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CASE REPORT

Extramedullary chronic phase chronic myeloid leukaemia (CML) involving the central nervous system: A case report

Akshay Deshpande | **Dina Osman** | **Vidhya Murthy** | **Hayder Hussein**

Department of Haematology, University Hospitals Birmingham NHSFT, Birmingham, UK

Correspondence
Akshay Deshpande, Haematology SpR, Department of Haematology, University Hospitals Birmingham NHSFT, Birmingham B15 2GW, UK.
Email: akshay.deshpande@nhs.net

Abstract

Chronic myeloid leukaemia (CML) has been classically described as a disease restricted to the bone marrow with very few reports of extramedullary involvement. CNS involvement with CML has been described in the literature as an aggressive disease in the leukaemic phase either preceding or coexisting with medullary blast crisis or seen in patients with long-term Imatinib therapy. No treatment consensus exists for this patient group and outcomes remain poor. We hereby present a very rare report of CNS involvement with chronic phase CML at diagnosis in a patient who presented with raised intracranial pressure and cranial nerve palsies.

KEYWORDS
chronic phase, CML, CNS infiltration

1 | INTRODUCTION

Chronic myeloid leukaemia (CML) is a myeloproliferative haematopoietic stem cell disorder characterised by the balanced translocation of t (9;22) (q34;q11) leading to the fusion of BCR and ABL1 genes [1]. The fused BCR::ABL1 oncogene subsequently results in constitutional activation of the tyrosine kinase pathway, which gives mutant haematopoietic stem cells a proliferative advantage [2]. The disease has two phases according to the fifth edition of the World Health Organisation (WHO) classification of haematolymphoid tumours, the chronic phase and blast crisis [3]. The differentiation can be made based on the lineage of blasts, blast percentage, and the presence of myeloid sarcoma [4]. The incidence of CML ranges between 10 and 15 cases/10 [6]/year and there are no known geographic or ethnic variations [4]. With a mean age of over 65 years, CML has been classically described as a disease of old age [5]. Tyrosine kinase inhibitors (TKIs) have revolutionised the management of CML with a near-normal life expectancy [6].

Extramedullary disease in CML is rare and most of the reported cases in the literature are in the form of myeloid sarcoma [7] with only a handful of cases with central nervous system (CNS) involvement [8]. CNS involvement in CML has either been reported as in blast crisis in isolation, concurrently, or preceding medullary blast crisis [8], [9] and in the relapse/refractory setting while on treatment with TKIs [10]. A large retrospective analysis of cerebrospinal fluid (CSF) cytology in CML patients over seven years only picked up ten samples with CNS infiltration [11] with a time interval for CSF positivity following CML diagnosis ranging from five months to 11 years [11]. No consensus on treatment exists for this patient group with reports of second-generation TKIs [10], [12], intrathecal chemotherapy [8], [10], cranio-spinal radiotherapy [10], [12] and systemic chemotherapy with allogeneic stem cell transplant consolidation being described. Overall outcomes have been poor [5].

We report a unique case of a newly diagnosed CML patient presenting with CNS infiltrative disease in the chronic phase.

1.1 | Case presentation

A 61-year-old previously fit and well gentleman presented with a subacute onset headache, diplopia, and left-sided ptosis. There was no history of fever, night sweats, or weight loss. Neurological examination showed a bilateral reduction in visual acuity, left complete 3rd cranial nerve palsy, and potentially 4th cranial nerve involvement. There was no relative afferent pupillary defect. Fundoscopy showed bilateral optic disc swelling with haemorrhages suggesting an infiltrative process of the optic nerves. The rest of the cranial nerves were intact and there was no motor or sensory deficit identified on upper and lower limb examination. There was no hepatosplenomegaly or lymphadenopathy detected on examination or any evidence of extramedullary involvement on imaging. His blood pressure was raised and that was the only identifiable cardiac risk factor.

Full blood count showed marked leucocytosis with a WBC count of 188.36 × 10^9/L, Hb 127 g/L, and thrombocytosis, platelets 468 × 10^9/L. The blood film was leucoerythroblastic with left-shifted neutrophils with plenty of myelocytes, basophilia (2%), and blasts constituting 2.4% of nucleated cells. This picture was highly suggestive of chronic phase CML. Liver and renal function tests were unremarkable; however, Hepatitis B surface antigen and anti-hepatitis B core antibody were positive suggesting chronic hepatitis B infection. BCR::ABL1 e13a2 gene fusion was detected by single-step RT-PCR consistent with the diagnosis of CML. Bone marrow trephine confirmed that the disease was in the chronic phase with <5% blasts detected. No additional cytogenetic abnormalities were identified through karyotype analysis. The disease was classified as low risk based on the EUTOS and Sokal scoring systems.

In light of the significant leucocytosis and neurological signs, cytoreduction with Hydroxycarbamide was started immediately and was substituted with Imatinib when the diagnosis of CML was confirmed. A CT Head was unremarkable and there was no detectable mass lesion. Perineural enhancement of both optic nerves and the chiasm was suspected on MRI of the orbits and base of the skull, though images were limited by motion artefact. Repeat neuroophthalmological review showed a reduction in the optic disc swelling prior to lumbar puncture which was thought to be attributed to Imatinib.

Cerebrospinal fluid (CSF) obtained by lumbar puncture was straw-coloured. CSF protein was elevated at 0.39 g/L, with normal glucose, and no growth after culture for 48 h. The CSF cytospin showed neutrophils and myelocytes with no blasts or red cell contamination (10 × 10^6/polymorphs and 45 × 10^6/L mononuclear cells) (Figure 1). Flow cytometry of the CSF sample showed 72% myeloid cells (CD33/CD13 positive, Figure 2A), 85% of which were mature (strongly positive for CD11b) (Figure 2B) and 0.6% blasts by CD34 and/or CD117(Figure 2C). These results were consistent with CSF infiltration with chronic phase CML. The Patient was switched to Dasatinib 140 mg OD and started on weekly intrathecal Methotrexate. Entecavir prophylaxis was started for chronic hepatitis B infection. Three doses of intrathecal Methotrexate were administered weekly including a dose of triple intrathecal chemotherapy including Cytarabine and Hydrocortisone. The CSF was clear after the second dose of intrathecal chemotherapy. The patient tolerated Dasatinib well with no side effects and achieved haematological response in 3 weeks. At 6-month follow-up, the patient continues to maintain an optimal molecular response with a BCR::ABL to ABL1 ratio of 0.54%. His CSF remains negative by immunophenotyping with complete resolution of cranial nerve palsies. He continues Dasatinib 140 mg with no plans for dose reduction for now.

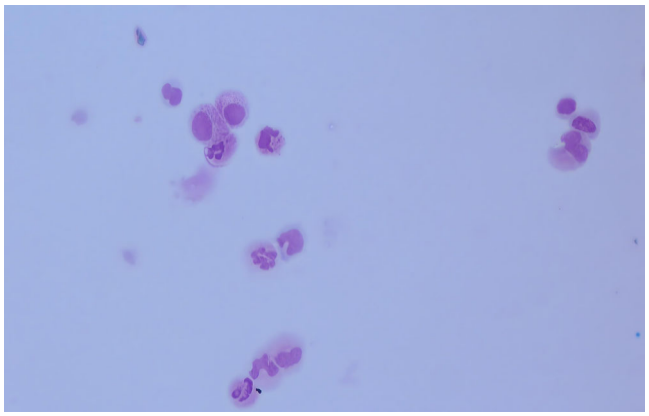

FIGURE 1 CSF cytospin showing neutrophils and myelocytes with no blasts or red cell contamination.

Due to the unusual nature of the patient's presentation, he was considered for an allogeneic stem cell transplant; however, there were no suitable donor options. Considering the complete resolution of his symptoms and optimal response by RT-PCR, he is currently continuing to be managed with Dasatinib monotherapy.

2 | DISCUSSION

Extramedullary CML blast crisis is defined as the infiltration of myeloid or lymphoid blasts outside the bone marrow regardless of the status of bone marrow disease [13], [14]. Synchronous medullary and extramedullary blast crises can occur; however, extramedullary blast crisis can start first and is almost always followed by bone marrow blast crisis in a few months [14]. The prevalence of extramedullary blast crisis is approximately 15% and the commonly affected sites are the bones, lymph nodes, skin, soft tissue, and CNS [5]. Extramedullary CNS blast crisis has been classically reported in patients on long-term Imatinib therapy [9]. Poor CNS penetration with Imatinib due to the P-glycoprotein efflux mechanism is postulated to be responsible for this complication [9]. Extramedullary blast crisis is reported in younger patients with a mean age of less than 30 years and is four times more common in males as compared with females [5]. Median survival in extramedullary CML blast crisis has been reported to be 16 months with stem cell transplant providing a survival benefit [5].

The reported cases in the literature are mostly of CNS blast crisis; however, we report a case of extramedullary CML in the chronic phase affecting the CNS at presentation. A case report by Sakakura

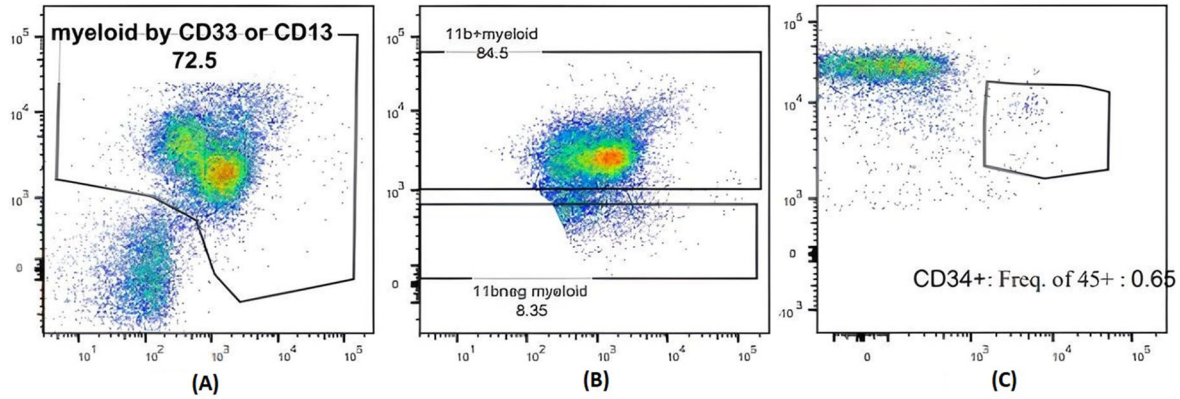

FIGURE 2 Flow cytometry performed on the CSF sample showed 72% myeloid cells (CD33/CD13 positive, A), 85% of which were mature (strongly positive for CD11b) (B) and 0.6% blasts by CD34 and/or CD117(C).

et al. [7], describes a patient with recently diagnosed chronic phase CML patient with a retroperitoneal mass representing extramedullary haematopoiesis from a CML clone positive for BCR-ABL1 fusion on FISH. Soni et al. [5] also report a case of presumed extramedullary CML in a patient with HIV and chronic phase CML who presented with leg weakness but with no obvious evidence of CML infiltrate on CSF examination. The recent WHO and ELN classifications do not provide sufficient clarity to classify this rare presentation as an accelerated phase/blast crisis.

There is no available good-quality evidence to guide the management of extramedullary chronic phase CML. Our patient received weekly intrathecal chemotherapy until clearance of the disease in combination with high dose Dasatinib which is known to have better CNS penetration and higher CSF concentration compared with Imatinib as inspired by the management of Philadelphia positive acute lymphoblastic leukaemia patients with CNS disease [15].

Some unanswered questions remain following this approach such as the recurrence rate, whether further treatment should be given and how best to monitor. It could be argued that intensive chemotherapy with CNS penetrating regiments like FLAG Ida with a TKI, followed by allogeneic stem cell transplant should be considered. However, the associated toxicities and treatment-related mortality should be carefully sought especially in chronic phase disease. Alternatively, the role of cranial radiotherapy remains unclear.

There is insufficient evidence regarding the role of consolidation with allogeneic stem cell transplant in this setting. The authors believe that this should be considered in the presence of an available donor as the presence of extramedullary disease in any form would be considered at risk of treatment failure.

3 | CONCLUSION

Extramedullary CNS chronic phase CML is extremely rare with no confirmed reported cases in the literature. We managed this patient with a combination of intrathecal chemotherapy with high dose Dasatinib, resulting in complete resolution of symptoms and optimal response by PCR in the peripheral blood. Whilst we would consider stem cell transplant because of the potential risk of treatment failure, this option was not available for this patient. However, at present his disease is well controlled and this case provides an example of a potential management strategy in this situation.

AUTHOR CONTRIBUTIONS

Akshay Deshpande and Dina Osman co-wrote the manuscript. All four authors commented on the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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PATIENT CONSENT STATEMENT

The authors confirm the patient's consented for the study.

CLINICAL TRIAL REGISTRATION

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ORCID

Akshay Deshpande https://orcid.org/0000-0002-5096-3839
Dina Osman https://orcid.org/0000-0002-3668-0250

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