Chronic myeloid leukaemia (CML) presenting with pleural effusion

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Abstract

Background: Chronic myeloid leukaemia presenting with pleural effusion as the initial clinical manifestation is very rare and poorly understood.

Case Presentation: We report a 34year old woman with CML (accelerated phase) in whom the initial clinical presentation was pleural effusion. She had a four week history of chest pain and cough, one week history of progressive difficulty in breathing and a history of weight loss and recurrent low-grade fever. On examination, she was a chronically ill-looking young woman in respiratory distress, pale, with tachycardia, tachypnoea and stony dull percussion notes and absent breath sounds on the right hemi-thorax. She also had splenomegaly and hepatomegaly. An initial diagnosis of disseminated Tuberculosis was ruled out by a full blood count and bone marrow aspiration cytology suggestive of a chronic myeloid leukaemia and confirmed by positive BCR-ABL transcripts. She was commenced on cytoreduction but demonstrated features of Tumour Lysis Syndrome after initiation of cytoreduction despite prophylaxis, warranting multidisciplinary care and haemodialysis. When she became clinically stable, she was referred for enrolment into Glivec International Patient Assistance Program (GIPAP) and she was commenced on Imatinib mesylate 600mg daily on account of CML in accelerated crisis. However, she was lost to follow up after her enrolment into the program.

Conclusion: Pleural effusion as the initial clinical manifestation of chronic myeloid leukemia (CML) is very rare so high index of suspicion should be maintained in the context of these unusual manifestations of CML.

Key words: chronic myeloid leukaemia, extramedullary, pleural effusion, tyrosine kinase inhibitors

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Introduction

Chronic myeloid leukaemia (CML) presenting with pleural effusion as the initial clinical manifestation is very rare and pleural effusion in CML patients is not only rare but also poorly understood.[1,2]

While the exact pathogenesis of pleural effusion in CML is poorly understood, some of the possible mechanisms include direct leukaemic infiltration of the pleural cavity, pleural space involvement in extramedullary haemopoiesis (EMH) and non-leukaemic pathways.[1,3]

This paper reports a rare case of accelerated phase CML presenting with pleural effusion.

Case Presentation

The patient was a 34 year old married Tiv woman of Benue state whose occupation was farming. She presented on referral from a private hospital on 1st October, 2022 with complaints of chest pain and cough, of four weeks duration and progressive difficulty in breathing of one week duration. She also had a history of weight loss, recurrent low-grade fever and progressive loss of energy since the onset of symptoms. She had no close contact with a person with chronic cough or diagnosed with tuberculosis. There was no history of bone pains, pruritus, night sweat and mucosal bleeds. She did subsistence farming and rarely used fertilisers or agro-chemicals on her farm. She also did not drink alcohol or use tobacco in any form. She did not have any significant medical or surgical history prior to index illness.

A physical examination revealed a chronically ill-looking young woman in moderate respiratory distress, pale, anicteric, acyanosed, and no significant peripheral lymphadenopathy.

Cardiovascular examination revealed a tachycardia (pulse rate of 108beats per minutes-bpm) with regular rhythm and full volume, normal blood pressure, jugular venous pressure was not elevated while her cardiac apex beat was in the normal position with normal heart sounds and no murmurs. She had a respiratory rate of 32 cycles per minute (cpm), stony dull percussion notes and absent breath sounds on the right hemi-thorax suggestive of a pleural effusion. She also had splenomegaly (4cm in length below the left costal margin), hepatomegaly (6cm below the right costal margin in the mid-clavicular line) with no ascites. A diagnosis of suspected Disseminated Tuberculosis was entertained by the Pulmonology unit which admitted her.

An urgent chest radiograph obtained confirmed a massive right sided pleural effusion and a chest tube was urgently inserted by the General surgeons to relieve her

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dyspnoea while the pleural fluid aspirate was sent for microscopy, culture, sensitivity and protein estimation.

Abdominopelvic ultrasound scan showed a right sided pleural effusion, hepatosplenomegaly, enlarged peri-pancreatic and peri-aortic lymph nodes, dilatation of the pelvicalyceal system of the right kidney (hydronephrosis) with both kidneys being echogenic, a right ovarian cyst and no ascites.

Pleural fluid protein was 39mg/dl (exudative) while culture showed no pathogenic growth. GeneXpert was negative for Mycobacterium tuberculosis.

Other investigations done included; Electrolytes/ Urea/Creatinine (E/U/Cr) which was thus: Na=128 mmol/L (135-145mmol/L), K=3mmol/L (2.9-5.0 mmol/L), Cl=92mmol/L (98-105mmol/L), HCO_3=30 mmol/L (22-29mmol/L), Urea=8.7mmol/L (2.5-6.5 mmol/L), Creatinine = 235µmol/L (53-106 µmol/L).

Full Blood Count (FBC) showed a total white blood cell count (TWBC) of 210 x 10^9/L with differential counts of; 4% lymphocytes, 94% neutrophils and 2% mixed differential count (combined eosinophils, basophils and monocyte counts), haemoglobin concentration (Hb) was 9.2g/dl, haematocrit (HCT) of 25.4% and platelet count (PLT) of 295 x 10^9/L while peripheral blood film (PBF) showed marked leucocytosis with predominance of myeloid cells, showing a full spectrum of maturing myeloid cells. There was no eosinophilia or basophilia.

On account of the FBC and PBF, the Haematologists were invited to review the patient. Following evaluation by the haematologists, a repeat PBF and bone marrow aspiration for cytology was done. Both films showed a hypercellular marrow with myeloid hyperplasia, with the myeloid cells showing a full spectrum of maturing myeloid cells. However, the typical peaks of myelocytes and mature neutrophils were not noted and blast count was not increased. Few eosinophils were noted and there was no basophilia. Although, this morphological finding did not describe a typical chronic phase CML, due to the leukaemia-range white cell count, CML was maintained as a differential diagnosis; hence an assessment of a neutrophilic leukaemoid reaction to rule out chronic phase CML was made and sample for BCR-ABL was sent to a referral molecular laboratory to confirm CML. Meanwhile she was commenced on cytoreduction on account of hyperleucocytosis with Hydroxyurea 1g b.d and prophylaxis for tumour lysis syndrome with Allopurinol 300mg daily.

However, on the 8th day of admission, her clinical condition deteriorated as she became restless, increasingly drowsy during the day and disoriented, whereas she stayed awake at night talking irrationally. There was also associated vomiting and itching of the body. Oxygen saturation (SPO_2) was 84% and Glasgow Coma Score (GCS) had dropped from 15/15 to 10/15.

An urgent PCV done was 18%, TWBC was 18.1 x 10^9/L; differential counts thus: L=0.8 x 10^9/L, M=0.2 x 10^9/L, N=17.1 x 10^9/L while E/U/Cr showed increasing urea and creatinine values (Urea= 19.2mmol/L, Cr=314µmol/L, Na=128mmol/L, K=4.3mmol/L, Cl=93mmol/L, HCO_3=20mmol/L).

An assessment of type 1 respiratory failure, worsening anaemia and pre-renal acute kidney injury (AKI) complicated by uraemic encephalopathy was made by the Nephrologists and she was commenced on intra-nasal oxygen, transfusion of packed cells with conservative management of the AKI. Samples were also sent for serum calcium, uric acid and phosphate.

Cytoreduction was withheld for continued monitoring of her WBC with serial FBCs.

A repeat E/U/Cr done the next day, showed worsening hyperkalaemic metabolic acidosis, increasing values of urea and creatinine (K=6.8mmol/L, HCO_3= 11mmol/L, Urea=24.2mmol/L, Cr=347µmol/L) with an Estimated Glomerular Filtration Rate (EGFR) suggestive of end stage renal disease (ESRD) despite conservative management and corrections of electrolyte imbalances. There was also hyperuricemia with hypocalcaemia and hyperphosphataemia indicative of a Tumour Lysis Syndrome while urinalysis showed leucocyturia, nitriuria, proteinuria and haematuria.

Following the above findings, she had two sessions of haemodialysis (HD), while allopurinol was increased to 600mg daily and she made marked clinical and laboratory improvement following haemodialysis. The FBC showed a TWBC of 6.8 x 10^9/L; L= 0.7 x 10^9/L, M=0.9 x 10^9/L, N=5.2 x 10^9/L, Hb=7.4g/dl, HCT= 22.3%, PLT=388 x 10^9/L while E/U/Cr showed Na= 143mmol/L, K =2.9mmol/L, Cl=100mmol/L, HCO_3 = 29mmol/L, Urea =6.4mmol/L, Cr = 138µmol/L.

The BCR-ABL result came out positive about two weeks after the sample was sent; BCR-ABL major transcript p210 (b2a2 and b3a2) detected.

When she was clinically stable, she was discharged by all managing teams (Haematology, Pulmonology, Nephrology, and General surgery) after 30 days on admission in stable clinical condition. Full Blood Count at discharge was thus: TWBC=18.1 x 10^9/L, Hb=8.7g /dl, HCT=26.6%, PLT=388 x 10^9/L.

She was also referred to the Obafemi Awolowo University Teaching Hospital Complex (OAUTHC) in Ile-Ife, Osun state, the only center in Nigeria providing free Imatinib (Glivec®, Novartis International AG, Basel, Switzerland) courtesy the Glivec International Patient Assistance Program (GIPAP).

She presented at OAUTHC one month after her discharge (approximately two months after her first

presentation at our hospital), where a repeat PBF showed evidence of CML in accelerated phase and she was commenced on Tabs Imatinib 600mg daily. She was thereafter referred back to us for follow up using serial PBFs. However, patient was lost to follow up as she did not present for any clinic visit and was unreachable till the time of this report.

Discussion

CML has some notable unusual first time clinical presentations as documented in the reports of previous studies which included recurrent painful priapism, syncope and myocardial infarction, *Haemophilus influenzae* pneumonia, chronic obstructive airway exacerbation and new-onset atrial fibrillation with rapid ventricular rate.[4,7]

Pleural effusion is a rare manifestation in CML and has been documented by only few researchers[1,3] and the strength of this case is that it was an unusual first time presentation of CML in our facility.

This patient presented with an exudative pleural effusion and other co-morbidities; renal impairment, ovarian cyst, intra-abdominal lymphadenopathy hence, she was initially being evaluated for a possible disseminated tuberculosis. However, the finding of a leukaemoid reaction on PBF raised the suspicion of CML which was further confirmed by BMA cytology and BCR-ABL test.

It is reported that, during the course of CML, about 37% of patients will develop extramedullary disease (EM) in sites such as lymph nodes, spleen or meninges but typically, excludes the pleura.[8]

The pathogenesis of pleural effusion in CML is poorly understood but few mechanisms are proposed;

1. **Leukaemic infiltration into the pleura;** this usually occurs at the time of or just prior evolution to blast crisis. Pleura involvement is rare, with isolated pleural blast crisis in the absence of medullary transformation being extremely rare. When the pleural effusion is caused by leukaemic pleural infiltration, the differential white blood cell count of the effusion is identical to that of the peripheral blood, while the fluid cytology reveals leukaemic blasts.[1] Furthermore, leucocyte alkaline phosphatise (LAP) known to be low in CML granulocytes of peripheral blood has been reported to be normal in the granulocytes of pleural effusion.[1] However, the differential white blood cell count of the effusion with cytology and LAP were not done for this patient.
2. **Bleeding into the pleural cavities**: this may cause a pleural reaction and hence, an effusion. Predisposing factors include leukostasis and platelet dysfunction therefore the cytologic findings will be that the ratio of red blood cells to nucleated cells in the blood and effusion should be similar.[1] This patient's pleural effusion was not bloody.
3. **Pleural extramedullary hematopoiesis:** although, the pleura are rare sites for EMH, cytologic finding in this case will include haematopoietic cells of the erythroid, myeloid, and megakaryocytic cells even though one lineage can predominate.[1]
4. **Non-malignant causes, such as infection and hypoproteinemia.** The presence of necrotic debris and/or the positive identification of micro-organisms by special stains may suggest an infectious process so an infectious process should be excluded.[8]

   The negative GeneXpert and microbial culture helped to exclude tuberculosis and other infections as a cause of her pleural effusion.
5. **Drug induced**. Dasatinib, nilotinib and imatinib are tyrosine kinase inhibitors (TKIs) with significant anti-leukaemic activity in CML patients but their use has been associated with pleural effusion in 15% cases in one study.[8] Our patient was treatment naïve when she presented with an effusion so this was also unlikely to be a cause.

From the above, the first pathogenetic mechanism may be the most likely explanation for this patient's pleural effusion. Unfortunately, a pleural fluid cytology was not done to confirm this mechanism which may have also indicated the presence of an accelerated phase CML even when there was no evidence in the bone marrow.

Pleural effusion in CML is an indicator of poor prognosis and there is no effective standard therapy for pleural effusion in CML.[2] Periodic pleural fluid withdrawal (thoracoentesis), pleurodesis, along with the treatment of underlying CML have been listed as options for management.[2,3] Moreso, management of blast crisis of CML remains a challenge, especially in those with EM presentation even with TKIs and the goal of therapy is to restore the patient to the chronic phase of the disease.[3] Hence, CML blast crisis can be treated with TKI alone in higher doses or in combination with myelosuppressive chemotherapy regimen for acute leukaemias.[9,10] The best outcomes may be observed in patients who successfully regress to the chronic phase and undergo a stem cell transplant.[11]

Our patient was commenced on Imatinib 600mg daily on account of CML in accelerated phase but she could not be followed up as she did not return to the clinic after the visit to OAUTHC, Ile-Ife, Osun state.

Conclusion

In conclusion, although pleural effusion as the first clinical manifestation of CML is rare, awareness of this seemingly uncommon presentation by both physicians

and haematologists is critical for the prompt diagnosis and management of such cases. A cautious approach and high index of suspicion are considered imperative in the context of these unusual extramedullary manifestations of CML.

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