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Case Report

Title:

Polymorphous Low-Grade Adenocarcinoma **of the Parotid gland: A rare entity in Asians with a unique cystic presentation.**

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Abstract

Polymorphous low-grade adenocarcinoma (PLGA) is a rare entity scarcely reported in major salivary glands, with minimal incidences in the Asian population. It generally presents as a solid tumor with morphological diversity and variable histological patterns. This article reports PLGA of the parotid gland, mimicking a

cystic lesion in an Indian male, with a review of relevant literature. A 64-year-old male patient presented with a slow-growing swelling of the left parotid region for the last 10 years. The cytology report suggested a cystic swelling. The patient underwent a superficial parotidectomy. A detailed histopathological examination confirmed it as PLGA. The patient remains disease over 24 months of post-surgery follow-up.

Key Clinical Message: PLGA is a rare malignancy arising de novo or ex-PMA from salivary glands' terminal (intercalated) duct cells. The recommended treatment of PLGA, independent of its location, consists of the wide local surgical excision, and neck dissection should be added only in cases with cervical lymphadenopathy.

Keywords: Lymphoepithelial cyst, Parotid gland, Pleomorphic adenoma, Polymorphous adenocarcinoma, Polymorphous Low-Grade adenocarcinoma, Salivary gland tumor.

INTRODUCTION

Polymorphous low-grade adenocarcinoma (PLGA) is a rare malignant epithelial tumor of salivary glands and was first described as a distinct clinicopathological entity-"Lobular carcinoma", by Freedman and Lumerman in 1983.[1] Evans and Batsakis suggested the term polymorphous low-grade adenocarcinoma for the tumor in 1984.[2] Due to its polymorphous histology and indolent clinical behavior, the WHO also adopted the term in its second classification of histological typing of salivary gland tumors in 1991.[3] The WHO classification of salivary gland tumors (2018) categorized the indolent PLGA as a classical variant of Polymorphous adenocarcinoma (PAC), being defined as "a malignant epithelial tumor characterized by cytological uniformity, morphological diversity, an infiltrative growth pattern, and low metastatic potential".[4]

PLGA has been reported in the 3rd to 7th decade of life, with over 90% of cases occurring above 40 years, with a mean age of 61.3 years at diagnosis.[5] This tumor has a clear female predilection in a ratio of 2.15:1.[6] Although rare, it is the second most common malignancy of the minor salivary glands (MiSG) located frequently in the posterior hard and soft palate (60% of cases, range: 49%-87%). The incidences of occurrence in the labial and buccal mucosa, retromolartrigone, tongue, floor of the mouth, nasal cavity, paranasal sinuses, larynx, trachea, and bronchi have also been reported.[5-7] It may occasionally originate in major salivary glands, particularly the parotid, in 3% (0% to 9%) case.[5,7] The tumor also shows racial preponderance, with 75 % of cases reported in whites and less than 2 % (0.5%-1.6%) in Asians.[6,7] As per the author's literary search, a total of nine cases of PLGA in the parotid gland have been reported by Asian authors till 01/06/2023 (Table 1). Only three cases (Case No.1,3,5) have been reported from India to date.The present case describes the rare occurrence of PLGA presenting with a unique cystic appearance, the first of its kind, in the parotid gland of an Indian male.

CASE HISTORY/EXAMINATION

A 64-year male patient reported having complained of left cheek swelling for the last 10 years. History revealed that it started as a small painless nodule that progressed slowly over time without any associated symptoms, such as dysphasia, dysphonia, dysphagia, odynophagia, otalgia, or odontophagia. He had visited several regional professionals for the same and was prescribed antibiotics for the aural and dental infections. The drainage through a local incision was also attempted three years back without significant results. No record of previous intervention was available with him.

Clinical examination recorded a swelling of 4×4 cm size in the left preauricular region with extension to the infra-auricular area (Fig. 1a).It was non-tender, non-fluctuant, localized, firm in consistency, and had well-defined margins without any fixation to the underlying structures on palpation. There was an absence of cervical lymphadenopathy, and the facial nerve functions were maintained without any evidence of weakness. The detailed head and neck examination identified no other significant etiological factor. The hematological and biochemical liver and renal function tests were within normal range. The viral markers were negative for HIV and Hepatitis B infection. Fine needle aspiration cytology using a 26 gauge needle suggested a cystic lesion (Fig. 1b). A rapid filling of the swelling immediately after the pathologist also reported FNAC. Pre-operative contrast-enhanced computed tomography (CECT) recorded a well-defined cystic mass of 43×41×39

mm in the left parotid with peripheral enhancement and extension into the deep lobe (Fig. 1c and 1d). A provisional diagnosis of a benign lymphoepithelial cyst or Warthin's tumor was suggested.

METHODS

Based on thefindings above, the case was planned for superficial parotidectomy with preservation of the facial nerve under general anesthesia, and written informed consent was taken. The site was approached through a modified Blair incision (Fig. 2a),and a single 5cm x6cm soft tissue mass was obtained (Fig. 2b).

The specimen was sent for a detailed histopathological examination. The postoperative flap necrosis was observed on day 5 (Fig. 3a)and managed conservatively. Sutures were removed on the 10^{th} day, and the patient was discharged on the 25^{th} day without any postoperative complications (Fig. 3b).

The histopathology reported that a 5x4x3cm mass exhibited a hemorrhagic, fluid-filled cut section macroscopically. Microscopically, an infiltrative pattern at the periphery was evident (Fig. 4a). The cells were arranged in various architectural patterns, including tubular, trabecular, solid, and cribriform (Fig. 4b and 4c). The small to medium-sized round tumor cells had a uniform shape, an indistinct border, and eosinophiliccytoplasm (Fig. 4d and 4e). Their nuclei were round to ovoid that contained open vesicular nuclear chromatin and inconspicuous nucleoli (Fig. 4d and 4e). Considering the histological features, the final diagnosis of PLGA was made. It was further confirmed by the positivity of S-100 on immunohistochemistry (Fig. 4f). The patient was informed about the diagnosis and potential complications and referred to a higher center for postoperative radiotherapy. However it was rigidly refused by himdue to anticipated complications. His postoperative CT recorded the signs of chronic parotitis without any evidence of residual disease. The patient was recalled monthly for the first 3 months, followed by every three months at the present institute. The patient was asymptomatic without evidence of recurrence, metastasis, or associated complications at the final follow-up of 24 months. The scheduled follow-ups are expected to be carried out in the future to assess the treatment's long-term outcome.

DISCUSSION

PLGA is a rare malignancy arising de novo or ex-PMA from salivary glands' terminal (intercalated) duct cells.[6] It generally presents as an oval, firm to solid, circumscribed, slow-growing swelling with variable histological pattern.[5,6] The FNAC is recommended to be the first-line tissue-based testing procedure for establishing the pre-surgical diagnosis for major salivary gland PGLA.[5,8] However, the procedure is challenging because of limited tissue access and variable cytoarchitectural findings.[8] The cytological smears of PLGA are hypercellular with branched papillary clusters and sheets of uniform cells with moderately eosinophilic cytoplasm; round-to-oval nucleus with bland or absent nucleoli; finely stippled chromatin; and abundant hyaline globules within the matrix.[8] Contrarily, these findings were completely absent in the present case, and the smear suggested a cystic lesion. Due to the absence of any specific radiographic features, the role of imaging for PLGA is also limited to assessing its origin, local extent, and any regional or distant metastasis rather than distinguishing a distinct diagnosis. The PLGAs of parotid gland had mostly been provisionally misdiagnosed as pleomorphic adenomas, adenoid cystic carcinoma, epidermal tumor, chronic parotitis, and multicystic lesion, etc., in the literature (Table 1), thereby revealing the lack of specificity of the pre-operative diagnostic testing for them.

Table 1.Summary of cases of PLGA of parotid gland reported in the Asia continent.

Case No.	Age/ Sex	Origin	Pre-operative Diagnosis	Treatment	Follow-up	Outcome
1	16/M	Ex -PMA	PMA on FNAC	Surgery, RT	33 months	NAD
2	21/F	denovo	Low-grade papillary neoplasm on FNAC	Surgery	NM	NM
3	25/F	denovo	Epithelial Parotid tumor on Punch biopsy	Surgery, RT	1 year	NAD
4	35/M	denovo	Multicystictumoral mass on USG	Surgery	NM	NM
5	25/M	de novo	Chronic Parotitis	Surgery	NM	NM
6	52/ F	de novo	Parotid Mass on CT	Surgery, RT	50 months	NAD

Case No.	Age/ Sex	Origin	Pre-operative Diagnosis	Treatment	Follow-up	Outcome
7	55/F	Ex-PMA	Parotid tumour on CT and MRI	Surgery	6years	Local Recu
8	79/M	de novo	ACC on excisional biopsy	Surgery	14 months	NAD
9	65/M	denovo	Carcinoma ex-PMA	Surgery	46 months	Local Recu

PMA -Pleomorphic adenoma, **FNAC** - Fine needle aspiration biopsy, **ACC** -Adeniod cystic carcinoma, **RT** -Radiotherapy,**NM** - Not Mentioned, **NAD** -No abnormality detected.

The present tumor was also, provisionally described as a lymphoepithelial cyst or Warthins tumor on the CECT examination. Predicting a benign neoplasm with negligible metastatic potential, the case was surgically managed by a minimally invasive option of superficial parotidectomy with facial nerve preservation. The pathology was disparate from the pre-operative diagnosis and reported as the rare polymorphous low-grade adenocarcinoma of the parotid gland. It was concluded to be the classical variant as per the WHO 2017 classification due to clinical evidence of slow growth with the absence of local or distant metastasis over the last 10 years and the presence of small to medium cells in multiple patterns, targetoid cells, and <30 % of cribriform areas.[4] It was further confirmed by the diffuse positivity for the S-100 stain, which is reported to be associated with more than 90 % of reported cases.[16]

The recommended treatment of PLGA, independent of its location, consists of the wide local surgical excision, and neck dissection should be added only in cases with cervical lymphadenopathy.[17] The complete surgical excision of the parotid gland was not accomplished for the present case as the initial treatment plan was framed, considering it a benign lesion. The role of postoperative radiotherapy is ambiguous in the treatment of PLGA. It may diminish the local recurrence of tumors having high-risk features, closed margins, perineural invasion, etc [6]. However, the recurrence might take years to develop in PLGAs without adverse features with negative or even positive margins.[6,17] The main limitation of the present case is the non-accomplishment of radiotherapy due to the patient's denial. As the tumor was a classical variant suspected to have an indolent course and the postoperative CT scan also recorded minimal residual disease, he is kept under the regular three-month follow-up to detect the earliest sign of any anticipated complications.

CONCLUSION AND RESULTS

PLGA of the parotid gland is a rare entity in the Asian population with diverse morphology and cytological patterns. The available pre-operative investigations have a limited role in its diagnosis, and a detailed histopathological examination is the standard for confirmation.

AUTHOR CONTRIBUTION: IPK, PD, MS Conceptualization; data curation; resources; software; writing – original draft; writing – review and editing. **VP, AM, JS, NS** Conceptualization; formal analysis; supervision; writing – original draft; writing – review and editing. All authors agreed to the final version of the manuscript.

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GUARANTOR

All the authors are nominated guarantors of the manuscript.

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Legends

Legend for Table

Table 1. Summary of cases of PLGA of parotid gland reported in the Asia continent.

Legend for Figure

Figure 1. Pre-operative presentation of the pathological swelling: (a) clinical view. (b) cytological smear-cystic fluid with scanty macrophages (100X). (c) CT scan-axial view showing left parotid swelling. (d) CT scan- coronal view showing left parotid swelling.

Figure 2 . Intra-operative presentation: (a) Modified Blair incision. (b) soft tissue pathological mass of size 5cm X 6cm.

Figure 3. Postoperative presentation of the surgical site: (a) flap necrosis on the 5^{th} day postoperative. (b) residual scar at the time of discharge.

Figure 4. Histopathological images of biopsy: (a) peripheral infiltration of tumor -H&E stain; 100X. (b & c) arrangement of the tumor cells in various architectural patterns-H&E stain; 100X. (d & e) round tumor cells with indistinct borders, eosinophilic cytoplasm, round to oval nuclei, and inconspicuous nuclei- H&E stain; 100X. (f) tumor cell positive with IHC stain - S100antigen; 400X.