Case Report

Primary amelanotic malignant melanoma of parotid and submandibular salivary gland: A rare case report

Mehebuba Sultana, Rudra Prasad Chatterjee, Sanchita Kundu, SK Abdul Mahmud

Department of Oral and Maxillofacial Pathology, GuruNanak Institute Of Dental Science And Research, Kolkata, West Bengal, India

Abstract

Primary amelanotic malignant melanomas (AMMs) of the parotid and submandibular salivary glands are extremely rare with only a few reported cases due to its low incidence and misdiagnosis. Malignant melanoma (MM) has a high predilection for the head-and-neck region and majority of the cases in the parotid gland reported as association with metastasis in and around the gland from a cutaneous primary tumor. Immunohistochemistry is solely needed for confirmation of diagnosis and MMs give positive reactivity for melan-A, HMB-45, and S–100. Prognosis for AMM in the mucosal or salivary gland regions is much poorer than cutaneous regions because of anatomic considerations and its delayed diagnosis. The treatment of choice is radical surgery and parotidectomy along with radiotherapy and chemotherapy.

Keywords: Amelanotic melanoma, immunohistochemistry, positron emission tomography-computed tomography, salivary gland, WT-BRAF

Address for correspondence: Dr. Mehebuba Sultana, Department of Oral and Maxillofacial Pathology, Guru Nanak Institute of Dental Sciences and Research, Panihati, Kolkata, West Bengal, India.
E-mail: mehebubasultan@gmail.com
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INTRODUCTION

Malignant melanoma (MM) is a neoplasm of epidermal pigment-producing cells, i.e., melanocytes. It is the third-most common cancer of epithelium after basal cell carcinoma and squamous cell carcinoma. In Africa and Asia, the annual incidence rate of MM is only 0.2–0.4 per 100,000 population, affecting mainly palms, soles and mucous membranes. The incidence of oral melanomas occurs more in males (male: female = 2.8:1) with an average age of 56 years.[1] Among the five types of MM. Amelanotic malignant melanoma (AMM) is a rare subtype with little or no pigmentation that has been observed only in 1.8%–8.1% of cases.[2]

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Majority of AMM cases in the parotid gland reported in association with metastasis from a cutaneous primary tumor, usually from nonpigmented nodular type, as the parotid gland is known to act as a filtering center for lymphatic drainage in the head-and-neck region. Primary AMM of the parotid and submandibular gland are extremely rare, and there are only a few AMM case reports in English literature due to both of its low incidence and misdiagnosis.[1,3]

Clinically, AMM in the parotid gland presents as a rapid painful growth with normal to the erythematous surface epithelium. Metastasis to regional lymph nodes as well as distant structures is very common, while radiologically, it

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appears as a dense radiopaque mass in radiograph with the destruction of underlying structures.

Fine-needle aspiration cytology (FNAC) can be a noninvasive and helpful procedure for diagnosis; however, its utility remains controversial.[4,5]

Histopathologically, in AMM, tumor cells are large, round to ovoid with enlarged, hyperchromatic nuclei along with prominent nucleoli with or without any pigment production. This tumor can be readily confused with some other mesenchymal neoplasms such as atypical fibroxanthoma, malignant fibrous histiocytoma, malignant schwannoma, or spindle cell squamous cell carcinoma.

Immunohistochemistry (IHC) is considered an essential tool to confirm the diagnosis. Melanomas typically give positive reactivity for S100, melanoma-associated antigen (MAA), melan-A and HMB-45 as reported by Gazit and Daniels (1994).[1]

Prognosis for AMM in the mucosal or salivary gland regions is much poorer than cutaneous regions because of anatomic considerations and its delayed diagnosis.[6,7] Indicators of poor prognosis of AMM are the presence of malignant melanocytes in blood vessels, multiple or atypical mitoses and metastasis of tumor cells to regional nodes or other sites.

The treatment of choice for primary AMM involving the parotid gland is radical neck dissection and parotidectomy along with chemotherapy and radiotherapy. Immunotherapy and gene therapy are also under trial. In MMs, 5-year survival rates range from 4.5% to 29% after initial diagnosis, with a mean survival rate of 18.5 months.[8]

Based on the aforesaid findings, a 60-year-old female patient with an extensive AMM involving parotid and submandibular gland is discussed in this article with detailed clinical, radiological and histopathological features along with treatment procedure.

CASE REPORT

A 60-year-old female patient from semiurban area reported to the Department of Oral and Maxillofacial Pathology, Gurunanak Institute of Dental Sciences and Research, Kolkata, with the chief complaint of a large swelling over the left cheek region associated with pain for the last 5–6 months. A detailed history from the patient revealed that initially swelling was small with occasional pain, which was relieved after the use of antibiotics and painkillers for the last 3 years. Recently, after extraction of a carious tooth 36 FDI, the swelling rapidly increased in size to attain the present dimension. The patient also visited to the Department of ENT in Kolkata Medical College, where she was advised for FNAC. The report of FNAC by medical college revealed the presence of malignant epithelial cells in sheets, clusters and scattered singly with enlarged pleomorphic nuclei and abundant cytoplasm in a background of mucoid material, inflammatory cells and blood elements. Squamous differentiation was seen in some clusters, suggesting mucoepidermoid carcinoma (MEC). Thereafter, the patient visited to our Department around 5 months ago along with the FNAC report.

Extraoral examination revealed the presence of a large diffused, firm to hard, moderately tendered swelling involving the left parotid region, extending up to the submandibular region, measuring about 10 cm × 6.5 cm × 4.5 cm with erythematous skin surface [Figure 1a and b]. Regional cervical lymphadenopathy was present. Intraorally, no abnormality was noted [Figure 1c].

The patient was advised to perform magnetic resonance imaging (MRI) of head-and-neck region which revealed the presence of a large, solid mass measuring about 50 mm × 52 mm × 63 mm involving superficial and deep lobe of the left parotid and submandibular gland with an obscure boundary without any bony abnormality, suggestive of salivary gland carcinoma [Figures 2a and b].

Then, the patient was referred to maxillofacial oncosurgeon for surgical treatment and management. After 1 week, with the patient's consent, modified radical neck dissection was performed by oncosurgeon along with parotidectomy and submandibulectomy preserving the facial nerve.

The tumor specimen was sent to our Department for histopathological evaluation. The sections stained with H and E showed the presence of sheets of round-to-ovoid noncohesive cells being characterized by pronounced cellular and nuclear pleomorphism, cellular atypia and abnormal mitosis with concomitant

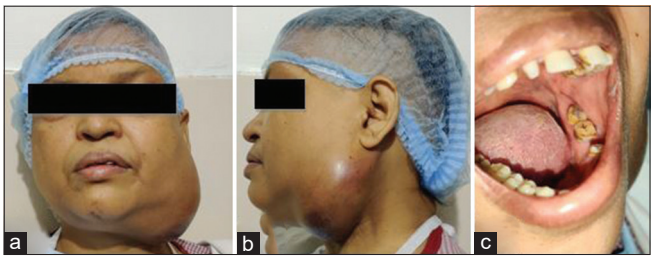


Figure 1: (a and b) Clinical image shows a large, diffuse swelling involving left parotid region extending upto submandibular region causing facial asymmetry. (c) Intraorally, no abnormality present

destruction of stromal architecture. Areas of extensive necrosis, hemorrhage and nonspecific inflammatory cell infiltration were also noted [Figure 3]. According to the light microscopic features, a primary diagnosis of "round cell malignant neoplasm" was made involving both the salivary glands.

To confirm the diagnosis, IHC was performed. Tumor cells showed positive staining for S-100, HMB-45 and Melan-A [Figure 4a-c] which confirmed the diagnosis of AMM. Moreover, the negative staining for pan CK, EMA, Vimentin, CD138 and leukocyte common antigen (LCA) [Figure 5a-c] excluded the differential diagnoses of epithelial carcinomas, ductal epithelial cell carcinomas, mesenchymal neoplasms, plasma cell tumor and hematopoietic neoplasms, respectively.

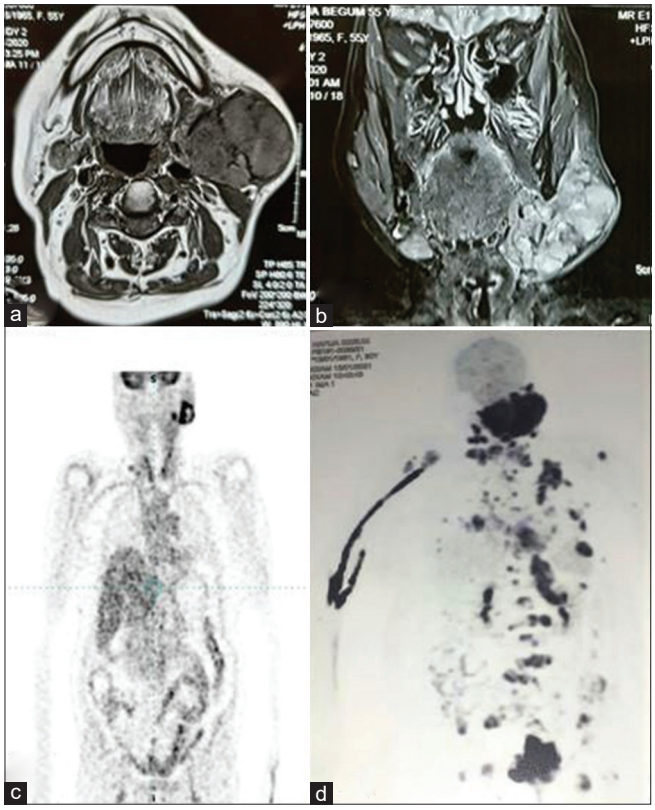
A confirmatory histopathological diagnosis of "primary AMM" was done after IHC staining, and the patient was referred to the medical oncologist for further necessary treatment and management.

A postsurgical whole-body positron emission tomography–computed tomography (PET-CT) with 18 fluorodeoxyglucose (F-FDG) injection of iodinized contrast was done as suggested by the medical oncologist, and the findings were suggestive of metastases of neoplastic cells in the masseter muscle, left upper buccal mucosa, left cervical and right supraclavicular lymph nodes along with multiple active skeletal metastases [Figure 2c].

Furthermore, the medical oncologist advised BRAF V600E-mutation analysis by RT-PCR method for more précised and targeted chemotherapy which revealed as wild type, i.e., WT-BRAF.

Meanwhile, after 3 months, the patient was followed up by the medical oncologist and received three cycles of chemotherapy consisting of cytotoxic and alkylating drugs such as cisplatin and dacarbazine, Aprecap as antiemetic drug, biologic response modifier like filgrastim which contains granulocytic colony-stimulating factor and bisphosphonate as zoledronic acid.

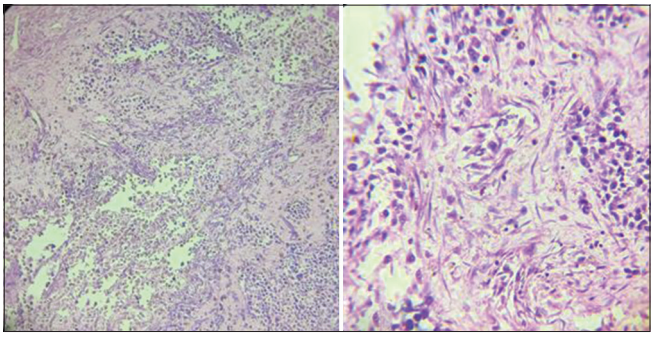
One week after the third chemotherapy, the medical oncologist advised for a repeat PET-CT to analyze the treatment protocol, prognosis and evaluation of metastases of the disease process, which revealed multiple active metastases throughout the body [Figure 2d]. However, within a week, the patient succum due to cardiorespiratory failure.



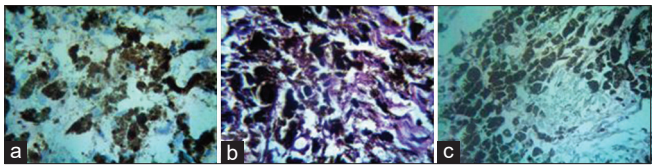
Figures 2: Radiographical images show (a) Axial view and (b) Coronal view of head and neck magnetic resonance imaging with the presence of a large, solid mass involving left parotid and submandibular salivary glands without any bony abnormality. (c) Postsurgical whole body Positron emission tomography–computed tomography scan with 18 fluorodeoxyglucose injection of iodinized contrast showing metastases of neoplastic cells in left masseter muscle, left buccal mucosa, left cervical and right supra-clavicular lymphnodes along with multiple active skeletal metastases. (d) Positron emission tomography–computed tomography scan after chemotherapy showing multiple metastases throughout the body

DISCUSSION

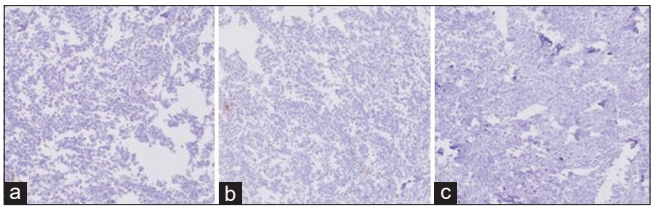
MMs of the head-and-neck region usually occur on facial skin, most commonly on the cheek. Amelanotic MM is a rare type of MMs, observed only in 1.8%–8.1% of cases.[3,9,10] Despite its rarity, melanoma is the most



Figures 3: Histopathological image shows the presence of sheets of round to ovoid noncohesive cells in a loose myxoid stroma (H and E stain, ×10, H and E, stain, ×40)



Figures 4: (a-c) Histopathological image shows positive staining for (a) S–100 (×100) (b) Melan-A (×100) and (c) HMB-45 (×100)



Figures 5: (a-c) Histopathological image shows negaitive staining for (a) EMA (×10) (b) LCA (×10) and (c) Vimentin (×10)

important pigmented lesion of the oral cavity due to its poor prognosis and high mortality rate. Primary AMM of the parotid gland along with submandibular salivary gland is exceptionally rare because of its wide-ranging clinical appearance without any pigmentation. To our knowledge, there was no previously reported case of primary AMM involving both parotid and submandibular salivary glands.

As melanocytes are derived from the neural crest cells and not a normal structural component of the salivary gland, the occurrence of primary melanomas. Of the parotid remains controversial.[3] Whereas, Greene and Bernier, in 1961 reported that these melanocytes rarely derived from melanoblasts which coalesce with the salivary gland tissue during the down growth of oral epithelium into underlying mesenchyme to form salivary ducts and tissues. They also reported that, certain cells from healthy normal parotid glands rarely tested positive for melanin, after staining with 3,4-dihydroxy-L-phenylalanine (L-DOPA) method. Green and Bernier (1961) published several criteria for the diagnosis of primary parotid MM (PPMM)[1,11] and in 1993, Woodward (WW's criteria) coined some criteria for the same, such as (i) The predominant tumor mass should be intra-parotid; (ii) there should be no identifiable lymph node tissue present in the mass; (iii) there should be no evidence of MM elsewhere after a diligent search of the eyes, skin, nose, pharynx, mouth, esophagus, anogenital region and meninges and (iv) there should be no evidence of the previous excision of a MM or progressing pigmented lesion.[3,4,11,12] Furthermore, later in 1997, Takada found melanocytes for the very first time in interlobular duct of the parotid gland in a Japanese male during performing autopsy.[3,13]

AMM most commonly affects older men compared to other types of melanomas,[2] while in the present case, the patient was a 60-year-old female having a diffused, large, firm to hard, moderately tendered swelling involving left parotidomasseteric region extending up to submandibular gland with erythematous overlying skin and mildly tendered and mobile regional cervical lymph nodes.

Radiologically, both head-and-neck CT scan and MRI of AMM usually presented as an intra-parotid mass with an undefined, obscure boundary with focal necrotic centers.[1,4]

Axial view of MRI of the present case was also showing a large, solid mass involving superficial and deep lobe of left parotid along with submandibular salivary gland without any bony abnormality, suggestive of malignancy involving the parotid and submandibular salivary gland.

FNAC is a noninvasive adjunct for diagnosis while its utility is still under controversy.[4,5] FNAC features of the present case were corroborating with MEC.

Histopathologically, AMM is characterized by the proliferation of large, mostly noncohesive, round, polygonal, spindle-shaped cells with large hyperchromatic nuclei along with areas of necrosis. A few cells may contain yellowish brown granules.[3,4] The H- and E-stained sections of our case, also revealed the presence of noncohesive, round-to-ovoid hyperchromatic cells with pronounced cellular and nuclear pleomorphism, cellular atypia, large nucleoli and abnormal mitosis along with the loss of stromal architecture and areas of necrosis, hemorrhage and nonspecific inflammatory cell infiltration, suggestive of round cell malignant neoplasm involving parotid and submandibular salivary gland.

To confirm the final diagnosis, IHC was performed and tumor cells showed positivity with S-100, melanin-A and HMB-45 antigens and negativity with pan CK, EMA, Vimentin, CD-138 and LCA antigens, which were satisfying the previously recorded IHC features of MM published in different case reports.[3,4,14,15]

Modern imaging techniques such as 18 F-FDG PET imaging is considered as more potent than CT and MRI in the assessment of metastases as it can detect primary melanoma at about 6 months earlier than other traditional imaging systems. While PET scan has limitations for metastases screening in the brain because of its physiologic uptake of FDG.[7] Whole-body PET-CT with 18 F-FDG findings of our case showed metastases in masseter muscle, left upper buccal mucosa, left cervical and right supraclavicular lymph nodes along with multiple active skeletal metastases.

The confirmatory diagnosis of primary amelanotic MM

in parotid gland has been established after assessing IHC and 18 FFDGPET-CT features along with the criteria laid down by Woodward in 1993.[3,4,12]

PPMMs are very rare and have a high potential for distant metastases to the lungs, brain, liver and bones.[16] Oral MMs are usually treated by surgical resection. The efficacy of chemotherapy and radiotherapy is difficult to evaluate because of the limited number of cases. Although our patient was treated by surgical resection along with three cycles of chemotherapy, the efficacy of these treatments was not judged as our patient died within 1 week after chemotherapy.

CONCLUSION

Primary AMM involving both parotid and submandibular salivary glands is extremely rare and aggressive neoplasm with controversial pathogenesis and very poor prognosis. To our knowledge, there are very few case reports of primary AMM involving the parotid gland, but this is the first reported case of primary AMM involving both parotid and submandibular salivary glands. It should be differentiated clinically, radiologically and immunohistochemically from other malignancies, such as adenosarcoma, squamous cell carcinoma, parotid lymphoma and other sarcomas of salivary glands. IHC, 18F-FDG-PET CT and WW's criteria are the main cornerstones for early diagnosis and better management of this aggressive malignant neoplasm.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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