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Pathology in Focus

Orbital and skin metastases in a polymorphous low grade adenocarcinoma of the salivary gland

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Abstract
We report the previously undocumented development of an orbital metastasis and skin metastases in a patient with polymorphous low grade adenocarcinoma (PLGA) 15 years after initial presentation. The clinical course, treatment and changing histological features are discussed.

Key words: Salivary gland neoplasms; Neoplasm metastasis; Orbit; Skin; Adenocarcinoma

Introduction

The tumour now generally known as low grade polymorphous adenocarcinoma (PLGA) was described by Batsakis *et al.* (1983) as terminal duct carcinoma and by Freedman and Lumerman (1983) as lobular carcinoma. The first name indicated its origin from the terminal duct and the second its infiltrating pattern resembling lobular carcinoma of the breast. The age range is from 21 to 94 years, and it occurs most frequently in the seventh decade. Two thirds of patients have been female. The tumour occurs almost exclusively in minor salivary glands, most commonly in the palate (60 per cent) followed by the lip, particularly the upper lip, (19 per cent) followed by the cheek (16 per cent) (Wenig and Gnepp, 1991). It has been described in major salivary glands arising in a pleomorphic adenoma (Tortoledo *et al.*, 1984) and there is a single case report of the tumour arising in the parotid gland with no evidence of any residual pleomorphic adenoma (Miliauskas, 1991).

By 1992 over 100 cases had been reported. This case was previously reported in this journal, forming one of only 12 cases reported in the United Kingdom at that time (Tay *et al.*, 1992). However, since then the patient has developed metastases in the skin of the shoulder and breast and in the orbit with slightly modified histology but still consistent with PLGA. Metastases to local lymph nodes are well recognized. Distant metastases have not previously been described.

Case report

In 1978 a 58-year-old lady presented with a three-year history of a lump in the floor of the mouth, diagnosed on a small biopsy as salivary gland adenocarcinoma. She received both radiotherapy and chemotherapy which produced only slight reduction in size. Tumour excision requiring a left paramedian mandibulotomy was performed. An apparently well encapsulated tumour involving the left sub-mandibular region, floor of the mouth to the mid-line, tongue base, vallecula and soft palate was removed with primary closure. The histology was reported as an adenocarcinoma of salivary gland incompletely excised.

She remained well at regular review until she developed a left neck swelling in April 1991. A radical neck dissection was performed. The histology showed a nodule 10 × 7 × 3 cm of PLGA and other lymph nodes free of tumour. Histological review of the tumour removed in 1978 led to a change of diagnosis from adenocarcinoma to PLGA.

In August 1993 she developed a right sided proptosis with chemosis, papilloedema and a right visual acuity of 6/24. She also had cystic skin lesions in the left post-auricular region, the left breast, thigh and shoulder. An emergency CT scan demonstrated a large retro-orbital mass compressing the right optic nerve (Figure 1). She was given intravenous dexamethasone and after 48 hours a right lateral orbitotomy was performed. A 2 × 2 cm cystic

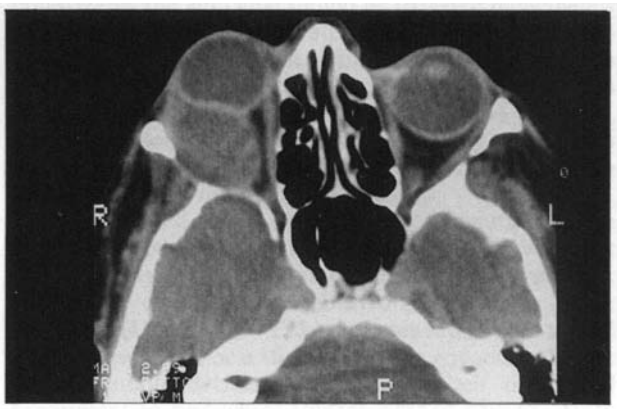

FIG. 1
Axial CT scan showing right-sided retro-orbital mass.

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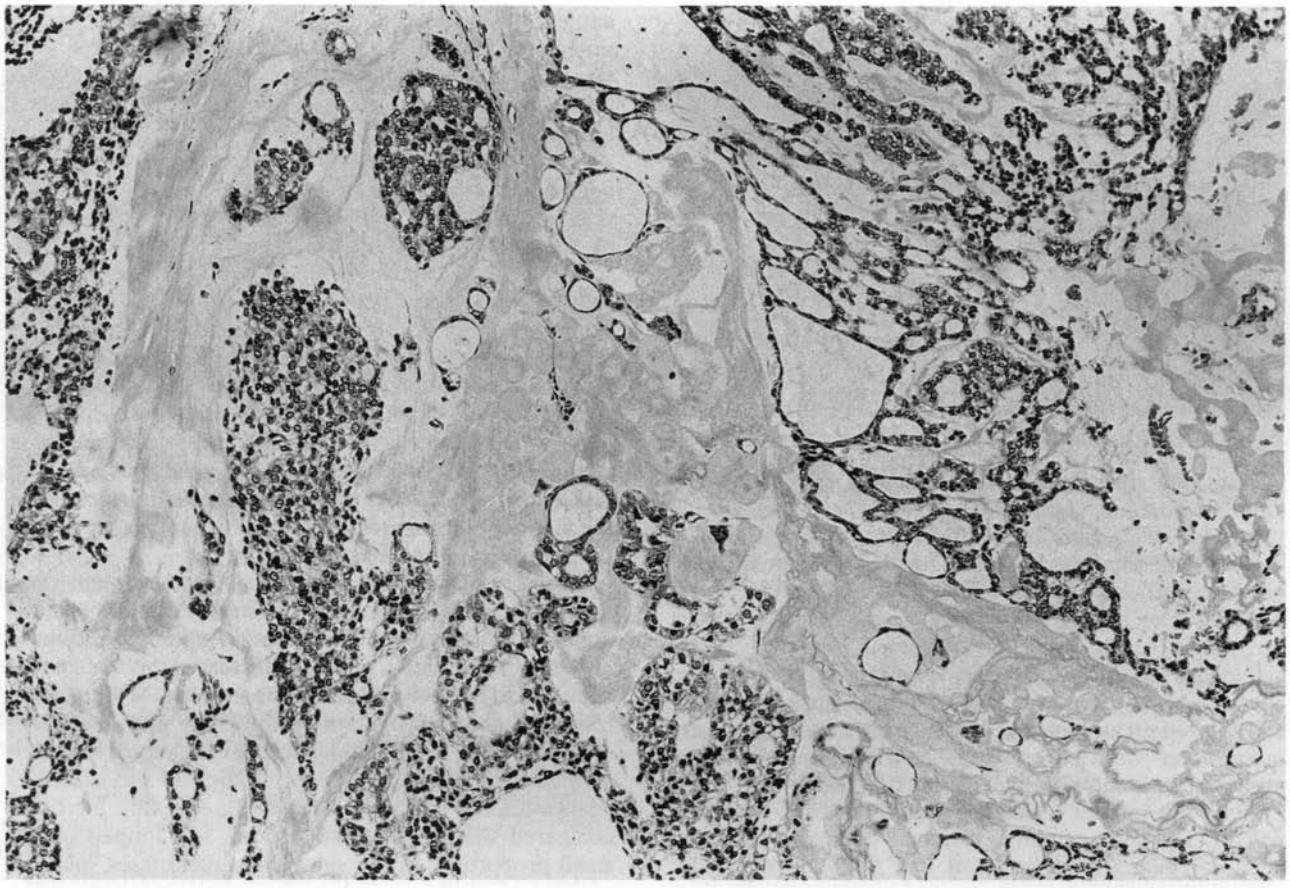

FIG. 2
Tumour removed in 1978 showing morphological diversity, cytological blandness, mucinosis and hyalinization. (H & E; × 100).

intra-periostial tumour was dissected out. The globe and optic nerve were intact. The left post-auricular region was biopsied and the cyst below the left breast was aspirated. Her visual function improved over the first week leaving mild proptosis and mild limitation of right abduction. She underwent six courses of mitozantrone and three months after surgery her visual acuity was 6/9 in both eyes and her eye movements normal. One year later she remains free of disease.

Pathology

The tumour removed from the floor of the mouth was an apparently circumscribed lobulated mass measuring 6.5 × 6 × 5 cm. The cut surface showed a varied appearance with haemorrhagic areas, grey areas and yellow necrotic areas. Microscopically the tumour showed the typical morphological diversity and cytological blandness characteristic of this tumour (Figure 2). The growth patterns included cribriform, ductal, trabecular, papillary and cystic areas. The nucleii were round or oval, vesicular with fine chromatin and inconspicuous nucleoli. Mitoses were exceedingly rare. There was stromal hyalinization, mucinosis and considerable necrosis. Although apparently circumscribed, the tumour was not encapsulated and extended to the resection line (Figure 3).

The left radical neck dissection in 1991 showed a nodule of tumour 3.0 cm in diameter, possibly replacing a level 1 lymph node. This showed the same morphological diversity and some central necrosis. Cribriform areas showed some increase over the original tumour but still formed less than 10 per cent of the tumour.

The tumour in the orbit was cystic. It showed small tubular and lobular areas but by now over 75 per cent was cribriform in appearance (Figure 4). These cribriform areas resembled those of the original tumour with the same cytological blandness but an increase in mitotic rate up to three per 10 high-power fields. The recurrence in the post-auricular scar was similar, and the aspirate from the skin nodule below the left breast showed identical cribriform tumour fragments (Figure 5).

Immunocytochemistry

Staining for S-100 was strongly and uniformly positive in all areas. Low molecular weight keratin (CAM 5.2) and epithelial membrane antigen (EMA) showed patchy staining with a predominance of tubular and luminal cells. Carcinoembryonic antigen (CEA) was patchy with some strong positivity in both luminal and myoepithelial cells. Vimentin showed weak, patchy staining unrelated to pattern. Actin staining was also patchy in both tubular and myoepithelial cells. In the predominantly cribriform pattern in the orbit, S-100 was uniformly positive. EMA was negative. Positive staining for actin was more uniform.

Discussion

Both the primary tumour in the floor of the mouth and its regional and distant metastases showed the characteristic features described in the WHO Classification of Salivary Tumours (Seifert, 1992) with cytological uniformity and morphological diversity. The tumour appeared well circumscribed clinically yet exhibited infiltration and was incompletely excised. The neoplasms that present most difficulty in differentiation from PLGA are pleo-

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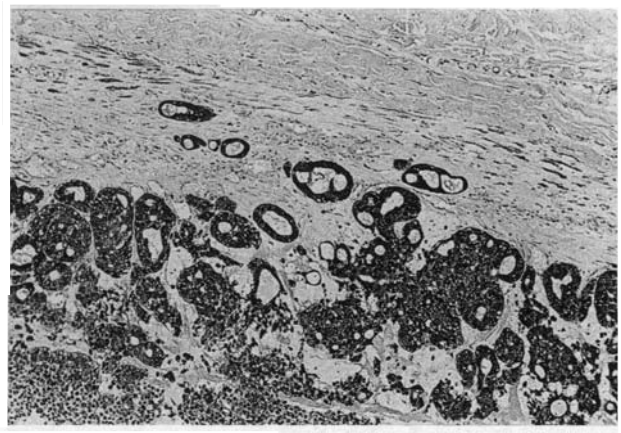

FIG. 3
Tumour infiltrating adjacent skeletal muscle. Stained for S-100 × 200.

morphic adenoma and adenoid cystic carcinoma. Pleomorphic adenoma does not exhibit an infiltrative growth pattern. The major distinction from adenoid cystic carcinoma, which also shows diverse morphology, is a cytological one. The cytological aspirate from a proven adenoid cystic carcinoma was examined for comparison and showed greater nuclear pleomorphism and hyperchromasia than was present in the cribriform fragments aspirated from the skin under the left breast.

A further tumour which has sometimes been confused wth PLGA, and sometimes grouped with it, is papillary adenocarcinoma. It is now felt that tumours which are entirely, or almost entirely, papillary have a worse prognosis (Shootweg and Muller, 1987; Wenig and Gnepp, 1991) and should be categorized separately. It has been suggested that tumours which are clearly PLGA but have a prominent papillary pattern may be more aggressive (Simpson *et al.*, 1991). In our case, the papillary component was a minor one in the original tumour and first recurrence, and non-existent in the orbital and skin metastases.

Immunocytochemistry and electron microscopy have supported an origin from the terminal duct. Our immunocytochemical findings were broadly in line with others in that both luminal and non-luminal cells stained with low molecular weight keratin, EMA and S-100. EMA and CAM 5.2 were stronger in luminal and tubular cells, but unlike others (Luna *et al.*, 1987) there was no difference in the intensity of S-100 staining between ductal cells and myoepithelial cells. Actin gave a more uniform staining in the large cribriform areas of metastatic tumour supporting their myoepithelial differentiation.

The role of radiotherapy in management is not clear (Aberle *et al*, 1985). Stromal hyalinization and mucinosis are well recognized in PLGA (Luna *et al*, 1987; Simpson *et al.*, 1991) but radiation may have increased this feature and almost certainly contributed to the necrosis. Myoepithelial cells are more resistant to radiotherapy and one might speculate on its role in modifying the histology of recurrent or metastatic tumour. However, in the first metastasis, 13 years later, myoepithelial cribriform areas, while increased compared with the original tumour, still formed only a small proportion. In the subsequent metastases, much of

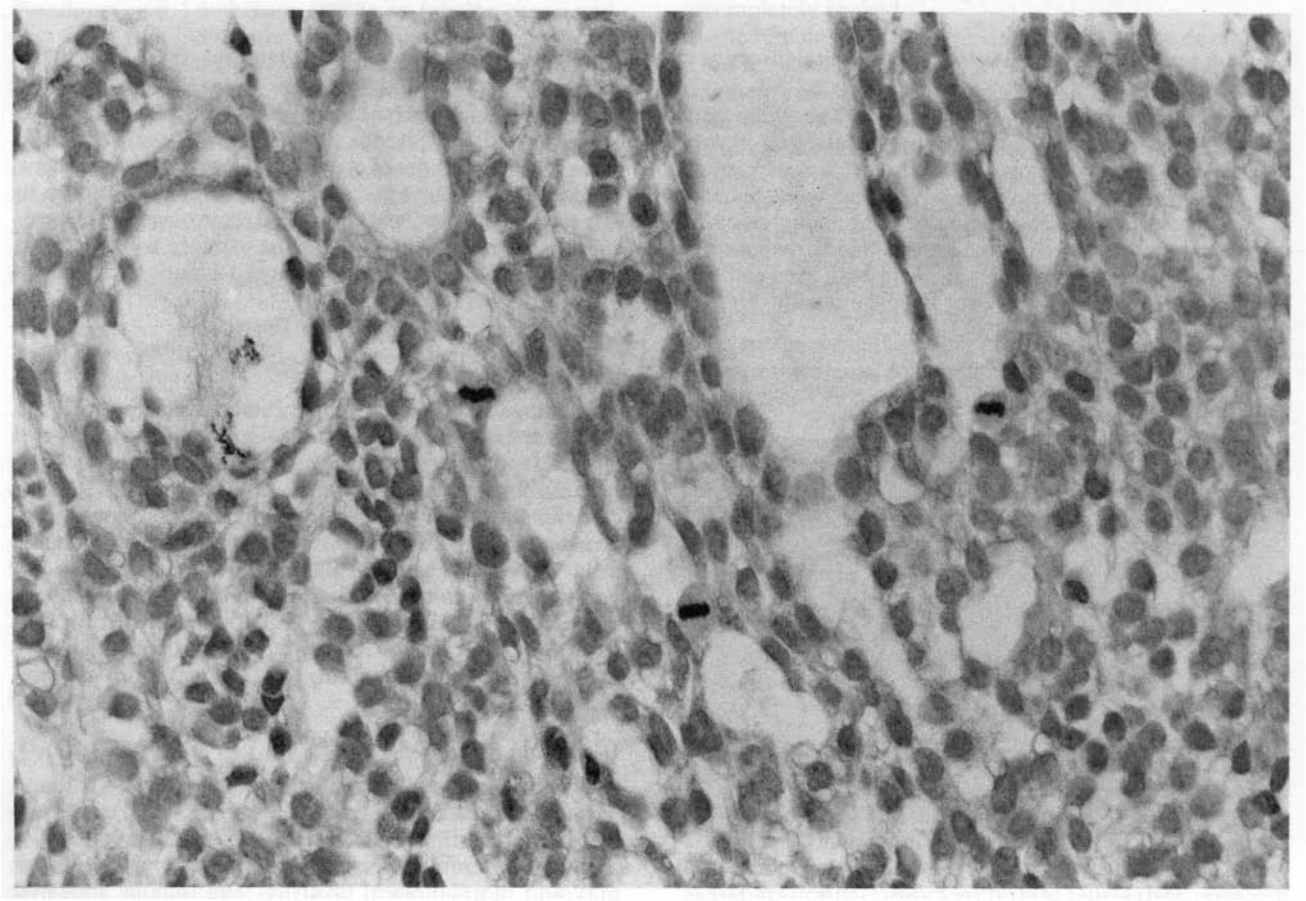

FIG. 4
Cribriform pattern in the orbital metastasis. Cytological blandness but increased mitotic rate (H & E; × 400).

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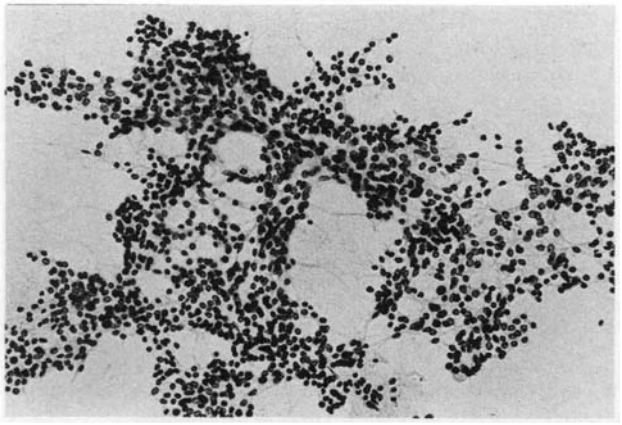

FIG. 5

Fragments of cribriform tumour aspirated from skin below the left breast. (H & E; × 200).

the tumour (over 75 per cent) was cribriform with only a little remaining morphological diversity.

PLGA is an indolent tumour. The local recurrence rate is about 25 per cent with a further 25 per cent of this group showing multiple recurrences and 10 per cent cervical lymph node metastases (Wenig and Gnepp, 1991). One patient died as a result of direct extension of the tumour to vital structures of the head (Aberle, 1985). Distant metastases of PLGA have not been reported, though one of nine patients who had PLGA arising in a pleomorphic adenoma died of distant metastases (Tortoledo *et al.*, 1984; Luna *et al.*, 1987).

This case represents the first report of a primary PLGA eventually undergoing distant metastases including a metastasis to the orbit.

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