A Case of Relapsed Chronic Myeloid Leukemia Admitted with the Complaints of Paraplegia and Urinary Incontinence

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Abstract Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell malignancy. In CML, extramedullary blastic crisis is a very rare condition in which the prognosis is even worse. Herein we presented a rare case of relapsed CML patient as blastic crisis with serious neurological symptoms because of central nervous system (CNS) infiltration. A 69-year-old male patient diagnosed with CML was admitted to hospital with complaints of weakness in legs, urinary incontinence, abnormal speech, and impaired vision. Deep tendon reflexes were bilaterally hypoactive in lower and upper extremities and Babinski reflex was negative. Immunophenotyping and cytological examination of CSF showed blastic cell infiltration. Also BCR-ABL mutation was positive in CSF and MR showed CNS involvement. So the patient diagnosed as “Myeloid blastic phase of CML with CNS involvement”. Imatinib therapy was replaced with dasatinib and intrathecal methotrexate, cytarabine and dexamethasone treatment was applied. Complaints of weakness, fatigue, urinary incontinence, leg weakness and inability to walk were completely resolved in three months. Extramedullary blastic crisis such as CNS involvement has been reported in a limited number in CML. Even if hematological and cytogenetic remission is provided, CML patients should be followed regularly. Any new clinical detail should be considered carefully and extramedullary involvement including CNS should be kept in mind.

Keywords: chronic myeloid leukemia, extramedullary blastic crisis, dasatinib, central nervous system infiltration


1. Introduction

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell malignancy [1]. The erythroid, monocye and megakaryocyte series are affected because of the impact of the abnormal myeloid hematopoietic stem cells in the bone marrow [2]. In CML, Ph chromosome which is a result of a reciprocal translocation between chromosomes 9 and 22, is present more than 90% of the cases [3]. This translocation causes the expression of BCR/ABL tyrosine kinase fusion protein which increases the proliferation of mature myeloid cell series and extends their life span [4]. CML has a three-stage course; the vast majority is diagnosed in the chronic phase, 10% are diagnosed in accelerated phase and 10% are diagnosed in blastic phase of the disease [1]. The patients in the blastic phase show poor response to treatment and has also a poor prognosis [5]. Extramedullary blastic crisis is a very rare condition in which the prognosis is even worse.

Tyrosine kinase inhibitors are used as effective treatment of CML. Imatinib is the first generation, nilotinib and dasatinib are the second generation tyrosine kinase inhibitors. In previous studies, it was shown that dasatinib is the best tyrosine kinase inhibitor passing to the cerebrospinal fluid (CSF) by crossing the blood brain barrier [6,7].

We herein presented a rare case of relapsed CML patient as blastic crisis with serious neurological symptoms because of central nervous system (CNS) infiltration, who was before BCR/ABL-negative and in hematological remission in his regular checkups.

2. Case Presentation

Sixty nine year old male patient with the diagnosis of CML for three years and under the treatment of imatinib 400 mg/day, was admitted to hematology clinic with the complaints of weakness in the legs which was started 10
days ago, urinary incontinence, fatigue, sleep talking and impaired vision. The patient was on regular outpatient control. His previous BCR/ABL mutation by molecular methods was negative and he was in hematological remission before. On neurological examination; bilateral muscle strength was 5/5 in upper extremities, 4/5 in lower extremities, deep tendon reflexes were hypoactive in all extremities and Babinski was negative. In his laboratory tests; hemoglobin (Hb):11.1 g/dL (N:12-15 g/dL), mean corpuscular volume (MCV):98.4/fL (N:80-96/fL), White Blood Cell (WBC):3.6x10^9/mm^3 (N:4-10x10^9/mm^3), neutrophils (Neu):2.62/mm^3 (N:1.7-7x10^9/mm^3), platelet (PLT):195.000/mm^3 (N:150-450.000/mm^3), sedimentation rate:2 mm/h, total protein:5.9 g/dl (N:6.6-8.2 g/dl), serum albumin:3.2 g/dl (N:4.1-5 g/dl), lactate dehydrogenase (LDH):291 U/L (N:125-243 U/L), uric acid:3.9 mg/dL (N:2.8-5.8 mg/dL), alanine amino transferase (ALT):13 U/L (N:0-55 U/L), aspartate amino transferase (AST):14 U/L (N:7-24 U/L), alkaline phosphatase (ALP):56 U/L (N:40-150 U/L), gamma-glutamyl transferase (GGT):14 U/L (N:0-7 U/L), total bilirubin:0.93 mg/dL (N:0.16-0.93 mg/dL), direct bilirubin:0.37 mg/dL (N:0.08-0.4 mg/dL), creatinine:1.02 mg/dL (N:0.6-1.1 mg/dL), iron:82 μg/dL (N:22-155 mg/dL), total iron binding capacity (TIBC):116 µg/dL (N:110-370 mg/dl), ferritin:404 ng/ml (N:13-150 ng/ml), folic acid:9.77 ng/ml (N:3.1-17.5 ng/ml), vitamin B12:378 pg/ml (N:191-663 pg/mL), TSH:3.54 μU/ml (N:0.56-5.57 μU/ml), CRP:3.44 mg/L (N:0-5 mg/L), INR:1.1 (N:0.8-1.3). He had a history of benign prostatic hypertrophy and had a complaint of urinary incontinence so urologic evaluation has been done. It has showed that patient had a loss of sensation to urinate despite the presence of 300 cc residual urine in his bladder. Only pathologic finding observed in abdominal ultrasonography was the presence of multiple millimetric cysts of renal cortex bilaterally.

The patient was consulted to neurology and thoracolumbar and brain magnetic resonance imaging (MRI) and electromyography (EMG) were taken. EMG revealed mild polyneuropathy. MRI assessment showed a signal increment in bilateral cerebellar peduncle, periaqueductal space and around the fourth ventricle in T2 and FLAIR sequences. There was bilateral thickening and contrast enhancement in optic nerves. Contrast enhancement was also detected in the third and fifth cranial nerves bilaterally and also in right-sided seventh and eighth cranial nerves. There was the appearance of the bilateral papilledema. Increased signal intensity on T2-weighted sequences in the dorsal spinal cord and a slight thickening of soft tissues in the paravertebral area were detected. There was a slight bilateral pleural effusion. It was reported that above described lesions could be a sign of metastasis and paravertebral findings were reported to be compatible with blast crisis or extramedullary hematopoiesis.

Lumbar puncture (LP) was performed for the detection of disease involvement in meningeal cord, spinal cord and cranial nerves. Cerebrospinal fluid (CSF) culture was negative. In CSF analysis; WBC:3.37x10^3/mm^3, Neu:0.023x10^3/mm^3, lymphocytes:1.2 x10^3/mm^3, monocytes:2.14x10^3/mm^3, microprotein:439.3 mg/dL, glucose:56 mg/dL, LDH:531 U/L. Evaluation of the CSF cytology of the patient was compatible with CSF involvement with CML (Figure 1). The study of viral and bacterial parameters in order to exclude the other causes of monocyte increase in the CSF were reported as normal. In bone marrow assessment, 75.6% myeloid blastic cells were detected in flow cytometry and 60-70% blastic cell population was detected in the marrow aspiration.

Figure 1. In smear examination of the CSF, there are cells of myeloid series in the band/granulocyte form fallen between the mature lymphocytes lonely or in groups on the clear background (Mgxs400)

Although the presence of normal blood platelet, slightly decreased hemoglobin and leukocyte counts and lack of any blast increase in peripheral blood smear, patient was diagnosed as CML myeloid blastic phase with bone marrow and CSF findings according to the pre-defined criteria. Intensive chemotherapy treatment was not planned because of the patient's age and performance status. Imatinib treatment switched to 140 mg/day
dasatinib treatment which CSF transition is better. Radiotherapy has been discussed with radiation oncology clinic and it has been decided not to be beneficial. Intrathecal methotrexate, cytarabine and dexamethasone for CSF involvement were administered four times with intervals. In order to evaluate the response, LP was repeated on the 10th day and no blastic cell was detected in the CSF. In posttreatment bone marrow evaluation, the blast rate was found under 10% both with flow cytometric analysis and pathological examination. We could not detect the concentration of dasatinib in CSF due to the technical shortcomings. About three months later, the MR evaluation revealed complete recovery of earlier views associated with blastic crisis.

Figure 2. Hypocellular bone marrow that containing 10% CD34 immunopositive blastic cell (HEx400)

With the treatments during follow-up, complaints of the patients such as fatigue, loss of strength in the legs and voiding dysfunction were all improved, and he became able to walk again.

His cytogenetic analysis was also very interesting. At the diagnosis, conventional cytogenetic analysis revealed no metaphase spread. Molecular cytogenetic analysis, FISH showed 94% of nuclei having BCR/ABL fusion. However the BCR/ABL positive cells had a deletion of ABL gene on BCR/ABL fusion. At the followed up stage the patient had 46,XY,Ph(+) [5]/41-45,XY,Ph(+) [10] (hypodiploidy). FISH analysis showed 90% of interphase nuclei having as at diagnosis. After three months of the last treatment, the patient applied to our clinic due to neurologic problems. Conventional cytogenesis analysis was failed because of no metaphases. FISH analysis revealed BCR/ABL fusion on 88% of interphase nuclei. FISH analyse was also performed in CSF. It showed BCR/ABL fusion on 86% of interphase nuclei. Molecular analysis by using real time PCR showed no major BCR/ABL gene fusion. This result was not concordant with cytogenetic and FISH analysis. This could be false negative, because FISH analysis showed a deletion of ABL part on the BCR/ABL fusion gene. After five months, the follow-up study was done on conventional cytogenetic analysis, no metaphase spread was obtained. FISH analysis revealed 25% of nuclei having BCR/ABL fusion and also partial ABL deletion of fusion part. Molecular analysis by using real time PCR showed major BCR/ABL gene fusion again indicating false negative, because of the presence of partial ABL deletion of BCR/ABL fusion gene. Three months later, the patient had normal karyotype and the decrease of BCR/ABL fusion gene in 8%. Another three months later, the patient karyotype was normal, FISH analyses revealed. Still presence of 7% of nuclei with BCR/ABL fusion.

3. Discussion

Although CNS infiltration by leukemic cells is common in Ph+ acute lymphoblastic leukemia, it is a rare clinical condition in patients who are under the treatment of adequate dose of tyrosine kinase inhibitors in CML. There are significant differences in peripheral blood, bone marrow, genetic, flow cytometry and radiological imaging findings of the CML cases who have extramedullary blastic crisis in another part of the body such as involvement of CNS in the literature. Extramedullary blastic crisis in CML is generally a situation that expected in patients with high leukocyte counts. There is no preferred standard therapeutic regimen in CML patients with CNS involvement. For CNS involvement, intrathecal chemotherapy, high-dose systemic chemotherapy, radiotherapy are available treatment options but problems such as significant treatment related toxicities, short-term treatment responses and poor quality of life can be seen. In previous studies, it was shown that dasatinib is the best tyrosine kinase inhibitor passing to the cerebrospinal fluid, so we used dasatinib and achieved complete response.

Lindhorst et al [8] reported a young female patient who presented with CNS relapse while she was receiving imatinib treatment for CML. In that case, peripheral blood leukocyte count was very high (385,000 / mm³), bone
marrow blast cells ratio was 5% but cell count was very low in the CSF. In our case, there was a significant increase in ratio of blasts in bone marrow while peripheral blood findings was in favor of remission. Xu Z et al [6] reported a 22-year-old CML patient who was presented with episodes of monocytic and lymphoid blastic crisis. But in her third attack there was CNS involvement without any abnormality in the bone marrow. In that case, young cells that detected in the CSF, have only been reported. Unfortunately there was not enough information about genetic analysis, flow cytometric evaluation, peripheral blood smear, radiological findings and bone marrow blast percentage during the attack of CNS involvement. Our case has been presented with myeloid blastic crisis and peripheral blood smear, bone marrow, genetic, cytometric and radiological examinations were all assessed in detail. Lai SW et al [7], reported a case of 22-year-old CML patient who was presented with myeloblastic crisis four years after diagnosis and her peripheral blood and bone marrow findings were consistent with acute leukemia (WBC: 330,000/mm³, BCR/ABL mutation negative). After the treatment of 7+3 induction for acute leukemia, recurrence with neurological symptoms occurred but aggressive treatment could not be given due to poor performance status. Complete remission was achieved with dasatinib and intrathecal injections. In our case, although over 50% blastic cells were detected, aggressive treatment was not considered because of the poor performance status. Gomez, J. et al [9] reported a 33-year-old male patient with CML who was admitted with neurological problems in the fifth year of imatinib therapy. His all imaging and bone marrow findings were found as normal but CSF examination with flow cytometry and genetic methods was showed the blast infiltration. Radhika N et al [10] reported 15 and 37-year-old two CML cases with isolated CNS involvement who were treated with imatinib, triple intrathecal chemotherapy and radiotherapy. The second case was lost due CNS involvement after three months. In these cases, flow cytometry and genetic characteristics findings of the CSF have not been reported. In our case, significant pathological findings were detected in radiologic, bone marrow, flow cytometry and genetic evaluations. Fuchs M et al [11] reported a 64-year-old case with highly aggressive CML, who was treated with allogeneic bone marrow transplantation (BMT) because of his recurrent blastic crisis. After BMT, in his second blastic crisis, CNS involvement was detected. After dasatinib and intrathecal treatments hematological remission was achieved. In our case, CNS involvement was detected in the first blastic crisis and yet it did not relapse in his follow-up.

4. Conclusion

All kinds of new signs and symptoms should be evaluated and investigated carefully for the relapse of the disease in the follow-up of the CML cases. We also think that FISH method should be used in addition to the molecular methods in the follow-up.

References