

CASE REPORT

A late solitary liver metastasis from
pleomorphic salivary adenomaNicolò FABBRI * ¹, Doemnico REALE ², Gloria FERROCCI ¹, Emanuela GHISELLINI ³, Giancarlo PANSINI ¹¹Division of General Surgery, Department of Morphology, Experimental Medicine and Surgery, S. Anna Hospital, University of Ferrara, Ferrara, Italy; ²Institute of Anatomical Pathology, Department of Oncology/Specialistic Medicine, S. Anna Hospital, University of Ferrara, Ferrara, Italy; ³University of Ferrara, Ferrara, Italy*Corresponding author: Nicolò Fabbri, Division of General and Thoracic Surgery, Department of Morphology, Experimental Medicine and Surgery, University of Ferrara, via Aldo Moro 8, 44100 Ferrara, Italy. E-mail: medicina100986@gmail.com

ABSTRACT

Pleomorphic adenoma (also known as mixed tumour) is the most common neoplasm of the salivary glands. It is usually a benign, slow-growing and well-circumscribed lesion. Metastasizing pleomorphic salivary adenoma is extremely rare, occurring in less than 1% of patients with pleomorphic adenoma. There are very few reports of a subset of these tumours metastasizing to distant sites without undergoing malignant transformation. There are as yet no statistics for this pathology – some aspects continue to be controversial and any patient may represent a diagnostic dilemma for the surgical oncologist and the cancer pathologist. A definitive diagnosis usually requires radical surgery, if possible. We present a review of the literature and an unusual case of a large liver mass found incidentally in an 87-year-old female. The patient was eligible for surgery and a successful liver resection was performed. The liver tumour was found to be a very large metastasis of pleomorphic adenoma with unharmed resection margins. This diagnosis is extremely rare and our patient seems to represent the oldest case described to date.

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KEY WORDS: Salivary gland adenoma, pleomorphic; Liver neoplasms; Neoplasm metastasis.

Salivary gland tumours represent 1% to 4% of all human neoplasms.¹ Pleomorphic adenoma (PA) is also termed *mixed tumour* and it is the most common lesion affecting the above-mentioned glands.¹ It has rarely been found in other tissues, such as lungs and breast.²

The first case of metastasizing pleomorphic adenoma (MPA) was reported in 1953.³ Clinically, the pleomorphic adenoma (PA) is a salivary gland tumour that appears as a slow-growing, painless volume enlargement of the parotid gland and most patients are 30 to 50 years old.⁴ The condition usually requires complete surgical resection rather than a simple tumour enucleation, which would increase the local recurrence rate. The MPA is a rare variant of the salivary gland tumour that histologically corresponds to a PA but is characterized by a tendency to spread to local lymph nodes and distant sites.⁴ The most common organ of the initial MPA tumour growth is the parotid gland

(74%), followed by the minor salivary glands (17%) and the submandibular glands (10%).^{1,5} The MPA usually occurs after multiple local recurrences, with a reported interval between diagnosis of primary PA and distant metastases ranging from 1.5 right up to 55 years.

The majority of MPA patients present with symptoms including head and neck mass, lower back pain, abdominal mass, cranial nerve palsy, nasal obstruction and anosmia, dyspnea, acute spinal cord compression, pathological fractures and hip pain.⁶ Most metastases from PA occur in patients that have undergone surgery on the primary tumour site one or more times. The metastatic process is explained by the theory of a “transplantation mechanism” initiated with the vascular implantation of tumour cells during the repeated surgical procedures for the local recurrences, which, prior to metastasizing, can increase the rate of direct tumour seeding and tumour embolisms in capsu-

lar blood vessels, followed by haematogenic dissemination—mostly to the bones, but also to the head, neck and lungs.^{7, 8}

Case report

An 87-year-old female was referred for investigation of a liver mass initially found by chance during an abdominal evaluation for suspected diverticulosis recommended by her general physician. An examination of her circumstances found no personal or family history of liver disorders as prognostic factors of liver cancer. She was positive for bilateral hearing loss, bilateral phacoemulsification, arterial hypertension and, more interestingly, had undergone previous left parotidectomy for PA in 2007. The procedure was complicated by damage to the VII cranial nerve and a tiny amount of local residual tissue was present at the first follow-up. In view of the high risk of post-surgical fibrosis injuring the facial nerve, the otorhinolaryngologist decided to extend the follow-up. Any further increase in size of the suspected remaining tissue in the subsequent surveillance was recorded. At the US scan, the liver mass was mostly located anteriorly and inferiorly to segment V and VI of the liver. The patient's liver tumour was completely asymptomatic and except for her recent fortuitous diagnosis, she had no other medical issues.

The CT scan (Figure 1) revealed multiple bilateral pulmonary nodules (which could no longer be evaluated owing to their very small, millimetric size) and the presence of a large solid mass 8 cm in diameter located in the right lobe of the liver between segments V and VI, with

peripheral vascularization and minimal dilation of the intrahepatic upstream biliary tract. These findings suggested a primitive tumour of the liver, identified as a possible intrahepatic cholangiocarcinoma. There was no evidence of any further metastatic deposits.

The case was discussed at a multi-disciplinary meeting. The CT images of the neoplasia failed to reveal any of the typical radiological features of a common benign hepatic lesion such as adenoma, focal nodular hyperplasia or hemangioma. That this was an example of metastasis of an unknown primary tumour seemed an unlikely hypothesis. Moreover, the patient had no history of viral hepatitis or alcohol abuse; nor were there any signs of hepatic decompensation or liver cirrhosis. Laboratory signs of infection were completely absent, so the hypothesis of a hepatic abscess or parasitic cyst was excluded. The conclusion was that this mass was possibly malignant in nature and that its radiological appearance might be mimicking a cholangiocarcinoma.

In spite of its malign aspect, the liver tumour was not immediately related to the previously treated PA, due to the extreme rarity of this occurrence. The tumour was found to be suitable for complete surgical resection and the elderly patient was eligible for safe surgery. No further investigation or treatment was deemed necessary. A percutaneous biopsy was not required for a conclusive assessment and treatment decision. The patient subsequently underwent an uncomplicated and complete removal of her liver tumour by means of a bi-segmental resection (V-VI), with intraoperative staging US, US-navigation-surgery and cholecystectomy (Figure 2).

The postoperative course was uneventful. The patient

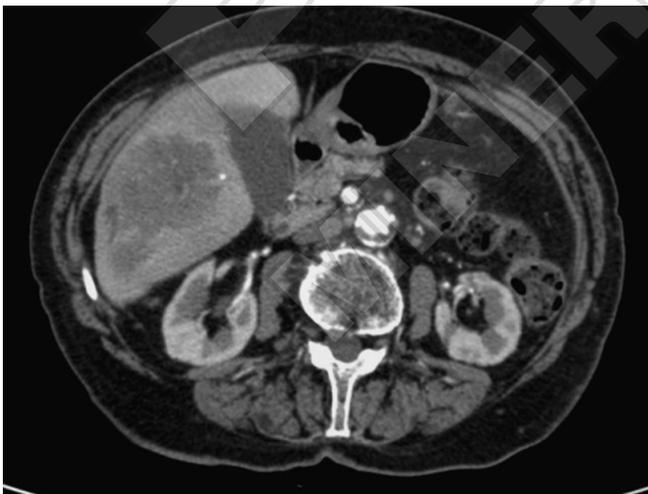


Figure 1.—Voluminous single metastasis of the right lobe of the liver on TC scan.

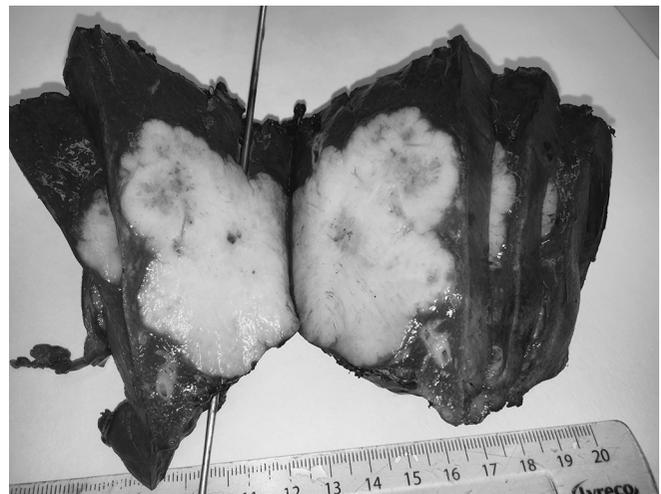


Figure 2.—Metastasizing pleomorphic salivary adenoma.

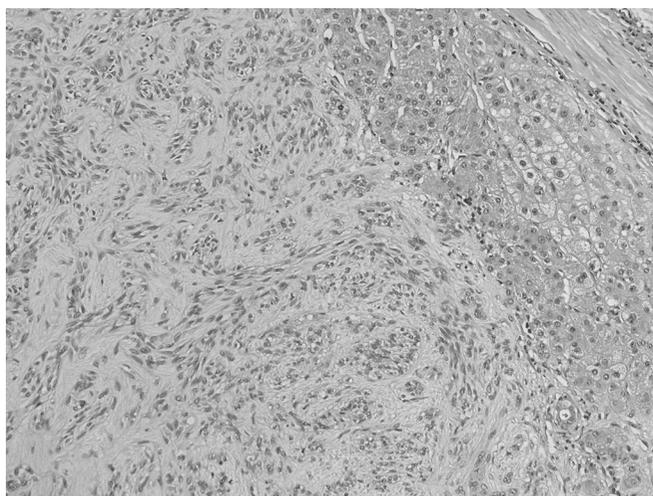


Figure 3.—Liver metastasis of pleomorphic adenoma (hematoxylin and eosin, 100x).

was discharged 8 days after the operation and she is at present in good health 5 months later.

Lastly, a prior history of pleomorphic adenoma was crucial in suggesting a diagnosis of MPA. But only after histological analysis of the liver lesions and comparison with the original salivary gland tumour could the diagnosis of liver metastasis of PA with unharmed resection margins be made (Figure 3). Immunohistochemistry staining revealed positive immunoreactivity for p16 (nucleus and cytoplasm) and Bcl2, whereas it was negative for p53; ki67 was 3%.

Discussion

Pleomorphic adenoma with metastases to the liver, which clinically may act as an indolent malignancy with no established characteristics on multimodality imaging, is extremely rare in the literature, as are discussions of its management. Most papers focus on case reports, while systematic reviews are conspicuous by their absence.

The malignancy can arise from a PA in three forms: carcinoma ex-pleomorphic adenoma (CEPA), carcinosarcoma and metastasising pleomorphic adenoma (MPA). The last two are exceptionally rare, with MPA accounting for 1% of all malignant PA.⁹ CEPA is an epithelial and/or myoepithelial malignancy derived from a pleomorphic adenoma. It can be further subdivided into intracapsular (typically ductal and high-grade carcinoma confined within the PA), minimally invasive (defined as < 4-6 mm extending beyond the PA border) and invasive carcinomas. The risk of transformation to CEPA has been estimated as approximately 1% per year, but may be as high as 25%.

Carcinosarcoma is a true malignant mixed tumour containing both epithelial and mesenchymal components. It is rare and has been described as arising both de novo or as recurrent PA. Carcinosarcoma is a highly aggressive tumour and, like CEPA, is associated with a poor, 5-year survival rate.¹⁰

MPA is a tumour that histologically corresponds to a PA, but may include local lymph nodes and distant metastasis;⁴ it is extremely rare¹⁰ and displays neither age nor sex predilection, nor any association with race or geographic location.¹

The most frequent site of the primary tumour is in the parotid gland, followed by the submaxillary gland, the palate, and the minor salivary glands (Table I).^{4, 6}

Clinical presentation is the painless augmentation of the volume in the affected salivary gland. The majority of MPA patients (60%) presents with symptoms. Among these MPA symptomatic patients, head and neck masses are the most common complaints, followed in descending order by lower back pain (16%), abdominal mass (8%), cranial nerve palsy (8%), nasal obstruction and anosmia (8%), dyspnea (8%), acute spinal cord compression (4%), pathological fractures (4%), and hip pain (4%). The MPA was detected as a result of the medical evaluation of a local recurrent PA in only 17% of patients.⁶ Local recurrence of PA is apparently related to incomplete resection of the dis-

TABLE I.—Main sites of primary neoplasia and metastasis.

Sites of primary neoplasia and metastasis	Author
Initial tumor site	
Parotid gland (74%),	Santaliz-Ruiz <i>et al.</i> ⁶
Minor salivary glands (17%)	
Submandibular glands (10%)	
Local recurrences	
Head and neck mass	Santaliz-Ruiz <i>et al.</i> ⁶
Symptoms:	
• cranial nerve palsy,	
• nasal obstruction,	
• anosmia,	
• dyspnea,	
• acute spinal cord compression,	
• pathological fractures	
Common site for metastasis	
Bone (45%),	Santaliz-Ruiz <i>et al.</i> ⁶
Head and neck (43%)	
(only 17% of cases metastasized to regional lymph nodes)	
Lungs (36%),	
Abdominal viscera (10%): ⁵	
• liver, ⁵	
• kidney ⁸	
• retroperitoneum ⁸	
Central nervous system (rare)	Soteldo <i>et al.</i> ⁴
Skin (rare)	

TABLE II.—*Risk factors not absolute for MPA.*

Risk factors of metastasising pleomorphic adenoma (MPA)	Author
Younger presentation of PA	Knight <i>et al.</i> ⁹
Surgical intervention that should favor seeding and permeation of blood or lymphatic vessels by tumor cells	Ranjbari <i>et al.</i> ¹
Long-standing pleomorphic adenomas	Soteldo <i>et al.</i> ⁴
Minimum one local recurrence of PA	Ranjbari <i>et al.</i> ¹
Previous radiation of the primary PA	
Higher mitotic rate of PA	

ease during the initial surgery.⁶ To date there are no agreed histopathological parameters that can distinguish between a nonmetastatic pleomorphic adenoma and a MPA.^{4, 6, 10} The mean time between initial presentation and the development of metastasis was 16 years, but this interval can vary from 1.5 right up to 55 years. Bone is the most common site for metastases (45%) followed by the head and neck (43%) and lungs (36%).^{5, 10} Within the head and neck area, only 17% of cases metastasized to regional lymph nodes.¹ Three cases of intracranial MPA have been reported; interestingly, in two of these cases the primary PA presented at age 9 and 12 years and the MPA 3 and 51 years later (Table II).^{1, 4, 9}

The diagnosis of MPA of salivary gland origin is challenging and remains a matter of debate. Controversy exists due to the discrepancy between the tumour's histologically benign behaviour and its biological behaviour.² Although apparently benign, MPA is associated with up to 22% mortality.⁶

In 2015, the World Health Organization (WHO) defined MPA as a "histologically benign pleomorphic adenoma that inexplicably manifests local or distant metastasis" and considered it to be a malignant epithelia tumour.¹¹ However, the 2017 WHO classification of salivary gland tumours categorizes both MPA and PA not as a malignant tumours but as a benign ones.¹² Most patients (81%) with MPA have a history of at least one local recurrence of PA prior to the detection of distant metastasis; recurrence occurring in about 90% of cases.¹ In cases of recurrent or longstanding PA, a high index of suspicion for MPA is advisable. Complementary studies, including full body CT, magnetic resonance, and/or PET, should be considered to rule out metastases.¹³ Many authors have reported cases of MPA without prior evidence of local recurrence.¹ A case of MPA was reported with a single kidney tumour displaying the histological features of a PA in the absence of salivary gland neoplasm. Thirteen months later, the patient presented an aggressive parotid tumour, which pathological examination revealed to be a CEPA.¹⁴ Another reported case was a cranial metastasis with a carcinomatous component,

albeit in conjunction with an apparently benign primary submandibular gland tumour.¹⁵ These last two cases have challenged the classical theory which suggests that the surgical manipulation of PA seeds tumour cells and allows them to permeate blood vessels, through which they spread and metastasize. New theories have been proposed as a result of the foregoing evidence.⁶

Immunohistochemical histologic examination of the tissue excised from the primary site and from the metastases usually shows the typical mixture of benign-appearing epithelial and mesenchymal components of a pleomorphic adenoma with abundant chondromyxoid stroma.^{1, 4} Mitotic figures and nuclear pleomorphism may be seen, but the tumour is not overtly histologically malignant. The histology is not predictive regarding its ability to metastasize.⁴ Analysis of apoptosis-related and cell proliferation markers p53, Bcl2, Ki67 in MPA did not reveal significant differences from a control group of conventional PA.¹⁶ More recently, it was discovered that malignant cell components of CEPA showed significantly lower p16 expression in the nuclei and significantly higher expression in the cytoplasm when compared with their benign components.¹⁷ The analyses of nucleic and cytoplasmic p16 immunoreactivity revealed a similar positive expression in both cell compartments of MPA.⁶ Though further studies are warranted, this could suggest that p16 overexpression in the cytoplasm, along with decreased p16 expression in the nucleus, may be important in the evolution of malignant transformation.⁶

The management of primitive PA typically involves curative surgical resection.⁹ The most widely accepted procedure is total parotidectomy with adequate margins and preservation of the facial nerve, unless this has been infiltrated by the tumour.^{4, 10} The decision regarding the most appropriate treatment is taken by intraoperative confirmation⁴ and intra-operative facial nerve monitoring is advisable. Revision surgery of the parotid can be extremely difficult due to the presence of fibrosis and should be reserved for experienced surgical teams dealing regularly with this cohort of patients. Tumour enucleation should never be performed as it increases the local recurrence rate.¹

Local recurrence may be the first step in the dissemination of these neoplasms and radical surgery and radiotherapy should therefore be considered in these cases.¹ The use of postoperative radiotherapy for recurrent PA has been widely discussed, with several studies indicating there is no benefit in the use of radiotherapy after uncomplicated parotidectomy for single, localized recurrences.¹⁰ Multidisciplinary teams may also take into account age, treatment morbidity, facial nerve involvement, and contraindications

to further surgery when considering radiotherapy.¹⁰ Selective neck dissection of the lymph nodes and postoperative radiotherapy are indicated for regional lymph node metastasis.⁶ Surgical resection of metastases, when feasible, is the mainstay of MPA treatment. It can confer a significant survival advantage over nonoperative treatment on log-rank analysis.⁶ In some cases the tumour is inoperable or the patient declines surgery. It is hard to provide a precise prognosis for MPA because such patients have not undergone a long-term follow-up, and some case reports often appear relatively soon after treatment.¹⁸ The prognosis of most histologically benign lesions is generally good.¹²

There are as yet no statistics for MPA and some aspects continue to be controversial. In one of the reported reviews, a period of 50 years was analyzed and 52 cases of MPA were recorded.⁵ Another systemic revision of the bibliography from 1942 to 2014 found 81 known cases worldwide, showing that the average age for diagnosis was 49.5 years.⁹ In the present review we searched for articles on MPA between 2015 and 2017 using Pubmed and Google Scholar databases, starting from the last MPA review of 2014. Keywords used were: metastasizing pleomorphic adenoma, metastasizing pleomorphic adenoma and mixed tumour (without-carcinoma).¹⁹⁻²²

We found 7 new published cases of MPA (6 females and 1 male) (Table III).^{4, 8, 10, 18, 23-25} The average age in this series in the literature was 50,7 years (ranging from 36 to 68 years), with the MPA affecting more females than males. Five primitive PA were in the parotid gland, one PA was in the submandibular gland and one tumour in a minor salivary gland. In only one patient was a local tumour recurrence or residual tumour detected at an early stage. When the time came to decide between treatment options, the patient refused to undergo reoperation.¹⁰ In the literature we reviewed, an average of 15,5 years elapsed between the diagnosis of pleomorphic adenoma and detection of metastasizing pleomorphic adenoma. Regarding the sites of metastases, the tumour recurred in the cervical lymph nodes in 2 patients, in the lungs in 2 patients and in both the liver and the thyroid in one patient, while in one other patient it was present in the liver alone. In the cases of hepatic metastasis, the MPA occurred about 20 years after the first diagnosis of PA.

An interesting aspect of our own case report is that to the best of our knowledge ours is the oldest patient with an MPA to have undergone successful surgery with curative intent.

TABLE III.—MPA world history between 2015 and 2017.

Age at the diagnosis of MPA (years)	Gender	Primary tumor and surgery	Distance from the first intervention for PA (years)	Side of MPA	Surgery for MPA	Author
36	Male	PA, excision of pleomorphic adenoma of the parotid gland	18	Cervical lymph node metastasis	Total left parotidectomy and selective left side cervical dissection	Javier Soteldo <i>et al.</i> 2017 ⁴
37	Female	PA, Left parotidectomy	14	Cervical lymph node metastasis	neck dissection	Ki HaHwang <i>et al.</i> 2015 ²³
40	Female	PA, Resection of right parotid gland	12	Lung, bilateral lobes	Double lung Wedge resections	Ayaka Nakai <i>et al.</i> 2017 ¹⁸
46	Female	PA of the submandibular gland	9	single metastasizing pulmonary pleomorphic adenoma	lobectomy	Seo Young Choi <i>et al.</i> ²⁴
63	Female	Resection of PA of minor salivary gland	20	bilateral MPA of the maxillary bone	Osteotomy	TakaharuTaketomi <i>et al.</i> ²⁵ 2017
65	Female	PA, parotidectomy	20	MPA of the liver	Wedge hepatectomy	Victoria Solveig Young <i>et al.</i> 2015 ⁸
68	Female	Double Resection of PA of the right parotid gland (52 and 35 years ago)	Recurrent PA in 1995 (untreated for patient's request)	MPA of the liver and thyroid gland	Right Thyroidectomy, right selective neck dissection, total right parotidectomy and left lobe hepatectomy	Mufaddal Moonim <i>et al.</i> ¹⁰ 2015.
87	Female	PA, left parotidectomy	Recurrent PA in 2007 (untreated, only follow up)	Single MPA in the right lobe of the liver	Right partial hepatectomy	Fabbri <i>et al.</i> 2017

Conclusions

Current methods of histological diagnosis cannot distinguish between an MPA and a benign PA. A history of previous or concurrent primary PA is essential to diagnose MPA.⁶ Local recurrence may be the first step in the dissemination of these neoplasms and therefore radical surgery and radiotherapy should be considered in these cases. There is currently no way to predict which locally recurrent PA will potentially give rise to MPA. Some suggest that local PA recurrence should be investigated for MPA with Positron Emission Tomography (PET). Due to the long latency between PA resection and MPA, it is suggested that patients with incomplete excision, surgical spillage or local recurrence have a long term follow-up for MPA, even though in practice this surveillance is likely to be difficult to maintain effectively.⁹ The liver may represent a target organ for late metastases from a PA. Once a mass has been revealed and a radiological diagnosis made, the various treatment options need to be considered. Although surgical excision is not usually required in asymptomatic patients, it can be offered to patients suitable for a safe liver resection, before the sinister complications of their progressive growth appear. Alternatively, a tissue biopsy from the liver mass could be obtained as a way of ensuring a correct diagnosis of MPA as against other, more common tumours of the liver. In case of fragile patients the informations from the biopsy could address more information for conservative or palliative treatments or simple clinical and radiological surveillance.

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