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Case Report

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Chronic Myeloid Leukemia Presenting as Cerebral and Deep Vein Thrombosis

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Introduction

Chronic myeloid leukemia is a myeloproliferative disorder characterized by increased proliferation of granulocytic and megakaryocytic cell lines. Consequently, the peripheral blood shows an increased number of granulocytes and their immature precursors including blast cells and thrombocytosis. The specific cytogenetic abnormality of CML is the reciprocal translocation between the long arm of chromosome 9 and Chromosome 22, t (9:22), forming a fusion gene BCR - ABL on chromosome 22, which has abnormal tyrosine kinase activity. It progresses through 3 stages clinically, which are differentiated by the percentage of blasts. Chronic phase (blast < 10%), accelerated phase (blast 10-19%) and blast crisis phase (>20% blast) [1]. CML can have various complications including bleeding manifestations, recurrent infections, problems due to leucostasis and extra medullary infiltrations [1-3]. Treatment options are Tyrosine kinase inhibitor, uricosuric agents and other supportive measures depending on the disease status. We had one patient who presented with cerebrovascular accident due to cerebral vein thrombosis with hemorrhagic transformation, along with deep vein thrombosis, loss of appetite and significant weight loss. On evaluation he was found to have a massive splenomegaly, maximally elevated white cell count, the highest ever we had come across, with leucoerythroblastic blood picture. Complications were primarily due to leucostasis and he had deep vein thrombosis in addition to cerebral vein thrombosis. He had developed almost all possible other complications seen with CML during the hospital stay. He had a very aggressive course in the hospital with waxing and waning at multiple occasions but eventually made a complete recovery.

Case History

68 years old male from Kerala, India who was working in the middle east for last several years had been symptomatic for six months with tiredness, anorexia, fatigue and weight loss, was getting treatment for gouty arthritis, he was asked to go home and get treated for his illnesses. He was brought straight from the airport to our outpatient section and by the time he was brought he was behaving abnormally. While narrating the history, we noticed that he had deviation of angle of mouth to the right side and on further asking we got a history, which was suggestive of left sided hemiparesis, which neither the patient nor the relatives told us; objects were falling from his left hand and was having difficulty in wearing chappal on the left foot. The patient did not complain of it, and the relatives also noticed that difficulty only after inquiring about it, and we realized that it was due to hemineglect in non-dominant cortical involvement. There was no history of fever, headache, seizures or trauma to head. He was getting treatment for hyperuricemia and HTN for the past two years. On examination he was conscious, co-operative and well oriented, vitals were stable, pallor was present, there was pitting pedal edema on left lower limb and swelling and erythema over the metatarso-phalangeal joint of left big toe, suggestive of gouty arthritis. There were skin and nail changes suggestive of chronic liver disease. Curiously there was massive splenomegaly; spleen was palpable up to the level of umbilicus, which somehow was not noticed by anyone before, in spite of having made several visits before to some clinics for gouty arthritis, in addition there was firm hepatomegaly of 2cm. Neurological examinations revealed minimal upper motor neuron facial palsy on left side, with, exaggerated deep tendon reflexes, grade 4 power and extensor plantar response on left side. Cardiovascular and respiratory system examinations were unremarkable. The clinical possibilities considered were myeloproliferative disorder (? Chronic Myeloid Leukemia / myelofibrosis) with CNS involvement due to Cerebral Vein Thrombosis (CVT) and deep vein thrombosis with possible underlying chronic liver disease.

Laboratory investigations - Hb was 9.4gm%, MCV:84fl, RDW:18.4, TLC:4,69,200/mm^3 (N56 / 30% myelocyte, 6% meta myelocyte, 2% promyelocyte) Platelet:2.88lakhs/mm^3. ESR:100mm, Uric Acid:9.8mg/dL, SGPT:8 IU, Albumin/Globulin:3.7/4; The albumin globulin reversal was concluded as due to coexisting Nonalcoholic Fatty Liver Diseases (NAFLD), since he never had alcohol intake and the viral markers were negative. Serum creatinine was 1.6mg/dL, and the blood urea was 88mg/dL. Plain CT scan of brain showed hemorrhagic space occupying lesion in the right temporoparietal region with some mass effect, which in the clinical context was supportive of our clinical diagnosis of cerebral vein thrombosis with hemorrhagic transformation (Figure 1). The peripheral smear showed leucoerythroblastic blood picture typical of Chronic Myeloid Leukemia (CML) in chronic phase. BCR - ABL quantitative analysis was positive with 100% fusion transcripts, which we got a week after initiation of treatment. MRI brain was done after a few days, which showed a well-defined hyperintense lesion in the right temporo-parietal area, the radiologist suggested only the possibility of acute intracerebral bleed and said in addition that there was nothing to suggest venous thrombosis, in spite of suggesting that diagnosis to the radiologist. We still retained our clinical diagnosis of cerebral venous thrombosis due to the strong clinical suspicion. We did not do MR venogram, for fearing of aggravation of the leucostasis.

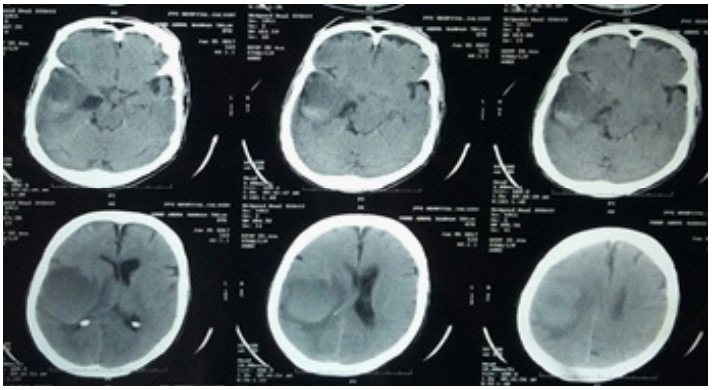

Figure 1: Venous infarct with hemorrhagic transformation with mass effect in right temporoparietal area.

He was started on Imatinib 400mg, Hydroxyurea 500mg three times daily and allopurinol on the first day itself and it was made sure that he was properly hydrated. In spite of the deep vein thrombosis on the left lower limb, anticoagulants were deferred initially in view of CT and MRI findings. Daily monitoring of the hemogram was done, his blood counts started falling and spleen also started to shrink. On the 5th day of hospitalization he developed extensive Deep Vein Thrombosis (DVT) on the left lower limb, then started him on heparin subcutaneous 5000 units 12th hourly, foot end was kept elevated, but 3 days later he had melena, hematuria, worsening of neurological status with features of raised intracranial tension, for which parenteral dexamethasone was used. We were then forced to stop heparin and was given fresh frozen plasma infusions. Along with white blood cells, the hemoglobin and platelets also started falling. Once the total count was within normal limits, hydroxyurea was discontinued after two weeks. In view of persistent melena, low Hb, low platelet counts during the course of treatment, and the possible underlying chronic liver disease, he was given multiple blood and blood products transfusion (Packed cells, FFP and PRP). Once the melena and hematuria settled, we restarted heparin 5000 unit's s/c bid, under the cover of FFP and PRP, in view of the deep vein thrombosis and possible cerebral vein thrombosis as the cause for the hemorrhagic ICSOL and hemiparesis. While on Imatinib he developed severe neutropenia with TLC of 500/mm^3 only (Table 1), which is often described as a side effect of the TKI inhibition; Imatinib was withheld temporarily and was given G-CSF (filgrastim 300 mcg for two days), there was prompt response and the total count reached 2460 and it was stopped. Due to the altered sensorium, during the course, he also suffered from aspiration pneumonia. Then we noticed that he had multiple sharp and loosened teeth, which caused bleeding and ulcers over both lips and tongue and underwent tooth extractions with appropriate precaution. During the third week of hospital stay, he also had upper urinary tract infection with neutropenic sepsis which was managed with multiple antibiotics. All the adverse events were tackled with prompt and optimal treatment and we ensured that he was getting a balanced diet in semisolid or liquid form in view of his teeth problems, during the entire course in the hospital. Adequate hydration also was ensured throughout hospital stay, to reduce the risk of leucostasis and we never thought of doing leukapheresis in view of the critical nature of his illness but continued to focus on hydration and correction of all the compilations.

Date	Hb g/dL	TTLC/mm^3	Platelet count lakhs/mm^3
28/12/16	9.4	469200	2.88
30/12/16	8	380270	3.7
31/12/16	5.9	274510	2.98
4/1/2017	7.7	107350	2.39
5/1/2017	6.2	59760	2
8/1/2017	7.7	22670	1.3
10/1/2017	7.4	16130	1.4
14/1/17	6.4	9830	98000
19/1/17	5.8	5100	46000
21/1/17	5.8	500	40000
23/1/17	7.6	2460	42000
3/2/2017	7.9	6330	92000

Table 1: Hemogram during the course in the hospital.

Once the Hb and platelet started rising and the total count was within normal limit, after four weeks of hospitalization, he was discharged on Imatinib, low dose anti-hypertensive and multi vitamin supplements. Reviewed in the outpatient section after one week with a normal hemogram except mild iron deficiency anemia. One week after discharge, he was reviewed with normal blood reports except for iron deficiency anemia, Iron supplements were added to the treatment. During subsequent follow up there was gradual improvement in all aspects. On subsequent follow up, he was fully conscious well oriented and was able to do all routine activities on his own. The hemiplegia improved, he started walking without support, hemogram was within normal limits, splenomegaly disappeared completely, urea and creatinine became normal and follow up CT showed resolution of lesion of the hemorrhage and the mass effect (Figure 2). While writing this article he has completed two and half years in remission and he had even gone back to work in the middle east for six months and came for review recently. Repeat BCR ABL, quantitative estimation showed zero percentage transcripts.

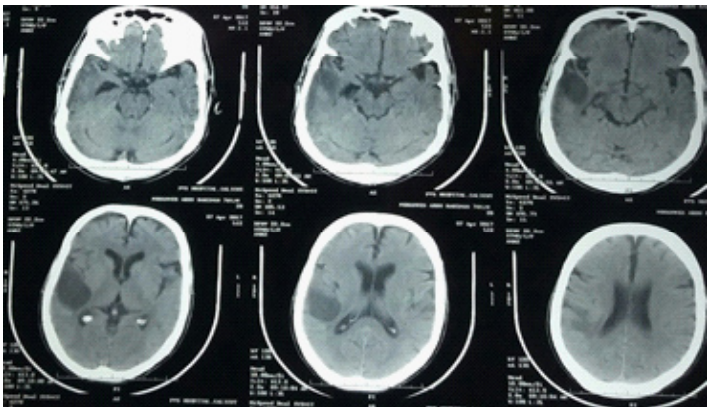

Figure 2: Showing resolution of the original lesion one week after discharge.

Discussion

The patient thus had all the possible manifestations described in CML with leukostasis and all its complications including renal involvement [4]. Cerebral vein thrombosis was considered in view of the clinical setting, the minimal neurological deficit and the evidence of cortical involvement in the form of hemineglect and the coexisting deep vein thrombosis [5]. In addition, he had features of chronic liver disease (skin and nail changes, firm hepatomegaly and albumin/globulin reversal) which also is known to predispose to venous thrombosis by protein c and s deficiency, because these are synthesized in the liver. Cerebral Venous Thrombosis (CVT) has to be suspected always clinically and CT scan and MRI are done only to look for alternate causes [5]. Proof of CVT is often difficult to get considering the dynamic nature of the thrombus which behaves differently at different sites in each patient [5]. With proper clinical diagnosis, timely and appropriate management, including heparin administration, and the use of steroid to reduce cerebral edema, with correction of all the predisposing causes, in spite of all the odds, the patient had a complete recovery. In cases of cerebral vein thrombosis, heparin has to be given, even if there is some hemorrhagic transformation [5]. We are certain that, if we had not suspected CVT and given FFP and Heparin, he would not have recovered. Similar would have been the situation, if there was any delay in initiation of treatment for CML, by waiting for BCR -ABL report. The development of cytopenia during Imatinib therapy is considered as a side effect, but it is in fact due to the prompt response to treatment with imatinib, which knocks out all the BCR-ABL positive abnormal clones, because in this patient 100% cells were BCR-ABL positive. After this the normal clone has to populate marrow, the GCSF given at this stage certainly would have helped in accelerating the process of mobilizing the normal stem cells and eventual recovery. Had we sent the patient for confirmation of CVT with MR venography, it would have only accelerated the cerebral vein thrombosis and the renal involvement by leucostasis. Patients like this need proper and prompt clinical diagnosis and early intervention based on clinical skill, rather than depending on investigations to prove everything. Unfortunately, in the present-day medical practice, clinical skill is lost due to too much of compartmentalization [6]. All the problems in this patient needed 'management' using clinical skill rather than protocol-based therapy alone, as is widely practiced now a day. We could manage him properly, only because of our strong internal medicine background and the rich clinical experience of managing all kinds of complex medical problems at a teaching hospital. We were also looking after large number of hematological problems, including CML for more than three decades. It was a unique set up which we had at the government medical college, Kozhikode. Unfortunately, too much of compartmentalization as is happening now is jeopardizing the clinical skill and patient outcomes these days [7]. The case is reported for the unusual presentation, the complications, the highest ever reported total leucocyte counts in CML, and to emphasize the need for clinical skill in managing patients.

Conclusion

CML, which was once considered an incurable disease, has become almost curable now with effective targeted therapy, but that also requires prompt clinical recognition of the other complications and comorbidities, with timely and appropriate interventions. Clinical skill is the corner stone, even today, for facilitating recovery of such critically ill patients and relying too much on laboratory alone for the confirmation of some clinical problems like cerebral vein thrombosis might adversely affect their outcome. Too much of compartmentalization and focus on protocol-based treatment alone may not be appropriate for better patient outcomes.

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