Original Article

Clinical Profile and Outcomes of Granulocytic Sarcoma among Myeloid Malignancies Treated in a Tertiary Care Center

Abstract

Introduction: Granulocytic sarcoma (GS) is a rare tumorous collection of immature myeloid cells in extramedullary sites. **Patients and Methods:** We reviewed all treated patients of myeloid malignancies presenting to a tertiary referral Centre for treatment of Malignant disorders in western part of India. Using the database for patients diagnosed between Jan 2010 and Dec 2015, a study was conducted to detect the incidence, clinical features, and outcomes in patient presenting with GS. **Results:** Our study had 400 patients with myeloid malignancies out of which GS was diagnosed in 07 patients which constituted 1.7% of patients of all myeloid neoplasms. All received standard protocol based treatment. Five patients were in complete remission and one had partial remission after treatment.

Keywords: *Granulocytic sarcoma, myeloid malignancy, outcomes*

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Introduction

Myeloid malignancies have protean presentations, which include features of marrow failure, infiltration into various organs, and extramedullary tumors. Granulocytic sarcoma (GS) is an uncommon presentation of extramedullary tumor consisting of immature myeloid cells.[1] GSs are also called as myeloid sarcoma, chloroma, myeloblastoma, and extramedullary myeloid cell tumor.[2] It is often subclassified as leukemic or nonleukemic GS depending on whether or not a concurrent myeloid neoplasm is diagnosed at the presentation of the extramedullary tumor.[3] As this disorder is rare, large series are rare and only case reports are available.[4] We undertook this study to detect and analyze patients presenting with GS among myeloid malignancies by reviewing the data of all patients presenting to our center over a 5-year period.

Patients and Methods

The database of our center included patients with chronic myeloid leukemia (CML), acute myeloid leukemia (AML), and myelodysplastic disorder (MDS) along with those who presented with GS from January 2010 to December 2015. We reviewed the clinical presentation, pathologic studies, and chemotherapy given along with the outcome of the patients. The evaluation of records included presenting complaints, clinical features, bone marrow (BM) studies, cytogenetic studies, and biopsies of the tumors along with standard blood counts, serum biochemistry and imaging studies. All patients received therapy according to the standard regimens of the center. All patients were advised follow-up as per institutional protocol.

End points

Complete remission (CR) was defined as complete absence of all disease-related symptoms and detectable clinical, radiological, and pathological evidence of disease. Partial remission was defined as a reduction by >50%. Other responses were considered failure. Survival was counted from the time of diagnosis to the last follow-up/death from any cause. We used the National Cancer Institute Common Toxicity Criteria for reporting adverse events.

Brief description of the cases [Case Table 1]

Case 1

An 11-year-old boy presented with progressively increasing proptosis of the right eye over a period of 1 month. Computed tomography (CT) imaging showed retro-orbital soft tissue mass and biopsy of the mass was done and reported as round cell tumor of high-grade malignancy/ lymphoma. Peripheral blood and BM studies

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Case Table 1: Brief description of cases

Case number	Clinical features	Investigations	Treatment	Results	Remarks
1	An 11-year-old boy presented with proptosis of the right eye	CT scan - Retro-orbital mass Biopsy - Round cell tumour high grade PBS - 70%-80% blasts, suggestive of myeloid origin Cytogenetics - t(8;21)	AML BFM 98 protocol	CR	No recovery of vision in the right eye
2	A 9-year-old girl presented with fever, swelling of the right eye with loss of vision in the same eye	CT scan - Retro-orbital mass FNAC - GS PBS - 50%-60% blasts of myeloid origin Karyotyping - Normal	AML BFM 98 protocol and RT to mass	CR	Lost to follow-up
3	A 21-year-old, male, presented with pain and swelling in the left thigh	Bone scan - Increased uptake in the lower end of the left femur and right tibia Biopsy - Malignant round cell tumor, positive for LCA but negative for CD99 and vimentin. Bone marrow - 40% MPO positive blasts IPT was consistent with AML-M4 and cytogenetics was normal (46 XY)	Idarubicin + cytarabine as per 3 + 7 protocol 2 cycles of high-dose cytarabine consolidation chemotherapy	CR	In CR
4	A 15-year-old, female, developed painful swelling involving bilateral elbows, wrists, and knees of 4-month duration for which she was evaluated at a rheumatology center and treated as juvenile rheumatoid arthritis	X-ray - Lytic lesion of the lower end of the left humerus Biopsy - Leukemic infiltration PBS - 76% promyelocytes and blasts Bone marrow - 90% abnormal promyelocytes and blasts. Cytogenetics showed t(15;17), consistent with AML-M3	Idarubicin + all-trans retinoic acid-based induction and consolidation as per Fenaux protocol	Molecular remission	Elbow lesion regressed with full range of movements
5	A 32-year-old, male, presented with mediastinal mass with SVC obstruction	CT chest - Anterior mediastinal mass PBS - AML-M2 Cytogenetics - Normal	Idarubicin and cytarabine	Induction death	Autopsy-mediastinal mass GS
6	A 56-year-old, female, presented with postmenopausal bleeding	USG - Bulky uterus HPE of the uterus revealed myeloid sarcoma infiltrating the fundus of uterus and bilateral fallopian tubes, MPO, CD34 positive	Idarubicin + cytarabine as per 3+7 protocol Refused to undergo consolidation	AML relapse after 6 months and expired	Refused to undergo treatment after the first induction
7	A 71-year-old, male, presented with multiple cervical lymphadenopathy of the left submandibular region	Biopsy - Myeloid sarcoma Bone marrow - 13% blasts Cytogenetics was t(8;21)	Cytarabine (twice daily for 7 days) RT to the left submandibular region	CR	Continues to be in CR after 15 months

CT: Computerized axial tomography, CR: Complete remission, PBS: Peripheral blood smear, RT: Radiotherapy, SVC: Superior vena cava, FNAC: Fine needle aspiration cytology, LCA: Leukocyte common antigen, HPE: Histopathological examination, MPO: Myeloperoxidase, IPT: Inflammatory pseudotumor, USG: Ultrasonography

were normal. A month later, his condition deteriorated and he presented to our center. On examination, he had proptosis with chemosis of the conjunctiva and complete blindness of the right eye. His peripheral blood smear examination and BM examination revealed 70%–80% blasts. Cytochemical study was positive for Sudan black, myeloperoxidase (MPO), and periodic acid-Schiff stain. Cytogenetics revealed t(8,21), and he was given standard AML induction and consolidation

as per AML BFM 98 protocol. He achieved CR at the end of induction with complete resolution of the orbital mass, though with incomplete visual recovery.

Case 2

A 9-year-old girl developed easy fatigability, intermittent fever of 1-month duration, along with swelling and blindness of the right eye of 15-day duration. On examination, she had purpuric spots, gum hypertrophy, and proptosis of the right eye. Her peripheral blood revealed leukocytosis of 23,000/cu mm with 50%–60% blasts. BM examination was suggestive of AML M_2. Karyotype was normal (46 XX) and a CT scan of the eye revealed right retro-orbital mass. Fine-needle aspiration cytology of the mass revealed features of GS. She was treated as per AML BFM 98 protocol and achieved a CR at the end of induction, with partial resolution of the orbital mass. She was subsequently treated with local radiotherapy after which the proptosis resolved, but her visual acuity did not recover. She was lost to follow-up 8 months after induction chemotherapy.

Case 3

A 21-year-old male presented with progressive pain and swelling of his left thigh of 6-month duration. There was no history of fever, bleeding tendencies, or easy fatigability. Clinically, he had no lymphadenopathy, gum hypertrophy, or bleeding diathesis. Examination of the lungs, abdomen, and testis was normal. Complete blood count (CBC) was normal, and X-ray of the left femur revealed osteoblastic lesion of the lower end. CT imaging of the chest was normal. Bone scan revealed increased uptake in the lower end of the left femur and right tibia. Biopsy of femur was suggestive of malignant round cell tumor, which was positive for leukocyte common antigen but negative for CD99 and vimentin. BM study revealed a hypercellular marrow with 40% MPO +ve blasts. Inflammatory pseudotumor (IPT) was consistent with AML-M4 and cytogenetics was normal (46 XY). He was given induction therapy with idarubicin + cytarabine as per 3 + 7 protocol, with which he achieved morphological remission in marrow. The painful swelling of the lower left thigh regressed clinically by more than 50%. He was subsequently given two cycles of high-dose cytarabine consolidation chemotherapy at the end of which there was a complete radiological resolution of the left femoral lesion. He continues to remain in remission on follow-up.

Case 4

A 15-year-old female developed painful swelling involving bilateral elbows, wrists, and knees of 4-month duration, for which she was evaluated at a rheumatology center and treated as juvenile rheumatoid arthritis, with analgesics, steroids, and oral methotrexate. Peripheral blood smear done at that time was normal. Five months later, she developed intermittent fever and X-ray revealed lytic lesion of the lower end of the left humerus. Biopsy of the lesion revealed leukemic infiltration, and so she was transferred to our center. Clinically, she had left elbow swelling with fixed flexion deformity at the elbow joint. She had multiple purpuric spots and left axillary lymph node enlargement. Hemoglobin was 7 gm/dl, total leucocyte count —was 50,000/cu mm, and platelet count was 39,000/cu mm. Phosphate-buffered saline (PBS) revealed 76% of promyelocytes and blasts. BM study showed 90% of abnormal promyelocytes and blasts. Cytogenetics showed t(15,17), consistent with AML-M3. She was managed as high-risk acute promyelocytic leukemia with idarubicin + all-trans retinoic acid (ATRA)-based induction and consolidation as per Fenaux protocol. She achieved morphological remission at the end of 35 days of ATRA induction, and a molecular remission after three cycles of consolidation. The left elbow lesion regressed completely within 2 months of starting therapy with complete recovery of range of movement after she started physiotherapy.

Case 5

A 32-year-old male was admitted as a transfer in case from a peripheral hospital as a case of mediastinal mass with superior vena cava obstruction diagnosed when he was evaluated for breathlessness. Peripheral smear done initially was reported as normal. Evaluation at this center revealed large anterior mediastinal mass on CT chest. PBS and BM studies were consistent with AML-M2 with normal cytogenetics. He was put on induction therapy with idarubicin and cytarabine, but on day 11 of the induction, he died due to neutropenic sepsis. Autopsy done revealed GS involving anterior mediastinum, bilateral lungs, both the kidneys, and heart.

Case 6

A 56-year-old female with a prior comorbidity of schizophrenia, well controlled on antipsychotic drugs, presented to her gynecologist with postmenopausal bleeding. Ultrasound of the pelvis revealed a bulky uterus. PAP smear cytology was normal, and she underwent a total abdominal hysterectomy. The high-permeability edema (HPE) of the uterus revealed myeloid sarcoma infiltrating the fundus of the uterus and bilateral Fallopian tubes. Positron emission tomography (PET) scan revealed no residual lesions and she was transferred to our center for further advice. The biopsy blocks were reviewed and MPO, CD34-positive myeloid sarcoma was confirmed. BM aspiration and biopsy was normal, without any leukemic involvement. She was given induction chemotherapy with idarubicin and cytarabine as per 3 + 7 protocol. She had neutropenic sepsis with pulmonary aspergillosis requiring 2 weeks of antifungal therapy. She recovered completely from neutropenia by day 34 and was discharged in good performance status. However, she was unwilling for consolidation therapy and did not come for follow-up for 6 months. In the 7th month postinduction chemotherapy,

she had a frank relapse of AML with 90% of peripheral blood blasts for which she received palliative care at her hometown and she died within 2 weeks.

Case 7

A 71-year-old male presented with multiple cervical lymphadenopathy of the left submandibular region. The nodes were firm, confluent, nontender, and measured between 1 and 2 cm in size. CBC, serum biochemistry, X-ray chest, and a dental examination were all normal. After preliminary infectious disease screen, he underwent excision biopsy of the lymph node mass. HPE including immunohistochemistry revealed myeloid sarcoma. A BM examination revealed cellular marrow with 13% blasts. IPT was consistent with AML-M4. Cytogenetics was t(8;21) by karyotyping and reverse transcription-polymerase chain reaction. PET scan revealed residual disease in the excised area. In view of his advanced age, he was given chemotherapy with intermittent doses of cytarabine (twice daily for 7 days). He also underwent radiotherapy to the left submandibular region, with complete resolution of the mass. BM on day 28 showed <5% blasts, with normal cellularity and normal CBC. He was given another three cycles each of intermittent dose cytarabine, for consolidation of the remission. Repeat PET scan showed no evidence of residual disease. This patient has been under follow-up postchemotherapy for 15 months, and is in CR.

Treatment summary

We treated five patients of GS with chemotherapy and two received chemotherapy plus radiotherapy. In all, five patients received idarubicin 12 mg/m^2 for 3 days plus Ara-C 100 mg/m^2 for 7 days as induction therapy (I A), one received idarubicin 12 mg/m^2 for 3 days and ATRA 45 mg/m^2 for 30 days, and one patient received low-dose Ara-C with radiation.

Results

In all, there were 400 patients with myeloid malignancies which included 135 patients with AML, 227 patients with CML, and 38 patients with high-risk myelodysplastic syndrome as shown in Table 1 and Figure 1. GS was diagnosed in seven patients which constituted 1.7% of patients of all myeloid neoplasms and 5.2% of patients with AML. No patient of CML or high-risk MDS had GS. Out of the seven cases, two patients initially presented with nonleukemic GS [Figure 2], but both subsequently developed AML, five patients presented with features of GS with concomitant AML.

The patient characteristics at presentation with GS are listed in Table 2. The site distribution is shown in Table 3; one patient had multifocal involvement of mediastinum, heart, and lungs. Cytogenetic analyses of the BMs were available for all patients, four out of whom had a normal karyotype. Two patients had t(8;21) and one patient had T(15;17) as shown in Table 4.

Table 1: Incidence of granulocytic sarcoma and association among other myeloid neoplasms (2010-2015)

Diagnosis	Number	GS/Dx ratio
GS	7	NA
AML*	135	0.05
MDS (high risk)	38	0.18
CML	227	0.03
All	407	0.02

*AML 135 patients not including the 7 GS patients. GS: Granulocytic sarcoma, AML: Acute myeloid leukemia, MDS: Myelodysplastic syndrome, CML: Chronic myeloid leukemia, NA: Not available

Table 2: Clinical and laboratory characteristics of patients with granulocytic sarcoma

Characteristic (*n*=7)	Mean	Range
Age	31	9-71
WBC (×1000)	28	5-77
Hemoglobin (g/dl)	9.9	5.8-14.5
Platelets (×1000)	78	17-334
Creatinine (mg/dl)	0.8	0.6-2.5
Bilirubin (mg/dl)	0.6	0.2-2.6
SGPT (IU/L)	42	10-69
SGOT	35	12-80
Albumin (g/dl)	3.1	2.2-4.5

WBC: White blood cell, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase

Table 3: Sites of involvement

Sites of involvement	*n*
Orbit	2
Bone	2
Lymph nodes	1
Uterus	1
Skin	1

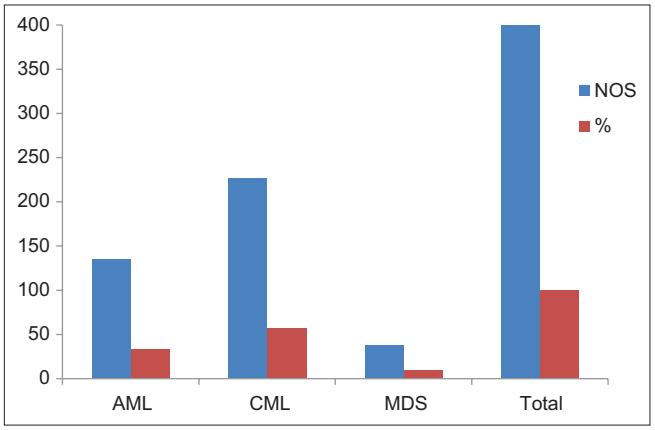

Figure 1: Distribution of myeloid disorders

Six patients were given standard protocol-based treatment. One patient due to advanced age received Ara-C and RT. CR in the marrow was achieved in six patients and five out of these had remission in the extramedullary mass also.

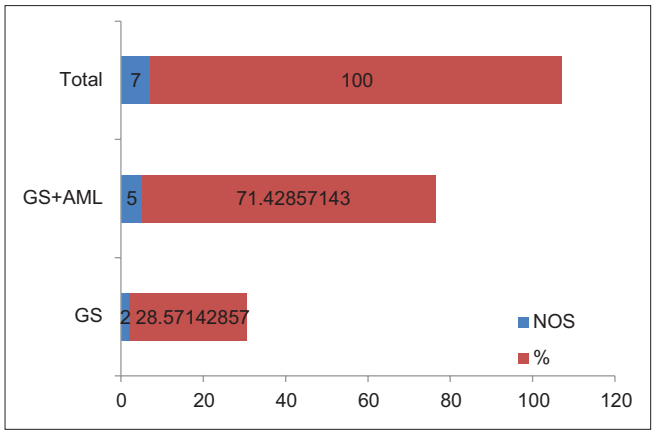

Figure 2: Initial presentation

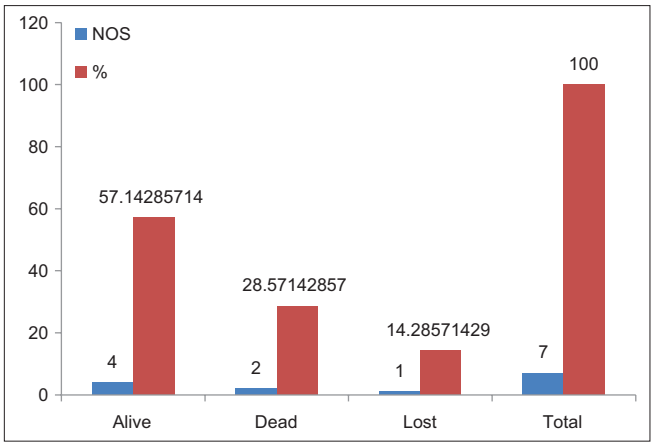

Figure 3: Outcomes

Table 4: Cytogenetics

Karyotype	Total (4)
t(8;21)	2
t(15;17)	1

One patient had partial response in the extramedullary myeloid mass, while one patient was unresponsive and expired after induction chemotherapy. Of the five patients who had CR of the extramedullary lesions, one patient subsequently died of medullary relapse.

Out of seven patients of GS in this study, four patients are alive and on regular follow-up. Two patients died, one during induction chemotherapy and one 7 months later with relapse. One patient was lost to follow-up 8 months after the diagnosis [Figure 3]. Median follow-up of patients who survived is 26 months (range: 12–44). Three patients had favorable cytogenetics [two t(8;21) and one t(15;17)], and all three have sustained remission posttherapy.

Discussion

The term GS refers to a tumor mass consisting of infiltrates of immature cells found in some cases of myeloid leukemia which are located in extramedullary sites. Leukemic infiltrates that are not in tumorous form are not considered as GS. It is also known as chloroma (owing to its green color attributed to the enzyme MPO).[2] It is often subclassified as leukemic GS or nonleukemic GS depending on whether or not a concurrent myeloid neoplasm is diagnosed at the presentation of the extramedullary tumor.[3] Some authorities have synonymously used the term myeloid sarcoma for GS. It can occur as primary GS without marrow involvement or after the appearance of blood or BM disease.[4] GS is also sometimes seen in patients with MDS and myeloproliferative neoplasm.[5] GS are often diagnosed as round cell tumors, and in most of the cases, they are misdiagnosed as lymphoma.[6,7] High index of suspicion and use of myeloid markers for any extramedullary site of round cell tumor and poorly differentiating neoplasm result in early diagnosis. Patients with extramedullary GS may subsequently progress to acute leukemia.[7,8]

GS is a rare disease; therefore, all treatment protocols cannot be based on prospective studies. Most literatures describing GS published from India have been case reports or short case series. This is also a retrospective analysis of all myeloid malignancies presenting as GS. We have put our data on GS in perspective to myeloid neoplasms seen in the population dependent on our center. In this study, the overall ratio of GS to AML is 5.2%. This is much higher than that reported in Western literature where it is quoted as between 1% and 2% of all AML patients.[9,10] CR was achieved in six patients with chemotherapy or chemo-radiotherapy. There were no patients of GS from the pool of CML patients including those in accelerated or blastic phase.

Extramedullary sites for primary GS may indicate an abnormal homing signal for the blast cells. On comparison of the chemokine receptors expressed on AML blasts in pediatric AML patients with or without skin involvement, Faaij *et al*. found that AML blasts from the skin had special chemokine receptors including CCR5, CXCR4, CXCR7, and CX3CR1, but these were not present on blasts in marrow.[11] In our study, though there were two patients with nonleukemic GS, one presented to us only after the disease had spread and involved the marrow. Only one patient took treatment at a nonleukemic stage and relapsed 6 months later.

Imrie *et al*. have recommended aggressive chemotherapy for extramedullary GS results in lower rates of progression to AML and increase in survival.[12] Following the second CR, transplant is also used as intensified postremission therapy with better results.[12,13] Byrd *et al*. reported that, among AML patients with t(8;21) (q22;q22) karyotype, those presenting with GS have lower rates of CR and survival.[14,15] Our study with good cytogenetics appeared to have similar response rates, significance of which is difficult to comment due to small number of patients.

Radiotherapy as a treatment option is used to treat tumorous growth of GS but its role is not well established. Avni *et al*. published data of 19 patients of GS treated with radiotherapy along with chemotherapy but found no difference in median time to death.[16] Two of our patients received radiotherapy with an intention to consolidate the extramedullary lesions after induction, but no radiation was given to others with good response with chemotherapy alone.

Despite the largest group of myeloid neoplasms being patients of CML, we did not encounter even one GS case from our database of 227 CML cases including 14 who were in accelerated or blastic phase. This may reflect the effect of disease control with tyrosine kinase inhibitor (TKI) therapy, which each of these CML patients were on. Most studies reporting GS in CML patients included patients from the pre-TKI era. The same can be said about the high-grade MDS patients who mostly exhibited hypomethylating agents. The fact that our database included only 34 patients with MDS, which is a small number, should also be kept in mind while considering the incidence of GS in these patients.

Conclusions

GS are tumorous collection of leukemic infiltrates at extramedullary sites. High index of suspicion and use of myeloid markers for any extramedullary site of round cell tumor result in early diagnosis. This study highlights the clinical presentation and outcome of this rare disease at a tertiary care hospital in India. Consensus on optimal therapy for extramedullary GS has not been reached.[14] High index of suspicion and use of myeloid markers for any extramedullary site of round cell tumor result in early diagnosis. Unlike some Western studies, our data show that intensive standard AML chemotherapy with or without radiotherapy was also an effective treatment for GS. However, larger studies or collaborative studies from India will further help in characterizing the presentations and outcomes of GS seen in our population with limited resources.

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Conflicts of interest

There are no conflicts of interest.

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