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Extramedullary blast crisis in chronic myeloid leukemia: A case report

CML with atypical EBC

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Abstract

BACKGROUND

Extramedullary blast crisis in chronic myeloid leukaemia (CML) is an uncommon occurrence that reflects leukemic blast infiltration in regions other than bone marrow. Malignant infiltration of the serosal membranes should be considered as a differential in instances with CML presenting with ascites or pleural effusion.

CASE SUMMARY

A 23-year-old girl with Chronic Myeloid Leukemia came with progressively worsening ascites and pleural effusion despite on first-line tyrosine kinase inhibitor treatment. Her blood work indicated leukocytosis with myelocyte bulge and 2% blasts, while her bone marrow confirmed chronic phase of CML. Ultrasound abdomen had hepatosplenomegaly with ascites. The fluid investigation of both ascites and pleural effusion revealed a neutrophilic predominance with an exudative picture, but no acid fast bacilli or growth on culture. Although hydroxyurea reduced cell counts, it had no effect on ascites or pleural effusion. Repeat investigation of the ascitic and pleural fluid revealed a polymorphous myeloid cell population consisting of myelocytes, metamyelocytes, band forms, neutrophils, and a few myeloblasts. With extramedullary

blast crisis in mind, mutation analysis was performed, and she was moved to Tab dasatinib, which she responded well to. Her symptoms eased, ascites and pleural effusion went away, and her spleen shrank.

CONCLUSION

We mention this case because serosal membrane involvement in CML is extremely rare, with just a few case reports of pleural effusion and ascites published thus far.

Key Words: chronic myeloid leukemia; extramedullary blast crisis; serosal infiltration; ascites; pleural effusion

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Core Tip: Extramedullary blast crises can exhibit diverse presentations, underscoring the importance of clinicians' awareness of possible sites of occurrence. In cases of CML with ascites or pleural effusion, it's essential to consider the possibility of malignant infiltration of serosal membranes as a potential diagnosis. Recognizing these early can lead to timely interventions and management.

INTRODUCTION

Extramedullary blast crisis in chronic myeloid leukaemia (CML) is an uncommon occurrence that reflects leukemic blast infiltration in regions other than bone marrow. The most prevalent site of involvement in EBC is the lymph nodes, followed by bone and skin.(1)

Serosal membrane involvement is exceedingly uncommon in CML, with just a few case reports of pleural effusion and ascites being described to far. We describe a case with

CML on TKI therapy who had extramedullary blast crisis with concomitant ascites and pleural effusion.

CASE PRESENTATION

Chief complaints

A 23 year old female presented to our hospital with chief complaints of progressive distension of abdomen, associated with swelling of legs for 2 mo, and right sided chest pain.

History of present illness

For a few weeks, she had been complaining of non specific malaise, growing weariness, and anorexia.

History of past illness

The patient was diagnosed with CML three years ago and was put on Tab imatinib 600mg once a day. She was compliant with her treatment.

Personal and family history

There was no history of similar illness in her family.

Physical examination

On examination, she was afebrile, with normal vitals. She had pallor and bilateral pitting pedal edema that extended above her ankles. An evaluation of the respiratory system indicated a dull note with reduced breath sounds at the right infraaxillary as well as the infrascapular area. Abdominal examination revealed tense ascites and splenomegaly extending up to umbilicus.

Laboratory examinations

Her initial investigations revealed anemia with haemoglobin of 8.9 g/dL, leukocytosis with white blood cell counts being 68000 with the following differential (P68/L24/B4/E2) and thrombocytosis with platelets 6 Lakhs. Hyperkalemia (5.7), hyperphosphatemia (6.9) and elevated LDH levels (572 IU/L) were also observed. The patient's liver and renal function tests, as well as her coagulation profile and serum procalcitonin, were all normal.

Thoracocentesis was performed under ultrasound guidance and the aspirated fluid was exudative in nature (protein 5.3gm/dL) along with 600 cells/mm^3 with polymorphic preponderance. The SAAG level in ascitic fluid was 0.9, and the cyto-biochemical profile was comparable (300 cells/mm^3, protein 5.1 gm/dL). In pleural and ascitic fluid, ADA was 4.3 and 8.1, respectively. There were no pathogenic organisms or acid fast bacilli found in the pleural and ascitic fluids, and the culture was sterile.

The peripheral smear showed leukocytosis with myeloid bulge with bimodal myeloid population, with both mature and immature myeloid proliferation with 2% blasts. Myelocytes made up 13% of the myelogram, metamyelocytes and band formations were 16%, and 5%, respectively. An impression of CML in chronic phase was reported. NAP score was 24. Her Mantoux, viral markers, thyroid function test and autoimmune profile were unremarkable, while blood and urine cultures showed no growth. The tumour markers CA 125, CEA, CA19-9 were within normal limits.

Imaging examinations

The chest X-ray (figure 1a) confirmed the pleural effusion (right>left) while the ultrasound revealed hepatosplenomegaly with ascites. A contrast enhanced computed CT (figure 2) confirmed the sonographic findings, revealing smooth enhancing peritoneum with omental caking in addition and ruling out any mass or space-occupying lesion.

Her 2D echocardiography was suggestive of mild pericardial effusion with normal ejection fraction.

FINAL DIAGNOSIS

Her ascitic fluid was sent for smear testing, which revealed the presence of malignant cells. It possessed a polymorphous myeloid cell population that included myelocytes, metamyelocytes, band forms, neutrophils, and a few myeloblasts. Keeping this report of ascitic fluid in mind, we studied the pleural effusion and found a similar picture with all kinds of myeloid cells present. In a known case of CML in mind, a possibility of extramedullary blast crisis in the form of ascites and pleural effusion was considered. We also tried a ultrasound-guided FNAC from the sites of omental thickening, but the results were ambiguous.

TREATMENT

She was started on hydroxyurea which reduced cell counts but no improvement in her symptoms. Since the patient was already on imatinib, mutation analysis was done which revealed G250E. She was started on Tab Dasatinib 100mg once a day and was planned for stem cell transplantation. However, the patient was gave negative consent for transplant.

OUTCOME AND FOLLOW-UP

The patient's peripheral smear was repeated one month after switching to dasatinib. There were no immature myeloid cells found. A chest X-ray (figure 1b) and ultrasound abdomen at 3 mo revealed that the pleural effusion and ascites had disappeared, the spleen had shrunk to 12 cm in size, and her overall health had improved. She continues to be on Dasatinib without any significant side effects.

DISCUSSION

Blast crisis in CML is classified according to the place of origin (medullary or extramedullary) and cell type (myeloid, lymphoid, or mixed). At least one of the following(2) characterises the CML blast crisis:

2

20% myeloblasts or lymphoblasts in blood or bone marrow

Large clusters of blast cells in bone marrow biopsies.

The emergence of chloroma

EBC is widely recognised in CML, being present in around 8 - 15% of patients over the course of the illness.(3,4) EBC often manifests as a tumorous mass known as a chloroma, however it can also manifest as a diffuse infiltrate. Lymph nodes (40 – 61% of cases) are the most often affected locations with extramedullary disease, followed by bone (22-37% of cases) and skin or soft tissues (20%).(5) Hepatosplenomegaly is not considered as EBC in CML patients. EBC is particularly common during the accelerated phase of CML or during the blast crisis. This may well be the first manifestation of blast crisis. Extramedullary disease in CML is considered as an indicator of poor prognosis, which should lead to a change in therapy and to the institution of treatments usually reserved for blast crisis.(6)

Serosal membrane involvement in CML is extremely rare, with just a few case reports of ascites and pleural effusion recorded thus far. During the chronic phase of CML, Aleem A *et al* described a patient, who presented with massive ascites, which they believe was caused by mesenteric/peritoneal infiltration. The response to imatinib was outstanding, with a full cytogenetic response and the complete elimination of ascites.(4) Likewise, Deshpande AS reported a case of CML with extramedullary illness manifesting as tense ascites in a 23-year-old girl. Both the ascitic fluid and a peripheral blood smear included all phases of granulocytes and a few blasts. A favourable response was reported after commencing therapy with Imatinib.(7) Ridha N described a CML patient who developed pleural effusion despite on therapy. A diagnosis of extramedullary blast crisis in the form of pleural effusion was established based on cytological investigation of the pleural fluid, which revealed cells with the morphological hallmarks of myeloblasts. They continued with Imatinib, but the patient succumbed to his illness within a month.(8) Nuwal P *et al* described a case of a 26-year-old man with CML who presented with pleural effusion as the initial clinical symptom.(6)

The following are some of the potential mechanisms hypothesized for pleural effusion in CML patients(8,9)

Leukemic infiltration into the pleura that frequently occurs during or soon before bone marrow progression to the blast crisis phase. The lymph nodes, bone, and nerve system are the most commonly affected, with infiltration of the brain, testis, skin, breast, soft tissue, synovial, gastrointestinal tract, ovaries, kidneys, and pleura occurring less frequently. Pleural involvement has been infrequent, and isolated pleural blast crises in the absence of medullary change are extremely unusual.

Extramedullary hematopoiesis is another probable source of pleural effusion in CML, albeit the pleura are an uncommon location for this process. Extramedullary hematopoiesis, as opposed to pleural leukemic infiltration, contains hematopoietic cells of the erythroid, myeloid, and megakaryocytic types.

Pleural effusions in CML can be caused by the probable blockage of pleural capillaries or penetration of interstitial tissue by leukemic cells during uncontrolled leukocytosis, as well as enhanced capillary permeability owing to cytokine release. Predisposing variables including leukostasis and platelet dysfunction which may play a role in CML hemorrhagic effusion.

Non-malignant causes of effusion have also been proposed, including as infection and hypoproteinemia. As a result, this option must be ruled out by blood investigations, using a specific stain to identify bacteria and/or the presence of necrotic material.

Drug-induced pleural effusion is another probable cause of pleural effusion in CML. Dasatinib and imatinib are tyrosine kinase inhibitors that have been shown to have strong anti-leukemic efficacy in CML patients. The pathogenesis remains unclear; however one finding suggested an off-target Tyrosine Kinase Inhibitor influence on the immune system.

The mechanism of ascites could be similar but is yet to be documented in literature due to dearth of cases. Despite our extensive literature search, we could not find a case in which the patient presented with concomitant ascites and pleural effusion as EBC in a case of CML. Moreover, our patient was already on TKI therapy.

The basic objective of CML blast crisis treatment is to return to the chronic phase, with intentions to proceed with allogeneic hematopoietic cell transplantation in the chronic

phase if possible. Treatment varies according to the blast lineage (i.e., myeloid (70%) *vs* lymphoid (30%)).(10,11)

The use of a TKI (with or without chemotherapy) followed by an allogeneic HCT is the chosen treatment in myeloid crisis. According to studies, treating de novo myeloid blast crisis with TKI alone and assessing response is recommended, while if myeloid blast crisis arises when a patient is already on a TKI, provide AML-type induction chemotherapy mixed with a more potent TKI for remission induction.(10,11)

We switched to a second generation TKI in our patient based on mutation analysis, and she had a favourable response. Patients who are presently being treated with a tyrosine kinase inhibitor (TKI) are more likely to experience lymphoid blast crisis. A transition to a second or third generation TKI is required for these individuals. TKIs can be used alone or in conjunction with lower-intensity chemotherapy.

There is a lack of data on which TKI should be utilised as the first line of treatment for patients with blast crisis, regardless of whether the patient is a candidate for HCT. In general, rather than imatinib, treatment with a second generation TKI (e.g., dasatinib, nilotinib) is recommended. If the disease progression/blast crisis happened while the patient was already receiving imatinib for early stage CML, second generation TKIs should undoubtedly be administered. Ponatinib can also be recommended if the progression occurred while the patient was on dasatinib, nilotinib, or bosutinib.

The limitations of our case include a lack of adequate investigations (no genetic tests were performed) at the time of the first diagnosis, as well as the failure to get evidence of chloroma on the USG guided FNAC of the omentum.

CONCLUSION

Extramedullary blast crises can manifest in a variety of ways, and it is critical for clinicians to be aware of potential sites of presentation. Serosal involvement in CML is highly unusual, and concurrent involvement of the peritoneum and pleura is yet to be described. As a result, in instances with CML, an investigation for malignant cells in the fluid should be performed on priority. Clinicians will be better prepared to manage

CML patients who present with blast crisis, taking this atypical presentation into account.

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