Metaplastic (infarcted) Warthin’s tumour of the parotid gland: a possible consequence of fine needle aspiration biopsy

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Aims: The metaplastic (or infarcted) variant of Warthin’s tumour is characterized by replacement of much of the original oncocytic epithelium by metaplastic squamous cells, along with areas of extensive necrosis, fibrosis and inflammatory change. The pathogenesis is unknown, but it is most likely to be vascular in origin. An association with a previous fine needle aspiration (FNA) has been suggested, and this is explored further.
Methods and results: Nine metaplastic Warthin’s tumours were collected from several centres: all arose in the parotid gland, and all showed the characteristic histological features. Eight had previously undergone FNA some 1–4 months before surgery; the other case had had an incisional biopsy.

Conclusions: It is important to recognize metaplastic Warthin’s tumour, because the differential diagnoses of this benign neoplasm include mucoepidermoid and squamous carcinoma, both primary and metastatic. The tumours in this study followed FNA or biopsy, and we believe this association is unlikely to be coincidental. Although many metaplastic Warthin’s tumours clearly arise spontaneously, we conclude that the balance of probabilities favours the view that FNA is capable of causing metaplastic change in a Warthin’s tumour, and may have done so in these cases. If so, this previously unusual subtype will become increasingly common, as FNA becomes more widely used (and its value appreciated) in the investigation of patients with a mass in the neck.

Keywords: biopsy, metaplasia, salivary gland, Warthin’s tumour

Introduction

Warthin’s tumour (adenolymphoma) is the second commonest neoplasm of the parotid gland, and is the easiest salivary tumour to recognize by microscopy.1 One of the few diagnostic pitfalls is the rare subtype variously termed infarcted, infected or metaplastic. It accounted for 6.2% (20/323) of Warthin’s tumours in one series1 and 7.5% (21/275) in another.2 The histopathological definition is a Warthin’s tumour in which much of the original oncocytic epithelium has been replaced by squamous cells, and it thus resembles a ruptured epidermoid or lymphoepithelial cyst.3 Other microscopic features include extensive necrosis, fibrosis and inflammatory change, including granuloma formation.4 It should be noted that this definition does not encompass minor microscopic foci of inflammation, necrosis and fibrosis, as these findings can be seen not infrequently in any Warthin’s tumour.1

The pathogenesis remains uncertain, but it has been suggested that some cases are a consequence of fine needle aspiration (FNA).4–6 If so, this is important as the increasing use of this technique may well lead to a greater frequency of metaplastic Warthin’s tumours in routine diagnostic histopathological practice. The present study consists of a further nine cases of this
lesion, all but one of which had previously undergone FNA, and we try to explore the relationship, if any.

Materials and methods

The surgical pathology archives and consultation practice of the Istituto Nazionale Tumori, Milan, the Departments of Pathology of the Royal Devon and Exeter Hospital, and Charles University in Pilsen contained nine neoplasms with the histopathological features of metaplastic Warthin’s tumour. Paraffin-embedded blocks were available from all cases. Sections were prepared in the conventional manner and stained with haematoxylin and eosin and by other methods including Perls’ Prussian blue. For immunohistochemistry, the following primary antibodies were employed: cytokeratins (AE1-AE3; Boehringer Mannheim, Germany, dilution 1 : 500, and CAM5.2; Becton-Dickinson, San Jose, CA, 1 : 50), S100 protein (polyclonal; DAKO, Glostrup, Denmark, 1 : 1000), muscle actin (HHF35, DAKO, 1 : 400), smooth muscle actin (1 A4; DAKO, 1 : 1000). The bound antibodies were visualized using the supersensitive streptavidin–biotin–peroxidase complex (Biogenex, San Ramon, CA) and 3,3′-diaminobenzidine (Sigma, St. Louis, MO) as chromogen.

Results

Clinical findings

These are summarized in Table 1. The sex incidence of our cases showed a male predominance (seven male, two female), and the mean age was 64 years (range 48–76). All the patients presented with parotid swellings and eight underwent diagnostic preoperative FNA at time intervals ranging from 6 to 101 days before surgical excision. No history of wound infection or any trauma was obtained. In case 5, the patient did not have an FNA but there was an incisional biopsy of the parotid gland performed 18 days before parotidectomy.

Table 1. Clinical findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age (years)</th>
<th>History</th>
<th>FNA</th>
<th>Needle</th>
<th>FNA findings</th>
<th>Pre-operative time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/57</td>
<td>Parotid mass, 50 mm diameter; 2 months</td>
<td>Yes</td>
<td>18, 22</td>
<td>Possible Warthin</td>
<td>41, 27</td>
</tr>
<tr>
<td>2</td>
<td>M/48</td>
<td>Firm parotid nodule 20 × 30 mm; 2 months</td>
<td>Yes</td>
<td>22</td>
<td>Warthin</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>M/66</td>
<td>Left parotid mass, 30 × 25 × 15 mm; (duration unknown)</td>
<td>Yes</td>
<td>22</td>
<td>Warthin</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>M/76</td>
<td>Right parotid nodule, 20 mm diameter; 2 months</td>
<td>Yes</td>
<td>Not known</td>
<td>Non diagnostic</td>
<td>97, 9</td>
</tr>
<tr>
<td>5</td>
<td>M/71</td>
<td>Right parotid swelling; 25 × 15 × 15 mm; 2 months</td>
<td>No</td>
<td>*</td>
<td>*</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>F/67</td>
<td>Parotid mass, 17 mm; (duration unknown)</td>
<td>Yes</td>
<td>22</td>
<td>Warthin</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>F/55</td>
<td>Left parotid mass, 16 mm; (duration unknown)</td>
<td>Yes, x2</td>
<td>22</td>
<td>Nondiagnostic</td>
<td>101, 87</td>
</tr>
<tr>
<td>8</td>
<td>M/66</td>
<td>Right parotid mass, 18 mm; 2 months</td>
<td>Yes</td>
<td>22</td>
<td>Nondiagnostic</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>M/76</td>
<td>Left parotid mass, 16 mm; 2 years</td>
<td>Yes</td>
<td>22</td>
<td>Probable Warthin</td>
<td>46</td>
</tr>
</tbody>
</table>

*Incisional biopsy; no tissue or information available.
CYTOPATHOLOGICAL FINDINGS

Not all the aspirates from consultation cases were available for review, and the findings in Table 1 include those reported by the referring pathologists. There were two aspirates in case 1: the first displayed only occasional lymphocytes and oncocytic cells with no evidence of inflammation (Figure 1a), while the second revealed numerous leukocytes, nuclear debris and a few oncocyttes with regressive changes (Figure 1b). In cases 2, 3, 6 and 9 the cytology was reported as Warthin’s tumour, and in cases 4, 7 and 8 as not diagnostic. No tissue or information were available from the incisional biopsy in case 5. In none of the aspirates available for review were squamous cells or macrophages seen (except for the repeat in case 1).

HISTOPATHOLOGICAL FINDINGS

The microscopic findings are summarized in Table 2. The most obvious feature was extensive necrosis of the centre of the lesions; in all cases the area involved exceeded 50%, and in cases 1, 3, 4, 5 and 9 it was almost total (Figure 2). The extent of the necrosis was not related to tumour size. Within the necrotic areas a ghost architecture of papillary structures suggestive of Warthin’s tumour could be seen (Figure 3); this was highlighted with Gomori’s reticulin stain. At the periphery, small areas with a residual lymphoid stroma were recognizable (Figure 4). In all cases there was dense hypocellular fibrosis as well as areas of myofibroblast spindle cell proliferation. Non-keratinizing squamous cell metaplasia was a prominent feature in every case: this consisted of tongues, cords and sheets of often spongiotic squamous cells extending into the fibrous tissue in a pseudoinfiltrative growth pattern. Cytological atypia was prominent in places (Figure 5), but mitotic figures were sparse and none was abnormal. Thus, the overall appearance resembled immature squamous metaplasia at other sites. In all tumours there were sheets of macrophages, some with foamy cytoplasm: lipogranulomas were noted in three cases. Neutrophils were a feature in every lesion and were intermingled with other inflammatory cells, but no abscess formation was observed. Other findings included haemosiderin deposition, and in some cases cholesterol granulomas. In three cases, there was an additional granulomatous reaction in the stroma consisting of epithelioid cells, in one case forming abundant noncaseating sarcoïd-like granulomas associated with Langhans-type multinucleated giant cells. Scanty mucous cell metaplasia was not infrequent and occasionally, goblet cells were associated with squamous epithelium (Figure 6). The appearance thus mimicked mucoepidermoid carcinoma, but the mucinous cells were present only in small numbers, even though they these could be highlighted by a mucin stain (e.g. PASD), and no ‘intermediate’ cells were observed. Significant areas of residual undamaged Warthin’s stroma and epithelium were seen in four tumours. The
Table 2. Pathological findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Necrosis</th>
<th>Fibrosis/ (myo)fibroblast proliferation</th>
<th>Squamous metaplasia</th>
<th>Granuloma</th>
<th>Acute inflammation</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Almost total</td>
<td>++ +</td>
<td>Peripheral</td>
<td>No</td>
<td>Focal</td>
<td>Moderate atypia</td>
</tr>
<tr>
<td>2</td>
<td>&gt;50%</td>
<td>++ +</td>
<td>Focal</td>
<td>Yes</td>
<td>Rare</td>
<td>Atypia</td>
</tr>
<tr>
<td>3</td>
<td>Almost total</td>
<td>++ +</td>
<td>Peripheral focal hyalinization</td>
<td>No</td>
<td>Abundant mixed inflammatory cells</td>
<td>Atypia, cholesterol clefts, macrophages +</td>
</tr>
<tr>
<td>4</td>
<td>Almost total</td>
<td>++ +</td>
<td>Peripheral</td>
<td>No</td>
<td>Focal inflammatory cells</td>
<td>Papillary ghosts ++</td>
</tr>
<tr>
<td>5</td>
<td>Almost total</td>
<td>+</td>
<td>Myofibroblast proliferation + ; hyalinization</td>
<td>No</td>
<td>Focal</td>
<td>Cholesterol clefts, macrophages +</td>
</tr>
<tr>
<td>6</td>
<td>&gt;50%</td>
<td>++</td>
<td>Peripheral</td>
<td>Yes</td>
<td>Focal</td>
<td>Goblet cells</td>
</tr>
<tr>
<td>7</td>
<td>&gt;50%</td>
<td>++</td>
<td>Peripheral</td>
<td>No</td>
<td>Focal</td>
<td>Papillary ghosts ++</td>
</tr>
<tr>
<td>8</td>
<td>&gt;50%</td>
<td>++ +</td>
<td>Peripheral</td>
<td>Yes</td>
<td>Focal</td>
<td>Goblet cells</td>
</tr>
<tr>
<td>9</td>
<td>Almost total</td>
<td>+</td>
<td>Peripheral</td>
<td>Lipogran ++</td>
<td>Focal</td>
<td>Cholesterol clefts, macrophages +</td>
</tr>
</tbody>
</table>

adjacent parotid gland in all cases showed a mixed inflammatory infiltrate and mild atrophy of the acini. Immunohistochemical examination showed strong positivity of the squamous epithelial cords with a broad spectrum cytokeratin antibody AE1–3, but CAM5.2 (cytokeratins 8 and 18) staining was only weak and patchy. S100 protein was negative. Actin positivity was seen in proliferating myofibroblasts in the stromal papillae at the periphery of the necrotic nodules.

**Discussion**

The age distribution and the sex ratio of patients with metaplastic Warthin’s tumour in this study was broadly

![Figure 2](image2.jpg) Case 4, a well-circumscribed, partly cystic and partly necrotic mass with only rare foci of recognizable Warthin’s tumour (H & E × 4).

![Figure 3](image3.jpg) Case 3, necrotic area with ghost outlines of papillae covered by columnar epithelium (H & E × 100).
similar to previous reports and also to that of the usual type of Warthin’s tumour.1,2

The typical microscopic features of metaplastic Warthin’s tumour of necrosis, inflammation and squamous metaplasia were well represented in the present study. The lesion can resemble both benign and malignant conditions; one of our cases in which no residual Warthin’s tumour remained was initially thought to be a ruptured and inflamed epidermal cyst. However, the more important histopathological differential diagnoses are squamous and mucoepidermoid carcinoma, arising either de novo, as an intraparotid lymph node metastasis, or rarely, as the malignant component in a pre-existing Warthin’s tumour.7-8 In the present study, the original diagnosis in two cases was well differentiated squamous cell carcinoma (SCC), and in another mucoepidermoid carcinoma. SCC generally displays invasion and cytologic atypia of the tumour cells, much more than in even the most florid areas of metaplastic Warthin’s tumour; this is true even in carcinomas arising in a Warthin’s tumour.8 Invasion is also an important feature in mucoepidermoid carcinoma where, in addition, the combination of mucinous, intermediate, clear and squamous cells can also be observed. However the presence of goblet cells is by no means diagnostic, as scanty examples are not infrequently seen in Warthin’s tumour, but they are only rarely present in large numbers1 and, if abundant, should raise the suspicion of malignancy. They were not prominent in our cases, although in one tumour a resemblance to mucoepidermoid carcinoma resulted from an intimate admixture of only small numbers of goblet cells with squamous epithelium.

It should generally be possible to make the diagnosis of metaplastic Warthin’s tumour on haematoxylin and eosin (H & E) morphology alone. Special stains are of limited value, but a reticulin stain can highlight the ghost papillary architecture in the necrotic areas; PAS-D or mucicarmine are good at demonstrating goblet cells. Immunohistochemistry has little or no practical value in making the diagnosis.

The pathogenesis of metaplastic Warthin’s tumour is not known for certain: infection was originally suggested as being responsible in two early cases.9 A history of radiotherapy was noted in 20–40% of one of the two large series.2 In the other,1 neither of these factors...
appeared relevant, as no patient had been irradiated and only two had clinical signs of acute inflammation and, even then, no bacteria were identified. These authors suggested a vascular cause for the necrosis, i.e. infarction. Support for this view (i.e. a vascular mechanism in the development of metaplastic Warthin’s tumour) comes from experimental studies in rats in which the arteries supplying the salivary glands were ligated.10 Within a few days squamous metaplasia had developed.

Some reports have suggested that a diagnostic FNA can in some way act on an ordinary Warthin’s tumour to produce the metaplastic subtype.4–6 This hypothesis is plausible, as post-FNA infarction is well described in other organs, in particular in the breast,11 lymph node12,13 and thyroid. In our series, the previous aspirates were either nondiagnostic or showed viable Warthin’s tumour cells, but evidence of necrosis or inflammation was lacking. This suggests that the infarction and squamous metaplasia happened after the FNA. Furthermore, the patient in case 1 underwent two distinct aspirates within an interval of 14 days. In the first smear inflammatory cells and necrosis were not seen, while in the second numerous granulocytes and necrotic debris accompanied degenerated oncocytic cells.

The view that trauma such as from an FNA could cause infarction and squamous metaplasia in a Warthin’s tumour is supported by the existence of an analogous lesion in non-neoplastic salivary glands, necrotizing sialometaplasia. It is usually seen in the minor glands of the palate and often follows a clear history of trauma. Microscopically, it is characterized by necrosis, inflammation and squamous metaplasia,3 and it is sometimes referred to as salivary gland infarction.

The postulated similar pathogenesis of necrotizing sialometaplasia and metaplastic Warthin’s tumour is also supported by comparable time intervals following trauma or FNA. A previous study of necrotizing sialometaplasia showed an average interval of 18 days (range 6–53 days) between surgery and the development of squamous metaplasia,16 whereas in our Warthin’s tumour cases the post-FNA interval ranged from 6 to 101 days.

If trauma is to be postulated as a cause of metaplastic Warthin’s tumour, the most likely mechanism would be direct injury of a blood vessel by the needle. Warthin himself commented that his eponymous tumours were ‘not very vascular; the arterial supply [was] small, and the veins [were] not large and were thin-walled’.17 Eveson and Cawson also observed few blood vessels within the substance of the lesions.1 Therefore, Warthin’s tumours could be at risk of anything damaging one of the relatively sparse feeder arteries. Also, possibly relevant was that focal haemosiderin was demonstrated in all of our cases.

Another factor that may be important in the pathogenesis of metaplastic/infarcted Warthin’s tumour is the constituent cell type. It is noteworthy that in other examples of FNA damage, infarction occurs particularly in tumours rich in oncocytic cells, such as Hürthle cell adenoma of the thyroid.6,15 Similarly, we have also seen several examples of necrosis of salivary oncocytomas following FNA,18 a finding also recorded by Batsakis et al.5 However, in neither tumour has squamous metaplasia been reported. Chan et al.6 speculate that the high energy requirements of these mitochondrion-rich tumours perhaps contribute to their tendency to undergo infarction after FNA injury.

It is clear that FNA is far from being the sole factor in inducing necrosis in Warthin’s tumour, since in many instances there is no history of FNA or other trauma, and indeed, some reports predate the widespread use of FNA. Other cases follow radiation or open biopsy, as in our case 5. Alternatively, the possibility also exists that any association between infarcted Warthin’s tumour and FNA may just reflect that in many institutions, most patients with a salivary mass will have had a preoperative FNA, and it would then be reasonable to suppose that a similarly high proportion of infarcted Warthin’s tumours would likewise have had an FNA as a matter of course. However, we have found only one report of the cytological findings in a lesion described as metaplastic Warthin’s tumour, i.e. the lesion was present before the FNA.19

Overall, therefore, we feel that the balance of probabilities favours the view that FNA is capable of causing metaplastic change in a Warthin’s tumour and,
if so, this previously unusual subtype will become increasingly common, as FNA becomes more widely used in the investigation of patients with a mass in the neck.

How often this might occur is difficult to assess, as there are no data on even the incidence of a previous FNA in metaplastic and non-metaplastic Warthin’s tumours. The only paper to address this point at all was the survey of FNA in salivary tumours by Abad et al.,20 in which none of the 10 Warthin’s tumours were of the metaplastic subtype. As our study was a multicentre one and included outside consultations, we too are unable to supply an answer.

Many studies attest to the diagnostic value of FNA in the investigation of salivary disease,20–23 and, for example, it has been claimed that surgery can be avoided in a third of patients.21 These papers discuss the problems of diagnostic accuracy, but little reference is made to adverse effects on the tumours themselves. This is because FNA is largely harmless to the patient and, for example, seeding of malignant cells along the needle tract has been reported very rarely.24 and not as yet from the salivary glands. In a review which specifically addresses histological changes induced by FNA, Chan et al.6 classify them as tissue injury with repair, infarction and reactive pseudomalignant epithelial changes. We believe that our cases illustrate some of these effects on one particular target lesion, i.e. Warthin’s tumour, and that histopathologists need to be aware of the resulting diagnostic difficulties in a situation likely to become increasingly frequent.

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References
