

CASE REPORT

Primary oral myeloid sarcoma: Report of a case

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ABSTRACT

Myeloid sarcoma is defined as a tumor mass of immature myeloid cells that may be observed in a variety of locations including bone, skin, lymph nodes and soft tissues. However, oral involvement of myeloid sarcoma is extremely rare. These tumors are considered as specific lesions of acute myeloid leukemia. We present a case of a myeloid sarcoma of the upper vestibular gingiva in a 29-year-old woman who has no hematologic disease history. Multiple metastases were found in floor of the nasal cavity, left breast, and left lacrimal gland 12 months after primary diagnosis.

Key words: Acute myeloid leukemia, myeloid sarcoma, maxillary gingiva

INTRODUCTION

According to the new World Health Organization classification, myeloid sarcoma (MS) is defined as a tumor mass of immature myeloid cells such as myeloblasts, promyelocytes and myelocytes in an extramedullary site or bone. It is also known as chloroma, granulocytic sarcoma or extramedullary myeloid tumor.^[1,2]

MS first described by Burns in 1811,^[3,4] was later named as “chloroma” which got its name from Greek word chloros (green).^[4-8] The high levels of myeloperoxidase enzyme in immature tumor cells are the cause for green discoloration of these tumors.^[6,7,9] In 1904, Dock and Warthin recognized the association between acute leukemia and chloroma.^[5,10] Rappaport used the term “granulocytic sarcoma” in 1966,^[11] because he recognized that the green color is not present in all types of this tumor.^[12-14] The tumor may precede or occur concurrently with acute or chronic myeloid leukemia (CML) or with other types of myeloproliferative disorders or myelodysplastic syndromes.^[15-20]

Myeloid sarcoma is known to be frequently occurring in bone structures such as skull, paranasal sinuses, ribs, sternum, vertebra, pelvis, and soft tissues.^[14] However, it may occur in any location such as skin, periosteum, lymph nodes, bronchi, pericardium, peritoneum, orbits, gastrointestinal tract, breast, kidney, bladder, mouth, jaws and reproductive

organs.^[1,3,5,6,10,21-24] Oral involvement of MS is extremely rare. It may be either intra-osseous or extra-osseous.^[1,15,25]

Intraoral MSs usually affect only one site; in English literature there are only two cases reported involving both maxilla and mandible. Clinically intraoral MS presents a non-specific mass, usually with ulceration. This mucosal mass may resemble any carcinoma, pyogenic granuloma, lymphoma, or periodontitis. Radiographically, MS may show destructive bone lucency if jaws are involved.^[1]

The exact prevalence of the disease is still unclear due to its low incidence. But according to Puranen *et al.*^[15] MS incidence associated with acute myeloid leukemia (AML) ranged between 3% and 4.7%. Although MS occurs at any age, the most reported cases were diagnosed before the age of 15 years and between the ages of 20 and 44 years.^[15,21]

Apart from histological diagnosis of MS which is not the only criteria, immunoreactivity with anti-myeloperoxidase is still thought to be the most useful marker.^[1] In flow cytometry, it is usually required for detecting myeloid linkage.^[5]

Here we report a case of MS that manifested in gingival mucosa primarily and later spread to multiple organs in 12 months. We aimed to point out the differential diagnosis of this tumor for pathologist due to its high frequency of poorly differentiated histological appearance.

CASE REPORT

A 29-year-old woman appealed to the faculty of Dentistry, Department of Maxillofacial Surgery in August 2009. The patient complained about a painful buccal gingival swelling and bilateral submandibular lymphadenopathy [Figure 1a]. She had the history of these complaints for 3 months. The

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patient was initially treated for periodontitis by a dentist. On clinical examination, of gray-brown keratinized, severely painful, sessile lesion at the anterior upper labial gingiva accompanied with submandibular lymphadenopathy was noted [Figure 1b]. There was no gingival bleeding on probing. In detailed medical history, we found out the patient had weight loss, malaise, night sweats and fever for a while. Radiological examinations did not show any bone pathology. The patient's blood test results were as follows: hemoglobin, 10.8 g/dl; hematocrit, 36.5%; white blood cell count was $9.2 \times 10^3/\mu\text{L}$ (52.9% monocytes, 23.2% neutrophils, 22.7% lymphocytes, 0.8% eosinophils, 0.4% basophils); platelets, $146 \times 10^3/\mu\text{L}$. A bone marrow aspirate showed 80-90% blastic cell infiltration.

An incisional biopsy was performed from the labial vestibular fornix under local anesthesia and sent to Department of Oral Pathology.

On gross examination, the excised material showed a central grayish-white non-specific soft tissue material. Histologic examination of the biopsy specimen showed monomorphous diffuse infiltrate with a population of immature blast-like cells beneath the intact oral epithelium on panoramic view. The tumor cells were intermediate in size and round to oval in shape with mild to moderate basophilic cytoplasm without granules [Figure 2a]. The tumor was composed of two different cell types. Some of these cells had pale nuclei containing conspicuous nucleoli, while the others had large angular shaped hyperchromatic nuclei. The tumor cells exhibited loss of cohesion with each other at these areas [Figure 2b]. Also the tumor cells had an increased nuclear-to-cytoplasmic ratio. Rare mitotic figures were observed whereas eosinophilic myelocytes were not seen. Immunohistochemical staining were performed

on the paraffin-embedded sections. Tumor cells demonstrated pale positive reaction to CD117(c-Kit) [Figure 3a] and strong positive reaction to myeloperoxidase (MPO) [Figure 3b] monoclonal antibodies; whereas, negative reactions to S-100, Melan-A, HMB-45, pan-keratin, kappa, lambda, alpha smooth muscle actin, desmin, CD3, CD15, CD20, CD34, CD45 and CD68 monoclonal antibodies was observed. Histopathological examination demonstrated an extramedullary myeloblastic malignancy. Diagnosis was MS.

The patient's submandibular lymph node induration and gingival swelling increased during the time period between biopsy and final histopatological diagnosis was made. After the diagnosis, we consulted the Medical Oncology Department.

In PET/CT (Positron emission tomography/computed tomography) scans, tumor masses were apparent in mandible and on the floor of nasal cavity [Figure 4a]. The patient received combination of idarubicin and ARA-C (cytosine arabinoside) chemotherapy regimen at first treatment phase. Because of the enlargement of the masses and development of AML, in second chemotherapy session 3-5-7 (daunorubicin, etoposide, ARA-C) regimen was performed. Bone marrow transplantation was planned after the fourth chemotherapy session but during this hold on period other aggressive tumor masses were found in left lacrimal gland and left breast [Figure 4b]. Histopathological diagnoses of the new lesions were also MS. Unfortunately, the patient died waiting for the appropriate bone marrow transplant and after 15 months of first diagnosis of MS.



Figure 1: (a) Bilateral painless submandibular swelling. (b) Upper buccal gingiva showing gray-brown keratinized swelling

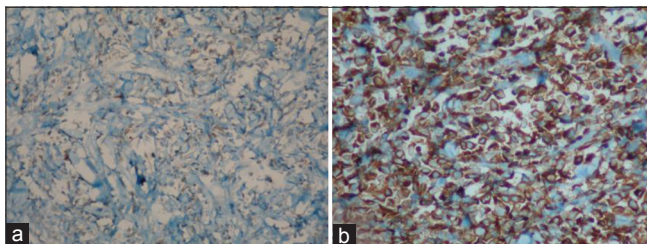


Figure 3: (a) Tumor cells demonstrated pale positive reaction with CD117 (IHC stain, x200). (b) Tumor cells strongly positive for myeloperoxidase (MPO) (IHC stain, x400)

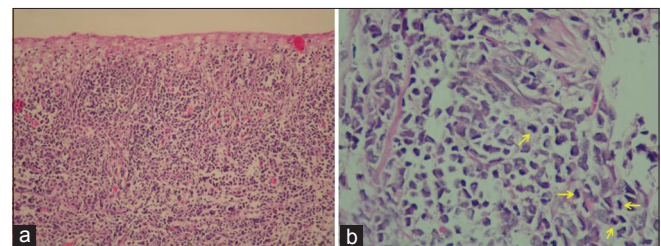


Figure 2: (a) Monomorphous diffuse malignant tumoral infiltrate was seen beneath the oral epithelium (H& E stain, x40). (b) Tumor cells exhibited loss of cohesion with each other at these areas. Rare mitotic figures were also seen (arrow) (H& E stain, x200)

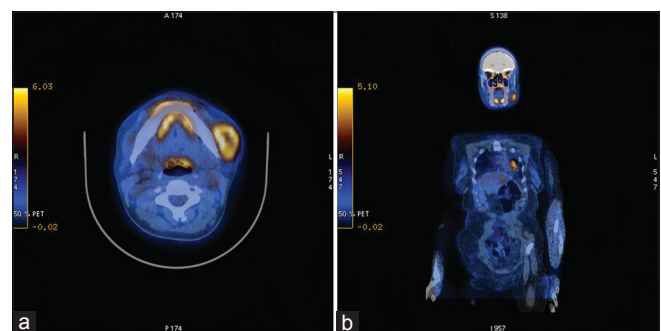


Figure 4: (a) Axial PET scan clearly depicts the tumor of the left mandible and floor of the nasal cavity. (b) Coronal PET scan view of the patient

DISCUSSION

MS is a solid, localized, extramedullary tumor mass of immature myeloid cells that is often associated with malignant hematopoietic disease such as AML, CMD.^[3,15,26]

Presence of MS in the oral tissues is rare, only about less than fifty intraoral MS cases are reported in the literature so far.^[1,7,15,26]

The primary oral manifestation of MS without presence of hematological findings is very rare. The most common intraoral locations of MS are the maxillary and mandibular gingiva and bones; followed by cheek, tongue, parotid, hard palate, soft palate, and lip.^[1,15,25]

The occurrence of intraoral MS as multiple masses involving multiple organs is extremely rare. Xie *et al.* reported only two cases in which the tumor involved both the maxilla and the mandibular gingiva.^[1] Thus, in the present case MS involved multiple regions including breast, lacrimal gland, nasal cavity, maxillary gingiva and mandibular soft tissue.

In patients who lack a history of pre-existing hematologic disorder, the diagnosis of MS based on just histopathological views is difficult. Differential diagnosis must include soft tissue sarcomas, non-Hodgkin's lymphoma (diffuse large cell type), Burkitt lymphoma, large-cell lymphoma, small round cell tumors, Ewing's sarcomas or poorly differentiated epithelial tumors.^[1,8,15] The case presented in this article did not have any diagnostic statement regarding hematologic disease so this case points out the importance of early and attentive diagnosis of oral manifestations.

Cheng *et al.* concluded that the survival rate of MS is only 30.8%.^[3] They reported only four intraoral primary MS cases and concluded that the survival rate of primary MS (50.00%) is higher than MS associated with malignancy (22.2%). The present case shows an intraoral primary MS associated with AML and the patient deceased about 15 months after diagnosis. Prognosis of MS depends on the medical history of patient and clinical presentation. Recently, it was reported that MS in patients with bone marrow involvement has a higher rate of relapse.^[13] Xie *et al.*, reported a case of relapse free patient with only 6-month follow-up.^[1] Although there is no consensus of follow-up periods in the literature, all authors agreed that a close clinical follow-up is critical.

Histologically, MS is composed of a relatively uniform population of immature cells. This may cause difficulty in differentiating MS from other malignancies such as large cell lymphoma, poorly differentiated carcinoma or even plasmacytoma. Crystalline, rodlike, intracytoplasmic acidophilic bodies (Auer rods) can establish the diagnosis of both MS and acute myeloid leukemia; however, they may be present in less than 10% of cases.^[27] Occasionally the

presence of immature eosinophils and maturing neutrophils may indicate the true nature of the lesion. Attempts at the histopathological classification have generally resulted in three levels of differentiations: blastic, immature and differentiated cells.^[14,28] Myeloid cells contain distinctive primary granules that are not seen in lymphomas or other small blue cell tumors. Immunohistochemically, MS myeloblasts usually express myeloid-associated antigens such as CD43, CD13, CD33 and CD117 but are not reactive with lymphoid antigens such as CD3 and CD20.^[29]

Histological appearance directed us to consider small round cell soft tissue tumors for differential diagnosis. A large immunohistochemistry panel was performed and other tumors were eliminated with the exception of tumors originating from hematopoietic tissues. Tumoral infiltration of case did not include conspicuous immature eosinophil and mature neutrophil. Positive staining with MPO and CD117 (c-Kit) was noted but CD3 and CD20 were negative, which gave important clues to indicate a myeloid neoplasm. Distinction of one subtype from the other variants of MS is difficult on the basis of histomorphology alone such as the present case. The co-expression of MPO and CD-117 (c-Kit) is useful to show granulocytic differentiation of the tumor.

Misdiagnoses are important issues in dental practice especially if malignant tumors are the subject. MS is a rare malignancy in head and neck region; hence it is difficult to calculate its incidence accurately. But malignancies diagnosed by dentists have increase in the number of cancers and also more cautious examinations by dentists. It is very well known that various systemic disorders including malignant tumors, even metastatic ones may occur in oral mucosa as the very first sign of disease. These conditions can be challenging not only for clinicians but also for pathologist. Gingival masses may be confusing due to high frequency of reactive or neoplastic lesions. A careful oral examination more than usual is needed, particularly in elderly patients or in patients who have primary disease.

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