Clinicopathological study of myoepithelial sialadenitis and chronic sialadenitis (sialolithiasis)

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SUMMARY To determine any overlap in pathological features between myoepithelial sialadenitis and chronic sialadenitis/sialolithiasis histological sections from 69 cases of myoepithelial sialadenitis (MESA) (n = 7) and chronic sialadenitis/sialolithiasis (n = 62) were reviewed over a 10 year period. Three of the cases with MESA contained calculi and four of those originally diagnosed as chronic sialadenitis/sialolithiasis showed epimyoepithelial island formation. The presence of calculi should not rule out a diagnosis of MESA, particularly in the parotid gland where calculi are uncommon; as the incidence of MESA may very well be underestimated and diagnosed as chronic sialadenitis, these patients, who are at increased risk of developing lymphoma, could be lost to follow up.

Myoepithelial sialadenitis (MESA) is characterised by the formation of epimyoepithelial islands accompanied by chronic lymphocytic infiltration of the salivary parenchyma and often glandular atrophy. It has largely superceded the earlier used term, benign lymphoepithelial lesion, which was coined by Godwin in 1952.13

Although the histological picture of well established MESA is usually so characteristic that there is little difficulty distinguishing it from other types of sialadenitis, we recently saw a case of MESA in which the excised parotid gland tissue contained several calcified laminated calculi situated within dilated ducts. This feature, which initially prompted some diagnostic confusion, led us to review all the cases of MESA and chronic sialadenitis/sialolithiasis from our files seen over the past 10 years. The aim of this study was to determine the incidence of calculi in cases diagnosed as MESA and the incidence of epimyoepithelial islands in otherwise typical chronic sialadenitis. We were particularly interested in cases which may represent the development of MESA in pre-existing chronic sialadenitis and the possibility of any overlap between these two types of disease.

Material and methods

Cases diagnosed as chronic sialadenitis, sialolithiasis, MESA, Sjögren’s syndrome, or lymphoma were obtained from the files of the department of pathology, University of Birmingham and the department of histopathology, General Hospital, Birmingham. Sections stained with haematoxylin and eosin were reviewed and the presence or absence of epimyoepithelial islands, ductal infiltration by lymphoid cells, and calcified material noted. Other features assessed were the prominence of lobular lymphoid infiltration, presence or absence of germinal centres, intra-acinar and ductal acute inflammatory cells, lobular and periductal fibrosis and atrophy, and epithelioid granuloma formation. Interval sections were cut in those cases showing epimyoepithelial island formation. The case notes of patients diagnosed as having MESA or chronic sialadenitis/sialolithiasis, in which epimyoepithelial islands were found were reviewed (table).

Results

Histological sections from a total of 73 salivary glands (56 submandibular, 17 parotid) were reviewed. Two submandibular glands and six parotid glands had been reported as MESA or Sjögren’s syndrome. This included one patient with two excisions over a period of several years. Chronic sialadenitis/sialolithiasis had been diagnosed in 54 submandibular glands and eight parotid glands; calculi were noted macroscopically, or microscopically, or a definite clinical history of sialolithiasis had been elicited in 29 (53%) of submandibular glands and three (38%) of parotid glands. Of the remaining three salivary glands, one was clearly a
Table  Clinical details of cases of MESA and chronic sialadenitis/sialolithiasis

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Salivary gland(s)</th>
<th>Duration of gland symptoms (months)</th>
<th>Calculi</th>
<th>Associated diseases</th>
<th>Serology and other relevant investigations</th>
<th>Clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>F</td>
<td>Parotid</td>
<td>12</td>
<td>Absent</td>
<td>Rheumatoid arthritis, Mixed collagen disease, autoimmune thrombocyto paenia</td>
<td>RhF positive, ANF positive</td>
<td>Sjögren's syndrome</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>F</td>
<td>Parotid</td>
<td>5</td>
<td>Present</td>
<td></td>
<td>RhF positive, ANF positive</td>
<td>Sjögren's syndrome</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>F</td>
<td>Parotid</td>
<td>12</td>
<td>Absent</td>
<td>Rheumatoid arthritis, Hashimoto's thyroiditis</td>
<td>Schirmer's test positive, ANF positive</td>
<td>Sicca syndrome</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>F</td>
<td>Submandibular</td>
<td>12</td>
<td>Absent</td>
<td>Rheumatoid arthritis, Sjögren's syndrome</td>
<td>Schirmer's test positive, ANF positive</td>
<td>Sjögren's syndrome</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>F</td>
<td>Submandibular</td>
<td>6</td>
<td>Absent</td>
<td>Rheumatoid arthritis</td>
<td>RhF positive, Schirmer's test positive</td>
<td>Sicca syndrome</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>F</td>
<td>Both parotids</td>
<td>12</td>
<td>Present</td>
<td>Rheumatoid arthritis</td>
<td>ANF positive, Polyclonal hypergamma-globulinaemia</td>
<td>Sjögren's syndrome</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>F</td>
<td>Parotid</td>
<td>60</td>
<td>Present</td>
<td>Rheumatoid arthritis</td>
<td>RhF positive</td>
<td>Sicca syndrome</td>
</tr>
<tr>
<td>8</td>
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<td>F</td>
<td>Parotid</td>
<td>180</td>
<td>Present</td>
<td></td>
<td></td>
<td>Sialolithiasis</td>
</tr>
<tr>
<td>9</td>
<td>77</td>
<td>F</td>
<td>Submandibular</td>
<td>36</td>
<td>Present</td>
<td></td>
<td></td>
<td>Sialolithiasis</td>
</tr>
<tr>
<td>10</td>
<td>57</td>
<td>F</td>
<td>Parotid</td>
<td>6</td>
<td>Present</td>
<td></td>
<td></td>
<td>Sialolithiasis</td>
</tr>
<tr>
<td>11</td>
<td>36</td>
<td>M</td>
<td>Submandibular</td>
<td>240</td>
<td>Present</td>
<td></td>
<td></td>
<td>Sialolithiasis</td>
</tr>
</tbody>
</table>

Fig 1  Typical epimyoeplithelial island in established MESA. Many infiltrating lymphoid cells have a centrocyte-like morphology at higher magnification (case 5).

Fig 2  Fragmented calculus within remains of intralobular duct (case 2).
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Fig 3  Dilated duct densely infiltrated by lymphoid cells and containing calcified material (case 6).

granulomatous sialadenitis, probably sarcoidosis, and in the two others there was a history of trauma or local tumour resection.

The mean age of patients with MESA was 59 years (range 43–68 years); all were women (table). Epimyoepithelial islands were found in all eight cases (fig 1). In addition, calculi were present in three (38%) cases, one of which was noted macroscopically on slicing glandular tissue as a 0.2 cm stone (case 7). In the other two cases calcified material was noted within dilated ducts on histological examination (fig 2). Apart from epimyoepithelial islands, an important histological feature was the presence of dilated ducts infiltrated by lymphoid cells. This was seen in six of the eight cases (75%) and was pronounced in three of these. In those cases containing calcified material this was characteristically within dilated ducts of this type (fig 3). A dense chronic lymphoid infiltrate was also present around ducts and within lobules, but in most cases occasional lobules were largely spared or completely devoid of infiltration. Germinal centre formation varied from abundant to absent, but was present in most cases (75%). No cases of salivary lymphoma had been seen over the 10 year period.

The mean age of patients in the chronic sialadenitis/sialolithiasis group was 44.6 years (range 13–77) for the submandibular cases, and 57.8 years (48–65) for the parotid cases. Male to female ratios were about 1:1 and 2:3, respectively. A review of these cases showed that epimyoepithelial islands were found in two (4%) of the submandibular glands and in two (25%) of the parotid glands. Calculi were identified either macroscopically or microscopically in all four cases (table).

Epimyoepithelial islands were small and sparse in these four cases but more typical examples were usually identified by interval sections through the tissue blocks (figs 4–6). A lymphoid infiltrate in the epithelium of dilated ducts as seen in MESA was present in both parotid tissue samples but not in submandibular tissue; otherwise, lymphoid infiltration of ductal epithelium was conspicuously absent in the cases of chronic sialadenitis/sialolithiasis.

Occasional intraductal lymphoid cells were also present as part of a granulomatous infiltrate in two of the four cases of chronic sialadenitis in which sparse epithelioid granulomas were noted. Acute inflammatory cells within ducts or acini were rare in the presence of epimyoepithelial islands, but particularly common in those cases of chronic sialadenitis with definite calculi (41%). A prominent lobular lymphoid infiltrate was present in seven of 54 (13%) submandibular glands, previously reported as being chronic sialadenitis/sialolithiasis, but this was usually less prominent than in the cases of MESA.
In the parotid gland specimens this feature was prominent only in those cases containing epimyoepithelial islands. Germinal centre formation was present in 42% of cases of chronic sialadenitis and was occasionally of a degree comparable with that seen in typical MESA. Focal fibrosis, both lobular and periductal, was common in cases of chronic sialadenitis/sialolithiasis and often present in those with MESA.

Discussion

Although the eye catching feature of epimyoepithelial island formation makes the histological diagnosis of MESA quite straightforward, it is a histopathological term without a precise clinical counterpart. The clinical setting in which MESA occurs is variable and the terminology confusing. Many cases occur in the context of Sjögren’s syndrome, a triad of keratoconjunctivitis sicca, xerostomia, and an underlying disease of connective tissue—most often rheumatoid arthritis. An incomplete, primary (or limited) form of Sjögren’s syndrome without an accompanying autoimmune disease is also recognised and commonly referred to as the sicca syndrome. This can also be part of a “sicca systemic syndrome” in which several other exocrine gland systems are affected and extraglandular manifestations can occur. The exact relation between this primary form and the classic secondary form is not fully resolved, but is considered to be a distinct clinical entity and more common than the latter.

The clinical manifestations of dry eyes and dry mouth are secondary to the degree of inflammatory changes occurring in glandular tissue and may be difficult to show in mild or early disease. Some workers suggest that xerostomia should be substituted by the more objective criterion of focal sialadenitis in a minor salivary gland biopsy specimen. In practice, many cases present as salivary gland swelling in a patient with confirmed connective tissue disease. In our series four of the cases diagnosed as MESA occurred in association with rheumatoid arthritis and one with mixed collagen disease; these cases thus fell into the classic secondary category of Sjögren’s syndrome. The other two could be regarded as examples of the primary form.

Although there was definite evidence of calculi in apparently half of the cases of chronic sialadenitis/sialolithiasis, this was probably a considerable underestimate as many stones are passed spontaneously or are not received by the pathologist. A recent study suggests that at least 82% of cases of chronic sialadenitis are related to calculi. The four patients with an original diagnosis of sialadenitis/sialolithiasis,
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Another epimyoepithelial island in a similar case (case 10).

Fig 5

in whom epimyoepithelial islands were found on review, had no pointers towards any underlying connective tissue disease (although serology had not been carried out) and all four had documented calculi.

Although our series is small, it suggests that calculus formation is not uncommon in otherwise typical MESA (three of eight cases). All the calculi identified were small and multiple, and in only one case was calcification noted macroscopically, necessitating decalcification of tissue. Thorough sampling of tissue in other cases would probably have shown more examples of microscopic calcification. Generally, calculi of the parotid gland are said to be rare. The reasons for this probably include the downward slope followed by Stensen’s duct and the relatively low viscosity of parotid secretions. This paucity of parotid calculus formation is reflected in our series: after cases diagnosed as MESA are subtracted only seven parotid glands remain showing features of chronic sialadenitis/sialolithiasis. Two of these on review contained scarce epimyoepithelial islands and large dilated ducts infiltrated by lymphoid cells. In view of this a careful search for features of MESA seems indicated in the presence of calculi at this site.

Dilated ducts showing variable degrees of lymphoid infiltration have often been noted in cases of MESA and account for the sialoectasia often seen radiologically (fig 7). Almost all our cases of MESA contained ductal lesions of the type and it is more likely that the calculi noted in our cases were the result of calcification of inspissated secretions in such abnormal ducts rather than MESA developing on a background of pre-existing sialolithiasis. Ductal lymphoid cell infiltrates, other than the very occasional intraepithelial cell, were not seen in any of the cases initially diagnosed as chronic sialadenitis/sialolithiasis, with the exception of two of the cases in which epimyoepithelial islands were also found and two cases in which small numbers of lymphoid cells were present as part of a granulomatous infiltrate. Gran-
ulomas have recently been described as an occasional feature of chronic sialolithiasis and are thought to be the result of duct rupture.9

It is difficult to categorise precisely the four cases in which epimyoepithelial islands were found in a clinical context of sialolithiasis. Two of these occurred in the parotid glands of women aged 57 and 65 years. One had multiple small stones present in Stensen’s duct and intraglandular ducts, the other a larger calculus in Stensen’s duct. Infiltrated dilated ducts as well as sparse epimyoepithelial islands were present. These cases most probably represent mild or early examples of MESA and would best fit into the clinical category of primary Sjögren’s syndrome in which the dominant clinical picture of sialolithiasis may have been coincidental or the result of calcification of inspissated secretions in dilated ducts. These women may develop full blown Sjögren’s syndrome. Epimyoepithelial islands without dilated duct lesions were noted in the submandibular glands of two other patients, one, a woman of 77 years, had a radiologically confirmed stone in Stensen’s duct. Interestingly, she also had clinical enlargement of her other submandibular gland and both parotid glands, again suggesting the possibility of more widespread salivary disease. The only male patient in the group (aged 36 years) had undoubted well formed epimyoepithelial islands surrounded by a dense lymphoid infiltrate within a gland which showed atrophy of occasional lobules but was otherwise unremarkable (fig 8). This case is closest to representing an example of the very rare occurrence of epimyoepithelial islands in otherwise straightforward sialolithiasis.3.10

Epimyoepithelial islands occurred in our series with one exception—in middle aged and elderly women, a group particularly prone to autoimmune disease. It is interesting to speculate that even in the absence of clinically overt MESA those lesions found incidentally in salivary glands in the clinical context of sialolithiasis are likely to represent an “autoimmune phenomenon” and their relation to full blown Sjögren’s syndrome may parallel that of focal lymphocytic thyroiditis to Hashimoto’s thyroiditis. In both these entities characteristic glandular epithelial changes occur to a lesser or greater extent and are associated with other organ specific autoimmune diseases.11

Our study shows that the presence of calculi should certainly not rule out a diagnosis of MESA, particularly in the parotid gland, where calculi are generally uncommon, a careful search should be made for epimyoepithelial islands and ducts infiltrated by lymphoid cells. Multiple sections may be helpful in this respect as these lesions may be very sparse. The overall
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incidence of MESA is probably underestimated as some cases are probably labelled as chronic sialadenitis. Such patients would be lost to follow up and may be at a slightly increased risk of developing a lymphoma.2

We are grateful to Mr M A Atkins for technical assistance, Mr A A Cooper for help with the photographs, and Mrs I F Pring for typing the manuscript.

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*J Clin Pathol* 1988 41: 403-409
doi: 10.1136/jcp.41.4.403

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