Dental Research Journal

Case Report

Unusual metastasizing pleomorphic adenoma of the parotid gland involving locoregional lymph nodes

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ABSTRACT

Carcinoma ex-pleomorphic adenoma (PA) is a complex group of malignant neoplasms arising in PA. When microscopic features of the neoplastic cells are representative of carcinoma, the pathologist can easily make a definite diagnosis, but when worrisome morphology is replaced by metastatic behavior, the metastasizing PA (MPA) is a diagnostic challenge for the pathologist. Here, we present an unusual MPA to cervical lymph nodes and discuss diagnostic challenges.

Received: 21-Jun-2024
Revised: 05-Nov-2024
Accepted: 15-Jan-2025
Published: 20-Feb-2025

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Key Words: Cancer of parotid, dissection, lymph node, lymphatic metastasis, mixed salivary gland tumor

INTRODUCTION

One to five percent of all human neoplasms are salivary gland tumors.[1] Pleomorphic adenoma (PA), commonly known as a mixed tumor, is a slow-growing, benign tumor that is often well circumscribed. The main treatment intervention is surgical management. Recurrence rates following tumor enucleation have been reported, ranging from 20% to 45%.[2] The parotid gland is the most commonly affected site by PA.[1] Metastasizing PA (MPA) is an extremely rare salivary gland neoplasm. The World Health Organization (WHO) classified MPA as "histologically identical to PA, but with inexplicable regional or distant metastases" in their classification of salivary gland neoplasms in 2005.[1] MPA has been moved from "malignancy" to "benign epithelial tumor" in the 2017 WHO classification due to recent reclassification that prioritizes histological appearance over clinical features; however, it still carries an alert due to its aggressive behavior. The importance of microscopic features in categorizing different types of neoplastic lesions of major salivary

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Website: www.drj.ir
www.drjjournal.net
www.ncbi.nlm.nih.gov/pmc/journals/1480
DOI: 10.4103/drj.drj_274_24

How to cite this article: SeyedForootan F, Motiee-Langroudi M, Moradi M, Aminishakib P. Unusual metastasizing pleomorphic adenoma of the parotid gland involving locoregional lymph nodes. Dent Res J 2025;22:4.

glands may be the reason for the emphasis on histopathological examination in the diagnosis of these conditions.[1]

Clinically, it manifests as a painless mass in the parotid that grows slowly. This malignancy is linked to the facial nerve's symptoms of fast development and compression.[3] On ultrasonography, MPA has rounded, hypoechoic, and well-delineated lobulated outlines. It appears uniform, smooth, and well-defined on computer tomography (CT) and has higher attenuation than the parotid parenchyma around it. Although the size varies, the little lesions are more confined and homogenous, whereas the greater lesions might have irregular borders, enhancement, calcifications, necrotic regions, and/or hemorrhagic areas.[4,5] Histologically, the primary salivary gland tumor and metastatic component reveal the typical combination of benign-appearing mesenchymal and epithelial PA. Although there may be rare mitotic figures and mild nuclear pleomorphism, the tumor is not clearly histologically malignant.[3]

The diagnosis of this malignant neoplasm is definitely made after histological assessment of both the initial tumor and any subsequent metastases. The pathogenesis is thought to take place hemogenously by surgical disruption or partial resection of original PAs. The common treatment approach for accessible tumors is full surgical excision of the main tumor and any metastases, as inadequate enucleation might result in recurrence.[6,7] The most common operation is total parotidectomy with facial nerve preservation, unless the nerve has been invaded by the tumor. Utilizing adjuvant radiation is recommended in advance cases.[8] Comprehensive reporting is necessary to better comprehend the biochemical differences, treatment outcomes, prognosis, and survival rates between non-MPA and MPA.[3,9]

CASE REPORT

A 34-year-old male patient was referred to our institution with a swelling on the right side of his face and submandibular region. Magnetic resonance imaging (MRI) study revealed multinucleated 30 mm × 21 mm mass at the deep lobe of the parotid gland with parapharyngeal extension. Furthermore, lower parapharyngeal area, submandibular region, and superior part of anterior neck space were infiltrated by tumoral nests. Furthermore, the lowest tumoral seeding is just superior to the level of the right thyroid lobe at anterior neck space and lymphadenopathy was significant at levels I and IIB [Figure 1b-d].

Based on the well-recognized microscopic features of PA, no significant differential diagnosis was considered until the occurrence of locoregional metastases to cervical lymph nodes, the primary diagnosis based on incisional biopsy was "PA." The complete superficial and deep parotid lobes were resected with facial nerve preservation [Figure 1a]. Furthermore, submandibular content and cervical lymph nodes at level I and IIB were resected. Histopathologic examination of the excised lesion showed a morphologically benign PA composed of duct-like structures lined by inner epithelial and outer myoepithelial cells in a fibromyxoid stroma [Figure 1e, f and i, j]. Forty-six out of 59 cervical lymph nodes were invaded by tumoral nests demonstrating locoregional metastasis [Figure 1g and h]. Then, the final diagnosis was made as "MPA."

The patient received 30 fragments of adjuvant radiation therapy. The patient reported asymmetry and swelling on the right side of his face during his postoperative visit. Because there was no sign of recurrence or metastasis, no more treatment, including chemotherapy, was administered, and after 12 months of follow-up, an MRI study revealed suspicious areas indicating a recurrence of the tumor. An incisional biopsy confirmed the recurrence of the lesion at the previous surgical site.

DISCUSSION

Malignant mixed tumors of the salivary glands are uncommon, making up <1% of all salivary gland tumors.[10] They are classified into three types, the first two of which have clearly malignant histologic characteristics: carcinosarcoma, carcinoma ex PA, and MPA.[11]

MPA is an uncommon malignant tumor that is histologically identical to PA but can nevertheless cause secondary tumors in distant locations,[9,12,13] particularly in cases where the excision was not completed.[14,15]

Histological analysis of removed tissue from the main site and metastases often reveals a PA with extensive chondromyxoid stroma and no evidence of malignancy.[16] These tumors are more likely to show with a localized absence of the pseudocapsule, as well as pseudopodia and satellite nodules.[17] Some experts believe that mitotic activity and infiltrative growth patterns in the initial tumor are crucial in determining

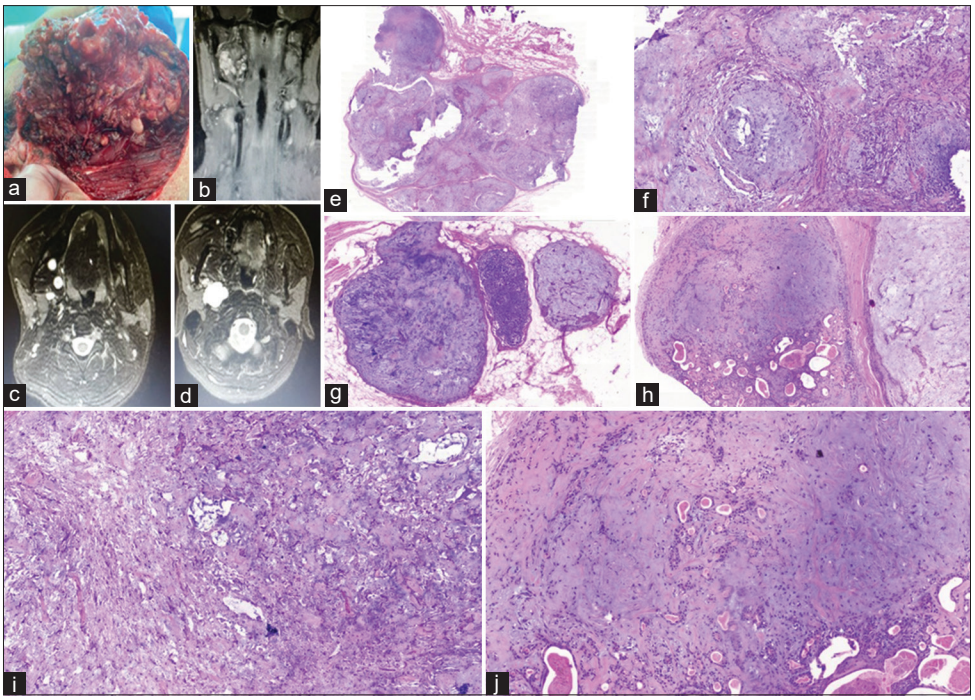

Figure 1: (a) Carcinoma ex-pleomorphic adenoma of the right parotid. Intraoperative view of parotidectomy and radical neck surgery (facial nerve invasion is noticeable); (b) neck region magnetic resonance imaging shows a mass at deep part of right parotid with parapharyngeal extension and cervical lymphadenitis; (c and d) head and neck computer tomography scan showing a well-circumscribed hypoecho mass lesion located in the right parotid gland space; (e) histopathology of the resected specimen reveals an encapsulated PA composed of myxoid, chondroid, and mucoid materials; (f) myoepithelial cells with spindle or stellate cytomorphology in myxochondroid background; (g) there is a rupture of the fibrous capsule and tumor cells are slightly invade the surrounding fat tissues; (h) there is mucinous metaplasia in some areas; (i and j) high magnification of the specimen demonstrates hypocellular areas with scattered various-sized ducts showing no significant cellular atypia in a chondroid stroma.

metastatic potential.[14] Furthermore, the histologic subtypes of primary and recurring PAs may differ, and metastatic deposits may consist mostly of cellular or myoepithelial components.[17]

However, the presence of both benign (PA) and malignant (carcinoma) components on histologic examination is necessary for the pathological diagnosis of carcinoma ex-PA; the ratio of carcinoma to adenoma varies greatly among patients. The malignant component can be identified by histopathologic examination as either of the following: adenocarcinoma not otherwise specified (the most common type), adenoid cystic carcinoma, squamous cell carcinoma, myoepithelial carcinoma, or salivary duct carcinoma. Mixed types can also be encountered.[18] The most common malignant signs include significant pleomorphism, elevated nuclear-to-cytoplasmic ratios, necrosis, bleeding, numerous mitotic figures, including atypical forms, and perineural and perivascular invasion. There is no dominant low-power architectural pattern; instead, there are several patterns.[19,20]

The parotid gland is the most common main location of a MPA. Complete excision of this gland is challenging because of important anatomical concerns such as the existence of the facial nerve.[15] According to earlier studies [Table 1], the primary PA and the discovery of metastases are frequently detected after a considerable amount of time (mean: 15 years; maximum: 51 years).[3,35,36] PA metastasizes most frequently to the lung (33.8%), cervical lymph nodes (20.1%), and bone (36.6%). The kidneys, skin, liver, and brain are other locations.[12,13]

The prognosis for MPA is challenging to determine due to limited reporting. This is mainly because of the lack of long-term follow-up and the publication of case reports shortly after treatment. The disease-free period and survival rates vary significantly. Multiple metastases are considered a poor prognostic factor and are typically fatal.[9] Complete resection is the basis of treatment. The possibility of distant metastases is increased when enucleation leads to incomplete resection, hence increasing the chance of local recurrence.[15] A superficial parotidectomy can be used to remove a benign salivary gland tumor located in the superficial lobe of the parotid gland.[37] If a facial nerve was unaffected, total

Table 1: Metastasizing pleomorphic adenoma with locoregional involvement of cervical lymph nodes according to previous case reports

Author	Year	Sex - age	Location	Age of LRM	Treatment	Follow-up
Collina *et al*.[21]	1989	Male - 8	Parotid	11	Parotidectomy and selective neck dissection	No evidence of recurrence at 3 years
	1989	Female - 26	Submandibular	35	Surgical resection and selective neck dissection	No evidence of recurrence at 1 year
Ferlito *et al*.[22]	1991	Female - 42	Parotid	44	Subtotal parotidectomy and selective neck dissection	NF
Wenig *et al*.[12]	1992	Male - 15	Parotid	27	Simple excision	Three recurrences at 1, 3, and 12 years
Commins *et al*.[23]	1995	Male - 23	Parotid	41	Total parotidectomy and en bloc neck dissection	No evidence of recurrence at 2 years
Chen and Tu[24]	2000	Female - 29	Parotid	51	Total parotidectomy with neck dissection	No evidence of recurrence at 8 months
Hay *et al*.[25]	2001	Female - 36	Parotid	47	Surgical resection and neck dissection	NF
Sabesan *et al*.[26]	2007	Male - 33	Parotid	61	Superficial parotidectomy and selective neck dissection	No evidence of recurrence at 2 years
Larbcharoensub *et al*.[27]	2009	Female - 27	Parotid	40	Surgical resection and radiotherapy	NF
	2009	Female - 32	Parotid	42	Surgical resection	NF
	2009	Female - 36	Submandibular	45	Surgical resection	NF
Qureshi *et al*.[28]	2009	NR	Parotid	65	NR	NF
	2009	NR	Submandibular gland	53	NR	NF
Soteldo and Aranaga[29]	2017	Male - 18	Parotid	36	Parotidectomy with selective cervical dissection	No evidence of recurrence at 2 years
Nagarajah *et al*.[30]	2017	Female - 40	Parotid	55	Superficial parotidectomy and neck dissection	No evidence of recurrence at 1 month
Wong *et al*.[31]	2019	Female - 31	Parotid	61	Resection of the tumor and selective neck dissection	No evidence of recurrence at 6 months
Wasserman *et al*.[32]	2019	Male - 34	Parotid	59	Surgical resection	Two recurrences at 6 and 25 years
Ko *et al*.[33]	2022	Male - 48	Parotid	48	Superficial parotidectomy with selective neck dissection	No evidence of recurrence at 2 years
Catarzi *et al*.[34]	2024	Female - 27	Parotid	35	Total parotidectomy with lymph node dissection	NF

LRM: Locoregional metastasis; NF: Not found; NR: Not reported; MPA: Metastasizing pleomorphic adenoma

parotidectomy was the most common treatment for recurrent MPA.[29] In terms of treating regional neck metastasis, elective neck dissection is advised in cases with high-grade histological malignancy and formal neck dissection should be carried out for clinically obvious nodal metastases of parotid malignancy.[38] For rare cases of unresectable MPA, radiotherapy may be used.[39,40] Surgical excision is the preferred treatment for metastases in accessible sites. The effectiveness of radiotherapy in treating metastases and preventing new lesions is limited.[14,41,42] However, some authors advocate for adjuvant postoperative radiotherapy to prevent the potential spread of hidden local recurrence to distant sites.[8]

To differentiate between MPA and the conventional type of this tumor, cytogenetic studies are necessary due to their different clinical evaluations. In addition, precise imaging of cervical regions should be included in routine clinical examinations and follow-ups of patients with PA to rule out any locoregional lymph node metastasis.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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