Surgical pathology of the mouth and jaws

R. A. Cawson, J. D. Langdon, J. W. Eveson

11. Non-neoplastic diseases of salivary glands

Investigation

Investigations will be discussed in relation to specific disorders and those more appropriate to neoplasms are discussed in the following chapter. However, it must be emphasized that chronic inflammatory swellings of the major salivary glands, in particular, sometimes cannot be distinguished from neoplasms clinically. Nevertheless, biopsy of the parotid glands is contraindicated because of the frequency of pleomorphic adenomas which can be seeded into the surrounding tissues to produce multiple recurrences. There are also the risks of damaing branches of the facial nerve or of producing a parotid fistula.

For imaging techniques, see Chapters 1 and 12.

Developmental disorders

Aplasia/agenesis. Complete absence of one or more salivary glands is very rare, but occasionally the parotid glands are absent. Absence of all major salivary glands is even more rare.

Duct atresia. This is also rare, but usually affects the submandibular duct in the floor of the mouth. Absence of the duct results in retention cysts of the submandibular and sublingual glands.

Salivary gland hypoplasia. This can be a feature of the Melkersson-Rosenthal syndrome. The hypoplasia possibly may be secondary to atrophy of parasympathetic nerves thought to be implicated in this syndrome.

Congenital salivary fistulae. These are sometimes seen in association with branchial clefts.

Aberrant salivary tissue. This is common in the cervical lymph nodes (where it should not be mistaken for a metastasis) and may be found in the middle ear cleft. Stafne's bone cavity is another example.

Acessory ducts and lobes. These are so common as to form normal variations rather than anomalies. A distinct accessory duct and lobe in the parotid is present in as many as 50% of patients.

Cysts. Cysts of salivary glands can be developmental or, more frequently, acquired. Both types are discussed below.

Infections and other inflammatory diseases

Acute bacterial sialadenitis

Ascending infection usually affects the parotid gland. The parotid duct is of larger calibre than the submandibular duct and the opening of the duct at the parotid papilla, unlike that of the submandibular gland, is not guarded by a sphincter-like mechanism.

Ascending parotitis was more common in the past when debilitated and dehydrated surgical patients were at risk from infection ascending from the oral cavity as a result of inadequate salivary flow and probably also oral sepsis. This is now unusual and the single most common predisposing cause is chronic failure of salivary flow usually as a result of Sjögren's syndrome or radiation damage, or occasionally a consequence of tricyclic antidepressant treatment. It can also occasionally affect healthy persons for no obvious reasons.

Clinically, the parotid gland is hot, red, tender and swollen. Frequently, pyrexia and lymphadenopathy are associated. If neglected, fluctuation will result from parotid abscess formation.

Staphylococcus aureus is the most common causative microbe; viridans streptococcal infection is less frequent and it may be difficult to exclude it as a contaminant. A wide variety of other bacteria has been incriminated, such as Gram-negative bacilli and anaerobes. In 23 cases reported by Brook (1992), anaerobes were isolated in 20 patients, but often in association with aerobes. Parotitis is occasionally a nosocomial infection or, in the past particularly, secondary to septicaemia.

Microscopy

Vasodilatation is followed by increasing infiltration by neutrophils into the ducts and parenchyma from blood vessels. Colonies of bacteria may be seen, particularly in the ducts, which become dilated and filled with neutrophils. Ducts and then acinar tissue are progressively destroyed, leading to formation of micro-abscesses. If neglected or if host defences are impaired, destruction progresses to gross abscess formation and destruction of large areas of the gland. With subsidence of the infection, healing by fibrosis follows.

Management

Antibiotics should be given as soon as pus has been obtained for culture and sensitivity testing. To prevent contamination from the mouth, pus should be milked from the duct after the mucosa round its orifice has been wiped dry with a sterile swab. Since staphylococci are so frequent a cause, flucloxacillin is usually the first choice, but changed if the microbiological findings dictate. Metronidazole can be added because of the frequency of anaerobic infections. Other investigations in the acute stage are a full blood picture and the temperature. A sialogram should never be taken in the acute phase, as this drives more organisms into the gland parenchyma and could result in bacteraemia or septicaemia. Early treatment with antibiotics, fluids to correct any dehydration and stimulation of salivary flow with tart drinks (lemon juice) is usually effective.

A comprehensive report by Raad and Sabbagh (1990) of 29 cases and review of earlier reports, from 1911 to 1969, comprised in all 722 cases. The earlier cases frequently required drainage and had a mortality of 10-50%. By contrast, none of the more recent cases required surgery but responded to fluids and antibiotics alone.

However, if an abscess forms it must be drained, with care not to damage branches of the facial nerve. Sharp dissection should therefore be confined to the skin and blunt sinus forceps used to perforate the parotid fascia and the abscess cavity.

Once the acute phase has resolved, a sialogram is useful to assess the functional state of the gland, and for this purpose the emptying film is essential. Sialography at this stage helps also to flush out the gland, and the iodized medium may possibly have some local disinfectant activity. In general, the parotid recovers well from acute infection, whereas the submandibular gland usually goes on to chronic sialadenitis which ultimately necessitates its excision.

Chronic bacterial sialadenitis

The submandibular are more frequently affected than the parotid glands. The serous parotid secretion and wider parotid duct probably allows infection to clear mechanically, whereas the more viscid mixed secretion and narrower duct of the submandibular gland predisposes to chronic infection. Chronic sialadenitis often follows an acute infective episode or is associated with chronic obstruction.

Clinically, the inflamed gland may form a painless tumour-like firm mass (a Küttner 'tumour'), but chronic sialadenitis is frequently also a chance finding on microscopy.

Microscopy

The main features are varying degrees of loss of acini, duct dilatation and a chronic inflammatory infiltrate, usually predominantly lymphocytic, with widespread interstitial fibrosis in the later stages. Squamous metaplasia and calculus formation may be seen in the dilated ducts.

Management

Sialography shows varying degrees of sialectasis and acinar atrophy, sometimes with dystrophic calcification in the gland itself. Again, the emptying film is essential, as this demonstrates the functional status of the gland. Often it also shows obstruction due to a calculus or stricture. In the case of the submandibular gland, the only effective treatment is excision. For the parotid, a superficial lobectomy with tying-off of the parotid duct is usually sufficient. Any functioning remnants of the deep lobe atrophy spontaneously.

Recurrent parotitis

This puzzling condition is seen in children starting at about 6 years of age and recurring usually only until adolescence. Boys are affected twice as often as girls. Occasionally, younger children and frequently adults are also affected. The history is usually

of recurrent unilateral or bilateral parotid pain and swelling ('recurrent mumps'), particularly at mealtimes. Heat, redness, fluctuation and pyrexia are absent. Sialography in the acute phase shows widespread punctate sialectasis with a snowstorm appearance.

An association with Epstein-Barr virus has been reported by Akaboshi et al (1983), in that children with recurrent parotitis often show a considerably higher incidence of antibody to EBV than controls, but this has not been generally confirmed. However, the histological findings suggest that obstruction, probably secondary to formation or transport of abnormal secretion, is probably a major factor in the aetiology.

Microscopy

Mild dilatation of ducts containing inspissated mucus and desquamated epithelial cells, but no significant inflammation in the early stages, may be seen. Oedema and swelling of acinar cells is followed by periductal inflammation and patchy destruction of the lobular structure. Ultimately fibrosis, dilatation of the proximal ducts and degeneration of the duct epithelium, which frequently undergoes metaplastic change, progresses until some lobules consist only of proliferated ducts and fibro-fatty tissue.

Management

Although there is no evidence of a bacterial cause, the episodes are usually treated with an antibiotic and resolve progressively in 5-10 days. Six or more months may elapse between attacks. It is not known if the sialographic changes resolve at puberty, but recurrent parotitis starting in childhood is usually self-limiting.

In adults, by contrast, persistent recurrent parotitis can be troublesome and difficult to treat, as indicated by the range of measures that have been recommended. These have ranged from duct ligation to low-dose radiotherapy or, if all else fails, parotidectomy. The only reliable treatment is to perform a superficial lobectomy with tying off of the main duct as far distally as possible.

Granulomatous infections and sarcoidosis

Tuberculosis, syphilis or toxoplasmosis can involve the salivary glands, but rarely do so. However, the incidence of tuberculosis is beginning to rise in several countries and O'Connell et al (1993) reported 6 cases of parotid swelling among 187 new cases of mycobacterial infections admitted to their hospital during the previous 3 years. These appeared clinically to be parotid gland tumours and diagnosis was only made after excision or enucleation. Fine-needle aspiration biopsy was unhelpful in 2 out of the 3 cases where it was used, all the patients had normal chest radiographs and all who were Mantoux tested showed weakly or strongly positive reactions. Diagnosis of mycobacterial infection of the parotid gland is, therefore, only likely to be made postoperatively by microscopy.

Sarcoidosis (Chapter 14) has a predilection for salivary tissue. It causes either diffuse enlargement, often involving all the major salivary glands, or it may affect a single gland, sometimes with rapid growth mimicking a tumour. The diagnosis is usually suggested by microscopy of an excised gland showing typical granuloma formation, and confirmed by

finding hilar lymphadenopathy or other signs of sarcoidosis, or a positive Kveim test. Usually there is a mumps-like salivary gland swelling, and this is occasionally the presenting feature of systemic sarcoidosis.

Less commonly, Heerfordt's syndrome (parotid swelling, uveitis and cranial nerve palsies, and fever) can develop. Facial palsy is the usual neurological complication. Rarely, sarcoidosis may give rise to a localized pseudo-tumour within a single parotid gland.

The labial salivary glands are involved histologically in a high proportion of cases of systemic sarcoidosis. When there are other suggestive features, particularly hilar lymphadenopathy and widespread pulmonary infiltration, labial gland biopsy may provide valuable confirmation of the diagnosis by avoiding more invasive procedures.

Microscopically, sarcoidosis is characterized by discrete non-caseating granulomas which may be surrounded by a dense lymphocytic infiltrate. It should benoted, however, that granuloma formation in salivary glands is often due to other causes, which are not necessary identifiable (Chapters 12 and 14).

Viral sialadenitis

Sialadenitis caused by the mumps virus is the most common cause of acute parotitis. Mumps is usually a disease of childhood, but can affect any non-immune adult. The parotid is involved in 70% of cases and the swelling may be unilateral or bilateral. The submandibular glands may also be involved. Immunity following a first attack is absolute and lifelong, so that patients claiming to have recurrent mumps probably suffer from recurrent non-specific parotitis. If there is any doubt about the diagnosis, it can be confirmed by a complement fixation test soon after the onset of the illness. The S (soluble) mumps antibody develops within a few days, then disappears after convalescence.

Microscopy

There is interstitial inflammation of the gland which is infiltrated predominantly by lymphocytes and plasma cells. Vacuolation of acinar cells, and small haemorrhages are widespread, but destruction of acini is probably less than appears microscopically, as full functional recovery of the glands typically follows.

Management

There is no specific treatment, and serious complications such as encephalitis or sensory nerve deafness are rare. Nevertheless, because of these risks, mumps vaccination with triple vaccine is strongly recommended for children.

Other viral infections of salivary glands

Congenital cytomegalovirus infection (salivary gland inclusion disease) gives rise to a characteristic picture with owl's eye viral inclusion bodies larger than the duct cells. However, salivary gland involvement is of little clinical significance in comparison with the congenital defects.

Acute parotitis may be caused by viruses such as Coxsackie, Echo, or Epstein-Barr or choriomeningitis viruses, but rarely in comparison with mumps. Chronic parotitis is a common feature, particularly of childhood AIDS, but its cause is as yet unclear.

Post-irradiation sialadenitis

All patients undergoing radiotherapy develop acute sialadenitis when the irradiated field includes the parotid or submandibular glands. Xerostomia and tender swelling of the glands develop within 24 hours, but the symptoms resolve spontaneously within about 3 days. During the acute phase there is a sharp rise in salivary amylase both in the serum and urine. More important are the chronic effects described later.

Sialadenitis of minor glands

The minor salivary glands may be involved in a variety of systemic diseases, particularly sarcoidosis and Sjögren's syndrome, as discussed later. So-called stomatitis nicotinica affects the palate of pipe smokers or those who practise reverse smoking. In this condition, the inflamed duct orifices stand out as red dots or small swellings within the white hyperkeratinized mucosa (Chapter 9). Necrotizing sialometaplasia by contrast gives rise to a tumour-like swelling.

Necrotizing sialometaplasia

This lesion is seen most commonly in the minor glands of the palate. It is of unknown cause, though thought to result in part from cigarette smoking. It is far more frequent in the USA than in Britain.

Middle-aged males are predominantly affected. Typically, the patient develops a relatively painless ulcerated swelling on the hard palate midway between the midline and gingival margin, often in the first molar region. The base of the ulcer is often on the underlying bone and the margins are irregular and heaped-up or everted. The ulcer, which may be 15-20 mm in diameter, clinically resembles a squamous cell carcinoma for which it has, in the past, also been mistaken on microscopy.

Microscopy

There is chronic inflammation of minor salivary tissue and necrosis of acini. The duct tissue undergoes squamous metaplasia and proliferates to produce a pseudo-epitheliomatous appearance. These lesions are often excised for diagnosis, but usually heal spontaneously over 8-10 weeks. An acrylic cover plate is sometimes needed to protect the healing area, particularly at meal times.

Allergic sialadenitis

Some foods, chloramphenicol, oxytetracycline, pollens and heavy metals have been reported to produce allergic parotitis. Eosinophilia in saliva and the peripheral blood are suggestive, but otherwise allergic sialadenitis is a questionable entity. Antihistamines are not reliably effective, and there is little reason why they should be expected to be. Iodides in

contrast media are a recognized but rare cause of salivary gland swelling. However, this appears to be an inflammatory reaction to the concentration of iodide in the salivary gland rather than an allergic reaction, and is not prevented by prophylactic administration of corticosteroids (Berman and Delaney, 1992).

Obstruction and trauma

Obstruction to salivary flow is frequently caused by calculi and can lead to chronic sialadenitis. Another consequence of obstruction is the formation of mucoceles.

Papillary obstruction

Trauma to the parotid papilla as a result of cheek biting, abrasion from a rough tooth or denture flange, or occasionally an aphthous ulcer, can cause inflammatory oedema. This may be sufficient to obstruct salivary flow. Typically, the patient complains of acute pain and swelling of the affected gland at mealtimes or other gustatory stimuli, but it resolves slowly over the ensuing 2 hours. Removal of the source of irritation relieves the symptoms permanently.

Chronic trauma from similar causes can eventually result in a stricture and stenosis of the parotid papilla. When established, this condition is best treated surgically by papillotomy. A probe is inserted through the duct opening and an incision made through the wall of the papilla down on to the probe. Once laid open, the papilla should not be sutured. Occasionally, after this procedure, some patients, particularly woodwind and brass instrument players, complain of swelling as a result of inflation of the parotid. Ascending infection does not appear to follow.

The submandibular papilla, although having a smaller orifice than that of the parotid, rarely becomes obstructed other than by a calculus impacting at the opening (see below). Occasionally, a child traumatizes the submandibular papilla by falling while holding a pencil or other object in the mouth. When the submandibular papilla becomes stenosed, a new opening of the submandibular duct into the floor of the mouth should be created proximal to the site of the papillary obstruction.

Stricture

Salivary duct strictures are usually secondary to ulceration of the duct wall from calculi and mostly affect the submandibular duct. Any trauma - accidental or surgical - to the floor of the mouth may result in stricture formation. Congenital submandibular duct strictures are rare.

Masseteric or buccinator hyperplasia is a rare cause of stricture of the parotid duct which becomes chronically irritated and fibrosed where it curves around the anterior border of the thickened masseter or perforates the buccinator muscle. Attempts may be made to dilate salivary strictures with graded bougies but often, for submandibular duct strictures, it is easier to bring the duct directly into the floor of the mouth proximal to the site of the stricture and make a new opening.

Tumours

Occasionally, benign parotid tumours can compress a duct and produce more rapid enlargement of the gland. Malignant parotid tumours may also cause duct obstruction by infiltrating the duct wall and blocking the lumen.

Calculi (sialolithiasis)

Radiopaque calculi consist predominantly of calcium phosphate and carbonate which crystallize round an organic nidus - usually cellular debris or casts from the duct walls. Microscopically, calculi have a lamellated or radial structure and the duct walls may undergo squamous metaplasia.

Submandibular calculi

The majority of calculi form within the ducts. The more viscid, mixed submandibular secretion probably predisposes to stasis and crystallization of mineral salts. Most submandibular calculi are radiopaque and show up on plain radiographs. They frequently impact at the junction of the main duct and deep lobe of the submandibular gland where the duct bends around the posterior border of the mylohyoid muscle. The other common site of impaction is in the distal third of the submandibular duct often just behind the papilla.

The typical presentation of a submandibular calculus is acute pain and swelling at mealtimes. Nevertheless, many submandibular calculi are asymptomatic or produce chronic obstruction with progressive atrophy and fibrosis of the affected gland. Eventually, infection in the damaged gland brings the patient to seek help.

Management

Radiopaque submandibular calculi are readily recognized on plain radiographs. If stones are in an accessible part of the duct (distal to the point at which the lingual nerve crosses the duct), they should be removed surgically through the floor of the mouth before sialography. A sialogram should not be taken as it can flush the calculus towards the gland where it may not be accessible through the floor of the mouth.

Surgical removal of submandibular stones in an accessible part of the duct (distal two-thirds) is straightforward and can be undertaken under local analgesia. A stay suture inserted around the duct proximal to the calculus prevents subsequent manipulation from milking the stone backwards towards the gland. A linear incision is made along the submandibular duct, to expose the calculus which is then readily teased out. The duct proximal and distal to the site of impaction is then gently irrigated to remove any gravel. The incision in the duct is left open, as closure invariably results in stricture formation.

After removal of the calculus, sialography should be undertaken to assess any damage within the gland. Anything more than mild sialectasis with minimal delay in emptying indicates permanent damage. In a fit patient, surgical removal of the affected gland is advisable, as the gland is otherwise liable to become chronically infected and the site of

recurrent calculi. Unlike the parotid, the submandibular gland has a poor capacity for recovery.

For a calculus in the proximal third of the duct or within the submandibular gland, excision of the gland from an external approach is advocated, with due care to avoid branches of the facial, lingual and hypoglossal nerves.

Parotid calculi

Only about 20% of parotid calculi are radiopaque. They rarely cause acute pain and swelling at mealtimes and many are probably flushed out spontaneously by the salivary flow and sometimes noticed by patients as gritty particles.

Most patients with larger, impacted parotid calcui have chronic diffuse swelling of the gland and discomfort, usually at the start of a meal. Sialography is then required to show the calculus and its site. The great majority of parotid calculi are lodged at the junction of the main duct and the two primary divisions, and have a staghorn shape.

On the rare occasions when parotid calculi impact near the duct papilla, it is often sufficient gently to dilate the parotid papilla and encourage salivary flow to flush out the calculus. Surgical removal of a staghorn calculus is indicated, as the parotid has such good powers of recovery after obstruction.

The surface marking of the parotid duct on the cheek is readily identified and constant. A conventional pre-auricular parotidectomy incision is used, but care must be taken to avoid the buccal branch of the facial nerve which is frequently running close to and parallel with the duct.

Piezoelectric shock wave lithotripsy offers an alternative to the surgical removal of salivary gland calculi. Iro et al (1992) report its successful use, without anaesthesia or sedation, in 81% of parotid gland and 40% of submandibular gland calculi in 51 patients. The only adverse effects were localized petechiae after 13% of treatments and transient swelling of the gland immediately after treatment in 3%.

Mucoceles

Mucoceles usually result from damage to the duct or obstruction to the drainage of a minor salivary gland. The common sites are the lower lip, particularly in class 2, division 2 malocclusions, and the retromolar pad and cheek from occlusal trauma from erupting upper wisdom teeth. Rarely, mucoceles form in the palate following trauma from sharp bones or crusts.

Microscopy

Mucoceles are usually mucous extravasation cysts rather than retention cysts. In their early stages, pools of extravasated mucus surrounding by an inflammatory reaction can be seen in the submucosal connective tissue. These pools coalesce to produce a macroscopic cyst with a wall of compressed but cellular connective tissue and the inflammatory reaction

progressively subsides. Occasionally, such cysts form immediately beneath the epithelium to produce a pemphigoid-like bulla.

Occasionally, obstruction causes the duct to become distended, resulting in a true retention cyst lined by duct epithelium, sometimes containing mucous cells.

Treatment

Mucoceles, if untreated, eventually burst and discharge spontaneously. As the overlying epithelium heals, the secretion accumulates again and the mucocele recurs. Surgery is, therefore, indicated. A linear incision is made just through the overlying mucosa and the lesion is excised *in toto* together with the underlying minor gland of origin. Occasionally, mucoceles recur after surgery either because the affected glandular tissue has not been completely excised or operation has caused further trauma or scarring which blocks adjacent glands. In this situation, cryosurgery or diathermy is often curative.

Ranula

Occasionally, damage to the duct of the sublingual gland causes the formation of a mucous extravasation cyst appearing as a tense bluish swelling in the inferior floor of the mouth just to one side of the midline. Such a ranula is submucosal but lies entirely above the mylohyoid muscle. It may reach 3 or 4 cm in diameter and cause speech disturbance.

A deep ranula lies entirely within the submental space or it may be plunging and hourglass in shape, lying partly superficial and partly deep to the mylohyoid. As the cyst expands, it passes through a developmental dehiscence in the mylohyoid muscle. The lining of an extensive ranula is difficult to excise and usually ruptures during surgery. However, this is unimportant as permanent cure is achieved by excision of the affected sublingual gland with little regard to the ranula itself. In the case of plunging ranula, Mizuno and Yamaguchi (1993) recommend transoral drainage in addition.

Other salivary cysts

Congenital cysts are occasionally seen and lymphoepithelial (branchial cleft) cysts can extend into the parotid area.

Benign lymphoepithelial parotid cysts, often bilateral, can be found on CT scanning, and in association with cervical lymphadenopathy are strongly suggestive of HIV infection, as discussed later.

Sjögren's syndrome

Sjögren's syndrome is a common, chronic connective tissue disorder characterized by dry mouth and dry eyes due to infiltration of salivary and lacrimal glands by T and B lymphocytes, and acinar destruction. PrimarySjögren's syndrome (sicca syndrome) consists of dry mouth and dry eyes in the absence of any other connective tissue disease. The glandular destruction tends to be severe and is more often associated with lymphomatous change. Secondary Sjögren's syndrome is the well-known triad of dry eyes, dry mouth and

a connective tissue disorder, usually rheumatoid arthritis. The sicca symptoms are frequently less severe than in the primary type.

Clinical features

Women, usually of middle age or older, are predominantly affected. Paradoxically, the majority do not complain of dry mouth, but rather of its effects, such as disturbed taste sensation, the need to take fluids with dry food, or soreness of the mucosa. Speech may be impaired as a result of the tongue sticking to the palate. Rarely, the mucosa is dry and parchment-like, but more frequently appears normal, though there may be no obvious flow of saliva from the parotid ducts or frothing in the floor of the mouth. In established cases, the tongue becomes partially depapillated and develops a lobulated surface. Redness and soreness of the mucosa is due to candidal infection. Intermittent salivary gland enlargement is seen in approximately 20% of patients, and persistent enlargement in 4%. In secondary Sjögren's syndrome, rheumatoid arthritis, the most common connective tissue disease, is most frequently associated. Sjögren's syndrome can also be associated with widespread changes of varying severity in many organ systems either as a result of associated autoimmune diseases or secondary to exocrine gland dysfunction (Table 11.1). Depressed lacrimal secretion (keratoconjunctivitis sicca) is particularly important but may be asymptomatic.

Table 11.1 Disorders of other organ systems that may be associated with secondary Sjögren's syndrome

Cutaneous: Rashes of lupus erythematosus or dermatomyositis.

Respiratory: Nasal crusting, or chronic bronchitis and dyspnoea associated with bronchiectasis.

Gastrointestinal: Hepatomegaly associated with primary biliary cirrhosis, chronic active hepatitis or cryptogenic cirrhosis. Acute or chronic pancreatitis. Pernicious anaemia.

Renal: Renal tubular acidosis, nephrogenic diabetes insipidus, nephrocalcinosis or other renal tubular dysfunctions.

Musculoskeletal: Rehumatoid arthritis. Polymyositis or myasthenia gravis. Sensory and/or motor neuropathy and cranial nerve palsies.

Microscopy

Sjögren's syndrome is characterized by lymphoplasmacytic infiltration of salivary tissue; this is initially periductal but leads to progressive destruction of acini, which are replaced by the lymphoid infiltrate. Persistent and proliferation of duct epithelium gives rise to so-called epimyoepithelial islands which may contain hyaline material. This lymphoproliferation, unlike a lymphoma, is polyclonal and respects the lobular septa. The same microscopic picture is typical of benign lymphoepithelial lesions.

Labial salivary glands show similar changes and have a close correlation with those in the parotid glands but rarely show epimyoepithelial islands. Labial glands are a more

convenient site for biopsy, to avoid risk of damage to branches of the facial nerve or parotid fistula. However, in assessing labial gland biopsies, non-specific sialadenitis must be excluded. This is characterized by scattered, rather than periductal infiltrates, variable numbers of neutrophils, acinar damage and ductal dilatation.

It is also important to assess several labial salivary gland lobules, as the greater the number of lymphocytic foci found, the greater the accuracy of diagnosis. If there are more than 5 foci per 4 mm^2 the accuracy of diagnosis is 95%.

Management

If the mouth is not obviously dry on clinical examination, depressed salivary function should be confirmed by measuring the total, unstimulated flow rate. Other causes of xerostomia (Table 11.2) should be excluded. However, it must be ephasized that though the patient may have a dry mouth, investigation of lacrimal function is more important, as keratoconjunctivitis sicca can damage or destroy sight and is therefore more disabling than the oral effects of the disease. The Schirmer test is a measure of tear secretion. A healthy eye should wet more than 15 mm of the standard filter strip in 5 min. A more reliable assessment is made by staining the cornea with 1% rose bengal dye and examination with a slit lamp show punctate or filamentary keratitis if the cornea is dry.

There is usually a raised erythrocyte sedimentation rate and frequently mild anaemia and leucopenia. Fifty per cent of patients have polyclonal hypergammaglobulinaemia. Autoantibodies, particularly rheumatoid factor and rheumatoid arthritis precipitin (RAP), are found in 90% and 75%, respectively, of cases of secondary Sjögren's syndrome, but in only 50% and 5%, respectively, in primary disease. SS-A antibodies are more specific and found in 5-10% of cases of the primary disease, but in 50-80% of cases of secondary disease. SS-B antibodies are found in up to 75% of cases of primary disease, but in 5% or less of secondary disease. Gastric parietal cell, thyroid microsomal, thyroglobulin and smooth muscle autoantibodies may also be detected.

A labial minor salivary gland biopsy, readily performed under local anaesthesia, will usually confirm the diagnosis by showing focal lymphocytic infiltration.

Diagnosis, therefore, depends on confirmation of depressed salivary output and exclusion of other causes of xerostomia, and in the case of secondary Sjögren's syndrome the association with another connective tissue disease. Labial salivary gland biopsy and the autoantibody profile are probably the most reliable confirmatory investigations. Sialography of the parotid glands usually shows varying degrees of sialectasis and duct atrophy as glandular destruction progresses, but is less useful.

Treatment is largely palliative. Immunosuppressive therapy has not been shown to be effective, as salivary gland destruction is usually too far advanced. Such treatment may increase the risk of malignant change. Treatment with hydroxychloroquine may cause a decline in autoantibody production, but does not improve salivary or lacrimal secretion.

Frequent use of lubricant eye drops is necessary when lacrimal secretin fails: fulguration of the nasolacrimal ducts also helps to conserve any secretin, but paradoxically

may lead to epiphora. For the dry mouth, frequent sips of water while eating and frequent rinsing with saliva substitute are the main aids. Meticulous oral hygiene is essential and, for dentate patients, restriction of dietary sugar, topical fluoride and chlohexidine mouthwashes help to control caries. Candidal infection may be troublesome, particularly for those wearing dentures, and topical antifungal agents should be given.

Table 11.2 Causes of xerostomia

Organic

Sjögren's syndrome
Irradiation
Mumps (transient)
HIV infection
Sarcoidosis
Amyloid
Iron deposition (haemochromatosis, thalassaemia)
Hypercholesterolaemia type V

Functional

Dehydration
Water deprivation or excessive loss
Haemorrhage
Persistent diarrhoea and/or vomiting
Diuretic overdosage

Drugs with antimuscarinic effects

Atropine, ipratropium, hyoscie and other analogues
Tricyclic and some other antidepressants
Antihistamines
Antiemetics (including antihistamines and phenothiazines)
Neuroleptics, particularly phenothiazines
Some antihypertensives, especially ganglion blockers and clonidine

Drugs with sympathomimetic actions

'Cold cures' containing ephedrine, etc.
Decongestants containing sympathomimetics
Bronchodilators containing sympathomimetics
Appetite suppressants, particularly amphetamines

Psychogenic

Anxiety states and depression.

Any underlying connective tissue disorder is treated as appropriate and all patients must be carefully followed up because of the increased risk of lymphoma.

Complications

These include:

- ocular damage from xerophthalmia

- those resulting from xerostomia (oral and salivary gland infections)

- those resulting from any associated connective tissue disease

- lymphomas of salivary glands or other sites.

Lymphomatous change may be preceded by a fall in serum immunoglobulin levels and may be suggested clinically by persistence or, particularly, late onset of salivary gland swelling. Approximately 5% of patients with Sjögren's syndrome develop lymphomas; this may represent more than a 40-fold increase in risk compared with normal. However, early lymphomatous change in Sjögren's syndrome may be difficult to recognize microscopically, as discussed later.

Functional xerostomia

In the differential diagnosis of xerostomia, organic diseases of the salivary glands, discussed earlier, must be distinguished from conditions where the glandular tissue is normal but salivary secretion is depressed as a result of dehydration or interference with the neurohumoral control.

An important difference between organic and functional causes of xerostomia is that the latter tend to be only temporary unless caused by long-term drug treatment.

Functional causes of xerostomia are summarized in Table 11.2.

It is important to re-emphasize that patients with objectively confirmed depression of salivary flow, as in Sjögren's syndrome, relatively rarely complain of dryness of the mouth itself, but often of its secondary effects such as disturbed taste sensation, or soreness resulting from candidal infection.

In anxiety states, excessive sympathetic activity can frequently depress salivary flow rates. Most people have experienced the dry mouth induced by anxiety before such occasions as examinations or public speaking. In a few, such as actors, this may become so great an occupational problem that treatment with a beta-blocker may have to be considered.

Other patients may complain of dry mouth as an essentially delusional symptom and salivary flow measurements do not confirm any reduction in secretin. Salivary flow studies may, therefore, be useful in helping to identify patients with psychiatric disorders presenting with this somatic symptom.

Despite statements to the contrary, there is no evidence that either benzodiazepies ('minor tranquilizers') or beta-blockers cause dry mouth.

HIV-associated salivary gland disease

Chronic parotitis in children is said by Prose (1990) to be virtually pathognomonic of HIV infection. In adults, swelling due to lymphocytic infiltration, often with cyst formation, of salivary glands and in some cases xerostomia are also well-recognized abnormalities. In some cases, the parotid swellings are bilateral, cystic and may be massive. Unlike patients with Sjögren's syndrome, most patients with HIV-associated sialadenitis are males in a consierably younger age group. An autoantibody picture typical of Sjögren's syndrome is also not associated with the sicca syndrome of HIV infection: SS-A or SS-B antibodies are not detectable and rheumatoid or antinuclear factors are no more frequent than in a healthy population. Another important difference is that in Sjögren's syndrome the infiltrate is mainly of CD4 lymphocytes, but in HIV infection there is typically dense CD8 lymphocytic infiltration.

Smith et al (1988) have reported typical Sjögren-like changes (benign lymphoepithelial lesions), but associated with microcyst formation, in parotid glands from males at high risk from AIDS. All patients had generalized lymphadenopathy concurrent with painless parotid swellings, which had developed over periods of one or more years, but none reported dryness of the mouth or eyes.

Table 11.3 Typical differences between Sjögren's syndrome and HIV-associated salivary gland disease

	Sjögren's syndrome	*HIV-associated salivary gland disease*
Sex	Up to 90% females	Predominantly males
Age	Mostly over 50	Usually 20-40
Lymphadenopathy	-	+++
Xerostomia/ xerophthalmia	++	Variable
Salivary gland cysts	-	+
Autoantibodies	RF, RAP, SS-A, SS-B, etc	None characteristic of Sjögren's syndrome
Lymphocytic infiltrate	CD-4	CD-8 (but microscopy otherwise similar)
HLA	DR3/DR4	DR5.

Holliday et al (1988) have also reported, painless facial swelling due to benign lymphoepithelial parotid cysts in patients with HIV infection. These were bilateral in most cases and visible in CT scans.

Microscopy

The lymphoplasmacytic infiltrate and formation of epimyoepithelial islands is essentially the same as that seen in Sjögren's syndrome and may also be found in labial salivary glands biopsies. However, there may be gross or microscopic cyst formation. Major cysts are lined by cuboidal and squamous epithelium overlying nodules of hyperplastic lymphoid tissue. Cervical lymphadenopathy due to follicular hyperplasia (Chapter 14) is usually associated.

Parotid swelling with changes typical of benign lymphoepithelial lesion, particularly with cyst formation, in an adult male below the age group at risk from Sjögren's syndrome, is therefore strongly suggestive of HIV infection. However, dryness of the mouth or eyes is not always associated, and an autoantibody picture typical of Sjögren's syndrome is not found. Typical differences between Sjögren's syndrome and HIV-associated salivary gland disease are summarized in Table 11.3. Other salivary gland lesions associated with HIV infection include parotid swellings due to involvement of intra- or paraparotid lymphoid tissues in the lymphoproliferative process of this disease, or a salivary gland lymphoma.

Irradiation damage

Salivary glands are sensitive to ionizing radiation. The acute self-limiting reaction has been described earlier, but long-term irreversible changes follow exposure to 16 Gy or more of irradiation. This destroys salivary acini and causes obliterative endarteritis.

Table 11.4 Sialosis: associated conditions and possible causes

Hormonal

- Ovarian insufficiency
- Hypothyroidism
- Acromegaly
- Diabetes mellitus

Metabolic

- Cirrhosis
- Alcoholism (with or without cirrhosis)
- Chronic pancreatitis
- Chronic renal failure
- Malnutrition

Drug-associated.

Microscopy

Progressive atrophy of gland acini leads to fibrosis: ischaemic damage due to obliterative endarteritis persists indefinitely. In severe cases, little of the gland may remain, apart from the remnants of ducts and obliterated blood vessels in a dense fibrous matrix.

Management

Symptomatic management of the dry mouth is the same as for Sjögren's syndrome and care should be taken to relieve this distressing symptom as far as possible. If enough salivary tissue is destroyed, the resulting xerostomia will lead to severe caries in any remaining teeth, and other oral infections if precautions are not taken. The consequences of any such dental disease are likely to be considerably more serious for the irradiated patient because of the risk of osteoradionecrosis if subsequent dental extractions are undertaken. Protection and preservation of the teeth are therefore particularly important in the patient who has therapeutic irradiation. Preventive measures are liberal uswe of artificial saliva, minimal sugar consumption, meticulour oral hygiene, regular application of fluorides and treatment of any infections secondary to the xerostomia. Acute candidosis (thrush) is common in such patients, but responds well to a course of miconazole gel.

Mikulicz's disease and Mikulicz's syndrome

These terms are an unnecessary source of confusion and are referred to here only for clarification. Mikulicz's disease is an alternative clinical term for benign lymphoepithelial lesion of the parotid glands, particularly when bilateral.

Mikulicz's syndrome refers to the much less common clinical condition of bilateral enlargement of the parotid, other salivary and lacrimal glands by definable disorders such as sarcoidosis, lymphoma or sialosis.

Sialosis (sialadenosis)

Sialosis is an uncommon condition consisting of bilateral, soft, painless enlargement of the parotids and occasionally of other glands. The pathogenesis is unknown, but sialosis seems particularly likely to develop in association with a variety of diseases (Table 11.4).

Microscopically, the acinar cells become swollen and there is loss of cytoplasmic granulation. The striated ducts may atrophy, fatty infiltration may increase and interstitial oedema may develop. In some cases, there is extensive fatty replacement of acinar tissue, but inflammation is notably absent.

There is no reliably effective treatment. The underlying condition should be controlled is possible, but regression of the salivary gland enlargement does not necessarily follow.