Benign lymphoepithelial salivary lesion to be distinguished from adenolymphoma

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SYNOPSIS  In a collection of 11 cases, the benign lymphoepithelial lesion presented clinically in every case as a tumour of a salivary gland. In eight cases the parotid was affected, in two a palatal salivary gland, and in one the submandibular gland was affected. Microscopically the lesion consisted of a mixture of lymphoid and epithelial components and, although the appearances in several cases suggested lymphosarcoma or reticulosarcoma, the arrangement of the epithelial component in characteristic islands (epi-myoepithelial islands) indicated the benign nature of the lesion. In one case incomplete excision of a lesion of the palate was followed by a recurrence that was cured by a radium mould.

The microscopical appearances of the benign lymphoepithelial lesion were identical with those of the salivary lesions of Sjögren's syndrome but in all the cases the lesion was an isolated one and the sicca syndrome was absent.

The following account is based on 11 cases of a tumour of salivary tissue for which the name 'benign lymphoepithelial' lesion seems appropriate. The name was suggested by Godwin (1952) who emphasized that the lesion responded to surgical treatment or irradiation and that none of his 11 cases ran a malignant course; the name has the advantage of indicating the characteristics of the lesion without being dogmatic about its aetiology.

CLINICAL FEATURES

In the present collection, six of the patients were female and five male; the youngest was a boy of 16 and the oldest a woman of 75 years. All complained of a single localized swelling and were referred to surgeons for what was thought, in most cases, to be a mixed salivary tumour. The glands affected were: the parotid (eight cases), a palatal salivary gland (two cases), and the submandibular gland (one case). The lumps felt firm but were not stone-like, and the range of their size was from about 1 cm. in diameter, in the cases with the palatal lesions, up to 5 cm. in diameter in the parotid and submandibular glands. During the excision of one of the parotid swellings a cystic area ruptured and, in the submandibular lesion, an abscess ruptured spontaneously about two weeks before operation, leaving a small sinus in the overlying skin. In lesions without cysts or abscess cavities the macroscopic appearance was of a lobulated mass with smooth contours surrounded, at least partially, by a capsule. The cut surface was smooth and white with occasional flecks of congestion or haemorrhage (Fig. 1). Three of the parotid swellings were described in the operation notes as superficial to, and easily separated from, the main parotid gland. In more than one case, however, the excision of the

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Received for publication 20 November 1964.
parotid swelling was complicated by involvement of the facial nerve or large branches of it, and the lingual nerve had to be divided during the removal of the submandibular lesion.

The swellings were painless with three exceptions: the palatal swellings were painful and tender because of trauma by dental plates, and the submandibular lesion formed a painful abscess.

FOLLOW-UP

It has been possible to keep track of six of the cases for over one year after treatment, and five of these have been followed for over three years; in all of them the lesion has been cured.

HISTOLOGICAL APPEARANCES

Lymphoid and epithelial components were present in every case but in several the epithelial structures were scattered inconspicuously in the lymphoid component and defects of fixation or other technical faults tended to obscure the epithelium in some cases. Sections seemed particularly liable to develop fractures in the immediate vicinity of epithelial islands. Thus in several cases there was anxiety as to whether the lesion might be a lymphosarcoma that had involved a salivary gland, and five of the cases became available because sections were sent to the Department of Pathology of Liverpool University for a second opinion.

The epithelial elements consisted of remnants of glandular acini, of ducts with a single, or in three cases, a double layer of lining cells (Fig. 2), and of solid, or almost solid, epithelial islands. The epithelial islands were the most characteristic structures so far as diagnosis was concerned and they appeared to be formed by proliferation of the epithelium or ducts (Figs. 3, 4, 5, 6). According to Morgan and Castleman (1953) the islands consist of a mixture of epithelial and myoepithelial cells, the myoepithelial cells being recognized by their elongated nuclei. Other writers (Lloyd, 1946; Godwin, 1952; Bauer and Bauer, 1953) have attributed the islands to squamous metaplasia but the complete lack of keratin in the present collection favoured the suggestion that the flattened cells with elongated nuclei were myoepithelial. The islands were bounded by a basement membrane that stained well by silver methods for reticulin (Fig. 7). The diagnosis of benign lymphoepithelial lesion was not made unless epithelial (epi-myoepithelial) islands were present. In one case they were the only epithelial structures present; in all the other cases they were associated with ducts or remnants of acini.

The lymphoid component had a recognizable follicular structure in six of the specimens. In some the follicles were inconspicuous but in others they were prominent. The cases without follicles were those that caused anxiety about the possibility of lymphosarcoma. In eight of the cases hyaline fibrous tissue was present in varying amounts in the lymphoid component.

Although lack of follicular structure and distortion of the lymphoid component by fibrous tissue caused anxiety, the chief cause of difficulty was a combination of degenerative and proliferative changes in the epithelial component. The following changes were seen: (a) Ducts had become dilated to form cysts (four cases) and the lining epithelium had become difficult to differentiate from the adjacent lymphoid tissue (Figs. 9 and 10). (b) Solid epithelial islands had become hydric (Fig. 11) with loss of the cytoplasmic details leaving relatively well preserved nuclei that resembled lymphocytes and made the islands almost indistinguishable from the lymphoid tissue in which they lay. Some degree of this change was present in seven of the cases. (c) Epithelial islands had become hyaline (five cases) and resembled the hyaline fibrous tissue commonly present in the lymphoid tissue (Figs. 12 and 13). (d) Ducts and epithelial islands had disintegrated leaving scattered epithelial cells (Figs. 14, 15, and 16) that resembled large reticulum cells.

Extravasated red cells were present in variable numbers among the lymphocytes in almost every case and haemorrhage had occurred into the ducts also in one case (Fig. 17). Granules of haemosiderin were present in three of the specimens. Combination of haemorrhage and epithelial disintegration caused a very disorderly picture in which epithelial cells with hyperchromatic or multiple nuclei were scattered in lymphoid tissue without follicles. Occasionally vacuoles of mucoid secretion could be demonstrated by mucicarmine or alcian blue within the epithelial cells but this was inconstant.

Although a capsule appeared to be present macroscopically, there was not usually any well-defined capsule microscopically; lymphocytic infiltration extended into the adjacent granular tissue and into adjacent fatty tissue. Commonly, in eight of the 11 cases, nerves were recognized microscopically in the lesion (Fig. 18); nerve fibres were absent from one of the specimens from the parotid and from the two lesions of the palate. A small focus of calcification was present in one of the parotid lesions. The abscess that developed in the submandibular lesion was suspected to have originated in a cyst but no epithelial lining remained when the tissue was examined. The lining was of granulation tissue that contained polymorphonuclear leucocytes, macrophages, and many plasma cells. This was the only lesion that contained plasma cells.
FIG. 2. Ducts lined by a double layer of epithelium in a parotid lesion. Haematoxylin and eosin × 315.

FIG. 3. Epithelial islands being formed from ducts. Haematoxylin and eosin × 150.

FIG. 4. Epithelial islands with technical fracture in the adjacent lymphoid tissue. Haematoxylin and eosin × 150.

FIG. 5. Epithelial islands with some elongated nuclei that may be in myoepithelial cells. Haematoxylin and eosin × 243.
FIG. 6. Epithelial island with a central area of cells resembling those of the background. Haematoxylin and eosin × 126.

FIG. 7. The basement membrane surrounding epithelial islands. Gordon and Sweet's reticulin stain × 126.

FIG. 8. Marked follicular structure in the lymphoid component of a lesion. Haematoxylin and eosin × 50.
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FIG. 9. Duct undergoing dilatation to form a cyst. Haematoxylin and eosin × 150.


FIG. 11. Hydropic change making the central cells of an epithelial island indistinguishable from those in the surrounding tissue. Haematoxylin and eosin × 315.

FIG. 13. Hyalinization of the periphery of an epithelial island. Haematoxylin and eosin × 315.

FIG. 14. Ducts disintegrating to leave scattered groups of epithelial cells. Haematoxylin and eosin × 126.
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FIG. 15. Small multinucleated cells, probably epithelial. Haematoxylin and eosin × 504.

FIG. 16. Dividing cell, believed to be epithelial, in background of irregular lymphoid tissue and extravasated red cells. Haematoxylin and eosin × 504.

FIG. 17. Haemorrhage into a duct and into the adjacent lymphoid tissue. Haematoxylin and eosin × 126.
ILLUSTRATIVE CASES

CASE 1 A boy of 16 had a painless swelling (2.5 x 1 cm.), that had been present for four to six weeks, excised from above the angle of the jaw on the right side. The original pathological diagnosis of heterotopic salivary tissue in a lymph node with follicular hyperplasia was later changed to the benign lymphoepithelial lesion. There was no recurrence and the patient was in good health 6 years later.

CASE 2 A woman of 52 had a tender, soft swelling, without ulceration, on the right side of the hard palate. She did not know how long it had been present and had noticed it only when it began to cause pain under her denture. Biopsy was carried out and, as epithelial structures were very scanty in the small specimen, the provisional pathological diagnosis was of lymphosarcoma. On consultation a few epi-myoepithelial islands were noticed and the diagnosis of benign lymphoepithelial lesion was made. Six weeks after the biopsy the lesion had not changed significantly and it was excised. Examination of the specimen, which was about 1 cm. in diameter, confirmed the pathological diagnosis. The lesion extended to the margins of the excision and, five months later, a nodule reappeared on the palate. This was successfully treated with a radium mould, there was no further recurrence, and the patient was in good health four years later.

CASE 3 A widow of 70 had noticed a slowly enlarging lump in the right side of her neck for four years. About two weeks before admission to hospital the swelling became painful and red and ruptured with the discharge of pus. In hospital, she had a swelling of the right submandibular gland, 5 cm. in diameter, with a small sinus in the overlying skin. Her general condition was poor: she was crippled with arthritis of 20 years' standing, she had lumbo-dorsal kyphosis, and she was anaemic (Hb 54%). She was treated with iron by mouth for two weeks before operation and was also given a transfusion of 3 pints of blood. The submandibular gland was then excised, sacrificing the lingual nerve, which was involved. The patient remained in poor health but the tumour did not recur. She died four years later of the combined effect of Parkinsonism, myxoedema, rheumatoid arthritis, and anaemia due to hiatus hernia. There was no necropsy.

DISCUSSION

The cases all have a pattern that has been built up from case reports during the past 30 years. There was, for example, the report by Sidahara (1937) of the surgical cure of a case of lymphosarcoma of the parotid. The photomicrographs of the specimen from this case contain the epi-myoepithelial islands of the benign lymphoepithelial lesion. Swinton and Warren (1938), in a study of salivary gland tumours, noted seven examples of the lesion, which they took to be Mikulicz's disease localized to a single gland. In 1940 Fein reported a case of 'lympho-epithelioma' of the parotid gland in a 28-year-old woman. The woman had had a long history of occasional parotid swellings and one swelling ruptured, with relief of pain and swelling. The case differs from any in this series in that the swellings were bilateral but the rupture and discharge are features that were present in the case of the submandibular lesion reported above. The photomicrographs in Fein's report show the appearances of the benign lymphoepithelial lesion and, according to Godwin (1952), the woman was well and free from recurrence 11 years later. Skorpil (1942) recognized the benign nature of the lesion in the parotid and described three cases in which it presented as a unilateral new growth. He described the microscopic appearances and included photomicrographs of the epithelial islands. In 1946 Lloyd reported seven cases of a solid variety of adenolymphoma (papillary cystadenoma lymphomatosum or Warthin's tumour). Six of these tumours were in the parotid region and were classified as benign; the seventh was in the left submandibular gland and was classified as a reticular (undifferentiated) reticulosarcoma. There was, however, no recurrence following surgical removal and the patient...
died of unrelated disease two years later. The illustrations leave little doubt that these cases, including the one regarded as malignant, were examples of the benign lymphoepithelial lesion.

In 1952 Godwin reported 11 cases of a lesion for which he suggested the name benign lymphoepithelial lesion. Lesions of this type had been reported in the past, he said, as lymphoepithelioma, lymphocytic tumour, chronic inflammation, Mikulicz's disease, and adenolymphoma; the names indicated the lack of agreement as to the nature of the process. The name suggested by Godwin has been used throughout the present communication; it is aetologically non-committal and includes the important word benign. Godwin's patients had the lesion in, or adjacent to, the parotid gland, were middle-aged, and mainly women. Their lesions were unilateral or bilateral. In some the parotids were affected successively and, in three cases there was dryness of the mouth and sore eyes. The swellings could be cured by excision or irradiation and, as had been noted by Lloyd (1946), recurrence following incomplete excision could be cured by irradiation.

The next year two papers on the subject were published: Bauer and Bauer (1953) described the histological appearances of six cases of the lesion under the title of 'lymphomatoid adenoma', and Morgan and Castleman (1953) described the same picture in a clinico-pathological study of 18 cases of 'Mikulicz's disease'. Bauer and Bauer believed the lesion to be a new growth, mainly because of its tendency to recur, but to be benign. Morgan and Castleman based their investigation on the observation that six patients diagnosed histologically as having malignant lymphoma of the salivary or lacrimal glands had survived without recurrence for nine to 16 years after surgery. They collected 12 other cases and concluded that the histological characteristic that distinguished the benign cases from cases in which malignant lymphoma of the salivary or lacrimal glands had been rapidly fatal was the formation, in the benign cases, of islands of epithelium that they believed to be mixtures of epithelium and myoepithelium (epi-myoepithelial islands). They went on to suggest that their cases of 'Mikulicz's disease' were, in fact, examples of Sjögren's syndrome (Sjögren, 1933). Comparison of the lesions in the present collection with the illustrations in papers on the pathology of Sjögren's syndrome (Sjögren, 1933; Ellman, Parks Weber, and Goodier, 1951; Morgan and Raven, 1952; Morgan and Castleman, 1953; Cardell and Gurling, 1954) and with material obtained at necropsy from a case of Sjögren's syndrome (case 1, of Cadman and Robertson, 1952) has confirmed the similarity of the salivary lesions. The present cases, however, with

FIG. 19. Epithelial island formed from a prostatic duct in an area of lymphocytic infiltration. Haematoxylin and eosin × 126.

FIG. 20. Epithelial island infiltrated by lymphocytes in an area of lymphoid tissue in an enlarged prostate. Haematoxylin and eosin × 105.
the exception of one case with rheumatoid arthritis, had none of the clinical features of Sjögren’s syndrome and the lesion was limited to a single gland or, in some cases, even to a single lobe of one salivary gland. Thus, despite the histological appearances of their lesion, there is no justification for identifying them as examples of Sjögren’s syndrome. There is even less justification for calling them cases of Mikulicz’s disease as there was no clinical resemblance to the massive enlargement of the lacrimal gland and of all the salivary glands, including the palatal salivary glands, that was so striking in the one case described by Mikulicz (1892). It is true that Mikulicz described a massive small cell infiltration of the interstitial tissue and that the one microscopic illustration contains what are probably epi-myoepithelial islands, but the definition of Mikulicz’s disease has been made so vague by papers published since Mikulicz’s death that the diagnosis is almost meaningless. Morgan and Castleman made a most useful contribution when they recognized the importance of the presence of epi-myoepithelial islands in differentiating between a simple lesion of a salivary gland and involvement of a salivary gland by a malignant lymphoid tumour, but they seem to have gone too far in asserting that all cases with lymphocytes and epi-myoepithelial cells in the salivary glands were examples of Sjögren’s syndrome. A histological appearance in a single organ is not a syndrome and the histological picture may not be quite as specific as they claim; for example, lymphocytic infiltration associated with epi-myoepithelial islands can be found occasionally in inflamed areas of hypertrophic prostate glands (Figs. 19 and 20). For cases similar to those that have been described above, with the lesion limited to a single salivary gland and without keratoconjunctivitis sicca, the name benign lymphoepithelial lesion seems preferable to either Sjögren’s syndrome or Mikulicz’s disease. There is no evidence that the solitary lesion may be followed in time by Sjögren’s syndrome (one of the patients had the benign lymphoepithelial lesion for 10 years without developing Sjögren’s syndrome), but there is a theoretical risk that the liberation of antigenic material from a solitary lesion might lead in time to widespread antiglandular autoimmune disease. Because of the theoretical risk the treatment of choice for the solitary lesion would seem to be surgical removal.

I am indebted to Drs. R. W. Evans, J. B. Lynch, E. Mavis McConnell, A. G. Rickards, C. A. St. Hill and Professor J. D. Kennedy for material. The photography is the work of Mr. A. C. Hemes, F.I.M.L.T., of the Department of Pathology, the University of Liverpool.

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