CASE REPORT

Chronic Myeloid Leukemia with Extramedullary Blast Crisis: Two Unusual Sites with Review of Literature

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Abstract Extramedullary blast crisis (EBC) in chronic myeloid leukemia (CML) is a rare phenomenon and represents infiltration of leukemic blasts in areas other than bone marrow. Lymph node is the most common site of involvement by EBC. We herein present a case of CML who suffered from two discrete episodes of EBC at atypical locations (scalp and paravertebral) within an interval duration of nine months. A-38-year-old female was diagnosed as a case of CML with extramedullary blast crisis in scalp at presentation. She received treatment with imatinib 600 mg once daily through Novartis Oncology Access Program (NOA). She achieved hematological remission. However nine months later she was readmitted with spinal shock due to cord compression secondary to paraspinal chloroma. She was started on tablet Nilotinib in view of failure to 1st line therapy. Her compressive myelopathy was treated with pulses of high dose dexamethasone. However soon she died due to pneumonia.

Case Report

A-38-year old lady was seen in February 2013 with complaints of scalp swelling in left parietal area of 5×5 cm in

dimension (Fig. 1A). Rest of general physical examination was normal. Per abdomen examination revealed splenomegaly of 6 cm below left costal margin. Her total blood count showed hemoglobin-114 g/L, platelet count- 417×10^9 /L, and total leukocyte count- 146×10^9 /L with predominance of myeloid precursors -12 % myelocytes, 11 % metamyelocytes. Excisional biopsy of scalp swelling confirmed MPO positive chloroma (Fig. 2). Bone marrow examination showed hypercellular marrow spaces with 2 % blasts, 5 % basophils, 15 % myelocytes and 14 % metamyelocytes with mild megakaryocytic hyperplasia. BCR-ABL quantitative transcript ratio from blood was 78.35 %. Hence diagnosis of CML with extra medullary myeloid blast crisis of scalp was made. She was started on imatinib 600 mg OD. Second generation tyrosine kinase inhibitors (TKIs) or allogeneic stem cell transplantation were offered to her but she could not afford due to financial constraints. Reassessment at 3 months showed complete hematological remission with hemoglobin-113 gm/L, platelet count- 135×10^9 /L, TLC- 4.97×10^9 /L and no immature cells on differential count analysis. There was significant reduction in size of chloroma. Her quantitative transcript for BCR-ABL translocation was found to be 7.37 % at end of 6 months. The dose of imatinib was increased to 800 mg/day as BCR ABL transcripts levels were above 1 % at 6 months. However, 3 months later, she presented with complaints of sudden onset quadriplegia with bowel and bladder incontinence. Neurological examination revealed features suggestive of compressive myelopathy with power of 0/5 in bilateral lower limbs and panto-sensory loss below D4 level. An urgent CEMRI of dorso-lumbar spine showed heterogeneously enhancing posterior epidural soft tissue component compressing and displacing the spinal cord at D4, 5, 6 and 7 level (Fig. 1B, C). In view of significant past history of scalp chloroma, clinical

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Fig. 1 **A** Well defined protuberant scalp swelling with intact overlying skin (Chloroma) **B** T2-weighted magnetic resonance imaging (MRI) and **C** Gadolinium-enhanced T1-weighted MRI showing heterogeneously enhancing posterior epidural soft tissue component compressing and displacing the spinal cord at D4, 5, 6 and 7 level

possibility of paraspinal chloroma as a cause of compressive myelopathy was considered. Fine needle aspiration cytology from this mass showed abundant blast cells confirming the diagnosis of chloroma. The peripheral blood showed WBC of $22 \times 10^9/L$ with 25 % blasts in peripheral blood. Bone marrow biopsy showed 38 % blast cells which were 2.5–4 times the size of mature lymphocytes with opened chromatin, round to oval to intended nuclear membrane and positive for myeloperoxidase stain. Flow-cytometric analysis confirmed 38 % of blast cells to be positive for myeloid series markers (CD13, CD33 and CD 117). Kinase domain mutation analysis from peripheral blood showed M351T mutation. Hence final diagnosis of imatinib resistant CML in myeloid blast crisis with paraspinal chloroma was made. In vitro sensitivity of BCR-ABL inhibitors showed that IC 50 values of imatinib,

dasatinib, nilotinib, bosutinib for M351T were 1.76, 0.88, 0.44, and 0.70 respectively. The clinical profile, disease status, BCR-ABL transcript load, site of extramedullary relapse at both the admissions have been mentioned in Table 1. She was given intravenous 1 gram of methylprednisolone for 3 days and local radiotherapy to spine with 10 fractions (30 Gray) for 2 weeks. She was started on nilotinib through Novartis Oncology Access program. However she succumbed to pneumonia related sepsis shortly afterwards.

Discussion

Blast crisis in CML is based on site of origin (medullary or extramedullary) and type of cell (myeloid, lymphoid or

Fig. 2 Histopathology. **A** Skin biopsy with dense infiltration in the dermis (Magnification $\times 40$). **B** Numerous myeloid precursors with eosinophils (Magnification $\times 200$). **C** Mitotic figures (Magnification

$\times 400$). **D** Myeloperoxidase immunostain showing strong cytoplasmic positivity

Table 1 Clinical and laboratory parameters at two admissions

Data	February 2013	October 2013
Site of extra medullary blast crisis	Scalp	Paravertebral
Hemoglobin (gm/L)	114	117
Total leucocyte count ($\times 10^9/L$)	146	72
Platelet count ($\times 10^9/L$)	417	127
Bone marrow examination	2 % blasts (CML in chronic phase)	38 % blasts (CML in myeloid blast crisis)
BCR-ABL1 kinase domain mutation	–	M351T mutation detected
Interpretation	CML in extra medullary blast crisis of scalp	Imatinib resistant CML in myeloid blast crisis with extramedullary (paravertebral) chloroma

mixed) [2]. The blast crisis in CML is characterized by at least one of the following [3]:

- >20 % myeloblasts or lymphoblasts in the blood or bone marrow.
- Presence of large clusters of blasts cells in bone marrow biopsy.
- Development of chloroma.

The most common sites of extra medullary involvement by CML are lymph nodes, bones and CNS [1]. In many of these patients, the bone marrow remains in chronic phase [4, 5]. A systematic review of all studies investigating extra medullary blast crisis in CML cases from 2000 to 2013 was done by us. The Pub Med database was systematically searched by using following Medical Subject Heading

Table 2 Tabulation of authors, year of publication, median interval from diagnosis to extra medullary blast crisis, total number of CML patients studied and percentage of extra medullary sites involved

Author	Median interval (months)	Total cases(n)	Total no. of extra medullary blast crisis (n)	Percentage (%) of number of sites involved							
				Lymph node	Bone	CNS	Pleura	Skin/soft tissue	Ocular region	Par spinal	Mediastinum
Inverardi et al. [6]	4	349	14	29	57	14	0	21	0	0	0
Specchia et al. [7]	NA	235	15	86	0	6	0	0	6	0	0
Maloisel et al. [42]	NA	227	16	6	3	5	0	0	0	0	0

(MeSH) term:–“Extra medullary blast crisis in CML”. We limited the literature search to articles on human subjects. Using pre-defined inclusion and exclusion criteria, we screened all the references. The selection of relevant studies was initially made by reviewing title and abstract, then for the remaining studies by reading the complete article which have been summarized in Tables 2 and 3. Two large series of extra medullary blast crisis were reported by Inverardi et al. [6] and Specchia et al. [7]. Inverardi et al. reported bone as the most common site (57 %) followed by lymph node (29 %) while Specchia et al. reported that 86 % of patients with extra medullary blast crisis had lymph node as the site of involvement. Contrary to common presentation, not only did our patient had uncommon extra medullary site of involvement, but also had recurrence at a different site within few months. Cervantes et al. showed that out of 113 cases of blast crisis of CML, 13 patients had extra medullary involvement, common sites being lymph nodes followed by osteoperiosteal and central nervous system [1]. Brien et al. reported extra medullary blast transformation in a patient who achieved cytogenetic remission following treatment with interferon alpha. In total patient suffered four episodes of extra medullary blast crisis. The first three episodes were lymphoid type and the last one was myeloid in nature and involved bone and pulmonary parenchyma [8]. Sun et al. reported a case of CML with extra medullary blast crisis at paraspinal area [9]. Ganessan et al. reported a 14-year old child who presented with mediastinal mass and generalized lymphadenopathy, work up of which revealed CML in chronic phase with extra medullary blast crisis as a presenting feature of the disease.

Literature review shows few rare case reports too in which immunohistochemistry of extra medullary granulocytic sarcoma had shown T cell lineage extra medullary blast crisis [2, 10–13]. Extra medullary blast crisis with biphenotypic picture (mixed myeloid and T cell features) were also reported separately by Hossain et al. [14], Cervantes et al. [15], Ganessan et al. [16] and Chen et al. [17].

Rare presentation of extra medullary relapse of CML in mediastinum have also been reported in literature [18, 19]. Simpson et al. [20] suggested that clinicians should consider the possibility of extra medullary disease in any case

of CML who present with unusual symptoms. They reported two cases who had extra medullary blast crisis in the form of skin infiltration and intestinal lump. Paravertebral involvement like in the index case has been reported by Pullarkat et al. [21] in past. Apart from common sites like lymph nodes, literature also mentions very rare unexpected sites of extra medullary crisis. One such case was reported by Palatnik et al. [22] which mentioned reproductive organs as the site of blast crisis which was initially believed to as tubo-ovarian abscess. Tsukamoto et al. [23] and Yu et al. [24] reported femoral head as site of extra medullary blast crisis. Abdominal symptoms [20, 25–27] as the first presentation of extra medullary blast crisis have been also been reported in English literature. Simpson et al. [20] reported a rare presentation of EBC as acute abdomen who also suffered later a second attack in left cerebral hemisphere.

First presentation of CML as tense ascites was reported by Aleem et al. [27] who reported CML with extra medullary blast crisis in the form of peritoneal and mesenteric deposits. Similarly Sakakura et al. [26] reported a case of newly diagnosed CML who presented with large intra-abdominal hematopoietic tumor as the first presentation. Charles and coworkers [18] and Kroschinsky et al. [19] have reported cases with mediastinal mass as the site of extra medullary blast crisis. Both these cases had two common facts as both presented with large mediastinal mass causing superior vena cava syndrome and both cases had post-allogeneic hematopoietic stem cell transplant status. Al-Rayes et al. [28] reported right shoulder joint leukemic synovitis as the initial presentation of CML with blast crisis in 2001. Testis as the site of T- cell lymphoid extra medullary blast crisis has been reported in a 29-year-old male who was being treated for thirty-one months with interferon-alpha for CML [29]. We have already reported a case of paraspinal chloroma in a case of CML [30] similar to the case of Sun et al. [9].

Extramedullary blast crisis as an initial presentation are commonly associated with blast and accelerated phase. However as only 5–10 % patients of CML present in BP or AP, thereby meaning that extramedullary crisis will further be a rare phenomenon [30]. Specchia et al. found in their study of fifteen cases of extramedullary blast crisis that

Table 3 Tabulation of authors, year of publication, median interval from diagnosis to extramedullary blast crisis, total number of CML patients studied and percentage of extramedullary sites involved

Author	Year of publication	Median interval (months)	Sites involved	Drugs which the patients were on while developing EMBC	Age/Gender
Sun et al. [9]	1993	NA	Paraspinal	NA	NA
Harada et al. [35]	2000	5	Cervical lymph node	Interferon	57/m
Beedassy et al. [29]	2000	31	Testis, meninges	Interferon	29/m
Apfelbeck et al. [2]	2000	13	Generalised lymphadenopathy	Interferon	48/f
Okazuka et al. [36]	2001	39	Lymph node	Interferon, CHOP, Post-ASCT	45/m
Al-Rayes et al. [28]	2001	0	Right shoulder monoarthritis	NA	NA
Gotoh et al. [37]	2002	2	Lymph node	Interferon	51/m
Zeppa et al. [25]	2002	24	Para-aortic lymph-node	NA	62/m
Kroschinsky et al. [19]	2003	30	Mediastinal mass	Post-ASCT	42/m
Naito et al. [38]	2003	24	Lymph node	Interferon	42/m
Madhumath et al. [39]	2003	NA	Lymph node	NA	NA
Charles et al. [18]	2004	5	Mediastinum mass	Post-ASCT	32/m
Breccia et al. [40]	2004	5	Pleural effusion	Interferon, Imatinib	71/m
Matsuda et al. [41]	2005	NA	CNS, subcutaneous tissue	Imatinib	NA
Maloisel et al. [42]	2005	68	Ischio-pubic bone	Hydroxyurea	44/f
Maloisel et al. [42]	2005	9	Right femur trochanter	Interferon	32/m
Maloisel et al. [42]	2005	13	C1 vertebra	Interferon	66/m
Aleem et al. [27]	2005	0	Peritoneal/mesenteric infiltration	NA	60/m
Rajappa et al. [43]	2005	7	Meningeal involvement	imatinib	39/m
Tondon et al. [44]	2005	NA	NA	NA	NA
Sakakura et al. [26]	2005	0	Abdominal hematopoietic tumor	NA	59/m
Simpson et al. [20]	2006	14	Small intestine, Left cerebral hemisphere	Imatinib	62/f
Simpson et al. [20]	2006	48	Skin	Imatinib, Interferon	54/m
Yu et al. [24]	2006	0	Femoral head	NA	3/f
Ganessan et al. [16]	2007	0	Lymph node	NA	14/m
Chauhan et al. [45]	2007	0.72	Paraspinal chloroma	Hydroxyurea	57/f
Kim et al. [46]	2008	5	Lymph node	Imatinib	72/m
Kim et al. [46]	2008	4	Lymph node	Imatinib	32/f
Kobayashi et al. [47]	2011	1200	Lymph node	Imatinib, Interferon	60/m
Chen et al. [17]	2012	NA	Lymph node	NA	NA
Shune et al. [48]	2012	6	Lymph node	Imatinib	50/f
Palatnik et al. [22]	2012	0	Reproductive system	NA	NA
Wei et al. [49]	2013	2	Lymph node	Imatinib	35/m
Chen et al. [17]	2013	0	Lymph node	Imatinib	14/m
Jin et al. [50]	2013	0	Lymph node	Imatinib	40/m
Tsukamoto et al. [23]	2013	0	Femoral head	NA	NA

patients of CML with CP, AP and BP were three, three and nine respectively [7].

The treatment of blast crisis consists of bringing the disease back into the chronic phase followed by allogeneic stem cell transplantation in a transplant eligible patient. This is achieved by combining 2nd generation TKI's (based on kinase domain mutation if present) with chemotherapy [31]. Newer third generation TKIs like

ponatinib also have shown promising results in such patients. In a study of 94 patients in BC, treatment with ponatinib resulted in CCR and MMR in 27 and 22 % cases respectively [32]. The most important factor determining the survival following HCT is the disease phase at the time of transplantation, with four year disease free survival rates of <10 % in BC, 30–40 % in AP and approximately 80 % in CP [33]. Study on imatinib in primary AP/BC by Talpaz

et al. showed that out of 119 patients with CML in AP, CHR and CCR was achieved in 37 and 19 % respectively [34]. Similar study was conducted by Silver RT et al. in 2004 who found that at 36 months of imatinib therapy with escalated dose of 600 mg/day, out of 260 patients with CML in BP only 14 % were alive and 7 % were disease free. Among the second line TKIs, dasatinib has been approved in BC. Study by Cortes J et al. on 116 patients with BC (myeloid -74, lymphoid -42) suggested that on 8 month follow-up with dasatinib, complete hematological response and major cytogenetic response were observed in 34 and 31 % patients of myeloid blast crisis versus 31 and 50 % of that achieved in cases of lymphoid blast crisis.

Conclusion

Very few reports of recurrent episodes of extramedullary blast crisis in the same individual have been reported [8]. Our case had recurrence of extra medullary blast crisis at two discrete sites namely paravertebral and scalp within short interval of time. Progression of this case from chronic to blast phase within 9 months suggests that those individuals of chronic myelogenous leukemia who at initial presentation have extra medullary sites of tumor load are comparatively at high risk of progressing to frank blast crisis in near future. Keeping this fact in mind, all such cases should be closely followed up and counselled regarding the need for allogeneic stem cell transplantation as definite therapy.

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