DOI: 10.7860/JCDR/2016/15813.7045

Review Article

Internal Medicine Section

Isolated CNS Blast Crises in Chronic Myeloid Leukaemia Presenting as Hypertrophic Pachymeningitis and Bilateral Optic Neuritis: A Case Report

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ABSTRACT

Extramedullary blast crises of Chronic Myeloid Leukaemia (CML) involving CNS is rare and usually accompanies systemic relapse. Isolated CNS blast relapse is an extremely uncommon event. A 35-year-old male was diagnosed with chronic phase (CP) CML two years back at our hospital and was started on imatinib 400 mg daily. Patient achieved haematological and cytogenetic remission at three and 12 months respectively but was non-compliant with medications thereafter. He presented to our emergency with headache and bilateral visual loss. CNS examination revealed neck rigidity and fundoscopy revealed disc edema with retinal vein dilatation and haemorrhages. Cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis and a positive cytospin for myeloid blasts. MRI brain suggested pachymeningeal enhancement involving falx cerebri and tentorium along with bilateral optic nerve thickening. Patient maintained cytogenetic remission at current presentation. A diagnosis of isolated CNS blast crises with pachymeningitis and bilateral optic nerve involvement was made and two doses of intrathecal chemotherapy were administered. However, patient died due to a rapidly downhill course. A previously unreported finding of pachymeningitis with bilateral optic neuritis has been highlighted in this case, along with a brief review of this rare condition.

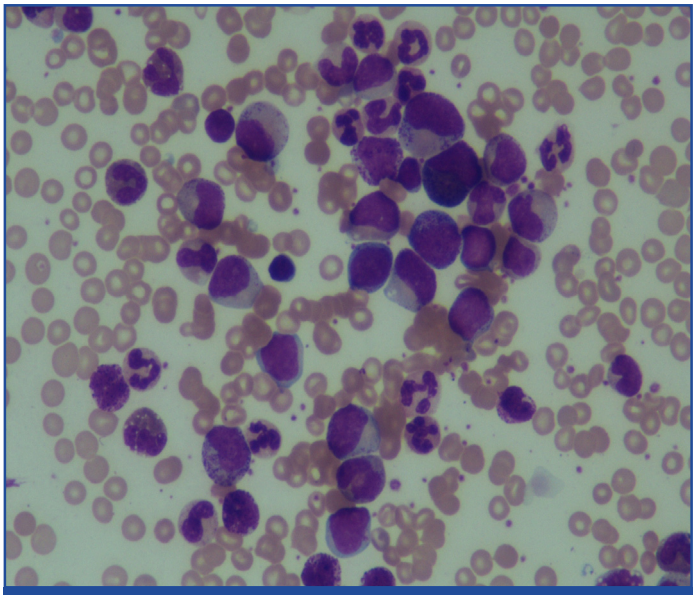
Keywords: Allogenic stem cell transplantation, Chemoradiotherapy, Extramedullary blast crises, Imatinib

CASE REPORT

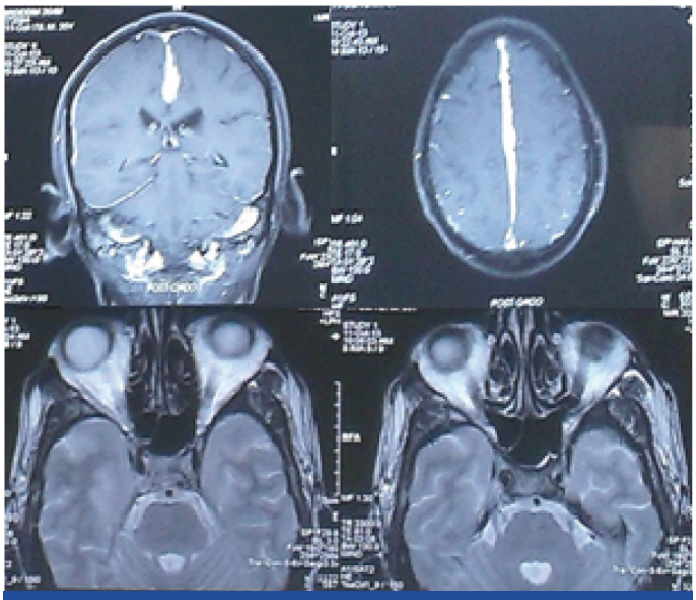
We report a case of a 35-year-old man, who presented to our haematology clinic in May 2012 with complaints of easy fatiguability and low grade fever for two months. Examination revealed pallor and 8 cm splenomegaly. Patient's complete blood counts were-Hb-92g/l, Total Leucocyte Counts (TLC)-56 x 10^9/L, Differential Counts (DLC)- polymorphs 76%, lymphocytes 5%, eosinophils 3%, basophil 1%, myeloblasts 4%, promyelocytes 2%, myelocyte 5%, metamyelocytes 4%, platelets-510 X 10^9/L, Erythrocyte Sedimentation Rate (ESR)-30mm/h, Lactate Dehydrogenase (LDH)-900 IU/L. Bone marrow was hypercellular with myeloid proliferation and shift to left and Fluorescence In Situ Hybridization (FISH) revealed 98% Philadelphia chromosome positive (Ph+) metaphases. Bcr-abl (a2b3) fusion product was detected by Polymerase Chain Reaction (PCR) in the peripheral blood. Patient was diagnosed as a case of CP- CML and was initiated on Imatinib Mesylate (IM) 400 mg once daily. Patient achieved complete haematological remission (CHR) at three months and Complete Cytogenetic Remission (CCR) at 12 months. However, he was non-compliant with his medications and had an irregular follow up thereafter. Patient presented to our emergency department in June 2014, with complaints of severe headache, vomiting and painless bilateral visual loss since three days. Patient denied any retro orbital pain, fever, cough, weight loss, night sweats, evening temperature rise and seizures. On examination, patient was afebrile and appeared pale. His vitals were: blood pressure-110/62 mm hg, pulse rate-120/minute. There was no lymphadenopathy. Nervous system examination revealed neck rigidity and presence of meningeal signs. Extraoccular muscle testing was normal; however there were sluggishly reacting and slightly dilated pupils. Patient's light perception was absent. Slit lamp examination was normal. Fundoscopy revealed bilateral disc edema with dilated, tortuous retinal veins and superficial flame shaped haemorrhages. Rest of the systemic examination was unremarkable. Patient's investigations are summarized in [Table/Fig-1]. Haemogram revealed Hb-102g/L, TLC- 97 x 10^9/L, DLC-60% polymorphs, 20% lymphocytes, 2% myeloblasts, 5% myelocytes, 3% metamyelocytes, 4% eosinophils and 4% basophils, platelets-420 x 10^9/L. Peripheral smear findings were suggestive of CML-CP [Table/Fig-2]. Bone marrow

Parameter	Patient's value	Parameter	Patient's value
Hemoglobin (g/L)	102	CSF analysis	Clear, cell count-100/cumm, 90% lymphocytes. Sugar-45mg/dl, protein-120mg/dl.
Total leucocyte counts (x 10^9/L)	97	CSF flow cytometry	Myeloid blasts positive for CD-13, CD-33, negative for CD-19, CD-10
Platelets (X 10^9/L)	420	CSF gram stain/ culture/ ZN stain	Negative
Bone marrow aspiration	CML-CP	HIV serology/ ACE levels/ RF/ANA/ ANCA/ VDRL tests	Non-reactive/ normal results
ESR (mm/hr)	24	CSF PCR for mycobacterium tuberculosis and herpes simplex	Negative
LDH (IU/L)	245	Bone marrow examination (FISH)	No Ph+ metaphase detected, suggestive of CCR
Bcr-abl mutational analysis for TKI resistance	No mutation detected	Chest X-ray, liver and kidney function tests	Normal

[Table/Fig-1]: Table summarizing investigations of the patient.
*ACE-Angiotensin Converting Enzyme, RF-Rheumatoid Factor, ANA-Antinuclear antibody, ANCA-Antineutrophil Cytoplasmic Antibody, VDRL-Venereal Disease Research Laboratory, PCR-Polymerase Chain Reaction, CCR-Complete Cytogenetic Response, FISH-Fluorescence In Situ Hybridization, TKI-Tyrosine Kinase Inhibitors, Ph-Philadelphia.



[Table/Fig-2]: Peripheral blood smear of the patient showing myelocytes, meta-myelocytes, myeloblasts, eosinophils and basophils consistent with CML-chronic phase (May Grunwald, Giemsa, 40X).



[Table/Fig-3]: MRI brain of the patient after gadolinium contrast administration showing the heterogenous and shaggy thickening and enhancement of dura matter along the falx cerebri and tentorium suggestive of pachymeningitis (upper two images) along with bilateral optic nerve thickening (lower two images).

examination done this time revealed myeloid proliferation with presence of 2% myeloblasts and was consistent with CML-CP. MRI brain of the patient revealed a heterogenous shaggy enhancement involving falx cerebri and tentorium suggestive of pachymeningitis along with the thickening and enhancement of bilateral optic nerves [Table/Fig-3]. A diagnosis of extramedullary isolated CNS blast crises (myeloid type) was made based on the presence of blasts in CSF (confirmed by flow cytometry to be myeloblasts) and bone marrow FISH results showing no Ph+ metaphases. Patient was administered intrathecal methotrexate (12mg) and dexamethasone (4mg) twice a week and imatinib was continued at 400 mg per day. However, patient had a rapidly progressive deterioration in his neurological status and died after two doses of intrathecal therapy.

DISCUSSION

CML, a clonal stem cell disorder is characterized by formation of Philadelphia chromosome and fusion of Bcr and Abl genes with constitutive overactivity of tyrosine kinase. CML runs a triphasic course, most patients being diagnosed in chronic phase, which evolves into blast phase within 4-5 years if untreated. Blast phase of CML is defined either by the presence of more than 20% blasts in the peripheral blood/bone marrow or alternatively in 5-10% of cases, by the focal accumulation of blasts in the extramedullary sites [1]. Lymph nodes, skin and soft tissues, bone, serosal surfaces, gastrointestinal and genitourinary tract are the commonest sites of extramedullary blast crises. CNS involvement by extramedullary blast crises is rare and usually accompanies systemic involvement [1,2]. Imatinib mesylate, a Tyrosine Kinase inhibitor (TKI) capable of inducing complete molecular and cytogenetic remission has changed the outlook for patients of CML by prolonging their 10 year overall survival from 20% to 80-90% and is effective in all the phases of CML [1]. However, CNS penetration of imatinib is poor (CSF concentration <1% that of the plasma) due to the P-glycoprotein mediated efflux mechanisms [3]. Hence, CNS serves as the sanctuary site for CML. Therefore patients on long term imatinib therapy with haematological and cytogenetic remission may rarely present with CNS blast crises. Isolated CNS blast crises however, is uncommon and is limited to occasional case reports [2]. We reviewed the clinical details of 23 reported cases of isolated CNS blast crises in CML including their imaging characteristics, fundus findings, treatment administered and final outcome [Table/Fig-4] [2,4-21]. CML involves retina, though rarely by direct infiltration as well as due to leukaemic retinopathy. Leukaemic involvement of macula and optic nerve leading to rapid visual loss has been reported [22]. Hypertrophic Pachymeningitis (HP) is a rare disorder characterized by fibrosis and thickening of the dura matter (in contrast to involvement of pia and arachnoid matter in leptomeningitis) [23]. It may be idiopathic or secondary to infections, malignancies, collagen vascular disorders and spontaneous intracranial hypotension [23]. HP has never been described in association with CML previously. From the review of 23 cases of isolated CNS relapse in CML, we summarize that males are affected more commonly (M: F -4.5:1) and the median age of presentation is 40 years. Disease occurred exclusively in patients who received imatinib (either alone or combined with SCT/chemotherapy) after a median period of 2.4 years and most of the cases were already in remission at the time of relapse, strengthening the fact that CNS acts as a sanctuary site for relapse in patients on imatinib. Headache and vomiting are the commonest clinical manifestations of CNS relapse and require CSF evaluation by cytospin and immunophenotyping of atypical cells for diagnosis. CNS infiltration is commonest with lymphoid blasts (followed by myeloid and bilineage). Papilloedema and leptomeningeal enhancement represents the commonest fundus and imaging findings respectively. Most of the reported cases were treated with combined intrathecal chemotherapy (variable combination of methotrexate, cytarabine and dexamethasone/hydrocortisone) and craniospinal irradiation. Combined therapy was found superior to the intrathecal treatment alone in terms of treatment outcome. Additional shunt surgery was done in two cases with hydrocephalus. Notably, one patient also received CD-14 depleted *intrathecal* Donor Lymphocyte Infusion (DLI). TKI's (imatinib and dasatinib) were employed for *maintenance* after eradication of CNS leukaemia. SCT was found to improve the survival of patients after successful CNS treatment compared to patients who were not transplanted. Five cases developed an isolated CNS relapse following Allo-SCT after a median duration of 3.1 years. History of CNS involvement prior to SCT, non remission at SCT and prophylactic intrathecal chemotherapy are potential risk factors for isolated CNS

S. No.	Author	Age (yr)	Sex	Treatment prior to presentation	Duration of treatment prior to CNS relapse	Disease status before CNS relapse	Clinical presentation	Blast type	Fundoscopy	MRI Findings	Treatment given	Outcome
1	Narayan et al., [4]	15	F	imatinib	4 year	HR	H,V	L	N	thrombosis of superior sagittal sinus	imatinib, IT CT, RT	loss to follow up
		37	M	imatinib	4 year	HR	H, V, altered sensorium	B	P	bilateral infarcts with features of meningitis	imatinib, IT CT,RT	Died
2	Gomez et al., [5]	33	M	imatinib	5 year	HR +CR	Post ME H,V, confusion	NA	OA	MRI brain and optic MRI normal	IT Mx,C,D +Dasatinib	improved with residual visual impairement
3	Fuchs et al., [6]	64	F	imatinib and dasatinib followed by HSCT	15 months	HR +CR+MR	Cognitive decline, disorientation	MY	NA	Communicating hydrocephalous	Shunt surgery, IT Mx,C,D +dasatinib	Improved initially, death due to vulvar cancer
4	Barlow et al., [7]	68	M	imatinib	2 year	HR+CR	H, tremor, poor balance	L	NA	Normal	IT Mx, D +dasatinib + RT	Alive
5	Oshima et al., [8]	23	M	Imatinib followed by BMT	671 days	CR	NA	NA	NA	NA	IT CT + RT	alive, developed systemic relapse 39 days after CNS relapse
		31	M	Imatinib followed by BMT	134 days	BP	NA	NA	NA	NA	IT CT + RT	alive, developed systemic relapse 115 days after CNS relapse
6	Neumann et al., [9]	25	NA	Allo-SCT, followed by three bone marrow relapses in 11 years, two treated by DLI and one by high dose imatinib	11 year	AP	H, V, photophobia	NA	NA	intraparenchmal tumor in left hippocampus and frontobasal area	IT Mx,C,D + CD-14 depleted DLI +Nilotinib	death after 17 months due to second CNS relapse
7	Park et al., [10]	54	M	Imatinib	7 months	HR+MCR	H	L	NA	leptomeningeal enhancement of both paramedian gyri	IT Mx, + RT +dasatinib	Alive
8	Kim et al., [11]	42	M	Imatinib	25 months	MCR	H + low back ache	L	NA	obstructive hydrocephalus and a mass lesion in right cerebellum	craniotomy, IT Mx,C,HY +Imatinib	died 15 days after craniotomy
9	Beyazit et al., [12]	46	F	HU and interferon for 2 years followed by imatinib for 2 months	26 months	CR	H and convulsion	NA	NA	infiltration of spinal cord	IT CT + RT + systemic CT	Died
10	Pfeifer et al., [13]	19	M	HU + Imatinib + prophylactic IT CT	41 days after starting imatinib	CR	H, V, meningism	B	NA	NA	IT CT + RT+ imatinib	Died
		68	M	HU+Imatinib	139 days after starting imatinib	HR	H, diplopia	L	NA	NA	IT CT + RT	Died
		45	M	HU, interferon, VCR + Pred + imatinib	191 days after starting imatinib	CR	H, hearing loss	B	NA	NA	IT CT + RT + imatinib	alive, repeat CNS relapse
11	Gaur et al., [14]	30	M	imatinib/ Nilotinib for 7 years, dasatinib for 6 months, ponatinib for 4 months	relapse after 2 months of stopping ponatinib	CR	H, visual loss,lower limb weakness	MY	NA	supratentorial and infratentorial leptomeningeal enhancement	IT C + RT+ dasatinib	Alive
12	Isobe et al., [15]	61	M	Imatinib	14 months	CR	H, V, tinnitus	L	P	normal CT scan	IT Mx, D, + imatinib followed by PBSCT	second CNS relapse after PBSCT, alive
13	Lindhorst et al., [16]	24	F	HU + imatinib	3 months	HR	H	MY	NA	increased signal intensity in periventricular area of third ventricle	IT C, H+dasatinib	Alive

S. No.	Author	Age (yr)	Sex	Treatment prior to presentation	Duration of treatment prior to CNS relapse	Disease status before CNS relapse	Clinical presentation	Blast type	Fundoscopy	MRI Findings	Treatment given	Outcome
14	Thomas et al [17]	33	M	HU + imatinib, followed by SCT and dasatinib	13 months after SCT	CR+MR	upper limb weakness, dysarthria, diplopia	MY	NA	NA	IT Mx + RT+nilotinib	Alive
15	Rytting et al., [18]	48	M	HU + imatinib + C + idarubicin	after 3 courses of CT	MCR	H, V	MY	NA	NA	IT Mx,C + RT+ imatinib+C + idarubicin followed by SCT	alive
16	Johnson et al., [19]	50	M	interferon for 2 months +imatinib for 1 yr	14 months after diagnosis	CR	H,V	L	NA	NA	IT Mx,C,HY + CT for ALL protocol followed by SCT	Died after SCT
17	Nishimoto et al., [20]	22	M	Imatinib	29 months	CR	H and blurred vision	L	NA	Optic nerve enhancement at chiasm	IT CT, RT followed by SCT and dasatinib	Alive
18	Rajappa et al., [2]	39	M	Imatinib	22 months	CR	H,V	NA	P	meningeal enhancement	IT Mx,C,HY+ RT+imatinib	Alive
19	Lee et al., [21]	39	M	Imatinib	36 months	CR	H, diplopia, eye pain	L	NA	abnormal enhancement around petrous areas	IT Mx,C +imatinib	Alive
20	Present case	35	M	Imatinib	25 months	CR	H,V, Bilateral visual loss	MY	P	Pachymeningitis with bilateral; optic neuritis	Imatinib+ IT Mx ,D	Died

[Table/Fig-4]: Table summarizing the clinical details of the 23 reported cases of isolated CNS relapse in CML along with findings of the present case
*Sex-M/F- male/female; NA- not available, HR-haematological remission, CR-cytogenetic remission, MR-molecular remission, MCR-major cytogenetic remission, BP-blast phase, CP- chronic phase, AP-accelerated phase, HSCT-hematopoietic stem cell transplant, SCT-stem cell transplant, PBSCT-peripheral blood stem cell transplant, BMT-bone marrow transplant, HU-hydroxyurea, C-cytarabine, IT CT-intrathecal chemotherapy, DLI-donor lymphocyte infusion, Pred-prednisolone, H-Headache, V-vomiting, L-lymphoid, MY-myeloid, P-papilloedema, OA-optic atrophy, IT-intrathecal, CT-chemotherapy, Mx-methotrexate, D-dexamethasone, RT-radiation, HY-hydrocortisone

relapse after SCT [8]. Presence of graft vs host disease was not found to affect the development of CNS relapse after SCT as CNS represents an immunologically privileged site [9]. This finding is supported by the observation that systemic infusion of donor lymphocytes do not affect CNS relapse [9]. In this respect, observations of Neumann et al., need a brief mention. Using *intrathecal* administration of CD-14 depleted peripheral donor lymphocytes, Neumann et al., could treat isolated CNS relapse of a patient after 11 years of Allo-SCT by exploiting the concept of Graft vs Leukaemia (GVL) effect [9]. As is evident from above review of the reported cases of isolated CNS relapse in CML, only one case with optic nerve enhancement has been reported and none of the reported cases till date had pachymeningitis though leptomeningeal enhancement is the commonest reported feature.

CONCLUSION

The present case not only reports a new finding of HP and optic neuritis in association with a rare event of isolated CNS blast crises in CML, but presents a brief review of the clinical features, available treatment options and overall survival of such patients. Intrathecal donor lymphocyte infusion (DLI) as a potential therapy for isolated CNS blast crises has been highlighted in this review.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jul 20, 2015**
Date of Peer Review: **Oct 14, 2015**
Date of Acceptance: **Nov 14, 2015**
Date of Publishing: **Jan 01, 2016**