

Oral manifestations of myeloid neoplasms and acute leukemia- a diagnostic perspective

Abstract

Hematologic malignancies constitute approximately 9 % of all cancer cases diagnosed in a year collectively and are amongst the top 10 malignant disorders with respect to the incidence as well as cause of death in cancer patients. Although the oral manifestations of these malignancies are non-pathognomonic, they may often represent the initial sign of the underlying hematopoietic disease. Knowledge of symptoms of hematologic malignancies at an early stage can help in early diagnosis and reduction in disease burden of patient as well as healthcare system.

Keywords: leukemics, nonlymphocytic, plasma cell tumors, HL, MM, NHL

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Introduction

Hematologic malignancies constitute approximately 9 % of all cancer cases diagnosed in a year collectively and are amongst the top 10 malignant disorders with respect to the incidence as well as cause of death in cancer patients.¹ Immune-phenotyping and cytogenetic and molecular genetic testing has thrown light on the genetic diversity and manifestations of hematologic diseases (Table 1).^{2,3} Same technology has made treating these diseases easy due to availability and delivery of new drugs through molecular genetics, and significantly extending survival. With this advantage, knowledge of symptoms of hematologic malignancies at an early stage can help in early diagnosis and can also provide baseline data on symptoms for standard treatments. This is also extremely useful in planning and evaluating clinical trial outcomes for new therapies.⁴ Although the oral manifestations of these malignancies are non-pathognomonic, they may often represent the initial sign of the underlying hematopoietic disease.⁵ Stafford et al. reported that dentists are responsible for early diagnosis in a large portion of acute nonlymphocytic leukemias as 65% of leukemics had some form of oral pathology.² In India the prevalence of leukemia is reported at higher rate compared to lymphomas with reported incidence being 84% and 16%, respectively, for leukemia and lymphoma in West Bengal, 90% and 10% in Odisha and 91% and 9% in Gujarat respectively.¹ Hence this review was undertaken to report the symptoms of myeloid hematopoietic neoplasms in oral cavity.

Table 1 WHO classification of myeloid neoplasms and acute leukemia³

Myeloproliferative neoplasms (MPN)

- Chronic myeloid leukemia (CML), BCR-ABL1
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
- PMF, prefibrotic/early stage
- PMF, overt fibrotic stage
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukemia, not otherwise specified (NOS)

MPN, unclassifiable

Mastocytosis

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCMI-JAK2

- Myeloid/lymphoid neoplasms with PDGFRA rearrangement
- Myeloid/lymphoid neoplasms with PDGFRB rearrangement
- Myeloid/lymphoid neoplasms with FGFR1 rearrangement
- Provisional entity: Myeloid/lymphoid neoplasms with PCMI-JAK2

Myelodysplastic/myeloproliferative neoplasms (MDS/ MPN)

- Chronic myelomonocytic leukemia (CMMI)
- Atypical chronic myeloid leukemia (aCML), BCR-ABL1
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/ MPN-RS-T)
- MDS/MPN, unclassifiable

Myelodysplastic syndromes (MDS)

- MDS with single lineage dysplasia
- MDS with ring sideroblasts (MDS-RS)
- MDS-RS and single lineage dysplasia
- MDS-RS and multi-lineage dysplasia
- MDS with multi-lineage dysplasia
- MDS with excess blasts
- MDS with isolated del(5q)
- MDS, unclassifiable
- Provisional entity: Refractory cytopenia of childhood
- Myeloid neoplasms with germ line predisposition

Acute myeloid leukemia (AML) and related neoplasms

Table Continued

AML with recurrent genetic abnormalities	B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);KMT2A rearranged
AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1	B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1);ETV6-RUNX1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11	B-lymphoblastic leukemia/lymphoma with hyperdiploidy
APL with PML-RARA	B-lymphoblastic leukemia/lymphoma with hypodiploidy
AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A	B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) IL3-IGH
AML with t(6;9)(p23;q34.1);DEK-NUP214	B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);TCF3-PBX1
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM	Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1	Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
Provisional entity:AML with BCR-ABL1	T-lymphoblastic leukemia/lymphoma
AML with mutated NPM1	Provisional entity: Early T-cell precursor lymphoblastic leukemia
AML with biallelic mutations of CEBPA	Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma
Provisional entity:AML with mutated RUNX1	
AML with myelodysplasia-related changes	
Therapy-related myeloid neoplasms	
AML, NOS	
AML with minimal differentiation	
AML without maturation	
AML with maturation	
Acute myelomonocytic leukemia	
Acute monoblastic/monocytic leukemia	
Pure erythroid leukemia	
Acute megakaryoblastic leukemia	
Acute basophilic leukemia	
Acute panmyelosis with myelofibrosis	
Myeloid sarcoma	
Myeloid proliferations related to Down syndrome	
Transient abnormal myelopoiesis (TAM)	
Myeloid leukemia associated with Down syndrome	
Blastic plasmacytoid dendritic cell neoplasm	
Acute leukemias of ambiguous lineage	
Acute undifferentiated leukemia	
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2);BCR-ABL1	
MPAL with t(v;11q23.3); KMT2A rearranged	
MPAL, B/myeloid, NOS	
MPAL,T/myeloid, NOS	
B-lymphoblastic leukemia/lymphoma	
B-lymphoblastic leukemia/lymphoma, NOS	
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities	
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);BCR-ABL1	

General manifestations of hematologic malignancies

The Hematologic Malignancies are a group of cancers that arise from a malignant transformation of cells of the bone marrow or the lymphatic system. They account approximately for one-third of total cancers occurring in early childhood, with ALL being the most common entity. There are three main groups of hematologic malignancies: leukemia, lymphoma and plasma cell tumors.⁶

Leukemia: It results from the proliferation of a clone of abnormal hematopoietic cells with impaired differentiation, regulation, and programmed cell death (apoptosis).

Lymphomas: They are solid tumors of the immune system. Hodgkin's lymphoma (HL) accounts for about 10% of all lymphomas and the remaining 90% are referred to as non-Hodgkin lymphoma. Approximately 95% of patients with HL will have the classic HL histology, which is characterized by the presence of rare malignant Hodgkin's Reed-Sternberg cells among an overwhelming number of benign reactive cells and NHL is known to be associated with chronic inflammatory diseases such as Sjögren's syndrome, celiac disease, and rheumatoid arthritis.

Multiple myeloma (MM): It is a neoplastic plasma cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction. It accounts for approximately 1% of neoplastic diseases and 13% of hematologic cancers.⁶

Though reported hematologic malignancy prevalence is 0.0127% in India, A study conducted in Gujarat pediatric population reported that within 2½ years duration nearly three lakh patients from indoor and outdoor departments of pediatrics were screened for hematological malignancies and had some form of clinical manifestation.^{7,8} Hence having a knowledge of general manifestations as well as oral manifestations of hematological malignancies is very important. Most common presentations reported clinically are fatigue, pyrexia, anorexia, pallor, weight loss, night sweats, pruritus, splenomegaly and hepatomegaly.⁸

Oral manifestations

Orofacial manifestations of malignant hematological diseases may present primarily with clinical features due to infiltration of oral soft and hard tissues, subsequent infiltration of bone marrow elements and side effects of treatment being the secondary and tertiary cause. Qualitative defects in granulocytes are also associated with oral manifestations; presenting with recurrent aphthous-like ulcers and periodontal disease. Specific or non-specific oral manifestations of individual myeloid neoplasms that have oral manifestation are discussed below.

Soft tissue findings

Oral mucosa: Common reported manifestations in oral mucosa include mucosal pallor or erythema, ulcerations, hemorrhage, mucositis, severe recurrent viral, bacterial and fungal oral infection. Mucosal pallor due to anaemia, spontaneous bleeding and petechial haemorrhages of gingiva, palate, tongue or lip as a result of thrombocytopenia, gingival hyperplasia due to leukaemic infiltration and severe recurrent viral, bacterial and fungal oral infection as a result of immunosuppression. Most of these manifestations are commonly seen in AML.³ Very few cases of eosinophilic leukemia have been reported with oral ulcerations, crusted erosions on the lips.⁹ Palatal ulcerations and necrosis may herald presence of mucormycosis of the nasal cavity and the paranasal sinuses. Exfoliative cheilitis and infections with herpes and *Candida*, followed by hemorrhagic lesions and mucositis were manifested in CML and 0² reported.⁸

Gingiva: Spontaneous gingival bleeding, gingival enlargement and discolorations were the commonly reported manifestations in gingiva. Gingival enlargement due to leukemic infiltrates is seen in AML than in other types of leukemia.¹⁰ Polycythemia vera present with engorged reddish-purple discoloration of the gingiva and tongue, petechiae, and ecchymoses, while spontaneous gingival bleeding may be rarely seen.³ In essential thrombocythemia only excessive dental hemorrhage has been reported. Tsuda et al.,¹¹ is also seen in Myelodysplastic syndrome.³ The increased tendency to oral bleeding predisposes to impaired oral hygiene and accumulation of microbial plaque and debris and an exaggerated response to plaque with subsequent reactive connective tissue hyperplasia of the gingival soft tissues and accelerated periodontal destruction.¹¹ In a rare case report Viviano et al.,¹² has reported Blastic plasmacytoid dendritic cell neoplasm manifesting as a lump on the mandibular gingiva and ipsilateral otalgia without any cutaneous lesion.¹²

Lymph nodes: Lymph nodes represent the most common extramedullary sites for manifestations of myeloid malignancies including CML, granulocytic sarcoma or lymphoblastic leukemia/lymphoma¹³⁻¹⁵. Frequency of lymph node swelling was as high as 50% in CML patients with extramedullary neoplasm.¹⁵ As there are plethora of benign and malignant clinical entities that can cause lymphadenopathy further investigations are always recommended to arrive at correct diagnosis.

Hard tissue findings

Tooth: The manifestations in teeth are more due to secondary or tertiary effect of the neoplasm rather than primary. Common findings are increased cervical caries and tooth pain, displacement and loosening due to destruction of alveolar bone and PDL. Increased incidence of dental caries specially in cervical aspect of tooth is due to reduced oral hygiene and salivation, where as displacement and

pain in tooth are due to bone invasion and leukemic infiltration of the pulp in acute leukemia.² Loosening of teeth noted in B-lymphoblastic leukemia/lymphoma, Acute leukemia.^{13,14}

Bone: Most commonly manifest as bony masses. In MFS long standing anemia manifests as masses in the mandible and maxilla.² Granulocytic sarcomas of jaw noted in CML are localized deposit of myeloid cells having a whitish or a green tinge color due to the production of myeloperoxidase.¹⁰ Though extremely rare there are 3 B-LBL and 1T-LBL cases reported to present in oral cavity as bony mass.^{13,14} B-LBL presentation in oral cavity ranges from swelling covered with healthy mucosa to a lobulated mass with red hue or fungating and friable mass. Radiologic imaging studies show lytic or sclerotic bone changes mimicking benign or malignant primary bone lesions.¹³ Apart from masses temporomandibular joint arthritis and osteolytic lesions in the mandible have been reported in AML.¹⁵

Neural manifestations

Adeyemo et al.,² has also reported neurologic manifestations such as facial paralysis, trigeminal neuralgia, inability to protrude the tongue, difficulty in swallowing, weakness in biting and paraesthesia or anesthesia of the face, lips or tongue. Less frequently, mental nerve neuropathy (numb chin syndrome) and Trismus in their review as a manifestation of acute leukemia.²

Conclusion

In this review we noted that though rare almost all forms of myeloid leukemia have manifested in oral cavity (Table 2). There are also reports that had oral lesions as the sole manifestation of the neoplasia. Hence oral physicians should always consider oral cavity as a part of the whole body while examining, rather than a separate entity. A thorough knowledge of general pathologies and neoplasms with a clear understanding of their corresponding oral manifestations will not only help in early and timely diagnosis but can also bring out a tremendous reduction in patients' disease burden. Also, as a dental practitioner, we have a defined role in treating some of the oral symptoms as it primary, secondary or tertiary thus giving dentist a role in multidisciplinary management.

Table 2 Oral Manifestations of myeloid neoplasms and acute leukemia

Neoplasm	Oral manifestation
Chronic myeloid leukemia (CML): Rare oral features. If present manifests as granulocytic sarcoma of jaws during chronic phase. ¹⁰	
Myeloproliferative neoplasms (MPN)	Gingival enlargement because of infiltration of premature leukocytes Chronic Eosinophilic leukemia: oral ulcerations, crusted erosions on the lips. ⁴ Essential thrombocythemia (ET): Excessive dental hemorrhage ³
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCMI-JAK2	Oral ulceration
Myelodysplastic/ myeloproliferative neoplasms (MDS/MPN)	Chloroma, gingival hyperplasia

Table Continued

Myelodysplastic syndromes (MDS)	mucosal pallor, Persistent recurrent mucosal ulcerations, gingival bleeding, and an increased susceptibility to viral, fungal, and bacterial infections of the oral cavity due to the ² Gingival hyperplasia, ¹¹ Behcet's disease, ⁷ chloroma ⁸ mucosal pallor due to anaemia, spontaneous bleeding and petechial haemorrhages of gingivae, palate, tongue or lip as a result of thrombocytopenia, and gingival hyperplasia due to leukaemic infiltration. ¹ Numb chin syndrome and other neurologic manifestations. ² arthritic changes of TMJ ¹⁶
Acute myeloid leukemia (AML) and related neoplasms	Gingival mass ¹³
Blastic plasmacytoid dendritic cell neoplasm	NA
Acute leukemias of ambiguous lineage	Very rare. Only 3 reported cases in literature. Painless swelling of jaws, paraesthesia, loosening of teeth and lymphadenopathy. ^{14,15}
B-lymphoblastic leukemia/lymphoma	Bony mass in oral cavity ¹⁵
T-lymphoblastic leukemia/lymphoma	

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Conflict of interest

Author declares that there is no conflict of interest.

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