Surgical pathology of the mouth and jaws

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14. Lymphoreticular and granulomatous diseases

Lymphoreticular diseases are diverse clinically and pathogenetically but can share a variety of features. In particular, immunity depends on normal function of the lymphoreticular diseases frequently lead to immunodeficiencies. Conversely, lymphomas are a recognized complication of AIDS and other immunodeficiencies.

Lymphoreticular tumours - lymphomas

The main examples of solid lymphoid tumours are the lymphomas. Leukaemias, by contrast, typically do not form solid tumours but affect the bone marrow and blood. However, lymphocytic lymphomas may have features of both diseases. Myeloma and Langerhans cell histiocytosis also arise from lymphoreticular cells, but particularly affect bones and are discussed in Chapter 5.

Lymphomas are solid tumours of any type of lymphocyte; they are all malignant. They comprise Hodgkin's disease and non-Hodgkin's lymphoma. Their aetiology is unknown, but lymphomas are more frequent in the following:

- rheumatoid arthritis, Sjögren's syndrome and benign lymphoepithelial lesion

- immunosuppressive treatment, particularly for organ transplantation, and cytotoxic chemotherapy

- AIDS

- irradiation.

Exposure to asbestos has been reported to be associated with an increased incidence of oral lymphomas, but this has not been widely confirmed.

Lymphomas, particularly Hodgkin's disease, are rare tumours in the mouths of otherwise healthy persons, though they relatively frequently involve the cervical lymph nodes. The majority of oropharyngeal lymphomas develop in Waldeyer's ring, but are usually in the tonsils. Salivary glands, particularly the parotids which have a lymphoid component, can occasionally also be affected. By contrast, lymphomas in AIDS can account for 2% of oral neoplasms.

Clinical features

Adults are predominantly affected and lymphomas within the mouth form nondescript, usually soft, painless swellings, which may become ulcerated by trauma. The regional lymph nodes are not necessarily involved at first and diagnosis depends on the microscopic findings and related investigations.

Nasopharyngeal lymphoma is a rare cause of midfacial destructive disease, and can cause swelling and ulceration of the palate as the presenting feature, as discussed later.

Microscopically, lymphomas consist of B or, less often, T lymphocytes which, according to their stage of differentiation, give rise to different types of tumour, but morphological differences between these cells are frequently very slight. This is, therefore, a particularly difficult area of light microscopy and there are many classifications, of which the Working Formulation (Table 14.1) and a simplified histological classification (Table 14.2) are given. The Working Formulation relates histology with behaviour but does not include T cell lymphomas. The simplified histological classification shows the main currently recognized types of non-Hodgkin lymphomas. However, precise categorization is best left to specialists.

Table 14. 1 Working Formulation for non-Hodgkin's lymphomas

Behaviour	*Histology*
I. Low grade	Small lymphocytic
	Follicular, small cleaved cell
	Follicular, mixed small cleaved and large cell
II. Intermediate grade	Follicular, large cell
	Diffuse, small cleaved cell
	Diffuse, mixed small and large cell
	Diffuse, large cell
III. High grade	Large cell, immunoblastic
	Lymphoblastic
	Diffuse, small non-cleaved cell.

Non-Hodgkin lymphomas appear as solid sheets of lymphocytes which may be predominantly small or large. Invasion or destruction of adjacent tissues may be seen and helps to confirm the malignant nature of these tumours. They may be diffuse or have a follicular pattern. Most (but not all) follicular lymphomas are low grade and have a better prognosis.

Table 14.2 Simplified histological classification of non-Hodgkin lymphomas

1. Lymphocytic
2. Follicle centre cell
3. Immunoblastic
4. Burkitt-type lymphoma
5. MALT cell lymphoma
6. T cell lymphomas.

An additional problem in the mouth is that, if traumatized, superimposed inflammatory changes can cause a lymphoma to resemble a reactive lesion microscopically.

Investigation

In addition to the cytological features, which are used to decide the grade of a tumour, a useful test is the detection of a change from polyclonality (production of both lambda and kappa immunoglobulin light chains) of benign lymphoepithelial or reactive lesions to monoclonal production, usually, of kappa light chains by the neoplastic cells. Immunophenotyping is used to establish the lineage of the tumour cells as a guide to treatment.

Management

Clearly, a critical factor is whether the tumour is primary or is the initial manifestation of disseminated disease. In addition to biopsy, therefore, staging investigation is necessary to determine the extent of spread of the tumour. Preliminary examination consists of physical examination, blood picture, chest radiographs, bone marrow biopsy and CT scanning to detect affected nodes in the abdomen.

The few cases with disease localized to a single node or extranodal sitre (stage I) and those with limited spread (stage II) are usually treated by irradiation. However, the majority of patients with oral or perioral lymphomas have disseminated disease (stage III or IV) and treatment is by combination chemotherapy. Oral disease, such as ulceration and infection, are common complications of such treatment. The overall 5-year survival rate for non-Hodgkin lymphomas is about 30%.

Burkitt's lymphoma

This type of lymphoma, endemic in East Africa, has its onset in childhood, and has aroused interest by its association with the Epstein-Barr virus (EBV).

Clinically, Burkitt's lymphoma is peculiar in its onset at an average age of 7 years, and its predominantly extranodal distribution, with jaw involvement as the single most common initial site. Spread to the surrounding oral soft tissues and parotid glands and involvement of non-lymphoid abdominal viscera are common.

Over 95% of cases respond completely to single dose chemotherapy and though there is a high relapse rate, especially in those with widespread disease, the overall survival rate is approximately 50%. Also unlike other lymphomas, there is little or no response to radiotherapy.

Microscopically, Burkitt's lymphoma is a small cell lymphoma containing scattered histiocytes which, characteristically, give the otherwise dark sheets of cells a so-called starry-sky appearance.

A histologically similar tumour is rarely encountered in children in the West, but differs in that gut-associated lymphoid tissue is predominantly affected and it is rarely associated with the EBV genome or high EBV antibody titres. Lymphoma resembling Burkitt's lymphoma microscopically can also be a complication of immunosuppressive treatment and of AIDS and, in about 50% of the latter, is associated with EBV.

Hodgkin's disease

Hodgkin's disease frequently involves the cervical lymph nodes (where it may be mistaken for a submandibular salivary gland tumour) but only exceptionally rarely affects the mouth and is not clinically distinguishable from a non-Hodgkin's lymphoma.

Microscopically, Hodgkin's disease typically shows a mixed and pleomorphic picture of large, pale Hodgkin's cells as well as lymphocytes, eosinophils and fibroblasts. Moreover, the cellular picture varies widely, as indicated in the classification (Table 14.3). Hodgkin's cells are histiocyte-like and have large nucleoli or have paired (mirror-image) nuclei (Reed-Sternberg giant cells); diagnosis depends largely on recognizing these cells. However, these cells are frequently difficult to find and, as with non-Hodgkin's lymphoma, any superimposed inflammation adds to the difficulties.

Table 14.3 Rye classification of Hodgkin's lymphoma

- Nodular sclerosis
- Lymphocyte predominant
- Mixed cellularity
- Lymphocyte-depleted.

Hodgkin's disease may not readily be distinguished from non-Hodgkin's lymphomas by the microscopic features. However, it is important to make the distinction, as the chance of permanent cure of some types of Hodgkin's disease is now high as a result of irradiation of localized disease or combined chemotherapy. The overall 5-year survival rate may be 80%.

Causes and management of enlarged cervical lymph nodes

Dental and periodontal infections are by far the most common causes of cervical lymphadenopathy, but there is a great variety of possible causes including life-threatening diseases and, as mentioned earlier, enlargement of the cervical lymph nodes is a well-recognized early manifestation of lymphomas.

In most cases the cause of cervical lymphadenopathy is readily apparent. However, in the case of metastases without an obvious primary tumour it is essential to exclude the rare, occult and often minute, nasopharyngeal carcinoma. Second, in conditions where lymph nodes show proliferative activity it is essential to confirm or exclude a lymphoma and, if present, to start treatment as soon as possible. At the same time, it is also important to exclude non-malignant lymphoproliferative disorders to avoid serious overtreatment. Finally, increasing numbers of cases of lymphadenopathy due to HIV disease must be expected and in such patients lymph node biopsy should usually be avoided to lessen the risk of transmission of infection. Several of the diseases listed in Table 14.4 have been discussed earlier and will not be considered further here.

Table 14.4 Important causes of cervical lymphadenopathy

I. Infections
- 1. Bacterial
  - (a) Dental, tonsils, face or scalp
  - (b) Tuberculosis
  - (c) Syphilis
  - (d) Cat scratch disease
  - (e) Lyme disease
- 2. Viral
  - (a) Herpetic stomatitis
  - (b) Infectious mononucleosis
  - (c) HIV infection
- 3. Parasitic
  - Toxoplasmosis
- 4. Possibly infective
  - Mucocutaneous lymph node syndrome (Kawasaki's disease)

II. Neoplasms
- 1. Primary
  - (a) Hodgkin's disease
  - (b) Non-Hodgkin's lymphoma
  - (c) Leukaemia, especially lymphocytic
- 2. Secondary
  - (a) Carcinoma - oral, salivary gland or nasopharyngeal
  - (b) Malignant melanoma
  - (c) Ewing's sarcoma
  - (d) Other mesenchymal tumours

III. Miscellaneous
- (a) Sarcoidosis
- (b) Sinus histiocytosis
- (c) Angiofollicular hyperplasia
- (d) Drug reactions
- (e) Connective tissue diseases.

Indications for lymph node biopsy

These can be summarized as follows (Stansfeld and d'Arcdenne, 1992):

For diagnosis of persistent unexplained lymphadenopathy. Infective causes can usually be readily eliminated, but persistently enlarged cervical nodes are often a cause for anxiety. Hard or rubbery nodes in older persons are especially likely to be due to neoplasms. Soft, slightly enlarged nodes in children are frequently of no serious significance.

To make or help in the diagnosis of lymphadenopathy associated with systemic disease. Biopsy is only justified if all other investigations have failed. One purpose of lymph node biopsy in such cases is to exclude lymphoma; however, the microscopic findings may reveal an infection such as tuberculosis or a connective tissue diseases such as lupus erythematosus, of which cervical lymphadenopathy is very occasionally the presenting feature.

To confirm an already suspected diagnosis. Removal or aspiration cytology of enlarged cervical nodes is mandatory in any patient with a carcinoma, treated or untreated, even when it seems that there is some other cause such as dental infection.

Similarly, in a patient with a known immunologically-mediated disease such as Sjögren's syndrome, enlargement of cervical lymph nodes may be due to infection secondary to the dry mouth, but may be due to lymphoma - recognized hazard of this disease.

To assess the extent of sprad of malignant disease. Block dissection of clinically affected nodes is frequently an essential part of the surgical treatment of carcinoma of the mouth, but removal of lymph nodes can also be part of a staging procedure for lymphoma to determine the choice of treatment.

To monitor the progress of lymphomas. Since the aim of treatment is curative, particularly in the case of Hodgkin's disease, further lymph node examinations may be required if nodes remain enlarged or enlarge during an apparent remission.

In such cases, the node may show persistence of the original tumour, the development of a different tumour (possibly as a consequence of cytotoxic chemotherapy) or an opportunistic infection secondary to immunosuppression by the tumour, or its treatment, or both.

Surgical considerations

Removal of cervical lymph nodes is not to be undertaken lightly. Though accessible, they are in close proximity to vital structrures. Skill is also needed to remove enlarged and diseased nodes without traumatizing them. Pulling on a node, squeezing or crushing with forceps can damage or tear the capsule or damage the architecture. From the pathologist's viewpoint, cervical lymph nodes are a preferred group as they are least likely to show scarring or fatty involution.

Generally speaking, the choice of node to be removed for diagnostic purposes is the largest or, better, a group of enlarged nodes if several are involved. Removal of the most accessible node may be easier, but may necessitate another operation if it provides insufficient information.

Surgical management of an excised lymph node

In view of the number of investigations that may have to be applied to lymph nodes, particularly to confirm the diagnosis of lymphoma and to assign it to a precise category, it is important to excise lymph nodes with great care to avoid trauma and to treat the node in a systematic fashion, to enable the widest range of investigations to be carried out. Investigations should include:

- light microscopy
- touch (imprint) preparations and cytochemistry
- fresh frozen material for immunocytochemistry
- special fixation for other immunocytochemistry or electron microscopy and, sometimes,
- fresh material for culture.

Discussion with the pathologist is desirable to confirm which of these investigations are required in the light of the clinical picture and other findings.

Avoidance of physical trauma is essential, as lymphoma and lymphocytic leukaemia cells are fragile and when damaged can appear as mere basophilic smears (nuclear streaking). This is seen particularly in small biopsies of intra-oral lymphomas, but is less likely when nodes are excised intact; the problem then may be to ensure complete fixation throughout the specimen.

Pathologists frequently prefer to cut up fresh lymph nodes themselves, but if this is not feasible, a lymph node may be cut across its long axis to provide immediate access of fixative to the full cross-section for light microscopy. The main specimen for light microscopy can be fixed in buffered formalin unless the pathologist prefers a mercury-based or other fixative such as Methacarn.

Touch preparations. The unfixed fresh-cut surface of the node can be touched on to a glass microscope slide and allowed to settle under its own weight. Undue pressure should be avoided and the specimen must *not* be smeared. The touch preparation should immediately be fixed and stained with haematoxylin and eosin when rapid diagnosis is required. Other touch specimens can be used for special stains and for immunocytochemistry.

Straight frozen sections are generally considered undesirable because of changes during freezing, the risk of using up too much material or damaging the specimen in the operating theatre. At worst the diagnosis may remain in doubt and inadequate or unsatisfactory material may be left for light microscopy and other important investigations.

Immunocytochemistryu. A thin (1 mm if possible) section should be taken from the unfixed specimen and placed in Methacarn or other preferred fixative for immunocytochemistry, particularly if a lymphoma is suspected, and B or T lymphocyte phenotyping is required, although nowadays many markers will react with paraffin-embedded, formalin-fixed material.

Plastic-embedded specimens and electron microscopy. Part of a 1 mm cross-section of the fresh node should be fixed in glutaraldehyde for electron microscopy if required, or alternativwely 'semi-thin' (1 microm) sections can be cut for light microscopy and show good nuclear detail.

Part of a slice should be sent fresh for culture if a mycosis or bacterial infection is suspected.

Tuberculous cervical lymphadenopathy

Tuberculous infection of the cervical lymph nodes is a primary infection, and accounts for less than 10% of tuberculosis in Britain. *Mycobacterium tuberculosis* (human) accounts for over 90% of the isolates, and most of the patients are adults, mainly immigrants of Asian or Afro-Caribbean origin in this area. Non-tuberculous ('atypical') mycobacteria, particularly *M. avium intracellulare* or *scrofulaceum* are not the major cause of cervical mycobacterial lymphadenitis in immunocompetent children. As discussed earlier (Chapter 2), the incidence of mycobacterial infections is growing and multiply resistant strains are emerging.

The site of entry of the infection is probably the tonsil in most cases, but entry through the oral mucosa with formation of a minute painless ulcer has been described in children.

Clinically, tuberculous involvement of cervical lymph nodes gives rise to firm swelling, usually of a group of nodes which typically become matted. Later an abscess or sinus may form, or there may be progressive fibrosis and eventual calcification. The clinical picture is therefore variable, and the diagnosis is usually only made after excision of a node. If a tuberculous ('cold') abscess and sinus form, excision should be carried out and incision is contraindicated.

Diagnosis depends on finding granulomas in which mycobacteria should be demonstrable by Ziehl-Nielsen staining or by immunofluorescence using auramine-rhodamine. However, infection by non-tuberculous mycobacteria even in immunocompetent children is likely to give rise to poorly defined or irregular granulomas without palisading, or ill-defined aggregates of epithelioid histiocytes. Caseation may not be seen, but there may be areas of necrosis with numerous neutrophils, Ziehl-Nielsen staining is also negative, as described by Pinder and Colville (1992). Culture of the mycobacteria is required, but the tuberculin skin test should be positive unless the patient is severely immunodeficient.

In addition to any surgery, a course of isoniazid should be given.

Syphilis

The cervical lymph nodes are enlarged, soft and rubbery when the primary chancre is in the mouth or on the lip. They are also involved in the widespread lymphadenopathy characteristic of the secondary stage.

Diagnosis is by finding *Treponema pallidum* in a direct smear from the oral lesion in the primary stage, and thereafter by the serological findings, as discussed earlier (Chapter 8). Lymph node biopsy is not indicated.

Only a few hundred cases of syphilis are detected annually in England, but even when it was more frequent oral lesions were rarely seen and some perhaps go unrecognized.

Cat scratch disease

This infection is very common in the USA and, though rare in Britain, is increasingly frequently found. The history is usually but not invariably of a scratch by a cat, followed by the appearance of a papule which may suppurate, at the site of inoculation. There is mild fever, malaise and regional lymphadenitis, which develops - weeks after exposure. The lymph nodes soften and typically suppurate. Conjunctivitis may be associated: encephalitis is a rare complication.

Microscopically, there is destruction of the architecture of the lymph nodes, necrosis and lymphocytic infiltration with formation of histiocytic granulomas and central suppuration.

These appearances can readily be mistaken for one of the deep mycoses. However, it may be possible to demonstrate the causative organism, *Afipia felis* (a small Gram-negative bacillus) by use of a silver (Warthin-Starry) stain at the site of inoculation or in the lymph nodes. Even if this fails, the clinical picture is characteristic and the diagnosis can be confirmed by a skin (Rose-Hanger) test using a sterilized extract of cat scratch disease pus.

The disease is typically mild and self-limiting but may lead to suppuration and sinus formation. The response to antibacterials is variable and difficult to evaluate in view of spontaneous resolution in many cases. However, Collipp (1992) has reported that treatment with sulphamethoxazole led to prompt healing without suppuration in 71 children, whereas 30 patients given other antimicrobials had more prolonged disease and, in 7 of them, suppuration that required drainage.

Lyme disease

Lyme disease is caused by a spirochaete, *Borrelia burgdorferi,* which is transmitted by insects, particularly by deer ticks. The disease is worldwide.

Clinically, the chief manifestations are a rash, enlarged regional lymph nodes, fever and often other systemic symptoms. The rash (erythema chronicum migrans) is characteristic and spreads outwards from the site of the insect bite. The main chronic effect is arthritis, particularly of the knees. The onset may be within weeks ormore than a year after acquisition of the infection. Involvement of the temporomandibular joint is rare.

Neurological complications develop in about 15% of patients. They are typically heralded by neck pain and stiffness, and include facial palsy or other cranial nerve lesions.

Diagnosis is by the clinical picture and confirmed serologically or sometimes by demonstration of the spirochaete by means of silver stains in a skin biopsy.

The spirochaete is sensitive to penicillin or tetracycline which should be given as early as possible. However, joint pain may recur or destructive arthritis may develop later.

Infectious mononucleosis

Infection by the Epstein-Barr virus causes a self-limiting lymphoproliferative disorder characterized by polyclonal activation of B lymphocytes. In children, especially, there is generalized lymphadenopathy, typically with conspicuous enlargement of the cervical nodes, sore throat and fever. In adolescents, lymphadenopathy may be less conspicuous and there is a vague illness with fever. In the anginose form of the disease, there is a sore throat, palatal petechiae, tonsillar exudate and pharyngeal oedema which may be severe. The clinical features are distinctive in most cases, but rarely there is more persistent lymphadenopathy which may mimic a lymphoma. Confusion may be compounded if a lymph node is taken for biopsy, as the appearances can also be mistaken for those of a lymphoma.

Syndromes clinically similar to infectious mononucleosis canalso result from toxoplasmal, cytomegalovirus or HIV infection.

Microscopically, the lymph node architecture is severely distorted or even destroyed and replaced by gross follicular hyperplasia with irregular germinal centres containing transforming lymphocytes which may show mitoses. Many histiocytes and large immunoblastic cells, which may resemble Reed-Sternberg cells, are associated. Lymphocytes may infiltrate the pericapsular tissues.

The diagnosis can be made on the microscopy of this lymphoma-like picture by a specialist, but is more likely to be made by a peripheral blood picture showing the atypical (monocyte-like) lymphocytes, a heterophil antibody (Paul-Bunnell) test and, if necessary, demonstration of a raised titre of EBV antibodies.

Patients are prone to characteristic macular rashes on the trunk when given ampicillin or amoxycillin, but are not necessarily allergic to penicillin.

Acquired immune deficiency syndrome

Lymphadenopathy is one of the most frequent manifestations of HIV infection, as discussed later in this chapter. Soon after infection there may be a transient glandular fever-like illness or later there may be generalized and persistent lymphadenopathy. Current estimates suggest thatover 50% of patients with lymphadenopathy as the sole manifestation of HIV infection will develop full-blown AIDS within less than 4 years.

Lymph node biopsy is not recommended for diagnosis. The microscopic appearances are described later, as are clinical features which may suggest the diagnosis.

Toxoplasmosis

Toxoplasma gondii is a common intestinal parasite of many domestic animals, particularly cats. It is a low-grade pathogen but can affect previously healthy persons, particularly young women. Infection can be acquired by ingestion of oocytes and four main types of disease can result:

1. Acute toxoplasmosis in normal children or adults can cause a disease very similar to infectious mononucleosis, with cervical lymphadenopathy as the most common feature. Parotid swelling has also been described. Atypical lymphocytes are present in the blood, but there is no heterophil antibody production. Usually the infection is self-limiting.

2. In immunodeficient patients, such as those with AIDS, toxoplasmosis causes disseminated disease and, particularly, encephalitis.

3. In pregnant women, toxoplasmosis is an important cause of fetal abnormalities.

4. Toxoplasmal chorioretinitis with impairment or loss of sight is usually a result of congenital infection, but can also occasionally result from severe infections in previously healthy adults.

The microscopic appearances are not in themselves diagnostic. However, follicular hyperplasia, sinus histiocytosis and scattered foci (rather than granulomas) of pale histiocytes standing out conspicuously against a dense background of lymphocytes is strongly suggestive. Merozoites are rarely seen.

The diagnosis is confirmed serologically by a high or rising titre of antibodies or by several other immunological methods.

Treatment

This is required only for severe infections and is with pyrimethamine and a sulphonamide.

Mucocutaneous lymph node syndrome (Kawasaki's disease)

Kawasaki's disease is endemic in Japan and there have been outbreaks in Hawaii and the USA. in Britain, it causes approximately 100 deaths per annum.

The distribution of cases suggests that the disease may be an infection, but no agent has been identified with certainty.

Children aged under 5 years are mostly affected. Typical features are a generalized, often morbilliform rash and erythematous stomatitis. Swelling and cracking of the lips and pharyngitis quickly follow and the palms and soles become red, swollen and indurated. A unilateral mass of cervical lymph nodes is characteristic, abdominal symptoms are common and change of mood ('extreme misery') is typical. Approximately 20% of patients develop heart disease. The overall mortality is 1-3% as a result of heart failure secondary to coronary artery disease or dysrhythmias secondary to myocardial ischaemia.

The diagnosis may sometimes be made early by lymph node biopsy showing microscopic vasculitis, associated with fibrinous thrombi in small vessels and patchy necrosis. Arteritis resembling polyarteritis nodosa has its main effect on the coronary arteries. However, the diagnosis is more likely to made from the clinical and, particularly, the electrocardiographic findings.

There is no specific treatment, but aspirin, despite the possible risk of Reye's syndrome, should be given to reduce vascular damage and thrombotic phenomena. Intravenous gamma globulin has also been advocated.

Sinus histiocytosis

Sinus histiocytosis is typically seen in nodes draining carcnomas, but is a rare cause of cervical lymphadenopathy. It is characterized by prominent distended lymphoid sinusoids. The sinuses are filled with histiocytes and the endothelial cells are often grossly hypertrophied. The condition is benign.

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)

This disease is also rare, but particularly affects Blacks. As the name implies, lymphadenopathy can be gross. Salivary glands and other sites are occasionally involved. Fever and neutrophil leucocytosis may be associated, but most cases resolve spontaneously.

Microscopically, the lymph node sinuses are filled with very large histiocytes, some of which have engulfed lymphocytes, and there is a reactive plasmacytosis.

Giant (angiofollicular) lymph node hyperplasia (Castleman's disease)

This rare condition usually affects the thorax, but can occasionally cause a cervical mass resembling a lymphoma. Its cause is unknown, but it can be a complication of HIV infection.

Microscopically, the salient features are gross hyperplasia of lymphoid follicles, with the lymphocytes forming tight concentric layers round blood vessels with swollen endothelial cells which frequently proliferate. The interfollicular tissue is highly vascular. Several variants of this picture have been described and in the rare plasma cell type there may be monoclonal immunoglobulin production and other abnormalities.

Though the condition is benign, the mass may be so large that resection may be justified. This not merely confirms the diagnosis, but is usually curative. Otherwise a short course of high-dosage corticosteroids or a single other immunosuppressive drug is effective, but combination cytotoxic chemotherapy should be avoided and the condition is not radiosensitive.

Lymphomatous change is a rare but recognized complication and malignant blood vessel tumours are another. In AIDS, giant lymph node hyperplasia may be associated with Kaposi's sarcoma.

Angiolymphoid hyperplasia with eosinophils (epithelioid haemangioma, Kimura's disease and related diseases)

Kimura's disease is rare in the West but common in China, Japan and Singapore. It is characterized by mucosal or cutaneous nodules which can be mistaken clinically for lymph nodes. However, these nodules, when in the mouth, are more likely to resemble pyogenic

granulomas. Involvement of the parotid and submandibular glands and of the cervical lymph nodes has been described in Oriental patients.

Microscopically, there is proliferation of lymphoid tissue and blood vessels leading to formation of thick-walled capillaries. Eosinophils are conspicuous in the stroma and may form dense foci with central necrosis. In addition to peripheral blood eosinophilia, serum IgE levels are frequently raised.

Excision is curative but may have to be repeated.

In the West, lesions with a somewhat similar histological picture may be seen, but peripheral eosinophilia is absent. Lymphoid hyperplasia is less prominent, but vascular proliferation may be conspicuous. These lesions should usually be categorized as epithelioid haemangiomas.

Phenytoin and other drug-associated lymphadenopathies

Of the many possible side effects of pheytoin, lymphadenopathy may rarely develop within a few weeks or months, but more frequently after long-term treatment. Lymphadenopathy caused by phenytoin (unlike that caused by many otbher drugs) is not generally associated with serum sickness-like symptoms of fever, rashes and joint pains. The importance of phenytoin-associated lymphadenopathy is that the microscopic changes can mimic a lymphoma.

Cervical lymph nodes are frequently first affected, but lymphadenopathy usually becomes widespread. The microscopic appearances are varied, but the nodal architecture can be completely obliterated by a pleomorphic picture with proliferation of large immunoblast-like cells which may be binucleate or multinucleate, and appearances which can closely mimic Hodgkin's disease. There also appears to be a slight risk of lymphoma if the condition is allowed to progress.

The diagnosis is likely to be made from the history of treatment with phenytoin, or suggested from the finding of associated gingival hyperplasia. If the latter is absent and the patient fails to disclose the necessary information about drug treatment so that lymph node biopsy is carried out, an expert opinion is needed to distinguish these changes from lymphoma.

Substitution of phenytoin with another anticonvulsant such as carbamazepine should allow the lymphadenopathy to subside and confirm the diagnosis.

Other drugs which can cause lymphadenopathy include penicillin (rarely), phenylbutazone (virtually obsolete) and some other non-steroidal anti-inflammatory drugs, and some antimalarials. As mentioned earlier, lymphadenopathy with these drugs is frequently associated with serum sickness-like features.

Immunodeficiency diseases

In immune deficiency states the activity of one or more components of the immune system is defective. The main consequence is that, in the more severe types, the ability to combat infections is so impaired that they are the chief cause of death. This is shown strikingly in the acquired immune deficiency syndrome (AIDS), which is both transmissible and exceptionally severe.

Table 14.5 Important causes of immunodeficiency

Primary (Genetic)

T or B lymphocyte defects (Swiss-type agammaglobulinaemia, Di George's syndrome, etc).
IgA deficiency.
Complement component deficiencies.

Secondary (Acquired)

Infections - HIV, other severe viral or bacterial infections, malaria, etc.
Drug induced - immunosuppressive and anticancer treatment.
Malnutrition (worldwide a major cause of immunodeficiency).
Cancer (particularly of lymphoreticular cells).
Diabetes mellitus.

Immune deficiencies can be primary or acquired (Table 14.5) and can affect B or T lymphocytes, or both. However, the role of T lymphocytes in regulating B lymphocyte activity often means that a T cell defect affects antibody production. Alternatively, there can be failures of production of individual antibodies such as IgA or of complement components.

Clinically, any patient who develops recurrent infections, particularly if the infections respond poorly to treatment or are caused by otherwise harmless microbes (opportunistic infections), must be suspected of being immunodeficient.

The severe primary immunodeficiencies are rare and, unless a marrow transplant can be given, are usually fatal in childhood. The main causes of *severe* immunodeficiency in the developed world are HIV infection and immunosuppressive treatment for organ transplantation or other purposes. Many cancer patients are also severely immunodeficient as a result both of the neoplasm and of the cytotoxic drugs used for its treatment.

Oral manifestations of immunodeficiencies

The main effect, as mentioned earlier, is the abnormal susceptibility to infections, particularly candidosis or viral infections such as herpes. Similar but generally less severe infectious complications to those seen in AIDS are to be expected and are usually the chief cause of death. Deficiency of complement components, particularly C3, also increases susceptibility to infection but is rare.

Acquired immune deficiency syndrome (AIDS)

The acquired immune deficiency syndrome is epidemic in parts of the USA and Africa. It is worldwide in distribution and several millions have been infected. It is almost useless to quote statistics because of the rate at which the disease is spreading. However, by 1992, more than 7000 cases and over 4000 deaths from this cause had been reported in Britain, despite the fact that the infection rate is the lowest in Europe. In the USA, cases of AIDS exceeded 100000 during 1989, but this figure had doubled by 1992. In addition, many times these numbers of personjs in all parts of the world have acquired the infection and may be able to transmit it, but have not yet had any clinical effects.

AIDS is transmissible to health care personnel, particularly surgeons, dental surgeons and nurses, via needles or other sharp instruments. However, the risk of acquiring the infection by this means is considerably smaller than that of hepatitis B.

Aetiology

AIDS is caused by a retrovirus, the human immunodeficiency virus (HIV), mainly HIV 1. HIV 2 is as yet only widely prevalent in West Africa. AIDS in the absence of HIV infection is currently a source of controversy.

The chief mode of transmission is by male homosexual activity which accounts for over 70% of cases in Britain. Heterosexual transmission is far less common in the Western world than in Africa. Once infected, pregnant women can transmit the infection to the fetus. Transmission by blood or blood products has caused intravenous drug abusers to be at risk. Many haemophiliacs have acquired the disease from infected blood products but heat treatment of clotting factor concentrates should have eliminated this risk.

The incubation period of AIDS is highly variable and may be related to the infecting dose of virus. In the case of male homosexuals, the incubation period is on average approximately 5 years, but study of sera stored before the disease was recognized shows that it can be as long as 14 years. Testing of apparently healthy infected persons also shows deterioration of immune function long before the disease becomes clinically apparent and it is still not clear whether all those who develop prodromal signs, such as generalized lymphadenopathy, will develop the full, lethal syndrome.

Immunology

The human immunodeficiency virus directly infects lymphocytes and other cells which carry the CD4 marker. In particular, the virus depresses the number of T helper (CD4) cells and reverses the ratio of helper to suppressor lymphocytes. Macrophages and monocytes can engulf the virus and some monocytes also express the CD4 receptor to which the virus binds. These cells probably have a major role in the propagation and pathogenesis of the infection.

Antibody is produced in response to the virus but is not protective and there is no evidence as yet that the virus is ever eliminated from the body. Antibodies to HIV indicate only that infection has been acquired and all seropositive persons must be assumed to be capable of transmitting the virus. Though the detection of these antibodies is often misnamed,

by the press, 'the AIDS test', it is of little value in predicting the development of full-blown disease. The immune responses and serological consequences of HIV are not as yet clear, but it has become apparent that, rarely, antibodies to HIV may not appear for periods of up to 3 years after infection. In others, antibodies may disappear from the blood late in the disease. Antibody detection is not therefore 100% reliable, but has been a useful means of detecting the majority of HIV-infected persons, particularly among blood donors.

Detection viral antigens, such as p24, in the blood provide a more direct and reliable indicator of infection. Moreover, minute amounts of the virus in the form of provirus DNA in lymphocytes can be detected by using the polymerase chain reaction. The presence or absence of viral antigens can, therefore, be correlated with the serological findings and can, for example, be used when the history and clinical features are at variance with the serological findings.

The main effect of depletion of T helper cells is deepening depression of cell-mediated immunity. This can be demonstrated by such means as declining responses of lymphocytes to antigens *in vitro,* and impaired or absent delayed hypersensitivity responses, long before any clinical signs of the disease appear. Apparently paradoxically, there is also polyclonal B lymphocyte activation resulting in hypergammaglobulinaemia and autoantibody production. The main effect of the immunodeficiency and chief cause of death is infection by a wide variety of microbes, particularly opportunistics.

In addition to its effects on the immune system, the human immunodeficiency virus also attacks the central nervous system, cells of which carry receptors for the virus.

Clinical aspects

The possible courses of events after infection by HIV are shown in Figure 14.20 but, as mentioned earlier, it is still uncertain whether any symptomless carriers of the virus will ultimately remain healthy.

As can be seen from Figure 14.20, the earliest clinical manifestation of infection can be a transient illness resembling glandular fever, associated with antibody production. Thereafter, in progressive cases, markers of declining cell-mediated immunity eventually become detectable and later various clinical syndromes, previously termed AIDS-related complex (ARC), may develop. The classification of HIV infection by stages has been developed by the Center for Disease Control (CDC) but a new, combined WHO/CDC clinical classification has been proposed to include specific diseases and immunological findings. Generalized lymphadenopathy syndrome (GLS), in which there is widespread persistent enlargement of lymph nodes, is a typical early sign of developing disease. However, the course of AIDS is highly variable and none of the prodromal symptoms appears to be obligatory. The first clinical sign may therefore be *Pneumocystis carinii* pneumonia or Kaposi's sarcoma.

The full syndrome of AIDS is characterized by multiple infections by bacteria, fungi, parasites and viruses (Table 14.6). Many of these infections, such as *P. carinii* pneumonia, are opportunistic and virtually unknown in normal persons.

Though infections are the main cause of death, there is also a greatly increased incidence of tumours, particularly Kaposi's sarcoma and lymphomas which frequently affect the oral or perioral tissues. In normal persons these tumours are not merely uncommmon or rare but are particularly rare in the oral tissues.

Table 14.6 Important opportunistic infections in AIDS

Viral
Herpes simplex
Varicella zoster
Cytomegalovirus
JC virus

Bacterial
Campylobacter spp
Legionellosis
Pseudomonas aeruginosa
Staphylococcus aureus
Streptococcus pneumoniae
Haemophilus influenzae
Mycobacterium tuberculosis
M. avium-intracellulare
Other non-tuberculous mycobacterioses
Shigellosis

Mycoses
Aspergillosis
Candidosis
Coccidioidomycosis
Cryptococcosis
Histoplasmosis
Mucormycosis

Parasitic and other
Cryptosporidiosis
Giardiasis
Isosporosis
Microsporidiosis
Pneumocystic carinii.

The second major manifestation of AIDS is, in addition to opportunistic infections or tumours involving the central nervous system, neuropsychiatric disease which can range from psychiatric disturbance resembling depression, to dementia and death. These neurological disorders may be associated with, but can develop in the absence of, immunodeficiency.

A third but lesser manifestation of AIDS in some patients is autoimmune disease, particularly thrombocytopenic purpura or, less frequently, a disease resembling lupus erythematosus.

Once AIDS has developed, the outcome is invariably fatal usually within 2-3 years, though the course of the disease may be modified to some degree by drugs such as zidovudine and vigorous treatment of the infections.

The terminal stages of AIDS can be horrifying. A young patient may be emaciated with persistent diarrhoea, suffering a multiplicity of infections, covered with skin lesions, breathless from *P. carinii* pneumonia, frequently with a malignant tumour, and sometimes also blind and demented.

Table 14.7 Oral disease in HIV infection

Infections
Fungal
- Thrush and other forms of candidosis
- Mucosal lesions of deep mycoses (cryptococcosis, histoplasmosis, etc)

Viral
- Herpes simplex
- Herpes zoster or varicella
- Oral hairy leucoplakia (EBV-associated)

Bacterial
- *Mycobacterium tuberculosis* and non-tuberculous ('atypical') mycobacterioses
- *Klebsiella pneumoniae*
- *Escherichia coli*
- *E. cloacae*

Tumours
Lymphomas
Kaposi's sarcoma

Salivary glands
Swelling (cystic, proliferative or neoplastic)
Xerostomia

Neurological
Facial palsy
Trigeminal neuropathy

Others
Purpura
Pigmentation
Major aphthae
Necrotizing gingivitis
Accelerated periodontitis
Delayed wound healing.

Orofacial manifestations of AIDS

More than 75% of patients with AIDS have orofacial manifestations, and thrush is a common early sign of the immunodeficiency. Orofacial manifestations of AIDS are listed in Table 14.7 and discussed in more detail below.

Prediction of progression of AIDS

The current estimate is that at least 60% of HIV seropositive individuals will develop the disease, but increasing evidence of silent infections with greatly delayed antibody production and retrospective studies of 'pre-AIDS' stored sera may cause such estimates to appear modest.

Haematological markers, indicative of progression to AIDS, include the presence of viral antigens in the serum, high beta 2 microglobulin levels and failure of or greatly depressed antigen-induced interferon gamma production. Fewer than 0.2×10^9 CD4 (T helper) lymphocytes per litre or a total lymphocyte count of less than 1×10^9 per litre represent advanced disease.

Clinical indicators of a poor prognosis are oral thrush or herpes zoster or other persistent or recurrent infections, hairy leukoplakia, unexplained constitutional symptoms, cutaneous anergy and lymphadenopathy. Between approximately 20% and 70% of such patients can be expected to develop full-blown disease within a period of less than 5 years.

The possibility of trasmission of HIV infection during oral surgery is a source of anxiety. Oral infections and other features of AIDS or its prodromes may enable patients to be recognized. A young adult male who develops thrush for no apparent reason is likely to have AIDS, but if he has oral Kaposi's sarcoma it is virtually pathognomonic. However, there are many more patients who are infective but without overt signs to suggest the possibility. At the time of writing there may be 20.000 or more antibody-positive, potentially infective persons in Britain and the number rises each month.

All patients must now, therefore, be regarded as potentially infective and treated with full aseptic precautions as for hepatitis B. The only small crumbs of comfort are that HIV is considerably less easily transmitted than hepatitis B.

Most health care workers who have developed AIDS have not acquired it as a result of their occupation. However, a few nurses have become infected as a result of needle-stick injuries and accidentally injecting themselves with a significant amount of infected blood. By contrast, many other needle-stick injuries have apparently failed to transmit the infection.

As to the risk to dental and general surgeons, at least two of the latter in the Western world are known to have died from the disease, acquired at operation. By contrast, only one dental surgeon is known to have acquired the disease as a consequence of his occupation. He was working in New York (by far the highest incidence area in the Western world), did not practise a high standard of infection control and had had many needle-stick injuries. No other dental surgeons, even in high incidence areas, are known to have acquired the disease occupationally.

Nevertheless, as mentioned earlier, all patients must be regarded and treated as potentially infective. Though the risk of acquiring AIDS during dental treatment may be very small, the consequences of doing so are so appalling as to be avoided by all means possible. Currently, the chance of acquisition of hepatitis B is considerably greater, because of its greater prevalence and ease of transmission, but is avoidable by immunization.

Oral lesions in AIDS

In a review of 2235 HIV-positive homosexual or bisexual men in San Francisco, Feigal et al (1991) found that the most frequent oral lesions were hairy leucoplakia (18.7%), thrush (6.6%) or erythematous candidosis (2.1%), Kaposi's sarcoma (1.6%) and oral ulcers (2%). However, the frequency of such lesions varies in other groups. Kaposi's sarcoma, for example, is particularly common in homosexual men.

Candidosis. Oral thrush may be seen in over 70% of patients at some stage. It is indicative of declining immunity, and other infections may be associated or are likely to follow. Thrush may be concurrent with oral herpes to produce a confusing clinical picture.

In approximately 50% of patients with HIV-associated thrush, AIDS is likely to develop within 5 years.

Most of the other types of candidosis, such as angular stomatitis, generalized mucosal erythema or hyperplastic candidosis, have also been reported in AIDS patients.

Viral infections. Herpetic stomatitis is less common than might be expected. Severe orofacial zoster may be indicative of a poor prognosis.

Cytomegalovirus can be found in some oral ulcers and the possible role of the Epstein-Barr virus in hairy leucoplakia is discussed below.

Papillomaviruses have been isolated from proliferative lesions, such as verruca vulgaris, condyloma acuminatum and focal epithelial hyperplasia in patients with AIDS.

Bacterial infections. A variety of infections by bacteria which rarely affect the oral tissues, such as *Klebsiella pneumoniae, Enterobacter cloacae* and *Escherichia coli,* have been reported.

In the later stages there may be oral lesions secondary to systemic infections, particularly mycobacterial ulcers.

Deep mycoses. Histoplasmosis or cryptococcosis can give rise to proliferative or ulcerative lesions. Histoplasmosis can also destroy the adrenal glands and occasionally cause Addison's disease with oral hyperpigmentation.

Hairy leucoplakia. This lesion, characteristic of HIV infection, is so called because hair-like filaments of keratin may extend from the surface, but more commonly the whitish surface has a vertically corrugated surface. The plaque is soft, usually painless and is most

frequently seen along the lateral borders of the tongue. It has been discussed more fully in Chapter 9.

The chief importance of hairy leucoplakia is as an index of prognosis. Over 80% of patients with this lesion are likely to develop full-blown AIDS within 3 years. However, hairy leucoplakia can also rarely be seen in immunodeficient patients such as those receiving renal transplants and does not appear to be unique to HIV infection.

Surgical excision of hairy leucoplakia is not indicated.

Tumours. Nearly 50% of patients with AIDS have a malignant tumour at the time of presentation. By far the most frequent are Kaposi's sarcoma and non-Hodgkin lymphomas. Unlike non-AIDS patients these tumours are particularly frequent in the head and neck region.

The aetiology of AIDS-associated tumours is unknown, though it is suspected that they may be viral and secondary to the immunodeficiency.

Kaposi's sarcoma. This tumour is particularly common in male homosexuals with AIDS, but uncommon in intravenous drug abusers and rare in haemophiliacs who have acquired the infection from contaminated blood products.

Clinically, a common oral site is the hard palate where the tumour forms a purple area or, later, a nodule which bleeds readily. Kaposi's sarcoma in the mouth, particularly in a young male who is not receiving immunosuppressive treatment, is virtually pathognomonic of AIDS. Kaposi's sarcoma has been discussed more fully in Chapter 13.

Non-Hodgkin lymphomas. AIDS-related lymphomas can develop in intra-oral sites, in salivary glands or in cervical lymph nodes. Typical sites within the mouth are the palate or alveolar ridge, where the tumours form soft painless swellings which do not ulcerate unless traumatized.

Microscopically, these tumours frequently resemble Burkitt's lymphoma and are of intermediate or, more frequently, high-grade malignancy as discussed earlier.

Lymphadenopathy

Enlargement of lymph nodes is particularly characteristic of AIDS and its prodromes, especially the early glandular fever-like syndrome and the later generalized lymphadenopathy syndrome (GLS). Cervical lymphadenopathy is probably the most common head and neck manifestation of HIV infection.

Microscopically, typical findings are smaller numbers of T-helper cells in the paracortical region associated with greater numbers of T-suppressor cells there and in the follicles. Follicles may initially be hyperplastic but later undergo involution. The lymph nodes become virtually or entirely functionless.

Enlargement of the cervical lymph nodes may also be due to lymphomas.

Autoimmune disease

The most common autoimmune phenomenon in AIDS is thrombocytopenic purpura. This can give rise to purple patches in the mouth and may be mistaken for Kaposi's sarcoma. As with other types of purpura, prolonged bleeding may follow surgery.

Other autoimmune diseases reported in AIDS are lupus erythematosus, but salivary gland disease resembling Sjögren's syndrome does not seem to have a similar basis.

Gingivitis and periodontitis

HIV-related periodontal disease includes necrotizing gingivitis and accelerated periodontitis.

Salivary gland disease

The main effects, which are described in more detail in Chapter 11, include:

- parotitis, possibly due to Epstein-Barr virus or cytomegalovirus, appears to affect children with AIDS particularly

- a Sjögren-like syndrome with xerostomia in adults, though autoantibodies characteristic of this disease are lacking

- parotid swellings due to benign lymphoepithelial lesion, which are frequently cystic, bilateral and identifiable by CT scanning.

Parotid swelling due to Kaposi's sarcoma has also been reported but it is rare in the salivary glands.

Recognition of parotid cysts or microscopic diagnosis of Sjögren-like changes, particularly in a young adult male, are important indicators of HIV infection of which the surgeon should be aware when dealing with a tumour-like lesion of salivary glands.

Neurological complications

Orofacial effects include facial palsy and trigeminal neuropathy.

Miscellaneous oral lesions

- Mucosal ulcers - these include major aphthae and can be a troublesome feature which can interfere with eating and accelerate deterioration of health.

- Necrotizing oral ulceration of an ill-defined nature has also been reported and aphthae-like lesions are common oral signs of HIV infection.

- Oral hyperpigmentation - in a few cases, pigmentation may be secondary to Addison's disease due to fungal destruction of the adrenals; alternatively, it appears to be a complication of treatment with zidovudine or to be due to an unknown mechanism.

No doubt, with the passage of time, yet other orofacial manifestations of AIDS will be reported. AIDS-related arthritis, for example, was only firmly identified approximately 7 years after the disease was first characterized.

Surgical considerations in AIDS and its prodromes

With the growing prevalence of HIV infection and the severity of its consequences, it is overwhelmingly important to the oral surgeon to recognize the oral and perioral manifestations. Though surgical intervention is rarely indicated for AIDS-related lesions, oral surgery may be necessary for treatment of concomitant disease. Prevention of cross-infection, as discussed earlier, and awareness of the patient's low resistance to secondary infection are then major considerations. However, it does not appear that patients with HIV infection are particularly prone to infective complications from dental procedures such as extractions. Occasionally, biopsy of a lesion, particularly if it proves to be a Kaposi's sarcoma, may suggest hitherto unsuspected HIV infection.

Primary IgA deficiency

IgA deficiency is common in that it affects approximately 1 in 700 of the population. The chief effects are:

- recurrent respiratory infections (especially if IgG_2 is also lacking)

- atopic disease (frequently)

- connective tissue disease (uncommonly).

Despite the fact that IgA is the only antibody secreted in the saliva in significant amounts, IgA deficiency may not be associated with any increase in frequency of oral infections. This may in part be due to secretion of other immunoglobulins in the saliva when IgA is absent. However, Porter and Scully (1993) have reported that in 39 of these children aphthae-like ulcers were present in 61%, thrush in 25%, recurrent herpes labialis in 25%, and only 9% had no orofacial lesions.

Hereditary angio-oedema

Hereditary angio-oedema causes localized areas of oedema resembling allergic angio-oedema, but results from a genetically determined deficiency of C1 esterase inhibitor. Deficiency of this enzyme results in prolonged complement activation and release of kinin-like substances, typically in response to minor trauma including oral surgery. Oedema typically affects the oral and perioral regions, where it can endanger the airway.

Significant clinical manifestations frequently do not appear until later childhood or adolescence and the abdomen or extremities are other sites which may be affected. Abdominal

pain, nausea or a rash may herald an attack. In the absence of treatment, the mortality may be as high as 30%.

The most effective treatment is with the androgenic steroids, such as stanozolol, which should be given daily, usually 2.5-10 mg for an adult.

Allergic angio-oedema

Allergic angio-oedema is typically an IgE-mediated reaction and can be precipitated by drugs such as penicillin or antisera. Acute oedematous swelling frequently affects the face and neck region and can endanger the airway. Such reactions should be managed as for anaphylactic emergencies with adrenaline plus intravenous antihistamines or corticosteroids. Mild cases may respond to oral antihistamines.

Granulomatous diseases

The term granuloma is traditionally used *clinically* for lesions characterized by proliferation of granulation tissue as in apical granulomas or, in a more specialized sense, for 'midline granulomas', as described below. *Histologically,* the term granuloma refers only to conditions where there is formation of tuberculosis-like follicles microscopically. These consist of rounded collections of large, pale histiocytes ('epithelioid cells'), sometimes surrounded by lymphocytes and often containing giant cells. The causes of this type of reaction are heterogeneous: it is usually a manifestation of cell-mediated immunity, but the immunological abnormalities associated with these diseases are very varied. The more important examples are shown in Table 14.8. Many of them can affect the cervical lymph nodes (as described above) or the mouth.

Table 14.8 Important examples of granulomatous diseases

Infections
Tuberculosis and non-tuberculous mycobacterioses
Leprosy
Syphilis
Deep mycoses, particularly histoplasmosis, cryptococcosis, blastomycosis and coccidioidomycosis
Cat scratch disease
Toxoplasmosis

Reactive
Foreign body reactions
Secondary to carcinoma or radiotherapy

Unknown causes
Wegener's granulomatosis
Sarcoidosis
Crohn's disease
Orofacial granulomatosis.

Midline granuloma syndrome
(lethal midline granuloma, midfacial destructive disease, etc)

Midline granulomas are granulomas mainly in the sense of the clinical appearance of granulomatous destruction of tissues, particularly of the nasal cavity, but sometimes extending into the mouth. Proliferation, ulceration and crusting of the nasal or paranasal tissues typically leads to destruction (occasionally gross) of the midfacial tissues. Later, other organs are involved and the outcome is typically fatal. One cause of this previously mysterious syndrome has now been identified as being a lymphoma, but since it is not clinically distinguishable from Wegener's granulomatosis it is also discussed here.

Specific infections such as tuberculosis, leprosy or the deep mycoses may rarely produce a somewhat similar clinical picture but only the idiopathic types are discussed here. These comprise two main diseases, namely:

- Wegener's granulomatosis - a form of necrotizing vasculitis

- peripheral T cell lymphomas.

Wegener's granulomatosis

Wegener's granulomatosis, in its fully developed form, typically comprises the triad of granulomatous inflammation of the nasal region and pulmonary and lung involvement.

Wegener's granulomatosis is frequently (but unjustifiably) classified with the connective tissue diseases, but there are no immunological abnormalities linking it with those diseases. Neutrophil anticytoplasmic antibodies have been detected in Wegener's granulomatosis, but are not specific to it.

Clinically, men seem to be more frequently affected and the peak age incidence is between 40 and 55 years.

Early features of Wegener's granulomatosis typically consist of granulomatous inflammation and variable degrees of destruction of the nasal cavity. Later, destruction of the nasal septum can lead to a saddle-nose deformity. Wegener's granulomatosis can also give rise to oral ulcers or to a dinstictive type of oral lesion, namely a proliferative gingivitis with a granular surface and deep red in colour. It has been described as 'strawberry gums' and can involve a few or many teeth. It can form the earliest clinical manifestation of the disease and, after confirmation by biopsy, can allow treatment to be started at an early stage. Approximately 10% of patients with Wegener's granulomatosis have oral lesions.

Microscopically, there is widespread inflammation with a mixed cellular picture and, frequently, numerous eosinophils. However, an essential feature is a necrotizing vasculitis of small arteries, associated with giant cells. The giant cells are not necessarily directly involved in the vasculitis and may as frequently be found in the adjacent tissues. They are typically compact with four or five nuclei and an irregular outline, but may resemble Langhans giant cells. Granulomas, though characteristic of this disease, are inconspicous, usually difficult to find and rarely seen in oral biopsies, as are foci of necrosis and microabscesses (Devaney et

al, 1990). Biopsies of gingival lesions typically show only the giant cells and are unlikely to show vasculitis, since arteries of sufficient size are unlikely to be included. In addition, gingival tissues show superficial proliferation throwing the epithelium up into folds which produce the granulomatous appearance seen clinically.

Diagnosis and management

Later manifestations are typically pulmonary cavitation, and renal disease which is likely to be fatal. Joint pains are common and rashes are sometimes a feature. The diagnosis must be confirmed by biopsy at the earliest possible moment and detection of neutrophil anticytoplasmic antibodies. Examination of the nasopharynx, chest radiographs, renal function tests and, if appropriate, lung biopsy should also be carried out. Haematuria is likely to indicate glomerulonephritis and a poor prognosis.

Early treatment with cytotoxic drugs such as cyclophosphamide or azathioprine may be successful. Arrest of the disease with cotrimoxazole has been reported on several occasions but remains a controversial treatment (Hoffman et al, 1992).

Peripheral T cell lymphomas

Some of these tumours, when in the nasopharyngeal region, can cause midfacial destruction. The cellular picture is pleomorphic and a variety of terms had been given to these lesions until the introduction of T cell markers confirmed their nature. Confusion has arisen particularly because of the tendency in these lymphomas for the tumour cells to surround or destroy blood vessels and so closely mimic true vasculitis.

Clinically, these tumours, by their involvement of the nasal passages, are not reliably distinguishable, in their earlier stages, from Wegener's granulomatosis. The age and sex distribution seems also to be similar.

Early features are nasal obstruction and serosanguineous discharge from or crusting of the nostrils. In advanced cases, massive destruction of the centre of the face and secondary infection may develop.

Oral lesions, unlike those of Wegener's granulomatosis, typically consist of palatal swelling, which is boggy in character, and ulceration. The latter may consist of no more than a small central crater or result from extensive palatal necrosis. Bone destruction can lead to loosening of upper teeth. Involvement of regional lymph nodes is unusual until the tumour disseminates.

Microscopically, the cellular picture is pleomorphic, with many large or immunoblast-like cells and relatively few small lymphocytes. A striking feature is the angiocentric distribution of the tumour cells and angiodestruction which mimics vasculitis. Epithelium may also be invaded and extensive areas of necrosis may be seen. Unlike Wegener's granulomatosis, giant cells are absent and granulocytes few unless infection is superimposed. However, in biopsies from the mouth the picture is frequently obscured by necrosis, superimposed inflammation and consequently a much more mixed cell population.

Diagnosis and management

Adequate biopsy is essential. In the case of palatal involvement the biopsy should extend deeply and be repeated if necessary to obtain material uncontaminated by superimposed inflammation or necrosis.

Some of these tumours have a slow and remittent course, but eventually disseminate. The main principles of treatment are radiotherapy, usually with combination chemotherapy.

Midline granuloma syndromes - summary

Wegener's granulomatosis and nasopharyngeal T cell lymphomas can present indistinguishable nasopharyngeal disease, comprising ulceration, discharge, granulation and crusting. Wegener's granulomatosis can cause destruction of the nasal septum, but T cell lymphomas can ultimately cause more severe midfacial destruction. Extension into the mouth of a T cell lymphoma is most likely to be via the palate which appears ulcerated as a result of perforation. Wegener's granulomatosis, by contrast, can cause a proliferative gingivitis (strawberry gums) or mucosal ulceration: either may be the presenting feature.

Microscopically, the essential lesion of Wegener's granulomatosis is a necrotizing arteritis with giant cells. T cell lymphomas present a pleomorphic cellular picture, but can show angiocentric and angiodestructive infiltrations which mimic arteritis. Identification of T cells by immunocytochemistry is required. Spread of Wegener's granulomatosis is particularly to the lungs and kidneys. Late-stage nasopharyngeal lymphoma disseminates in a generally similar way to other lymphomas.

Tuberculosis

This infection has been discussed earlier in this chapter and in Chapter 8.

Deep mycoses

Granuloma formation is typical of mycoses such as histoplasmosis, as discussed in Chapter 2.

Sarcoidosis

Sarcoidosis is a chronic disease of unknown cause, in which non-caseating epithelioid cell granulomas form, particularly in the lungs, lymph nodes (especially the hilar nodes), liver, skin (frequently of the face), eyes, bones, nerves and salivary glands.

Oral lesions are uncommon, but the most frequently affected sites are the gingivae, lips, palate and buccal mucosa, usually with painless swelling, or solitary or multiple soft nodules. In over 50% of patients with bilateral hilar lymphadenopathy, biopsy of the minor labial salivary glands shows typical granulomas. Clinically evident involvement of the major salivary glands is uncommon, but can cause tumour-like swelling or so-called Mikulicz's syndrome (Chapter 11).

Microscopically, the essential features of sarcoidosis are non-caseating epithelioid-cell granulomas, sometimes compact and numerous, surrounded by lymphocytes and containing variable numbers of multinucleated giant cells.

Many minor abnormalities of immune responses but, in particular, limited depression of cell-mediated immunity (as shown by anergy to some antigens such as tuberculin) and frequently hypergammaglobulinaemia are detectable. Paradoxically, patients are not unusually susceptible to infection, and frequently also treatment with immunosuppressive drugs, namely corticosteroids, is effective.

Diagnosis

This depends on the combined clinical and laboratory findings and, in particular, evidence of pulmonary involvement, biopsy of affected tissue and a positive Kveim test. Granuloma formation in labial salivary glands may obviate the need for pulmonary biopsy and thus facilitate diagnosis.

Treatment

Treatment with systemic corticosteroids is effective but justified only to control pulmonary fibrosis, eye or cerebral lesions or hypercalcaemia.

Crohn's disease

Crohn's disease is of unknown aetiology. It most frequently affects the ileocaecal region causing thickening and ulceration. Effects include abdominal pain, variable constipation or diarrhoea and sometimes obstruction and malabsorption.

Many other sites may become involved either before or after gut involvement. Orofacial involvement is relatively frequent and may occasionally also precede abdominal changes. The main effects are diffuse soft or tense swelling of the lips, or mucosal thickening. A cobblestone-like thickening of the buccal mucosa, with fissuring and hyperplastic folds, is characteristic. The gingiva may be erythematous, diffusely enlarged and granular. A minority of patients have painful ragged, linear or aphtha-like oral ulcers. Some patients have glossitis due to iron, folate or vitamin B_{12} deficiency that can result from malabsorption. Abdominal symptoms such as colicky pain, and alternating constipation and diarrhoea, if associated with the characteristic oral changes, are strongly suggestive of Crohn's disease.

Microscopically, oral lesions typically show dilated lymphatics, focal aggregations of lymphocytes and irregular, perivascular mononuclear cell infiltrates and, in particular, loose, non-caseating granulomas, with or without multinucleate giant cells in the corium, but often few in number. The overlying oral epithelium may be normal or ulcerated.

The oral symptoms may resolve when intestinal Crohn's disease is under control, or may respond to oral sulphasalazine or to intralesional injections of triamcinolone. No special precautions are necessary for oral surgery unless the patient is having systemic corticosteroids or is anaemic due to malabsorption.

Melkersson-Rosenthal syndrome and cheilitis granulomatosa

Melkersson-Rosenthal syndrome, in its rare complete form, comprises facial palsy, facial swelling and fissured tongue. The aetiology is unknown.

Zimmer et al (1992) have described 42 patients and reviewed the findings in 220 reported cases. Labial swelling was most common (84% of cases). Initially recurrent, it tends to become persistent due to progressive fibrosis. Facial swelling is less common. The buccal mucosa may have a cobblestone pattern indistinguishable from that in Crohn's disease. Facial palsy, which can be the first sign, develops in up to 36% of cases. It is typically recurrent over many years, is usually unilateral, and can be partial or complete. Permanent weakness of the facial muscles may follow. The tongue is fissured in 50-60% of cases, but has no other special features.

Microscopy

Typical epithelioid granulomas may be close set, contain many large Langhans-type giant cells and be surrounded by lymphocytes. Fibrosis is seen in long-standing cases. The appearance cannot be distinguished microscopically from sarcoidosis and other granulomatous diseases, and like sarcoidosis the serum angiotensin-converting enzyme level may be raised.

Treatment

Persistent lip swelling sometimes responds to intralesional injection of corticosteroids, but relief is usually only temporary. After some years, the lip swelling becomes permanent, in which case surgical reduction may be indicated. Dramatic effectiveness has been claimed for methotrexate (Leicht et al, 1989), but enthusiasm for treatment with cytotoxic drugs may not be widespread.

Isolated swellings of the lips, with similar microscopical appearances, is termed *cheilitis granulomatosa (Miescher's syndrome),* but may be an incomplete form of Melkersson-Rosenthal syndrome.

Foreign body reactions

Granulomas in response to implantation of foreign bodies are usually readily recognizable because of the clinical circumstances, most frequently implantation of amalgam or extrusion of root canal filling material. Such material is usually visible microscopically either directly or by polarized light. Amalgam frequently, however, causes no reaction in the tissues.

In starch granulomas (from glove powder), the granules should be recognizable by polarized light, but may cause confusion because they can induce caseation. Beryllium and zirconium (once used in dentifrices) can cause widespread and severe foreign body reactions.

Food implanted into the tissues can sometimes cause a florid reaction with giant cells, while leguminous matter can produce a particularly characteristic reactin (pulse granuloma -

Chapter 2). A granulomatous reaction can also develop in relation to endogenous material such as keratin (as in ruptured epidermal cyst) or sequestra.

Granulomatous reactions secondary to radiotherapy or chemotherapy

After treatment (usually radiotherapy) of oral carcinoma, regional lymph nodes may become enlarged and firm, as if due to tumour spread. Removal of such a node sometimes shows only a granulomatous (sarcoid-like) reaction, probably as a response to reaction products from treatment of the tumour.

The finding is of no clincal significance apart from the need to reassure the patient.

Granulomatous reactions of unknown cause

The diagnosis of granulomatous reactions in oral tissues frequently depends on ancillary investigations, as suggested earlier. However, once the major causes have been eliminated, a significant proportion of oral granulomatous reactions are of unknown cause. In some, the patient may develop Crohn's disease or sarcoidosis some time later. Many others, however, remain healthy. In some of them the granulomatous reaction appears to result from common food additives such as cinnamon or tartrazine. Such causes can only be confirmed by an exclusion diet which, if faithfully maintained, may sometimes greatly lessen the swellings.

The term *orofacial granulomatosis* has been introduced for this otherwise healthy group. However, this term must not be confused with midline (midfacial) granulomas which are potentially lethal diseases, as discussed above, in view of their utterly different effects and outcomes.

Otherwise, it is essential to maintain regular follow-up to ensure that systemic disease such as Crohn's disease or sarcoidosis is not missed before it reaches an advanced stage. Symptomatic treatment can be given as for granulomatous cheilitis.

Differential diagnosis of oral granulomatous lesions

It is frequently impossible to identify the cause of a granulomatous disease from an oral biopsy alone, but various clinicopathological features are helpful and suggest appropriate systemic and laboratory investigations (Tables 14.9 and 14.10).

Table 14.9 Major features of important granulomatous diseases

Disease	*Oral mucosal lesions*	*Cervical lymph nodes*	*Salivary glands*	*Systemic or other lesions*
Tuberculosis	Ulceration, usually tongue	-	Rarely	Pulmonary cavitation (reactivation)
Tertiary syphilis (granulomas exceptionally rare)	Leucoplakia (premalignant or malignant)	-	Historically mainly	CVS or CNS disease
Deep mycoses	Ulcers and/or tumour-like lesions	Rarely	Rarely	Usually disseminated disease
Cat scratch disease	-	++	Rarely	Conjunctivitis, fever, encephalitis
Sarcoidosis	Typically gingival swelling	+++	++ especially minor glands	Lungs; facial palsy, xerostomia
Crohn's disease	Cobblestone mucosal swellings, ulcers	+	-	Ileitis, fistulas, malabsorption*
Melkersson-Rosenthal syndrome	Lip swelling, fissured tongue	-	Minor glands	

			Facial palsy
Cheilitis granulomatosa			
	Lip swelling		
		-	
			Minor glands
			-
'Orofacial granulomatosis'			
	Lip or gingivalswelling		
		-	
			-
			-
Wegener's granulomatosis			
	Gingival swelling; mucosal		
		-	
			Rarely
			Nose, lung and renal disease
Foreign body reactions			
	Minor swelling or pigmentation		
		-	
			Mainly with tumours+
			-

* Malabsorption due to ileal disease can cause anaemia and consequent oral lesions.
+ Particularly in Warthin's tumour and occasionally in mucoepidermoid carcinomas.

Table 14.10 Oral features of important granulomatous disease and confirmatory findings

Disease
Oral features of granulomas
Confirmatory tests

Tuberculosis
Numerous epithelioid follicles, Langhans giant cells, caseation, dense peripheral lymphocytic infiltrate
Sputum culture, chest radiograph (bacteria rarely found in oral granulomas)

Sarcoidosis
Many compact epithelioid follicles, no caseation, peripheral lymphocytic infiltrate
Chest film, labial gland biopsy, blood picture serum ACE and calcium levels, Kveim test

Crohn's disease
Isolated, loose, poorly formed follicles, often deeply situated; occasional giant cells, scanty inflammatory cells
History of bowel dysfunction or pain, abdominal radiographs (if appropriate); blood picture

Deep mycoses
Organisms typically difficult to find if granulomas prominent; sometimes central necrosis in granulomas; dense inflammatory infiltrate; special stains may show many yeast forms or hyphae
Culture of any unfixed material; immune function (?HIV+); patient from endemic area?

Cat scratch disease
Multiple epithelioid granulomas with central suppuration, in lymph nodes; dense surrounding infiltrate; bacteria may be demonstrable with Warthin-Starry stain
Papule or pustule at inoculation site, conjunctivitis? Rose-Hanger skin test

Tertiary syphilis
Plasma cells prominent but granulomas rarely seen; inflammation may be non-specific
Both specific and non-specific serological tests positive if untreated

Wegener's granulomatosis
Dense mixed inflammatory infiltrate, granulomas ill-defined and hard to find; arteritis; giant cells randomly distributed
Raised titres of anti-neutrophil cytoplasmic antibodies.