Original Article

Myeloid Sarcoma as the First Sign of Progression of Chronic Myeloid Leukemia in Medullary Chronic Phase: Experience from a Tertiary Cancer Centre in Southern India

Lokanatha Dasappa, Aditi Harsh Thanky, Lakshmaiah Chinnagiriyappa Kuntegowdanahalli, Govind Babu Kanakasetty, Linu Abraham Jacob, Suresh Babu Chikkadasappa Mallekavu, Rajeev Krishnappa Lakkavalli, Lokesh Nagendrappa Kadabur, Rudresha Haleshappa Antapura

Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, India

Abstract

Introduction: Myeloid sarcoma (MS) in chronic myeloid leukemia (CML) is a rare entity which is suggestive of advanced phase of the disease and poorer outcomes. There is little data in literature available regarding its presentation in medullary chronic phase (CP) as well as outcomes in the era of tyrosine kinase inhibitors (TKI) and needs to be carefully evaluated as it can present the first sign of progressive disease before haematological progression.

Methods: We identified cases of MS presenting with medullary CML–CP from January 2002 to December 2015. We analyzed their clinical profile and outcomes with TKI.

Results: Only 8 out of 615 CML–CP cases developed MS. Median age of presentation was 43 years with male:female ratio of 1.7:1. Sites of presentation were soft tissue deposits (7 cases) and lymph nodes (2 cases). All the cases had myeloblastic morphology. With higher dose Imatinib/Nilotinib, median overall survival was 14 months with longest survival of 36 months in a case on Nilotinib while 4 patients progressed to medullary BP at a median duration of 9 months (2–10) and expired.

Conclusion: MS in medullary CML–CP carries better prognosis than medullary CML–BP. Due to rarity of presentation, MS presenting in soft tissues might be overlooked as an infection/hematoma unless proven otherwise. Our series emphasizes the need of meticulous examination and investigation of such presentations for earlier intervention to improve patient outcomes.

Keywords: myeloid sarcoma, chronic myeloid leukemia, chronic phase

Introduction

Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder characterized by reciprocal translocation between chromosome 9 and 22. Up to 80% of the cases present in early phase of the disease known as chronic phase (CP) (1). Advanced phases of the disease, better known as accelerated phase (AP) or blast phase (BP) are mainly evolved through CML–CP and less commonly present as de novo disease. The most important prognostic factor for the disease is the phase at presentation with advanced phase of CML having significantly poor prognosis as compared to early chronic phase. Historically median overall survival for CML–CP, AP and BP were considered to be 5 years, 1–2 years and 3–6 months respectively (2).

Progression to CML–AP or CML–BP may be heralded by some of the unique characteristics of the disease. These mainly are reflected by changes in haematological parameters as defined by World Health Organisation (WHO) including blast and basophil percentage in peripheral blood or bone marrow, changes in WBC count and platelet count on therapy and cytogenetic clonal evolution (3). However extramedullary deposits if any, also represent a rare manifestation of blast crisis and need to be evaluated carefully.

Extramedullary deposits, better known as myeloid sarcoma (MS) in CML are a rare entity. We here report...
Results

Total 615 cases with CML–CP were identified out of which 8 cases (0.013%) developed extramedullary disease during the disease course with medullary CP. Median age at presentation was 43 years (35 – 54). Male: female ratio was 1.7:1. Baseline haematological parameters are described in Table 1.

6 cases out of these had presented with only soft tissue deposits, 1 case had only inguinal lymphadenopathy and another patient presented with cervical lymphadenopathy as well as soft tissue deposit. Figure 1 shows plain radiograph of MS involving left shoulder in case 5. All the cases were diagnosed with fine needle aspiration cytology (FNAC) suggestive of myeloblasts morphologically, however further immunophenotyping was not performed. At the detection of MS, Imatinib resistance mutation analysis was performed. None of the cases showed positive mutation.

The course of disease is described in Table 2. Due to financial constraints, second generation TKI was offered to only 1 case, while for the rest, Imatinib dose was increased to 600–800mg per day. 4 patients progressed to medullary BP at a median duration of 9 months\(^2\)\cite{2-10} and expired. Median overall survival (OS) post detection of MS was 14 months (3–26 months).

<table>
<thead>
<tr>
<th>No</th>
<th>Age/ Sex</th>
<th>Initial treatment</th>
<th>Response to initial treatment</th>
<th>MS after initial diagnosis</th>
<th>Site of MS</th>
<th>Treatment change after chlorma detection</th>
<th>Medullary progression if any</th>
<th>OS after MS detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35/M</td>
<td>Imatinib 400mg/d</td>
<td>CHR at 3 months</td>
<td>3 years</td>
<td>Right Leg</td>
<td>Increased Imatinib to 600mg/d</td>
<td>BP at 10 months</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>39/F</td>
<td>Imatinib 600mg/d</td>
<td>CHR at 3 months</td>
<td>At baseline</td>
<td>Right gluteal region</td>
<td>Started Imatinib at 600mg/d</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>47/M</td>
<td>Imatinib 400mg/d</td>
<td>CHR at 3 months</td>
<td>8 months</td>
<td>Right gluteal region</td>
<td>Changed to Nilotinib 800mg/d</td>
<td>-</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>54/F</td>
<td>Imatinib 600mg/d</td>
<td>No CHR</td>
<td>At baseline</td>
<td>Left thigh</td>
<td>Started Imatinib at 800mg/d</td>
<td>AP at 8 months, BP at 10 months</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>36/M</td>
<td>Imatinib 400mg/d</td>
<td>No CHR</td>
<td>3 months</td>
<td>Left shoulder, cervical lymph node</td>
<td>Increased Imatinib to 800mg/d</td>
<td>BP at 8 months</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>47/M</td>
<td>Imatinib 400mg/d</td>
<td>CHR at 3 months</td>
<td>2 years</td>
<td>Upper back</td>
<td>Increased Imatinib to 800mg/d</td>
<td>-</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>54/F</td>
<td>Imatinib 400mg/d</td>
<td>CHR at 2 months</td>
<td>11 months</td>
<td>Right leg</td>
<td>Increased Imatinib to 600mg/d</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>38/M</td>
<td>Imatinib 400mg/d</td>
<td>No CHR</td>
<td>6 months</td>
<td>Right inguinal lymph node</td>
<td>Increased Imatinib to 800mg/d</td>
<td>BP at 2 months</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2: Course of MS with medullary CP on Imatinib
Chloroma/myeloid sarcoma is an extramedullary deposit containing immature myeloid cells. The entity was first described by a British physician A. Burns in 1811 (4), however the term “Chloroma” was first coined by King A in 1853 (5). It derives its origin from the Greek word “Chloros” which means green color, imparted by myeloperoxidase in myeloblasts. However in 1967 Rappaport proposed a new term, “granulocytic sarcoma” for the same, to describe granulocytic origin of the tumor, as up to 30% of the tumor deposits may be white, grey or brown due to rapid fading of green color on exposure to air or masking of the green pigment by red color of blood (6). However as we now recognize that all AMLs do not originate from granulocytes, the term “myeloid sarcoma (MS)” is preferred. Other terminologies commonly used are extramedullary sarcoma and extramedullary myeloid tumor. Based on the site involved the entity may be termed as leukemia cutis, for cutaneous involvement.

MS and its link to acute leukemia was first established by Dock and Warthin in 1902 which remains the most common disease entity associated with this presentation with incidence being 2.5–9% in various series (7). Here it can be seen along the course of leukemia in majority of the cases or before the detection of the myeloid disease in up to one fourth of the cases. Isolated extramedullary relapse post transplantation is more frequently identified especially for the patients with chronic graft versus host disease and longer interval between transplant and relapse (8).

Uncommonly it can be seen in association with CML, myelodysplastic syndrome and other myeloproliferative disorders (9, 10). In autopsy series MS was found in association with acute and chronic myeloid leukemia in 2–8% of cases. Inverardi and colleagues had reported extramedullary deposits in 4% (n=14) cases of CML overall (11). In CML, most common association is with medullary AP or BP while rarely it can be associated with medullary CP and even rarer presentation can be as the first evidence of medullary CP (12). Specchia and colleagues reported that 60% of MS were associated with CML–BP, while 20% each had medullary CP and AP (13). However in Inverardi’s series up to 50% of cases were associated with medullary CP (11). Both of these studies were in pre–Imatinib era. In our study less than 1% of all CML–CP cases developed MS on Imatinib.

Common sites of presentation for myeloid sarcoma are soft tissue, bone and periosteum, lymph node, central nervous system (CNS) and gastrointestinal tract in acute myeloid leukemia (AML) (14). In CML, MS was found in bone (57%), lymph nodes (29%), skin and soft tissues (21%) and CNS (14%) in the series by Inverardi and colleagues (11). Specchia and colleagues reported 15 cases of EMD in CML patients with majority (n=13) having lymph node disease, 1 with CNS involvement and 1 with suborbital mass lesion (13). In our series 7 out of 8 cases had involvement of soft tissue and 2 cases also had lymph node involvement.

It is important to avoid misdiagnosis of myeloid sarcoma. Clinically many of these cases may be overlooked as abscess or hematoma because of association with haematological malignancy. Imaging, especially magnetic resonance imaging for soft tissue and CNS lesions can be helpful in characterizing the lesion. However, even for those cases which are attempted to get a pathological diagnosis by fine needle aspiration cytology, which is the more commonly used method, rate of misdiagnosis was as high as 75%, especially in those cases with isolated myeloid sarcoma according to historical reports (15). In one series most common misdiagnosis were lymphoma, small cell carcinoma, sarcoma (Ewing’s sarcoma), melanoma and undifferentiated neoplasm (16). Therefore it cannot be overemphasized to get adequate tissue sample for all ancillary tests including immunohistochemistry, flow cytometry, fluorescent in situ hybridization (FISH) and molecular analyses as and when required. We had performed FNAC for all our cases and diagnosis was based mainly morphologically. All our cases showed myeloid phenotype. Specchia and colleagues showed that 73% of their MS in CML were myeloid while the rest had
lymphoid phenotype \cite{13}. Amongst lymphoid cases, 3 cases had B-cell phenotype and 1 case had T-cell phenotype. Diagnosis of our cases was dependent on morphology on FNAC, no further immunophenotyping was performed. All our cases showed myeloid morphology.

Prognosis of MS in AML in initial reports was poor however later report have denied the possible poor prognostic impact of the same and recommended the therapy similar to acute leukemia with or without local radiotherapy \cite{17, 18}. Similarly it remains important to treat advanced disease in CML at the earliest detection as overall outcomes remain poor. Response rates to therapy documented by Kantarjian and colleagues were 23% complete remissions and 13% partial remissions in CML–BP with median OS of only 18 weeks was gained \cite{19}. Inverardi and colleagues reported a median time to develop medullary BP after MS development of 4 months with median OS being only 5 months after development of MS \cite{19}. Response to treatment may also depend on phenotype of MS as suggested by Specchia and colleagues as all of their 4 cases with lymphoid phenotype achieved CR with chemotherapy while only 1 of the 11 cases with myeloid phenotype achieved the same \cite{13}. Thus in pre-tyrosine kinase inhibitor (TKI) era, median overall survival (OS) reported for myeloid sarcoma was only 3–6 months while that for medullary BP was similar \cite{20}.

However, use of TKI has improved OS in medullary BP to 6–11 months, actual OS for MS is unknown due to its rare occurrence \cite{20}. Investigators at MDACC reported a significantly better median OS of 40 months for 11 cases of myeloid sarcoma presenting with medullary CP as compared to medullary BP in TKI era \cite{21}. This probably reflects a probable difference in disease biology when MS presents early rather than as a part of progressive medullary phase. These cases probably have less resistance to TKI therapy and thus fare better with early intervention. In our series also cases presenting with MS with medullary CP had a median OS of 14 months. However due to financial constraints only one case was offered second generation TKI while rest were managed by increasing Imatinib doses and none of the cases underwent stem cell transplantation.

In today’s era where clinical examination is becoming less vigilantly practiced and laboratory medicine is becoming more prominent, we would like to emphasize on early detection of clinical signs of progression in form of new skin/soft tissue deposits or lymph nodes in a case of CML–CP to treat the disease at the earliest and improve outcomes for these patients. It cannot be overemphasized to be attentive as a clinician for the possible diagnosis of myeloid sarcoma in a CML case presenting with these features and to communicate the possibility with the pathologist to avoid delay in diagnosis and management.

**Conclusion**

MS is a rare presentation in CML with medullary CP. It carries better prognosis as compared to CML with medullary BP. Due to rarity of presentation, MS presenting in soft tissues might be overlooked as an infection/hematoma unless proven otherwise. Our series emphasizes the need of meticulous examination and investigation of such presentations for earlier intervention to improve patient outcomes.

**References**


