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CASE REPORT

Metastasising Pleomorphic Salivary Adenoma: A Rare Case Report of a Massive Untreated Minor Salivary Gland Pleomorphic Adenoma with Concurrent Ipsilateral Cervical Node Metastases

Melanie Watson[1] · Peter McAllister[2] · Brendan Conn[3] · Morna MacNeill[4] · Thomas P. B. Handley[5]

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Abstract
Salivary gland tumours constitute approximately 1–5% of all human neoplasms. Pleomorphic adenoma (PA) is the commonest benign neoplasm affecting the parotid gland most often (> 75%), followed by the submandibular gland (13%), then the palate (9%). Metastasising pleomorphic adenoma (MPA) is extremely rare. The effects can be severe and a reported 40% of MPA patients die with disease. This case represents the first known case in English literature of an untreated minor salivary gland PSA of the palate metastasising to an ipsilateral cervical node. We report a 61 year old female who presented with a large tumour occupying the palatal vault, and cervical neck mass. The oral tumour was believed to have been growing over four decades. The patient died eight months following surgical resection. Of known cases, male: female ratio is 35:51 and the mean age at diagnosis is 49.2. Most commonly, MPA is detected in bone 33.3% (n = 29), lung 31% (n = 27) and cervical lymph nodes 20.7% (n = 18). Thorough reporting is deemed essential to further understand the biological differences of non metastasising and metastasising PAs, treatment outcomes, prognosis and survival rates.

Keywords Metastasising · Metastasizing · Pleomorphic adenoma · Salivary metastases

Introduction

Salivary gland tumours constitute approximately 1–5% of all human neoplasms [1]. Pleomorphic salivary adenoma (PSA) is the commonest benign neoplasm affecting the parotid gland most often (> 75%), followed by the submandibular gland (13%), then the palate (9%) [1].

✉ Melanie Watson
melanie.watson8@nhs.net

Brendan Conn
brendan.conn@nhslothian.scot.nhs.uk

1 OMFS DCT3, St John's Hospital, Howden Road West, Livingston, Scotland EH54 6PP, UK

2 OMFS ST4, St John's Hospital, Livingston, Scotland, UK

3 Oral/H&N Pathology, Department of Pathology, Royal Infirmary of Edinburgh, 51 Little France Drive, Edinburgh, Scotland EH16 4SA, UK

4 Department of Pathology, Royal Infirmary of Edinburgh, 51 Little France Drive, Edinburgh, Scotland EH16 4SA, UK

5 OMFS Consultant, St John's Hospital, Livingston, Scotland, UK

Metastasising pleomorphic adenoma (MPA) is an extremely rare salivary gland tumour. In the 2005 classification of salivary gland tumours, the World Health Organisation (WHO) described MPA as 'histologically identical to PSA, but with inexplicable regional or distant metastases'. The tumour was accordingly grouped along with carcinoma-ex-pleomorphic adenoma in the malignant epithelial tumours section [1]. Recent reclassification favours designation by histological appearance above biological behaviour and, as such, MPA has been downgraded from "malignancy" to "benign epithelial tumour" in the recently updated 2017 WHO classification, yet retains an advisory in consideration of its aggressive nature [1]. Despite its rarity, the effects can be severe and 40% of MPA patients die with disease [2].

The most recent systematic review documented 81 reported cases since 1942 in the English literature [3]. Since then, at least a further five cases plus the author's own have been reported [4–8]. Diagnosis follows histopathological assessment and must exclude malignancy in both the primary tumour and resultant metastasis. Pathogenesis is hypothesised to occur haematogenously through incomplete resection of primary PAs or surgical disruption, aspiration of seeded tumour cells, or a lymphatic metastatic route. Total

surgical excision of the primary tumour and metastasis is the treatment of choice for accessible tumours, as incomplete enucleation can lead to recurrence [9, 10].

MPA is extremely rare. Of 87 known cases, male: female ratio was 35:51 (a single case did not report the subject gender) and the mean age at diagnosis was 49.2 (age 11–83) [3]. Most commonly, MPA was detected in bone 33.3% (n = 29), lung 31% (n = 27) and cervical lymph nodes 20.7% (n = 18).

This represents the first known case in English literature of an untreated minor salivary gland PSA of the maxilla metastasising to an ipsilateral cervical node. The patient died with disease 8 months following surgical resection. Thorough reporting is essential to further understand the biological differences of non-metastasising and metastasising PAs, treatment outcomes, prognosis and survival rates [3].

Case presentation

A 61 year old lady was referred to OMFS by her general medical practitioner regarding a maxillary tumour with recent fatigue and weight loss. On presentation, the patient complained of difficulty eating due to a growing palatal mass, reporting a 12–19 kg weight loss over the previous six months. The swelling was painless but causing mobility of her remaining upper teeth. A small palatal "lump" present since the age of 17 had never been formally investigated. She felt this swelling had grown insidiously then expanded over the preceding 24 months.

Investigations

Clinically, a pedunculated, firm mass filled the palatal vault. Its appearance was lobulated and the overlying mucosa smooth and pale. A mobile, left level II neck mass was identified. Given the obvious feeding difficulties, the patient was admitted for nutritional support and further investigation.

The clinical presentation was highly suspicious of malignancy. A Computed Tomography scan showed a 3.6 × 6.6 × 5.2 cm mass expanding into the left maxillary alveolus, sclerotic pterygoid plates and a 1.2 × 2.4 × 3.5 cm level II node with focal necrosis and internal attenuation similar to the dominant mass (Fig. 1). A CT head and chest were clear.

Two intraoral incisional biopsies showed myoepithelial cells, some scant ductal elements and chondroid stroma, consistent with pleomorphic adenoma (PA) (Fig. 2). Whilst there were no classic cytological features associated with malignancy, discrete, unencapsulated lobules anteriorly were considered to be highly suggestive of low-grade infiltrative behaviour although the possibility that these may represent

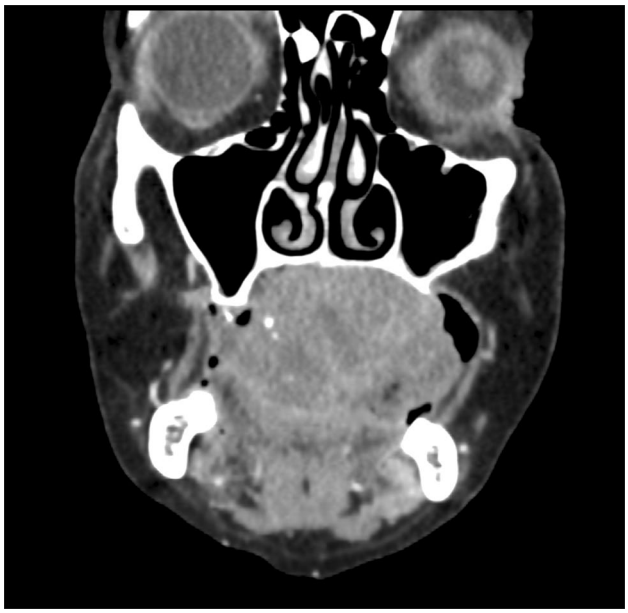

Fig. 1 CT scan (sagittal section) showing a mass causing bony destruction of the palate

satellite nodules/pseudocapsular invasion was also considered. Immunohistochemistry showed a predominance of myoepithelial cells (p63+, p40+, Vimentin+, CK5/6+, CK14+, S100 weak+, in chrondroid areas, SMA weak+, CK7−) and a secondary population of inner luminal ductal cells (CK7+, myoepithelial markers−).

Surgical management was staged. The first operation provided dental extractions and debulking of the tumour to allow formal histology, improve ease of feeding and allow impressions for an obturator. A panendoscopy and core biopsy of the cervical node were also completed. Subsequent surgery involved a hemimaxillectomy and left level I–IV neck dissection and reconstruction with a zygomatic and maxillary implant-supported obturator.

Results

The whole tumour in the resected specimen was blocked out. Histopathological analysis of the neoplasm (Fig. 3) showed elements of PA with lobules of closely packed plasmacytoid myoepithelial cells situated close to the epithelial surface. Whilst chondromyxoid stroma was not present in the original biopsy it was seen within the resected specimens. The tumour was partially encapsulated with small nests and single cells outwith the capsule. Immunohistochemical staining of the resected specimen (CK7/p40/p63/Vimentin/Alcian Blue PAS stain) confirmed a dual population of epithelial and myoepithelial cells typical of PA. A mucin stain confirmed the presence of acidic mucous substance within the

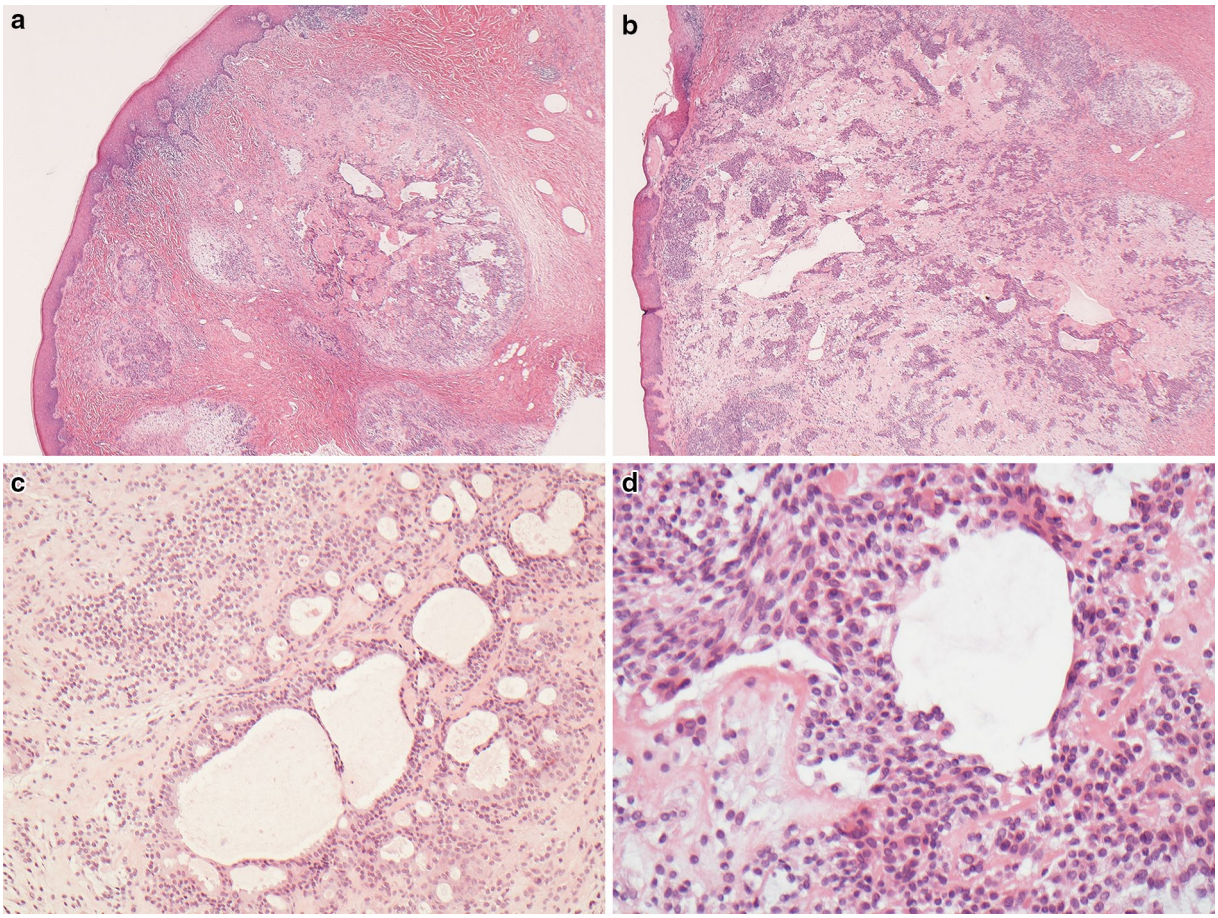

Fig. 2 **a** (H&E ×20) Discrete unencapsulated lobules of tumour in the incisional biopsy. **b** (H&E ×20) Trabeculae of myoepithelial cells set in myxoid stroma. Some dilated ductal structures are seen within the groups furthest from the epithelial surface. **c** (H&E ×100) Complex, variably sized bilayered ductal structures among a background of myoepithelial cells. **d** (H&E ×200) Epithelioid myoepithelial cells. A luminal structure lined by flattened ductal epithelium viewed centrally

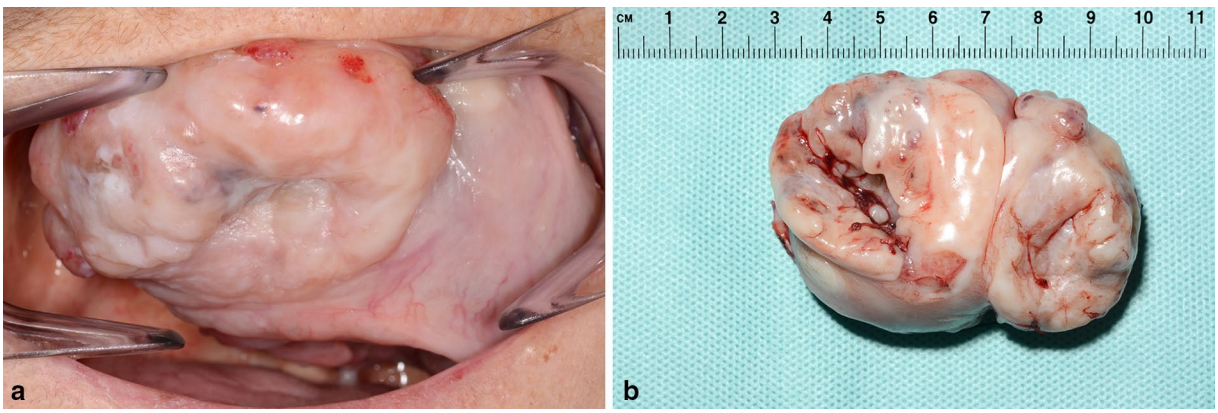

Fig. 3 **a** Extra-oral view of lobulated maxillary mass with superficial ulceration filling palatal vault. **b** Overlying bulbous tissue of the debulked maxillary mass measured 7.1 cm×4.9 cm×2.9 cm with deep surface ulceration

myxoid stroma (Fig. 4). The core biopsy of the level II mass also showed elements of PA.

The resected maxilla, sinus floor lining, left nasal floor and dissected cervical nodes were sent for analysis. Both

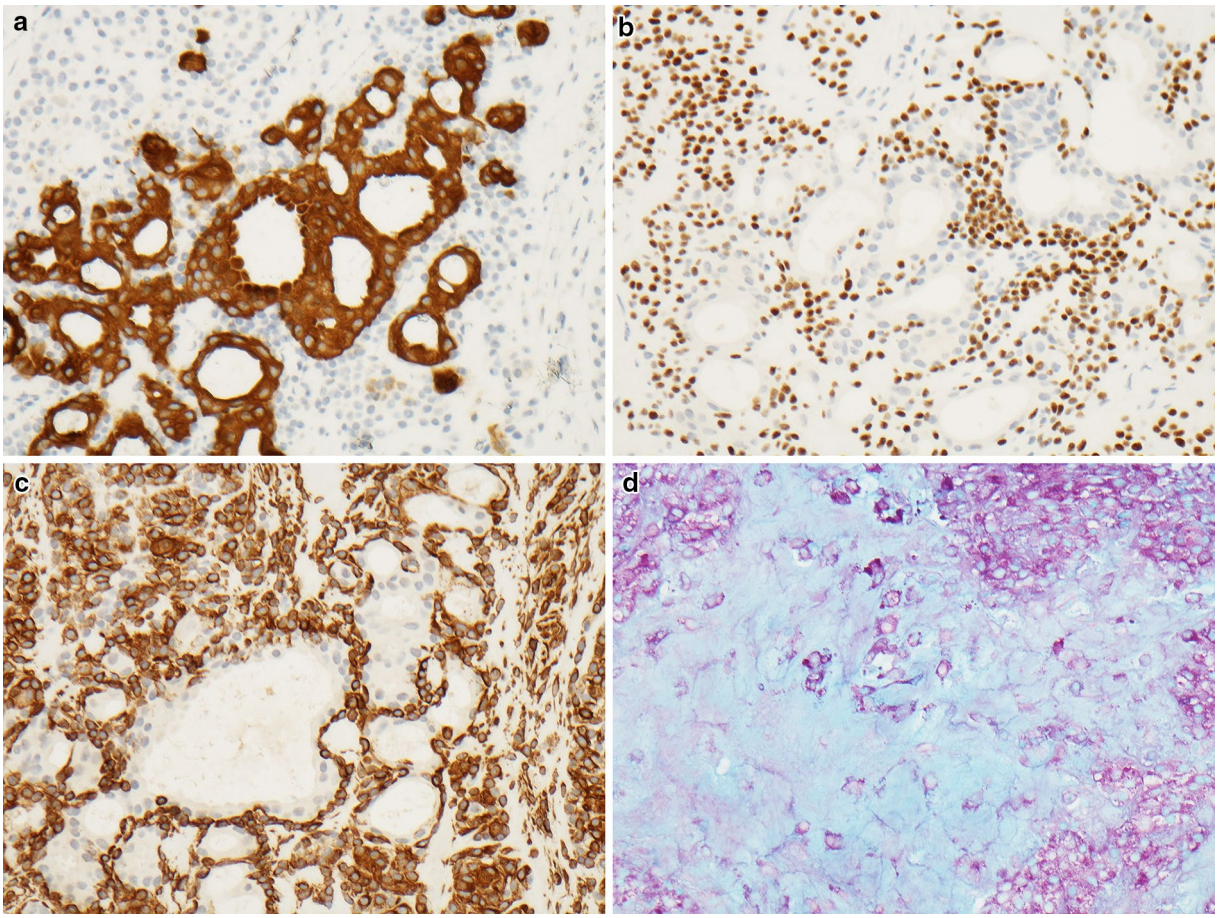

Fig. 4 **a** (CK7 ×200) Immunohistochemistry for CK7 highlights the luminal layer while the abluminal myoepithelial cells are negative. **b** (p40 ×200) Immunohistochemistry for p40 shows abluminal staining of the myoepithelial cells while the inner luminal layer is negative. **c** (Vimentin ×200) Immunohistochemistry for Vimentin shows abluminal staining of the myoepithelial cells while the inner luminal layer is negative. **d** (ABPAS ×200) Alcian Blue PAS stain shows sky-blue staining of the myxoid stroma confirming acidic mucous substance typical of pleomorphic adenoma stroma

tumours were resected completely, with clear margins. The left hemi-maxillectomy showed residues of tumour with elements of PA, the sinus and nasal floor were clear and there was one positive level II node, which was firm, rubbery, 34 mm at maximal diameter and showed typical features of PA. Again, lymph node deposit showed no cytological characteristics of malignancy (Fig. 5).

Sections on tumour and metastasis were subsequently submitted to members of the Scottish, Irish and Newcastle Oral Pathology group for discussion at an educational meeting. The group consensus, including respected authorities in salivary gland pathology, was that the features satisfied a diagnosis of MPA.

A subsequent multidisciplinary team (MDT) meeting concluded oncological management was not indicated, however, close clinical surveillance should be carried out given the high risk of recurrence. Post-surgical follow-up by OMFS showed poor recovery and increasing frailty (WHO performance status 3). The patient unfortunately died eight

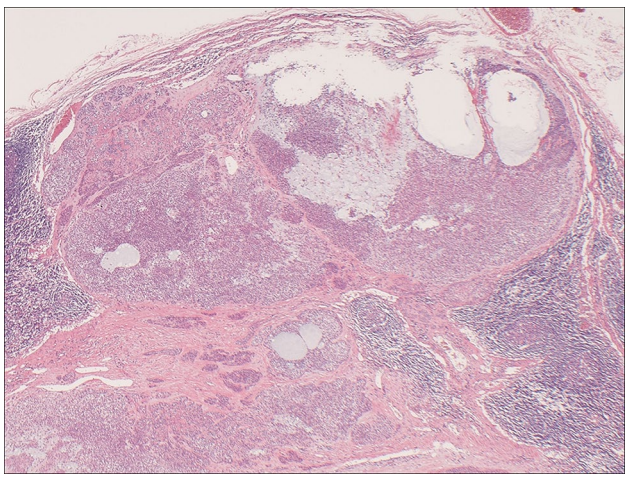

Fig. 5 (H&E ×20) lymph node shows a metastatic deposit predominantly of myoepithelial elements with focal myxoid stroma

months post-surgery, 10 months after her initial assessment. The family declined the option of post-mortem examination.

Discussion

Aetiology

MPA is a rare entity, whereby benign histological features accompany aggressive biological behaviour. In MPA, most primary PAs are diagnosed before the fifth decade [3]. The mean presentation to metastasis latency has been reported as 16 years [11]. Of 85 cases, 71.8% reported recurrence prior to MPA and 35% were associated with multiple local recurrences [3].

Approximately 6% of all PAs undergo malignant transformation to carcinoma ex-pleomorphic adenoma (CEPA), which is postulated to be linked to genetic instabilities of long-standing PAs [1]. One author proposed that MPA is positioned within a continuum between PA and CEPA and is likely to occur secondary to an accumulation of genetic mutations [12].

Genetic studies have not established a specific link with MPA tumorigenesis, however PAs have been associated with key genetic alterations [13]. PA gene 1 (PLAG1), detected by immunohistochemical staining, can result from chromosomal rearrangement of 8q12 and is involved with tumour progression [14]. Chromosomal translocation of 3p21 and trisomy 8 have also been implicated [14]. Approximately one-third of all PAs demonstrate allelic loss patterns in the absence of chromosomal arm 12q13-15 (a protooncogene) [15]. Further studies in gene fusions and key mutations are required to understand the molecular mechanisms involved in the biological progression of MPA and possibly lead to diagnostic biomarkers in future [2].

Diagnosis

Diagnosis of this challenging case required full correlation between the histochemical findings alongside radiological and clinical features at the local Head & Neck cancer MDT meeting. It was suggested that the presence of nests outwith this large oral lesion could be akin to satellite nodules seen more commonly in lesions of the parotid than in the oral cavity. Though PSAs are ordinarily well circumscribed, minor gland tumours do not always present with a capsule: 'psuedocapsular invasion' describes neoplastic advancement into and beyond a capsule with no evidence of infiltration of adjacent structures and should be distinguished from malignancy [16, 17].

While consideration was given to the possibility of PA arising from a salivary inclusion within lymph node capsule, the lack of ectopic salivary tissue and finding microscopic deposits of tumour under the subcapsular sinus was entirely consistent with metastatic spread. Initial biopsy of the primary tumour strongly suggested PA however given the size and dramatic clinical presentation, CEPA was favoured in the differential diagnosis until excluded following full histopathological assessment of the resected neoplasm and neck dissection. Myoepithelial carcinoma was excluded on the basis of myxoid stroma and bilayered ducts although it is generally accepted that PA of the minor glands may have minimal ducts and stromal components [18].

Multiple authors consider current case reports of MPA to be misdiagnosed and urge greater scrutiny [10]. Examples of reasons why cases are excluded are the presence of malignant histological changes at the primary or distant site, histological differences between the primary and distant site, or insufficient clinical and histological information [11].

Spread

Metastasis is classically theorised to result from intravascular or lymphatic seeding of tumour cells [11]. Haematogenous spread believed more common than lymphatic dissemination and is thought to occur through incomplete resection of primary PA, idiopathic tumour spillage or 'seeding' by surgical disruption [19–21]. This causes implantation of tumour cells into capsular blood vessels, resulting in formation of tumour emboli [22]. Microscopic lobules of PA outwith thin pseudo-capsules can become iatrogenically detached during enucleation, leaving residual disease [23]. Collina et al. have described metastatic lymphatic spread and Wermuth et al. proposed lung metastases caused by tumour cell aspiration from the minor salivary glands [24, 25].

This case, similar to those reported by Czader and Perrin, was not subject to previous surgical manipulation [12, 26]. This is different to the vast majority of reported cases of MPA, which support Wenig's theory of intravascular spread. However, this case is unique in terms of the size, location and duration for which the primary lesion had been present. The uninvestigated palatal lesion had been present for more than four decades, which may have influenced metastatic spread in this individual case given its obstructively large dimensions and vulnerability to local trauma. Certainly, evidence of cervical node metastases supports lymphatic metastatic seeding and at the very least dismisses the idea that surgical disruption is an absolute prerequisite to metastasis [27]. In our example, metastasis followed an untreated, long-standing single primary tumour, though the most recent systematic review of MPA reports 73% of cases are precipitated by local recurrence and 37% are associated with multiple local recurrences [3].

Treatment

Historically, PA was commonly treated by enucleation, however this was linked to high recurrent rates and MPA [1, 8, 10, 22]. Incomplete tumour enucleation is associated with 20–45% risk of local recurrence and 1–5% after partial or total parotidectomy [5]. Therefore total surgical excision of the primary tumour and metastasectomy with wide tissue margins is advocated as the treatment of choice for MPA, if the tumours are technically accessible [11, 27, 28].

One retrospective study presented mounting evidence that postoperative adjunctive radiotherapy resulted in significantly better local control of multifocal seeded recurrent PA [3]. Fast neutron-beam radiation therapy or accelerated hyperfractionated photon-beam schedules have been effective in the treatment of inoperable, unresectable, recurrent salivary gland tumors [29]. According to Ellis and Auclair, however, radiotherapy for MPA would be no more effective than when treating benign PA [30]. Similarly, chemotherapy has equivocal results in the literature but is not generally regarded as effective primary or adjunctive treatment. Klijanienko reported, in 1998, a case of pulmonary and paravertebral MPA in a 66 year old woman, which was initially treated with methotrexate and other chemotherapy drugs [31]. Eight years later, the paravertebral MPA was treated with chemotherapy and radiotherapy with no effect. Again, eight years later the patient presented with breast MPA, which regressed significantly with tamoxifen. Unfortunately, one year later multiple pulmonary metastasis were diagnosed. This case highlights the aggressive recurrent potential of MPA and places emphasis on the surgeon to achieve careful, clear margins during resection of the primary tumour.

Survival

Survival rates are poorly documented and cases often lack long-term follow-up. This is in part attributed to the often long latent periods between initial diagnosis of PA and recurrence/MPA diagnosis. Wenig illustrates this in his report of MPA diagnosed 52 years after excision of a primary tumour [21]. This underlines the importance of thorough history taking but also raises the issue of whether all cases of recurrent PA should undergo life-long follow-up. Fine-needle aspiration cytology has been suggested for monitoring recurrent PA and MPA due to its aggressive nature [32]. Another study argued that recurrent PA should investigate for distant metastases using PET scanning since it is impossible to determine which of the locally recurrent PA has the potential to metastasise [1].

MPA is potentially lethal and the WHO advise 40% of patients with MPA die with disease. Nouraei reported significant morbidity and mortality with 5-year disease-specific and disease-free survival of 58 and 50% respectively [11]. The study concluded that development of metastases within a decade of primary tumour and multiple recurrence reduced survival, as did non-operative management. Contrastingly, Wenig found that of 11 patients diagnosed with MPA, 82% (n = 8) were alive and disease-free after 16 years and two had died from unrelated causes [21].

Conclusion

This report marks the first known case of an untreated primary PA of the minor salivary gland metastasising to a cervical lymph node. There was no local recurrence prior to MPA, however significant tumour growth at the primary site over four decades. The patient has no evidence of MPA at seven months. Long term follow-up is recommended in view of recurrence potential, disease latency periods and fatal outcome. Further genetic studies are essential to discover what molecular machinery drives a small subset of PA to follow a lethal malignant course. Ongoing documentation of case reports is also essential in gaining greater understanding about the biological behaviour and prognosis of MPA.

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Compliance with Ethical Standards

Conflict of interest All authors named in this case report declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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