MYELOID SARCOMA – A CLINICOPATHOLOGICAL ANALYSIS OF 25 CASES

Usha Amirtham[1], Shankaranand Siddappa Bharatnur[2], Shanthi Velusamy[3], Mangalagowri Mayanna[4], Prasanna Kumari[5], Lakshmaiah Chinnagiriyappa Kuntegowdanahalli[6], Rekha Vijaykumar[7]

[1]Associate Professor, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore, India.
[2]Assistant Professor, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore, India.
[3]Fellow in Oncopathology, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore, India.
[4]Assistant Professor, Department of Pathology, Cytogenetic Unit, Kidwai Memorial Institute of Oncology, Bangalore, India.
[5]Associate Professor, Department of Pathology, Cytogenetic Unit, Kidwai Memorial Institute of Oncology, Bangalore, India.
[6]Professor, Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bangalore, India.
[7]Professor, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore, India.

ABSTRACT

INTRODUCTION

Myeloid sarcoma (MS) is defined as "a tumour mass consisting of myeloid blasts with or without maturation, occurring at an anatomical site other than bone marrow". It rarely arises as the only lesion, referred to as primary myeloid sarcoma. Secondary myeloid sarcomas precede or develop concomitantly with acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN) or MDS/MPN. MS developing in a known patient of AML is considered as relapse irrespective of blood and bone marrow findings. This study retrospectively analyses the clinicopathological, morphological and immunohistochemical profiles along with available data on cytogenetics and followup of 25 patients diagnosed as myeloid sarcoma in a regional cancer centre in South India.

MATERIALS AND METHODS

All cases diagnosed histopathologically as myeloid sarcoma between 2006 and 2015 were retrieved from the archives of the department of pathology. The clinicopathological profile of these cases was reviewed, including age, sex, site of involvement and accompanying haematological findings. Immunohistochemical and cytogenetic findings were noted along with laboratory data and median survival time.

RESULTS

Of the 25 cases studied, 18 patients were male and 7 patients were female. The age ranged from 14 months to 65 years. The commonest site of involvement was lymph node followed by bone, skin and soft tissue. Twenty cases represented primary MS and the remaining five cases were secondary myeloid sarcomas. Of the latter, four cases were associated with AML and one with chronic myeloid leukaemia (CML). One case of primary lesion in the radius subsequently developed another lesion in calcaneum after 3 years. Trisomy 8 was the commonest cytogenetic abnormality seen. Two patients of the series are alive and on treatment whereas 7 patients died within a year of diagnosis and the remaining were lost to followup.

CONCLUSION

Myeloid sarcoma is a rare disease with a higher incidence in males. It was seen more commonly as an isolated lesion in our study involving the lymph nodes. It requires early diagnosis and appropriate management including bone marrow transplantation, considering the high mortality.

KEYWORDS

Blastic transformation, Cytogenetics, Lymph node, Myeloid sarcoma.

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INTRODUCTION: First described by Burns[1] in 1811, myeloid sarcoma was termed chloroma by King et al[2] to describe the green colour of the tumour on exposure to air due to the enzyme myeloperoxidase. It is synonymous with extramedullary myeloid tumour and granulocytic sarcoma. The skin, lymph node, gastrointestinal tract, bone, soft tissue and testis are the most frequently involved sites,[3,4] though the tumour may arise at any site. Rarer sites reported include heart, spinal cord and liver.[5,6-9] The tumour has the morphological features of a round cell tumour with definitive diagnosis necessitating immunohistochemistry. Early and accurate diagnosis is necessary to provide appropriate treatment which includes chemotherapy and bone marrow transplantation.

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Corresponding Author:
Dr. Shanthi Velusamy,
Fellow in Oncopathology, Department of Pathology,
Kidwai Memorial Institute of Oncology,
Dr. M. H. Mari Gowda Road, Hombe Gowda Nagar,
Bengaluru-560030.
E-mail: shanz84@gmail.com
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MATERIALS AND METHODS: Patients who underwent incisional or excisional biopsy and histopathological examination with immunohistochemistry and thereby diagnosed as myeloid sarcoma were selected for the present study. The study period was ten years (2006 to 2015) and was conducted at a regional cancer center which caters to a large population of southern India. A review of case records, histopathology and immunohistochemistry was done correlating with the cytogenetics and bone marrow findings. Immunohistochemistry was done with avidin-biotin using Biogenex and Daco antibodies. Cytogenetic analysis was done in 14 cases on the available bone marrow and/or fine needle aspirates (FNA) of the lesion. Standard culture and G-banding technique was followed. Followup of these patients was done and the results are summarised in table 1.

RESULTS: A total of 25 patients were found to be diagnosed as myeloid sarcoma during the study period. This included 18 males (72%) and 7 females (28%). The male to female ratio is 2.6:1. The age ranged from 14 months to 65 years. The commonest presenting symptom was localised swelling in accordance with the site. The duration of symptoms varied from two to six months. The paediatric population included 11 cases (44%). The commonest location was lymph node constituting 24% (6 cases). The other sites encountered were skin and soft tissue (5 cases), bone (5 cases) including mandible, radius, calcaneum, rib and sacrum), orbit (4 cases), mediastinum (3 cases), testis (1 case) and endometrium (1 case).

A complete haematological workup was done for all cases including bone marrow study to rule out synchronous leukaemia and it was found that 20 cases were isolated lesions. One patient (Case 22) developed myeloid sarcoma of testis one year after the initial diagnosis of chronic myeloid leukaemia while on treatment with tyrosine kinase inhibitors (imatinib).

One patient (Case 21) who presented with pancytopenia was lost to followup after an inconclusive bone marrow aspiration. Eight months later, she presented with myeloid sarcoma of lymph node. Bone marrow studies revealed synchronous acute myeloid leukaemia. The patient defaulted induction chemotherapy and was on low intensity treatment due to poor performance status and died one week later.

One out of the 25 patients presented with myeloid sarcoma in the lower end of the radius, which was followed 3 years later by a metachronous lesion in calcaneum. The patient had defaulted chemotherapy in the intervening period. This patient is currently undergoing chemotherapy.

Case 25 presented with abnormal vaginal bleeding. Endometrial biopsy revealed large foci of infiltration by blasts. The cells showed clear cytoplasm, large round nucleoli with 1-2 nucleoli. The tumour cells were positive for MPO and C117.

Sl. No.	Age	Sex	Site	MPO	CD68	CD117	KI67 (%)	TdT	LCA	Cytogenetics	Survival/ Disease status at last followup
1	39	M	Mediastinum	+	+		60	-	+	NA	NA
2	34	M	Radius, calcaneum	+	+			-	+	46XY	3 yrs./AWD
3	20	M	Sacrum	+	+	-		-	-	46XY	I yr./DOD
4	12	F	Lymph node	+	-		90	-	+	58-60,XX, del(1)(p36)x2, inv(3)(q21q26),+4,+8,+9,+11,+13,+13,+16,+19,+20,+20	NA
5	11	M	Skin	+	-	-		-		46 XY	15 days/DOD
6	54	F	Jaw	+		+	70		+	48XX,+8,+10	4 days/DOD
7	5	M	Mandible	+				+		NA	NA
8	42	M	Presacral region	+	-				+	NA	NA
9	54	M	Lymph node	+	-			-	+	No metaphase	NA
10	26	M	Mediastinum	+	+			-	+	46XY, del (12)(p11)	NA
11	65	M	Orbit	+	-	+	70		+	NA	NA
12	5	M	Orbit	+	-	-	50	-		NA	1 month/DOD
13	35	M	Rib	+	-	+	80		+	Poor morphology	20 days/DOD
14	45	M	Lymph node	+	+					46,XY	NA
15	10	M	Lymph node	+	+					46,XY	NA
16	12	F	Lymph node	+	+			-		NA	NA
17	9	F	orbit	+	+					NA	NA
18	11	M	Infratemporal fossa	+	+		70		-	NA	NA
19	2	F	Orbit	-	+	+	80			NA	NA
20	35	M	Skin	+	+	+		-		47 XY, +8	NA

Table 1: Primary Myeloid Sarcoma

NA – Not Available; DOD – died of disease; AWD – alive with disease.

Sl. No.	Age	Sex	Site	MPO	CD68	CD117	KI67 (%)	TdT	LCA	Cytogenetics	Survival/Disease status at last followup
21	44	F	Lymph node	+	-	+	90	+	+	Poor morphology	8 months/ DOD
22	35	M	Testes	+	+	-				49 XY,+8,+der i(22) t(9;22)(q34;q11.2)x2	NA
23	9	M	Mediastinum	+	-	+	80			45X,- Y,t(8,21)(q22,q22),del (9)(q22)	AWD
24	14 MON	M	Eyelid	-	+	+		-		NA	5 days/DOD
25	39	F	Endometrium	+	_	+		-		49 XX,+8, t(8;21)(q22;q22), +15, +der(21)t(8;21) (q22;q22)	NA

Table 2: Secondary Myeloid Sarcoma

NA – Not Available; DOD – died of disease; AWD – alive with disease.

Pathologic Findings: Diffuse pattern of infiltration of mononuclear cells were seen in all cases. The cells showed scanty cytoplasm, round nuclei, fine nuclear chromatin and prominent nucleoli (Fig. 1 & 2). These neoplastic cells were seen to efface the architecture of the underlying tissue with a high mitotic rate.

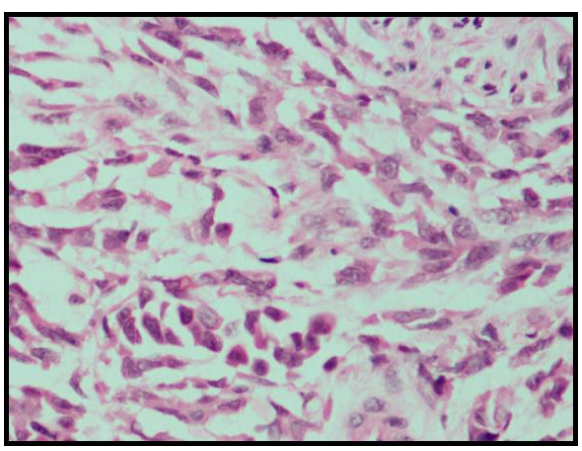

Fig. 1: Mononuclear Cells with Scant Cytoplasm, Round Nuclei, Fine Nuclear Chromatin and Prominent Nucleoli. (x400, Haematoxylin & Eosin)

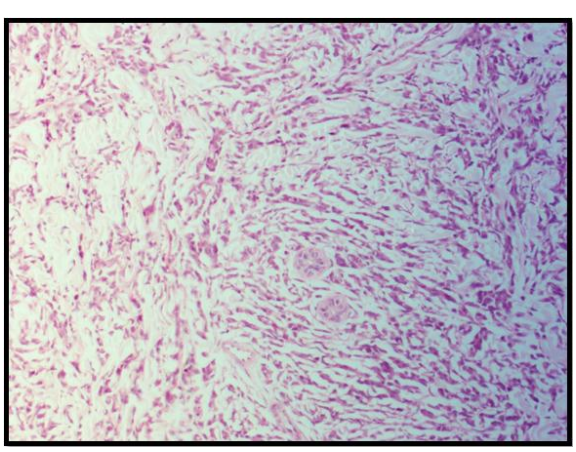

Fig. 2: Shows Blasts Infiltrating the Subcutaneous Tissue (Case 5). (x100, Haematoxylin & Eosin)

IHC panel included LCA, MPO, CD 68, CD 117, Ki 67, CD3, CD20 and TdT. Immunohistochemically, 92% of the cases were positive for MPO (23 cases, Fig. 3) and 52% of cases were positive for CD68 (13 cases). All cases were negative for B-cell and T-cell markers.

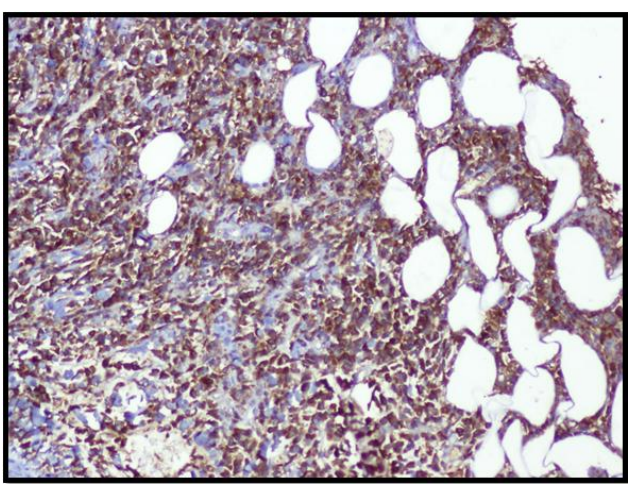

Fig. 3: Neoplastic Cells Showing Strong Cytoplasmic Staining for Myeloperoxidase (x100)

Of the 25 cases, cytogenetic evaluation was attempted for 14 cases, of which 12 cases were successfully cultured and karyotyped. Five cases showed normal karyotype, two cases showed one chromosomal abnormality and the other five cases had more than one chromosomal abnormality. Trisomy 8 (Cases 4, 6, 20, 22, 25) was the commonest chromosomal abnormality in our series, followed by del (12) (p11) in one (Case10) and inv (3) (q21q26) in another case (Case 4). Cytogenetic analysis of testicular and bone marrow aspirates showed a complex karyotype with trisomy 8 and double Ph chromosome favouring myeloid blast crisis in a known case of CML (Case 22). The lymph node and bone marrow aspirates of Case 23 revealed 45X, del Y, t(8;21) (q22;q22), del (9) (q22) compatible with synchronous presentation of acute myeloid leukaemia and myeloid sarcoma of mediastinum.

Followup data was available only for nine cases, all of whom received chemotherapy. Only two patients are alive and on follow up with the remaining seven patients dying of the disease. Two cases died before completing the first cycle of chemotherapy (within 4 to 15 days of diagnosis). The longest survival period is three years which is the case of metachronous lesion in calcaneum (Case 2).

DISCUSSION: Primary myeloid sarcoma is a rare disease with limited data available from a few case reports and series. The incidence of myeloid sarcoma in patients without leukaemia (primary myeloid sarcoma) is 2 per million in adults.[10] In adults, roughly one third of myeloid sarcomas present with concurrent myeloid neoplasm and one third have a history of myeloid neoplasms. The secondary forms of myeloid sarcoma occur in 1.4% to 9% of patients with AML.[11,12] 20 cases in our study were isolated myeloid sarcomas and the 5 secondary myeloid sarcomas were associated with AML (4 cases) and CML (1 case). Gulsah et al, in their study of 20 cases report association of MS with AML (10 cases), progressive myelofibrosis (1 case) and CML (2 cases).

Adult males were predominantly affected in our study, similar to WHO and the reports from other studies[13,14] and WHO. The commonest site was lymph node; other predominant sites included bone, with one case presenting with a metachronous lesion. Involvement of non-osseous sites and multiple tumours[15] have been reported in the literature.

The diagnosis is relatively easy in the presence of concurrent or preceding haematological neoplasms. Leukemic infiltrates that do not form tumour are not considered to be myeloid sarcomas. The presence of admixed maturing granulocytes or erythroid precursors should suggest the possibility of myeloid sarcoma in an extramedullary site. Important differentials include undifferentiated carcinomas and Non-Hodgkin lymphomas (diffuse large B-cell lymphoma, lymphoblastic lymphoma, blastoid mantle cell lymphoma). Morphological subtypes based on degree of maturation are not warranted as these have no clinical significance. A high degree of suspicion and immunohistochemistry are necessary to arrive at a diagnosis.

The immunophenotype of MS includes variable positivity for MPO, CD68, CD34, CD117, lysozyme, TdT, CD43 and glycophorin A. MPO, which is commonly expressed by cells of the myeloid lineage was positive in 92% cases. CD68, which is more common in cells of monocytic lineage, was also expressed in 44% of the cases (11 cases). All cases were negative for B-cell and T-cell markers.

Chromosomal abnormalities are detected in 55% of myeloid sarcomas. These include del 5(q), monosomy 7, trisomy 8, 11 and 14, monosomy 16, del 16(q), inv (16) and del 20(q). Multiple chromosomal abnormalities were seen in five of eleven cases (45%) in our study. Trisomy 8 was the commonest abnormality in our series which is similar to other studies.[13,14] Another abnormality that is commonly reported is inv 16 which was not seen in any of the cases. One case of CML showed complex karyotype with the presence of double Ph chromosome. For the first time, inv(3)(q21q26) is documented in this study.

A case of endometrial myeloid sarcoma (Case 25) was reported with the karyotype 49XX, +8, t(8;22)(q22;q22), +15, +der(21), t(8;22)(q22;q22)x2.[16] One of the cases (Case 23) showed loss of sex chromosome and del(9)(q22) along with (8;21). The prognostic value of the additional abnormality {t(8:21)} is still unclear.[17] We opine that additional abnormalities in a complex karyotype are an indication of disease progression.

MS is associated with a high mortality rate in most studies. The median survival time reported by Hani et al[13] is 24.7 months. Various studies show that patients who receive myeloablative allogeneic bone marrow transplantation have a longer disease free survival than patients who do not receive the same (58.6 months versus 11.1 months[13]). Appropriate chemotherapy followed by bone marrow transplantation at the first remission should be considered for all cases.[16] Other options are local radiotherapy and targeted therapy. The stage of presentation and socio-economic factors played an important role in the management and survival of our cases.

CONCLUSION: Myeloid sarcoma usually exhibits a diffuse pattern of mononuclear cells but a conclusive diagnosis requires immunohistochemical and cytogenetic analysis. Further inclusion of in situ hybridisation with appropriate probes will help to increase the detection rate of chromosomal abnormalities. A high index of suspicion and application of myeloid markers for any poorly differentiated neoplasm at any extramedullary site should help in their identification. This study highlights the rare incidence and advanced presentation of myeloid sarcoma in a southern Indian population. Longer disease free survival is being quoted following early diagnosis, intensive chemotherapy and allogeneic bone marrow transplantation in other studies[13] and the role of the same in the Indian population requires further investigation.

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