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CASE REPORTS

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DIAGNOSTIC CHALLENGES WITH INTRAORAL MYELOID SARCOMA: REPORT OF TWO CASES & REVIEW OF WORLD LITERATURE

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***Background*: Myeloid sarcomas (MS) are rare extramedullary tumors composed of blasts of myeloid lineage that either precede, follow or present concomitantly with acute myeloid leukaemia (AML) or myeloproliferative neoplasms. The diagnosis of MS is especially challenging in patients without an antecedent history of leukemia. *Methods*: We present 2 cases of intraoral MS that presented as *de novo* lesions. A detailed review of cases of intraoral MS that either preceded or presented along with leukemia has been done with emphasis on diagnostic criteria used. *Results*: Two male patients aged 28 and 5 years presented with MS with one patient presenting with concomitant AML. A combination of morphological and immunohistochemical methods was used for diagnosis. A thorough review of world literature revealed 44 cases of intraoral MS that presented as *de novo* lesions. *Conclusion*: Intraoral MS is a rare tumor with poor prognosis. It may be diagnostically challenging due to its protean clinical manifestations and histological overlap with other tumors.**

***Key Words*: myeloid sarcoma, leukemia, granulocytes, immunohistochemical method.**

Myeloid sarcoma (MS) is a pathologic diagnosis for an extramedullary proliferation of blasts of one or more myeloid lineages that leads to effacement of the tissue architecture in which it is found [1]. Originally called chloromas due to the greenish color on gross examination attributed to production of myeloperoxidase, it has subsequently undergone numerous changes in nomenclature including granulocytic tumor, extramedullary myeloid tumor and myeloblastoma. This change in nomenclature reflects the various facets of the historical evolution of this tumor corresponding with molecular and cytogenetic understanding of the neoplasm.

MS is usually observed in a setting of acute myeloid leukemia (AML), myeloproliferative neoplasms and mixed myelodysplastic/myeloproliferative neoplasms (50%). Appearance of MS in an AML patient in remission is an indication of relapse. Rarely MS has presented after allogenic stem cell transplantation [2, 3]. 15–35% of MS cases are detected concomitantly with AML, however, it is the remaining 25–27% that precede AML that create a diagnostic dilemma.

Intraoral MS is an exceedingly rare lesion with only about 75 cases reported since its first description in 1811. Almost all intraoral sites can be involved including the jaws, gingiva, hard and soft plate, tonsils, maxillary sinus, tongue and lips. Here we present two cases of intraoral MS along with review of world literature. Emphasis has been placed on the diagnostic criteria used by various authors. We also present differential diagnosis, approaches to diagnosis and pitfalls in diagnosing MS when it precedes or is diagnosed with AML based on review of world literature.

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Abbreviations used: AML – acute myeloid leukemia; MPO – myeloperoxidase; MS – myeloid sarcoma.

CASE REPORTS

Case I

A 28 year old monoplegic male presented with a progressively enlarging swelling on left side of face, since 5–6 months (Fig. 1, *a*). He had undergone extraction of 36.2 months ago due to mobility. Physical examination revealed ill defined bony hard swelling extending from the left ala tragus line up to lower border of mandible with involvement of ramus and angle of mandible. Intraorally, expansion on buccal aspect of #34 to #37 and healed extraction socket of #36 were noted. Orthopantomogram showed ill defined mixed radiolucent and radiopaque lesion with respect to left angle of mandible extending up to the ramus of mandible (Fig. 1, *b*). Laboratory studies including complete blood count and serum chemistry were within normal range.

Incisional biopsy was performed via intraoral approach. Histopathological examination revealed a diffuse infiltration of large atypical cells with vesicular nuclei with predominance of crushed nuclei. The atypical cells were seen infiltrating in between and splaying the muscle fibers (Fig. 1, *c*). A basic immunohistochemical panel consisting of pancytokeratin, vimentin, S100, CD45, and desmin was performed. The tumor cells were positive for CD45 (Fig. 1, *d*) and a presumptive diagnosis of non-Hodgkin's lymphoma was made. However, the cells were negative for CD3 and CD20. The H&E slides were re-examined and a population of large cells containing eosinophilic granules (Fig. 1, *e*) was seen intermingling with the tumor cells with areas of degranulation.

Based on all previous investigations and histopathological findings, anti-myeleoperoxidase antibody (anti-MPO) staining (Fig. 1, *f*) was performed which showed strong diffuse positivity. Bone marrow biopsy was within normal limits. A diagnosis of MS in the absence of AML was thus made.

Patient underwent induction chemotherapy with cytarabine and idarubucin with lesion regression. He has remained in remission for 14 months after diagnosis with normal blood counts.

Case II

A 5 year old male child was referred to our Centre by a private dentist with rapidly progressing mildly tender swelling in left posterior mandibular region (Fig. 2, *a*), since last 10 days. History of trauma was elicited 25 days prior to commencement of swelling and there was no history of any systemic disease. Examination revealed a well defined bony hard swelling with expansion of buccal and lingual cortices. The left deciduous molars were mobile and displaced due to the swelling (Fig. 2, *b*). A large area of ulceration was noted on the linguo-occlusal aspect. Orthopantomogram showed an ill defined mixed radiolucent radiopaque lesion causing resorption of molar roots

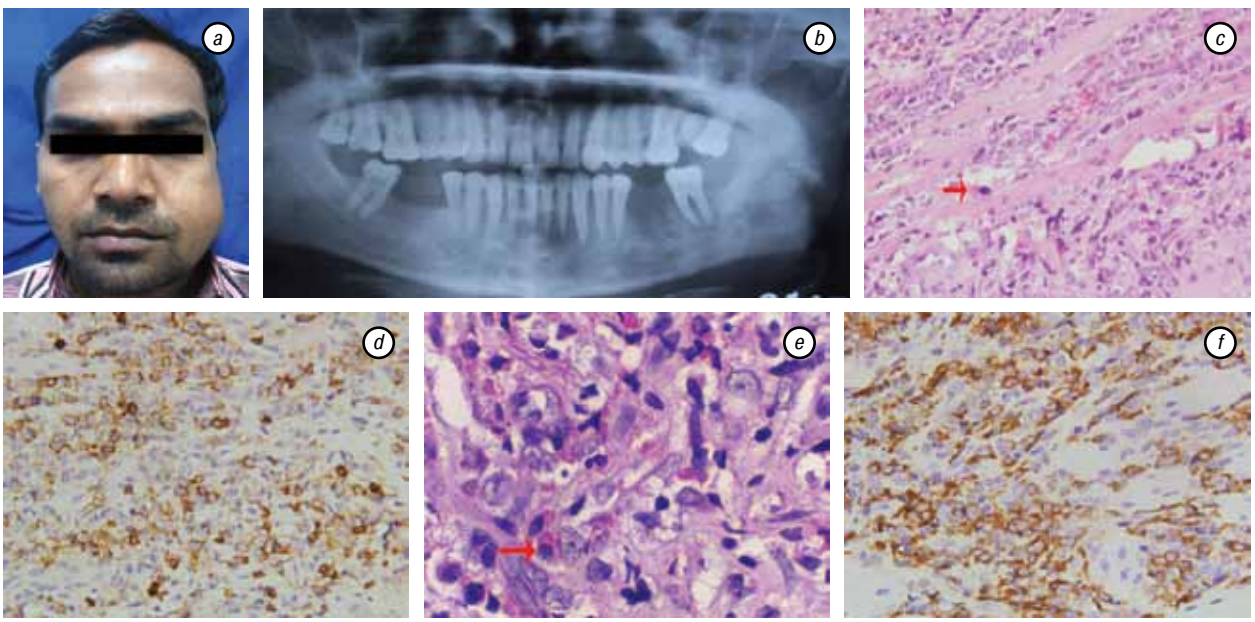

Fig. 1. Clinical, radiographic, histological and immunohistochemical findings of Case #1: *a* — extra oral photograph showing diffuse swelling over left mandible; *b* — orthopantogram showing poorly defined mixed radiolucent-radio opaque mottled lesion with partially healed socket of #36; *c* — microphotograph showing tumor cells invading in between and splaying muscle fibers (H & E, × 100); *d* — microphotograph showing diffuse positivity for CD45; *e* — higher magnification showing granular eosinophilic myelocytes (arrow) intermingling with immature tumor cells (H & E, × 1000); *f* — microphotograph showing strong positivity for MPO

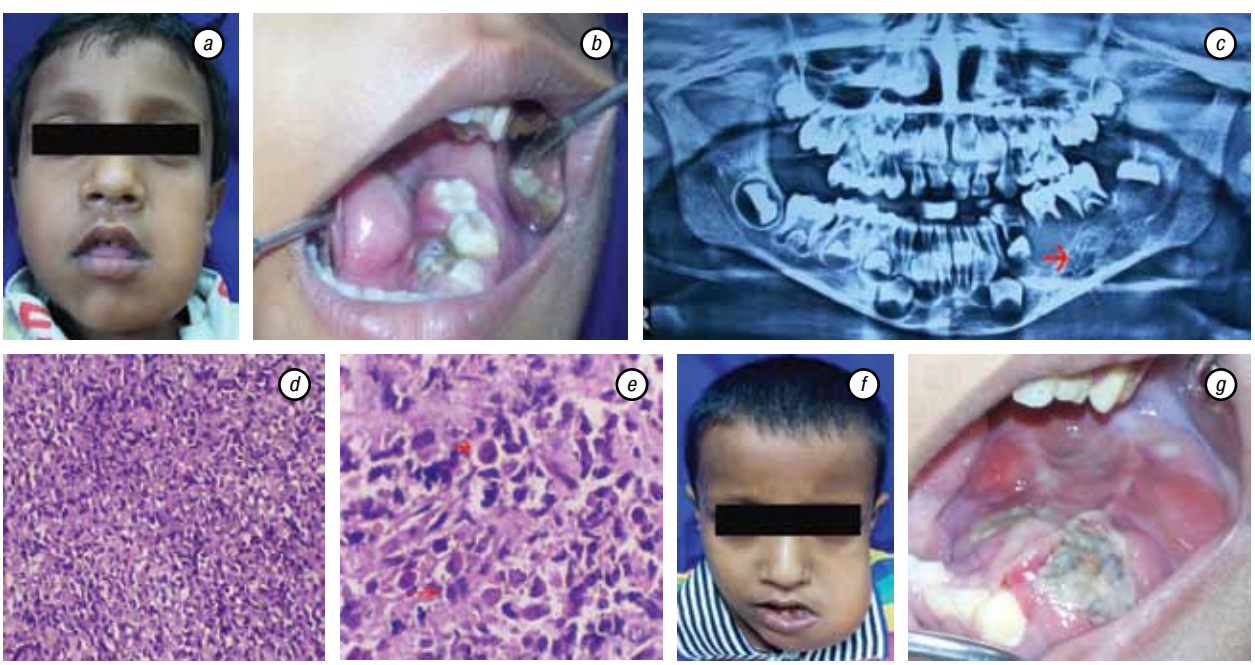

Fig. 2. Clinical, radiographic and histological findings of Case #2: *a* — extra oral photograph showing swelling over left angle of mandible that showed rapid expansion over a period of 1 week post incisional biopsy (*f*); *b* — intraorally, swelling with expansion of buccal and lingual cortices and ulcer over the linguo-occlusal surface covered by grayish pseudomembrane was observed at first visit; *c* — orthopantogram showing ill defined radiolucent lesion involving left posterior mandible causing resorption of molar roots (note the sunburst pattern at the periphery); *d* — microphotograph with pleomorphic round to spindled tumor cells (H & E, × 100); *e* — microphotograph showing immature tumor cells with varying degree of pleomorphism and mitotic activity (H & E, × 1000); *f* — 1 week post biopsy, a massive increase in swelling; *g* — 1 week post biopsy, the lesion showing massive expansion with an irregular, granular and necrotic appearance

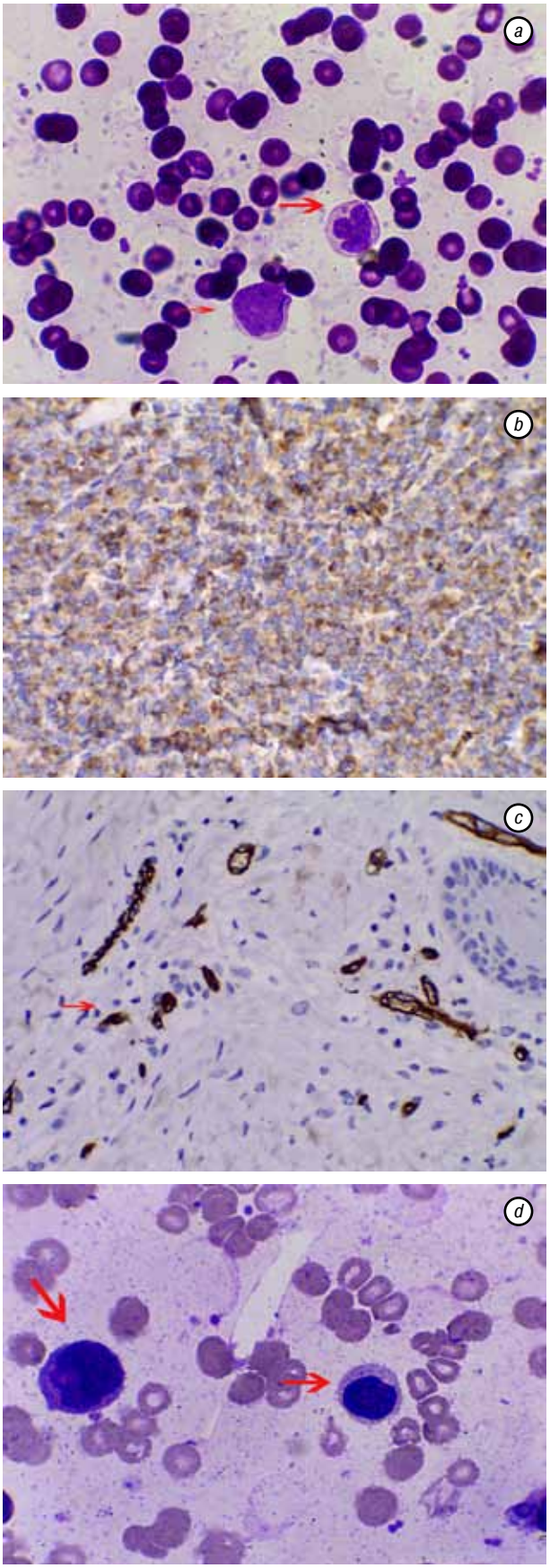

Fig. 3. Cytological and immunohistochemical findings of Case #2: *a* — peripheral smear showing presence of band forms and myeloblasts (Giemsa, × 100); *b* — diffuse positivity for MPO seen in all tumor cells (× 100); *c* — focal positivity for CD34 observed in some tumor cells (× 100), *d* — bone marrow aspirate showing numerous blast cells (Giemsa, × 100)

and a periosteal reaction giving a sunburst appearance (Fig. 2, *c*). Other than decreased hemoglobin level of 10.5 gm/dl, all other hematological parameters were within normal limits.

An incisional biopsy was subsequently performed along with extraction of the mobile teeth. Biopsy showed diffuse infiltration of predominantly round cells effacing the tissue architecture. The cells had sparse to moderate eosinophilic cytoplasm with prominent nuclei. Abundant mitotic figures were seen with mitoses ranging from 5–6 per high power field (Fig. 2, *d*, *e*).

Based on H & E sections, Ewing's sarcoma, embryonic rhabdomyosarcoma, and neuroblastoma were included in the differential diagnosis. The tumor cells were negative for vimentin, desmin, CD99, CD45 and NSE. In the mean time, the patient reported with a massive increase in swelling (7 days post biopsy) (Fig. 2, *f*, *g*).

A peripheral smear was repeated and numerous immature blasts including myeloblasts, and band forms were observed (Fig. 3, *a*). Immunohistochemistry was then done using anti-MPO (Fig. 3, *b*) and anti-CD34 (Fig. 3, *c*). The tumor cells were diffusely positive for MPO and focally positive for CD34. The lesion was thus diagnosed as MS. Subsequently, bone marrow biopsy was performed that showed marrow involvement with atypical cells with high nuclear-to-cytoplasmic ratio, focal nuclear convolutions and moderate to scant cytoplasm (Fig. 3, *d*). These atypical cells constituted more than 50% of marrow population. Strong MPO activity was also noticed in these atypical cells. MS presenting with AML was the final diagnosis. The left deciduous second molar was decalcified and showed dense diffuse infiltration by tumor cells completely obliterating the pulpal architecture (Fig. 4).

Patient underwent chemotherapy with cytarabine followed by successful lesion regression. He is currently in remission, one year post diagnosis.

A thorough search of world literature revealed 77 cases of intraoral MS, of which 44 lesions either preceded or presented concomitantly with leukemia. Diagnostic criteria used for these lesions (MS presenting with or preceding leukemia) have been compiled in Table 1 [1–46].

DISCUSSION

The diagnosis of MS can be a clinical challenge when there is no antecedent myeloid neoplasm. It has been reported that up to 27% cases present *de novo* and there may be a lag of up to 10 months between first presentation and bone marrow involvement [45, 46]. A high degree of clinical suspicion thus becomes mandatory in order to establish diagnosis. In a study of 26 MS cases by Menasce *et al*. [47], 14 were initially misdiagnosed, all 14 being without prior history of leukemia or myeloproliferative disorders. Further Byrd *et al*. [48] in their study found that up to 46% of published isolated cases were misdiagnosed, commonly as large cell lymphomas. The differential diagnosis of MS is quite large and clinical features such as age

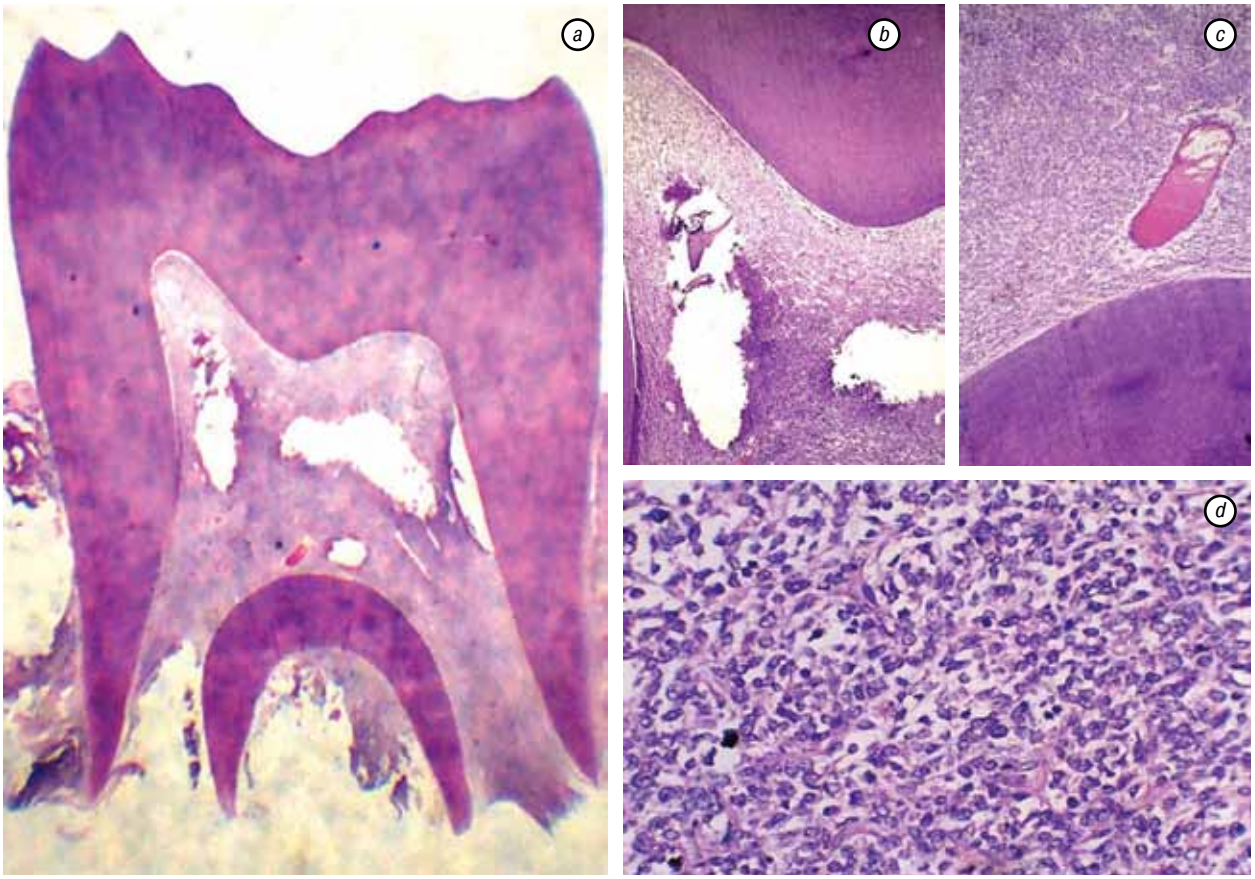

Fig. 4. Decalcified section of left permanent first molar (Case #2) showing diffuse infiltration and effacement of pulpal architecture by tumor cells: *a* — H&E, × 20; *b* — H&E, × 40; *c* — H&E, × 40; *d* — H&E, × 400

along with presence of a preexisting or concurrent myeloid neoplasm must be factored in.

The pathogenesis of MS has been attributed to an aberrant homing signal for the leukemic blast cells rather than their localization within the bone marrow [1]. Studies have shown that this homing and retention of the blasts may be mediated by different chemokine/chemokine receptor activations and the invasive potential of the cells is due to interactions between MMPs and integrins [49–51].

The clinical features of oral MS can be extremely variable and nonspecific. Patients may present with swelling, sore throat, purulent discharge, jaw pain, mobile teeth, sinus pain, tonsillar enlargement and lymphadenopathy amongst others [41]. MS has been reported at almost all intraoral sites with the mandible accounting for the maximum number of cases (35%). The most common site for extraoral MS is the skin (leukemia cutis) where it presents as multiple papules, plaques and nodules [34]. Radiographically, intraosseous oral lesions vary from innocuous appearing periapical granulomas/abscesses and superficial bony erosion to massive destructive expansile lesions involving large areas of the jaw [1, 9, 11, 52]. Periosteal reactions around the lesion and sinus haziness are some of the other reported findings.

Morphologically, MS classically presents as a tumor composed of immature cells namely myeloblasts, monoblasts and rarely promyelocytes that partially or completely efface the overall architecture of the tissue involved. The cells show scant cytoplasm with multilobed round to oval nuclei, fine or dusty nuclear chromatin and one or two small basophilic nucleoli [53, 54]. MS were historically divided into granulocytic sarcoma and monocytic sarcoma. Pileri *et al*. [45] in 2007 further classified GS into three variants as per the morphological type. Blastic variant shows predominance of myeloblasts with little evidence of maturation and no cytoplasmic granules, immature type (intermediate grade) consists of myeloblasts, promyelocytes and eosinophilic myelocytes and differentiated or mature type shows promyelocytes, and more mature cells with abundance of eosinophils. According to this classification, Case #1 belongs to the differentiated type and Case #2 to the blastic type. However, the cytomorphologic classification has no bearing on prognosis and is hence clinically irrelevant [47, 55].

With increase in cytogenetic and molecular understanding of these tumors, the abovementioned morphological distinctions seem less relevant. At the same time, sufficient knowledge regarding the immunohistochemical makeup of the various subtypes may prove critical in establishing diagnosis. A number of studies describing the immunophenotype of MS have shown that the tumor can show features of any myeloid lineage and often may show multiple lineage expression in the same tumor [34, 53]. A number of enzyme cytochemical stains such as myeloperoxidase, sudan black B, chloracetate

Table 1. Diagnostic criteria used for intraoral MS preceding or presenting with leukemia

No.	Authors/Reference	Year	Age/ Sex	Location	Type of malignancy	Diagnosis based on:	Marrow status at the time of diagnosis	Time to leukaemia diagnosis
1	Wiernick *et al*. [4]	1970	35/F	Cheek	AML	H & E	Uninvolved	10 months after MS
2	Brooks *et al*. [5]	1974	8/M	Maxillary sinus	AML	H & E	Uninvolved	4 years
3	Hansen *et al*. [6]	1982	83/F	Maxilla	AML	NA	Uninvolved	3 months after MS
4	Conran *et al*. [7]	1982	2/F	Mandible	None	H & E Ultrastructural analysis	Uninvolved	DF
5	Takagi *et al*. [8]	1983	25/F	Mandible	AML	IHC – MPO	Uninvolved	1 year 6 mos after MS
6	Reichart *et al*. [9]	1984	35/F	Mandible	AML, promyelocytic	CS – chloracetate esterase	Uninvolved	3 months after MS
7	Castella *et al*. [10]	1984	89/F	Hard palate	None	CS – chloracetate esterase Ultrastuctural analysis	DF	Died of unrelated cause
8	Timmis *et al*. [11]	1986	52/M	Mandible	LL	CS – Sudan black, chloracetate esterase IHC – HLA, Leu-M3 Ultrastructural analysis	Involved	Diagnosed with MS
9	Ficarra *et al*. [12]	1987	67/F	Hard palate	AML	CS – chloracetate esterase		1 year 3 mos after MS
10	De Vicente Rodriquez *et al*. [13]	1990	56/M	Left mandible	AML	CS – chloracetate esterase IHC – lysozyme	Involved	Diagnosed with MS
11	Eisenberg *et al*. [14]	1991	33/M	Multiple sites	None	CS – Sudan black, MPO, α-naphthyl butyrate esterase	Uninvolved	DF
12	Stack *et al*. [15]	1994	70/M	Mandible	CML	CS – chloroacetate esterase; IHC – antilysozomal peroxidase	Involved	Diagnosed with MS
13	Roth *et al*. [16]	1995	47/M	Gingiva	AML	NA	NA	NA
14	Lynch *et al*. [17]	1998	86 /F	Maxillary gingiva	AML	IHC – MPO	Uninvolved	2 years 5 mos after MS
15	Tong *et al*. [18]	2000	76 /F	Maxillary gingiva	AML	IHC – MPO	Uninvolved	7 months
16	Amin *et al*. [19]	2002	58/M	Hard palate	AML	IHC – CD34 (weak) FC – HLA-DR, CD11c, CD13, CD15, CD34, TdT CG – trisomy 13 (47,XY,+13)	Involved	Diagnosed with MS
17	Jordan *et al*. [20]	2002	62/F	Mandible	AML	CS – chloracetate esterase IHC – CD43, MPO, CD15 CG – normal	Uninvolved	6 weeks
18	Antmen *et al*. [21]	2003	12/F	Gingiva	AML	IHC – MPO, lysozyme	Uninvolved	Few weeks after MS
19	Stoopler *et al*. [22]	2004	50/M	Multiple sites	AML	IHC – LCA, CD43, CD34 (rare)	Involved	Diagnosed with MS
20	Colella *et al*. [23]	2005	62/F	Maxillary gingiva	AML	IHC – MPO, lysozyme, CD45, CD68	Uninvolved	Few weeks after MS
21	Koudstaal *et al*. [24]	2006	36/M	Hard palate	AML	IHC – CD45, CD43, HLA-DR, CD4 (weak) FC – CD117, CD56, CD13, HLA-DR, CD45, CD33 (weak) CG – abnormal	Uninvolved	2 years
22	Goteri *et al*. [25]	2006	84/F	Hard palate	None	IHC – CD45, CD43, CD34, MPO, CD68	Uninvolved	DF
23	Yinjun *et al*. [26]	2006	44/F	Gingiva	None	IHC – MPO, CD68 CG – trisomy 21	Uninvolved	DF
24	Yoon *et al*. [27]	2006	63/M	Gingiva	AML	IHC – CD117, MPO	Involved	Diagnosed with MS
25	Matsushita *et al*. [28]	2007	50/M	Maxillary gingiva	AML	IHC – MPO, CD43	Involved	Diagnosed with MS
26	Mohmedbhai *et al*. [29]	2008	45/M	Tongue	AML	IHC – CD45, MPO, CD68 FC – MPO, CD33, CD117 CG – t(15;17) (q22;q12)	Involved	Diagnosed with MS
27	Kim *et al*. [30]	2009	4 /F	Mandible	AML	IHC – MPO, CD34, CD43, CD79a, FC – CD13, CD33, CD38, CD117, HLA-DR, MPO	Involved	Diagnosed with MS
28	Lu *et al*. [31]	2009	63/F	Maxillary gingiva	AML	IHC – MPO, CD34, CD3 (rare), CD20 (rare)	Involved	Diagnosed with MS
29	Lu *et al*. [31]	2009	39/F	Maxilla	None	IHC – MPO, CD34	Uninvolved	DF
30	Papamanthos *et al*. [32]	2010	70/F	Mandible	AML	IHC – CD43, lysozyme, MPO	Involved	Diagnosed with MS
31	Qiu *et al*. [33]	2010	16/F	Condyle	AML	NR	Involved	Diagnosed with MS
32	Klco *et al*. [34]	2011	39/M	Maxillary gingiva	AML	IHC – MPO, CD117, CD4, CD34	Uninvolved	DF
33	Colović *et al*. [35]	2011	55/F	Mandible	None (HIV)	IHC – CD117, CD45, CD68, lysozyme, CD13 (weak)	Uninvolved	Dead at 8 months (HIV related sepsis)
34	Seema *et al*. [36]	2011	5/M	Mandible	AML	IHC – MPO, TdT	Involved	Diagnosed with MS
35	Mei *et al*. [37]	2011	56/M	Multiple	None	IHC – CD34, CD45, CD56, CD117, MPO	Uninvolved	DF
36	Yamashita *et al*. [38]	2012	1/M	Mandible	AML	IHC – CD45 FC – CD33, CD65, MPO	Involved	Diagnosed with MS
37	Kurdoğlu *et al*. [39]	2013	29/F	Gingiva	AML	IHC – CD117, MPO	NR	NR
38	Guastafierro *et al*. [40]	2013	56/F	Maxillary gingiva	None (pleural effusion)	IHC – CD45, CD68, lysozyme, MPO	Uninvolved	Died due to other causes
39	Zhou *et al*. [41]	2013	77/F	Tongue	MDS	CS – chloracetate esterase IHC – CD4, CD1c, CD33, CD43, CD68, CD117, CD163, MPO, lysozyme CG – 47,XX,+8[20]	Involved	Diagnosed with MS
40	Zhou *et al*. [41]	2013	55/M	Mandible	CML	IHC – MPO, CD43 CG – 46,XY,t(9;22) (q34;q11) [20]	Involved	Diagnosed with MS
41	Zhou *et al*. [41]	2013	47/F	Tonsil	AML	IHC – CD4, CD1c, CD33, CD43, CD45, CD68, CD117, MPO, lysozyme, CD163 CG – normal	Involved	Diagnosed with MS
42	Sharma *et al*. [42]	2014	9/M	Maxillary sinus	DF	IHC – CD31, MPO, vimentin, CD99	Uninvolved	DF
43	Ponnam *et al*. [43]	2014	45/F	Mandible	NA	IHC – CD45, CD68, CD117, MPO	NR	NR
44	Moshref *et al*. [44]	2014	45/M	Multiple sites	DF (MI)	IHC – CD45, C-Kit	Uninvolved	Died due to MI after 10 months

No.	Authors/Reference	Year	Age/ Sex	Location	Type of malignancy	Diagnosis based on:	Marrow status at the time of diagnosis	Time to leukaemia diagnosis
45	Present case	2016	28/M	Left mandible	DF	IHC – CD45, MPO	Uninvolved	DF
46	Present case	2016	5/M	Left mandible	AML	IHC – MPO, CD34	Involved	Diagnosed with MS

Notes: CG – cytogenetics; CML – chronic myeloid leukemia; CS – cytochemical staining; DF – disease free; F – female; FC – flow cytometry; HIV – human immudeficiency virus; HLA – human leukocyte antigens; IHC – immunohistochemistry; LL – lymphoblastic lymphoma; M – male; MDS – myelodysplastic syndrome; MI – myocardial infarction; NA – not available; NR – not reported.

Table 2. Immunohistochemical differential diagnosis of MS

Antibody	Specificity	MS		Non-Hodgkin's lymphoma		Ewing sarcoma	Epithelioid sarcoma	Poorly differentiated carcinoma	Melanoma	Langerhans cell histiocytosis
		Nonmonocytic	Monocytic	B cell	T cell					
CD43	T cells, myeloid cells, subset of B cells, T & B cell lymphomas	+++	+++	++	+++	–	–	–	–	–
Lysozyme	Myeloid & monocyte/macrophage lineage cells	+++	+++	–	–	–	–	–	–	–
MPO	Myeloid lineage cells	+++	–	–	–	–	–	–	–	–
CD68	Monocyte/macrophage lineage cells	++	++	–	–	–	–	–	–	–
CD34	Vascular progenitor cells, endothelial cells, interstitial cells of cajal, leukemic blasts, some soft tissue tumors	++	–	–	–	–	++	–	–	–
CD45	T & B lymphocytes, monocytes, macrophages, mast cells & weakly on granulocytes	+	+	+++	+++	–	–	–	–	–
CD117	Interstitial cells of cajal, germ cells, bone marrow stem cells, breast epithelium, melanocytes & mast cells	++	–	–	–	–	–	–	–	–
CD33	Cells of myeloid lineage, some lymphoid cells	++	+	–	–	–	–	–	–	–
CD3	T lymphocytes	+	–	–	+++	–	–	–	–	–
CD20	B lymphocytes	–	–	+++	–	–	–	–	–	–
CD99	Ewing sarcoma, primitive neuroectodermal tumor, peripheral neuroepithelioma	+	–	+	++	+++	–	–	–	–
Others					CD79a	FLI1 S100 NSE	CK INI-1 Vimentin EMA	High & low weight CK	HMB 45 Melan A S 100	CD1a S100

Note: +++ strongly positive, ++ frequently positive, + rarely positive, – negative.

esterase, α-naphthyl acetate esterase and α-naphthyl butyrate esterase have also been described.

Although the immunohistochemical panel for MS is well established, diagnosis may still be difficult for tumors presenting in the absence of a known primary. CD43 and lysozyme having a high sensitivity but low specificity are the most commonly used markers. Other routinely used markers include MPO, CD68 (KP-1 clone), CD34, CD45, CD117 and CD33. However, tumors of purely monocytic origin are negative for CD34, CD117 and MPO and positive for CD68, CD43, and CD33 [34, 53, 56].

A guide to the immunohistochemical differential diagnosis of MS is given in Table 2.

The most common differential diagnosis for MS in the adult population is non-Hodgkin's lymphoma (T & B cell type) [47]. It is especially true for T cell neoplasms as MS may express many markers of T cell differentiation namely, CD2, CD4, CD7, CD43, and CD45. Immature MS with no evidence of differentiation is usually misdiagnosed as diffuse large B cell lymphoma which has thick nuclear membrane and basophilic nucleoli, unlike myeloblasts or monoblasts, which have thin nuclear membranes and pinpoint nucleoli [57]. The use of a comprehensive immunohistochemical panel including lysozyme, MPO and CD68 thus becomes mandatory when dealing with such lesions. Other neoplasms that need to be differentiated are poorly differentiated carcinomas, melanomas and epitheloid sarcomas.

In pediatric population, differentiating MS from small round blue cell tumors such as Ewing's, primitive neuroectodermal tumors, neuroblastoma and alveolar rhabdomyosarcoma may become challenging. As seen in the case reported here, the radiographic appearance of a destructive radiolucent lesion surrounded by periosteal reaction giving a sun burst appearance may also favor a diagnosis of Ewing's sarcoma. The expression of CD99 by a large number of nonmonocytic MS further impedes diagnosis. However, positive expression of CD43, lysozyme and MPO swings the diagnosis in favor of MS. While dealing with children and young adults, it is prudent to exclude Langerhans cell histiocytosis from the differential diagnosis. The grooved coffee bean like nuclei of Langerhan's cells and abundance of eosinophils in the background is often seen in the monocytic MS [58].

Apart from immunohistochemistry, flow cytometric analysis using CD13, CD33, CD117 and MPO for non-monoblastic MS and CD14, CD163, and CD11c in monoblastic MS is well established when fresh tissue is available [1]. Cytogenetic abnormalities have been reported in approximately 50% of the MS cases and mirror the cytogenetic changes associated with AML. Interestingly, *de novo* cases of MS may lack these abnormalities. Pileri *et al*. [45] through FISH demonstrated trisomy 8 and monosomy 7 as the most common abnormalities. Trisomy 8 and inv (16) as determined by conventional cytogenetics was reported by Alexeiv *et al*. [59]. Pediatric patients having t(8;21)(q22;22) karyotypic abnormality have been shown to have a predilection for head and neck involvement including the orbit and CNS [60].

Molecular abnormalities in MS are not very well established. Mutations in nucleophosmin (*NPM*) 1 and

its resultant aberrant cytoplamic expression have been reported in approximately 15% of MS patients [61]. The prevalence of Fms like tyrosine kinase-3 (*FLT3*) mutations has been reported in a small subset of MS cases [62]. The significance of these mutations on the prognosis of MS patients is yet unknown.

With respect to available therapeutic options, there is a lack of consensus on treatment of MS with the recommended treatment regimen being conventional AML type chemotherapeutic protocols [1]. The role of radiotherapy in addition to chemotherapy is not well established with many studies showing no additional benefit [63, 64]. Other therapeutic modalities include hematopoietic stem cell transplantation and targeted therapy [1]. The prognosis of patients with MS is usually poor with slightly better outcomes when compared to primary or relapsed AML without extramedullary involvement. MS accompanying chronic myeloid leukemia or myelodysplastic syndrome is said to have a worse clinical outcome when compared to MS with AML.

To conclude, intraoral MS is a rare tumor with poor clinical outcome. It has protean clinical manifestations and histological overlap with numerous tumors making it a diagnostic challenge for clinicians and pathologists alike. When evaluating a tumor of unknown etiology, it is wise to maintain a high degree of suspicion especially if common antibody panels are negative for epithelial, mesenchymal or lymphoid markers. Apart from immunohistochemistry, use of ancillary techniques such as cytogenetics and bone marrow examination may assist in diagnosing. Arriving at prompt accurate diagnosis facilitates timely and effective therapeutic intervention thus improving patient outcomes.

Conflict of interest: Nil.

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