The Pathology and Surgery of the Salivary Glands

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Chapter 8: Mesenchymal, lymphoreticular, metastatic and periglandular tumours and other uncommon types of salivary gland tumours

Non-epithelial tumours of salivary glands are rare. They accounted for 4.5% of the material described by Seifert *et al* (1986) and 4.7% of the BSGTP material. As mentioned in Chapter 4, the most common types of non-epithelial tumours of salivary glands in adults are lymphomas. Some of these lymphomas are primary tumours whilst in others, the salivary gland mass is the initial manifestation of disseminated disease. Next in frequency is juvenile haemangioma; it is by far the most common salivary gland tumour of childhood and overall (with other types of vascular malformation) accounted for 52.5% of the series of 120 non-epithelial tumours (excluding lymphomas) of Seifert *et al* (1986). The next most common non-epithelial tumours in this series were lipomas (18.5%) and neural tumours (17.5%), while other benign mesenchymal tumours accounted in all for only 4.5%. Sarcomas formed 7.5%. Sarcomas formed 7.5% of this series and only isolated examples of the last two categories have been reported. They do not differ from their counterparts in other sites and the only important diagnostic consideration is to distinguish connective-tissue tumours from spindle cell myo-epithelial tumours.

Haemangioma of the Parotid Glands

Haemangiomas, or rarely lymphangiomas, may be present at birth, are most common before the age of 10 years and are exceedingly rare in adults.

Clinical features

Girls are affected more frequently than boys. The tumour forms a diffuse soft swelling of the parotid gland and if particularly widespread, may appear bluish. Rarely, the vascular channels can be so extensive as to form an arteriovenous shunt and there have been occasional reports of high output failure as a consequence. Other salivary glands are hardly ever involved.

Microscopy

The appearance is distinctive and consists in most cases of a multiplicity of capillaries, among which are isolated remnants of glandular tissue, particularly ducts (Fig. 8.1). In the rare angiomas of adults, thromboses can lead to phlebolith formation, which can also follow regression of haemangiomas in children.

Occasionally, these haemangiomas are partly or predominantly cavernous or are mixed haemangiomas and lymphangiomas. Some are highly cellular and their infiltrative appearance can mimic a malignant vascular tumour. Lymphangiomas, haemangiopericytomas and haemangioendotheliomas of the parotid glands have also been described. In patients with AIDS, Kaposi's sarcoma occasionally involves a salivary gland.

Behaviour and management

Spontaneous regression of juvenile haemangiomas is well recognized and operation should therefore be delayed if possible, until the age of about five years if the tumour shows no signs of regressing. The difficulties of surgery and the risk of damage to the delicate developing facial nerve are then less. Because of these problems, attempts have been made to reduce the bulk of large infantile haemangiomas, to delay surgery as long as possible, by such means as injection of sclerosing agents or cryosurgery. However, complications can outweigh any benefits. Irradiation is effective but its carcinogenic potential, in particular, rules out its use. Corticosteroids have been reported to control rapidly growing haemangiomas but this does not appear to have been widely confirmed.

Once operation has been decided on, total excision is curative but recurrence can follow incomplete removal. However, as mentioned earlier, avoidance of damage to the developing facial nerve is likely to be difficult.

Lymphangioma

Pure lymphangiomas of salivary glands are very uncommon. Even more rarely they can be very large, cause thinning of the overlying skin and may be fluctuant.

Unlike haemangiomas, lymphangiomas do not regress spontaneously and need to be excised. Aspiration cytology is helpful, but once the diagnosis has been confirmed, surgery is difficult and may have to be carried out in stages.

Embryoma (Sialoblastoma)

The variety of appearances is suggested by the names that have been given to these tumours. These include 'sialoblastoma' (Vawter and Tefft, 1966), 'embryoma' (Roth and Micheau, 1986), 'congenital basal cell adenoma', 'embryonal carcinoma' and 'congenital basal cell adenoma-adenoid cystic carcinoma' (Simpson *et al,* 1986).

Batsakis *et al* (1988) comment on the confusing nomenclature and suggest guidelines for the terminology of congenital and perinatal salivary gland tumours namely:

➤ Tumours indistinguishable from adult-type salivary gland tumours such as pleomorphic adenoma or undifferentiated carcinoma should be categorized accordingly.

➤ Tumours which have no adult counterparts should be termed 'embryoma' and subclassified as benign or malignant.

Batsakis *et al* (1988) emphasize that a property of embryonic tissue is infiltrative growth and that criteria for malignancy in an embryoma should include invasion of nerves or blood vessels, necrosis and greater atypia than expected of embryonic epithelium.

A sialoblastoma appears to have been first reported by Vawter and Tefft (1966) and described in detail by Taylor (1988). In the latter case, a large firm fixed mass extended from the mid-cheek to the tragus, deformed the otic canal and caused difficulties in delivery at birth. Facial palsy was associated. Computerized tomography scanning showed large feeder arteries from the left carotid and costocervical trunk. Batsakis *et al* (1988) also reported a case of a congenital parotid tumour and reviewed earlier reports. They noted that of 16 previously reported perinatal salivary gland tumours. Twenty-five per cent of these perinatal tumours were malignant. Apart from a single pleomorphic adenoma, all of these tumours shared a structure suggestive of embryonic salivary gland epithelia at varying stages of differentiation in a loose mesenchymal stroma. Harris *et al* (1990), in another review of the subject, also reported a congenital submandibular gland tumour which had grown since birth, in a 10-month infant.

Microscopy

The tumour reported by Taylor (1988) consisted predominantly of uniformly sized cells with relatively little amphophilic cytoplasm and some mitotic activity. The cells were mostly in solid lobules but with some duct-like structures budding from them. In other areas, more pronounced ductal differentiation and rare foci with a cribriform pattern were evident. The tumour reported by Batsakis *et al* (1988) also consisted predominantly of small, dark epithelial cells in the form of solid masses and ducts, but without acinar differentiation. Mitoses were frequent in the undifferentiated areas which had an embryonic appearance. The stroma was loose and vascular.

The tumour reported by Harris *et al* (1990) was circumscribed and consisted of aggregates of basaloid cells, ducts, acini and associated myoepithelial cells (Fig. 8.2). The acinar cells contained secretory granules which stained positively with periodic acid-Schiff. The epithelial structures were surrounded by a moderately vascular stroma containing nerve fibres. Overall, there were many features in common with fetal salivary tissue, but it was difficult to be certain whether it was a neoplasm or hamartoma.

It seems, therefore, that most congenital salivary gland tumours, apart from haemangiomas, can justifiably be designated 'embryoma'. Though there are some variations, these tumours have many microscopic features in common, namely, solid masses of small, dark cells with variable mitotic activity and some duct differentiation in a loose mesenchymal stroma. These appearances may be mistaken for a basal cell adenoma or adenoid cystic carcinoma.

Behaviour and prognosis

As an example of the behaviour of a malignant embryoma, the example reported by Taylor (1988) was excised 10 after birth but recurred six months later. A further operation at 13 months of age did not allow total excision because of extension into the skull. Radioactive gold implants were inserted but were followed by two further recurrences in the succeeding 30 months. However, there were no signs of metastases.

Some of these embryomas are benign, despite appearances suggesting invasion, but others are malignant as shown by both the microscopic features and behaviour. The treatment must therefore be planned accordingly but clearly this may present considerable difficulties.

Mixed Hamartomas of Salivary Glands

Some congenital tumours previously categorized as neoplasms have been found on further examination to be hamartomas with proliferation of all major components of normal salivary gland tissue, but particularly, ducts.

Other Salivary Gland Tumours in Childhood

In addition to embryomas and hamartomas, any of the salivary gland neoplasms of adult life can occasionally be seen in childhood. Seifert *et al* (1986) on the basis of earlier reports suggested that 3.5-5% of salivary gland tumours were in children up to the age of 16 years, but included in this estimate the vascular tumours described earlier.

Shikhani and Johns (1988), in a review of the English-language literature, concluded that 472 cases had been reported and presented 21 new ones (excluding vascular tumours), seen over a 30-year period. These 21 cases represented 3.7% of all 575 salivary gland neoplasms seen during this period. However, for this series, an upper age limit for childhood was set at 20 years and only 12 patients were < 17 years old. Three of these 21 tumours were mucoepidermoid carcinomas and the remainder (18) were pleomorphic adenomas. All of the latter were treated by local excision or superficial parotidectomy, eight recurred and four were left with facial-nerve weakness. The high incidence of facial nerve injury illustrates the surgical difficulties presented by parotid gland tumours in children. Of the three mucoepidermoid carcinomas, one was treated by total parotidectomy alone and showed no signs of recurrence after four years. The other two had local excisions followed by radiotherapy; one of these was still free of disease 25 years later.

Shikhani and Johns (1988) analyzed the relative incidence of different histological types among 472 previously reported and their own cases of childhood salivary gland tumours. No fewer than 50% were malignant and confirmed that malignant salivary gland tumours were relatively considerably more frequent than in adults. These malignant tumours were mainly in older children and more frequently in the parotid glands.

Of the 229 benign tumours, pleomorphic adenomas formed 86.6%. Of the 243 malignant tumours, mucoepidermoid carcinomas comprised 49.6%, acinic cell carcinomas 12.2%, undifferentiated carcinomas 8.9% and adenoid cystic carcinomas 6.5%. They also summarized the treatment and outcome of 272 cases where sufficient data were available and noted that the recurrence rate of pleomorphic adenomas after enucleation was > 39% but 19.5% after superficial parotidectomy. They considered that these exceptionally high recurrence rates were probably a reflection of the difficulties of operating on small glands. Two of these recurrent tumours underwent transition to highly aggressive carcinomas. Overall, 32 patients (11.4%), including one who had had a pleomorphic adenoma, died from their tumours.

Callender *et al* (1992) reviewed the results of surgery of 29 non-vasoformative salivary gland tumours in children aged 3-16 years. Of the eight pleomorphic adenomas, there were no recurrences after parotidectomy after a mean follow-up period of 15.9 years. Mucoepidermoid carcinoma was the most common of the malignant tumours and of 21 of the latter, 17 remained free from disease after surgery for periods of between 3.5 and 30.5 years (mean 13.6 years).

Lack and Upton (1988) also reviewed their experience of salivary gland tumours (including vascular malformations) in children and described the findings in 80 patients below the age of 18 years. Of the 25 epithelial tumours, 10 were pleomorphic adenomas, six were mucoepidermoid tumours and two were congenital carcinomas. Of the 55 non-epithelial tumours, 46 were vascular; six were neural and frequently associated with neurofibromatosis.

In summary, then, the most common salivary gland tumours of early infancy or the neonatal period are haemangiomas. In older children, the most common type of epithelial tumour is the pleomorphic adenoma but approximately 50% of tumours are malignant. Of the latter, mucoepidermoid carcinomas are most frequent. Enucleation or superficial parotidectomies of pleomorphic adenomas have been followed by exceptionally high recurrence rates and, in a few cases, malignant change. Shikhani and Johns (1988) recommend total parotidectomy for pleomorphic adenomas in children, but the chances of damaging the facial nerve are high.

Neurilemmomas and Neurofibromas

Neural tumours appear to be the most common connective-tissue tumours in salivary glands in adults; they formed 8% of the non-epithelial tumours in the BSGTP material and 17.5% of the material presented by Seifert *et al* (1986).

Clinically, neural tumours are not distinguishable from other benign tumours of salivary glands. The only condition likely to suggest their nature is when Von Recklinghausen's disease (neurofibromatosis type I) is present.

Microscopy

In the BSGTP material, of 11 nerve sheath tumours, three were neurilemmomas, four neurofibromas and four plexiform neuromas. The patients with neurilemmomas or neurofibromas were all > 30 years while all those with plexiform neuromas were < 18 years and were found to have neurofibromatosis (Palmer *et al,* unpublished data).

In a typical neurilemmoma with Antoni A tissue of compact masses or whorls of Schwann cells with nuclear palisading, the diagnosis should be obvious (Fig. 8.3). Foci of hyalinization which may undergo calcification or Verucay bodies are also distinctive. Antoni B tissue has a more nondescript appearance and consists of a loose mass of irregularly arranged elliptical or spindle cells in a myxoid matrix. Mast cells may be prominent and are a clue to the diagnosis. However, distinction from well-differentiated neurofibrosarcomas can be difficult.

Solitary neurofibromas are rare in any site and should lead to the suspicion that the patient has neurofibromatosis. The appearances are variable but most characteristically consist of irregularly interlacing bundles of spindle-shaped cells with bent nuclei separated by fine, sinuous collagen fibres. These cells are sometimes in a myxoid matrix and either component may predominate. Other cells, in addition to mast cells, which may be present are occasional inflammatory or xanthoma cells, or squamous epithelial inclusions. The possible role of mast cells in nerve sheath tumours, including neurofibromatosis, has been reviewed by Claman (1987).

Plexiform neurofibromas consist of spindle cells with myxoid areas mixed with normal nerve fibres in a highly irregular pattern. They may contain Wagner-Meissner corpuscles and as indicated earlier, are frequently associated with or possibly pathognomonic of peripheral neurofibromatosis (Fig. 8.4).

Neurofibrosarcomas or malignant schwannomas are particularly rare in salivary glands; they may arise *de novo* or from a neurofibroma of Von Recklinghausen's disease. Seifert *et al* (1986) mention only two cases among 120 non-epithelial tumours. Like neurofibrosarcomas in other sites, they may be difficult to distinguish microscopically from other soft-tissue sarcomas but frequently consist of plump spindle cells, typically with sinuous or bent nuclei, in a swirling pattern of fibrous stroma more irregular than that of fibrosarcomas. In some cases, the tumour cells may have an epithelioid appearance and form nests resembling an amelanotic melanoma. Occasionally heterotopic tissues such as cartilage or muscle may form. Myxoid areas or others resembling Antoni A tissue are suggestive, but the diagnosis can be confirmed if an origin from a branch of the facial nerve or a pre-existing neurofibroma can be seen. Staining for S-100 protein may be positive but sometimes electron microscopy is needed to demonstrate an origin in Schwann cells.

Treatment

Most neural tumours are recognized only after parotidectomy. Rarely, a neural tumour arises from a major branch of the facial nerve and it may be difficult to resect completely and restore nerve continuity. In neurofibromatosis, surgery is likely to be needed to confirm the diagnosis, or if the tumour is large, excision is necessary for cosmetic reasons.

In the case of neurofibrosarcoma, total parotidectomy is necessary and followed by radiotherapy. Insufficient data on the prognosis of these tumours are available, but overall, it is poor, particularly when associated with neurofibromatosis. Spread is mainly to the lungs and rarely to lymph nodes, except in the later stages when metastases become widespread.

Five-year survival rates may range from 25 to 75% according to stage and other variables, but if associated with neurofibromatosis, survival is likely to be only half as good as for a comparable solitary tumour.

Lipomas

Lipomas form virtually exclusively in the parotid glands which have a significant fat content as a normal feature. In the BSGTP material they formed 4.3% of the non-epithelial tumours. As described below, liposarcomas are particularly rare in salivary glands.

Lipomas affect adults, particularly males. If sufficiently extensive, a parotid gland lipoma may feel soft.

Microscopy

Salivary gland lipomas, like those in other sites, consist of fat globules and mature adipocytes, and resemble normal fat. They are distinguishable from lipomatosis only in that a capsule may be discernible.

Treatment

Excision of the tumour, the nature of which is likely to become apparent at operation, us curative and there should be no hazard to the facial nerve.

Other Soft-Tissue Tumours

Isolated examples of other non-epithelial tumours of salivary glands have been reported. Seifert *et al* (1986) mention fibroma, osteochondroma, granular cell tumour, malignant fibrous histiocytoma, rhabdomyosarcoma and angiosarcoma. In the BSGTP material, there have been 163 non-epithelial tumours (5% of all salivary gland tumours or 4% if lymphoepithelial lesions are excluded). In an analysis of the AFIP material, Auclair *et al* (1986) found that sarcomas formed 1.5% of all salivary gland tumours but this figure probably exaggerates their true incidence, because of the greater numbers of more unusual types of tumours referred to that Institute. Among more than 3500 salivary gland tumours in the BSGTP material, sarcomas formed only 0.3% and a somewhat similar proportion appeared in the Hamburg Salivary Gland Tumour Register (Seifert *et al*, 1986). Auclair *et al* (1986) also reviewed 33 previously reported cases and the rarity of sarcomas of salivary glands is suggested by the series reported by Farhood *et al* (1990) where, among 176 soft-tissue sarcomas of the head and neck, 2% were stated to have arisen in the parotid region, but none appeared to have arisen in the parotid or any other salivary gland.

In the material analyzed by Auclair *et al* (1986), malignant schwannoma and undifferentiated sarcomas were the most common types, followed by fibrosarcoma, malignant fibrous histiocytoma and rhabdomyosarcoma. Ellis and Gnepp (1988) point out that in the past, rhabdomyosarcomas have been the most frequently reported sarcomas of salivary glands, but that this may be misleading in that improved diagnostic methods, especially immunocytochemistry, have shown that many of these poorly differentiated tumours should be recategorized. As a result, Auclair *et al* (1986) were able to reclassify 12 of 27 tumours. Five were found to stain for keratin and five to react strongly for S-100 protein and were therefore recategorized as spindle cell carcinomas and malignant melanomas, respectively. In addition, one fibrosarcoma was recategorized as an angiosarcoma by its reaction for factor VIII-related antigen. Another fibrosarcoma had some reactivity for S-100 protein and was recategorized as a malignant schwannoma. Renick *et al* (1988) have also reported an embryonal rhabdomyosarcoma of the parotid gland and in a review of earlier reports found 12 examples of these tumours.

Ellis and Gnepp (1988) also point out that, compared with the rest of the body where malignant fibrous histiocytomas and liposarcomas are the most common types of sarcoma, they appeared to be underrepresented in salivary glands in the AFIP material and no cases of liposarcoma were found there or in a review of the literature. More recently, Luna *et al* (1991) reported 11 primary salivary gland sarcomas and reviewed 74 previously reported cases. Of the total of 85 sarcomas, the single most frequent types were rhabdomyosarcomas (18 cases) and malignant fibrous histiocytomas (15 cases). Eight tumours were of unspecified type but reports of two cases of liposarcoma were found.

Kaposi's sarcoma involving both parotid glands has been reported by Yeh *et al* (1989) in a patient with AIDS.

Clinically, 88% of the sarcomas reviewed by Ellis and Gnepp (1988) were in the parotid glands. They were found in patients with a mean age of 40 years but the range was from 1 to 91 years. The age of presentation was, overall, somewhat earlier than for soft-tissue sarcomas in other sites.

Most of these tumours formed painless swellings, but growth was rapid and the average history was only four months. Haematogenous spread was considerably more common than nodal spread.

Behaviour and management

Because of the rarity of these tumours, it is impossible to suggest a definitive plan of management other than that radical parotidectomy is the first requirement and other treatment does not differ from current protocols for such tumours in other sites. The value of chemotherapy, for example, is difficult to assess. As adjunctive treatment of rhabdomyosarcomas in particular, it appears to have improved the prognosis, but in their review, Ellis and Gnepp (1988) found little evidence for the value of either adjunctive radiotherapy or chemotherapy for salivary gland sarcomas. Only 40% of the 33 patients followed by Auclair *et al* (1986) were free of tumour and one-third of the cases died from their disease. The mean survival time of the latter was only 2.6 years and only one patient survived for more than five years. Of the 11 patients reported by Luna *et al* (1991), seven died from their disease within periods of six months to four years: three patients had no evidence of disease after periods of five to nine years.

It might be expected that salivary gland sarcomas would be recognized at an unusually early stage because of their relatively superficial site, and therefore have a more favourable prognosis. However, the survival figures suggest that is not the case and any benefit from early recognition may be nullified by their proximity to vital structures.

Nodular Fasciitis

In the body as a whole, nodular fasciitis is one of the most common causes of tumour-like fibrous masses. It is a benign proliferative lesion but its rapid growth and microscopic appearances cause it to be readily mistaken for a sarcoma. Nodular fasciitis particularly affects the upper extremities in adults and is common in the head and neck region only in children.

Nodular fasciitis has been reported as a rare cause of parotid tumours by Fischer *et al* (1989) who reviewed previous reports. However, Enziger and Weiss (1995) point out that some 50% of cases in several reports had originally been mistaken for sarcomas, so that it is possible that some of the earlier reported sarcomas of salivary glands might now be recategorized as nodular fasciitis.

Microscopy

The mass is non-encapsulated and may be intermingled with the gland parenchyma at its periphery. It consists of short irregular bundles of immature fibroblasts, many of which show mitotic activity. There is an abundant myxoid matrix, which can spread the fibroblasts to form feathery patterns and contains scattered inflammatory cells. Later the lesion may shrink as a result of fibrosis or undergo cystic change.

Nodular fasciitis must be distinguished from a fibrosarcoma to avoid unnecessarily extensive surgery. Points which help to make this distinction are that in fibrosarcomas, the neoplastic fibroblasts are closely packed and lack a conspicuous matrix. These cells form streaming, interlacing bundles which characteristically appear as herring-bone patterns. Their nuclei are also more pleomorphic and mitoses may be atypical.

Nodular fasciitis can, if necessary, be distinguished from spindle cell myoepitheliomas by failure of its fibroblasts to stain for keratins or S-100 protein.

Behaviour and management

As mentioned earlier fasciitis, despite its rapid initial rate of growth and microscopic appearances, is benign and self-limiting. In most cases the lesion will have been treated as a tumour and the diagnosis made postoperatively. It is important therefore not to extend the original excision but to keep the patient under review.

Solitary Plasmacytoma of Salivary Glands

Several cases of this tumour have been reported. El Naggar *et al* (1991) described a new case with typical crystalline inclusions and found reports of eight previous cases, though there are several others.

Patients are typically of middle age or over and males predominate in the ratio of > 2:1 but the tumour presents no distinctive clinical features.

Microscopy

The neoplastic plasma cells may be well or poorly differentiated but pyroninophilia and immunoglobulin or light-chain production can be readily demonstrated in them. A monoclonal component in the serum is rarely found in solitary soft-tissue plasmacytomas and electrophoresis may not be of value in confirming the diagnosis.

Treatment

In the absence of a clinical diagnosis, the tumour is likely to have been excised, but radiotherapy is very effective and should certainly be given if excision has been incomplete or if there is a recurrence. The prognosis is considerably better than for multiple myeloma but the disease can progress to multiple myeloma within a few years or only after several decades.

Giant-Cell Tumours of Salivary Glands

Very rarely, salivary gland tumours consisting largely of osteoclast-like giant cells are seen, as may happen in other organs, notably the thyroid. Among them, the most readily identifiable are giant-cell fibrous histiocytomas. The nature of others is more difficult to define and they probably form a heterogeneous group.

Ellis and Gnepp (1988) reviewed these tumours and describe them as consisting of osteoclast-like giant cells, containing 5-30 nuclei and acidophilic cytoplasm, in a stroma of mononuclear cells, but the appearances are variable (Fig. 8.5). In particular, the mononuclear cells range from a uniform bland appearance to atypia with nuclear pleomorphism and hyperchromatism. In two of the three tumours described by Eusebi *et al* (1984), there was osteoid formation and bony trabeculae in one of them. One of those containing osteoid abutted on, or was admixed with, a carcinoma arising in a pleomorphic adenoma. Of the four additional cases described by Ellis and Gnepp (1988), two had osteoid and bone formation. Two of these tumours were circumscribed and the others were infiltrative.

In view of the rarity of these tumours and the short periods of follow-up, it is impossible to generalize about treatment or prognosis, but it is likely that their behaviour will correlate to some extent with the degree of atypia and local signs of aggressiveness.

So-Called 'Benign Lymphoepithelial Lesion'

The term 'benign lymphoepithelial lesion' was introduced by Godwin in 1952 to describe lymphoid infiltration of salivary gland tissue associated with acinar atrophy but with proliferation of ductal elements. Mason and Chisholm (1975) give a useful account of the historical background to the ideas about the nature and confusing terminology of these lesions since they were first reported by Mikulicz in 1892. Salivary lymphoepithelial lesion has been discussed in relation to Sjögren's syndrome in Chapter 4.

The term 'benign lymphoepithelial lesion' is distinctly misleading in view of the risk of lymphoma in these patients and is only used here as the traditional term in the UK. Some prefer the term 'autoimmune sialadenitis' whether or not it is associated with clinical symptoms of Sjögren's syndrome. Another term, 'myoepithelial sialadenitis' (MESA) is widely favoured even though, as mentioned earlier, myoepithelial cell proliferation is not a feature of this disease. More recently, Batsakis (1987) has suggested the noncommittal term 'lymphoepithelial sialadenopathy' for lesions which can range from limited salivary gland diseases to Sjögren's syndrome with widespread systemic manifestations, and this may be a more appropriate term.

Clinical features

Benign lymphoepithelial lesion, as seen by the surgeon, appears as a diffuse swelling of the parotid gland in the great majority (80%) of cases; in the BSGTP material, 20% were bilateral. The swelling is typically firm but not fixed to skin or deep tissues but in about 40% of patients is painful.

In 36 patients with the primary diagnosis of benign lymphoepithelial lesion, reported by Gleeson *et al* (1986b), only 50% had or developed Sjögren's syndrome, or related autoimmune disease, most commonly, rheumatoid arthritis, but the period of follow-up was limited. Nevertheless, like Sjögren's syndrome, 83% of these patients were women and the majority were > 50 years of age. Further, patients will frequently not volunteer that they have dry mouth or eyes or both, or apparently not regard these symptoms as abnormal (Chapter 5). Alternatively, salivary or lacrimal secretion may be impaired but asymptomatic as also discussed earlier.

Microscopy

The salient features are a lymphoplasmacytic infiltrate, which is initially periductal but extends and progressively replaces acinar tissue. Ducts are disrupted but tend to persist and some of the ductal epithelium proliferates to form so-called 'epimyoepithelial islands' (Fig. 8.6). The latter is a misnomer in that electron microscopy and immunocytochemistry have shown that myoepithelial cells are absent (Fig. 8.7).

Epimyoepithelial islands are irregular in shape but sharply demarcated from the surrounding lymphocytes. Their epithelium appears squamous; they are usually solid, but sometimes contain minute lumens and are surrounded by a conspicuous basement membrane. The latter may be hyalinized and some of this hyaline material may be enclosed within the islands (Figs 8.8 and 8.9). Occasional small ducts may also persist, at least in the penultime stages, and may rarely form minute cysts.

The final picture is one of total replacement of acinar tissue by a dense lymphocytic infiltrate in which epimyoepithelial islands are scattered.

The lymphocytic infiltrate is confined within the capsule of the gland, is polyclonal and includes variable numbers of plasma cells. Germinal centres may form and occasionally become so numerous as to give an appearance superficially resembling a follicular lymphoma.

Diagnosis

Benign lymphoepithelial lesion should be suspected in patients with a tumour-like parotid swelling with any of the following characteristics or associations:

- ➤ Diffuse swelling of the parotid gland particularly in women of middle age or older.
- ➤ Bilateral parotid swellings.
- ➤ Salivary gland swellings in patients with:

rheumatoid arthritis
any other connective tissue disease or related autoantibody findings (Table 4.3);
dry mouth or eyes or other dry gland complications (Table 4.2);
microscopic changes of Sjögren's syndrome in a minor (labial) gland biopsy.

Management

In addition to the medical management of Sjögren's syndrome or associated disease, the two major problems are the risk of lymphomatous change and the operative difficulties in excising benign epithelial lesions. The risk of lymphoma is greatly increased in benign lymphoepithelial lesion, particularly when associated with rheumatoid arthritis, but it may be difficult to recognize lymphomatous change in a limited area of this lymphoproliferative lesion.

In most cases, a preoperative diagnosis cannot be made with certainty, but even if a benign lymphoepithelial lesion is suspected this hardly alters the surgical approach except in so far as it is a warning that it is likely to be difficult. Because of the risk of lymphomatous change, it is important that the lesion should be removed in its entirety if only for adequate microscopic examination. The surgical problem is that the lesion is diffuse and obliterates the normal planes of cleavage protecting the facial nerve and its branches, which as a consequence, are very difficult to define.

Even when the patient is known to have Sjögren's syndrome, the treatment of persistent parotid swelling, particularly when painful, does not differ. Treatment with corticosteroids may relieve the pain but their long-term use is undesirable. In any case, since the parotid glands of these patients are non-functional and are a potential site for lymphomatous change, parotidectomy is the treatment of choice.

Postoperative histological confirmation of the diagnosis of benign lymphoepithelial lesion should also not lull the surgeon into a false sense of security. Because of the increased risk of lymphoma, prolonged follow-up is essential, and further investigation should be initiated at the slightest suggestion of any change in the glands or lymph nodes.

Even if the diagnosis of benign lymphoepithelial lesion is made postoperatively, investigation or referral to a physician is desirable to treat or exclude any autoimmune disease or complications.

Benign Lymphoepithelial Lesion and Sjögren's syndrome

Although it is probable that there is no real distinction between these diseases, the fact remains that many surgeons, in particular, remain uncertain about their nature.

Though the microscopic features of benign lymphoepithelial lesion are the same as those of well-established Sjögren's syndrome, it was suggested by Mason and Chisholm (1975) that these are separate entities, and clearly, many still believe this to be the case. The difficulty is created by the fact that Sjögren's syndrome is not frequently associated with salivary gland swelling and that salivary function or autoimmune disease is frequently not considered when the tumour-like mass of benign lymphoproliferative lesion is first seen. This

is confirmed by Ostberg (1983) who investigated 19 patients in whom the diagnosis of benign lymphoepithelial lesion had been made, and found that 84% of them had symptoms or immunological abnormalities of Sjögren's syndrome. Gleeson *et al* (1986b), also found that most cases of benign lymphoproliferative lesion had been treated as tumours without investigation of the possibility of autoimmune disease. As recently as 1989, Pall commented on the lack of awareness of primary Sjögren's syndrome. Even if Sjögren's syndrome is suspected, the diagnosis may not be easy, as discussed earlier (Chapter 5).

In practice, therefore, there are two groups of patients, distinguished mainly by their mode of presentation. The first have clinical manifestations of Sjögren's syndrome and are seen by physicians. In these patients, salivary gland swelling rarely warrants excision. The second group of patients have a tumour-like salivary-gland swelling, are referred to surgeons, and the possibility of Sjögren's syndrome is not considered. The enlarged parotids are therefore excised. However, it seems likely that if such patients were fully investigated, most (if not all of them) would be found to have Sjögren's syndrome in complete or incomplete form.

Lymphoma in Benign Lymphoepithelial Lesion or Sjögren's syndrome

As mentioned earlier, lymphomatous change in benign lymphoepithelial lesion is a recognized risk. In addition, there is also an increased risk of extrasalivary lymphomas in Sjögren's syndrome and related connective-tissue diseases, particularly rheumatoid arthritis, whether or not they are associated with benign lymphoepithelial lesion. Estimates of the level of risk vary widely. Symmons (1984) for example reported lymphomas in 2.2% of 489 patients with rheumatoid arthritis after a mean interval of 11.8 years, but in such connective-tissue diseases, salivary gland lymphomas are not necessarily secondary to Sjögren's syndrome. Among the 38 lymphomas involving salivary glands reported by Colby and Dorfman (1979), where a clinical history was available, five patients had arthritis or were rheumatoid-factor positive and four others had Sjögren's or sicca syndrome. Of seven lymphomas developing in benign lymphoepithelial lesion reported by Gleeson *et al* (1986), there was a history of rheumatoid arthritis in two, but none of Sjögren's syndrome. Hyman and Wolff (1976) reported 33 new cases of which four had arisen in benign lymphoepithelial lesions, whilst Colby and Dorfman (1979) reported 59 new cases, seven of which contained areas which resembled benign lymphoepithelial lesion. Shin *et al* (1991) have also noted a strong association between the recently recognized entity, monocytoid B-cell lymphoma and Sjögren's syndrome.

Of 36 cases of benign lymphoepithelial lesion accessioned by the BSGTP between 1971 and 1984, 14% were found to have lymphomatous change in the lesion, while three others, among 24 available for follow-up, developed systemic lymphomas in a mean period of 3.8 years. Earlier, Schmid *et al* (1982) had reported 26 lymphomas arising in benign lympho-epithelial lesion as well as 25 primary lymphomas which had arisen in previously normal glands, while more recently, Seifert *et al* (1986) has reported that 23% of salivary gland lymphomas in his series had arisen in benign lymphoepithelial lesion ('myoepithelial sialadenitis') and this closely correlates with the 22% of malignant lymphomas associated with benign lymphoepithelial lesion in the series reported by Gleeson *et al* (1986b). Shin *et al* (1991) also noted the high frequency of association between Sjögren's syndrome and monocytoid B-cell lymphomas which are now accepted as being MALT lymphomas.

Undoubtedly, therefore, the risk of salivary gland lymphomas is significantly raised in benign lymphoepithelial lesion and particularly when associated with rheumatoid arthritis.

The possibility that lymphomatous change may have taken place in a benign lymphoepithelial lesion must always be considered and should not be dismissed because of persistence of, for example, epimyoepithelial islands (Fig. 8.10).

The persistence of epimyoepithelial islands or of germinal centres, in salivary gland lymphomas is well recognized (Fig. 8.11). Among 59 salivary gland lymphomas, either primary or secondary, reported by Colby and Dorfman (1979), for example, epimyoepithelial islands were found in no fewer than 14, despite the fact that few of them showed unequivocal signs of having originating in benign lymphoepithelial lesions. The diagnosis of lymphoma, therefore, depends on recognizing its cytological characteristics, in particular the more homogeneous cellular picture, and alternatively or in addition, signs of invasion (such as obliteration of interlobular septa or capsule, or both) or destruction of tissues such as nerves. In addition, immunostaining to show monoclonal immunoglobulin production is helpful as emphasized by Schmid *et al* (1982), and may be conclusive.

The incidence of lymphoma in salivary lymphoepithelial lesion or Sjögren's syndrome may be ≥ 20% as reported by Gleeson *et al* (1986a) in a study of 36 cases. Takahashi *et al* (1992) found that in 32 salivary gland lymphomas the initial diagnosis had been myoepithelial sialadenitis in nine cases. Lymphoma is typically a complication of long-standing disease and is therefore more likely to be seen in the elderly, particularly women. There is also a greater risk of lymphoma in patients with connective-tissue diseases, particularly rheumatoid arthritis, as mentioned earlier.

Lymphomatous change may be difficult to recognize among the lymphoproliferation characteristic of these diseases. Persistence of epimyoepithelial islands or of germinal centres does not preclude its presence. It is indicated by cytological features of malignancy, signs of invasion and destruction of adjacent tissues. A more sensitive indicator is provided by evidence of expansion of a monoclonal B-cell population. Schmid *et al* (1982), for example, considered areas of monotypic B-cell proliferation to represent lymphomatous change in Sjögren's syndrome. Fishleder *et al* (1987) and Freimark *et al* (1989) also proposed that foci of monoclonality represented 'prelymphomatous change'. Even in histologically benign lesions, Falzon and Isaacson (1991) have argued that a monoclonal B-cell population precludes the diagnosis of benign lymphoepithelial lesion. Moreover, immunoglobulin gene rearrangement is such a population may be identical to that in extrasalivary lymphomas in the same patient. Extensive areas of monoclonality are detectable by simple immunostaining but a limited area may be masked by the general polyclonal infiltrate and a more sensitive method is required.

Jordan *et al* (1995) have pursued the detection of monoclonality in salivary lymphoepithelial lesions using the polymerase chain reaction as well as immunohistochemistry and *in situ* hybridization, and reviewed previous work in this field. These methods in combination identified light-chain restriction in 77% (17 of 22 cases). The single most sensitive method was by the polymerase chain reaction which detected B-cell monoclonality in 68% of cases. Seven sequential biopsies were available from other sites and six of them also showed B-cell monoclonality. By contrast, Pablos *et al* (1994) found by the polymerase chain reaction, clonal expansion of the heavy-chain immunoglobulin gene in the labial

salivary glands of 13 patients with Sjögren's syndrome, but none developed a lymphoma within a mean period of follow-up of four years after biopsy. A B-cell lymphoma developed in another patient but the clonal rearrangement of the tumour differed from the predominant rearrangement in the labial salivary glands at that time.

It may be noted that lip biopsies are frequently carried to confirm the diagnosis of Sjögren's syndrome and they can be used for quantification of kappa to lambda ratios and may therefore be valuable for early detection of malignant lymphoproliferation. Thus Speight *et al* (1994) have shown that lymphomatous change in Sjögren's syndrome can be predicted by *in situ* hybridization for kappa and lambda light-chain MRNA in labial salivary glands. Of seven cases showing light-chain restriction, four developed low-grade mucosa-associated lymphoid tissue (MALT) lymphomas while a fifth died from disseminated lymphoma. They concluded that when lymphoma develops in Sjögren's syndrome, lymphoma cells may disseminate to labial salivary glands before the onset of symptoms. Jordan *et al* (1995) have also shown by *in situ* hybridization in 70 labial salivary gland biopsies, that 18.6% showed light-chain restriction. Subsequently 30.7% of these patients were found to have extrasalivary lymphomas within a follow-up period of 18-156 months.

Although small areas of monoclonality can be identified by molecular techniques, they are so sensitive that the significance of positive findings is as yet controversial.

It would be surprising if light-chain restriction in 77% of salivary lymphoepithelial lesions, as reported by Jordan *et al* (1995) represented early lymphomatous change in every case. Though detection of a small focus of monoclonality may be a controversial as an indication of the presence or likelihood of lymphoma, it should at least serve as a warning of the possibility and the need to keep the patient under observation. In view of the age of most affected patients, lymphoma may not develop within the patient's lifetime, but expansion of a monoclonal B-cell population in salivary lymphoepithelial lesion must be regarded with some anxiety.

Kassan *et al* (1978) quoted a 40-fold increased risk of lymphoma in Sjögren's syndrome compared with the general population but many of these lymphomas were more frequently extraglandular. However, in view of the findings of Falzon and Isaacson (1991) it seems possible that many of these may have been MALT lymphomas which homed from areas of light-chain restriction in salivary lymphoepithelial lesions.

The fact that salivary lymphoepithelial lesions, rheumatoid arthritis, other connective-tissue diseases and, particularly, Sjögren's syndrome are more common in women may explain the higher incidence of salivary gland lymphomas in females in most series.

Primary Lymphomas of Salivary Glands

Primary lymphomas of salivary glands are rare and, for example, were not described by Foote and Frazell (1954) in their monograph on salivary gland tumours. Lymphomas are also mentioned only as a complication of benign lymphoepithelial lesion by Thackray and Lucas (1974) in their data based on over 700 salivary gland tumours. Nime *et al* (1976) could find reports of only 29 cases of adequately documented primary salivary gland lymphomas and only a single example, among 2636 lymphomas (all sites), in three earlier reports. Of 473

lymphomas (all sites), in three earlier reports. Of 473 lymphomas reviewed by Anderson *et al* (1982), the great majority (316) were in lymph nodes and only one was known to have been in a salivary gland. Ellis and Gnepp (1988) have reviewed earlier reports of salivary gland lymphomas and noted that > 400 had been accessioned, but it was rarely possible to determine what proportion of them were primary tumours of salivary glands. The main reports of series of salivary gland lymphomas have been mentioned earlier, in relation to benign lymphoepithelial lesion.

Lymphomas found in salivary glands can be of different origins and present specific problems for both clinician and pathologist if the patient is not already known to have disseminated disease. Otherwise, the diagnosis is likely to be made only after excision and histological examination.

Since lymphomas are far more commonly nodal than extranodal, it seems probable that salivary gland lymphomas most frequently arise in intra- or juxta-glandular nodes and though they may then extend into the glandular parenchyma, the possibility that they are manifestations of disseminated disease, must be excluded. Of 59 salivary gland lymphomas described by Colby and Dorfman (1979), for example, 37 patients had disseminated disease and in 11 of then the diagnosis had already been established. In the material described by Seifert *et al* (1986), 30% of 139 non-Hodgkin lymphomas of salivary glands were secondary to systemic spread. In many cases, however, destruction of the nodal architecture may make it impossible to be certain whether the tumour has arisen in an intra- or periglandular lymph node, but it is also possible for true extranodal lymphomas to develop in the parenchyma or as a result of lymphomatous change in benign lymphoepithelial lesion.

In addition, salivary gland lymphomas have been reported in patients with AIDS. Lymphomas of the head and neck region are considerably more common than in a non-infected population, and among the lymphomas in patients at high risk of, or with AIDS, 2 of 21 lymphomas in the series reported by Ioachim *et al* (1988) and 2 of 31 in the series reported by Egeter and Beckstead (1988) were in salivary glands. The mean age of such patients is lower than for similar tumours in non-infected patients and all the patients in these reported series were males.

If therefore, these series are representative, then the incidence of salivary gland lymphomas, in association with HIV infection, appears to be high.

Yet another possibility is that of lymphoma developing in Warthin's tumour, but this is remarkably rare as discussed later. In summary, therefore, lymphomas in salivary glands can arise:

- ➤ as the first manifestation of disseminated disease;
- ➤ in juxta- or intraglandular lymphoid tissue;
- ➤ in the gland parenchyma;
- ➤ in benign lymphoepithelial lesion or Sjögren's syndrome;
- ➤ in association with other connective-tissue disease, particularly rheumatoid arthritis;
- ➤ as a complication of HIV infection; and
- ➤ rarely in Warthin's tumour.

Clinical aspects

Partly because of these variables, and because it is frequently unclear from reports whether a salivary gland lymphoma has arisen there or is secondary to disseminated disease, the incidence of primary salivary gland lymphomas is uncertain.

In the series of Seifert *et al* (1986) of 2913 salivary gland tumours, 4.5% (approximately 8% of all malignant salivary gland tumours) were lymphomas, while in the BSGTP series of 3500 salivary gland tumours, 2.4% were lymphomas.

In most series, the parotid gland has been the most frequent site. In the series of Seifert *et al* (1986), 60% were in the parotids whilst in the BSGTP material 50% were in those glands. The submandibular gland accounts for 15-20% and the remainder are in the minor glands, particularly of the palate. By contrast, in the series of Seifert *et al* (1986), Hodgkin's disease affected the submandibular gland (or more strictly, the juxtaglandular lymph nodes) slightly more frequently than the parotid gland. This is merely a reflection of the frequent early involvement of the cervical nodes in Hodgkin's disease.

The peak age incidence for non-Hodgkin lymphomas is in the sixth and seventh decades. Those in benign lymphoepithelial lesion are typically a complication of long-standing disease and are also therefore more likely to be seen in the elderly. Women are more frequently affected in the ratio of nearly 2:1. This is partly a reflection of lymphomatous change in Sjögren's syndrome. In such cases, symptoms of Sjögren's syndrome, sometimes of long duration, may be associated, or there can be features of another connective-tissue disease.

With regard to Hodgkin's disease, the juxtaglandular nodes, rather than the salivary glands are involved and there is a peak in the third and fourth decades. Males predominate in the ratio of 4:1.

A salivary gland lymphoma usually causes a firm swelling which in the majority of cases is painless. There is sometimes fixation to deep or superficial tissues and rarely (Gleeson *et al*, 1986a) facial palsy.

In 15 cases reported by Takahashi *et al* (1990) from Japan, 93% were in the parotid and the remainder in the submandibular glands; the mean age was 59 years and the male-to-female ratio was nearly 3:1. One patient had clinical evidence of Sjögren's syndrome.

Microscopy

Non-Hodgkin's lymphomas

The variety of classifications has made analysis of reports difficult. In the 59 cases reported by Colby and Dorfman (1979), salivary gland involvement in disseminated disease was included and all types of non-Hodgkin's lymphoma were represented.

In the 40 primary lymphomas reported by Gleeson *et al* (1986a), the single most common type was the follicular, predominantly small cleaved cell type, although there was little difference in frequency between follicular and diffuse types, and the majority were Grade I tumours. In the much larger series of 118 non-Hodgkin's lymphomas in salivary glands described by Seifert *et al* (1986) 90% were well differentiated (immunocytoma or centrocytic-centroblastic) and 10% were poorly differentiated (centroblastic or lymphoblastic).

The origin of salivary gland lymphomas has frequently been assumed to have been from MALT. To distinguish their site and cell origins, Kerrigan *et al* (1990) made use of specific gene rearrangements to provide a molecular marker. These are the immunoglobulin heavy-chain gene on chromosome 14 and *bcl-2* gene on chromosome 18. A search was made for the t(14:18) translocation in extranodal lymphomas, but it was not found in any samples from the extranodal lymphomas of the stomach, intestine or skin, but was found in 3 of 7 salivary gland lymphomas, all of which were nodular. The remainder, lacking *bcl-2* rearrangement were diffuse type and had histological or clinical features consistent with a MALT origin.

These preliminary findings therefore suggest that many salivary gland lymphomas are of MALT origin and that others which contain the *bcl-2* rearrangement differ morphologically.

Hodgkin's disease

In most series including our own, primary manifestations of Hodgkin's disease in salivary glands are rare. However Schmid *et al* (1982) found four cases among 25 salivary gland lymphomas and (as mentioned earlier) Hodgkin's disease formed 15% of primary lymphomas in the series of Seifert *et al* (1986). In this latter series, 75% of the tumours were the result of disseminated disease so that 80% of the parotid tumours and 90% of the submandibular tumours were in lymph nodes only. The gland parenchyma was involved in only a minority and in none was the gland parenchyma alone involved. It appears therefore that the unusually high incidence of Hodgkin's disease in the material described by Seifert *et al* (1986) mainly results from inclusion of disseminated disease involving the cervical lymph nodes rather than Hodgkin's disease of salivary glands. Taking no account of whether these were primary or secondary lesions, there were virtually equal numbers of lymphocyte-predominant, nodular sclerosing or mixed type but only two were lymphocyte-depleted.

Prognosis and management

From the limited amount of published data it appears that salivary gland lymphomas are frequently well differentiated. However, as with lymphomas in other sites, the first essential is precise histological categorization followed by staging to determine whether the tumour is a primary salivary gland tumour or, if not, the extent of the disease.

If it can be established that the lymphoma is limited to a salivary gland, parotidectomy should be carried out and followed by radiotherapy. However, the treatment and prognosis will be determined by the stage and histological subtype and should be according to currently accepted protocols.

In the rare cases of Hodgkin's disease involving salivary glands, histological categorization is of even greater importance in determining whether radiotherapy or combination chemotherapy, or both, are most appropriate and should also be according to currently accepted protocols.

According to reports, such as those of Nime *et al* (1976) and Schmid *et al* (1982), the prognosis of primary salivary gland lymphomas appears to be better than that of nodal lymphomas. This is perhaps to be expected, in that a salivary gland lymphoma may be of relatively low grade and, in any case, is likely to be recognized at an earlier stage than a more deeply situated tumour.

Lymphoma in Warthin's Tumour

Lymphoma in Warthin's tumour is exceptionally rare. Rekers (1952) was probably one of the first to report a case. Colby and Dorfman (1979) noted lymphomatous stroma in 2 cases of Warthin's tumour, but it is not clear whether these represented lymphomatous change in Warthin's tumour or involvement of the latter in disseminated disease. More recently, Bunker and Locker (1989) reported a case on which they carried out DNA analysis and in a review of the literature concluded that 12 other cases had been reported; of these 8 appeared to be primary lymphomas arising in Warthin's tumours. They also concluded that 11 cases had been previously reported but that 3 of these had not arisen primarily in the lymphoid stroma. Medieros *et al* (1990) have also reported a case and carried out immunophenotyping and gene rearrangement analysis on cryostat material. A typical Warthin's tumour was present but the majority of the stroma had been replaced by non-Hodgkin lymphoma which they categorized as being follicular and diffuse, of mixed small cleaved cell and large-cell type. Monotypic surface immunoglobulin could not be demonstrated but analysis showed rearrangement of both the immunoglobulin and kappa light-chain genes. The T-cell receptor beta-chain retained its germline configuration and confirmed the monoclonality and B-cell origin of the tumour.

The patient was a 71-year-old man who had had a mass at the angle of the jaw for five years but the growth of the mass had rapidly accelerated over the last two months. After partial parotidectomy the patient remained well four years later.

Clearly, it is impossible to make any useful statement about treatment of tumours as rare as these, but there seems to be no reason to suggest that they should be managed differently from other lymphomas of salivary glands.

Juxtaglandular Tumours

Tumours from adjacent tissues, other than lymph nodes, that involve salivary glands, or clinically appear to be salivary gland tumours are uncommon. The skin is probably the most frequent site of origin, but the cutaneous origin of such tumours is usually evident clinically.

Tumours of the mandible, such as an ameloblastoma, can also extend into the parotid but only very rarely. In any case mandibular tumours are uncommon and rarely extend outside the ramus.

Among the BSGTP material is a jugulotympanic paraganglioma which was initially mistaken for a clear cell acinic cell carcinoma of the parotid gland (Fig. 8.12). Its true nature was suggested by an astute surgeon who was impressed by its vascularity and the fact that it was fungating into the external auditory meatus. Paragangliomas stain in a generally similar manner to neuroendocrine cells but are negative for epithelial markers. Their cells are typically also in nests *(Zellballen)* and as the operative picture suggested, are more vascular than acinic cell carcinomas.

Tumours of the masseter muscles are exceedingly rare but a rhabdomyosarcoma can arise there and mimic a parotid tumour clinically.

Metastatic Tumours

Metastases to salivary glands are so uncommon that data on the relative frequency of the different types are conflicting. The most important in most respects, though not necessarily the most frequent, is a renal cell carcinoma, which as discussed earlier, must be distinguished from a clear-cell salivary gland tumour as has been well illustrated by Thackray and Lucas (1974).

In the BSGTP material there were only 19 metastatic tumours. Of these, 12 were in the parotid, six in the submandibular and one in the minor glands.

One difficulty is that secondary deposits in juxtaglandular parotid lymph nodes may extend into, and appear to have formed in, the gland, though from the viewpoint of management or prognosis, the distinction is unlikely to be of any significance. Despite the fact that adenocarcinomas are, overall, the most common malignant tumours in the body and might therefore be expected to be the most frequent type of metastasis in salivary glands, this does not seem to be the case. However, then a metastasis from a distant primary adenocarcinoma forms in a salivary gland, it may sometimes be difficult to distinguish it from a primary salivary gland tumour and it is possible that this problem may have distorted the reported data.

Conley and Arena (1963) have reported that the most frequent types of metastases from skin tumours, in salivary glands, were malignant melanomas (45%) and epidermoid carcinomas (37%) but these metastases were in parotid lymph nodes rather than the salivary gland. Pope and Lehmann (1967) have also stated that head and neck melanomas are the main source of metastases to parotid lymph nodes. Nevertheless, only a single case of metastatic malignant melanoma has been seen among 3500 salivary gland tumours in the BSGTP material and, in this case the primary tumour was in the eye. Ball and Thomas (1990) have reviewed previous cases and discussed their management.

Diagnosis and management

Diagnosis, obviously enough, depends on recognition of any feature that suggests that the tumour is a secondary deposit. This may be more easily said than done, unless the patient is known already to have a distant primary. It is reasonable to assume, for example, that a melanoma would be a secondary deposit, but as indicated earlier, this may not be the case, or alternatively, the tumour may be in some hidden carcinoma, the differential diagnosis from

a primary clear-cell carcinoma, has been discussed earlier (Chapter 7) but as indicated there, it is not always possible to make the distinction on the microscopic features alone. Ultimately, therefore, whenever a salivary gland tumour has microscopic features suggestive of a secondary deposit, confirmation of the diagnosis usually depends on investigation to confirm the presence of the primary tumour. This may be greatly facilitated by modern imaging techniques.

In the case of salivary gland metastases from distant sites, the prognosis is usually poor and palliative treatment is likely to be all that can be offered. In the case of metastases to the parotid glands, the diagnosis is usually made only after parotidectomy and, unless the tumour recurs in this site, no further treatment of this area is usually necessary or helpful. One exception may be the case of metastatic melanomas for which Ball and Thomas (1990) suggest that, though the long-term prognosis is poor, parotidectomy and elective neck dissection provide valuable loco-regional palliation. Another may be that of a renal cell carcinoma as discussed in Chapter 7.

In the case of spread to salivary glands of tumours from adjacent tissues (usually either from the skin into the parotid gland or from the oral mucosa to the submandibular gland), there is unlikely to be any problem of diagnosis. Moreover, the involvement of a salivary gland is usually evident clinically and removal of the primary tumour, and of the gland, may be manageable by a single wide resection, together with any lymph nodes that are involved. Nevertheless, the prognosis under these circumstances is also likely to be poor.

Intraosseous Salivary Gland Tumours

Salivary gland tissue is occasionally found within the body of the mandible. The usual site is near the angle of the jaw where an extension of the submandibular gland indents or may have become entrapped in the bone during development of the jaw. The defect is asymptomatic and only noticed by chance in a routine radiograph, as a sharply circumscribed, cyst-like area of radiolucency near the angle (Stafne bone cavity) or more rarely in the anterior part of the mandible (Chapter 3).

Rarely, salivary gland tumours develop within the jaw and presumably arise from these foci of ectopic tissue. Two trabecular adenomas, a few pleomorphic adenomas and adenoid cystic carcinomas have been reported in this site but most intraosseous salivary gland tumours have been mucoepidermoid carcinomas. Waldron *et al* (1987) reported 16 intraosseous mucoepidermoid carcinomas among 426 tumours of minor salivary glands. Waldron and Koh (1990) reported four more of these tumours and concluded that, so far, 66 central mucoepidermoid carcinomas had been reported. Hirota and Osaki (1989) reported a case of central adenoid cystic carcinoma in the mandible but were able to find reports of only seven other cases.

Clinical and radiographic features

The mandible is affected almost three times as frequently as the maxilla. Moreover, it is difficult to be certain that intraosseous maxillary tumours have not arisen in antral mucous glands rather than within the bone. In any case, unlike the mandible, there appears to be no ectopic salivary tissue within the maxillary bones from which these tumours could

arise. Of the 66 central mucoepidermoid carcinomas reviewed by Waldron and Koh (1990), the age range was 1-85 years, with a mean age of approximately 50 years. Swelling of the jaw was the main clinical feature in > 50% of cases and there was pain or paraesthesia in 30%.

The radiographic appearance of intraosseous salivary gland tumours is variable. They may appear as uni- or multilocular rounded areas of radiolucency which, if benign or of low-grade malignancy, appear well circumscribed and typically resemble odontogenic cysts. Their nature is only recognized after a biopsy or excision has been carried out (Fig. 8.13 and 8.14). High-grade tumours or central adenoid cystic carcinomas are likely to show some signs of peripheral bone destruction and appear less sharply circumscribed.

Microscopy

Intraosseous salivary gland tumours do not differ microscopically from their soft-tissue counterparts. It is important not to mistake them for one of the many types of odontogenic tumours, but most of the reported intraosseous salivary tumours have been of readily recognizable types.

Management

Once the histological diagnosis has been made it may be thought necessary to exclude the possibility that the tumour is a secondary deposit by screening other organs. However, this is extremely unlikely and all the cases reviewed by Waldron and Koh (1990) appear to have been primary tumours. Adenocarcinomas of other organs can occasionally resemble salivary gland tumours microscopically, so that metastases from other sites should be excluded (Fig. 8.15).

Most information is available about the results of treatment of central mucoepidermoid carcinomas, but the numbers are so small and treatment options that have been adopted have been so varied as to yield little useful information. However, in view of the unpredictable behaviour of mucoepidermoid carcinomas, it seems that wide excision, or if necessary, resection of the jaw and bone grafting, should be carried out. Some central mucoepidermoid carcinomas appeared to have responded to simple enucleation but nearly 45% of those so treated have recurred. As with mucoepidermoid carcinomas in salivary glands, the behaviour is unpredictable and Lebsack *et al* (1990) have reported a central mucoepidermoid carcinoma of the jaw that metastasized to a clavicle. The primary tumour was excised and radiotherapy given to both the mandible and clavicle. They also reviewed seven previously reported cases of metastases to lymph nodes, two of which were in adolescents. In the case of an adenoid cystic carcinoma, spread along the inferior dental nerve may necessitate even wider excision.

Radiotherapy appears to be of uncertain value. For example, one of the patients reported by Waldron and Koh (1990) died within nine months of initial surgery followed by external-beam irradiation.

An intraosseous salivary gland adenoma if completely encapsulated, may shell out, as in the case reported by Bret Day and Cawson (1969), and cause no further trouble.

Histogenesis

Though there may be doubt whether salivary gland tumours arise within the substance of the jaws, the fact that they do not arise from overlying minor salivary glands is shown by the absence of a soft-tissue mass, but central bone destruction with, initially, intact cortical plates. Though they are rare, the existence of benign intraosseous salivary gland tumours also indicates an origin within the bone. Credence is lent to this idea by the known presence of ectopic salivary tissue in Stafne bone cavities and in other parts of the jaws. Development of a plemorphic adenoma has also been reported in a Stafne bone defect and presumably arose in an extension of the submandibular gland. Aberrant salivary tissue has not apparently been described in maxillary bone where salivary gland tumours are considerably less frequent and their central origin more difficult to confirm.

Waldron and Koh (1990) consider the possibility, among others, that a salivary gland tumour might arise from a glandular odontogenic cyst or from the mucous cells frequently seen in odontogenic cyst linings. Nevertheless, ectopic salivary tissue seems to be the most obvious source of neoplastic change, but the frequency with which this takes the form of mucoepidermoid carcinoma is puzzling.

Note

1. Friedrich Daniel von Recklinghausen (1833-1910).