REVIEW ARTICLE

Chloroma: A Diagnostic Dilemma

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Abstract

Introduction: Chloroma is an extramedullary neoplasm of immature myeloid cells. It may develop during the course of or precede a myelogenous leukemia. Occasionally, extramedullary neoplasms composed of immature myelogenous cells may occur in patients without evidence of a leukemia. Though originally reported as an ocular tumor, it has since been reported in many organs of the body, including the oral cavity.

Objective: Difficulty in diagnosis of this neoplasm has long since been noticed as a major issue, especially in dental practice. This study aims to assimilate the facts regarding granulocytic sarcomas, thereby increasing the awareness of dental professionals to this life-threatening neoplasm.

Materials and methods: Published articles on granulocytic sarcomas (1853–2015) in established journals across the world are considered for our study.

Conclusion: Facts regarding the chloroma has been put together for the benefit of dental professionals so that diagnosis and treatment may be instituted at the earliest.

Keywords: Extramedullary, Immature, Leukemia, Myeloid, Neoplasm.

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Introduction

Chloroma is an extramedullary solitary tumor of immature myeloid cells—myeloblasts, promyelocytes, and myelocytes.[1,2] This rare lesion is found in association with an acute or chronic granulocytic leukemia, other myeloproliferative disorders, or myelodysplastic syndromes.[1,3,4] The term "granulocytic sarcoma" (GS) is used when a mass of blast cells are found outside the bone marrow, whereas leukemia cutis specifically refers to dermal infiltration by blast cells.[5]

This solid tumor was first described by Burns in 1811. King in 1853, named it as chloroma for its green color and as per his description, chloromas represented a separate disease entity.[6] Later in 1966, Rappaport renamed it as granulocytic sarcoma because about 30% of the tumors appeared white, gray, or brown. The term granulocytic sarcoma seems to be appropriate because it is composed of immature cells of the granulocytic series and has resemblance to a sarcoma.[7] The association of granulocytic sarcomas with leukemia was first noticed by Dock in 1892 and it was firmly established by Warthin and Dock in 1904. In 1912, the myelogenous origin of chloromas was established with convincing evidence, using a peroxidase stain.[7]

Etiopathogenesis

Myeloid neoplasms originate from hematopoietic progenitor cells capable of giving rise to terminally differentiated cells of the myeloid series such as erythrocytes, granulocytes, monocytes, and platelets. The disease primarily involves the bone marrow and, to a lesser extent, the secondary hematopoietic organs (spleen, liver, and lymph nodes), and present with an altered hematopoiesis. Myeloid neoplasms are classified into three major categories—acute myelogenous leukemias, myelodysplastic syndromes, and chronic myeloproliferative disorders. Homeostatic feedback mechanisms involving cytokines and growth factors play a major role in normal hematopoiesis. Myeloid neoplasms develop from transformed hematopoietic progenitor cells, where all these mechanisms are deranged. Granulocytic sarcoma is an extramedullary manifestation of myeloid neoplasms.[8]

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Granulocytic sarcoma is thought to originate in the bone marrow, from where it migrates to extra-osseous locations via the haversian canals.[9] Low socioeconomic status, decreased cellular immunity, and poor nutrition are considered to be predisposing factors for the development of extramedullary manifestations in leukemias. Cytogenetic abnormalities and certain cellular surface markers might contribute to the formation of this extramedullary disease.[5] Genetic alterations with a greater risk for development of GS include t (8; 21), t (15; 17), and inv (16). Individuals with elevated peripheral WBC counts are also included among the high risk group.[10] Most common sites are the bone and periosteum owing to their close proximity to the bone marrow. The tumor cells from the bone marrow travel through the haversian canals and infiltrate the periosteum. From here these cells invade the blood and other internal organs (the peritoneum, pericardium, bronchus, bladder, mediastenum, kidneys, and lungs) (Fig. 1). Frequent sites in the head and neck region are the soft palate, rhinopharynx, orbit, salivary glands, scalp, and face.[11]

Clinical Findings

Granulocytic sarcomas are rare neoplasms associated with acute and chronic leukemias but occasionally precede the development of a systemic disease by weeks or years. It occurs in 3.1–9.1% of patients with an acute myelogenous leukemia, most frequently in the monocytic form (AML M5).[7,9] There is a predilection for young individuals, with an incidence of about 5% in adults and 13% in

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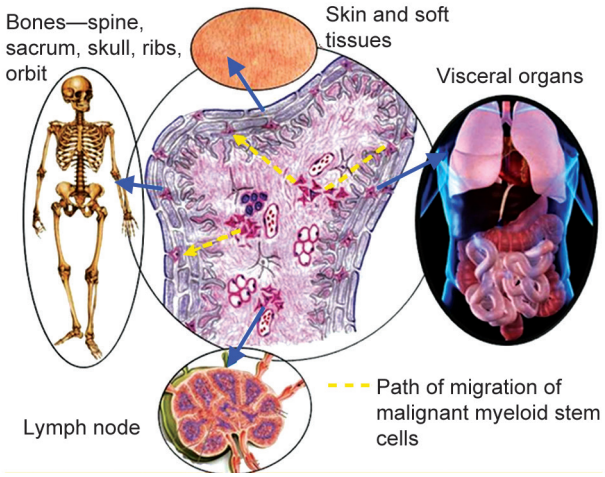

Fig. 1: Schematic representation of the pathogenesis of a chloroma from the bone marrow

children without any difference between sexes. Around 60% of the patients are aged less than 15 years.[11,12] Most of the chloroma patients were not having any previous history of associated malignancy of the myeloid series; however, these patients were diagnosed with leukemia within a period of about 10 months.[13]

The common location for chloroma is the bone, periosteum, skin, soft tissues, lymph nodes, and visceral organs.[5,13] Frequent sites of bone involvement include the orbit, sacrum, spine, and ribs.[12] Other sites reported in the literature are the genitourinary system and central nervous system. The clinical presentation of this neoplasm is highly variable, with the signs and symptoms closely related to its size and location.[24] Involvement of the head and neck is known to be around 12–43%.[14] They are frequently asymptomatic, with 50% of the cases diagnosed at the time of autopsy.[12] The presence of granulocytic sarcoma in leukemic patients is considered to be a sign of poor prognosis.[11] Sometimes, the appearance of myeloid sarcoma may represent a blast crisis in a myelodysplastic syndrome or chronic myeloproliferative disorder and hence has a significant role as a prognostic factor.[15] It can sometimes present an aggressive course with rapid enlargement. Intra bony lesions with extensive destruction of the bone and invasion to the adjacent tissues have also been reported.[10]

Oral Manifestations

Granulocytic sarcomas are rare in the oral cavity, with less than 50 cases reported in the literature till 2014.[7,16] More than 60% of these cases occur in association with an acute myelogenous leukemia, predominantly AML-M4 and AML-M5.[13,16] Oral granulocytic sarcoma is widely distributed among different age groups (ranging from 1 to 89 years) with a mild female predilection.[14] They may be either intra-osseous or extra-osseous or may present as a localized mass in the jaws, gingiva, palate, tongue, buccal mucosa, or extraction sockets.[1,13] Intraoral granulocytic sarcoma involving multiple sites is extremely rare with only three cases reported so far.[17] In the soft tissues, they present as asymptomatic nonspecific masses usually associated with ulceration.[1] The color of the overlying surface mucosa is pale gray, red, brown, or black.[14]

Radiography

Bone lesions involving the jaws are osteolytic with diffuse margins.[1,10] Occasionally, periosteal elevation is seen, producing a sunburst appearance. Rarely, perforation of cortical plates may also be noticed.[10]

Diagnosis

Diagnosis of GS is challenging especially if there is no previous history of any hematologic disorders such as leukemia. The clinical, radiographic, and histopathologic findings are nonspecific and hence not very helpful in diagnosis. The cut surface of the gross specimen appears green, which is due to high levels of myeloperoxidase (verdoperoxidase) enzyme within the tumor cells.[14] Myeloperoxidase catalyzes the oxidation of amino acids by hydrogen peroxide.[18] The green color fades rapidly when exposed to the air.[9] Some of the tumors appeared white, gray, or brown, and this variation in color depends on the concentration and the state of oxidation of the enzyme myeloperoxidase.[12,19] The tumor presents a characteristic red fluorescence under ultraviolet light, which is closely related to the physical property of myeloperoxide. It appears green in the crystalline form but fluorescent red under ultraviolet light.[20]

Optimally fixed, processed, embedded, and hematoxylin and eosin-stained sections are utilized for histopathologic diagnosis. The neoplasm is composed of a uniform population of immature cells of varying sizes and nuclear configurations.[11] Hence it is difficult to differentiate it from other malignant lesions such as the Hodgkin lymphoma, Burkitt's lymphoma, large cell lymphomas, neuroectodermal tumors, poorly differentiated carcinomas, or plasmacytoma.[10,13] There is a marked similarity in histology on routine paraffin sections between a granulocytic sarcoma and a histiocytic lymphoma owing to the presence of immature blast cells in both the lesions.[21] Auer bodies are crystalline, rod-like, and azurophilic structures representing intracytoplasmic, clumped primary lysosomal granules of myeloid cell precursors.[13] These structures, if present (10% of cases), can establish a definitive diagnosis of granulocytic sarcoma or AML. The presence of myeloperoxidase-positive Phi bodies and rods are considered to be diagnostic of the granulocytic sarcoma[22] (Fig. 2).

On the basis of histopathologic criteria, GS can be classified into three levels: blastic, immature, and differentiated. All three types show a diffuse cellular proliferation. Differentiated tumors show evidence of myeloid maturation with the presence of

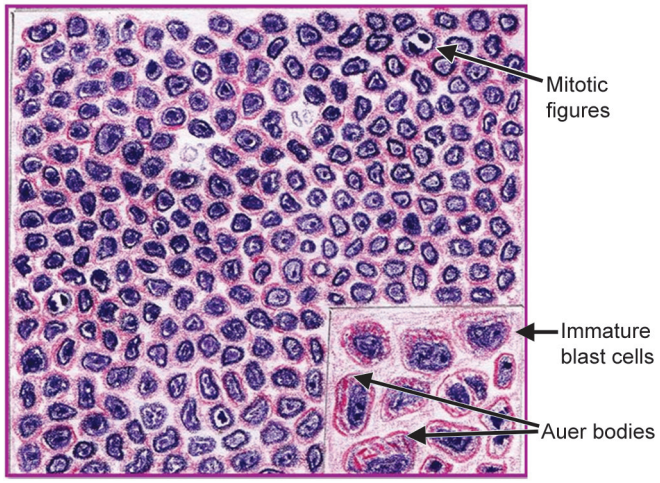

Fig. 2: Diagrammatic representation of the histopathology of chloroma

Table 1: Granulocytic sarcoma involving the oral cavity[27–76]

S. no.	*Author*	*Age/sex*	*Oral site*	*Lesion*	*History of leukemia*	*Prognosis/death*
1	King[27]	4/M	Mn	NA	NA	NA
2	Wiernik[18]	35/F	Cheek	Enlarging swelling	NAD 10 m PD	DD 2 years PD
3	Brooks[28]	8/M	Mx sinus	NA	NAD AML 4 years PD	DD
4	Nieman[29]	NA	Soft palate	NA	NA	NA
5	Hansen[30]	83/F	Mx AB	Periodontitis	NAD AML 3 m PD	DD
6	Conran[31]	23/F	Mn	Gingival enlargement with AB involvement	NAD	NRR
7	Takagi[32]	25/F	Mn	Firm swelling with periodontitis	NAD AML 18 m PD	DD
8	Chiari[33]	6/M	Mx AB	NA	NA	NA
9	Castella[34]	89/F	Hard palate	Grayish white swelling	NAD	DD
10	Reichart[35]	35/F	Mn	Brownish swelling with bone resorption	NAD AML 3 m PD	DD
11	Timmis[36]	54/M	Retromolar pad of Mn	Firm swelling	Simultaneous LL	DD
12	Muller[37]	39/F	Tonsil	Swelling	NAD	NA
13		37/F	Tonsil	Swelling	Known AML	DD
14	Welsch[38]	3/F	Mx	Firm swelling with invasion into the maxillary sinus and the base of the skull	NAD	DD 3 years PD
15	Dreizen[39]	NA	Mx gingiva, palatal mucosa	Exophytic growth with a reddish irregular surface	NAD AML PD	DD
16	Saleh[40]	62/F	Mn	NA	Simultaneous AML	DD
17	Ficarra[41]	67/F	Palatal mucosa	Swelling	NAD AML 15 m PD	DD 15 m PD
18	Barker[42]	4/F	Mx AB and palate	A firm bluish lesion with periodontitis and Mx sinus invasion	Known AML	DD
19	Alessi[43]	6/F	Mx AB and sinus	Swelling	Known AML	DD
20	Rodrigues[44]	56/M	Mn	An ulcerated lesion	NAD AML 6 m PD	NRR
21	Cho[45]	3/ M	Mn	NA	Known AML	DD
22	Eisenberg[46]	33/M	Max and mand AB	NA	Simultaneous AML	NRR
23	Stack[47]	70/M	Mn	Firm swelling	Simultaneous CML	DD
24	Ritter[48]	41/F	Gingiva	NA	Known AML	DD
25	Tuset[49]	77/M	Mn	NA	Known MDS	DD
26	Roth[50]	47/M	Gingiva	Enlargement	Simultaneous AML	DD
27	Wiernik[51]	1/M	Mn gingiva	Enlargement	Known AML	NA
28		19/M	Gingiva	Enlargement	Known AML	NA
29		56/M	Gingiva	Enlargement	Known AML	NA
30		5/F	Mn gingiva	Enlargement	Known AML	NA
31	Lynch[52]	86/F	Gingiva, maxillary bone	Brownish enlargement with bone resorption	NAD AML 29 m PD	DD
32	Menasce[53]	NA	Palate	NA	NA	NA
33	Carmona[54]	60/F	Mn extraction tooth socket (AB)	Swelling with an irregular surface	Known CML	DD 3 m PD
34	Tong[55]	76/F	Mx buccal alveolar mucosa	Granular and ulcerative lesion	NAD AML 7 m PD	DD 20 m PD
35	Bassichis[56]	8 months/M	Masseteric muscle	Swelling	Known AML	DD
36	Lee[25]	43/F	Mx gingiva	NA	NAD	NRR
37	Amin[57]	58/M	Palate	Solid swelling	Simultaneous AML	DD 1 m PD

(*Contd...*)

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S. no.	*Author*	*Age/sex*	*Oral site*	*Lesion*	*History of leukemia*	*Prognosis/death*
38	Jordan[58]	62/F	Mn AB	NA	NAD. AML in 2 m	DD
39	Asna[4]	72/F	Tongue	A large fleshy red lesion and a central crater	Known MDS	NRR
40	Antmen[59]	12/F	Gingiva	Enlargement	NAD	DD
41	Stoopler[60]	50/M	Buccal mucosa	Ulcer	Known AML	DD few m PD
42	Colella[61]	62/F	Mx gingiva Buccal vestibule	Swelling	NAD	DD 6 m PD
43	Ferri[11]	72/F	Max sinus	Solid growth filling the sinus	Known AML	DD 10 days PD
44	Goteri[15]	84/F	Hard palate	Ulcerated nodular infiltrative growth	NAD	NRR
45	Koudstal[7]	36/M	Hard palate	Swelling with a smooth surface	Simultaneous AML	Recurred after 2 years
46	Puranen[62]	59/M	Mx and Mn gingiva radicular cyst capsule	Gingival enlargement, decayed teeth with apical radiolucencies	Simultaneous AML	DD 1 year PD
47	Yinjun[63]	44/F	Mx gingiva	Enlargement	NAD	DD—few m PD
48	Yoon[64]	63/M	Mx gingiva	Enlargement	NAD	DD—few m PD
49	Matsushita[65]	50/M	Mx gingiva	A diffuse ulcerative granular lesion	Simultaneous AML	NRR
50		59/M	Mn gingiva	An ulcerative lesion	Known CML	DD 7 m PD
51	Xie[66]	32/F	Mx and Mn gingiva	Enlargement	Known CML	NRR after chemo
52	da Fonseca[67]	10/F	Soft tissue around Mn angle	Swelling and induration with lymphadenopathy	Simultaneous AML	DD 15 m PD
53	Srinivasan[68]	77/M	Lower lip	Solitary swelling	Known AML	DD 6 m PD
54	Kim[69]	4/F	Mn, facial swelling	NA	Known AML	DD few m PD
55	Cheng[13]	56/M	Buccal mucosa	Swelling	Simultaneous AML	DD 11m PD
56	Osterne[14]	23/F	Gingiva alveolar and lingual mucosa	Reddish enlargement	NAD AML 1 m PD	DD 2 m PD
57	Fasanmade[70]	75/F	Extraction socket	Ulcero-proliferative growth	Known MDS	Under radio-therapy
58	Qiu[71]	16/ F	Mn condyle	Swelling in the preauricular region	Simultaneous AML	NRR
59	Pau[72]	NA	Mx AB	A firm reddish lesion with periodontitis and periapical involvement	CML in remission. Presently diagnosed as AML	NRR
60	Papamanthos[73]	70/F	Alveolar socket, hard palate, Mx gingiva	Ulcero-proliferative growth	NAD	DD 5 m PD
61	da Silva-Santose[74]	47/F	Gingiva AB	Gingival enlargement with bleeding	Known AML	DD 3 m PD
62	Seema[75]	5 months/M	Mn alveolar ridge	Firm swelling with irregular necrotic surface and bone loss	Simultaneous AML	DD within a short period
63	Dym[76]	16/F	Lip, gingiva, palate	Erethema and ulceration	Simultaneous AML	NRR
64	Kurdoglu[1]	29/F	Buccal gingiva	Gingival enlargement and lymphadenopathy	Simultaneous AML	DD 15 m PD
65	Ponnan[10]	42/M	Mx gingiva	Enlargement	NAD	DD 2 m PD
66	Sharma[16]	9/M	Max sinus	Diffuse swelling of face, Mx AB	NAD	NRR
67	Moshref[17]	45/M	Max gingiva, palatal mucosa	Reddish soft irregular gingival enlargement	NAD	DD 10 m PD

NAD, nill at the time of diagnosis of chloroma; LL, lymphocytic lymphoma; MDS, myelodysplastic syndrome; NR, not reported; PD, post diagnosis; NRR, no recurrence; DD, died of disease; NA, not available; AB, alveolar bone; Mx, maxilla; Mn, mandible; m, months

eosinophilic myelocytes and are cytochemically positive for chloracetate esterase. Immature tumors are poorly differentiated with irregular nuclei and vesicular chromatin, and resemble large cell lymphomas. Cytoplasmic granules are not a common finding. The blastic type presents with a fine nuclear chromatin and a high mitotic rate without any obvious cytoplasmic granules.[23] Histopathologic diagnosis by hematoxylin and eosin stain may become difficult owing to poor myeloblastic differentiation. Adjuvant diagnostic techniques such as immunohistochemistry, flow cytometry, fluorescence in situ hybridization, or molecular analysis are also recommended.[24] For a confirmatory diagnosis, immunohistochemistry has become the gold standard.[14] Myeloblasts in GS usually express myeloid-associated antigens such as CD13, CD33, CD43, and CD117 and are negative for the lymphoid antigens CD3 and CD20. CD45 positivity confirms a hematologic origin, whereas positivity for myeloperoxidase and CD68 points to its myeloid lineage.[14] Once a granulocytic sarcoma is confirmed via diagnosis, a bone marrow biopsy and aspiration are to be performed to rule out any associated hematological malignancies. Tumors where a tissue biopsy is contraindicated, a fine needle aspiration may be recommended.[24]

Management

The prognosis for granulocytic sarcoma is poor, but not well documented.[24] Treatment methods include surgical decompression, chemotherapy, radiotherapy, or a combination of these three. Granulocytic sarcomas are radiosensitive and hence treated by localized radiotherapy and systemic chemotherapy because cures are not obtained with radiotherapy alone.[9] Recurrence is reported in 23% of the cases. Another line of an effective therapeutic option for myeloid sarcoma is hematopoietic stem cell therapy with a longer survival rate.[24] CT scan and MRI are useful tools in diagnosis, treatment plan, and evaluation of therapeutic response of granulocytic sarcomas.[12,25] The probability of developing acute myelogenous leukemia in individuals with an isolated chloroma is less with a longer survival if antileukemic chemotherapy is initiated at the time of diagnosis.[26] Even then the final answer to the treatment of this tumor resides with the development of methods to control or cure myelogenous leukemias.

Discussion

We have searched the literature on extramedullary granulocytic sarcomas from 1870 to 2015 and came across 66 cases involving the oral cavity[27–76] (Table 1). In our search, a slight female predominance was noticed. The disease was distributed over a wide age range with a peak incidence in the first decade of life. The most common site in the oral cavity was the gingiva, with very few cases reported in other areas such as the alveolar bone, palate, lips, buccal mucosa, tonsils, and maxillary sinus. Most of them presented with an enlargement/swelling, but a few had an ulcerated or a necrotic surface. An estimated 50% of the cases did not have a previous history of leukemia. Most of the patients underwent chemotherapy followed by radiotherapy. Prognosis for oral granulocytic sarcoma appears to be poor, as the mortality rate was found to be greater than 70%, with less than 10 cases showing remission. Appearance of a granulocytic sarcoma without a previous history of a leukemia complicates the diagnosis. All these facts points out that the dental surgeons need to be aware of such oral malignancies for early detection and treatment of these cases.

Conclusion

Difficulty in diagnosis or misdiagnosis is an important issue in dental practice, especially with malignant tumors or metastatic tumors from elsewhere. Myeloid sarcoma is a rare entity and hence a diagnostic challenge to dentists, physicians as well as pathologists especially if not associated with a myelogenous leukemia. A careful and thorough oral examination along with previous history followed by histopathology and histochemistry is of utmost importance in coming to a correct diagnosis.

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References

1. Kurdoglu B, Ostemal A, et al. Primary oral myeloid sarcoma: Report of a case. J Oral Maxillofac Pathol 2013;17:413–416. DOI: 10.4103/0973-029X.125209.
2. Cavder AO, Arcasoy A, et al. Ocular Granulocytic Sarcoma (chloroma) with acute Myelomonocytic Leukemia in Turkish Children. Cancer 1978;41:1606–1609. DOI: 10.1002/1097-0142(197804)41:4<1606::AID-CNCR2820410451>3.0.CO;2-Y.
3. Skarin A. Diagnosis in oncology. J Clin Oncol 2000;18:3993–3997. DOI: 10.1200/JCO.2000.18.23.3993.
4. Asna N, Cohen Y, et al. Primary Radiation Therapy for Solitary Chloroma of Oral Tongue. Isr Med Assoc J 2003;5:452.
5. Warme B, Sullivan J, et al. Chloroma of the forearm: A case report of leukaemia recurrence presenting with compression neuropathy and tenosynovitis. Iowa Orthop J 2009;29:114–116.
6. Austin JH. Chloroma: Report of a patient with unusual rib lesions. Radiology 1969;93:671–672. DOI: 10.1148/93.3.671.
7. Koudstaal MJ, van der Wal KGH, et al. Granulocytic sarcoma (chloroma) of the oral cavity: Report of a case and literature review. Oral Oncol Extra 2006;42:70–77. DOI: 10.1016/j.ooe.2005.09.003.
8. Kumar V, Abbas AK, et al. Robbins and Cotran. Pathologic Basis of Disease, 7th ed., Pennsylvania: Saunders; 2004.
9. Kalayci M, Sumer M, et al. Spinal granulocytic sarcoma (chloroma) presenting as acute cord compression in a nonleukaemic patient. Neurol India 2005;53:221–223. DOI: 10.4103/0028-3886.16418.
10. Ponnan SR, Srivastava G, et al. A fatal case of rapid gingival enlargement: Case report with brief review. J Oral Maxillofac Pathol 2014;18:121–126. DOI: 10.4103/0973-029X.131938.
11. Ferri E, Minotto C, et al. Maxilla-ethmoidal chloroma in acute myeloid leukaemia: case report. Acta Otorhinolaryngol Ital 2005;25:195–199.
12. Guermazi A, Feger C, et al. Granulocytic Sarcoma (Chloroma) Imaging Findings in Adults and Children. Am J Roentgenol 2002;178:319–325.
13. Cheng CY, Tzen CY, et al. Buccal granulocytic sarcoma (chloroma). J Dent Sci 2009;4:202–206. DOI: 10.1016/S1991-7902(09)60028-3.
14. Osterne RL, Matos-Brito RG, et al. Oral Granulocytic Sarcoma: A case report. Med Oral Patol Oral Cir Bucal 2009;14:232–235.
15. Goteri G, Ascani G, et al. Myeloid sarcoma of the maxillary bone. J Oral Pathol Med 2006;35:254–256. DOI: 10.1111/j.1600-0714.2006.00336.x.
16. Sharma A, Singh HP, et al. Granulocytic sarcoma in non-leukaemic child involving maxillary sinus with long term follow up: a rare case report. Ann Maxillofac Surg 2014;4:90–95.
17. Moshref M, Lotfi A, et al. Granulocytic Sarcoma (Chloroma) Presenting as Multiple Sites in Oral Cavity: Report of a Case. Iran J Cancer Prev 2014;7:53–57.
18. Wernik PH, Serpick AA. Granulocytic sarcoma (chloroma). Blood 1970;35:361–369.
19. Muss HB, Molony WC. Chloroma and other myeloblastic tumours. Blood 1973;42:721–728.
20. Schultz J, Shay H, et al. The Chemistry of Experimental Chloroma: I. Porphyrins and peroxidases. Cancer Res 1954;14:157–162.

21. Mason TE, Demaree Jr RS, et al. Granulocytic sarcoma (chloroma) Two Years Preceding Myelogenous leukaemia. Cancer 1973;31:423–432. DOI: 10.1002/1097-0142(197302)31:2<423::AID-CNCR2820310220>3.0.CO;2-J.
22. McCarty Jr KS, Wortman J, et al. Chloroma (granulocytic sarcoma) without evidence of leukaemia: facilitated light microscopic diagnosis. Blood 1980;56:104–108.
23. Gnepp DR. Diagnostic Surgical Pathology of the Head and Neck, 2nd ed., Saunders Elsevier; 2009. pp. 965–966.
24. Yilmaz AF, Saydam G, et al. Granulocytic sarcoma: a systematic review. Am J Blood Res 2013;3(4):265–270.
25. Lee SS, Kim HK, et al. Granulocytic sarcoma occurring in the maxillary gingiva demonstrated by magnetic resonance imaging. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:689–693. DOI: 10.1067/moe.2001.118287.
26. Imrie KR, Kovacs MJ, et al. Isolated Chloroma: The effect of early antileukemic therapy. Ann Intern Med 1995;123:351–353. DOI: 10.7326/0003-4819-123-5-199509010-00005.
27. King A. A case of chloroma. Monthly J Med 1853;17:97.
28. Brooks HW, Evans AE, et al. Chloromas of the head and neck in childhood. Arch Otolaryngol 1974;100:306–308. DOI: 10.1001/archotol.1974.00780040316014.
29. Neiman RS, Barcos M, et al. Granulocytic sarcoma: A clinicopathologic study of 61 biopsied cases. Cancer 1981;48: 1426–1437. DOI: 10.1002/1097-0142(19810915)48:6<1426::AID-CNCR2820480626>3.0.CO;2-G.
30. Hansen LS, Merrell PW, et al. Granulocytic sarcoma: an leukemic oral presentation. CDA J 1982;10:41–46.
31. Conran MJ, Keohane C, et al. Chloroma of the mandible:A problem of diagnosis and management. Acta Paediatr Scand 1982;71:1041–1043. DOI: 10.1111/j.1651-2227.1982.tb09573.x.
32. Takagi M, Ishikawa G, et al. Granulocytic sarcoma of the jaw. Bull Tokyo Med Dent Univ 1983;30:1–7.
33. Chiari H. Zur kenntniss des chloroms. Prog Ztschr F Heilk 1883;4: 177–187.
34. Castella A, Davey FR, et al. Granulocytic sarcomaof the hard palate: Report of the first case. Hum Pathol 1984;15:1190–1192. DOI: 10.1016/S0046-8177(84)80316-0.
35. Reichart PA, von Roemeling R, et al. Mandibular myelosarcoma (chloroma): Primary oral manifestation of promyelocytic leukemia. Oral Surg Oral Med Oral Pathol 1984;58:424–427. DOI: 10.1016/0030-4220(84)90337-2.
36. Timmis DP, Schwartz JG, et al. Granulocytic sarcoma of the mandible. J Oral Maxillofac Surg 1986;44:814–818. DOI: 10.1016/0278-2391(86)90161-8.
37. Muller S, Sangster G, et al. An immunohistochemical and clinicopathological study of granulocytic sarcoma ('chloroma'). Hematol Oncol 1986;4:101–112. DOI: 10.1002/hon.2900040202.
38. Welch P, Grossi C, et al. Granulocytic sarcoma with an indolent course and destructive skeletal disease. Tumor characterization with immunologic markers, electron microscopy, cytochemistry, and cytogenetic studies. Cancer 1986;57:1005–1010. DOI: 10.1002/1097-0142(19860301)57:5<1005::AID-CNCR2820570523>3.0.CO;2-P.
39. Dreizen S, McCredie KB, et al. Mucocutaneous granulocytic sarcomas of the head and neck. J Oral Pathol 1987;16:57–60. DOI: 10.1111/j.1600-0714.1987.tb00688.x.
40. Saleh MN, Rodu B, et al. Acute myelofibrosis and multiple chloromas of the mandible and skin. Int J Oral Maxillofac Surg 1987;16:108–111. DOI: 10.1016/S0901-5027(87)80039-5.
41. Ficarra G, Silverman Jr S, et al. Granulocytic sarcoma (chloroma) of the oral cavity: a case with aleukemic presentation. Oral Surg Oral Med Oral Pathol 1987;3:709–714. DOI: 10.1016/0030-4220(87)90375-6.
42. Barker GR, Sloan P. Maxillary chloroma: a myeloid leukaemic deposit. Br J Oral Maxillofac Surg 1988;26:124–128. DOI: 10.1016/0266-4356(88)90006-X.
43. Alessi DM, Karin R, et al. Granulocytic sarcomas of the head and neck. Arch Otol Head Neck Surg 1988;114:1467–1470. DOI: 10.1001/archotol.1988.01860240117036.
44. Rodriguez JC, Arranz JS, et al. Isolated granulocytic sarcoma: report of a case in the oral cavity. J Oral Maxillofac Surg 1990;48:748–752. DOI: 10.1016/0278-2391(90)90065-A.
45. Cho JS, Kim EE, et al. Mandibular chloroma demonstrated by magnetic resonance imaging. Head Neck 1990;12:507–511. DOI: 10.1002/hed.2880120611.
46. Eisenberg E, Peters ES, et al. Granulocytic sarcoma (chloroma) of the gingiva: report of a case. J Oral Maxillofac Surg 1991;49:1346–1350. DOI: 10.1016/0278-2391(91)90317-F.
47. Stack Jr BC, Ridley MB. Granulocytic sarcoma of the mandible. Otolaryngol Head Neck Surg 1994;110:591–594. DOI: 10.1177/019459989411000621.
48. Ritter JH, Goldstein NS, et al. Granulocytic sarcoma: an immunohistologic comparison with peripheral T-cell lymphoma in paraffin sections. J Cutan Pathol 1994;21:207–216. DOI: 10.1111/j.1600-0560.1994.tb00262.x.
49. Tuset E, Ribera JM, et al. Granulocytic Sarcoma: a study of five cases. Med Clin (Barc) 1995;104:377–380.
50. Roth MJ, Medeiros LJ, et al. Extramedullary myeloid cell tumors. An immunohistochemical study of 29 cases using routinely fixed and processed paraffin-embedded tissue sections. Arch Pathol Lab Med 1995;119:790–798.
51. Wiernik PH, De Bellis R, et al. Extramedullary acute promyelocytic leukemia. Cancer 1996;78:2510–2514. DOI: 10.1002/(SICI)1097-0142(19961215)78:12<2510::AID-CNCR10>3.0.CO;2-Z.
52. Lynch DP, Conlon TO, et al. Exophytic gingival mass in a geriatric patient. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85: 5–7. DOI: 10.1016/S1079-2104(98)90390-0.
53. Menasce LP, Banerjee SS, et al. Extra-medullary myeloid tumour(granulocytic sarcoma) is often misdiagnosed:A study of 26 cases. Histopathology 1999;34:391–398. DOI: 10.1046/j.1365-2559.1999.00651.x.
54. Carmona I T, Cameselle Teijeiro J, et al. Intra-alveolar granulocyticsarcoma developing after tooth extraction. Oral Oncol 2000; 36:491–494. DOI: 10.1016/S1368-8375(00)00024-5.
55. Tong AC, Lam KY. Granulocytic sarcoma presenting as an ulcerative mucogingival lesion: report of a case and review of the literature. J Oral Maxillofac Surg 2000;58:1055–1058. DOI: 10.1053/joms.2000.8752.
56. Bassichis B, McClay J, et al. Chloroma of the masseteric muscle. Int J Pediatr Otorhinolaryngol 2000;53:57–61. DOI: 10.1016/S0165-5876(00)00301-3.
57. Amin KS, Ehsan A, et al. Minimally differentiated acute myelogenous leukemia (AML-M0) granulocytic sarcoma presenting in the oral cavity. Oral Oncol 2002;38:516–519. DOI: 10.1016/S1368-8375(01)00085-9.
58. Jordan RC, Glenn L, et al. Granulocytic sarcoma: Case report with an unusual presentation and review of the literature. J Oral Maxillofac Surg 2002;60:1206–1211. DOI: 10.1053/joms.2002.35036.
59. Antman B, Haytac MC, et al. Granulocytic Sarcoma of Gingiva: An Unusual Case with Aleukemic Presentation. J Periodontol 2003;74:1514–1519. DOI: 10.1902/jop.2003.74.10.1514.
60. Stoopler ET, Pinto A, et al. Granulocytic sarcoma: An atypical presentation in the oral cavity. Spec Care Dentist 2004;24:65–69. DOI: 10.1111/j.1754-4505.2004.tb01681.x.
61. Colella G, Tirelli A, et al. Myeloid sarcoma occurring in the maxillary gingiva: a case without leukemic manifestations. Int J Hematol 2005;81:138–141. DOI: 10.1532/IJH97.E0410.
62. Puranen MH, Ropponen KM, et al. Myeloid sarcoma: Case report with an unusual presentation in radicular cystcapsule. Oral Oncol Extra 2006;42:190. DOI: 10.1016/j.ooe.2005.11.008.
63. Yinjun L, Jie J, et al. Granulocytic sarcoma of the gingiva with trisomy 21. Am J Hematol 2006;81:79–80. DOI: 10.1002/ajh.20469.

64. Yoon AJ, Pulse C, et al. Myeloid sarcoma occurring concurrently with drug-induced gingival enlargement. J Periodontol 2006;77:119–22. DOI: 10.1902/jop.2006.77.1.119.
65. Matsushita K, Abe T, et al. Granulocytic sarcoma of the gingiva: Two case reports. Quintessence Int 2007;38:817–820.
66. Xie Z, Zhang F, et al. Intraoral granulocytic sarcoma presenting as multiple maxillary and mandibular masses: a case report and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:e44–e48. DOI: 10.1016/j.tripleo.2006.12.028.
67. da Fonseca MA. Head and Neck Extramedullary Disease as the Initial Presentation of Acute Myelogenous Leukemia in a Child. J Dent Child 2007;74:241–244.
68. Srinivasan B, Ethunandan M, et al. Granulocytic sarcoma of the lips: report of an unusual case. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:e34–e36. DOI: 10.1016/j.tripleo.2007.07.020.
69. Kim K, Velez I, et al. A rare case of granulocytic sarcoma in the mandible of a 4-year-old child: a case report and review of the literature. J Oral MaxillofacSurg 2009;67:410–416. DOI: 10.1016/j.joms.2008.04.008.
70. Fasanmade A, Pring M, et al. Rapidly progressing mass of anterior mandible following a dental extraction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:330–334. DOI: 10.1016/j.tripleo.2009.10.051.
71. Qiu YT, Yang C, et al. Primary granulocytic sarcoma of the mandibular condyle presenting with the characteristic green color. J Oral Maxillofac Surg 2010;68:2575–2579. DOI: 10.1016/j.joms.2009.09.049.
72. Pau M, Beham-Schmid C, et al. Intraoralgranulocytic sarcoma: A case report and review of the literature. J Oral Maxillofac Surg 2010;68:2569–2574. DOI: 10.1016/j.joms.2009.09.040.
73. Papamanthos MK, Kolokotronis AE, et al. Acute myeloid leukaemia diagnosed by intra oral myeloid sarcoma: A case report. Head Neck Pathol 2010;4:132–135. DOI: 10.1007/s12105-010-0163-9.
74. da Silva-Santos PS, Silva BS, et al. Granulocytic sarcoma of the oral cavity in a chronic myeloid leukemia patient: An unusual presentation. Med Oral Patol Oral Cir Bucal 2010;15:e350–e352. DOI: 10.4317/medoral.15.e350.
75. Seema S, Jay GR, et al. Granulocytic sarcoma of the oral cavity. Indian J Cancer 2011;48:378–380. DOI: 10.4103/0019-509X.84929.
76. Dym H, Movahed R. Granulocytic Sarcoma of Palate: Case Report and Review of Literature. NYDDJ 2011;24–27.