Case Report:

Unprecedented behaviour of chronic myeloid leukaemia

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ABSTRACT

We report the occurrence of leukaemic infiltration of cervical spinal cord secondary to chronic myeloid leukaemia (CML) in a 31-year-old male patient. He presented with left upper limb monoplegia. On examination he had asymmetric quadriparesis, graded sensory loss and urinary retention. Diagnosis was suggested by magnetic resonance imaging. He responded dramatically to radiotherapy and corticosteroids treatment. Infiltration of the cervical spinal cord in a patient with CML has seldom been reported in literature till date, and hence we are reporting this case.

Key words: *Leukemic infiltration, Chronic, Myelogenous, Leukaemia, Cervical cord, Leukemic infiltration, Quadriplegia*

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INTRODUCTION

Leukaemic infiltration of the spinal cord is uncommon, and occurs variably among haematological malignancies. The incidence of leukemic infiltration of central nervous system (CNS) occurs in the following descending order: acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic lymphocytic leukaemia and chronic myeloid leukaemia (CML).[1] The few available case reports of CNS involvement in CML mention granulocytic sarcomas causing compressive myelopathy, but direct symptomatic invasion of the spinal cord, particularly cervical cord is extremely rare. Thus it is noteworthy to discuss thoroughly the present case.

CASE REPORT

A 28-year-old male presented with multiple swellings in the bilateral cervical, axillary and inguinal regions of 15 days duration along with low-grade fever of 4 days duration in June 2012. On physical examination, he had bilateral cervical, axillary, inguinofemoral, epitrochlear lymphadenopathy along with bilateral tonsillar enlargement and also massive splenomegaly. Fine needle aspiration cytology from the peripheral lymph node revealed non-specific lymphadenitis. Complete blood picture revealed a total leucocyte count of 284,600 cells/mm^3 with a differential count of myeloblasts 12%, promyelocytes 10%, myelocytes 16%, metamyelocytes 19%, band forms 15%, neutrophils 11%, basophils 5%, monocytes1%, eosinophils 2% and lymphocytes 9%**.** The peripheral smear was suggestive of CML in chronic phase (Figures 1 and 2A). Abdominal ultrasonography revealed multiple periportal and mesenteric lymphadenopathy and splenomegaly. Bone marrow trephine biopsy showed features

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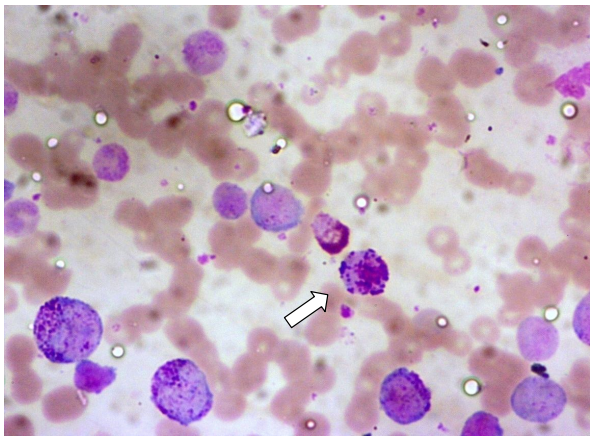

Figure 1: Photomicrograph of peripheral blood smear showing immature myeloid series cells. Arrow points to a basophil (Leishman × 400)

consistent with CML (Figures 2B and 2C**).** Bone marrow cytogenetic study detected a balanced reciprocal translocation t(9;22), the Philadelphia chromosome (ONCQUEST Laboratories Ltd., New Delhi). He was initiated on oral imatinib 400 mg once daily.[2] After two weeks of imatinib therapy, splenomegaly disappeared and lymphadenopathy grossly reduced.

After two months i.e., in August 2012, he presented with pedal oedema, puffiness over face and features suggestive of myelo-suppression. Ratio of break point cluster region (BCR) Abelson 1 (ABL1)/ABL1 transcript was detected to be 66.89% in the leukocytes (Oncquest Laboratories Ltd., New Delhi-)**.** Imatinib was withheld for about two weeks and he was managed with symptomatic and supportive treatment. His symptoms improved and Imatinib was restarted. However lymphadenopathy persisted. Excision biopsy of peripheral lymph node showed leukaemic infiltrates. Immunohistochemistry (IHC) was positive for leucocyte common antigen (LCA), CD3, CD20, CD34, and CD117 and negative for CD15. Imatinib was continued and he achieved complete haematological remission.

In March 2013, he presented with bleeding per rectum, epistaxis, progressive lymphadeno-pathy and tender splenomegaly**.** Per-rectal examination revealed a posterior fissure-in-ano**.** Laboratory testing revealed haemoglobin 6 g/dL, total leucocyte count 2000/mm^3 and platelet count 34,000 /mm**.**^{3} Imatinib resistance was suspected and so imatinib was withheld and he was managed conservatively**.** He was advised to get tested for imatinib resistant mutation analysis. However, the patient could not afford to undergo the testing. After symptomatic improvement, he was empirically initiated on oral dasatinib 100 mg once daily,[3] with which he attained complete haematological remission and was doing well until October 2014.

In October 2014, he presented with weakness of left upper limb of four days duration, along with neck pain radiating to interscapular area and left upper limb. He also complained of difficulty in raising the right arm above the shoulder, which was insidious in onset and gradually progressive. He also had difficulty in sitting from squatting position, difficulty in getting up from the bed, tingling sensation in

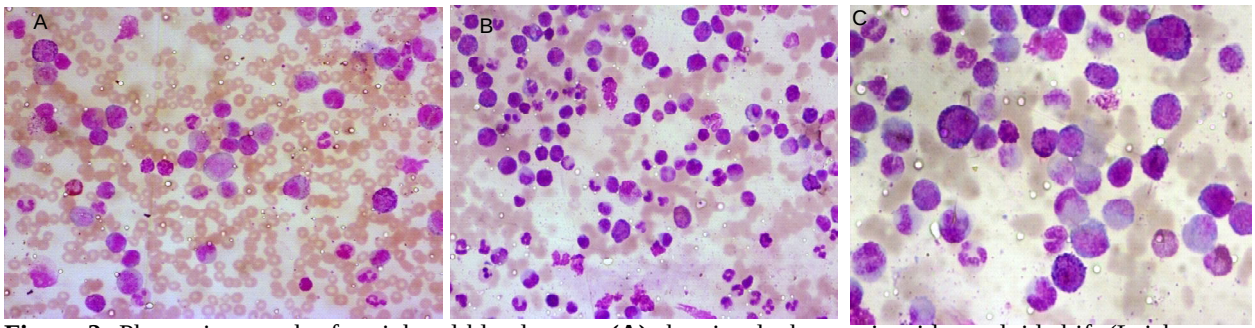

Figure 2: Photomicrograph of peripheral blood smear **(A)** showing leukocytosis with myeloid shift (Leishman × 100). Photomicrograph of bone marrow trephine biopsy showing increased myelopoiesis with immature forms and an occasional basophil (Leishman × 100) **(B)**, (Leishman × 200) **(C)**

both upper limbs, radicular pain in left upper limb, shock like sensation through all four limbs on bending the head, urgency and difficulty in initiating micturition.

General physical examination was unremarkable. Neurological examination revealed asymmetrical quadriparesis. Motor system examination revealed hypotonia in left upper limb. Power in the left upper limb was 0/5 while it was 3/5 in right upper limb. Power in both lower limbs was 4/5. Marked lower limb hyperreflexia with inverted supinator reflex was present. Plantar response was extensor bilaterally. Ankle clonus was present in both lower limbs. Sensory system examination revealed graded sensory loss.

Cerebrospinal fluid (CSF) analysis was unremarkable. Magnetic resonance imaging (MRI) brain was normal. MRI cervical spine revealed bulky cervical and dorsal spinal cord with altered signal intensity extending from cervico-medullary junction to D5 level which was hypointense on T1-weighted images (TIWI), hyperintense on T2-weighted images (T2NI) and Short Tau inversion recovery (STIR) images were consistent with leukaemic infiltrates (Figure 3). Bone marrow trephine biopsy showed reactive marrow with mild myeloid hyperplasia **(**Figures 4A and Figure 4B). He was treated with radiotherapy with 15 Gray (Gy) in 10 fractions at 1.5 Gy per fraction and intravenous methyl prednisolone 1g once-a -day for one week , followed by oral prednisolone in tapering doses. Patient had a dramatic response while on radiotherapy with improvement of the power in left upper limb to 4/5. MRI was repeated after the completion of treatment which showed marked reduction in edema surrounding the lesion (Figure 5).

DISCUSSION

At some point of time in the disease course of leukaemic patients, approximately 25%-50% will suffer a central nervous system (CNS) complication. In leukaemic patients with neurological symptoms, the differential diagnoses include direct spread to the CNS as well as cerebrovascular, infectious, and treatment related complications. Uncommonly, involvement of the CNS is the first manifestation of systemic leukaemia.[3]

CML is a chronic myeloproliferative disorder characterized by a reciprocal translocation between chromosomes 9 and 22 and thereby formation of the Philadelphia chromosome.[4] Leukaemic deposits may involve any part of the CNS leading to varied symptoms and signs depending on the extent of infiltration and the area of localization. These complications include cranial nerve palsies, hemiplegia, aphasia, hemianopia, ataxia, convulsions, cortical blindness etc.[5]

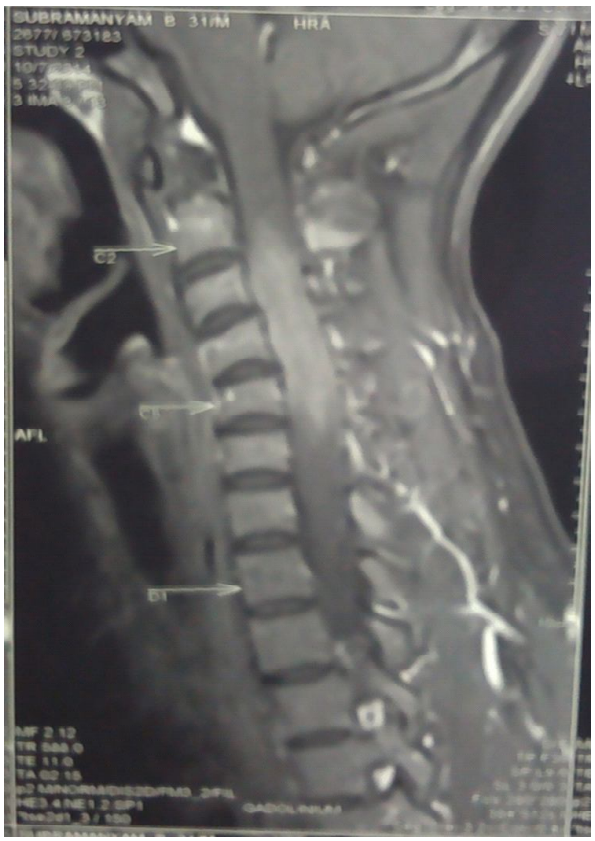

Figure 3: MRI cervical spine, sagittal view, showing bulky cervical and dorsal spinal cord with altered signal intensity extending from cervico-medullary junction to D5 level suggestive of leukaemic infiltrates
MRI = magnetic resonance imaging

Clinically significant spinal cord involvement is unusual in leukaemia. The clinical syndromes relating to spinal cord involvement range from complete cord syndrome (transverse lesion of the spinal cord with paraplegia, sensory loss below the involved segment and urinary retention) to partial cord syndromes; anterior or posterior cord syndromes or the Brown-Sequard syndrome. Back pain, frequently with root involvement, and progressive paraparesis or quadriparesis over days or weeks is another manifestation of progressive spinal cord compression from extra-dural deposits. The extradural deposits are commonly seen in the thoracic; cervical cord; conus medullaris and cauda equina are rarely involved.

Cord syndromes arise from compression by extradural deposits, direct infiltration of the spinal cord and nerve roots, vascular occlusion by thrombus, leukaemic cells or mixture of leukaemic cells and thrombus, or haemorrhage, and rarely acute paraneoplastic necrotizing myelopathy.[5] The precise mechanism of leukemic infiltration into the CNS is unknown, but may involve haematogenous spread as well as direct spread from adjacent involved bone marrow.[3] The diagnosis is suggested by MRI, the characteristics include hyperintense signal on T2WI and enlargement of the spinal cord. MRI is also useful in differentiating neoplastic infiltration from chloroma, epidural abscess and vertebral fracture from trauma among others.

Our patient was diagnosed as having CNS involvement in CML with leukaemic infiltration of the cervical cord. There are very few case reports, but none with cervical cord involvement.[4,6,7] Because of the rarity, no clear guidelines of management are available. The possible management includes radiotherapy, intravenous methyl prednisone and treatment of underlying disease along with symptomatic and supportive care, which was given to our patient. In an autopsy study[1] of 100 patients with both acute and chronic leukaemia, a single case of CML with CNS involvement was documented. Most of the case reports in the literature mention granulocytic sarcomas, which are extra-medullary solid tumours consisting of myelogenous leukaemic blasts. Myelopathy due to granulocytic sarcoma in chronic phase of CML has been reported.[4] A similar case causing compressive myelopathy has also been documented.[7] Isolated blast crisis in CNS in a case of CML on imatinib has been reported.[7]

In pre-imatinib era, where disease free survival and overall survivals were low, CNS involvement was seen rarely, but in the era of tyrosine kinase inhibitors (TKI), because of improved survivals, more and more CNS involvement is being seen. Among the TKIs, imatinib has limited activity against CML in the CNS due to poor blood brainbarrier penetration, possibly due to the P-glycoprotein mediated efflux.[8] But dasatinib which our

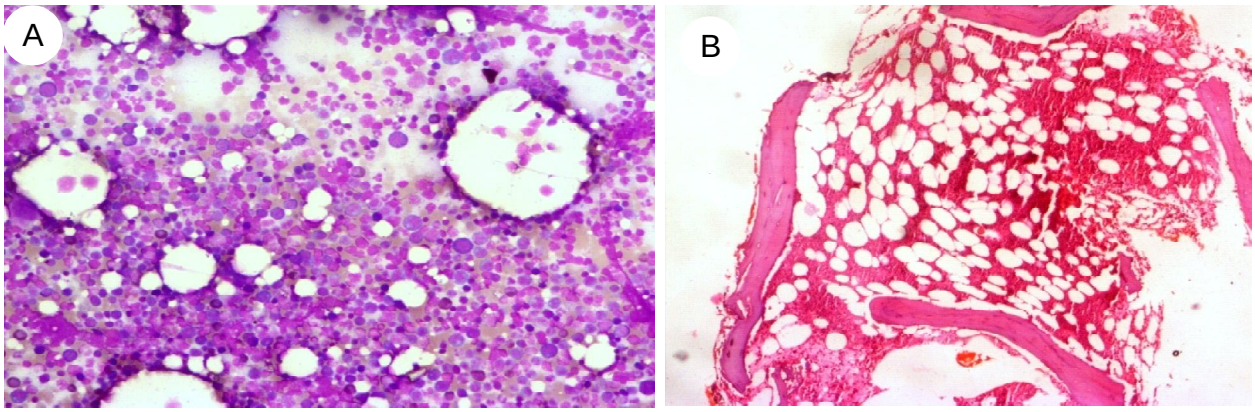

Figure 4: Photomicrograph of bone marrow trephine biopsy showing reactive bone marrow with mild myeloid hyperplasia (Leishman × 100) (A), (Haematoxylin and eosin × 40)

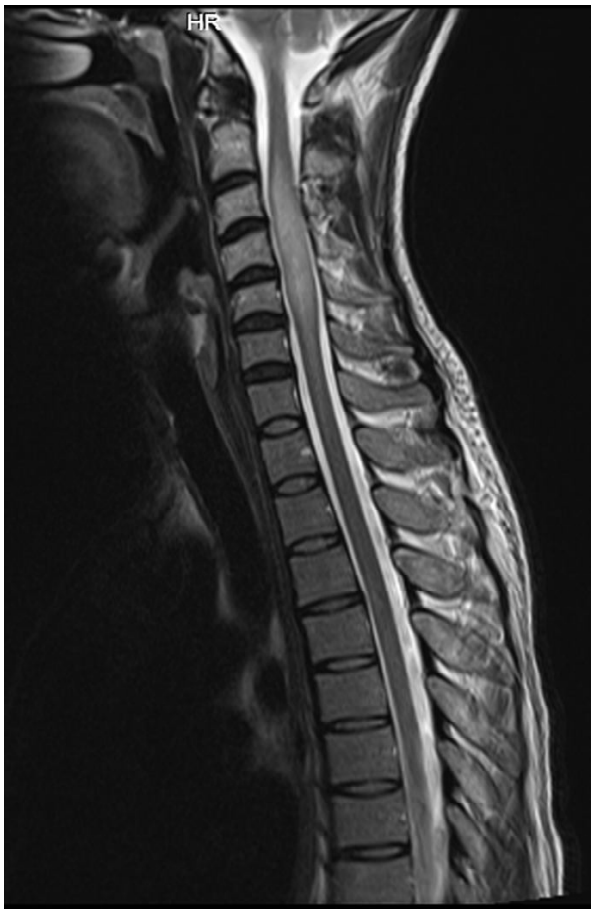

Figure 5: Repeat MRI of the cervical spine 8 days after of treatment showing significant decrease in oedema and infiltration
MRI = magnetic resonance imaging

patient received is known to cross blood-brain-barrier and has considerable CNS activity.[8]

Involvement of spinal cord in chronic phase of CML is rare. In fact CNS involvement is considered to herald blast crisis.[9]

Unique features of our patient were that he developed leukaemic infiltration in chronic phase of CML, with involvement of cervical cord. We want to emphasise that this possibility should be kept in mind whenever a CML patient presents with CNS involvement. A high index of suspicion, early diagnosis and aggressive management may help in preventing this devastating complication.

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