

Granulocytic sarcoma in non-leukaemic child involving maxillary sinus with long term follow up: A rare case report

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ABSTRACT

Granulocytic sarcoma (GS) is a rare extramedullary malignant tumor composed of immature myeloid cells. It is strongly associated with acute myeloid leukaemia, chronic myeloproliferative diseases. Occurrence of GS in the oral cavity is extremely uncommon. Present case reported an unusual occurrence of GS without leukemia involving maxillary sinus of a child. The patient underwent chemotherapy followed by radiotherapy with complete remission. A long-term follow-up of the patient was carried without any evidence of recurrence with special focus on diagnostic difficulties. The present case highlights the perplexity in diagnosing such lesions with emphasis on the need of careful interpretation of all clinical, radiographic, histopathological and immunohistochemical details as it is one of the most frequently misdiagnosed disorder.

Keywords: Granulocytic sarcoma, leukemia, myeloid, myeloproliferative diseases

INTRODUCTION

World Health Organization (WHO) classification of lymphoid and hematopoietic neoplasms has described granulocytic sarcoma (GS) as a rare localized solid tumor mass consisting of myeloblasts or immature myeloid cells in an extramedullary site.^[1] It can occur in any part of the body, with skin, soft-tissues, bone and lymph nodes as most common sites.^[2] but oral cavity is an extremely rare site.^[3] It is rare in childhood and is more commonly associated with acute myeloid leukemia (AML). In general, non-leukemic patients develop overt leukemia in a mean period of 10.5 months from diagnosis of GS.^[4] We hereby report a rare occurrence of non-leukemic presentation of GS involving maxillary sinus in a child with a long-term follow-up with special emphasis on diagnostic difficulties.

CASE REPORT

This was a case report of 9-year-old male patient who reported with the complaint of swelling over the left side of face since

1 month. The swelling was initially small in size and has increased to the present size over a period of 1 month [Figure 1]. There was no history of fever, pain, tenderness or numbness, trauma and weight loss. Extraoral examination revealed diffuse swelling on the left middle one-third of the face, which was non-warm, non-tender, non-fluctuant and slightly compressible. It measured 3 cm × 3 cm in size and extends antero-posteriorly from 1 cm lateral to left ala of the nose until anterior to the tragus of the left ear and supero-inferiorly from left infra-orbital margin to the left corner of mouth [Figure 1]. None of the lymph nodes were palpable.

Intraorally single ill-defined, diffuse swelling, extending from permanent left maxillary central incisor to primary left second molar labially with slight obliteration of the vestibule and from primary left lateral incisor to the second molar palatally was observed. Bony expansion in relation to buccal and palatal side was also found. Overlying mucosa was normal with no ulceration [Figure 2].



Figure 1: Extraoral photograph showing diffuse swelling on left middle third of face extending antero-posteriorly from 1 cm lateral to left ala of the nose till anterior to the tragus of the left ear and supero-inferiorly from left infra-orbital margin to the left corner of mouth



Figure 2: Intraoral photograph showing single ill-defined, diffuse swelling on left buccal side of maxilla slight obliteration of vestibule along with expansion of buccal and palatal cortical bone



Figure 3: Orthopantomograph showing haziness in left maxillary sinus and is more radiopaque as compared to contralateral sinus

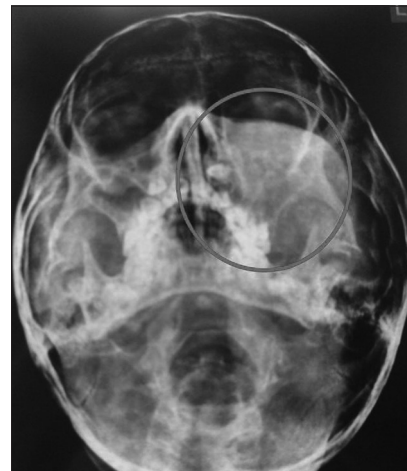


Figure 4: X-ray Water's view, demonstrating haziness in left maxillary sinus with more radiopacity than contralateral sinus

Orthopantomograph (OPG) revealed a marked area of haziness in left maxillary sinus and is more radio-opaque than contralateral sinus [Figure 3]. X-ray water's view, reconfirmed the findings as observed in OPG [Figure 4]. Computed tomography scan showed the extent and involvement of surrounding structures by the lesion. It extends superiorly to infra-orbital margin medially to nasal cavity and inferiorly to maxillary alveolar ridge and laterally expansion of zygoma [Figure 5]. Clinical differential diagnosis of dentigerous cyst, Ewing's sarcoma (EWS), adenomatoid odontogenic tumor, malignant epithelial carcinoma and odontoma were considered. Blood investigations were carried out which showed that differential blood count, total leucocyte count, prothrombin time, random blood sugar levels were all in normal range values. All liver function tests and renal function tests were in normal range values. Incisional biopsy was carried out and tissue was submitted to the department of oral pathology. Histopathologic examination showed diffuse monotonous infiltrate of medium sized or large cells, with interspersed eosinophilic cells. Most of the atypical myeloid cells showed increased nucleo-cytoplasmic ratio with round to ovoid, vesicular, reniform, or multilobated nuclei and finely granular eosinophilic cytoplasm [Figures 6 and 7]. Histopathologically neuroectodermal tumors, EWS, hematolymphoid tumors such as myeloid sarcoma (MS), malignant lymphomas (MLs) and myogenic tumors such as rhabdomyosarcoma (RMS) and malignant

epithelial tumors were considered as differential diagnosis. As there was considerable ambiguity regarding diagnosis, these lesions were differentially ruled with the application of the panel of immunohistochemical (IHC) markers. Positive reactivity was observed with CD99 [Figure 8], vimentin [Figure 9], CD31 [Figure 10], myeloperoxidase (MPO) [Figure 11], whereas Desmin, Actin, epithelial membrane antigen [Figure 12], synaptophysin [Figure 13], leukocyte-common antigen (LCA) and CD20 [Figure 14] showed a negative staining.

Bone marrow biopsy from right posterior iliac bone was also performed, which revealed normocellular bone marrow. Myeloid, erythroid precursors were well-preserved and normal myeloid erythroid ratio (2:1) was observed. Normoblastic erythropoiesis with no atypical cells were observed. Overall findings suggested Bone marrow uninvolved with any malignancy. Complete evaluation of clinical, radiographic, histopathological and IHC findings confirmed the diagnosis of an Aleukemic presentation of GS.

Patient was referred to oncology department where two courses of induction chemotherapy with cytarabine, daunorubicin and

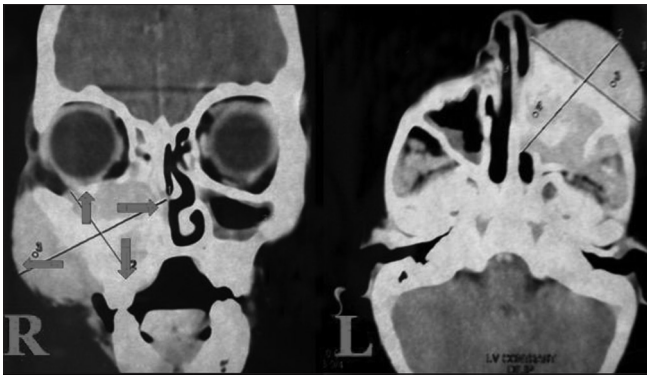


Figure 5: Computed tomography scan revealing the extent of lesion which extends superiorly to infra-orbital margin medially nasal cavity and inferiorly to maxillary alveolar ridge and laterally expansion of zygoma

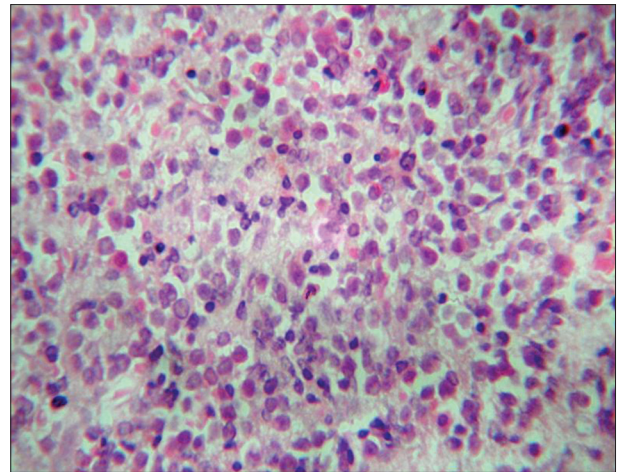


Figure 6: Diffuse monotonous infiltrate of medium sized or large cells, with interspersed eosinophilic cells (H and E, ×40)

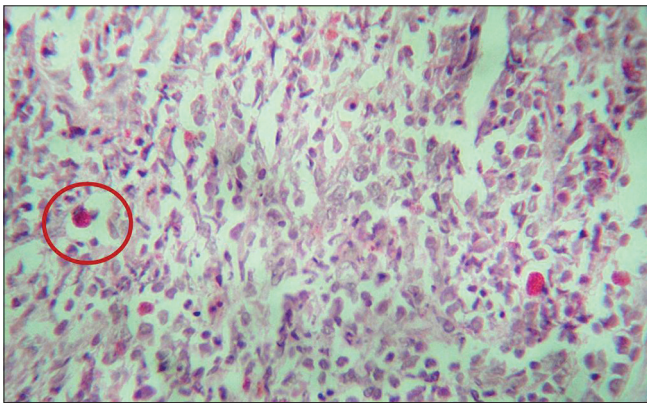


Figure 7: Myeloid atypical cells showing eosinophilic cytoplasm with fine granularity (H and E, ×40)

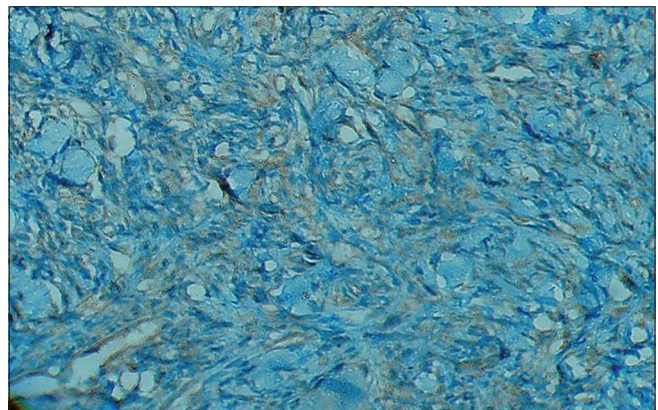


Figure 8: Immunohistochemical stained photomicrograph showing CD99 positive cells (×40)

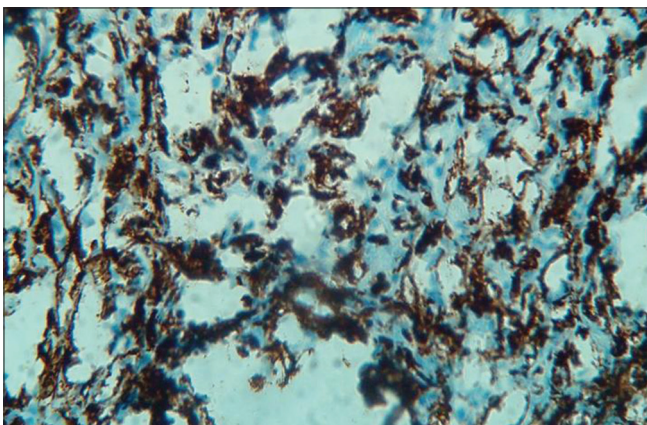


Figure 9: Photomicrograph showing Vimentin positive cells (×40)

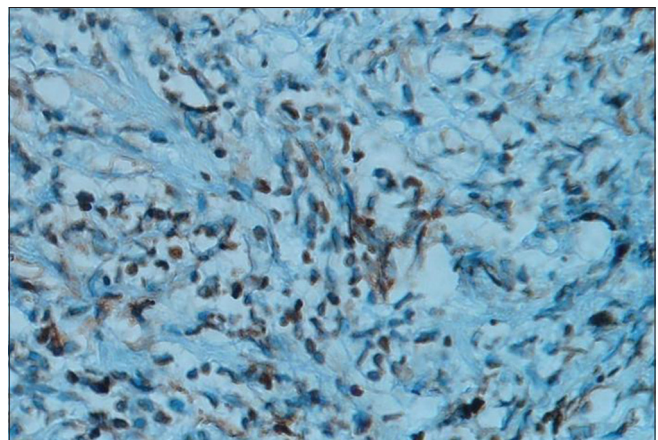


Figure 10: Immunohistochemical stained photomicrograph showing CD31 positive cells (×40)

three consolidation courses of chemotherapy with cytarabine was initiated followed by radiation dose of 50 Gy/25 fractions for 5 days a week for 5 weeks. This case has an isolated limited gross residual tumor after chemotherapy for GS. Further chemotherapy plus limited-field radiation therapy (RT) is potentially curative for this case at the present time. A complete remission of the disease, with the disappearance of the swelling was observed [Figure 15]. Patient was followed-up for 2 years without any evidence of recurrence of disease.

DISCUSSION

GS is a malignant neoplasm composed of progenitor cells of granulocytic lineage. It is believed that GS begins in the bone marrow and reaches the subperiosteal through haversian channels and then spreads to other parts of the body. The region of head

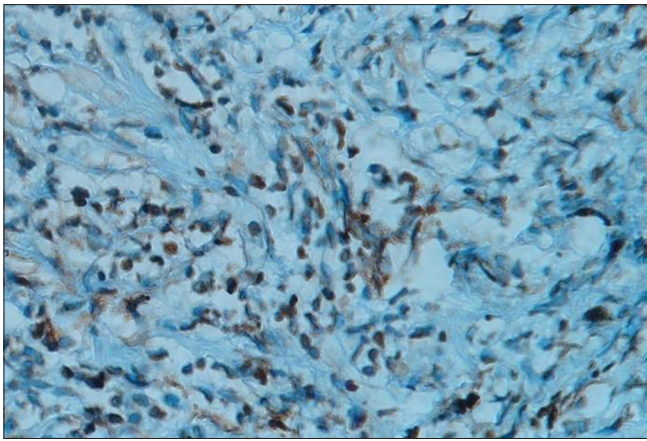


Figure 11: Immunohistochemical stained photomicrograph showing myeloperoxidase positive cells (x40)

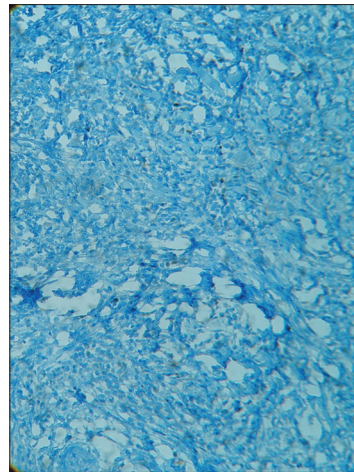


Figure 12: Immunohistochemical stained photomicrograph showing epithelial membrane antigen negative cells (x40)

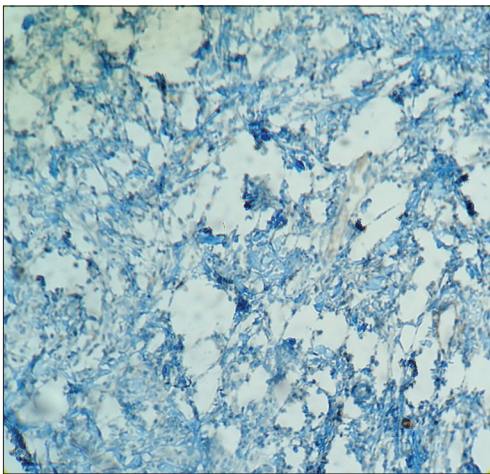


Figure 13: Immunohistochemical stained photomicrograph showing negative staining for synaptophysin marker (x40)

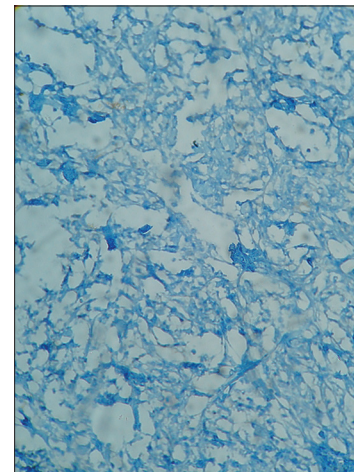


Figure 14: Immunohistochemical stained photomicrograph showing negative staining for CD20 marker (x40)



Figure 15: Postoperative photograph showing complete remission of disease

and neck is affected in 12-43% of the cases.^[5] Oral GS occur in a wider age group, ranging from 1 to 89 years of age, affecting both males and females with slight predilection for females, in the ratio of 4:3. The tumor may occur in the palate, mandible,

gingiva, lips, intra-alveolar space, tongue, tonsils, buccal mucosa.^[5,6] The intraoral GS is frequently associated with AML. AML-M4 and AMLM5 were the most commonly involved types. The GS can appear months or years before the AML manifests, during the course of the disease or represent a leukemia relapse or remission.^[6]

Only 46 intraoral cases have been reported in PubMed database search to the best of our knowledge, out of which only 18 cases manifested in the maxilla and very few of them involved maxillary sinus. Five patients were aleukemic at the time of diagnosis and even follow-up of these patients did not reveal any evidence of leukemia [Table 1]. Three of them manifested in the maxilla and only 2 showed involvement of maxillary sinus. Among 46 cases with intraoral presentation, 78% cases were misdiagnosed with unknown hematologic disease, which were later confirmed as MS with IHC.^[7] Present case described here, also occurred in the maxilla with involvement of maxillary sinus in a male child. Patient presented as a leukemic at the time of diagnosis and interestingly long term follow-up of 2 years revealed no evidence of leukemia or recurrence. Diagnosis of GS may be difficult when it occurs in the oral cavity, especially when it presents as an isolated finding

with no history of hematological disorders or peripheral blood or bone marrow involvement.^[8,9] Present case did not reveal any kind of abnormality in bone marrow and peripheral blood. Hence, it confronted a great challenge for diagnosis.

The differential diagnosis must include reactive lesions, benign neoplasms and malignant neoplasms, such as sarcomas, lymphomas, epidermoid carcinomas and metastasis of other neoplasms.^[10,11]

Histologically, GS presents a polymorphic picture, which usually has sheets of relatively monomorphic intermediate to large size polyhedral cells with irregular nuclear contours, vesicular chromatin, variably prominent nucleoli and frequent mitotic figures. Diagnosis of it is complicated by the diversity and inconsistency of its morphologic features.^[12] Due to poor myeloblastic differentiation the histopathological diagnosis by hematoxylin and eosin staining can be difficult and may result in erratic diagnosis.^[13] For example, it may be misdiagnosed as ML, EWS, acute lymphoblastic leukemia, or other small blue cell tumors. In such cases, use of histochemical staining, immunophenotyping with flow cytometry or IHC studies may help to arrive at a definitive diagnosis^[14-16] [Table 2].

Immunohistochemically, in addition to being reactive to antibodies against MPO, lysozyme and chloroacetate esterase, GS 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.^[17]

According to Anderson vimentin is expressed generally in sarcomas, melanomas and lymphomas and in myogenic tumors also and it was found to be positive in our case also.^[18] According to Fletcher, LCA (CD45) is positive in all MLs and may be positive in few MS but was observed negative in our case.^[18] Muscle specific Actin and Desmin are expressed in both smooth

and striated muscles and they came negative in our case. Hence, we can easily rule out any muscle tumor such as RMS.^[19] Chromagranin and synaptophysin are specific markers for neuroectodermal tumors and were negative in the present case. Hence, neuroectodermal tumors were also removed from differential diagnosis.^[20] Wick suggested that CD99 is expressed virtually in all primitive neuro-ectodermal tumor/EWSs, great variety of lymphoblastic lymphomas and minority of alveolar RMS as well.^[20] CD99 showed positivity in our case. Grenspan^[21] and Markoc et al.^[22] demonstrated that GS may be positive for CD99 similar to EWS, similar results were observed in the present case also. According to Fletcher, CD20 is expressed by B-lymphocytes^[18] and was negative in our case and CD13 for myeloid lineage^[18] and it showed positivity in our case. So, any tumor of lymphocytic origin was ruled out.

According to WHO, Traweek et al.^[16] and Fletcher,^[18] MPO is single most specific and sensitive marker to detect GS and it was found positive in our case and confirmed the diagnosis of GS. So, IHC forms the ground for definitive diagnosis of GS. According to Meis et al., vast majority of non-leukemic patients with GS, go on to develop acute leukemia within a matter of months (mean interval 10.5 months), with poor prognosis.^[23] So, it is very important to diagnose it early because any delay can be fatal for the patient. Meis et al.^[23] and Markoc et al.^[22] in two different studies, also found, patients of GS of extraoral sites without AML and who did not later develop AML had normal karyotype. In our case, bone marrow aspirate showed blast cells with normal karyotype.

Most of the non-leukemic patients affected by GS have been aggressively treated with chemotherapy or radiotherapy or both; however, the regimens employed have been quite heterogenous. Many patients have received more than one chemotherapeutic schedule and some have been treated for lymphoma for at least part of their therapy. More importantly, only a few patients

Table 1: Review of aleukemic cases of intraoral granulocytic sarcoma reported in English literature

Authors	Tumor location	Clinical and radiologic features	Correct diagnosis delay	Follow-up
Castella et al. ^[7]	The Hard palate	Painful, gray-white lesion with enlarged cervical lymph nodes	0	Died of disease
Conran et al. ^[8]	Mandible	Lesion with greenish pus-like discharge, bony erosion on plain radiograph and CT scan	2 months	No evidence of disease
Welch et al. ^[9]	Dentate maxilla	Firm lesion; invasion of maxillary sinus, bone erosion, and spread to skull base on plain radiograph and CT scan	30 months	Died of disease
Lee et al. ^[10]	Dentate maxilla	Firm, black-pigmented lesion with enlarged cervical lymph nodes; bone resorption on plain radiograph and low signal intensity on MR imaging	7 months	No evidence of disease
Goteri et al. ^[11]	Edentulous maxilla	Infiltrative mass, infiltration of maxillary sinus mucosa on CT scan	0	No evidence of disease

CT = Computed tomography, MR = Magnetic resonance

Table 2: The immunoprofile of common differential diagnosis of myeloid sarcoma

	CD13	CD20	CD99	CD45	Actin	Desmin	Synaptophysin	Vimentin	MPO	EMA
EWS	-	-	+	-	-	-	+	-	-	-
PNET	-	-	+	-	-	-	+	-	-	-
ML	-	+	-	+	-	-	-	+/-	-	-
MS	+	-	+/-	+/-	-	-	-	-	+	-
RMS	-	-	+/-	-	+	+	-	-	-	-
MEC	-	-	-	-	-	-	-	-	-	+

EWS = Ewing's sarcoma, MS = Myeloid sarcoma, PNET = Primitive neuro-ectodermal tumor, RMS = Rhabdomyosarcoma, ML = Malignant lymphoma, MEC = Malignant epithelial carcinoma, MPO = Myeloperoxidase, EMA = Epithelial membrane antigen

received RT for local control of the primary tumor and the total doses and timing of treatments varied widely from patient to patient.^[4] Since, present case was also a leukemia presentation of GS, it was successfully treated by combined chemotherapy followed by radiotherapy.

CONCLUSION

Albeit, GS is an uncommon tumor but it should not be overlooked especially in children. Physicians, oral surgeons and oncologists should always consider GS when evaluating swellings in patients with a history of hematologic disease and in patients presenting atypical clinical features without hematologic disease. It presents a great diagnostic challenge especially when it occurs as an isolated lesion. Confirmation of the diagnosis of GS relies on vigilant comprehensive analysis of pathologic examination and application of auxiliary studies, such as histochemical, IHC and flow cytometry studies.

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