amyloidosis patients, a mean age of onset of 65 years was found with a slight male preponderance [5]. Although the current series of patients presented complaints

Table II: Patients' data

Case No.	Sex	Age (y)	Presenting oral complaint	Other sites with proven depositions	Diagnosed underlying disorder	Ig + light chain isotype	Rx	FU
1*	F	74	swelling of floor of mouth	skin	MGUS	Gλ	none	6 mos; DOD
2**	M	67	indurated tongue and floor of mouth	CTS kidney heart	myeloma	Gκ	chemo	3 mos; DOD
3**	F	82	macroglossia	none	myeloma	Gλ	chemo	14 mos; A&W
4	F	50	tongue nodules and ulceration	kidney intestines	myeloma	Gλ	chemo	9 mos; DOD
5	F	62	macroglossia	CTS chorioidea lungs heart joints	MGUS	Gλ	chemo	47 mos; DOD
6	F	80	macroglossia	CTS skin heart proximal muscles	myeloma	Gλ	chemo	14 mos; DOD
7	M	59	tongue nodules	none	lymphoplasma-cytoid NHL / immunocytoma	Gκ	chemo + surgery	120 mos A&W
8	F	66	indurated tongue, floor of mouth and buccal mucosa	CTS	myeloma	Gλ	chemo	6 mos; DOD
9	F	77	macroglossia swelling of gingiva and buccal mucosa	heart intestines	myeloma	Gλ	chemo	34 mos; DOD
10	F	63	macroglossia	CTS kidney heart	MGUS	Gλ	chemo	14 mos; A&W
11	F	73	macroglossia swelling of floor of mouth	heart skin	myeloma	Gλ	chemo	8 mos; DOD

M = male; F = female; CTS =carpal tunnel syndrome; MGUS = monoclonal gammopathy of undetermined significance; NHL = Non-Hodgkin lymphoma; Ig = immunoglobulin; λ = lamba; κ = kappa; Rx = treatment; chemo = chemotherapy; mos = months; A&W = alive and well; DOD = died of disease

* From Van der Waal I, Fehmers MCO, Kraal ER. Amyloidosis: Its significance in oral surgery. Review of the literature and report of a case. Oral Surg Oral Med Oral Pathol 1973;36:469-81.

** From Van der Wal N, Henzen-Logmans S, van der Kwast WAM, van der Waal I. Amyloidosis of the tongue: A clinical and postmortem study. J Oral Pathol 1984;13:632-9.

at a similar mean age, most of them were females (nine women vs. two men). This may represent an artifact due to the small number of patients.

Amyloid involvement of the oral tissues is rather rare, the tongue being the most encountered subsite and usually manifesting as rubbery or firm macroglossia, as was also found in the present series of patients [4,6]. The differential diagnosis of macroglossia occurring in adults includes hypothyroidism and squamous cell carcinoma. Amyloidosis of the tongue less often presents as localized induration, yellowish nodules, or raised white lesions. Sometimes, petechiae, ecchymoses, and hemorrhagic blisters can be present. The submandibular salivary glands are frequently involved with amyloid, particularly when the tongue is enlarged. All patients in this series were found to have AL type amyloid.

Medical work-up of the present group of patients revealed a hematologic disorder in all of them. One patient (patient #5) was already known with a monoclonal gammopathy of undetermined significance prior to developing the oral amyloidosis lesions. Therefore, amyloidosis of the tongue should be considered as a paraneoplastic manifestation of the underlying plasma cell dyscrasia. This is also supported by the observation of reduction of amyloid infiltration and prolonged survival when treatment of the underlying hematologic disorder is successfully carried out [7].

Although this study is hampered by the retrospective study design and the small number of patients, the importance of histopathological examination of acquired macroglossia at adult age in the absence of other known causes remains valid. In case of amyloidosis, further investigations, especially in search for an underlying lymphoid or plasma cell dyscrasia, or even overt myeloma, should be undertaken. The diagnostic work-up scheme includes a full blood count, erythrocyte sedimentation rate, urea, creatinine, uric acid, calcium, albumin, alkaline phosphatase, and immunoelectrophoretic examination of plasma and urine. Further investigations comprise radiological imaging series of the skeleton and a bone marrow biopsy [4].

We emphasize that macroglossia can be an important clinical feature in the detection of amyloidosis and, as a result, also of underlying hematological disorders, possibly aiding in earlier diagnosis, treatment, and improved prognosis.

Conclusions

Amyloidosis of the oral cavity predominantly involves the tongue, mainly manifesting as macroglossia. In this retrospective series, an evident association was shown with occult underlying plasma cell dyscrasia, in particular myeloma. Amyloidosis of the tongue should be regarded as a paraneoplastic marker of these hematologic diseases.

Hence, whenever amyloidosis of the oral cavity is suspected -in a patient not known with an associated disorder-, a biopsy is mandatory. When AL amyloid deposits are present, a medical work-up should be carried out in search for underlying disorders, especially focusing on the existence of gammopathies and their underlying lymphoid and plasmacellular malignancies.

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Chapter IV

Cheilitis granulomatosa

Cheilitis granulomatosa: a review of the literature
J Eur Acad Dermatol Venereol 2001;15:519-23.

Cheilitis granulomatosa: an overview of 13 patients with long-term follow-up. Report of management
Int J Dermatol 2002;41:225-9.

Cheilitis granulomatosa and optic neuropathy as rare extra-intestinal manifestations of Crohn's disease
J Clin Gastroenterol 2002;34:557-9.

Orofacial granulomatosis in a patient with Crohn's disease
J Am Acad Dermatol (in press).

4.1

Cheilitis granulomatosa: a review of the literature

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Abstract

Cheilitis granulomatosa, a rare inflammatory disorder with unclear etiology, is a disorder characterized by recurrent or persistent swelling of one or both lips that may be part of the Melkersson-Rosenthal syndrome or may be a manifestation of Crohn's disease.

An overview of the clinical features, histopathology, differential diagnosis, management strategies, and prognosis of cheilitis granulomatosa is presented and discussed with regard to the literature.

Cheilitis granulomatosa, the Melkersson-Rosenthal syndrome, and orofacial granulomatosis: nomenclature

Cheilitis granulomatosa, first described by Miescher in 1945 [1], is a rare inflammatory disorder that is clinically characterized by generally painless enlargement of one or both lips (Fig. 1), primarily affecting young adults. Although the swelling may initially be episodic, in the long-term the enlargement of the lips often persists. Histologically, non-necrotizing granulomas are seen, as well as oedema, lymphangiectasia, and perivascular lymphocytic infiltration (Fig. 2). Cheilitis granulomatosa can be part of the Melkersson-Rosenthal syndrome, the other manifestations being facial nerve paralysis and fissured tongue [2,3]. It should be stressed, that it is rare for all components of the Melkersson-Rosenthal syndrome to occur at the same time [4]. Often this diagnosis can only be established after several years of follow-up.

The term orofacial granulomatosis was introduced [5,6] to encompass the broad spectrum of non-necrotizing granulomatous inflammation in the oral and facial region, including patients with cheilitis granulomatosa, the complete Melkersson-Rosenthal syndrome, sarcoidosis, Crohn's disease, and infectious disorders, e.g. tuberculosis. Thus, orofacial granulomatosis is a unifying term representing a variety of diseases, consequently permitting the possibility of several underlying etiologic mechanisms, and also recognizing the problem that similar clinical and pathological presentations, often manifesting at different localisations in time, may sometimes only render a final diagnosis after years.

The differential diagnosis of acquired swelling of the lip is outlined in Table 1.

Table I: Differential diagnosis of acquired swelling of the lip

Acute	**Chronic**
Trauma	Post-traumatic
Infection	Odontogenic (post-) infection
– Herpes simplex	Non-odontogenic (post-) infection
– Streptococcus	– Tuberculosis
– Staphyloccus	– Atypical mycobacteria
– Trichophytosis	– Leprosy
– Diphteria	– Syphilis
– Syphilis	– Leishmaniasis
– Leishmaniasis	– Rhinoscleroma
– Trichiniasis	Neoplasm
Erythema multiforme	Actinic cheilitis
Angio-oedema	Orofacial granulomatosis
Allergic reaction	– Cheilitis granulomatosa
(Actinic cheilitis)	– Melkersson-Rosenthal syndrome
	– Sarcoidosis
	– Crohn's disease
	Idiopathic
	– Amyloidosis
	– Cheilitis glandularis

Etiology

The cause of cheilitis granulomatosa is unknown. In view of the fact that patients demonstrating cheilitis granulomatosa alone are regarded as a monosymptomatic 'forme fruste' or incomplete variants of Melkersson-Rosenthal syndrome [4,7,8], the reports suggesting a genetic predisposition, i.e. autosomal dominant inheritance with variable expression, to Melkersson-Rosenthal syndrome [9,10] might also be applicable to cheilitis granulomatosa; nevertheless, the possibility exists that these are separate diseases.
A few patients with orofacial granulomatosis, including patients with cheilitis granulomatosa, have undergone patch testing and revealed reactions to cobalt [11] or to food additives [12-14]. These reactions do not automatically imply to be clinically relevant [15], nor should they prompt routine allergology testing in every patient with orofacial granulomatosis. There is no conclusive evidence that cheilitis granulomatosa is due to atopy or an infective agent [4,8,16,17], although elimination of existing odontogenic foci has been reported to generate improvement in some Melkersson-Rosenthal patient [18]. Some patients with cheilitis granulomatosa may represent a localized form of sarcoidosis [19,20], although oral manifestations of sarcoidosis usually coincide with systemic signs and symptoms and consist of focal nodular elements [19,21], as opposed to the more diffuse lip swelling in cheilitis granulomatosa.
Cheilitis granulomatosa has been reported representing extra-intestinal Crohn's disease [21], with oral manifestations of this disease most often found after the diagnosis of Crohn's disease has already been established or coinciding with the onset of gastrointestinal and systemic signs and symptoms [22]. Cheilitis granulomatosa is found in only 0.5 % of patients with Crohn's disease [23]. Vice versa, Kano reported that some patients with cheilitis granulomatosa are predisposed to Crohn's disease [24], preceding intestinal Crohn's disease up to several years [25,26]. The histopathologic specimens of the lip lesions of patients diagnosed with Crohn's disease do not show specific features. Therefore, patients with cheilitis granulomatosa and persistent gastrointestinal complaints -not being diagnosed before-, should be advised to undergo additional investigations of the gastrointestinal tract to rule out Crohn's disease.

Epidemiological and clinical features

Although cheilitis granulomatosa is a rare disease combined with the fact that most data on this entity have been reported in studies that also included cases with the oligosymptomatic or complete variants of Melkersson-Rosenthal syndrome, cheilitis granulomatosa may have its onset at all ages, but most often develops in the second and third decades of life [9,21,27]. There is no gender or racial predilection [18,21,23].
The first manifestation is often an acute diffuse swelling involving the upper lip and - less often - the lower lip [18]. The first episode of oedema usually subsides completely in hours to days, making angio-oedema one of the differential diagnoses. Recurrent, painless attacks are

the rule with episodes usually increasing in duration as the disease progresses, as well as leading to persistent swelling that gradually becomes firmer. After some years, the swelling may slowly regress. Also, spontaneous resolution of cheilitis granulomatosa in its pure form, although uncommon, has been reported [9].
Since cheilitis granulomatosa is generally regarded as a monosymptomatic 'forme fruste' or abortive form of the Melkersson-Rosenthal syndrome [4,6,9] and is often reported upon as variant of this syndrome, it is noteworthy to state that in Melkersson-Rosenthal syndrome labial swelling occurs in about 75% [9]. Intraoral involvement may appear as swelling of the gingiva, buccal and palatal mucosa, sublingual area, tongue, and even the pharynx and larynx [21,28]. Occasionally involvement of oral tissues is accompanied by erythema, erosions, and pain. Furthermore, facial swelling occurs in 50% of Melkersson-Rosenthal cases, as does enlargement of regional lymph nodes [9]. The attacks of swelling are sometimes accompanied by fever and mild constitutional symptoms, including headache and even visual disturbance. Melkersson-Rosenthal syndrome is a neuro-mucocutaneous disorder, involving remittently both the mucocutaneous tisses and the orofacial innervation in a pathosis of complex origin by recurrent oedema [29]. Facial nerve palsy of the lower motor neuron type is reported as the initial symptom in 30 to 50% of patients with Melkersson-Rosenthal syndrome [18]. Although intermittent at first, the palsy may become permanent. It may be unilateral or bilateral, partial or complete [18]. Although, it may precede the attacks of cheilitis granulomatosa by months or years, it has been reported commonly to develop later [21]. Apart from the facial nerve, other cranial nerves - including the olfactory, auditory, glossopharyngeal and hypoglossal - may occasionally be involved.
A fissured tongue is reported in 20 to 60% of Melkersson-Rosenthal cases and may be associated with burning sensation, swelling, loss of sense of taste, and decreased salivary gland secretion [18,21]. The plicated tongue is present from birth in some patients, which may indicate genetic susceptibility [18,21]. On the other hand, the fissured tongue has also been described as a common anomaly in the general population [30] making its presence of less value in reaching a diagnosis of Melkersson-Rosenthal syndrome.
Although the diagnosis of cheilitis granulomatosa can actually be made based on the history and the clinical findings, the taking of a biopsy is indicated to rule out any other disease, e.g. amyloidosis, neoplastic disease. One may consider the use of fine needle aspiration cytology, but because of the accessibility of the lesion for biopsy and the more reliable nature of a histologic specimen, a biopsy is recommended indeed.

Histopathology

Biopsy of the swollen lip or facial tissues during the early stages of the disease often only shows oedema and perivascular aggregations of lymphocytes. In some cases of long duration no other changes are seen, but in others the infiltrate of the submucosal connective tissue becomes denser and focal non-necrotizing granulomas are formed with epithelioid cells and Langhans' type giant cells. These granulomas are often indistinguishable from those in sar-

coidosis or Crohn's disease. Similar changes may be present in submandibular and cervical lymph nodes [18,31,32]. In general, stains for mycobacteria and fungal organisms are recommended to exclude specific infectious disease.

Differential diagnosis

The differential diagnosis of swelling of the lip is extensive (Table I) but a good history and careful clinical examination will usually eliminate many diagnostic possibilities. The essential feature of the - variants of the - Melkersson-Rosenthal syndrome is the granulomatous swelling of lip, tongue or face. In the early presentations clinical differentiation from angio-oedema may be impossible in the absence of either fissured tongue or facial nerve palsy. Persistence of the swelling between attacks should suggest the diagnosis of cheilitis granulomatosa, which can sometimes be confirmed by biopsy. Necrotizing granulomas are not always present but can be helpful in establishing the diagnosis of cheilitis granulomatosa. However, the histological changes are neither always conspicious or specific nor are they a prerequisite for establishing the diagnosis of cheilitis granulomatosa. Ultimately, the diagnosis of cheilitis granulomatosa is made by correlation of the patient's history and clinical features, and possibly supported by the histopathological findings.

Management and prognosis

A rational treatment for cheilitis granulomatosa is difficult because of its unknown etiology. Furthermore, evaluation of treatment is often hampered by the nature of cheilitis granulomatosa, being a disorder characterized by recurrent swelling.

Removal of odontogenic foci may elicit a good response in some patients [15,18]. Initial treatment with antihistamine therapy brought relief in most patients. Reactions to dietary components should be sought in the history and possible antigens avoided.

Most therapeutic regimens include corticosteroid therapy - either topical, intralesional or systemic -, as an empiric approach to this inflammatory disease [33]. Response to such treatment is generally favorable but temporary. Patients with mild episodes of cheilitis granulomatosa benefit from treatment with triamcinolone in orobase or clobetasol in orobase.

Injections of up to 1 ml triamcinolone acetonide (10 mg/ml) into each side of the affected lip should be repeatedly given to patients with more pronounced manifestations [34,35]. The patients' compliance to intralesional therapy can sometimes be increased if mental nerve anesthesia is given before injection of the corticosteroid, thus also allowing higher-volume injections [35,36]. The injections may initially have to be administered every two weeks, and thereafter at monthly intervals once a response plateau has been reached [34]. This treatment has also been successfully combined with surgical reduction (Fig. 3) [34,37]. This cheiloplasty should only be performed in severely disfiguring cases and only once the disease is brought into a quiescent phase and should thereafter be treated with biweekly to monthly injections of triamcinolone 0.1 % injections for two to six months to prevent massive relapse [30,34]. The results of surgery alone have often been disappointing [18,39]. Systemic corticosteroids are rarely indicated, but can be of use when deterioration of the lip swelling occurs [33]. However, not all patients with cheilitis granulomatosa respond and adverse effects may be a problem [23,34].

Non-corticosteroidal regimens are alternatives for corticosteroid therapy. In small studies clofazimine has been reported to help the majority of patients [40,41], in a dose of 100 mg twice daily for 10 days, then twice to four times per week 100 mg for two to 12 months [33]. Metronidazole may also produce resolution in granulomatous cheilitis.[42,43] Other treatments which have occasionally been helpful include long-term penicillin, erythromycin, sulphasalazine, dapsone, ketotifen, and hydroxychloroquine sulfate [4,21,44].

The rationale for using hydroxychloroquine sulfate is based on the reported improvement of the specific cutaneous lesions of sarcoidosis with antimalarial therapy [45,46]. Although cheilitis granulomatosa and sarcoidosis are separate and distinct entities, the clinical presentation and histopathologic characteristics may be indistinguishable. For this reason hydroxychloroquine sulfate, or for that matter other antimalarials, might be beneficial in the management of cheilitis granulomatosa.

In view of reports that patients with cheilitis granulomatosa are predisposed to Crohn's disease, sulphasalazine and mesalazine have been used with variable success in treating cheilitis granulomatosa [24].

So far, none of the aforementioned therapies has proved uniformly and predictably successful. Therefore, management still consists of attempting to reduce swelling to an acceptable state for the patient, preferably by conservative means, but sometimes combined with surgical intervention. Non-corticosteroidal systemic modalities - such as clofazimine, hydroxychloroquine or sulfasalazine -, form alternative treatment options, thus avoiding the long-term side effects of corticosteroids. Surgical reduction should only be performed in severely disfiguring cases and only once the cheilitis granulomatosa is in a quiescent phase and it is recommended that the intralesional treatment postoperatively be continued to prevent relapse [30,34]. When management of cheilitis granulomatosa is carried out according to the described strategy, outcome is usually satisfactory.

Nevertheless, due to the nature of the affliction, minor recurrences of lip swelling can still occur. Furthermore, as in any chronic relapsing disease, support of the patient is important, not overlooking the evident cosmetic and psychological impact of cheilitis granulomatosa. Additional investigations to rule out other relevant causes or associated diseases are to be carried out guided by the history of every individual patient. Of course pulmonary symptoms should hint for sarcoidosis, as should gastro-intestinal complaints for Crohn's disease, but in our experience, most patients do not present with positive histories on possibly related diseases. Routine examinations, e.g. full gastrointestinal tract examinations to rule out Crohn's disease, in a patient without other complaints than the local swelling is not indicated and at the same time introduces the chance of morbidity. Instructing every patient to report their complaints on relevant disease entities during follow-up is foremost important in planning further investigations.

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4.2

Cheilitis granulomatosa: Overview of 13 patients with long-term follow-up. Results of management

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Abstract

Cheilitis granulomatosa, often regarded as a subtype of orofacial granulomatosis, is characterized by recurrent or persistent swelling of one or both lips. Classically, a non-necrotizing granulomatous inflammation is seen at histological examination. Although a relationship has been proposed between Melkersson-Rosenthal syndrome (and the monosymptomatic form cheilitis granulomatosa) and Crohn's disease on the basis of the orofacial swelling and similar histology, several other studies of Melkersson-Rosenthal syndrome have not found an association with Crohn's disease.

The clinical features, histopathology, association with Crohn's disease, and results of non-surgical and surgical therapy in this retrospective case study of 13 patients with a mean follow-up period of 8.2 years are presented and discussed with regard to the literature.

Since this study revealed a low chance of developing Crohn's disease, it does not seem justified to inform patients with cheilitis granulomatosa on the possibility that they might develop Crohn's disease. Patients with a negative history of gastrointestinal complaints should not be exposed to routine investigations of the gastrointestinal tract.

Management of cheilitis granulomatosa remains a challenge. Most patients in this study responded to non-surgical treatment modalities. Patients with deterioration of lip swelling usually respond to intralesional injections with triamcinolone or to short courses of systemic glucocorticoids. Furthermore, non-steroidal systemic modalities, such as clofazimine, hydroxychloroquine or sulfasalazine, form alternatives to glucocorticoid regimens, thus avoiding the long-term side effects of corticosteroids. Surgical intervention should only be performed in severely disfiguring cases.

Introduction

Cheilitis granulomatosa, first described by Miescher in 1945 [1], is a rare idiopathic inflammatory disorder clinically characterized by generally painless enlargement of one or both lips, primarily affecting young adults. Although the swelling may initially be episodic, in the long-term the enlargement may persist [2]. Actually, cheilitis granulomatosa is often regarded as an entity within the spectrum of orofacial granulomatosis. The term orofacial granulomatosis was introduced [3] to encompass the broad spectrum of non-necrotizing granulomatous inflammation in the oral and facial region, including patients with the complete triad of Melkersson-Rosenthal syndrome -the other manifestations being peripheral facial nerve palsy and fissured tongue-, cheilitis granulomatosa - often regarded as monosymptomatic from of Melkersson-Rosenthal syndrome [4] -, sarcoidosis, Crohn's disease, and infectious disorders, e.g. tuberculosis. Thus, orofacial granulomatosis is a unifying term representing a variety of diseases, consequently permitting the possibility of several underlying etiologic mechanisms, and also recognizing the problem that similar clinical and pathological presentations, often manifesting at different localisations in time, may sometimes only render a final diagnosis after years.

Histologically, non-necrotizing granulomas are seen, as well as oedema, lymphangiectasia, and perivascular lymphocytic infiltration. However, the histological changes are neither always present or specific, nor are they a prerequisite for establishing the diagnosis of cheilitis granulomatosa [4]. Ultimately, the diagnosis of cheilitis granulomatosa is made by correlation of the patient's history and clinical features, and supported by the histopathological findings.

Cheilitis granulomatosa may occur without other signs of disease but may also be part of the Melkersson-Rosenthal syndrome [5] or may be a manifestation of Crohn's disease [6] and, rarely, of sarcoidosis [7].

Management of cheilitis granulomatosa is difficult, as is shown in the literature. This applies both to the type of diagnostic work-up that should be done, as well as to therapy. Different treatment modalities have been reported, varying from various conservative treatments to surgical interventions with variable outcome [5].

In a retrospective study of 13 patients with cheilitis granulomatosa, we evaluated the association with systemic disease and analysed the clinical efficacy of several non-surgical and surgical treatment modalities.

Patients and methods

Patients diagnosed with cheilitis granulomatosa in the period January 1977 - January 2001 at the departments of Oral and Maxillofacial Surgery/Oral Pathology and Dermatology of the University Hospital Vrije Universiteit, Amsterdam, The Netherlands, were included in this retrospective case study. The diagnosis of cheilitis granulomatosa was established on the patient's history, clinical features as well as histopathological features, if applicable. Follow-up

time was measured from first visit until the last visit for the cheilitis granulomatosa; only patients with a minimum follow-up period of one year were included.
The patients' histories were reviewed via the medical records in order to detect systemic signs and symptoms, with special regard to respiratory and gastrointestinal complaints, possibly pointing to sarcoidosis or Crohn's disease, respectively.
In evaluating treatment results, the outcome of non-surgical and surgical therapeutic modalities, as established at the patient's last visit, was recorded as "none", "moderate" or "good".

Results

The included group of patients consisted of seven females and six males (female to male ratio of 1.17). The mean age at first presentation to our departments was 32.8 years (range 15 to 56). Patients had a mean follow-up time of 8.2 years (range 1.1 to 24 years). A summary of the patients' data is presented in Table I.
Apart from lip lesions, other involved sites included the tongue, gingiva, eyelids, philtrum, nose, cheeks, and facial nerves. Three of the 13 patients revealed the complete triad of Melkersson-Rosenthal syndrome (patients #7, #10, and #12), based on the signs and symptoms at presentation and a previous history of temporary facial nerve palsy.
In 11 of the patients a biopsy had been performed, whereas in two patients no permission for a biopsy was obtained. The results of all histopathological examinations were consistent with the diagnosis of cheilitis granulomatosa. Stains for acid-fast bacilli, fungi, and spirochetes were negative in all reported patients. Although most specimens showed granulomas, some being composed of epithelioid cells and accompanied by giant cells, other specimens did not show a specific inflammatory pattern.
None of the reported patients had a history pointing to a possible allergic etiopathogenesis nor did any of the patients have a history of respiratory complaints or was diagnosed with sarcoidosis prior to the first visit. Although both patient #12 and patient #13 had suffered from gastrointestinal complaints during several years before presenting to our departments, repeated gastroenterologic investigations in that period had not revealed any abnormalities of the gastrointestinal tract.
Patients with mild lip swellings (patients #4-5, #9-11) were started on topical steroids. More pronounced swelling of the lip or deterioration of lip swelling was treated with intralesional triamcinolone 0.1 % injections, whereas patients with more extensive lip swellings were initially treated with systemic medication (patients #1-3, #6-8, #12). Surgery had solely been performed in severely disfiguring cheilitis and only once the disease had been brought into a quiescent phase and could thereafter be treated with biweekly to monthly triamcinolone 0.1% injections for six months to prevent relapse [8]. In this series, cheiloplasty was undertaken in only two of the patients (patients #3 and #6), using the technique as described by Habel [9].
During follow-up, the patients # 8 and # 13 provided a history of watery and at times also bloody stools, prompting additional investigations. In both cases Crohn's disease was diagnosed on histologic specimens, obtained via colonoscopy, five years after the diagnosis of

Table I: Overview of patients' data

Pat	Sex	Age	Site(s)	Pathology	Treatment	Result	Feats.	FU
1	F	31	upper lip^{R} eyelids^{R} lingua plicata^{R}	epithelioid cell granulomas	hydroxychloroquine TCA injections	none moderate		23
2	F	24	upper lip^{R}	ND	clofazimine TCA injections	none good		2.1
3	M	44	lower lip^{R}	granulomas +	clofazimine TCA injections prednisolone cheiloplasty	none none moderate moderate		13.3
4	M	19	upper lip^{R} lower lip^{R}	non-specific	TCA in orabase	good		5.3
5	M	56	lower lip^{R} cheeks^{R}	epithelioid cell granulomas + giant cells	TCA in orabase	good		1.8
6	M	38	upper lip^{R} lower lip^{R}	non-specific granulomatas	prednisolone TCA injections cheiloplasty	moderate none moderate		1.7
7	F	41	left facial nerve^{R} upper lip^{R} lower lip^{R} lingue plicata^{F} nose^{F} cheeks^{F} right facial nerve^{F}	non-specific granulomas	clofazimine hydroxychloroquine dexamethasone metronidazole sulfasalazine TCA injections	none none moderate none none good	MRS	14.2
8	F	29	upper lip^{R} lower lip^{R}	granulomasa + giant cells	prednisolone hydroxychloroquine mesalazine	good none moderate	CD	24
9	M	15	lower lip^{R}	ND	clobetasole in orabase	good		1.8
10	F	21	upper lip^{R} gingiva^{R} lingua plicata^{F} right facial nerve^{F}	non-specific	clobetasole in orabase prednisolone	good good	MRS	8.1
11	F	53	lower lip^{R} upper lip^{R} lingua plicata^{F}	non-specific	clobetasole in orabase	moderate		1.3
12	F	25	upper lip^{R} lingua plicata^{R} philtrum/nose^{R} left facial nerve^{R}	non-specific	clofazimine	moderate	MRS	1.1
13	M	30	upper lip^{R} lower lip^{R} gingiva^{R}	non-specific granulomas	TCA injections mesalazine	moderate moderate	CD	9.3

Pat = patient. F = female; M = male.
Site(s) = site and chronological ordered onset of manifestation: R = manifestation prior to or at referral; F = manifestation occurring in follow-up period.
ND = not done. TCA = triamcinolone 0.1 %.
Feats. = specific features in particular patients
MRS = Melkersson-Rosenthal Syndrome (complete triad); CD = Crohn's disease.
FU = follow-up in years from referral to our departments

cheilitis granulomatosa had been established. Histopathologic results of the lip specimens from these patients diagnosed with Crohn's disease did not show distinguishing features.

Comment

The etiopathogenesis of cheilitis granulomatosa is still unknown. In the past, allergic reactions to cobalt [10] and food additives [11-13] have been implicated as an etiologic mechanism in cheilitis granulomatosa but none of the reported patients had a history pointing to a possibly relevant allergy. Although patients demonstrating cheilitis granulomatosa in its pure form are regarded as monosymptomatic variants of Melkersson-Rosenthal syndrome [5], only three of the present 13 patients were diagnosed with the complete triad of Melkersson-Rosenthal syndrome (patients #7, #10, and #12). Whether the reports suggesting a genetic predisposition to Melkersson-Rosenthal syndrome [14,15] are also applicable to cheilitis granulomatosa is uncertain. Taking the long follow-up time of the present study into account, the possibility exists that cheilitis granulomatosa and Melkersson-Rosenthal syndrome are separate diseases.

Although cheilitis granulomatosa has been suggested to represent a localized form of sarcoidosis in some patients [7], none of the reported patients in our series developed sarcoidosis prior to the onset of lip swellings or during follow-up. Lip lesions do occur in sarcoidosis [7,16], but in our experience these lesions consist of focal nodular elements on the lips as opposed to the more diffuse lip swelling in cheilitis granulomatosa.

Cheilitis granulomatosa has been reported representing extra-intestinal Crohn's disease, with oral manifestations of this disease most often found after the diagnosis of Crohn's disease has already been established or coinciding with the onset of gastrointestinal and systemic signs and symptoms [6]. Cheilitis granulomatosa is found in only 0.5 % of patients with Crohn's disease [6]. Kano reported that some patients with cheilitis granulomatosa are predisposed to Crohn's disease [17], preceding intestinal Crohn's disease up to several years [18,19]. In our study this was demonstrated by only two patients (patients # 8 and # 13). In both cases Crohn's disease was diagnosed five years after the diagnosis of cheilitis granulomatosa had been established. The histopathologic specimens of the lip lesions of patients diagnosed with Crohn's disease did not show specific distinguishing features. In view of the fact that only two of the patients in this long-term follow-up series developed Crohn's disease and reviews of larger numbers of patients did not bear out a relationship of cheilitis granulomatosa with Crohn's disease [4,20,21], we do not recommend routine investigations of the gastrointestinal tract in patients with cheilitis granulomatosa or Melkersson-Rosenthal syndrome with a negative history of gastrointestinal complaints. Also, it does not seem justified to inform patients with cheilitis granulomatosa on the possibility that they might develop Crohn's disease.

In our experience, management of patients with cheilitis granulomatosa remains a challenge and should be guided by the severity of the clinical manifestations. Non-surgical treatment was the most used modality. In about half the patients, treatment had been commenced with topical steroids (patients #4-5, #9-11). Due to the extensive lip swelling, treatment of most patients had

initially consisted of systemic medication, varying from prednisolone to clofazimine or hydroxychloroquine (patients #1-3, #6-8, #12). Six patients at some stage underwent triamcinolone 0.1% injections, as previously described [4], with variable result (patients #1-3, #6-7, #13). The two patients who were diagnosed with Crohn's disease (patients #8 and #13) showed a moderate reduction of cheilitis granulomatosa while being treated for their enteritis with mesalazine. Surgical intervention had only been performed in two of the patients (patients #3 and #6) with a moderately effective outcome. Both patients have thereafter maintained a remarkably reduced lip size, although minor recurrent episodes of lip swelling still occurred.

Although this study is hampered by the retrospective study design, the small number of patients, and the subjective evaluation of treatment results, most patients with cheilitis granulomatosa did benefit from long-term topical treatment with triamcinolone in orobase or clobetasol in orobase. Deterioration of the lip swelling usually responded to intralesional therapy with triamcinolone injections or short courses of systemically administered glucocorticoids. Other non-surgical interventions, such as clofazimine, hydroxychloroquine or sulfasalazine, form attractive alternatives to glucocorticoid regimens, thus avoiding many of the steroid-associated side effects. Surgical intervention should only be performed in severely disfiguring cases and only once the disease is brought into a quiescent phase and should thereafter be treated with biweekly to monthly injections of traimcinolone 0.1 % injections for two to six months to prevent relapse [8]. When management of cheilitis granulomatosa is carried out according to the above-described strategy, outcome is usually satisfactory. Nevertheless, due to the nature of the affliction, minor recurrences of lip swelling can still occur. Unfortunately, to date, there is no good study evaluating different treatment modalities. Therefore, treatment is currently mainly empiric, based largely on severity of symptoms. A prospective study is required to adequately and objectively assess the outcome of different treatment modalities.

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4.3

Cheilitis granulomatosa and optic neuropathy as rare extra-intestinal manifestations of Crohn's disease

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Abstract

Crohn's disease can be accompanied by extra-intestinal manifestations. We report a 39 year-old patient who presented with cheilitis granulomatosa as the first manifestation of Crohn's disease. Four years later, intestinal Crohn's disease was diagnosed. One year thereafter, acute loss of visual acuity due to optic neuropathy developed as another, rare extra-intestinal manifestation of Crohn's disease.

Introduction

Crohn's disease is a chronic, relapsing, inflammatory bowel disease of unknown etiology. Although any part of the gastrointestinal tract may be involved, inflammation of the terminal ileum, colon and anorectal area is most common. Transmural intestinal ulceration, fistula formation, and stricturing fibrosis are characteristic of inflammation due to Crohn's disease.
A spectrum of extra-intestinal diseases has been associated with Crohn's disease. The diagnosis of associated manifestations can precede, accompany or follow the diagnosis of intestinal Crohn's disease. We present a patient with two rare extra-intestinal manifestations of Crohn's disease: cheilitis granulomatosa and, even rarer, optic neuropathy.

Case report

In 1991, a 39-year-old Caucasian male was referred to the Department of Oral and Maxillofacial Surgery/Oral Pathology with recurrent swelling of both lips. His medical history stated a period in 1985 of abdominal cramps and diarrhea with mucus, but endoscopic examination and biopsy specimens had revealed no abnormalities. At the time of presentation gastrointestinal complaints were absent. On examination a lobulated swelling of the buccal mucosa was noted. Diffuse, firm elastic swelling of the lower lip could be palpated. There was no evidence of facial palsy or a fissured tongue. A biopsy of the lower lip showed non-caseating granulomas and confirmed the tentative diagnosis of cheilitis granulomatosa. Intralesional injections with up to 2 ml triamcinolone acetonide 10 mg/ml per session at monthly intervals for six months provided temporary relief.
In 1995, recurrent periods of abdominal cramps and diarrhea with mucus were evaluated at the Department of Gastroenterology. Routine laboratory investigations showed normal erythrocyte sedimentation rate and hemogram. Gross examination revealed patchy erythema in the sigmoid, and multiple biopsy specimens of the colonic mucosa showed focal granuloma formation, consistent with Crohn's disease. Although sulfasalazine 500 mg bid reduced the abdominal complaints and resulted in a normalised intestinal mucosa, as was confirmed by repeated colonoscopic investigations, the lip swelling persisted.
In 1996, an acute bilateral reduction in visual acuity developed, without concomitant gastrointestinal complaints. Slit lamp examination revealed no symptoms of optic neuritis, retinal vasculitis, macular edema or diffuse retinal pigment epitheliopathy. Serum concentrations of vitamin B12, folic acid and calcium were within the normal ranges. Additional investigations by MR-imaging showed no abnormalities of both optic nerves and excluded maxillary sinusitis or intracranial disease. Based on increased latency times in visual evoked potentials, neuropathy of both optic nerves was established. The bilateral central scotoma of seven degrees was suggestive for retrobulbar neuritis. Two intermittent courses of systemic steroids for three weeks in dosages up to 60 mg resulted in stabilisation of the visual acuity. Furthermore, the lip swelling decreased during this regimen

Discussion

Between 25 and 35% of patients with Crohn's disease develop at least one extra-intestinal manifestation [1]. A spectrum of manifestations, comprising dermatological (erythema nodosum, pyoderma gangrenosum), ocular (episcleritis, uveitis), skeletal (peripheral arthropathy, ankylosing spondylitis, sacroileitis), vascular (thromboembolic disease, vasculitis, arteritis), and hepatobiliary disorders (fatty liver, chronic active hepatitis, cirrhosis, primary sclerosing cholangitis, cholelithiasis, cholangiocarcinoma) has been described accompanying intestinal Crohn's disease [2]. Arthralgias, ocular and skin manifestations typically - but not exclusively, as demonstrated in the present patient - occur when intestinal disease is active [3].

Cheilitis granulomatosa is a rare idiopathic inflammatory disorder, clinically characterised by painless enlargement of one or both lips, primarily affecting young adults [4]. Cheilitis granulomatosa is found in only 0,5% of patients with Crohn's disease [5]. Histologically, noncaseating granulomatous inflammation, edema, lymphangiectasia, and perivascular lymphocytic infiltration are seen. Cheilitis granulomatosa has been reported as an extra-intestinal manifestation of Crohn's disease, preceding the diagnosis of intestinal Crohn's disease up to several years [6].

Ocular complications occur in 4 to 6% of patients with Crohn's disease [7]. Acute episcleritis, acute anterior uveitis, marginal keratitis, conjuctivitis, scleritis, orbital inflammatory disease, optic neuritis, ischemic optic neuropathy and retinal vasculitis have been described in patients with Crohn's disease. Optic neuropathy has been previously reported in association with Crohn's disease as an extremely rare complication [8].

In general, treatment of extra-intestinal symptoms of Crohn's disease starts with the treatment of the underlying disease. Treatment of Crohn's disease is usually performed by a step up strategy starting with mesalazine or antibiotics, followed by steroids, and eventually immunosuppression. In our experience, the relapse rate following treatment with systemic cyclosporine for refractory lesions in Crohn's disease is high. Sulfasalazine induced a satisfactory reduction of the intestinal inflammation in the patient. The optic neuropathy and cheilitis granulomatosa proved to be more refractory. Eventually, high dose steroids during several weeks induced remittance of both extra-intestinal complaints.

Depending on the extent of clinical manifestations of cheilitis granulomatosa, its treatment primarily consists of topical clobetasol cream, intralesional triamcinolone acetonide injections, or systemic corticosteroids [9]. Unfortunately, there is no uniformly and predictably effective treatment for cheilitis granulomatosa. Clofazimine, metronidazole, long-term penicillin, erythromycine, sulphasalazine, ketotifen, and hydroxychloroquine sulphate have been mentioned as therapeutic modalities in case reports. Combination with surgical intervention, such as cheiloplasty, can be considered in severely disfiguring cases.

Corticosteroids are the mainstay of treatment for ocular inflammation accompanying Crohn's disease. Severity of inflammation and response to therapy determine the need for topical, transseptal or systemic corticosteroids. Other therapeutic modalities for ocular inflammatory disorders include hydroxychloroquine sulphate, azathioprine, cyclophosphamide, cyclosporine, and non-steroidal anti-inflammatory drugs, such as indomethacin and oxyphenbutazone [10]. The latter class of drugs, however, is contraindicated in Crohn's disease. Rapid control of ocular inflammation can be achieved in most patients with inflammatory bowel disease, but severe visual loss and blindness have occurred.

Recently, a new form of biological therapy has revolutionized the therapy of refractory Crohn's disease. Anti-tumor necrosis factor alfa treatment (infliximab) has been reported to be beneficial in about 60-70 % of patients unresponsive to immunosuppressive therapy [11]. Also, efficacy of anti-tumor necrosis factor alfa has been reported in case of extra-intestinal Crohn's disease, such as arthritis [12] and pyoderma gangrenosum [13]. The effect of this new class of drugs on cheilitis granulomatosa and optic neuropathy has not yet been documented.

In view of the fact that patients who develop one extra-intestinal manifestation are at risk of developing other extra-intestinal manifestations, we emphasize that joined effort of the gastroenterologist, ophthalmologist, oral surgeon and dermatologist is mandatory for the adequate treatment of extra-intestinal manifestations of inflammatory bowel disease.

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Orofacial granulomatosis in a patient with Crohn's disease

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Abstract

Orofacial granulomatosis encompasses previously recognised clinical entities of Melkersson-Rosenthal syndrome and cheilitis granulomatosa. We report a 39 year-old patient who presented with cheilitis granulomatosa, intestinal Crohn's disease, and optic neuropathy. Cheilitis granulomatosa and optic neuropathy represent two rare manifestations of orofacial granulomatosis in Crohn's disease.

Introduction

The term orofacial granulomatosis has been put forward to encompass a spectrum of previously described conditions and implies the possibility of more than one underlying etiology.[1] Orofacial granulomatosis may present with diffuse swelling of the buccal mucosa, lips, cheeks, nose, eyelids, and forehead with histological evidence of noncaseating granulomatous inflammation [1]. Other, less common clinical manifestations of orofacial granulomatosis include oral ulceration, angular cheilitis, oral mucosal edema, hyperplasia and inflammation of the gingiva. Orofacial granulomatosis also includes Melkersson-Rosenthal syndrome. Facial nerve paralysis, orofacial swelling, fissuring of the tongue, lagophthalmus, keratitis, retrobulbar neuritis, diplopia, and paralysis of the medial rectus muscle have all been described in Melkersson-Rosenthal syndrome. We present a patient with cheilitis granulomatosa and optic neuropathy as two rare manifestations of orofacial granulomatosis in a patient with Crohn's disease.

Case report

In 1991, a 39-year-old Caucasian male was referred to the Department of Oral and Maxillofacial Surgery/Oral Pathology with recurrent swelling of both lips. His medical history stated abdominal cramps and slimy diarrhea, but gastrointestinal analysis in 1985 had revealed no abnormalities. At the time of presentation gastrointestinal complaints were absent. On examination a lobulated swelling of the buccal mucosa was noted. Diffuse, firm elastic swelling of the lower lip could be palpated. There was no evidence of facial palsy or a fissured tongue. A biopsy of the lower lip showed noncaseating granulomas and confirmed the tentative diagnosis of cheilitis granulomatosa. Repeated intralesional injections with up to 2 ml triamcinolone acetonide 10 mg/ml per session provided temporary relief.

In 1995, complaints of recurrent abdominal cramps and frequent diarrhea were evaluated at the Department of Gastroenterology. Routine laboratory investigations revealed normal sedimentation rate and hemogram. Colonoscopy and biopsy samples showed chronic inflammation and focal granuloma formation of the sigmoid. A diagnosis of intestinal Crohn's disease was established. Although sulfasalazine 500 mg bid reduced the abdominal complaints and resulted in a normalised intestinal mucosa, as was confirmed by repeated colonoscopic investigations, the lip swelling persisted.

In 1996, an acute bilateral reduction in visual acuity developed. Funduscopical symptoms of optic neuritis, retinal vasculitis, macular edema or diffuse retinal pigmentepitheliopathy were absent. Blood levels of vitamin B12, folic acid, calcium, and cortisol were within the normal ranges. Additional investigations by MR-imaging showed no abnormalities of both optic nerves and excluded maxillary sinusitis or intracranial disease. Because of increased latency times in visual evoked potentials, the ophthalmological diagnosis of neuropathy of both optic nerves was made. The bilateral central scotoma of seven degrees was suggestive for retrobulbar neuritis.

Treatment with intermittent courses of systemic steroids in dosages up to 60 mg resulted in moderate improvement of the gastrointestinal complaints and stabilisation of the visual acuity. Furthermore, the lip swelling decreased during this regimen. Maintenance therapy with mesalazine 500 mg tid remained necessary for clinical consolidation.

Discussion

Orofacial granulomatosis describes a clinical entity including Melkersson-Rosenthal syndrome, granulomatous cheilitis, and sarcoidosis [1,2]. Food and contact allergies, tuberculosis, leprosy, and tooth-associated infections have also been implicated [1,3,4]. Furthermore, in patients with orofacial granulomatosis the development of intestinal Crohn's disease is well documented [5,6].

In addition, it has been described that twenty-five to 36% of patients with Crohn's disease develop an extra-intestinal manifestation [7,8]. Reported manifestations accompanying intestinal Crohn's disease include dermatological (erythema nodosum, pyoderma gangrenosum), ocular (episcleritis, uveitis), skeletal (peripheral arthropathy, ankylosing spondylitis, sacroileitis), vascular (thromboembolic disease, vasculitis, arteritis), and hepatobiliary disorders (fatty liver, chronic active hepatitis, cirrhosis, primary sclerosing cholangitis, cholelithiasis, cholangiocarcinoma).

The combination of two extra-intestinal manifestations of Crohn's disease in the spectrum of orofacial granulomatosis in a single patient is noteworthy. Some of the extra-intestinal manifestations of Crohn's disease manifest as orofacial granulomatosis. Cheilitis granulomatosa and optic neuropathy represent two such entities. Cheilitis granulomatosa is regarded as orofacial granulomatosis, being a monosymptomatic variant of Melkersson-Rosenthal syndrome [9]. Likewise, cheilitis granulomatosa has been reported as an extra-intestinal manifestation of Crohn's disease, preceding the diagnosis of intestinal Crohn's disease up to several years [10]. Optic neuropathy has been described as an ophthalmologic manifestation in Melkersson-Rosenthal syndrome [11], consequently forming part of orofacial granulomatosis, as well as being a rare extra-intestinal manifestation of Crohn's disease [12-14].

Treatment of cheilitis granulomatosa primarily consists of intralesional triamcinolone acetonide injections or systemic corticosteroids [15]. Clofazimine, metronidazole, long-term penicillin, erythromycine, sulphasalazine, ketotifen and hydroxychloroquine sulphate have been mentioned as therapeutic modalities in case reports. Combination with surgical intervention, such as cheiloplasty, can be considered [16].

Corticosteroids are the mainstay of treatment for ocular inflammation in Crohn's disease [17]. Other therapeutic modalities for ocular inflammatory disorders include hydroxychloroquine sulphate, azathioprine, cyclophosphamide, cyclosporine and nonsteroidal anti-inflammatory drugs, such as indomethacin and oxyphenbutazone. Severe visual loss and blindness have been described in association with inflammatory bowel disease [18].

We suggest careful history-taking of patients with orofacial granulomatosis at each visit. It is important that patients with manifestations of orofacial granulomatosis are aware of the need

to report persistent gastrointestinal complaints to their physician or specialist. Crohn's disease should be considered in the differential diagnosis in patients with orofacial granulomatosis. We stress that joined effort of the gastroenterologist, ophthalmologist, oral surgeon and dermatologist is mandatory for an adequate analysis and treatment of orofacial granulomatosis.

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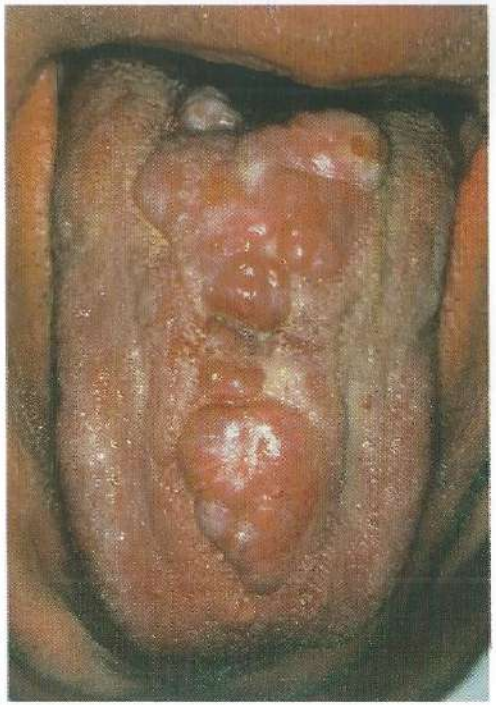
Fig. 1. Amyloidosis of the tongue may manifest with nodular lesions.



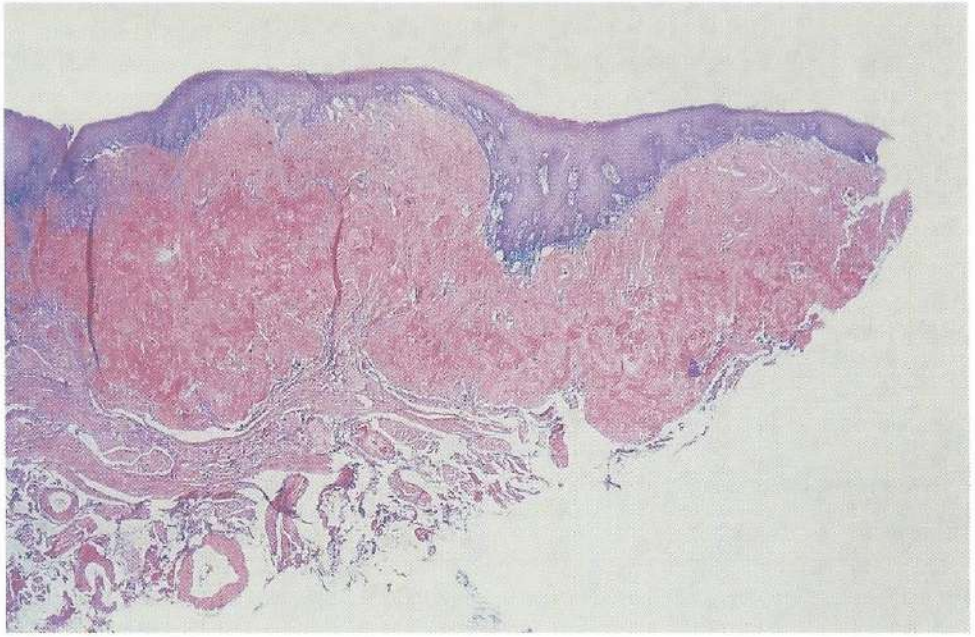


Fig. 2. Histopathology (Congo red staining, original magnification x 40): amyloid deposits in the connective tissue.

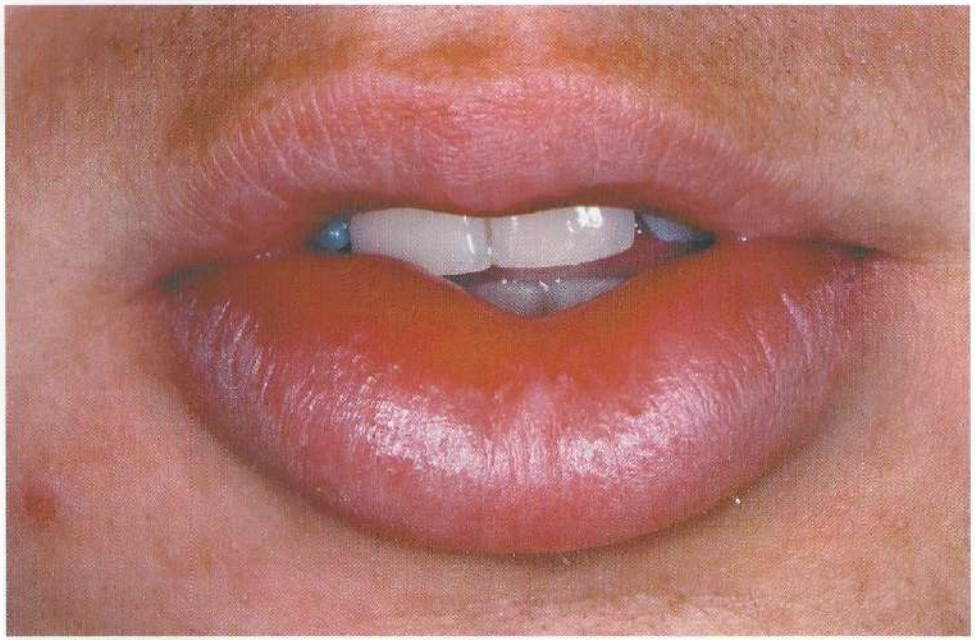


Fig. 1. Clinical appearance of cheilitis granulomatosa: Diffuse swelling of the lower lip.

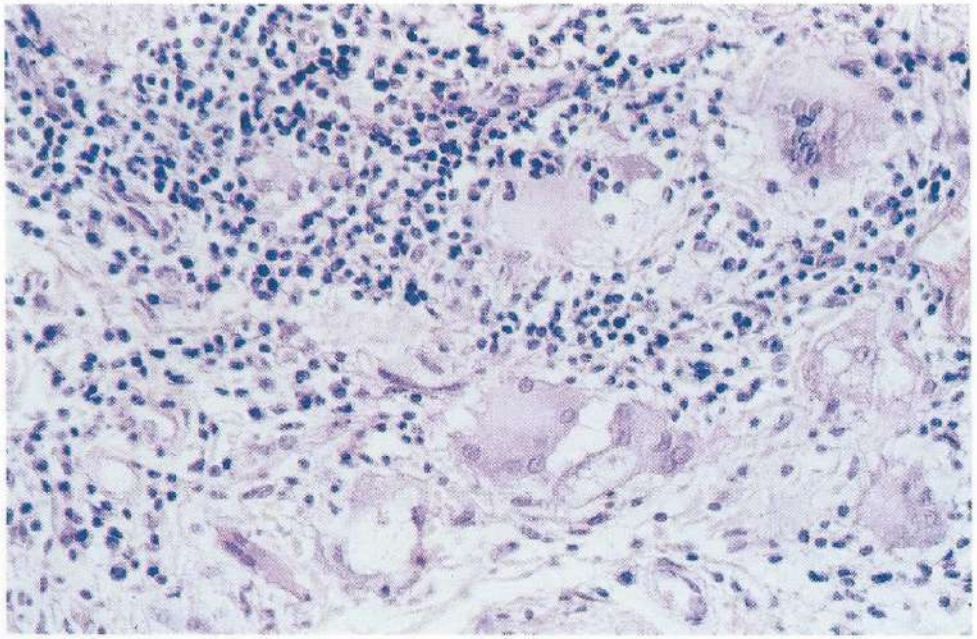


Fig. 2. Histopathology (H&E stain, original magnification x 500): dense infiltrate of the submucosal connective tissue with focal non-necrotizing granulomas.

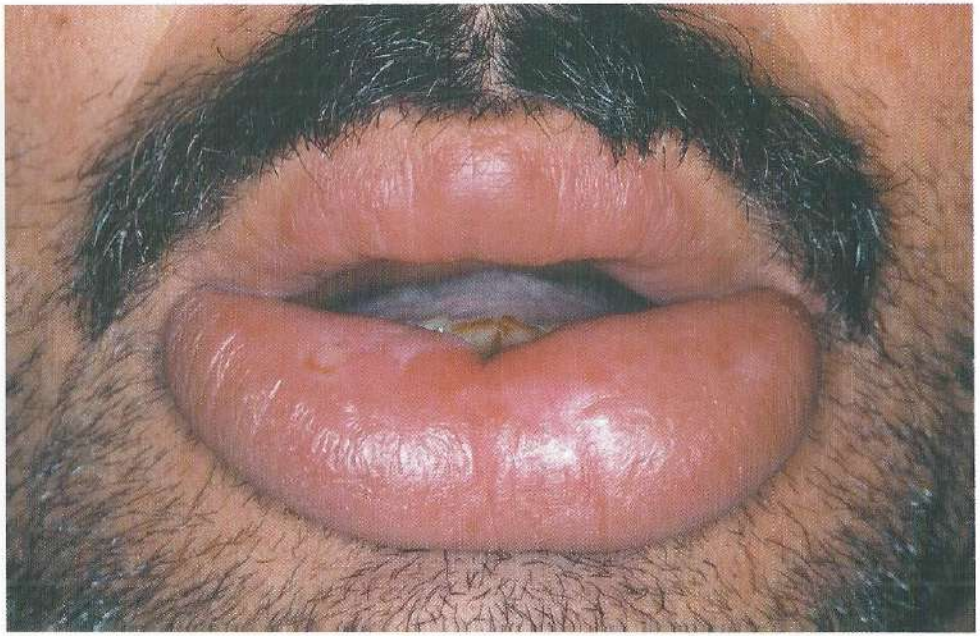


Fig. 3 A. Prominent swelling of the lower lip before cheiloplasty.

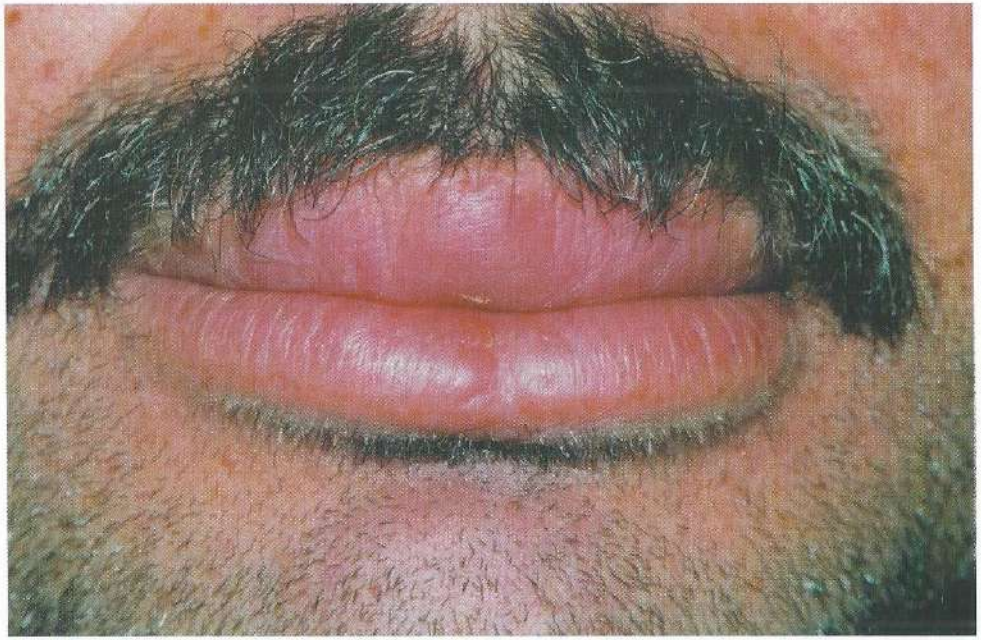


Fig. 3 B. Gross reduction of the lip swelling after cheiloplasty.

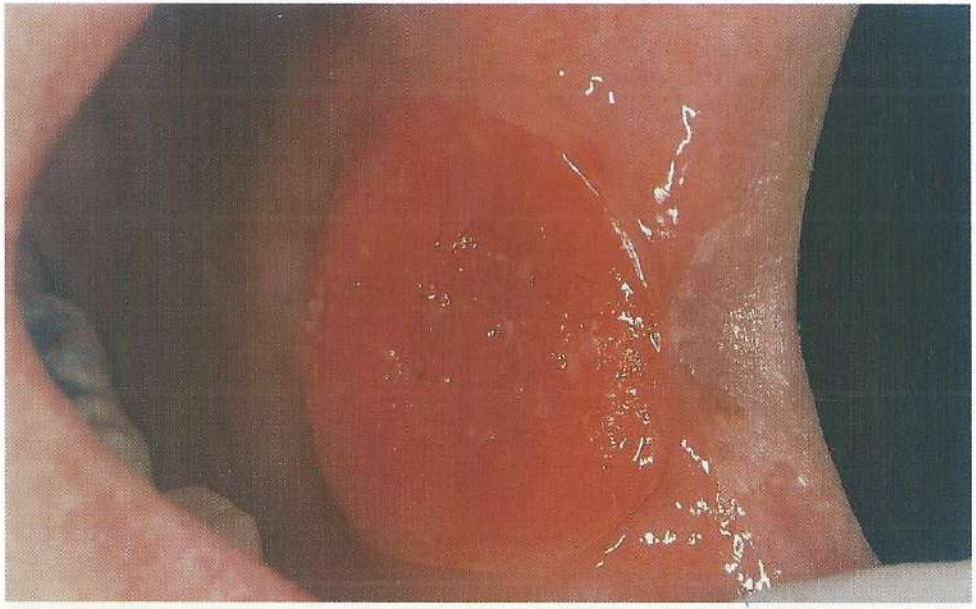


Fig. 1. Squamous cell carcinoma of the left buccal mucosa in a 20-year-old man.

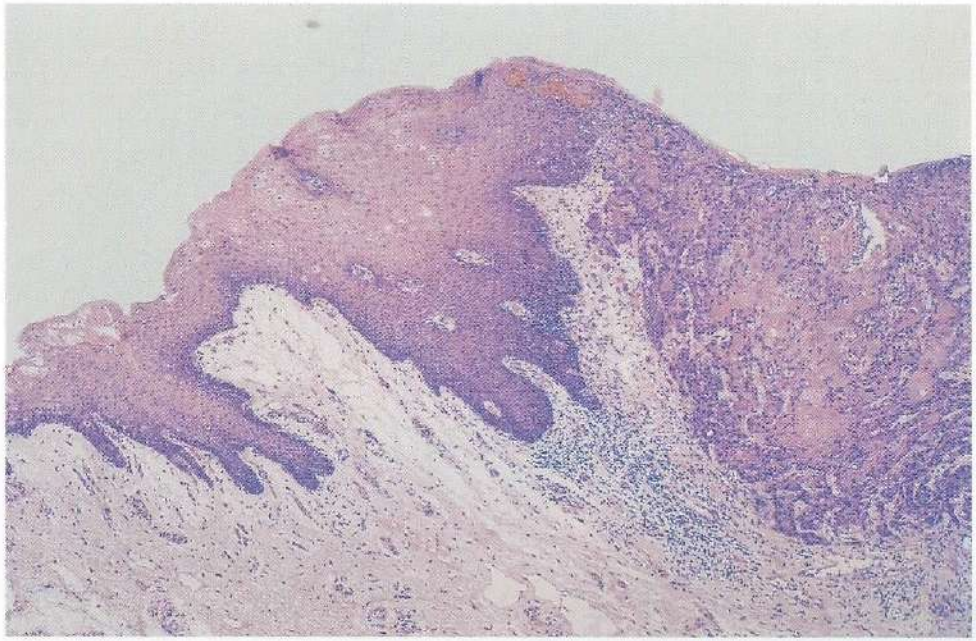


Fig. 2. Low-power view of the edge of the surgical specimen (H&E stain, original magnification x 40).

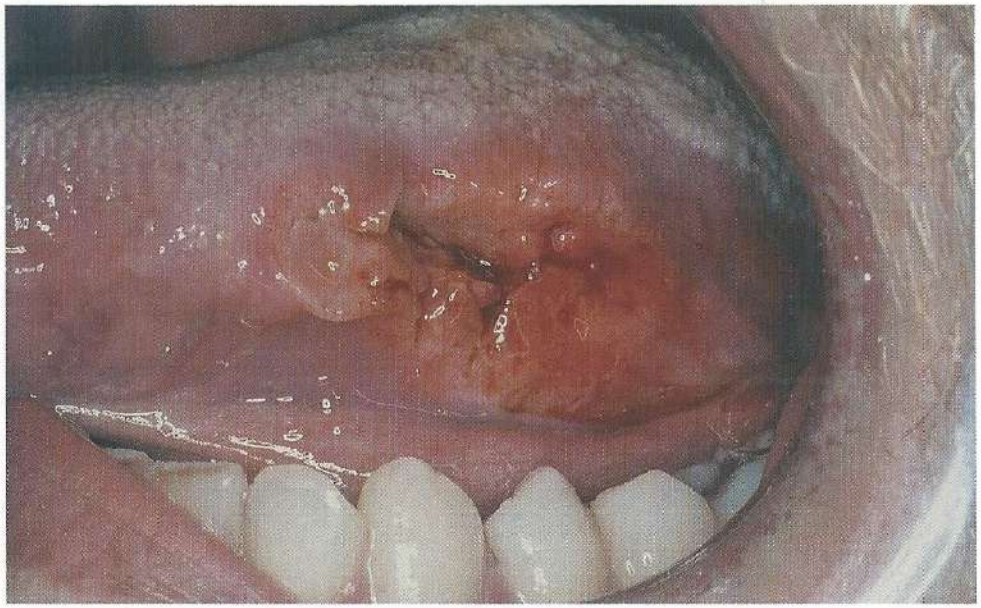


Fig. 1. Clinical appearance of squamous cell carcinoma of the border of the tongue in a 32-year-old man.

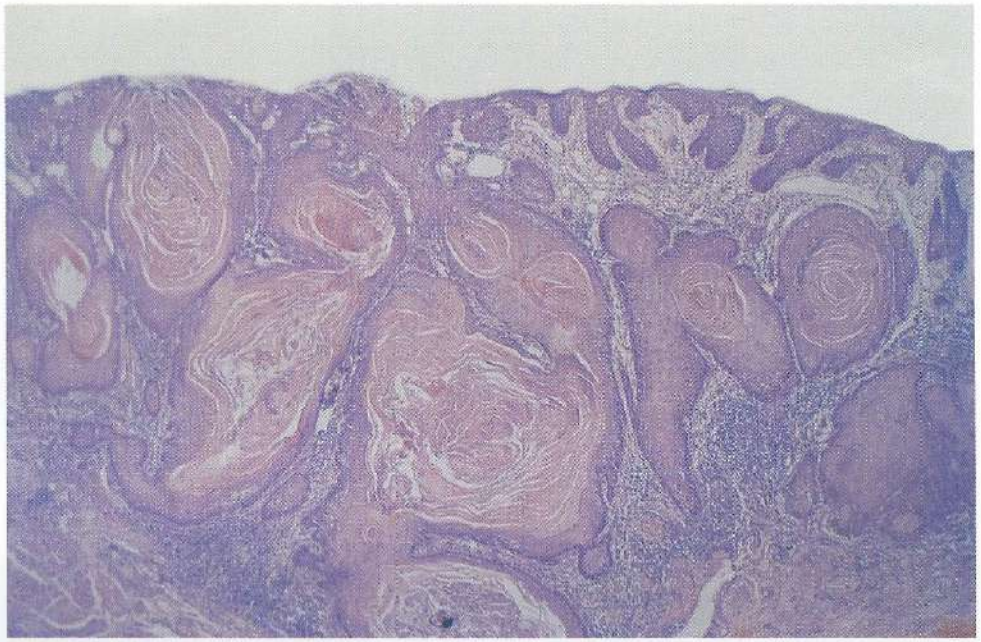


Fig. 2: Low-power view of sqaumous cell carcinoma (H&E stain, original magnification x 33).

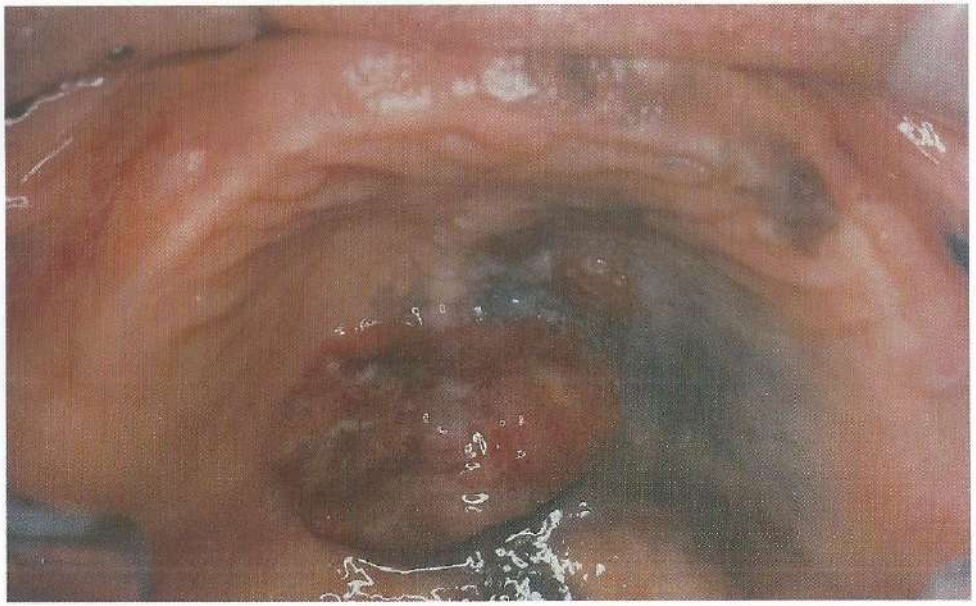


Fig. 1. Malignant melanoma in the midline of the palate. Note the pigmentation in the surrounding mucosa.

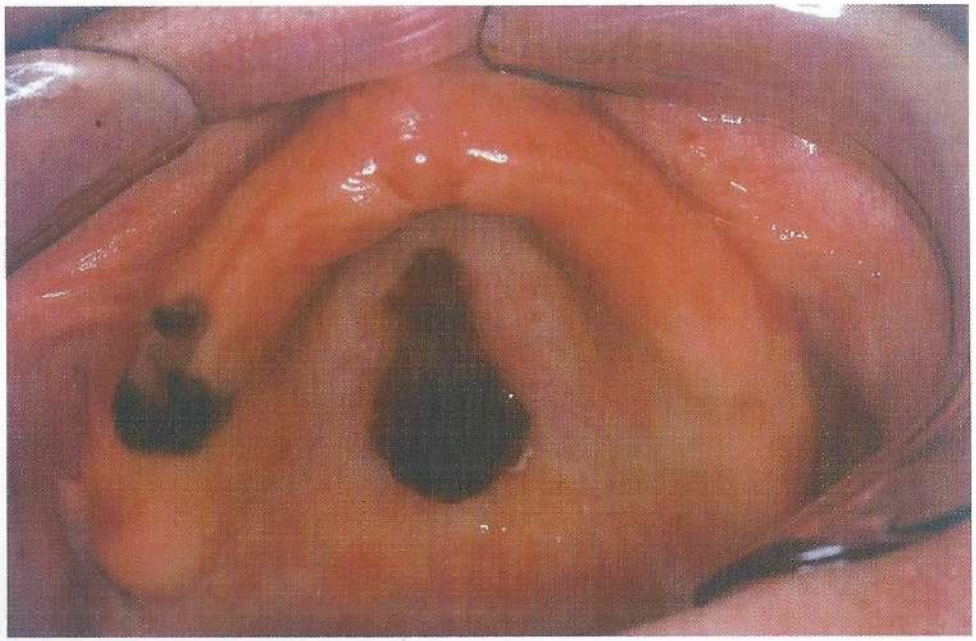


Fig. 2. Malignant melanoma of the palate and an in situ melanoma on the upper alveolar ridge.

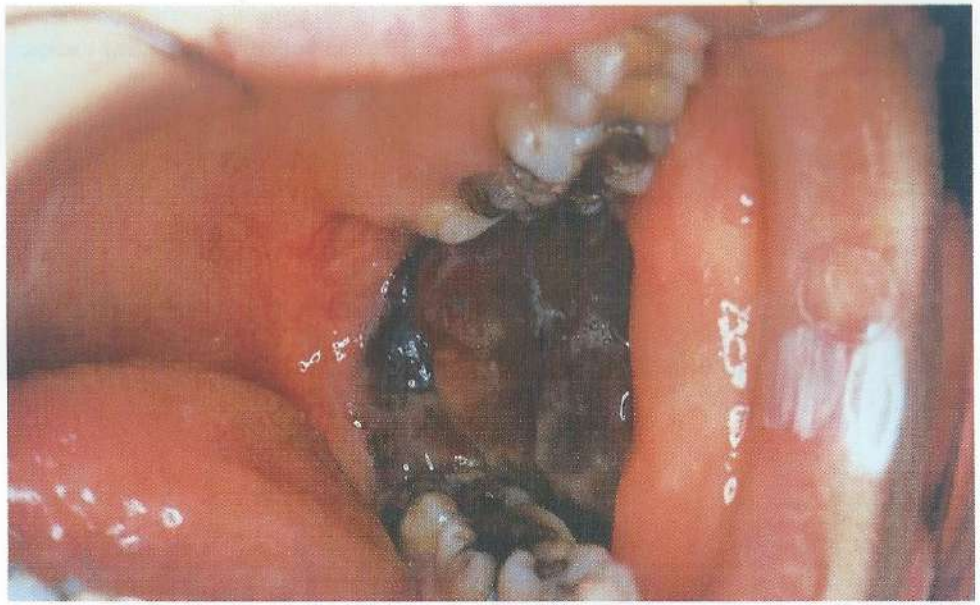


Fig. 3. Extensive malignant melanoma arising from the buccal mucosa.

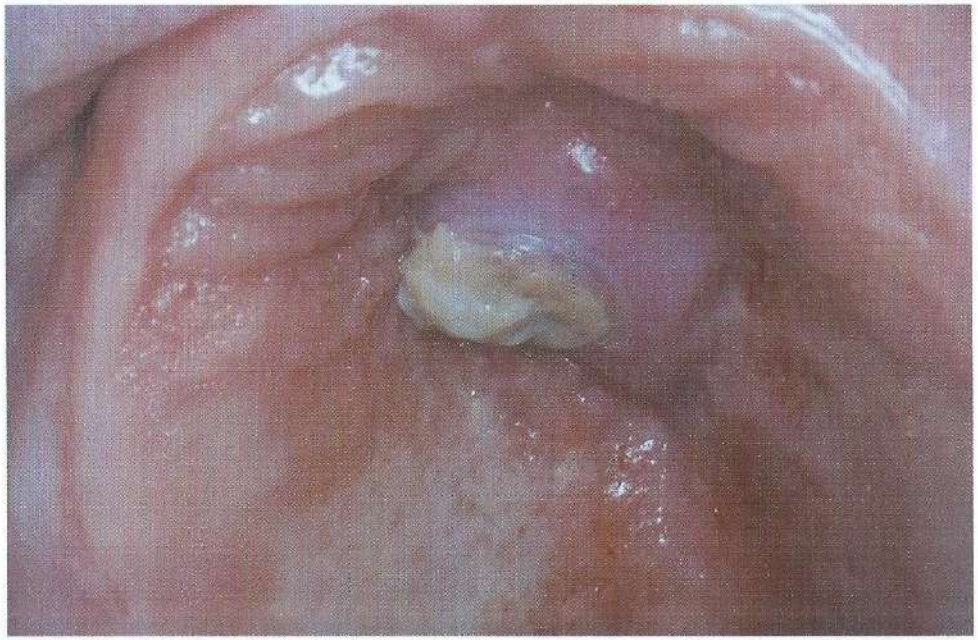


Fig. 4. Amelanotic melanoma of the palate.

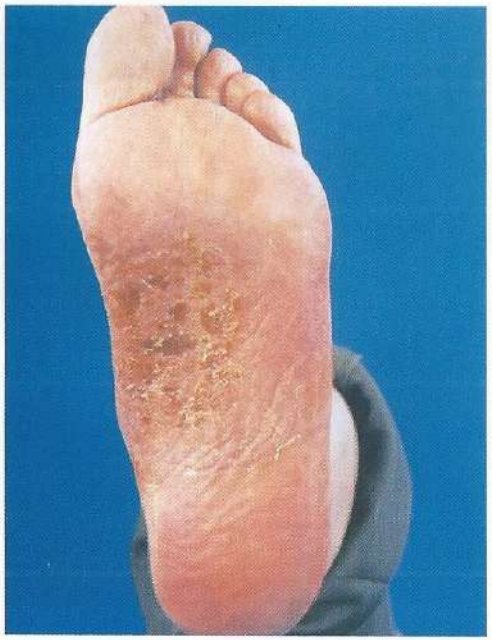


Fig. 1. Initial clinical presentation with vesicles and bullae on the patient's soles.

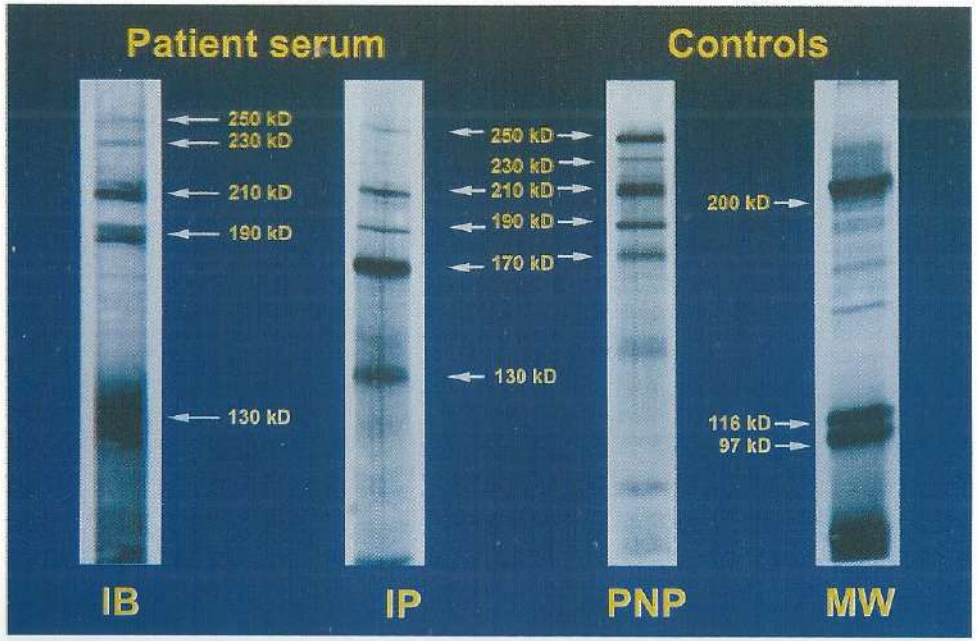


Fig. 2. IB=immunoblotting; IP=immunoprecipitation; PNP=immunoprecipitation of a control with paraneoplastic pemphigus; MW=molecular weights references with immunoprecipitation.

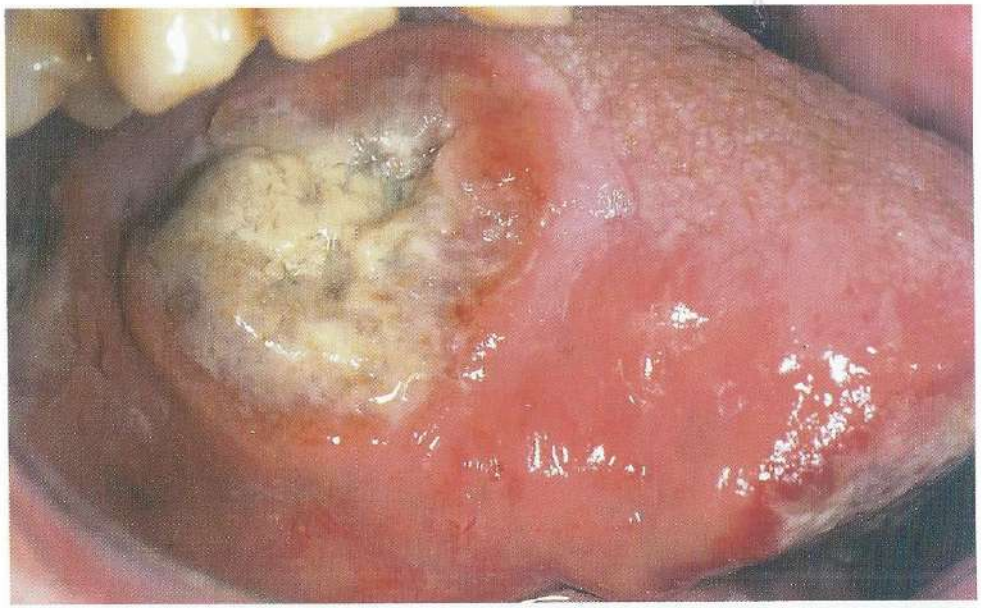


Fig. 3. Several gray well-defined, necrotic ulcers with a 0.5-1.5 cm diameter were noted on the tongue and similar sized erosive lesions were seen on the buccal mucosa.

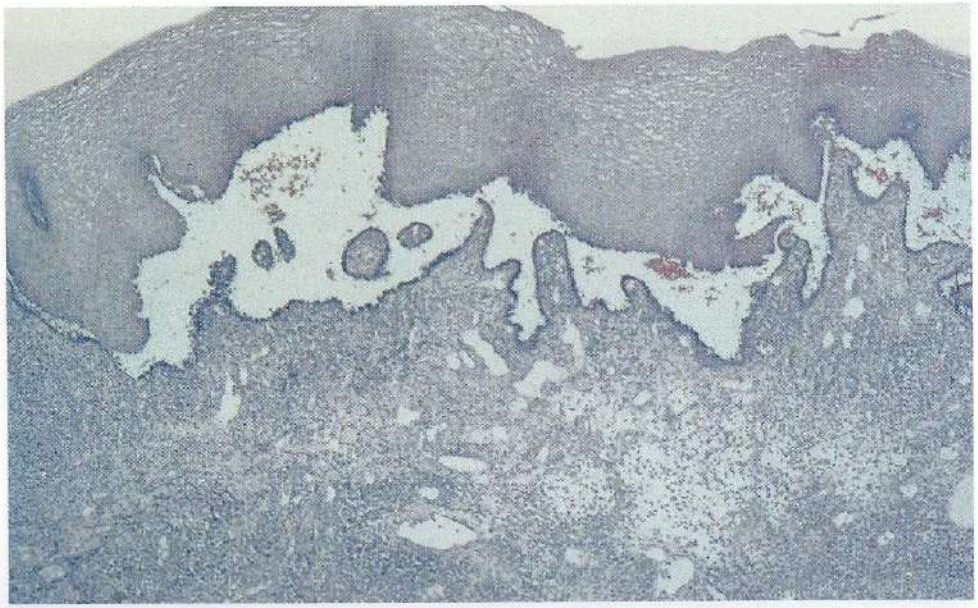


Figure 4. Perilesional biopsy of tongue lesion shows suprabasilar splitting of the epithelium and underlying lymphoma (H.E., original magnification x 130).

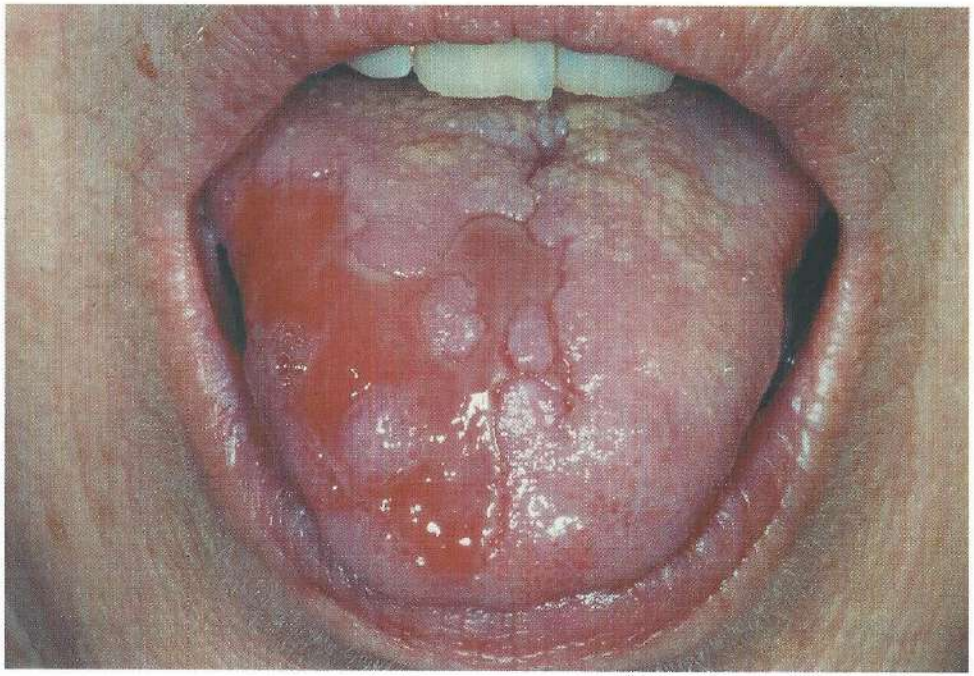


Figure 1. Multiple erosions on the tongue.

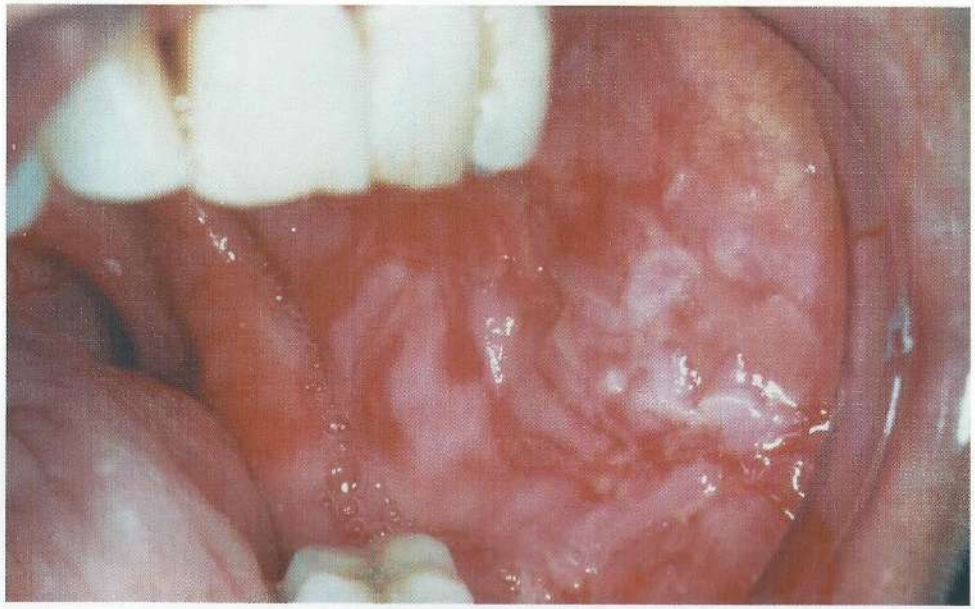


Figure 2. Multiple erosions on the left buccal mucosa.

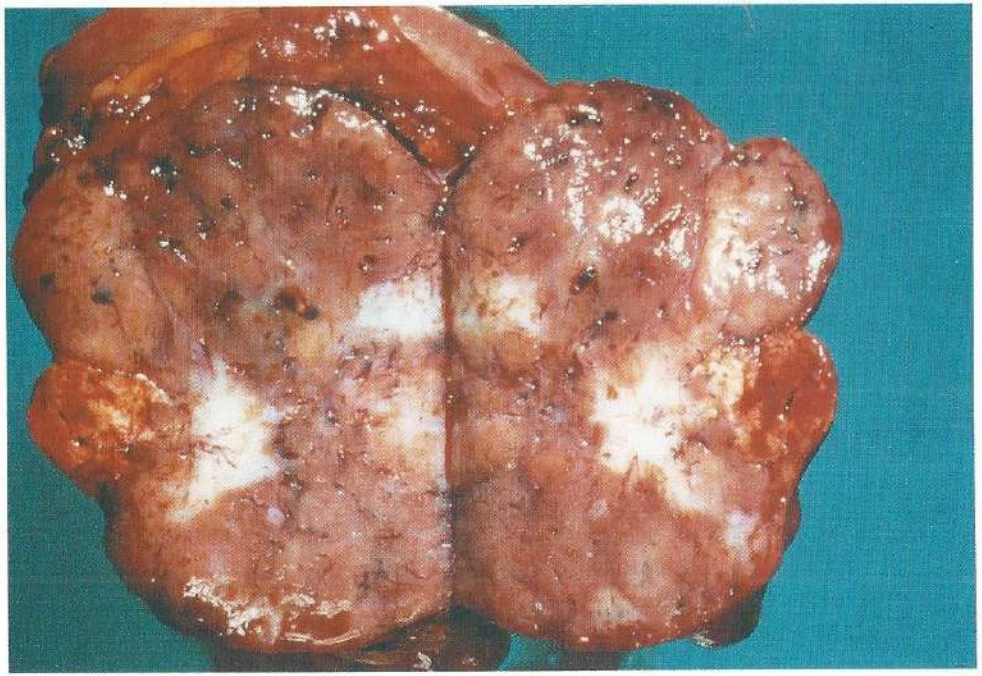


Figure 4. Transverse section of the epithelioid leiomyosarcoma.

Chapter V

Characteristics of 40 primary extranodal non-Hodgkin lymphomas of the oral cavity in perspective of the new WHO classification

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(submitted).

Abstract

Background

Non-Hodgkin lymphomas (NHLs) often present outside the lymph nodes. Although primary extranodal NHLs (PE-NHL) form a substantial part of all NHLs, reports on oral PE-NHLs are rare.

Objectives

To study patients with PE-NHL of the oral cavity for the distribution of gender, age, oral subsite and presenting complaint, histological subtype according to the WHO classification, clinical stage, treatment, and follow-up. Data of 40 oral PE-NHLs are reviewed against the background of the literature and the new WHO classification.

Patients and Methods

Six patients diagnosed with an oral PE-NHL during the period 1 January 1997 to 1 January 2002 at the department of Oral & Maxillofacial Surgery/Oral Pathology of the VU Medical Centre, Amsterdam, The Netherlands, were retrospectively identified and added to 34 earlier published cases from the same department in the period 1973-1993.

Results and Conclusions

All patients had a lymphoma of B-cell lineage. Two-thirds of patients presented with locoregional disease, while one-third had more extensive disease. Mean survival time was 38 months, with a mean recurrence-free survival time of 31 months.

Introduction

Lymphomas are a heterogeneous group of clonal malignant diseases that share the single characteristic of arising as the result of a somatic mutation in a lymphocyte progenitor. The progeny of the affected cell usually carries the phenotype of a B-, T-, or natural killer-cell as determined by immunophenotyping and/or gene rearrangement studies [1]. A lymphoma may arise in lymph nodes or any organ, either by spread from lymphatic sites or as a manifestation of primary extranodal disease [1].

Irradiation and immune deficiencies have been implicated as possible aetiologic factors in non-Hodgkin lymphoma (NHL). The incidence of lymphoma has increased dramatically in the second half of the past century [2], only partially associated with the AIDS-era. This increase has affected men and women, all age groups, and most histological types and has been documented both in industrialized European countries and in the United States [2]. For example, in the United States lymphomas currently comprise 4% of cancer incidence and 4% of cancer-related deaths [2].

While there is a preadolescent peak in lymphoma incidence, there is generally a logarithmic increase with age [3]. Generally, moderate male preponderance is noted. Variations in racial incidence, histology, and immunological subtypes of lymphomas are found throughout the world [3,4]. For example, in the United States lymphoma is more common in Whites than in African-Americans. Another example of this variation is the higher incidence of lymphomas in the United Sates than in Japan, while the incidence of extranodal disease is higher in Japan [5].

Within the lymphoma group, Hodgkin lymphoma is defined by the presence of the Reed-Sternberg cells in an appropriate cellular background [1]. All other neoplasms of the lymphoid system are called NHL. The classification of the subtypes of lymphomas, such as the revised European-American classification of lymphoid neoplasms (REAL) [6] that has recently been incorporated with minimal change into the World Health Organization (WHO) classification of haematopoietic and lymphoid neoplasms [7] (Table I), is aimed at combining clinical aspects, histomorphologic features, immunologic phenotype -nowadays readily achieved using formalin-fixed paraffin-embedded materials-, and genetic features [1]. Unlike earlier classifications, such as the Kiel scheme and Working Formulation, the WHO classification states no indication as to prognosis [7]. Histologically, grading of lymphomas as low-, intermediate, or high-grade malignancy has become somewhat out-dated, since it has become evident that so-called 'low-grade' (i.e. small cell) lymphomas can behave badly (e.g. mantle cell lymphomas), whereas, on the other hand, the formerly termed 'high-grade' (i.e. large cell) lymphomas may be curable (e.g. some anaplastic large cell lymphomas). Currently, each type of lymphoma is seen as a separate disease entity that may be more or less aggressive in individual patients. Because the Ann Arbor staging system [8] (Table II) was inconsistent in predicting outcome, the International Prognostic Index (IPI), incorporating several parameters (Table III), has been developed and validated to provide prognostic information for a variety of types of lymphoma [9]. The IPI is used within the histological subtypes to stratify patients into different prognostic groups [9]. It is expected that application of

Table I: WHO classification of lymphoid neoplasms[7]

B-cell neoplasms

I. Precursor B-cell neoplasm
- B-cell lymphoblastic lymphoma

II. Peripheral B-cell neoplasms
- B-cell chronic lymphocytic leukaemia / small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Lymphoplasmocytic lymphoma
- Splenic marginal zone B-cell lymphoma (± villous lymphocytes)
- Hairy cell leukaemia
- Plasmacytoma / plasma cell myeloma
- Extranodal marginal zone B-cell lymphoma of MALT type
- Nodal marginal zone lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Burkitt lymphoma (including Burkitt-like lymphoma)

T-cell and NK-cell neoplasms

I. Precursor T-cell neoplasm
- T-cell lymphoblastic lymphoma

II. Peripheral T-cell and NK-cell neoplasms
- T-cell prolymphocytic leukaemia
- T-cell granular lymphocytic leukaemia
- Aggressive NK-cell leukaemia
- Adult T-cell lymphoma (HTLV1+)
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic gamma-delta T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides / Sézary syndrome
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, T-null cell, primary cutaneous type
- Anaplastic large cell lymphoma, T-null cell, primary systemic type
- Peripheral T-cell lymphoma, not otherwise characterised

MALT = mucosa-associated lymphoid tissue
NK = natural killer
HTLV1 = human T-cell leukaemia-lymphoma virus type 1

molecular genetics, especially DNA micro-arrays, will aid in the understanding of lymphomas.

As opposed to Hodgkin's disease, NHLs often present outside the lymph nodes at sites such as the stomach, skin, lung, central nervous system, orbit, salivary glands, and oral cavity [10]. Although primary extranodal NHLs (PE-NHL) form a substantial part of all NHLs throughout the body [10], reports on oral PE-NHLs are rather rare.

In the present study, a series of 6 cases of PE-NHL of the oral cavity is presented and put in

Table II: Ann Arbor staging system[8]

Stage	Defining status
Stage I*	Restricted to single lymph node region (I) or a single extranodal site (I-E)
Stage II*	Two or more areas of nodal involvement on same side of the diaphragm (II) or one or more lymph node regions with an extranodal site (II-E)
	Stage III* Lymphatic involvement on both sides of the diaphragm (III), possibly with an extranodal site (III-E), the spleen* (III-S), or both (III-SE)
Stage IV	Liver, marrow, or other extensive extranodal disease

* The spleen is considered nodal.

Substages

Substage E =	localised, extranodal disease
Substage A =	absence of systemic signs
Substage B =	presence of unexplained weight loss (≥ 10 % in 6 months), and/or unexplained fever, and/or night sweats

perspective of a review of the literature together with 34 cases of our institute that have been published earlier [11].

Patients and Methods

In the studied period 1 January 1997 to 1 January 2002, 263 new cases of oral malignant tumours of which 6 NHLs were identified at the VU University medical centre, Amsterdam, The Netherlands. In all cases, oral lesions were the primary manifestation of the disease. The patient data, including gender, age, oral site of presentation, histological subtype according to the WHO classification [7], clinical stage according to the Ann Arbor conference [8], primary mode of treatment and follow-up results, were retrospectively retrieved via the medical records.

Table III: International Prognostic Index for NHLs[9]

Parameters
Age ≥ 60 years
Advanced stage (III or IV)
Extranodal involvement of > 1 site
Performance status ≥ 2
Serum lactate dehydrogenase level raised

Risk group stratification
(according to total number of above-listed features)

0 -1	Low-risk
2	Low intermediate risk
3	High intermediate risk
4 -5	High risk

Biopsy specimens were reviewed and classified using the WHO classification [7]. Beside routine haematoxyline-eosine stainings, immunohistochemical methods were used to investigate the origin of the tumour cells. Antibodies used were L26 (CD20, a pan-B-cell marker), CD79a (the immunoglobulin anchoring molecule, thus a B-cell marker), CD3 and UCHL1 (CD45RO) (both pan-T-cell markers), BerH2 (CD30), and MB2 (staining predominantly B-cells). For the differential diagnosis with epithelial malignancies keratin antibodies AE1/AE3 and CAM5.2 were used.

The patients were treated with radiotherapy, chemotherapy, or a combination of these modalities. When radiotherapy was applied, cumulative radiation doses of 28 to 40 Gy fractionated over 2 - 4 weeks. Chemotherapy regimes for the, at the time classified, low-grade NHLs consisted most often of chlorambucil with or without prednisolone. Intermediate- and high-grade NHLs were treated with polychemotherapy (CHOP; cyclophosphamide, doxorubicin, vincristine, and prednisolone).

Results

The data of the 6 patients, including gender, age, oral site of presentation, histological subtype of NHL according to the WHO classification [7] and clinical stage according to the Ann Arbor conference [8], primary mode of treatment and follow-up results are summarized in Table IV.

These 6 patients taken together with the earlier described 34 PE-NHL patients, accumulate to a total of 40 PE-NHLs, 24 men and 16 women, with a mean age of 59 years (range 3 - 88 years). None of the patients had a medical history of irradiation, immune deficiencies, or long-term immunosuppressive therapy. The duration of oral signs and symptoms ranged from 14 days to 4 months, often with sudden onset and rapid progression. In 29 cases the initial symptom was a diffuse, non-tender swelling of the soft tissues, ulcerating in 14 of these patients. Nine patients complained of spontaneously occurring pain, whereas mental nerve numbness was noted in 3 patients. In 4 patients, computerised tomography showed destruction of the palate, and spread into the nasal cavity, the maxillary sinus, and -sometimes- the orbit. Six patients presented with 'B' symptoms: 3 had tumour-related fever, and another 3 had extensive weight loss.

Table IV: Data of six patients with an oral PE-NHL

Case	Sex	Age	Oral site of presentation	Histologic type of NHL	Clinical stage	Rx	Follow-up	Outcome
1	M	61	maxillary gingiva	DLBCL	I - E	chemo	30 mos	A & W
2	M	61	mandible	DLBCL	IV	chemo	14 mos	A & W
3	F	28	mandible	DLBCL	I - E	chemo	20 mos	A & W
4	F	53	palate	plasmacytoma	I - E	RT	35 mos	A & W
5	M	86	palate	DLBCL	I - E	RT	6 mos	DOD
6	M	75	tongue	DLBCL	III	chemo	18 mos	DOD

DLBCL = diffuse large B-cell lymphoma; chemo = chemotherapy; RT = radiotherapy; mos = months; A & W = alive and well; DOD = died of disease

Table V: Primary site of 40 oral PE-NHLs

Oral subsite of presentation	Tissue of origin: Soft tissue	Tissue of origin: Bone	Total
Upper jaw	20	7	27
Lower jaw	–	7	7
Buccal mucosa & Tongue	6	n.a.	6
Total	26	14	40

The primary oral sites, with reference to initial localisation in soft tissue or bone following clinical and radiographical investigations, are listed in Table V. Using the WHO classification and Ann Arbor system, patients were categorised as shown in Tables VI and VII, respectively. One patient did not undergo staging because of poor physical condition and advanced age. Mean survival time was 38 months in the earlier described group of 34 patients, with a mean recurrence-free survival time of 31 months [11]. There was no statistically significant difference in survival time between patients with bone versus soft tissue localisation of the PE-NHL. Locoregional disease, i.e. stages I and II, and disseminated disease, i.e. stages III and IV, showed significant differences both for overall survival (P=0.0001) and recurrence-free survival (P=0.001).

Discussion

Lymphoma is the second most common neoplasm of the head and neck following squamous cell carcinoma [12]. Most occur in Waldeyer's ring, i.e. the tonsils, pharynx, and the base of the tongue, whereas lymphomas arising within the oral cavity account for 3.5% of all oral

Table VI: WHO subtype of 40 oral PE-NHLs

B-cell neoplasms	Cases
I. Precursor B-cell neoplasm	
B-cell lymphoblastic lymphoma	2
II. Peripheral B-cell neoplasms	
Plasmacytoma / plasma cell myeloma	1
Burkitt lymphoma (including Burkitt-like lymphoma)	1
Extranodal marginal zone B-cell lymphoma of MALT type	2
Mantle cell lymphoma	6
Follicular lymphoma	8
Diffuse large B-cell lymphoma	20
Total	40

Table VII: Clinical stage of 40 oral PE-NHLs

Stage	Number of patients
I-E	24
II-E	1
III-E	2
IV	12
Unstaged	1
Total	40

malignancies [12]. The reported percentage of PE-NHL of all NHLs ranges from 24 [13] to 48 [14,15]. In a Dutch study, PE-NHLs accounted for 41 % of all NHLs, 3% of which were primarily located in the oral cavity [10].

The clinical characteristics of the 6 PE-NHL patients taken together with the earlier described is conform the literature [11,16]. In this single institution series of 40 patients, there was a slight male predominance (24 men,16 women; male-female ratio of 1.5) and a mean age of 59 years (range 3 - 88).

In the oral cavity, lymphomas usually present as an extranodal, soft-elastic, asymptomatic lesion [12,17], hardly ever being accompanied by 'B' symptoms [18,19]. In our study oral PE-NHLs arose in two-thirds of patients (26/40) from soft tissues, 77% of these located in the upper jaw (20/26). Although lymphoma sites of the upper jaw are commonly separately indicated as palate and maxilla, in clinical practice this subdivision is often not clear-cut. Hence, we prefer the more realistic term upper jaw. In the remaining one-third of patients (14/40), the lesions originated from the bone, equally distributed over the mandible (7/14) and the upper jaw (7/14). On radiographical investigations, lymphoma with bone involvement predominantly causes diffuse bone destruction, leading to disappearance of the lamina dura of the teeth or appearing as a solitary radiolucent defect. In our patients, NHLs of the upper jaw most often originate from soft tissue (20/27), whereas NHLs of the lower jaw all arise in bone (7/7).

Most PE-NHLs are of B-cell lineage, as was also the case in our series (Table VI). Diffuse large B-cell lymphomas (DLBCL) represent approximately 40% of adult lymphomas [1] and, in our series, comprised 50% of oral PE-NHLs (20/40). Furthermore, as has been reported in the literature [1,9], most of these DLBCLs presented with locoregional disease, i.e. stages I or II.

Mean survival time was 38 months in the earlier described group of patients, with a mean recurrence-free survival time of 31 months [11]. Although PE-NHL arising in skeletal bone [20], and reports on small series of oral PE-NHL suggested a better prognosis for bone localisation, reported larger series of oral PE-NHL do not show this prognostic impact of primary tumour localisation [18,21]. Follow-up of the newly included 6 PE-NHL patients was too short to include for statistical analysis, but in our previous study there was no statistically significant difference in survival time between patients with bone versus soft tissue localisation of the PE-NHL [11]. Besides, determination of tumour localisation, primarily having an intraosseous or soft tissue origin, carries some subjectivity. Furthermore, cases of intraosseous localisation in the upper jaw, i.e. palate and maxilla, may represent local extension from nasal and/or paranasal sinus processes and vice versa. Locoregional disease, i.e. stages I and II, and disseminated disease, i.e. stages III and IV, showed significant differences both for overall survival (P=0.0001) and recurrence-free survival (P=0.001).

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Chapter VI

Oral squamous cell carcinoma in patients following primary malignancies elsewhere in the body

Oral squamous cell carcinoma following treatment of acute lymphoblastic leukaemia
J Oral Pathol Med 1997;26:98-9.

Oral squamous cell carcinoma as a second primary malignancy in a patient with previously diagnosed osteosarcoma of the femur
J Oral Maxillofac Surg 1997;55:1156-8.

Oral squamous cell carcinoma following treatment of acute lymphoblastic leukaemia

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Abstract

With substantially increased survival after most paediatric cancers over the past decades have come the late sequelae of treatment. Of all late complications of treatment, second malignancies are generally considered to be the most serious.
We report on a 20-year-old man with an oral squamous cell carcinoma 17 years after initial chemotherapy and irradiation for acute lymphoblastic leukaemia.
Although occurrence of the oral malignancy in this patient could have been treatment-related, one should keep in mind that the occurrence may also be based on a shared genetic aetiology.

Introduction

As treatment and survival of acute leukaemia in children as well as other types of paediatric cancers improve, the number of second primary malignancies (SPMs) in these treated patients will increase. To date, there a few reports of SPMs in the head and neck region.
A patient is discussed who presented with a squamous cell carcinoma of the oral cavity 17 years after initial treatment for acute lymphoblastic leukaemia (ALL).

Case report

In December 1993, a 20-year-old man presented to the outpatient clinic of our department with a 10-week-history of a painful swelling of the left buccal mucosa close to the commissure (Fig. 1). There were no other complaints. The patient did not smoke and did not use alcohol. His family history was insignificant.
His past medical history revealed treatment for ALL at the age of three years. He had received multidrug chemotherapy (vincristine, 6-mercaptopurine, methotrexate, and prednisone) and prophylactic cranial irradiation (2500 cGy). Initially, complete remission was achieved. Thereafter, he suffered four meningeal relapses, two of which occurred in combination with bone marrow recurrences. All relapses were adequately treated with chemotherapy.
At oral examination a tender 3 cm mass was noticed in his left buccal mucosa. No cervical masses were detected by palpation. Ultrasonography of the neck revealed no positive lymph nodes. A biopsy of the buccal lesion showed a well-differentiated sqaumous cell carcinoma. Under general anaesthesia a radical trans-oral excision was performed. The maximum thickness of the tumour measured 0.6 cm. There was no distinct evidence of perineural or vascular invasion. A mild lymphoplasmacytic infiltrate was observed at the tumour front. A rather sharp transition was noticed between the tumour and adjacent, non-dysplastic epithelium (Fig. 2).
Four months later, fine-needle aspiration of a left submandibular lymph node revealed metastatic disease and the patient underwent a radical neck dissection. Since histopathologic examination revealed two lymph nodes with extracapsular spread, post-operative irradiation was delivered with a total dose of 6250 cGy.
Thirty months after the first treatment of the oral lesion, the patient died of progressive regional recurrence. No autopsy was performed.

Discussion

Treatment for ALL now produces remission in over 95 per cent of patients and results in survival rates above 70 per cent at five years [12]. The ability to cure ALL occurring in childhood is regarded as one of the landmark developments of the past 30 years in cancer therapy [1]. With this success, however, have come late complications of treatment, second malignancies

generally being considered to be the most serious [3]. According to the Late Effects Study Group, the average latent period for a SPM following childhood leukaemia is 5.5 years [4]. The Children's Cancer Study Group included 9,720 ALL patients with a median follow-up of 4.7 years and noted 43 SPMs after a median interval of six years [1]. Only two of these concerned oral malignancies: both were mucoepidermoid carcinomas of the parotid [1]. Among a British cohort of 10,106 three-year survivors of childhood cancer, of which 2,082 children had been treated for leukaemias, not a single oral cancer was observed as a SPM [5].
A further search of the literature disclosed only two patients with carcinoma of the head and neck region after treatment for ALL: a 12-year-old patient with a squamous cell carcinoma of the tongue and a 13-year-old boy with a mucoepidermoid carcinoma of the left parotid [6,7]. No report was available on the occurrence of a squamous cell carcinoma of the buccal mucosa following treatment for ALL in childhood.
The presentation of two primaries in one individual may have several causes. It is tempting to speculate that its presence in our patient was related in some manner to the previous treatment, either the irradiation [1,4] or to the chemotherapy [8], rather than to a random event. However, second cancers may also be due to an underlying systemic disease (such as Von Recklinghausen's neurofibromatosis) or to chromosomal abnormalities shared by multiple organs in which they are tumorigenic (such as occurs in some congenital tumours) [9]. Thus, the sequential appearance of two different neoplasms in one person or within multiple individuals of one family may be a clue to a shared genetic aetiology [9]. Our patient had no history of underlying disease or family history that could explain the development of his SPM.

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6.2

Oral squamous cell carcinoma as a second primary malignancy in a patient with previously diagnosed osteosarcoma of the femur

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Introduction

Because treatment and survival of osteosarcoma have improved since the introduction of effective chemotherapy regimens, the number of second malignancies in these patients will increase. Occurrence of such second primary malignancies (SPMs) other than squamous cell carcinoma in the head and neck region is not frequently reported.
This report describes a patient who presented with a squamous cell carcinoma of the oral cavity nearly 3 years after initial treatment of osteosarcoma (OS) of his right femur.

Report of a case

In May 1980, a 32-year-old man presented to the outpatient Oral and Maxillofacial Surgery Clinic complaining of a sore on the left side of his tongue. There were no other complaints. The patient did not smoke and did not use alcohol. His medical history showed idiopathic acute renal failure at the age of 10 years. Furthermore, in 1977, he had undergone cardiac surgery for an atrial septum defect. The same year he was also diagnosed as having OS of the distal metaphysis of his right femur. Treatment had consisted of femur amputation followed by multi-agent adjuvant chemotherapy (methotrexate with leucovorin rescue, adriamycin, and vincristine). In 1979, the upper lobe of his right lung had been removed for a metastasis of his OS.
The patient had no siblings, but the family history indicated that his mother had died of breast cancer and his father had suffered from a non-Hodgkin's lymphoma. Remarkable as well was the number of deaths of cancer on the maternal side of the family. No further study of these family members could be performed.
On oral examination, a 1.5-cm diameter ulcer was found on the left border of the tongue (Fig. 1). No suspicious cervical lymph nodes were detected by palpation. A biopsy of the lesion showed a well-differentiated sqaumous cell carcinoma for which he underwent a radical partial tongue resection (Fig. 2). Three months later, an ipsilateral radical neck dissection was performed because of presence of two metastatic lymph nodes. Postoperative irradiation was delivered with a total dose of 62 Gy. Further follow-up of the head and neck region was unremarkable.
Almost two years after the first treatment of his tongue cancer, the lower lobe of his left lung had to be removed for a second metastasis of his OS. Finally, in June 1984, the patient developed a rapid progressive painful swelling of his left buttock. Further investigation showed this process to be a third metastasis of OS and, despite immediate commencement of chemotherapy, the patient subsequently died on July 1, 1984, of a hemorrhagic septic shock stemming from this third metastasis.

Discussion

With the introduction of effective chemotherapy regimens during the early 1970s, the dismal prognosis of OS has dramatically improved [1,2]; 5-year disease-free survival rates of 40 % are common nowadays [3]. However, these treatments may be associated with late neoplastic sequelae. The number of second primary malignancies (SPMs) among childhood cancer survivors is low, and the risk attributable to therapy is small when compared with the improvement in survival rates achieved by the use of cancer treatments [4]. Neither the Childhood Cancer Study Group [4] nor the Late Effects Study Group [5,6] found an increased incidence of SPMs among survivors of OS. It is yet unclear whether these observations also apply to malignancies occurring in adults. A further search of the literature disclosed no report of the tumor pair of a squamous cell carcinoma of the head and neck region after treatment for OS elsewehere in the body. One case was found of a carcinoma of the tongue in a 21-year-old man who was a long-term survivor of a stage III clear cell sarcoma of the kidney (CCSK) [7]. The CCSK patient had been treated at the age of 2.5 years by nephrectomy, postoperative actinomycin D for 15 months, and radiation therapy (24 Gy) to the tumor bed.

The occurrence of two primaries in one individual may have several causes. It is tempting to speculate that its presence in our patient was related to the previous chemotherapy [8] rather than to a random event. However, second cancers also may be due to an underlying systemic disease (such as Von Recklinghausen's neurofibromatosis) or to chromosomal abnormalities shared by multiple organs in which they are tumorigenic, such as occurs in some congenital tumors [9]. Thus, the sequential appearance of two different neoplasms in one person, or within multiple individuals within one family, may be a clue to shared genetic etiology [9]. Furthermore, the history of idiopathic renal disease and a congenital cardial defect could well represent a developmental syndrome involving (spontaneous) mutations leading to oncogenesis. Perhaps cytogenetic aberrations involving the long and short arms of chromosome 1 or chromosome 11 played a role in the pathogenesis of the sqaumous cell carcinoma of the tongue [10,13]. In our case, no suitable material was available to carry out cytogenetic studies.

Acquired mutations in the p53 tumor suppressor gene are the most common tumor-specific genetic changes observed to date, having been identified in most major cancer types [14-16]. In addition, germline mutations in p53 have been identified in families with the Li-Fraumeni syndrome, a rare familial cancer syndrome characterized by an unusually high incidence of sarcoma, breast cancer, and other neoplasms [17,18]. No such genetic pattern has been identified yet for osteosarcoma in combination with head and neck cancer.

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Chapter VII

Oral metastases: report of 24 cases

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Summary

Aim

To study patients with oral metastatic tumours for the distribution of sex and age, the oral site and histopathological type of the metastasis, the primary tumour site and length of follow-up.

Patients and methods

All patients who had an oral metastasis diagnosed during the period January 1970 - January 2001 at the department of Oral and Maxillofacial Surgery/Oral Pathology, VU Medical Centre, Amsterdam, The Netherlands, were included in this retrospective case study.

Results

Of 1537 patients with newly diagnosed oral cancers, 24 had metastatic tumours. There was an equal sex distribution and age at the time of diagnosis ranged from 8 - 90 years (median 60). The metastatic tumours most commonly involved the bone (18/24), the mandible being the most common (15/18). The predominant histological type was adenocarcinoma. In most patients (n=16) the primary tumour was already known before the oral metastatic lesion appeared. The most common primary tumours were breast, lung, kidney, and prostate, in that order. Prognosis was poor (median survival 6 months, range 1-60).

Conclusions

Oral metastases are rare and may present at any age in both sexes and predominantly involve bony structures, particularly the mandible. A third of oral metastases appeared to be the first indication of an occult malignant process elsewhere.

Introduction

About 1% of all oral cancers are metastases of primary tumours elsewhere in the body, and are located in the soft tissues as well as in the jaw bones.
Almost all types of malignancy may metastasise to the mouth. Although no particular malignancies seem to favour spread to the oral cavity, some primary tumours are found more often than others. For instance, primary lung tumours are more likely to metastasise to the mouth in men than in women, because men have a higher incidence of lung cancer [1,2]. Oral metastatic tumours from breast cancer, on the other hand, are extremely rare in men [3-5]. In most patients who present with an oral metastasis, the distant primary tumour has already been diagnosed, and in most cases treated. Sometimes, however, the discovery of an oral metastasis leads to the detection of an occult primary malignancy elsewhere in the body. In some cases, the histopathological features of the oral metastasis provide a clue as to the site of the primary tumour. On the other hand, the histopathological picture of an oral tumour may not be identifiable as a primary oral cancer, until the primary tumour is eventually detected. Most patients with a metastatic tumour in the oral cavity have also developed metastases at other sites, often leaving no other option than palliation. Only when extensive searches for other metastases have shown the oral metastatic tumour to be the sole metastasis combined with an identified primary tumour that seems to have been treated or controlled successfully, can curative treatment of an oral metastasis be considered.

Patients and methods

All patients who had an oral metastasis diagnosed in the period January 1970 - January 2001 at the VU University Medical Centre were studied retrospectively from the histopathological database and the medical records (ICD-9 codes 140,141, and 143-45). Apart from sex and age of the patients, the clinical presentation and histopathological picture of the oral metastasis were recorded as well as the site of the primary tumour, the results of further dissemination studies, treatment, and the course of the disease.

Results

In the 30-year period studied, 1537 new cases of oral malignant tumours were identified. The present study concerns our experience of 24 patients in whom the diagnosis of an oral metastasis from a primary tumour located elsewhere had been established (Table I).

Discussion

Metastasising is a complex process [5], the biological basis of which requires tumour cells to breach a sequence of barriers [5]. First, they have to detach from the primary tumour; then they must spread in the tissue, invade the blood or lymphatic vessels, and survive travel in the circulation. After this they have to settle in the microvasculature of the organ, extravasate through the vessel wall, invade the target organ, and proliferate within the target tissue [5,6]. For a micrometastasis to grow beyond the size of 2-3 mm, tumour cells have to induce the formation of new blood vessels (angiogenesis) for adequate supply of oxygen and nutrients [5].

Metastatic tumours to the oral cavity are uncommon, comprising about only 1% of newly-diagnosed oral malignancies in our department. As reported elsewhere [4], these metastases presented most commonly as lesions of the jaw bones (18/24), the mandible being the most common (15/18). In one case both jaw bones were involved. Only six of the oral metastases were in the soft tissues of the mouth. The clinical presentation varied from local swelling or pain to paraesthesia. Most patients had a swelling of the mandible with local tenderness. Metastases in the jaw bones were usually seen as radiolucent areas on the radiographs.

Oral metastases are as common in men as in women and may appear at any age; in this series the ages ranged from 8 - 90 years. The fact that the overall median age was 60 years and proved to be lower in women (median age 53) than in men (median age 66) is probably because we studied so few patients.

In all but one patient the histological type of the metastasis could be classified, adenocarcinoma being the most common (15/23). The most common primary sites were the breasts and the lungs, which is not surprising in view of the incidence of these tumours in The Netherlands (Table II). However, it was striking that so many renal cell carcinomas were identified as the primary tumours, because this cancer is not among the most common among the Dutch population (Tables II and III). This is probably because renal cell carcinoma tends to disseminate widely during an early phase of the disease. On the other hand, the relative large proportion of primary prostate cancers is less surprising, given its second ranking on the overall incidence (Table II). Prostate cancer prefers to metastasise to bone, as was shown in this series.

When the relative numbers of primary tumours published elsewhere are compared, the incidence of the specific primary lesions in that particular population should be taken into account. Indeed, the incidence of oral cancer may vary considerably depending on the geographical area studied. When data among populations are compared, standardisation for age is necessary, as age has a powerful influence on the risk of cancer [2]. An age-standardised rate (expressed per 100,000 world standard population) is a summary measure of a rate that a population would have if it had a standard age structure [2]. The rates of cancer of the oral cavity in men may be as low as 4.4 in the United Kingdom, but 12.8 in India.[2] For women the corresponding rates are 2.0 and 7.5, respectively [2].

Unfortunately, oral metastases are not separately reported by cancer registries, and estimates cannot be derived from age-standardised rates. Apart from these rates, local factors that in-

Table I: Clinical details

Site of primary	Sex	Age (years) at time of diagnosis	Site of oral metastasis	Histological type	Time relation between detection of metastasis and primary tumour (months)		Follow-up (months) before death
					Before	After	
Breast	Female	48	Gingiva	Adenocarcinoma	–	13	7
Breast*	Female	54	Mandible	Adenocarcinoma	–	12	6
Breast*	Female	57	Mandible	Adenocarcinoma	–	59	10
Breast*	Female	61	Mandible	Adenocarcinoma	–	48	60
Breast	Female	62	Gingiva	Adenocarcinoma	1	–	2
Breast	Female	63	Mandible	Adenocarcinoma	–	108	6
Lung	Male	55	Mandible	Squamous cell carcinoma	1	–	12
Lung	Male	59	Mandible + maxilla	Squamous cell carcinoma	1	–	2
Lung	Male	60	Mandible	Adenocarcinoma	3	–	25
Lung	Male	68	Gingiva	Squamous cell carcinoma	–	2	26
Lung	Male	78	Mandible	Adenocarcinoma	1	–	3
Kidney*	Female	62	Soft palate	Clear cell carcinoma	–	6	1
Kidney	Female	64	Maxilla	Clear cell carcinoma	–	6	2
Kidney	Male	48	Mandible	Clear cell carcinoma	–	32	21
Kidney	Male	67	Buccal mucosa	Clear cell carcinoma	–	9	22
Prostate	Male	64	Mandible	Adenocarcinoma	–	9	4
Prostate	Male	74	Mandible	Adenocarcinoma	–	13	7
Prostate	Male	90	Mandible	Adenocarcinoma	–	16	4
Cerebellum*	Female	8	Mandible	Medulloblastoma	–	12	1
Colon	Female	70	Hard palate	Adenocarcinoma	–	43	6
Oesophagus	Male	60	Hard palate	Adenocarcinoma	–	10	7
Unknown primary	Female	45	Tongue	Undifferentiated carcinoma	–	–	4
Unknown primary	Female	53	Mandible	Adenocarcinoma	–	–	5
Unknown primary	Male	77	Mandible	Adenocarcinoma	–	–	11

* Cases have previously been reported in detail.[7]

Table II: Ten most common malignant tumours in The Netherlands[8]

	Men	Percent		Women	Percent
1	Lung and bronchus	19.7	1	Breast	32.0
2	Prostate	18.8	2	Colon and rectum	13.2
3	Colon and rectum	13.1	3	Lung and bronchus	6.7
4	Bladder and urinary tract	5.6	4	Uterus	4.7
5	Skin, other	5.5	5	Ovary	4.4
6	Head and neck	4.9	6	Skin, melanoma	4.1
7	Stomach	4.2	7	Skin, other	3.9
8	Malignant lymphoma	3.7	8	Malignant lymphoma	3.5
9	Kidney	2.6	9	Stomach	2.4
10	Skin, melanoma	2.5	10	Pancreas	2.4
	Unknown primary	4.1		Unknown primary	3.8

fluence the epidemiology of oral cancer should be taken into account. India, for example, has high rates for primary oral neoplasms in both sexes as a result of reported additional specific risk factors such as reverse smoking and chewing betel nuts and tobacco [9]. Hence India is expected to have a lower percentage of oral metastases in their oral cancer subgroup than the 1% in the present study.

The primary tumour was already known before the oral metastatic lesion appeared in most patients (16/24). Nevertheless, in one third of patients (8/24) the oral lesion was diagnosed before the primary tumour. In five of these the primary tumour was detected, but in three patients it remained unknown despite additional investigations.

Most patients who present with a metastatic tumour in the oral cavity have also developed metastases at other sites, so a palliative regimen is the only management option. Local treatment of jaw bone metastases -nearly always by radiotherapy- usually relieves pain and may prevent loss of function. Metastases in the soft oral tissues may more readily be approached surgically, with similar palliative results for the patient.

Follow-up until death was available for all patients and the prognosis was poor, as shown by the median survival of 6 months (range 1- 60).

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Table III: Most common malignant tumours in The Netherlands according to 15-year-age groups[8]

Age group (years)	Sex	1	2	3	4	5
0-14	Both	Leukaemia	Brain	Malignant lymphoma	Kidney	Soft tissue
15-29	Male	Testis	Malignant lymphoma	Skin, melanoma	Brain	Leukaemia
	Female	Skin, melanoma	Malignant lymphoma	Breast	Ovary	Colon + rectum
30-44	Male	Testis	Skin, melanoma	Malignant lymphoma	Colon + rectum	Lung + bronchus
	Female	Breast	Skin, melanoma	Cervix	Lung + bronchus	Colon/rectum ovary
45-59	Male	Lung + bronchus	Colon + rectum	Prostate	Head and neck	Skin, melanoma
	Female	Breast	Lung + bronchus	Colon + rectum	Uterus	Ovary
60-74	Male	Lung + bronchus	Prostate	Colon + rectum	Bladder + urinary tract	Skin, other
	Female	Breast	Colon + rectum	Lung + bronchus	Uterus	Overy
≥75	Male	Prostate	Lung + bronchus	Colon + rectum	Skin, other	Bladder + urinary tract
	Female	Breast	Colon + rectum	Skin, other	Stomach	Lung + bronchus

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Chapter VIII

Primary malignant melanoma of the oral cavity: a review of eight cases

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Summary

A review of oral malignant melanoma and data of eight patients are presented. The dismal prognosis of the condition is probably mainly due to its long, 'silent' course. In one-third of cases melanosis precedes the tumour - it is this condition that should alert clinicians. Therefore, pigmented oral lesions should be viewed with suspicion and biopsy is mandatory when the clinical diagnosis is uncertain. Early detection is essential to successful treatment. In spite of aggressive treatment modalities, survival in patients with advanced stage disease remains poor.

Introduction

Malignant melanoma is a potentially aggressive tumour deriving from melanocytes. Intra-oral occurrence is rather rare. The prognosis is poor, especially in late cases. The present review is based on the relevant literature of the past decade and on experience with eight patients with a primary malignant melanoma of the oral cavity. These patients were referred to the Free university Hospital, Amsterdam, The Netherlands between 1978 and 1993 (Table I).

Epidemiology

The incidence of melanomas at all sites ranges from 4 to 8 per 100,000 population per year, thereby accounting for 1- 3 % of all cancers [1]. Involvement of mucous membranes, particularly of the oral cavity is rare; only 2 -5 % of all melanomas are oral primaries [2]. Oral malignant melanoma (OMM) appears to be slightly more common in men and negroids, and most frequently occurs between the ages of 40 and 70 [3]. The highest incidence of OMM is after the fifth decade, which is approximately 10 years beyond the highest incidence of malignant melanomas of the skin [4].

Aetiology

The aetiology of mucous membrane melanoma is unknown. Primary melanomas of the digestive tract may originate *de novo* [4]. However, pre-existing pigmentation - melanosis - occurs in at least one-third of OMMs [5]. Therefore, the importance of oral pigmentation has been stressed and prophylactic excision of such areas is generally advocated [5]. Unlike cutaneous melanoma, its oral counterpart is clearly not related to excessive exposure to solar radiation. Though repeated trauma to a pigmented lesion has been implicated as a cause of skin

Table I: Data of eight patients with an oral melanoma

Case	Age (yrs)	Sex	Site	TNM	Rx	FU	Status
1	91	F	palate	I	S+R	–	NDA
2	82	F	palate	I	S+R	19	DOD
3	71	M	palate	I	R	36	A&W
4	61	F	palate	I	S	77	DOD
5	59	F	palate	I	S	17	DOD
6	54	M	palate	I	S+L+R	80	DOD
7	38	F	tongue	I	S+R+C	16	DOD
8	31	F	buccal mucosa	IIb	S+R+I	16	DOD

F = female, M = male. Rx = treatment; S = surgery; R = radiotherapy; L = laser; C= chemotherapy; I=immunotherapy. FU = follow-up in months fom diagnosis. NDA = no data available; A&W = alive and well; DOD = died of disease

melanoma, to date there has been no proof that dentures, tobacco use, or other possibly irritating factors are, indeed, relate to the development of OMM [2]. Nevertheless, it its striking that all our palatal cases of OMM were seen in edentulous patients, possibly pointing to mechanical irritation as a predisposing factor.

Clinical features

Symptoms

There are few 'early' symptoms other than pigmentation. Ulceration, swelling, loosening of teeth, and ill-fitting dentures are the most common late symptoms [6]. The absence of pain appears to cause considerable patient's delay, the duration ranging from 2 weeks to 10 years [3]. No data are available in the literature about the doctor's delay with regard to the diagnosis of OMM. The patient's and doctor's delay in our own group was insufficiently recorded in the medical records.

Signs

OMM shows a predilection for the palate and maxillary gingiva, accounting for nearly 80 % of all cases [3,5,7]. Oral melanomas may present in various forms, ranging from non-pigmented [8], i.e. amelanotic, to deeply pigmented bluish, brown or even almost black lesions [7], with or without ulceration, and can be flat, swollen, or elevated. Satellite foci may attend the primary in any stage of the disease (Figs. 1-4). Regional, i.e. cervical, lymphadenopathy may occur already in an early stage of the disease.

Differential diagnosis

Localised blue-black pigmented lesions of the oral mucosa may be due to amalgam or any other heavy metal deposits, focal haemorrhage, melanocytic lesions, including the blue naevus, and Kaposi's sarcoma. Generalised oral discolouration is a physiological condition in negroids, and is referred to as racial pigmentation. In addition, it may be drug-induced or result from an endocrine disorder, such as Addison's disease, or from heavy smoking, smoker's melanosis [9].

Biopsy and histology

When an oral pigmentation cannot be diagnosed on clinical grounds alone a biopsy is mandatory, in particular to rule out the presence of a malignant melanoma. No scientific evidence exists that an incisional biopsy causes or promotes dissemination. The extent of oral lesions often makes such excisional biopsy unfeasible. Therefore, the incisional option is acceptable [6].

Histologically, OMM is often indistinguishable from its cutaneous counterpart. Malignant melanoma has a biphasic growth pattern consisting of a radial phase with lateral spread - subdivided into nodular, flat elevated, and ulcerated types - and a vertical phase with downward growth. The wide variety of morphological features and the various degrees of melanin production, ranging from absent to abundant, often complicate microscopic interpretation [10]. Two major cytological characteristic types have been recognized: the spindle cell type and the epithelioid cell type. Apart from the H&E stain, additional diagnostic tools such as the Fontana stain, DOPA reaction, S-100 protein marker, and electron microscopy may be helpful in establishing the final diagnosis.

Staging

The International Union Against Cancer does not provide a clinical classification for OMM Most authors adhere to the following system [11]:

Stage I	Primary tumour present only
Stage II	Metastases present
Stage IIa	Adjacent skin involved
Stage IIb	Regional lymph nodes involved
Stage IIab	Both adjacent skin and regional lymph nodes involved
Stage III	Metastases beyond regional lymph nodes

The value of this staging system seems somewhat questionable. When looking at the TNM stages of our own patients, mentioned in Table I, all but one could be staged as stage I, being suggestive of early malignancies carrying a fair prognosis. Nevertheless, the majority died of their disease.

Treatment

Surgery is the treatment of choice in OMM. The overall aim should be radical excision of all tumour tissue [5]. Unfortunately, often only partial removal is feasible due to anatomical limitations. The generally poor therapeutic results obtained with surgery coupled with incomplete excision have prompted alternative forms of therapy. Irradiation may be effective in early melanomas or in melanomas *in situ*. Immunotherapy is generally considered a palliative measure. Nevertheless, increased survival time following this modality indicates its effectiveness [12]. Chemotherapy is usually reserved for metastatic melanoma. Combination of treatment modalities are currently under investigation.

Prognosis

Most OMMs are large at presentation and have a poorer prognosis than cutaneous melanoma: 5-year survival rates of 10 - 20 % versus a 75 % long-term survival rate in skin melanoma [6]. Primary OMM has a marked propensity to metastasise locally to the submucosa and to regional lymph nodes. Distant metastases occur with considerable frequency to the lungs, brain, liver, and bones. These distant spreads result in a poor prognosis despite aggressive local and regional treatment and are the commonest causes of death in the majority of patients [4]. Although the overall outlook for a patient with OMM is rather unfavourable, the survival time may vary considerably [13]. In our patients the survival time after treatment varied form 16 to 80 months.

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Chapter IX

Paraneoplastic pemphigus

Paraneoplastic pemphigus as the presenting symptom of a lymphoma of the tongue

Oral Oncol 1998;34:567-70.

Paraneoplastic pemphigus caused by an epithelioid leiomyosarcoma and associated with respiratory failure

Oral Oncol 2000;36:390-3.

Paraneoplastic pemphigus as the presenting symptom of a lymphoma of the tongue

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Oral Oncol 1998;34:567-70.

Abstract

A patient is described who initially presented with an acrovesicular eczema which subsequently developed into erythema multiforme with histopathological features of bullous pemphigoid. Although the various laboratory studies pointed to the diagnosis of paraneoplastic pemphigus (PNP), the underlying neoplasm was not detected until six months later when the biopsies of an oral lesion showed the presence of an underlying non-Hodgkin lymphoma.

Introduction

The concept of paraneoplastic pemphigus (PNP) was first put forward in 1990 by Anhalt et al. [1], with the description of a distinct variant within the pemphigus spectrum associated with underlying neoplasms, especially lymphoreticular malignancies. This variant is characterized by atypical, erythema multiforme-like clinical and histopathological features and the occurrence of additional anti-epithelial IgG-type antibodies.
We describe a patient who initially presented with an acrovesicular eczema which subsequently developed into erythema multiforme with histopathologic features of bullous pemphigoid. Immunofluorescence microscopy, immunoblotting and immunoprecipitation proved this case to be a PNP, although initially no underlying neoplasms could be detected.

Case report

A 75-year-old Caucasian man was referred to the department of Dermatology in December 1996 with a three month history of multiple painful vesicles and bullae on palms and soles, which were initially diagnosed as acrovesicular eczema (Fig. 1). Treatment was initiated with prednisone 30 mg daily. Repeated relapses occurred after tapering of the prednisone dose. In addition, he developed multiple urticarial plaques on trunk and limbs as well as painful erosive lesions in the mouth. The patient also complained of general malaise and weight loss of 15 kilograms over the past two years.
Physical examination on admission showed an erythema multiforme-like skin eruption with some target lesions on trunk and upper limbs, blisters on the soles, and erosive lesions on the buccal mucosa. Nikolsky's sign was positive. General physical examination revealed no abnormalities.
Routine laboratory examination showed: raised white blood cell count (under current oral corticosteroid regimen) with 88% polymorphs; normal levels of erythrocyte sedimentation rate (ESR), haemoglobin, haematocrit, platelets, electrolytes, blood urea nitrogen, creatinine, blood glucose, and liver enzymes. A chest radiograph showed no abnormalities. Blister cultures remained negative.
Histological examination of a skin lesion showed an interface dermatitis with a band-like inflammatory infiltrate in the superficial dermis consisting of numerous eosinophils. Also mild vacuolar degeneration, spongiosis, and infiltration with inflammatory cells -especially neutrophilic eosinophils- were found in the epidermis. Apoptotic keratinocytes were sporadically present.
Direct immunofluorescence microscopy (DIF) of perilesional skin revealed intercellular IgG-deposits. The epidermal basement membrane zone showed linear deposits of C3d and C3c, as well as weak deposits of IgG.
Indirect immunofluorescence microscopy (IIF) of the patient's serum demonstrated IgG-autoantibodies directed to the intercellular epithelial substance of monkey oesophagus (titer 1:512) and rat bladder (titer 1:64). Immunoblotting (IB) was performed by sodium dodecyl

sulfate-polyacrylamide gel electrophoresis on keratinocyte cell extracts as previously described [2]. IB analysis of the patient's serum revealed multiple bands, including the 230 kD bullous pemphigoid antigen, suggestive of PNP (Fig. 2). Immunoprecipatation (IP) with the patient's serum was carried out as previously described [3], and showed clear identification of all five bands characteristic of PNP (Fig. 2).

On the basis of these results a preliminary diagnosis of PNP was made and a search for underlying neoplastic disease was carried out. However, except for a histologically proven benign prostate hyperplasia, no neoplasm could be detected.

Therapy was recommenced with prednisone 40 mg daily and azathioprine 100 mg daily. Initially, the bullous lesions responded well to treatment but six months later painful bullous and erosive lesions developed in the oral cavity (Fig. 3). Also on the trunk a few sharply demarcated erythematous lesions were found with central bleaching. The skin of the palms and soles was not involved. Again, general physical examination was unremarkable otherwise.

Laboratory investigations now revealed a raised ESR (46 mm/hr) and gamma-GT (123 U/l), whereas other results remained within normal range. Paraproteinaemia was excluded and a chest radiograph showed no abnormalities. Serologic tests were negative for syphilis and HIV. The oral blister cultures showed a mixed bacterial flora.

Using local anaesthesia, biopsies were taken from the lesions of the tongue. Immunohistopathologic examination revealed acantholysis and intercellular deposition of IgG and complement in the epithelial layers. The underlying connective tissue was filled entirely with a diffuse growing, polymorphous centroblastic CD79A-, B2-, and CD20-positive large B-cell lymphoma located underneath an ulcerative lesion (Fig. 4).

Additional investigations revealed an enlargement of the minor curvature of the gastric wall, suspicious of lymphoreticular tumour. No retroperitoneal or mesenterial lymphadenopathy was found. On gastroscopy, several suspicious areas were seen and biopsied. Histopathologically, these were identified as lymphoma localizations. Bone marrow involvement was excluded by marrow aspiration. Finally, the patient was diagnosed as having a paraneoplastic pemphigus caused by a polymorphous centroblastic large B-cell non-Hodgkin lymphoma, stage III.

Treatment was started with chemotherapy consisting of cyclophosphamide, adriamycine, vincristine, and prednisone (CHOP). Shortly after receiving the first chemotherapy course the pemphigus lesions rapidly diminished. The patient was discharged from hospital and currently has undergone five CHOP-courses. Sixteen months after the diagnosis of PNP had been established, the patient is alive without signs of relapse of his PNP-lesions. The oral localizations of the lymphoma have shown complete regression.

Discussion

PNP is defined by five criteria [1]: (1) a polymorphous eruption of skin and mucous membranes; (2) histopathological features of epidermal acantholysis and dyskeratosis, with basal layer vacuolar changes [3]; (3) depositions of IgG and C3 with an intercellular pattern in the

epidermis and/or a linear pattern at the epidermal basement membrane zone by DIF; (4) circulating autoantibodies which bind to the intercellular spaces of multiple epithelia and to other tissues which contain desmosomes as detected by IIF. Binding on rat bladder transitional epithelium in particular has been shown to be quite specific for paraneoplastic pemphigus [4,5]; and (5) IP studies show the unique complex of 250, 230, 210, 190, and 170 kD antigens [6,7].

Our patient's first symptom was an acrovesicular eczema and the first skin biopsy specimen was considered to be most consistent with bullous pemphigoid. DIF directed the diagnosis more towards pemphigus. However, a preliminary diagnosis of PNP was made on IIF studies.

The diagnosis of PNP was further supported by the results of IB and IP. The 170 kD antigen was not detected on IB, as in accordance with literature [8]. IP of the patient from this case report clearly identified strongly labeled bands at 250, 210, 190, and 170 kD. In addition, the 230 kD antigen band was faintly labeled. Due to different techniques, the IP did not reveal the 130 kD pemphigus vulgaris antigen (desmoglein 3) as in the IB. IP of the control serum identified all five bands characteristic of PNP quite strongly and these comigrated precisely with the antigen bands of our patient. These findings are diagnostic for PNP.

Several PNP patients have previously been described with an atypical blistering condition [9,10]. The development of painful blisters and erosions of the oral mucosa is a well known feature of PNP and sometimes even the sole manifestation [11,12].

Almost all cases of PNP have been associated with a lymphoreticular malignancy, especially arising in longstanding non-Hodgkin lymphoma and chronic lymphocytic leukemia [1,6,11,13]. About two thirds of reported cases arise in the context of a known neoplasm -either of benign or malignant origin [6]. In some cases the PNP occurred during chemotherapy or radiation treatment [14,15]. In approximately one third of PNP cases, no neoplastic lesions have been manifest at the time of development of mucocutaneous disease. As in our case, screening for an occult neoplasm is than mandatory [6].

Most reported PNP patients have had a poor prognosis, although occasionally substantial survival times have been described [16]. Treatment of the underlying malignancy has been reported to not affect the course of the PNP [17]. Nevertheless, we found a striking correlation between the rapid regression of PNP lesions and the diminishing sizes of our patient's oral lymphoma immediately after the first chemotherapy courses.

The present case is remarkable because of the initial clinical presentation of acrovesicular eczema and because the PNP preceded the discovery of the neoplasm for a rather long period of nine months.

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9.2

Paraneoplastic pemphigus caused by an epithelioid leiomyosarcoma and associated with fatal respiratory failure

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Abstract

A patient is described who initially presented with pemphigus vulgaris, limited to the oral cavity, and weight loss. Although the various laboratory studies pointed to the diagnosis of paraneoplastic pemphigus (PNP), the underlying neoplasm was not detected until six months later, when the patient developed shortness of breath and routine physical examination on admission revealed an abdominal mass, which eventually was proven to be an epithelioid leiomyosarcoma. In spite of radical excision of the tumour and intensive treatment of the dyspnoea, the patient died of respiratory failure 19 months after the PNP had been diagnosed. Early diagnosis of PNP is stressed to possibly prevent fatal pulmonary involvement.

Introduction

Paraneoplastic pemphigus (PNP) is a clinically, histologically, and immunologically distinct autoimmune bullous disease characterised by severe mucosal erosions and polymorphous skin lesions, acantholysis with interface dermatitis or keratinocyte necrosis, and autoantibodies to various epidermal proteins in the context of underlying neoplasia [1-4]. Recently, a number of PNP cases with pulmonary involvement, resulting in respiratory failure have been reported [5-12].

In the present paper, a patient who initially presented with abundant oral lesions with clinical and histopathological features of pemphigus vulgaris is described.

Case report

A 56-year-old Caucasian woman was referred to the Department of Dermatology in July 1997 with a five month history of multiple, progressive, painful vesicles, bullae, and ulcerations of the buccal and lingual mucosa. Furthermore, the patient complained of general malaise and weight loss of 13 kg over the past five months without complaints of the gastrointestinal tract.

On intraoral examination multiple erosions throughout the oral cavity were seen (Figs.1 and 2). General physical examination did not reveal any other abnormalities.

Routine laboratory examination, including sedimentation rate, white blood cell count, haemoglobin, haematocrit, platelets, electrolytes, blood urea nitrogen, creatinine, glucose, and liver enzymes, did not show any abnormalities. A chest radiograph did not show any abnormalities either. Cultures taken from the oral lesions remained negative.

Histological examination of the buccal mucosa lesions showed suprabasilar cleft formation with acantholysis. The submucosa showed a predominantly lymphocytic infiltrate. Although the histopathologic features were compatible with pemphigus vulgaris, a diagnosis of PNP was suspected in view of the history of profound weight loss.

Direct immunofluorescence microscopy of perilesional mucosa showed intercellular IgG-deposits. The mucosal basement membrane zone revealed weak deposits of IgG, but prominent linear deposits of C3c and C3d. Indirect immunofluorescence microscopy of the patient's serum demonstrated IgG autoantibodies directed to the intercellular epithelial substance of monkey oesophagus (titre 1: 256) and rodent urinary bladder (titre 1: 64) as well as antibodies to cytoplasmatic, striated muscle (titre 1: 1024) and antinuclear antibodies (titre 1: 256). Immunoblotting analysis of the extract of cultured keratinocytes [13] disclosed antibodies to the 250-, 210-, 190-, and 130-kd proteins, respectively desmoplakin I, envoplakin-desmoplakin II, periplakin and desmoglein 3 (Fig.3). In addition, immunoprecipitation [14,15] detected the 170-kd protein, an as yet unidentified transmembranous antigen. The bullous pemphigoid 230-kd protein was not immunoreactive with the serum. On the basis of these results, a preliminary diagnosis of PNP was made. Subsequently, a search for an underlying neoplasm was carried out. At that time no neoplastic disease could be detected.

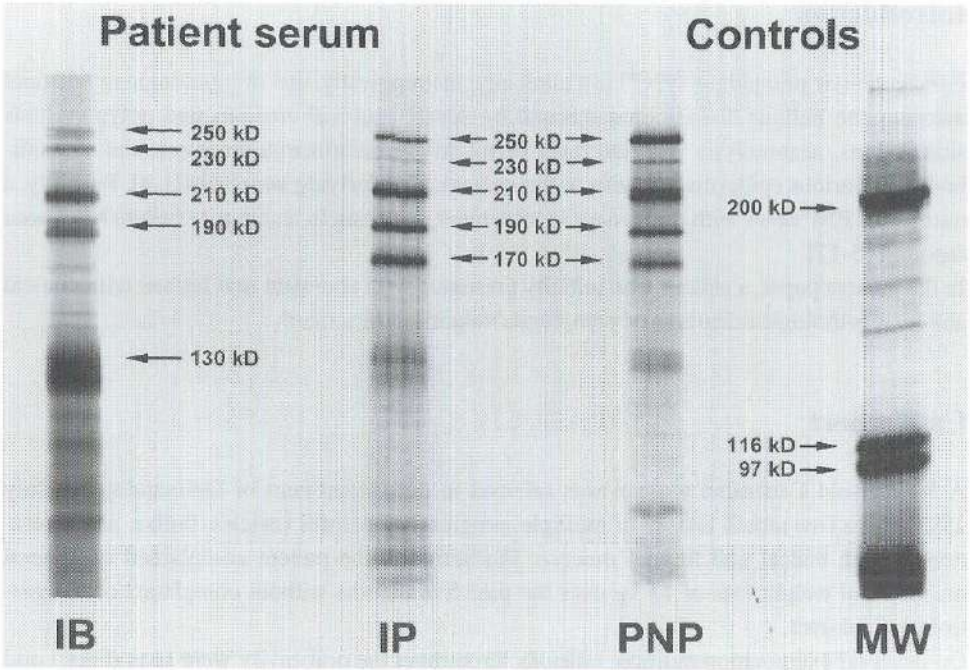

Figure 3. IB=immunoblotting; IP=immunoprecipitation; PNP=immunoprecipitation of a control with paraneoplastic pemphigus; MW=molecular weight references with immunoprecipitation.

Therapy was started with 60 mg prednisolone and 100 mg azathioprine daily. Initially, the bullous lesions responded well to treatment and allowed tapering of the prednisolone. Six months later, however, again painful erosive and bullous oral lesions had again developed and the patient also complained of progressive shortness of breath. The dyspnoea was analysed through chest radiographs, computed tomographic (CT) scanning, scintigraphy, pulmonary function tests, and bronchoscopy and diagnosed as bronchiolitis obliterans. Consequently, high dosages of prednisolone were given.

Physical examination on admission also revealed an asymptomatic abdominal mass in the left lumbar region. Ultrasonography and a CT scan of the abdominal tumour showed it to be a solid retroperitoneal process. No other abnormalities were found on imaging or on laboratory investigations. Eight months after the diagnosis of PNP had been established, surgical excision of a 15-cm-diameter tumour was performed (Fig.4). Histopathological investigations revealed a radically excised epithelioid leiomyosarcoma, a rare sarcoma variant.

Despite high-dose corticosteroids, intensive pulmonary treatment and ten plasmapheresis procedures, the patient's respiratory status continued to deteriorate. Although the oral lesions slowly healed, the patient died of respiratory failure nineteen months after the initial diagnosis of PNP had been established. No post mortem examination was performed.

Discussion

PNP, as first outlined by Anhalt et al. in 1990 [1], occurs in association with an underlying neoplasm and is characterised by five diagnostic criteria: (1) a polymorphous eruption of skin and mucous membranes; (2) histopathological features of epidermal acantholysis and dyskeratosis, with basal layer vacuolar changes; (3) depositions of IgG and C3 with an intercellular pattern in the epidermis or with a linear pattern at the basement membrane zone by direct immunofluorescence; (4) circulating autoantibodies which bind to the intercellular spaces of multiple epithelia and to other tissues which contain desmosomes as detected by indirect immunofluorescence; and (5) immunoblotting and immunprecipitation studies show the unique complex of 250, 230, 210, 190, 170, and 130 kd antigens [7, 16].

The most frequently observed clinical feature of PNP are persistent oral vesiculobullous lesions and erosions, usually as the presenting sign - as in the presented case - sometimes as the only clinical manifestation [8], and often resistant to treatment. The oral lesions in the described patient are probably on account of the desmoglein 3 autoantibodies, similar as in oral pemphigus vulgaris [16].

Most cases of PNP have been associated with a lymphoreticular malignancy, especially with non-Hodgkin lymphoma and chronic lymphocytic leukaemia [1,3,7,11,17]. An association with retroperitoneal sarcoma has been reported in only six per cent of PNP cases [7]. Approximately two-thirds of reported PNP cases arise in the context of a known neoplasm - most frequently of malignant and sometimes of benign origin [7]. In some cases, the PNP became manifest during radiation treatment [18,19] or chemotherapy [20]. In the remaining one-third of PNP cases, no neoplastic lesions have become manifest at the time of development of the mucocutaneous disease [7, 21]. As in the presented case, screening for an occult neoplasm is mandatory in suspected cases of PNP, especially with CT scanning of the chest, abdomen, and pelvis [7].

In PNP patients with a benign neoplasm, the disease usually clears substantially once the tumour is surgically excised. Reported cases of PNP with an underlying malignancy have generally followed a rapidly progressive and fatal course [1,7]. Although oral lesions in PNP are known to be persistent, excision of the tumour in the reported patient was followed by healing of the lesions of the oral cavity.

Pulmonary involvement occurs in about 30 per cent of PNP patients [11]. It has been found that autoantibodies directed against plakin proteins may cause acantholytic changes in the respiratory epithelium, leading to bronchiolitis obliterans [11]. The irreversible restrictive changes due to scarring of the bronchi and alveoli in bronchiolitis obliterans [5-11] is known to progress to fatal respiratory insufficiency [5,11,18,19,20], also in the event of an early excised underlying benign neoplasm. In spite of radical excision of the retroperitoneal sarcoma, high-dose corticosteroids and repeated plasmapheresis, the presented patient died of bronchiolitis obliterans with severe respiratory failure 19 months after the initial diagnosis of PNP had been established. Therefore, early diagnosis of PNP is thought to be important to possibly prevent pulmonary involvement since there is no effective treatment yet available.

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Chapter X

Summary

&

Samenvatting

Summary

In **Chapter II** a brief overview has been presented of some systemic diseases, not dealt with in the other chapters, that may present with oral manifestations and oral lesions that may have a systemic background.

In **Chapter III** eleven patients with amyloidosis of the oral cavity have been highlighted. In this retrospective series, an evident association was shown with occult underlying plasma cell dyscrasia, in particular myeloma. Amyloidosis of the tongue should be regarded as a paraneoplastic marker of these hematologic diseases. This is also supported by the observation of reduction of amyloid infiltration and prolonged survival when treatment of the underlying hematologic disorder is successfully carried out.
Hence, whenever amyloidosis of the oral cavity is suspected -in a patient not known with an associated disorder-, a biopsy is mandatory. When AL amyloid deposits are present, a medical work-up should be carried out in search for underlying disorders, especially focussing on the existence of gammopathies and their underlying lymphoid and plasmacellular malignancies.
We emphasize that macroglossia can be an important clinical feature in the detection of amyloidosis and, as a result, also of underlying hematological disorders, possibly aiding in earlier diagnosis, treatment, and improved prognosis.

In **Chapter IV** an overview of the literature on cheilitis granulomatosa has been presented. Furthermore, the clinical features, histopathology, association with sarcoidosis or Crohn's disease, and results of non-surgical and surgical therapy in this retrospective case study of 13 patients with a mean follow-up period of 8.2 years have been presented and discussed with regard to the literature.
Although cheilitis granulomatosa has earlier been suggested to represent a localized form of sarcoidosis in some patients, none of the reported patients in our series developed sarcoidosis prior to the onset of lip swellings or during follow-up. In view of the fact that only two of the patients in this long-term follow-up series developed Crohn's disease -years after their cheilitis granulomatosa- and reviews of larger numbers of patients did not bear out a relationship of cheilitis granulomatosa with Crohn's disease, it does not seem justified to recommend routine investigations of the gastrointestinal tract in patients with cheilitis granulomatosa or Melkersson-Rosenthal syndrome with a negative history of gastrointestinal complaints. Instructing every patient to report their complaints on relevant disease entities during follow-up is foremost important in planning further investigations.
Management of patients with cheilitis granulomatosa remains a challenge and should be guided by the severity of the clinical manifestations. Most patients in this study responded to non-surgical treatment modalities, commonly consisting of topical steroids. Patients with deterioration of lip swelling usually respond to intralesional injections with triamcinolone or to short courses of systemic glucocorticoids. Furthermore, non-steroidal systemic modalities, such as clofazimine, hydroxychloroquine or sulfasalazine, form alternatives to glucocorti-

coid regimens, thus avoiding the long-term side effects of corticosteroids. Surgical intervention should only be performed in severely disfiguring cases. When management of cheilitis granulomatosa is carried out according to the above-described strategy, outcome is usually satisfactory. Nevertheless, due to the nature of the disease, minor recurrences of lip swelling can still occur. A prospective study is required to adequately and objectively assess the outcome of different treatment modalities.

In **Chapter V** an overview of the oral manifestations of non-Hodgkin lymphoma (NHL) is presented. In the oral cavity, lymphomas usually present as an extranodal, soft-elastic, asymptomatic lesion. In the comprehensive series, oral primary extranodal (PE) NHL arose in two-thirds of patients from soft tissues, most commonly in the upper jaw. In the remaining one-third of patients, the lesions originated from the bone, equally distributed over the mandible and the upper jaw. In our experience, NHLs of the upper jaw by and large originate from soft tissue, whereas NHLs of the lower jaw all arise in bone.
The clinicopathologic features of oral PE-NHL correspond with those of PE-NHL in general. Most NHLs are of B-cell lineage, and, in our experience diffuse large B-cell lymphomas comprised half of oral PE-NHL cases. Furthermore, as has been reported in the literature, most of these diffuse large B-cell lymphomas presented with locoregional disease.
We conclude that PE-NHL of the oral cavity is a rather rare phenomenon; the clinical and radiological features are not pathognomonic. Obviously, this may delay the diagnosis. Recognition of oral PE-NHL in an early stage may be of vital importance with regard to prognosis.

In **Chapter VI** two reports have been presented of patients with a squamous cell carcinoma of the oral cavity as second primary malignancy following treatment for cancer in their past medical history. With the introduction of effective chemotherapy regimens during the early 1970s, the dismal prognosis of some malignancies has dramatically improved. However, these treatments may be associated with late neoplastic sequelae. Fortunately, the number of second primary malignancies among cancer survivors is low, and the risk attributable to therapy is small when compared with the improvement in survival rates achieved by the use of cancer treatments.

In **Chapter VII** an overview is given of 24 patients with a metastatic tumour of the oral cavity. Oral metastases are rare and may present at any age as well in males as in females and predominantly involve bony structures, especially the mandible. The predominant histologic type of the metastatic process was an adenocarcinoma. In the evaluation of the relative numbers of primary tumours, the incidence rates of the specific primaries in that particular population should be taken into account. Although most primary tumours are known at the time of occurrence of an oral metastasis, one third of oral metastases in this study appeared to be the first manifestation of an initially occult malignant process elsewhere in the body.
Since most patients presenting with a metastatic tumour in the oral cavity also have developed metastases at other sites, a palliative regimen often is usually the only management option. The prognosis of the patients studied proved to be poor with a median survival of six

months. Local treatment of a jaw bone metastasis -nearly always by means of radiation therapy- usually relieves pain and may prevent loss of function. Metastases in the soft oral tissues may be more readily approached surgically, with similar palliative results for the patient.

In **Chapter VIII** a review of the literature on oral malignant melanoma and data of eight patients have been presented. Oral malignant melanoma may present in various forms and shows a predilection for the palate and maxillary gingival. It was striking that all the palatal cases of melanoma in this study were seen in edentulous patients, possibly pointing to mechanical irritiation as a predisposing factor.
Most oral malignant melanomas are large at presentation and have a poorer prognosis than cutaneous melanoma. The dismal prognosis of the condition is probably mainly due to its long, 'silent' course, causing considerable patient's delay. Since there are no recent advances in the treatment of malignant melanoma, early detection is essential to successful treatment of melanomas. Therefore, pigmented lesions of the oral cavity should be viewed with suspicion and a biopsy is mandatory when the clinical diagnosis is uncertain.

In **Chapter IX** two reports have been presented of patients with paraneoplastic pemphigus. In both patients, the various laboratory studies pointed to the diagnosis of paraneoplastic pemphigus. However, both cases were remarkable because, in contrast to most described cases, the occurrence of paraneoplastic pemphigus preceded the detection of their underlying neoplasms for a long period of time. As in the presented cases, screening for an occult neoplasm is mandatory in suspected cases of paraneoplastic pemphigus, especially with computed tomography scanning of the chest, abdomen, and pelvis.
Pulmonary involvement occurs in approximately one-third of paraneoplastic pemphigus patients. It has been found that autoantibodies in this disease directed against plakin proteins may cause acantholytic changes in the respiratory epithelium, leading to bronchiolitis obliterans. The irreversible restrictive changes due to scarring of the bronchi and alveoli are known to progress to fatal respiratory insufficiency, as described in the second report. Unfortunately, continued follow-up after publication of the first case report also showed this fatal respiratory complication in that particular patient.
In paraneoplastic pemphigus patients with a benign underlying neoplasm, the disease usually clears substantially once the tumour is surgically excised. Reported cases of paraneoplastic pemphigus with an underlying malignant process have generally followed a rapidly progressive and fatal course, despite surgical excision or aggressive treatment. Therefore, early diagnosis of PNP is thought to be important to possibly prevent the fatal pulmonary involvement since there is no effective treatment yet available.

Samenvatting

Samenvatting

In **hoofdstuk II** is een beknopt overzicht gepresenteerd van enkele systeemziekten die zich met mondafwijkingen kunnen presenteren alsook van mondafwijkingen die een systemische achtergrond kunnen hebben. De in de volgende hoofdstukken nader besproken aandoeningen zijn hier bewust niet opgenomen.

In **hoofdstuk III** zijn elf patiënten met amyloidose van de mondholte besproken. In dit retrospectieve onderzoek werd een duidelijke associatie gevonden met occulte, onderliggende plasmacel dyscrasieën, in het bijzonder met multipel myeloom. Amyloidose van de tong zou beschouwd moeten worden als een paraneoplastisch kenmerk van deze hematologische ziekten. Dit wordt ook ondersteund door de observatie van de reductie van amyloid infiltraat en verlengde overlevingsduur aansluitend aan succesvolle behandeling van de onderliggende hematologische afwijking.
Wanneer amyloidose van de mondholte vermoed wordt, dient dan ook een biopsie verricht te worden. Indien AL amyloid afzettingen aanwezig zijn, moet aanvullende diagnostiek plaatsvinden naar onderliggende afwijkingen, waarbij met name gezocht dient te worden naar gammopathieën en onderliggende lymfoïde en plasmacellulaire maligniteiten.
We willen benadrukken dat macroglossia een belangrijke klinisch presentatie kan zijn om amyloidose te detecteren en, zoals besproken, ook onderliggende hematologische afwijkingen op te sporen. Mogelijk leidt dit tot vroeger stellen van diagnose en instellen van behandeling, hopelijk resulterend in een betere prognose.

In **hoofdstuk IV** is een literatuuroverzicht van cheilitis granulomatosa gepresenteerd. Voorts werden in een retrospectief onderzoek van 13 cheilitis granulomatosa patiënten met een gemiddelde volgduur van 8,2 jaar de klinische verschijnselen, de histopathologie, de associatie met sarcoïdose of de ziekte van Crohn en de resultaten van conservatieve en chirurgische therapie gepresenteerd in relatie tot de literatuur.
Hoewel in het verleden is gesuggereerd dat cheilitis granulomatosa bij sommige patiënten een gelokaliseerde vorm van sarcoïdose zou zijn, had geen der besproken patiënten sarcoïdose doorgemaakt voor het ontstaan van de lipzwelling, noch in de gevolgde periode nadien. Aangezien slechts twee van de patiënten in dit lange termijn volgonderzoek de ziekte van Crohn hebben ontwikkeld -jaren na hun cheilitis granulomatosa- en overzichtsliteratuur van grote aantallen patiënten geen relatie heeft aangetoond tussen cheilitis granulomatosa en de ziekte van Crohn, lijkt het niet gerechtvaardigd routine-onderzoek van de tractus digestivus aan te bevelen bij patiënten met cheilitis granulomatosa of het Melkersson-Rosenthal syndroom die geen gastro-intestinale symptomen in de anamnese hebben. Het is belangrijk dat deze patiënten geïnstrueerd wordt om klachten van relevante ziektes in de toekomst te melden teneinde eventueel aanvullende diagnostiek gericht op te zetten.
De behandeling van cheilitis granulomatosa patiënten blijft een uitdaging en zou ingesteld moeten worden op geleide van de ernst van de klinische verschijnselen. Het merendeel van de patiënten in dit onderzoek reageerde op conservatieve behandelingen, meestal bestaande

uit locale applicatie van steroïden. Excacerbatie van de lipzwelling is in het algemeen goed behandelbaar met intralesionale injecties met triamcinolon of stootkuren systemische glucocorticoïden. Voorts vormen niet-steroidale systemische behandelmodaliteiten, zoals clofazimine, hydroxychloroquine of sulfasalazine, alternatieven voor glucocorticoïd regimes, waarbij de lange-termijn bijwerkingen van corticosteroïden worden voorkomen. Chirurgische interventie dient slechts in ernstig verminkende gevallen te worden verricht. Wanneer de behandeling van cheilitis granulomatosa volgens bovenstaande wordt uitgevoerd, is het resultaat over het algemeen bevredigend. Desalniettemin kunnen als gevolg van de aard van de aandoening milde recidieven optreden. Een prospectief onderzoek is aangewezen om objectief de resultaten van de verschillende behandelmogelijkheden te bepalen.

In **hoofdstuk V** is een overzicht gegeven van de mondmanifestaties van het non-Hodgkin lymfoom (NHL). In de mondholte presenteren lymfomen zich meestal als extranodale, vastelastische, asymptomatische laesies. In een uitgebreide patiëntengroep bleek tweederde van de primaire extranodale NHL te ontstaan in de slijmvliezen, meestal de bovenkaak bekledend. In de resterende eenderde der patiënten ontstonden de afwijkingen in het bot, met gelijke frequentie in onder- en bovenkaak. In ons onderzoek bleken NHL van de bovenkaak voornamelijk te ontstaan in slijmvliesweefsel, terwijl NHL van de onderkaak allen in bot ontstonden.
De clinicopathologische kenmerken van primaire extranodale NHL van de mondholte corresponderen met die van primaire extranodale NHL in het algemeen. De meeste NHL zijn van B-cel origine waarbij het, in ons onderzoek, in de helft der patiënten een diffuus grootcellig B-cellymfoom betrof. Zoals uit de literatuur bekend, presenteren deze diffuus grootcellige B-cellymfomen zich veelal als een loco-regionaal ziekteproces.
We concluderen dat primaire extranodale NHL van de mondholte vrij zeldzaam zijn en dat klinische noch radiologische karakteristieken pathognomonisch zijn. Dientengevolge kan dit het stellen van de diagnose bemoeilijken en vertragen. Het in een vroeg stadium (h)erkennen van primaire extranodale NHL van de mondholte kan van vitaal belang zijn voor de prognose van de patiënt.

In **hoofdstuk VI** worden twee patiënten gepresenteerd met een plaveiselcelcarcinoom van de mondholte als tweede primaire maligniteit na behandeling van kanker in hun respectievelijke voorgeschiedenissen. Met de introductie van effectieve chemotherapie schema's begin jaren '70, is de sombere prognose van sommige maligniteiten sterk verbeterd. Deze behandelingen kunnen echter ook gepaard gaan met late neoplastische gevolgen. Gelukkig is het aantal tweede primaire maligniteiten onder overlevenden van kanker laag en is het aan behandeling toe te schrijven risico klein in vergelijking met de door deze behandeling bereikte verbeterde overlevingskansen.

In **hoofdstuk VII** is een overzicht gepresenteerd van 24 patiënten met een metastase in de mondholte. Orale metastasen zijn zeldzaam, kunnen voorkomen op iedere leeftijd, zowel bij mannen als bij vrouwen, en zijn voornamelijk in botweefsel gelokaliseerd, met name in de

mandibula. Het meest gesignaleerde histologische type van een dergelijk metastatisch proces bleek een adenocarcinoom te zijn. Bij de evaluatie van relatieve aantallen van de primaire tumoren dienen de incidentie cijfers van de specifieke primaire in de betreffende populatie te worden betrokken. Hoewel de meeste primaire tumoren bekend zijn ten tijde van ontstaan van een orale metastase, bleek eenderde van de orale metastasen in ons onderzoek de eerste manifestatie te zijn van een initieel occult maligne proces elders in het lichaam.
Aangezien de meeste patiënten met een metastase in de mondholte veelal tevens metastasen op andere lokalisaties hebben ontwikkeld, is palliatieve behandeling in het algemeen de enige optie. De onderzochte patiënten bleken een slechte prognose te hebben met een mediane overleving van zes maanden. Lokale behandeling van een kaakbot metastase -nagenoeg altijd met radiotherapie- vermindert veelal de pijn en kan verlies van functie voorkomen. Metastasen in slijmvliesweefsel van de mondholte kan eenvoudig chirurgisch worden benaderd, met soortgelijke palliatieve resultaten voor de patiënt.

In **hoofdstuk VIII** is een overzicht gegeven van de literatuur aangaande het maligne melanoom van de mondholte en de data van acht patiënten. Het maligne melanoom van de mondholte kan zich in verschillende vormen presenteren en vertoont daarbij een voorkeur voor het palatum en de gingiva van de maxilla. Opvallend in dit onderzoek was dat alle op het palatum gelokaliseerde melanomen gesignaleerd werden in edentate patiënten, mogelijk wijzend richting mechanische irritatie als een predisponerende factor.
De meeste maligne melanomen van de mondholte zijn groot bij presentatie en hebben een slechtere prognose dan cutane melanomen. De sombere prognose van deze aandoening berust waarschijnlijk op het lange, asymptomatische beloop dat leidt tot een aanzienlijke vertraagde signalering door de patiënt. Vroege detectie is essentieel voor succesvolle behandeling van melanomen. Gepigmenteerde afwijkingen in de mondholte dienen dan ook met verdenking te worden benaderd en een biopsie is geïndiceerd bij twijfel over de klinische diagnose.

In **hoofdstuk IX** worden twee patiënten gepresenteerd met paraneoplastische pemphigus. In beide patiënten wees laboratoriumonderzoek naar de diagnose paraneoplastische pemphigus. Echter, beide patiënten waren opmerkelijk omdat, in tegenstelling tot de meest gerapporteerde casus, het optreden van paraneoplastische pemphigus lange tijd voorafging aan de detectie van hun beider onderliggend neoplasma. Zoals bij beiden besproken, dient in voor paraneoplastische pemphigus verdachte gevallen aanvullende diagnostiek te worden verricht naar een occult neoplasma, in het bijzonder met CT-scans van de thorax, het abdomen, en het bekken.
Longbetrokkenheid treedt bij circa eenderde der paraneoplastische pemphigus patiënten op. Beschreven is dat bij paraneoplastische pemphigus auto-antilichamen gericht tegen plakine proteines acantholytische veranderingen kunnen induceren in het respiratoire epitheel, resulterend in bronchiolitis obliterans. De irreversibele restrictieve pulmonale veranderingen als gevolg van verlittekening van de bronchi en alveoli kunnen leiden tot fatale respiratoire insufficiëntie, zoals beschreven in de tweede patiënt.

Paraneoplastic pemphigus bij patiënten met een benigne onderliggend neoplasma verbetert veelal substantieel na excisie van de tumor. In de literatuur gerapporteerde gevallen van paraneoplastische pemphigus met een maligne onderliggend proces hebben een snel progressief en fataal beloop, ondanks excisie van de tumor of agressieve behandeling. Aangezien voor deze patiënten geen effectieve therapie voorhanden is, zou het vroeg stellen van de diagnose van belang kunnen zijn om de fatale pulmonale betrokkenheid te trachten te voorkomen.

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Curriculum vitae

The author of this thesis was born in Rotterdam, The Netherlands, on 31 January 1968. After graduating from the Rijnlands Lyceum in Oegstgeest, The Netherlands, in 1986, he attended Medical School at Leiden University, The Netherlands, from 1986 to 1994, of which one year was spent at the Manchester Royal Infirmary and Manchester University, United Kingdom. After fulfilling his National Service with the Royal Netherlands Navy as a Medical Officer, he has been resident at the department of Dermatology (head: Prof.dr. Th.M. Starink), VU Medical Centre, Amsterdam, The Netherlands. During his residency, he also performed clinical work and research in the field of Oral Medicine at the department of Oral and Maxillofacial Surgery/Oral Pathology, VU Medical Centre/Academic Centre for Dentistry (ACTA), Amsterdam, The Netherlands. On June 1, 2002, he completed his dermatology training.

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