Malignant lymphoma of parotid associated with Mikulicz disease (benign lymphoepithelial lesion)

J. G. AZZOPARDI AND D. J. EVANS

From the Department of Morbid Anatomy, Royal Postgraduate Medical School, London

SYNOPSIS Benign lymphoepithelial lesion (Mikulicz disease) is generally regarded as an inflammatory disorder of unknown aetiology, characterized by epimyoeplithelial islands, and unrelated to malignant lymphoma. Five cases have been collected which show evidence at the same site of both Mikulicz disease and a malignant lymphoma. The latter took the form of reticulum-cell sarcoma or Hodgkin's disease. The two diseases were discovered simultaneously or the malignant lymphoma was detected at a subsequent date. The probable sequence of events is discussed. These cases are regarded as one of the best illustrations in man of an autoimmune disorder being followed by the development of malignant lymphoma. It is concluded that so-called benign lymphoepithelial lesion is not always innocuous and an attempt is made to establish histological criteria which might be regarded with suspicion in a particular case.

In the older literature a disorder causing enlargement of the salivary glands, in particular the parotids, was variously designated lymphomatoid adenoma (Bauer and Bauer, 1953), lymphoepithelioma (Fein, 1940), solid variant of adenolymphoma (Lloyd, 1946) by pathologists, and Mikulicz disease by both clinicians and pathologists. Godwin (1952) coined the term 'benign lymphoepithelial lesion' because of the doubt that existed about the precise nature of the condition and suggested that the name Mikulicz disease be dropped. Morgan and Castleman (1953) gave a detailed pathological account of this condition to which little has been added since, and they retained the eponymous designation of Mikulicz disease. These authors stressed the importance of an epithelial proliferation affecting salivary ducts that takes the form of epimyoeplithelial islands which were regarded as characteristic and diagnostic of the condition. Finding of epimyoeplithelial islands came to be regarded as diagnostic of a pathological entity which is benign and unrelated to malignant lymphoma.

Our purpose is to report on five patients who had evidence of Mikulicz disease (benign lymphoepithelial lesion) and a malignant lymphoma at the same site, either simultaneously or consecutively.

Source of Material

Two cases were found in an analysis of pathological material from patients indexed as Mikulicz disease

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at the London Hospital, one case was sent to us by Professor R. Goudie of the Royal Infirmary, Glasgow, one was a referral to Professor C. V. Harrison from Dr A. G. Marshall of Wolverhampton Royal Hospital, and one was a referral to Dr B. Castleman at the Massachusetts General Hospital, Boston, USA.

CASE 1 E.C. (GLASGOW VICTORIA INFIRMARY AND ROYAL INFIRMARY)

A woman aged 53 years developed painless swelling of the right parotid region and was seen at the Victoria Infirmary in 1961, at the age of 56. Unilateral parotid swelling was found, together with a discharge from the right ear. The swelling fluctuated spontaneously in size. A biopsy was reported as consistent with a diagnosis of Sjögren's syndrome. Two years later the left parotid gland also became enlarged. It was noted that she had had xerostomia for some years but the eyes were normally moist. There was no arthritis and no lacrimal gland swelling. A left parotid sialogram showed some dilatation of the common duct and saccular dilatation of its branches. In 1964 there was septic infection of both parotid glands, one of which required surgical drainage. Within a few months she had massive bilateral parotid enlargement with shotty nodes on the left side of the neck. Bilateral partial parotidectomies were performed. At operation there was thought to be infiltration of masseter and sternomastoid muscles. Enlarged cervical lymph nodes were considered to be neoplastic. However, histology

of both parotid glands was again reported as showing features of Sjögren's syndrome without evidence of malignancy. The serum albumin was 2.9 g/100 ml, globulin 2.7 g/100 ml, haemoglobin 11.6 g/100 ml, and white blood cell count 3,350/cmm. The left parotid swelling recurred within a month of operation. By April 1965 the left parotid was painful and swollen and there was pharyngeal ulceration centred around the left tonsil; an emergency tracheostomy was performed together with a biopsy of the parotid. Following a diagnosis of reticulum-cell sarcoma, the patient was treated with prednisolone and cyclophosphamide with temporary improvement. Two months later a nodule appeared under the angle of the left mandible and this was biopsied. The patient died shortly afterwards at the age of 60. Biopsies or excisions were carried out in 1961, 1964, April 1965, and June 1965. Necropsy was performed in 1965.

1961 Biopsy specimen

This shows histology typical of a benign lymphoepithelial lesion (Fig. 1).

1964 Excision specimen

In 1964 an excision specimen, 90 g of parotid tissue from the left side and 65 g from the right side, was received in the laboratory. Four blocks of tissue are available for study. They all show the general structural features of benign lymphoepithelial lesion, but with a few additional features. (1) There is a marked histiocytic infiltration throughout most of the lymphoid background (Fig. 2). (2) In one block there are a few foci of necrosis on the lymphohistiocytic background. These measure up to 2 mm in diameter and are not obviously related to epithelial tissue. (3) Perhaps the most sinister feature is the presence in one area of one block of a quite different cytology from the rest of the tissue (Fig. 3). Here epimyoeplithelial islands are absent and, instead of a lymphoid and histiocytic background, there is a mass of pleomorphic reticulum cells with prominent nucleoli and numerous mitoses. We regard this focus as probable malignant lymphoma.

April 1965 biopsy specimen

Four blocks of parotid and one block of lymph node are available for study. The parotid tissue shows a reticulum-cell sarcoma with sparse remnants of ductal epithelium, including epimyoeplithelial islands (Fig. 4). The node is replaced by reticulum-cell sarcoma.

June 1965 biopsy specimen

Two blocks of lymph nodes show replacement by reticulum-cell sarcoma.

Necropsy (Dr W. P. Duguid at Glasgow Royal

Infirmery) showed grossly enlarged lymph nodes (some of which were necrotic) extending from the angle of the jaw to the hilum of the lungs. The spleen (80 g), liver, and femoral bonemarrow showed no evidence of tumour.

CASE 2 P.W. (LONDON HOSPITAL)

A woman aged 52 years complained of a lump anterior to the left ear present for four years. A tense swelling of the parotid was found on examination. This was excised and, following a diagnosis of Hodgkin's disease, she was given a course of deep x-ray therapy. Four years later she developed a swelling under the left jaw. Enlarged lymph nodes were palpated in the posterior triangle and below the angle of the jaw. A further course of deep x-ray therapy was given. Two years later an enlarged node was again palpated in the neck but no treatment was given. After another three years the position appeared unchanged, haemoglobin was 14.8 g/100 ml, white blood cell and differential counts were normal, and the erythrocyte sedimentation rate (Westergen) was 36 mm in one hour. Three years later the spleen was palpable and a 'small dose' of x rays was given to the region. Her condition remained fairly static for about nine years. She underwent partial gastrectomy for a benign peptic ulcer and was found at this time to have atrial fibrillation. A biopsy of a cervical node was again diagnosed as Hodgkin's disease. Three years later bilaterally enlarged cervical nodes were present, larger on the left side than the right. A lump was again palpated at the angle of the left jaw. Enlarged axillary nodes were now present. The spleen was palpable two fingerbreadths below the costal margin and the liver four fingerbreadths below the costal margin. Five months later the cervical nodes had enlarged considerably in size and a biopsy at this time was reported as showing necrotic malignant tumour. She died 16 months later with clinical evidence of persistent malignant lymphoma. No necropsy was carried out.

Biopsies were carried out in 1936, 1959, and 1962.

The 1936 specimen consists of fragmented resected parotid tissue. The changes can be divided into two: changes in the salivary parenchyma and an infiltration by malignant lymphoma. The changes in the parenchymal tissue consist of acinar atrophy with persistent salivary ducts. The ducts are in parts virtually normal, in parts hyperplastic but with two cell layers and a central lumen still identifiable, while in other areas there are solid epimyoeplithelial islets with varying amounts of associated 'hyaline' material (Fig. 5). In addition there is a pleomorphic infiltration with Hodgkin tissue. Reed-Sternberg cells are plentiful. Numerous histiocytic foci are

Fig. 1.

Fig. 1 Case 1: benign lymphoepithelial lesion with characteristic epimyoepithelial islands, acinar atrophy, and lymphoid infiltrate. Haemalum and eosin (H and E) $\times 150$.

Fig. 2.

Fig. 2 Case 1: epimyoepithelial islands on a lymphohistiocytic background. H and E. $\times 150$.

Fig. 3.

Fig. 3 Case 1: focus of pleomorphic reticulum cells from same specimen as in Figure 2. H and E. $\times 330$.

Fig. 4.

Fig. 4 Case 1: appearance of frank reticulum-cell sarcoma in parotid tissue in 1965 specimen. H and E. $\times 525$.

Fig. 5 Case 2: epimyoepithelial island with hyaline material in centre. H and E. $\times 330$.

Fig. 6 Case 2: histiocytic aggregate forming a 'sarcoid' in the Hodgkin tissue. H and E. $\times 330$.

present and sometimes these are discrete enough to resemble miniature 'sarcoids' (Fig. 6). There is heavy infiltration with eosinophils, with a tendency for them to be aggregated in the histiocytic foci.

1959 biopsy

This is a lymph node with destruction of the architecture and replacement by Hodgkin tissue. Histiocytes are somewhat less conspicuous than previously while plasma cells are more numerous. Typical Reed-Sternberg cells are again present.

1962 biopsy

This shows a partially necrotic malignant lymphoma without evidence of preexisting nodal tissue. There is infiltration of fibrous tissue and muscle by the pleomorphic infiltrate.

Comment

The disease ran an indolent course, the patient dying 28 years after the diagnosis of Hodgkin's disease.

CASE 3 I.B. (LONDON HOSPITAL)

A woman aged 35 years at the time of the first surgical intervention had a swelling of the right side of the face for three days in 1945, at the age of 25. This subsided completely and spontaneously. The following year there was a recurrence of the swelling for a few days, with a discharge into the mouth from the right cheek. Two years later there was recurrent painful swelling in the same site which lasted four to five weeks. There was no further trouble until six years later when in 1954 a lump appeared in the parotid region. This persisted for five months. On examination there was diffuse swelling of the right parotid with a more definite nodular swelling, 2.5 cm diameter, at the angle of the jaw. A mass of tissue $3 \times 2.5 \times 2.5$ cm was excised from the parotid. Five years later she presented herself at Oldchurch Hospital, Romford, where she was referred to the radiotherapy department. A chest radiograph showed a right hilar mass. Enlarged bilateral cervical nodes were present and a large right axillary node.

A cervical node was biopsied. Following a diagnosis of reticulum-cell sarcoma, deep x-ray therapy was given to the chest and neck, but her general condition was too poor to complete the course. She died within a month of presenting herself at Oldchurch Hospital. No necropsy was carried out.

1955 Excision specimen

A mass of parotid parenchyma, $4 \times 3 \times 1.5$ cm, which on section consists of whitish, friable nodular areas up to 0.8 cm diameter. Sections show features typical of a benign lymphoepithelial lesion as described by Morgan and Castleman (1953) as well as certain unusual features. The typical features include lymphoid infiltration of salivary parenchyma that respects lobular boundaries, acinar atrophy, and epimyoeptithelial islands (Fig. 7). In other respects, however, the lesion was not typical and was picked out as unusual while studying a series of 10 unselected cases indexed as 'Mikulicz disease' from the London Hospital. The subsequent behaviour was not known at the time. It differs in three essential

respects: (1) it contains large numbers of immature cells of the lymphoid series in addition to mature lymphocytes (Fig. 8). These immature cells, constituting about 50% of the lymphoid cells, are arranged in anastomosing bands and clumps, often clearly related to the epithelial element. While this appearance is described and illustrated by Morgan and Castleman in 'Mikulicz disease', these authors do state that in 17 of their 18 cases mature lymphoid cells predominated. (2) There are focal areas, mainly in the bands of immature lymphoid cells, with large numbers of mitoses, up to five per high-power field. (3) Areas of necrosis are present in the lymphoid tissue, mainly in relation to epithelial zones. There is no evidence that this necrosis is related to inflammation in the ducts. This feature is not present in our other cases of benign lymphoepithelial lesion nor, to our knowledge, has it been noted by other workers. On these grounds, we regard this as at least an unusually active variant of benign lymphoepithelial lesion, with a suspicion that incipient neoplastic change may also be present.

Fig. 7 Case 3: running across the top of the photomicrograph is the edge of a large epimyoeptithelial island; this is set in a lymphoid background. H and E. $\times 330$.

Fig. 8 Case 3: low-power view showing broad bands of paler-staining immature cells between the usual mature lymphoid infiltrate. H and E. $\times 110$.

1960 Biopsy specimen

This consists of two cervical nodes. The architecture of these is completely destroyed and replaced by a reticulum-cell sarcoma with some histiocytic differentiation.

CASE 4 E.W. (ROYAL HOSPITAL, WOLVERHAMPTON)

A woman aged 60 years complained of a painless swelling in the left parotid region for eight years. A superficial parotidectomy was carried out. Investigations at this time were normal. The patient presented six years later with a three months' history of right-sided painless parotid swelling. Examination revealed a diffusely enlarged mobile right parotid gland without evidence of facial palsy. On exploration, the parotid gland appeared normal but pushed forwards by several enlarged lymph nodes at the lower and posterior margins. The nodes were biopsied and a diagnosis of Hodgkin's disease was made. The

haemoglobin was 11.7 g/100 ml but the rest of the blood count was normal. The chest radiograph was normal. Examination revealed a little firm swelling below the lobe of the left ear. One large, mobile, firm gland was palpated in the right axilla. There was no other lymphadenopathy and no splenomegaly. She was referred for deep x-ray therapy but failed to keep her appointment and was lost to follow-up for five-and-a-half years. In September 1967, her general practitioner was contacted and elicited the information that the patient still had swelling in the right parotid region. This was said to fluctuate in size from time to time and was described as the size of a 'small lemon'. A few months later she was admitted to another hospital with what was now 'an enormous swelling on the right side of her face and neck'. A biopsy was taken. She was seen at the radiotherapy department of the Royal Hospital where, apart from a huge soft swelling of the right parotid region, she was found to have discrete enlarged nodes in both

Fig. 9 Case 4: epimyoeptithelial islands set in a mature lymphoid background. H and E. $\times 140$.

Fig. 10 Case 4: higher magnification of an epithelial island from same specimen as in Figure 9. H and E. $\times 330$.

Fig. 11 Case 4: Hodgkin tissue in node that also contains epimyoeipithelial islands. *H* and *E*. $\times 330$.

cervical chains, more marked on the right than the left, and enlarged right axillary nodes. She was treated with deep x-ray therapy with remission of the swelling. She was admitted to yet another hospital on 1 February 1969 with a history of left lower chest pain, sweats, and fever. There was progressive dysphagia, some epigastric pain, and weight loss. Prominent nodes were present in the right inguinal and axillary regions but there was no obvious recurrence in the parotid area. There was a central tender epigastric mass and an enlarged spleen. Chest radiographs showed enlarged mediastinal nodes and clear lung fields. Barium swallow showed a deformity in the gastric fundus. It was considered likely that she now had extensive malignant lymphoma. She was finally admitted to the Royal Hospital on 12 February 1969 for chemotherapy for Hodgkin's disease but she died on 15 February. Unfortunately, no necropsy was carried out.

Excisions or biopsies were carried out in 1955, 1962, and 1968.

Excision specimen from left parotid in 1955

Parotid tissue consisted of soft enlarged lobules. The general architectural features are characteristic of benign lymphoepithelial lesion, with preservation of lobular outlines, parenchymal atrophy, conversion of ducts to epimyoeipithelial islands, and a massive infiltration with lymphoid cells that are predominantly mature (Figs. 9 and 10). More detailed examination, however, reveals a few unusual features. (1) Eosinophil polymorphonuclear cells, rare in our control series of benign lymphoepithelial lesion, are sprinkled through the tissue in large numbers. (2) Plasma cells, uncommon in this condition, except at the 'advancing edge' of the lesion, are easily found. (3) Abnormal reticulum cells are present. These are sometimes sparse (1/HPF), sometimes concentrated with as many as 20/HPF. They have a copious cytoplasm, a large usually ovoid or reniform nucleus, and between one and three nucleoli. The most disturbing reticulum cells have a single large, eosinophilic nucleolus and a folded nucleus. Very occasional cells of this type with mirror-image nuclei are present.

1962 Biopsy

Three right juxta-parotid lymph nodes show destruction of architecture and replacement by Hodgkin tissue (Fig. 11). Mitoses are numerous. Of the three nodes, two have salivary duct inclusions. These have been converted to epimyoeipithelial islands. The islands are sometimes apparently distorted into linear streaks as if by tumour compression. No parotid gland proper is included in the sections but the point to be stressed is the existence side by side of epimyoeipithelial islands and of malignant lymphoma.

1968 Biopsy

A lymphoid mass is divided by broad fibrous trabeculae. The lymphoid mass consists of Hodgkin tissue which, compared with the previous biopsy, shows lymphocytic depletion. There is some histiocytic proliferation but eosinophils and plasma cells are scanty.

Comment

The illness spanned a period of 22 years. Hodgkin's disease was known to be present for 14 years.

CASE 5

This is a brief note on a case included by courtesy of Dr B. Castleman.

A woman aged 69 years complained of an asymptomatic mass in the parotid gland. Hepatosplenomegaly was found on examination. Malignant lymphoma was suspected clinically. Bone marrow

aspiration showed 'slight lymphocytosis' which was not considered diagnostic. The parotid mass was resected. Subsequently she was found to have a positive rheumatoid factor and a serum albumin-globulin ratio of 1:1 with elevation of the β -globulin fraction. The patient had no arthritis and no clinical evidence of the sicca syndrome. Nine weeks after the first surgical operation, she was readmitted for excision of ipsilateral enlarged cervical nodes.

Excisions were performed in August 1969 and November 1969. Two slides of the original material were sent to Dr Castleman for consultation: these were considered to be representative of the total material blocked. The general pattern of the parotid tissue in these slides is characteristic of benign lymphoepithelial lesion. However, on closer inspection, two features deserve further comment: (1) bands of immature lymphoid cells cuff some of the epithelial islands, though they constitute a much smaller proportion of the total infiltrate than in case 3; reticulum cells and some histiocytes are also scattered randomly through the infiltrate especially in one of the two slides. (2) There are two foci, the larger 4 mm in maximum diameter, in which epimyoeplithelial islands are absent and in which the infiltrate consists mainly of reticulum cells, as seen in the 1964 specimen of case 1. The second specimen consisted of seven lymph nodes between 1 and 2 cm diameter. A section of one of these was sent to Dr B. Castleman who diagnosed Hodgkin's disease. Professor C. V. Harrison also made a diagnosis of Hodgkin's disease, of the diffuse lymphocytic and histiocytic variety, though with capsular invasion. Both thought that, in retrospect, Hodgkin tissue was probably present in the first specimen also.

Discussion

Because of the confusion over nomenclature, we have been obliged sometimes to use the term 'Mikulicz disease'. It is used here in the sense of the pathological process that also goes by the name of benign lymphoepithelial lesion. We are not describing a clinical syndrome. It is worth pointing out that none of our five cases had rheumatoid arthritis and therefore none falls into the clinical category of Sjögren's syndrome. Our pathological findings, in cases of Mikulicz disease, are essentially similar to those of Morgan and Castleman (1953), but we would stress especially the dominance of mature lymphoid elements. Bands of immature lymphoid cells, related especially to epithelial elements, are a very prominent feature of our case 3. They are described as a feature of Mikulicz disease by Castleman, but on present evidence we reserve judgment about the significance of this finding.

The distinctive feature of these five patients is that they all had histological evidence of benign lymphoepithelial lesion, and that they also had evidence, simultaneously or at a later date, of malignant lymphoma in the same anatomical site. Since the malignant lymphoma started at the same site as the other very rare disease in all five cases, the relationship is clearly not fortuitous. Nor can the malignant lymphoma be attributed to radiotherapy or other treatment, since both diseases were either present from the start or else diagnosed before any radiation therapy was given.

The precise relationship of the two diseases is complex and may not be uniform in all cases. Malignant lymphoma may have led to the development of epimyoeplithelial islands in patients in whom the two pathological processes were discovered simultaneously. This applies particularly to the cases of Hodgkin's disease, in which lymphocytes are considered to be reactive rather than neoplastic. Though impossible to exclude, we regard this as less likely than the alternatives. The second possibility is that Mikulicz disease may progress into a malignant lymphoma or, thirdly, both diseases may be expressions of the same underlying host defect. This defect might consist of mutant cells giving rise to an autoimmune process on the one hand and to malignant disease of lymphoid tissue on the other. The concept of a relationship between autoimmune disease and malignant lymphoma is not a new one. Some workers believe that Hashimoto's disease of the thyroid is complicated occasionally by malignant lymphoma of this organ (Cox, 1964). Idiopathic steatorrhoea may be complicated by the development of malignant lymphoma in the jejunum, though the relationship in this case is more complex, involving ingestion of a foreign protein in the pathogenesis of the initial disorder. Interestingly enough, reticulum cell sarcoma and Hodgkin's disease are also the two types of malignant lymphoma that develop in patients with idiopathic steatorrhoea. A related but complex situation may be found also in the development of malignant lymphoma following the administration of antilymphocytic sera in patients with renal transplants (Doll and Kinlen, 1970). In mice autoimmune haemolytic anaemia precedes the development of certain malignant lymphomas (Mellors, 1966). In this paper we have put forward what we regard as strong evidence of a relationship between benign lymphoepithelial lesion and malignant lymphoma. That Mikulicz disease is an autoimmune disorder is strongly supported by clinical studies, morphological patterns, and the serological evidence (*British Medical Journal*, 1967). We believe that the patients reported on here represent one of the most convincing instances of a relationship between autoimmune

disease and the subsequent development of malignant lymphoma in man.

Talal and Bunim (1964) and Talal, Sokoloff, and Barth (1967) described the development of reticulum cell sarcoma in distant sites in five patients with Sjögren's syndrome. In none of these cases was there any involvement of the salivary glands by malignant lymphoma, though this may be inherent in their method of selection. These authors described other extrasalivary lymphoid abnormalities in their patients: these include primary macroglobulinaemia and a peculiar disorder which they regarded provisionally as a pseudolymphoma. In view of the fact that one of the latter patients had reticulosarcoma at necropsy, we have reservations about this concept of a pseudolymphoma.

Our main purpose here is to draw attention to the fact that epimyoepithelial islands are not necessarily indicative of a benign pathological process. Certainly they are usually diagnostic of specific benign disease processes that affect the salivary and certain other glands. However, the pathological picture of benign lymphoepithelial lesion does not exclude a malignant lymphoma developing simultaneously or subsequently in the same anatomical region. Doubtless, the majority of cases remain benign throughout their course but equally malignant lymphoma must be recognized as a complication of some cases. Since our cases are derived from several sources it is impossible to estimate the incidence of this complication. This can only be determined from the study of a large series with a prolonged follow up. While we cannot yet draw conclusions about the relationship between our cases and the type of patient reported on by Talal *et al*, we suspect that they may represent different aspects of a spectrum.

It would clearly be valuable if one could distinguish cases of benign lymphoepithelial lesion that were completely innocent from those with a malignant potential. In one of our cases (case 2) the diagnosis of Hodgkin's disease was fairly obvious pathologically from the start. Interest centres chiefly on the other four cases. In one case (case 1) there was nothing to distinguish the original specimen from a typical benign lymphoepithelial lesion. In the other three cases, however, there were certain debatable features that might have had a bearing on the subsequent course. These include tracts of immature lymphoid cells, unexplained foci of necrosis, and a diffuse or focal histiocytic reaction on the general

lymphoid background. In one case eosinophil and plasma cell infiltration, together with scattered abnormal reticulum cells, were the first indicators of complicating Hodgkin's disease. In another case, paucity or absence of epimyoepithelial islands over relatively large tracts of tissue (with their presence elsewhere) was one of the features arousing suspicion. At present we can only conclude that the finding of these features in a case of benign lymphoepithelial lesion may indicate a greater likelihood of the development of malignant lymphoma. On the basis of our case 1, however, we think that probably all cases of benign lymphoepithelial lesion have a degree of malignant potential though the degree of risk has still to be determined.

We wish to thank Professor I. Doniach for allowing access to the London Hospital material and Professor R. Goudie and Dr A. G. Marshall for supplying clinicopathological data from cases 1 and 4. We are indebted to Dr B. Castleman for allowing us to include case 5 and for his opinion on this case. We are grateful to Professor C. V. Harrison for his criticism of the manuscript. Our thanks are due also to the technical staff of the department of morbid anatomy and to Miss Anne Walker for secretarial help.

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