Metastatic benign pleomorphic adenoma. Report of a case and review of the literature

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Abstract

Pleomorphic adenoma (PA), originally called mixed tumour, is the most common neoplasm of the salivary glands and is generally accepted as benign biologically. Occasionally PA may give rise to metastasis. The metastasis may develop in a PA in which a malignant transformation occurs, either arising a carcinoma in the PA (carcinoma ex-mixed tumour) or as a carcinosarcoma (so–called true malignant mixed tumour). However, very rare benign PA eventually metastasise, usually after having a previous recurrence, displaying benign histological features as well in the primary tumour as in the metastasis. These tumours have been termed metastatic PA or metastatic mixed tumours. The aim of this paper is to report one case of metastatic histological benign pleomorphic adenoma, and to consider the clinical, pathological and therapeutic consequences of these rare tumours as well as its possible causes and mechanisms for its behaviour.

Key words: *Salivary, neoplasm, metastasis, adenoma, pleomorphic, surgery.*

Introduction

The pleomorphic adenoma is the most common tumour of glandular origin in the head and neck (1). In the 1991 WHO classification of tumours of the salivary glands, the term "Malignant Mixed Tumour" comprises three different pathologies. These pathologies, which should not be confused, are the Carcinoma Ex Pleomorphic Adenoma (CEPA), the Carcinosarcoma (or True Malignant Mixed Tumour) and the Metastatic Mixed Tumour.

Malignant Mixed Tumours represent 3.6% of all neoplasms of the salivary glands and 12% of all malignant neoplasms of the salivary glands (2).

Described by Kirklin (3) in 1951, True Malignant Mixed Tumours account for less than 1% of all Malignant Mixed Tumours. According to Tortoledo (4), they are biphasic tumours that are also able to metastasise. They can appear de novo, or less frequently, in existing pleomorphic adenomas, though this fact does not mean that they should be considered CEPA. Their metastases generally contain an epithelial component (carcinoma) and a mesenchymal component (sarcoma).

Metastatic Mixed Tumours are less common. Authors such as Wenig (5) suggest that Metastatic Mixed Tumours appear after multiple recurrences of the pleomorphic adenoma in the primary site and that many surgical manipulations can contribute to disseminate metastasis. Although apparently benign, mortality can be as high as 22%, according to Ellis and Auclair (6). Other authors such as Fujimura (7), Minic (8) and Czader (9) suggest that this type of tumor could be the intermediate link in the transformation of a pleomorphic adenoma into a CEPA.

The probability that a pleomorphic adenoma will become

malignant is directly proportional to the length of time it has been allowed to develop without treatment. According to Steifert (10), the probability of malignancy ranges from 1.5% in the first five years to 9.5% after 15 years.

Case Report

A 54-year-old female presented to our office with a left preauricular tumor that was 4 x 3 cm in diameter. The first symptoms had been observed 17 months earlier. No pain or facial palsy was described at that time. A fine-needle biopsy was performed and pleomorphic adenoma was diagnosed. The tumour was excised with a superficial parotidectomy that spared the facial nerve. The histopathologic diagnosis of the tumor was "pleomorphic adenoma" (Fig.1 A,B,C,D). There was no evidence of extracapsular growth, atypia or vascular- perineural involvement. Margins of the surgical specimen were free of tumour. Only scattered mitotic figures were present. After two years the patient developed a local recurrence consisting in a 3x3 cm. tumor mass that affected the deep parotid lobe, and had a clinical ipsilateral neck node at level II. A total conservative parotidectomy with functional neck dissection was performed, and a diagnosis of recurrence of PA was made (Fig. 4A). After the second surgery on the parotid, the patient developed right facial palsy. The lymph node metastasis showed the same histological picture as the tumor recurrence. The patient underwent radiotherapy after surgery. One year later the patient was treated for pulmonary metastasis (Fig. 4B). The lung metastasis (Fig 2,3) presented again the same histopathologic features as the primary neoplasm (Fig. 4 C&D). Five years later the patient died of the disease.

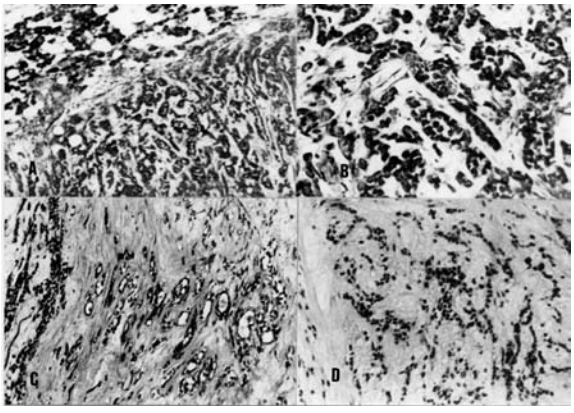

Fig. 1. A) Margin of the primary parotid tumour that shows duct-like structures. The tumour is well demarcated by a thin capsule of connective tissue that separate it from the parotid gland perenchyma (H&E, 25x); B) Higher magnification of a field of A) showing duct-like structures surrounded by a loose connective tissue (H&E, 50x); C) Panoramic view of another field which shows ductules and strands of epithelial cells set in a fibromyxoid matrix (H&E, 42x); D) In this field , the tumour has a predominant spindle cell morphology, comprised of epithelial and myoepithelial cells immersed in a myxoid stroma (H&E, 50x)

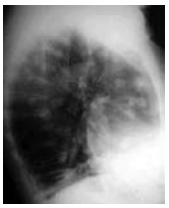

Fig. 2. Lateral chest X ray was done after cervical recurrence of the histologically benign pleomorphic adenoma.

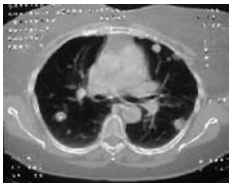

Fig. 3. CT scan showing multiple nodal lung metastasis.

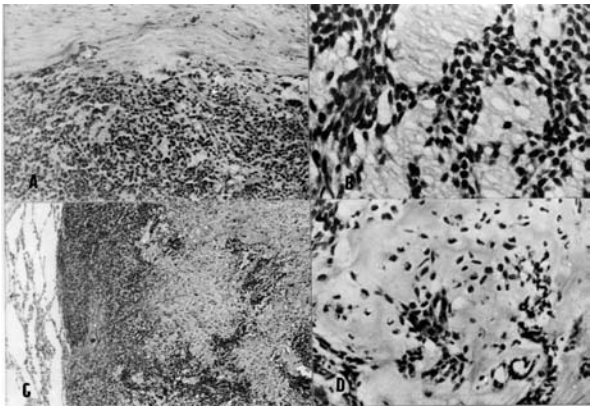

Fig. 4. A) Low power micrograph of the local recurrence showing that the tumour is demarcared by a fibrous pseudocapsule. (H&E, 50x). B) High power micrograph of another field of the local tumour recurrence. The neoplasm has sheets of basaloid cells with little intervening myxoid stroma (H&E, 100x); C) Low power micrograph depicting the pulmonary metastasis. Lung parenchyma seen adjacent to the well demarcated tumour which shows in the periphery higher cellularity than in central areas, where a fibromyxoid stroma predominates beeing very scarce the epithelial cells (H&E, 15x); D) A field of the pulmonary metastasis that shows anastomosisng strands of epithelial and myoepithelial cells surrounded by a fibrochondroid mesenchyma (H&E, 54x).

Discussion

Foot e and Frazell (11) described histological benign mixed tumors that were invasive and could eventually metastasise keeping their benign cytological features from the primary site. It is clear that they are more uncommon than carcinoma in pleomorphic adenoma (CEPA). Chen (12) reported one case and reviewed seven others in 1978, while Ellis and Gnepp found only two cases that had metastasised, out of the many specimens in the American Forces Institute of Pathology (1).

Malignant mixed tumors account for 3.6% of all neoplasms of the salivary glands and 12% of all malignant neoplasms (13). The largest series published are - in order of size, those of Spiro (14), Tortoledo (4) and Livolsi (15).

Authors such as Czader (9) have described the metastatic mixed tumor as a link between a pleomorphic adenoma and a CEPA and suggested that metastases of pleomorphic adenomas may be the first stage in the transformation of a tumor into a carcinoma, though this does not occur in the majority of cases. Other authors have defended this hypothesis (7,8).

Metastatic PA of the salivary glands is a very infrequent neoplasm. Wenig et al (5) could find 32 case reports in the literature and added 8 new cases to their series for a total of 11 cases; Qureshi et al reported one case (16) and Czader et al one more (9). This entity has raised controversy over its nomenclature and its true biological nature. These tumors were termed in early reports metastatic benign mixed tumors, a term that is a misnomer, given that the terms benign and metastatic are paradoxical. This paradox occurs also with other neoplasms of different organs, like the metastatic giant cell tumour of bone (17) and the metastasising leiomyoma of the uterus (18). Metastatic PA presents the same histological features than non-metastatic PA, showing an admixture of two components: An epithelial component, consisting of benign ductal structures and myoepithelial cells and a metaplasic mesenchymal appearing component, showing fibrous, chondroid or myxoid features. Histopathologic criteria as well as clinical criteria are absent. In most cases reported, as in our case, the patients had at least one episode of tumour recurrence at the primary site, before the development of metastasis, which may occur many years later after the presentation of the PA (5,24). Qureshi et al (16) reported a case in which bone metastasis appeared 16 years after a PA of the parotid gland was treated. Usually metastatic PA produces haematogenous metastasis to the lungs, bone and other organs, although lymphatic metastases have been also reported (5). The percentage of patients dying of metastatic disease is quite high 22% (19), and therefore these neoplasms should not be considered as benign in spite that the metastatic foci show benign histological features. Some authors have favoured to classify metastatic PA as low-grade malignant salivary gland neoplasms. Unfortunately the clinical, histopathologic and DNA-content findings were not predictive of which salivary PA will metastasise and which patients will die of metastatic disease (19).

Some hypothesis have been raised in order to explain how a histological benign tumour may produce metastasis, such as previous radiation of the primary tumour or previous surgical intervention that should favour permeation of vessels by tumour cells, followed by metastatic spread. However the data reported in the literature do not support such hypothesis (5) having shown that they are not absolute requisites for the production of metastasis.

More probably, the metastatic capability of PA reflects the accumulation of key genetic alterations, since the malignant transformation of neoplasms, according to the actual knowledge in the genesis of tumours, is a sequential process in which the accumulation of genetic alterations causes histological and biological progression. For instance, the development of a carcinoma ex mixed tumour apparently could be, in part, the consequence of the accumulative loss of chromosomal loci at 3p, 9p, and 17p (20-28).

The order of genetic alterations along tumor progression is not absolute and may vary for each tumor (21), which would explain certain cases. Hellquist and Michaels (22) reported the metachronous development of metastasis to a regional lymph node and subsequent carcinoma ex mixed tumour in a PA. Minic (8) described a carcinoma ex mixed tumour that produced lymph node metastases in which benign and malignant histological features were alike present. Czader et al (9) reported a unique case of metastatic PA in which the patient presented a solitary kidney tumour that showed the histological features of a PA in the absence of a previous or concurrent salivary gland tumour. One year after the removal of the kidney tumour, the patient presented an aggressive parotid tumour. After surgical excision the pathological examination discovered a high grade carcinoma arising from a PA.

The most widely accepted procedure today is total parotidectomy with conservation of the facial nerve unless this has been invaded by the tumor (23). Since conventional aspiration biopsy does not predict preoperatively how the tumor will behave, there is a great deal of uncertainty about which surgical attitude should be taken inn every case.

Intraoperative confirmation is the only procedure that can suggest a particular therapy i.e. whether radical exeresis including removal of the facial nerve or neck dissection is needed. Radiotherapy alone is not considered to be effective. Some authors, however, do consider radiotherapy to be efficient as a complementary treatment (9,15).

One decisive criteria in prognosis is the infiltration of the margins of resection. Local recurrence, regional metastasis and survival all depend on whether the margins are affected. In a study of 40 cases, Tortoledo (4) linked survival to the spread of invasion beyond the capsule in carcinomas ex-pleomorphic adenomas. Nourei on his analysis of 42 published cases of metastatic PA, revealed the relation between improper resection and recurrence. This relation is even more significant when dealing with carcinoma ex- pleomorphic adenomas (28)

Local recurrence makes prognosis worse and is apparently related to incomplete resection at first surgery. Uncontrolled recurrence is a risk factor for distant metastasis. This group of patients should be scheduled for a postoperative radiotherapy treatment in order to prevent possible distant spread. The metastatic disease, if respectable, should be treated surgically (29).

Conclusions

Metastatic pleomorphic adenoma is a very infrequent neoplasm. Some hypothesis have been raised in order to explain how a histological benign tumour may produce metastasis, such as previous radiation of the primary tumour or previous surgical intervention that should favour permeation of vessels by tumour cells, followed by metastatic spread. However the data reported in the literature do not support such hypothesis having shown that they are not absolute requisites for the production of metastasis. Tumour enucleation should never be performed as it increases local recurrence rate. Local recurrence may be the first step in the dissemination of these neoplasm and therefore radical surgery and radiotherapy should be considered in these cases.

Bibliografía

1. Gnepp DR, Wenig BM. Surgical Pathology of the Salivary Gland. Philadelphia: WB Saunders; 1991 p. 350-68.
2. Eneroth CM. Incidence and prognosis of salivary-gland tumours at different sites. A study of parotid, submandibular and palatal tumours in 2632 patients. Acta Otolaryngol Suppl. 1969;263:174-8.
3. Kirklin JW, Mcdonald JR, Harrington SW, New GB. Parotid tumors; histopathology, clinical behavior, and end results. Surg Gynecol Obstet. 1951 Jun;92(6):721-33.
4. Tortoledo ME, Luna MA, Batsakis JG. Carcinomas ex pleomorphic adenoma and malignant mixed tumors. Histomorphologic indexes. Arch Otolaryngol. 1984 Mar;110(3):172-6.
5. Wenig BM, Hitchcock CL, Ellis GL, Gnepp DR. Metastasizing mixed tumor of salivary glands. A clinicopathologic and flow cytometric analysis. Am J Surg Pathol. 1992 Sep;16(9):845-58.
6. Ellis Gl, Auclair PL. Malignant epithelial tumors. In: Ellis GL, Auclair PL, eds. Tumors of the salivary glands. Washington, DC: Armed Forces Institute of Pathology, 1996:39 –136.
7. Fujimura M, Sugawara T, Seki H, Otawara Y, Sakuma T, Nakano Y, et al. Carcinomatous change in the cranial metastasis from a metastasizing mixed tumor of the salivary gland--case report. Neurol Med Chir (Tokyo). 1997 Jul;37(7):546-50.
8. Minić AJ. Unusual variant of a metastasizing malignant mixed tumor of the parotid gland. Oral Surg Oral Med Oral Pathol. 1993 Sep;76(3):330-2.
9. Czader M, Eberhart CG, Bhatti N, Cummings C, Westra WH. Metastasizing mixed tumor of the parotid: initial presentation as a solitary kidney tumor and ultimate carcinomatous transformation at the primary site. Am J Surg Pathol. 2000 Aug;24(8):1159-64.
10. Seifert G, Sobin LH. The World Health Organization's Histological Classification of Salivary Gland Tumors. A commentary on the second edition. Cancer. 1992 Jul 15;70(2):379-85.
11. Foote FW and Frazell EL. Tumors of the major salivary glands. Atlas of tumor pathology: Section IV- Fascicle 11, 1954. Washington: Armed Forces Institute of Pathology.
12. Chen KT. Metastasizing pleomorphic adenoma of the salivary gland. Cancer. 1978 Nov;42(5):2407-11.
13. Rosai J. Major and minor salivary glands. In: Ackerman´s Surgical Pathology. CV St. Louis Mosby. 1989:125-96.
14. Spiro RH, Huvos AG, Strong EW. Malignant mixed tumor of salivary origin: a clinicopathologic study of 146 cases. Cancer. 1977 Feb;39(2):388-96.
15. LiVolsi VA, Perzin KH. Malignant mixed tumors arising in salivary glands. I. Carcinomas arising in benign mixed tumors: a clinicopathologic study. Cancer. 1977 May;39(5):2209-30.
16. Qureshi AA, Gitelis S, Templeton AA, Piasecki PA. "Benign" metastasizing pleomorphic adenoma. A case report and review of literature. Clin Orthop Relat Res. 1994 Nov; 308:192-8.
17. Bertoni F, Present D, Sudanese A, Baldini N, Bacchini P, Campanacci M. Giant-cell tumor of bone with pulmonary metastases. Six case reports and a review of the literature. Clin Orthop Relat Res. 1988 Dec; 237:275-85.
18. Wentling GK, Sevin BU, Geiger XJ, Bridges MD. Benign metastasizing leiomyoma responsive to megestrol: case report and review of the literature. Int J Gynecol Cancer. 2005 Nov-Dec;15(6):1213-7.
19. Batsakis JG. Malignant mixed tumor. Ann Otol Rhinol Laryngol. 1982 May-Jun;91(3 Pt 1):342-3.
20. Johns MM 3rd, Westra WH, Califano JA, Eisele D, Koch WM, Sidransky D. Allelotype of salivary gland tumors. Cancer Res. 1996 Mar 1;56(5):1151-4.
21. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990 Jun 1;61(5):759-67.
22. Hellquist H, Michaels L. Malignant mixed tumour. A salivary gland tumour showing both carcinomatous and sarcomatous features. Virchows Arch A Pathol Anat Histopathol. 1986;409(1):93-103.
23. Paris J, Facon F, Chrestian MA, Giovanni A, Zanaret M. Recurrences of pleomorphic adenomas of the parotid: changing attitudes. Rev Laryngol Otol Rhinol (Bord). 2003;124(4):229-34.
24. Yoshizaki T, Kinsen H, Minato H, Kita T, Furukawa M. Metastasizing mixed tumour of the parotid gland presenting as multiple lung metastases. J Laryngol Otol. 2004 Sep;118(9):724-6.
25. Steele NP, Wenig BM, Sessions RB. A case of pleomorphic adenoma of the parotid gland metastasizing to a mediastinal lymph node. Am J Otolaryngol. 2007 Mar-Apr;28(2):130-3.
26. Van der Schroeff MP, De Ru JA, Slootweg PJ. Case-report: metastasizing pleomorphic adenoma of the parotid gland. B-ENT. 2007;3(1):21-5.
27. Nouraei SA, Ferguson MS, Clarke PM, Sandison A, Sandhu GS, Michaels L, et al. Metastasizing pleomorphic salivary adenoma. Arch Otolaryngol Head Neck Surg. 2006 Jul;132(7):788-93.
28. M Mateos, J. Rodriguez, G Forteza, A Raventós, JJ Sirvent. Metástasis clavicular por carcinoma ex-adenoma pleomorfo de glándula submaxilar. Rev Esp Cir Oral Maxilof 2003 mar-abrl; 25 (2):55-9.
29. Bradley PJ. 'Metastasizing pleomorphic salivary adenoma' should now be considered a low-grade malignancy with a lethal potential. Curr Opin Otolaryngol Head Neck Surg. 2005 Apr;13(2):123-6.