A case of chronic myeloid leukaemia in blast transformation with leukemic ascites

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SUMMARY

Chronic Myeloid Leukaemia (CML) is a disease characterised by a distinctive marker that is the Philadelphia Chromosome and an ability to transform into blast phase, which confers a poor prognosis. The median survival was reported to be between three to six months in correlation to blast phase. Extramedullary involvement with CML to sites such as pleural, meningeal and bones have been reported. We report a case of 41-year-old man who was diagnosed with CML in blast phase and presented with ascites. Ultrasound of abdomen showed coarse echotexture of liver suggestive leukaemic infiltration to the liver. The liver profile was severely deranged and associated with coagulopathy. Flow cytometry analysis of the peritoneal fluid revealed presence of myeloblasts consistent with CML in blast crisis with leukaemic ascites. Bone marrow biopsy also confirmed disease transformation. He received standard induction chemotherapy for acute myeloid leukaemia with dose modifications based on liver enzymes performance. Our case highlights an unusual presentation of CML in blast crisis with leukaemic ascites and the challenges in managing cytotoxic treatments due to the liver infiltration.

KEY WORDS:
CML, blast phase, liver infiltration, leukaemic ascites

INTRODUCTION

Chronic myelogenous leukaemia (CML) is a myeloproliferative disorder with a unique marker that is Philadelphia Chromosome with translocation between long arms of chromosome 22 and 9.[1] Arion *et al.* reported that this mutation is detected up to 95% of newly diagnosed cases. Median survival is improved by 88% when treated with tyrosine kinase inhibitor. Even though the disease is commonly diagnosed during average age of 55 to 60 years in Western population, it is diagnosed in younger population in Malaysia with incidence rate of one in 100 000 patients.[1, 2] Extramedullary presentation of CML in blast phase has been reported and our article illustrated atypical presentation of CML with leukaemic ascites.[3]

CASE REPORT

A 41-year-old Indian man presented with symptomatic splenomegaly and leucocytosis of 43 x 10^9/L in 2008. Examinations of peripheral blood and bone marrow were consistent with the diagnosis of chronic myeloid leukaemia (CML) in chronic phase. The cytogenetics and molecular analysis confirmed the presence of t(9;22) and BCR-ABL fusion protein. Sokal score was 1.38. He received Imatinib 400mg daily, however there were treatment interruptions for poor compliance and dose reductions due to Grade 4 thrombocytopenia and therefore achieved only minimal cytogenetic response. Due to resource limitation, second or third generation tyrosine kinase inhibitors were not available to him. The patient had no matched sibling on HLA typing screening for consideration of allogeneic stem cell transplantation.

He presented in January 2015 with fever and left upper quadrant pain. Computed tomography (CT) of abdomen showed splenic abscess. Microbiology and serology tests for tuberculosis, meliodosis, bacteria, fungal and cytomegalovirus were negative. He improved with intravenous meropenem and discharged well. A repeated CT abdomen demonstrated resolved splenic abscess. Due to persistent bicytopenia with haemoglobin of 6.5 x 10^12/L and platelets of 5 x 10^9/L, a bone marrow biopsy was performed. Flow cytometry was inconclusive due to haemodiluted marrow blood. The trephine was coarsely fibrosed (Grade 3 reticulin). Immunohistochemical (IHC) stain with CD117 showed presence of >20 percent blasts, consistent with blast transformation. In addition, chromosome analysis and FISH identified BCR/ABL fusion in 41% of the interphase nuclei analysed with major fragments detected from RT-PCR analysis for *BCR-ABL* mRNA. However, the patient declined any definitive cytotoxic treatment at that point.

Four months later, he returned with fever, abdominal distension and diarrhoea for three weeks. There were bilateral pedal oedema with orthopnoea and reduced exercise tolerance. On general examination, he was febrile but haemodynamically stable. On physical examination, there was gross ascites with generalised tenderness and bilateral pedal oedema up until mid-shin. There was no other stigma of chronic liver disease. Otherwise, the rest of physical examination was normal. Blood investigations revealed further elevation of total white cells to 37.9 x 10^9/L and similar bicytopenia features with haemoglobin of 5.0g/dL and platelets of 34 x 10^9/L. There was circulating blasts of 2%.

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Table I: Summary of case reports for CML with extramedullary leukaemic infiltration.

Author, Year	Patient's Demographic	CML Phase	Extramedullary Sites	Treatment	Patient Survival from Diagnosis
Kim HW, et al, 2006	83, Male	Chronic	Pleural	Gefitinib, Hydroxyurea	6 months
Eden OB, Innes EM, 1978	13, Female	Blast	Meningeal	Vincritisne, Prednisolone	Multiple haematological relapse within 12 months
Our patient	40, Male	Blast	Ascites	Cytarabine, Idarubicin	Five months

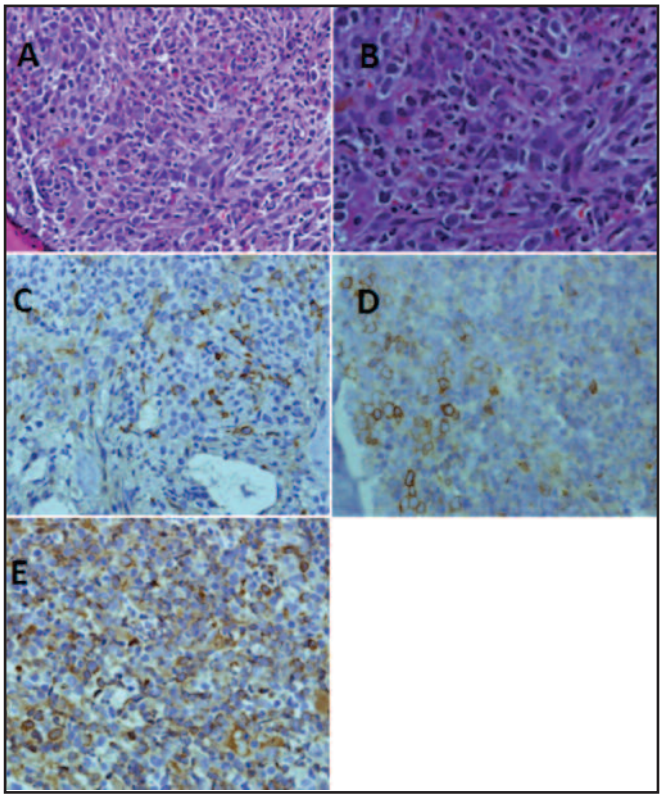

Fig. 1: Haematoxylin and eosin stain of trephine biopsy, which showed presence of more than 20% blasts. (A) At x 40 magnification. (B) At x 60 magnification. Immunohistochemical staining of the trephine biopsy was positive for CD34 (C), CD 117 (D) and MPO (E).

The renal function was deranged with urea of 11.6mmol/L and creatinine of 119mmol/L. Alkaline Phosphatase was elevated to 358U/L with concomitant coagulopathy, PT of 18.8 seconds and INR of 1.62 ratio. However, albumin and bilirubin were within normal range with 23g/L and 22µmol/L respectively.

Flow cytometry analysis of peritoneal fluid was positive for CD34, cyMPO (heterogeneous), CD33, CD38 (heterogeneous), CD11b (heterogeneous), CD13 (heterogeneous), D=CD33, CD38 (heterogeneous) and CD56 (heterogeneous). However the blast was negative for HLA – DR, cyCD79a, cyCD3, CD3, CD7, CD14, CD15, CD16 and CD64, thus suggesting presence of myeloblasts. Biochemical analysis revealed fluid albumin of 15g/L and total protein of 27g/L. Due to the raised peritoneal fluid polymoprhs, he also received treatment with intravenous ceftriaxone for spontaneous bacterial peritonitis.

Ultrasound scan (USS) of abdomen showed hepatomegaly of 16cm with coarse echotexture, splenomegaly of 16.3cm with normal echogenicity. Free fluid was seen in the peritoneal cavity and hepatorenal space (Morrison's pouch). A liver biopsy was deemed too risky due to concomitant coagulopathy and severe thrombocytopenia.

Following diagnosis of CML in blast phase with leukaemic ascites and infiltration to the liver, the patient finally consented to chemotherapy. He received standard induction chemotherapy with Cytarabine and Idarubicin. Due to initial concern regarding possibility of cirrhosis based on the USS appearance, the anthracycline dose was modified to limit the hepatotoxicity. Close monitoring of abdominal girth circumference showed reduction of ascites however the ensuing complications were stormy. He developed Grade 4

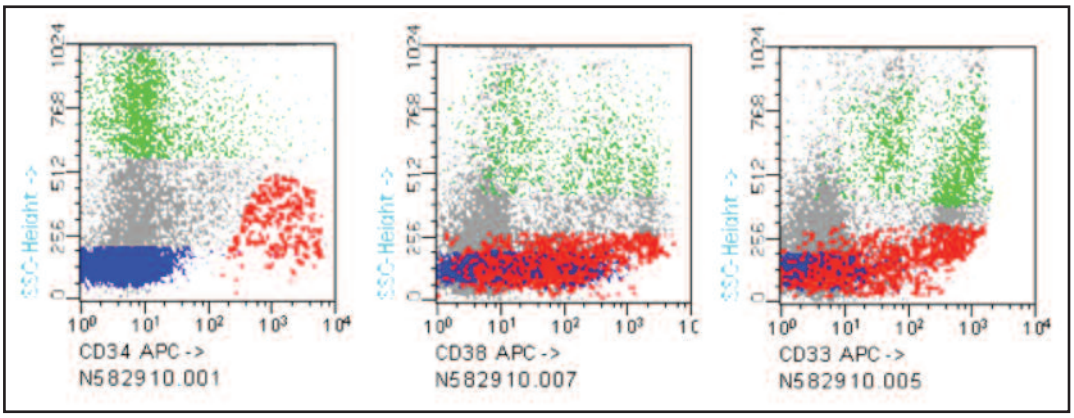

Fig. 2: Flow cytometry analysis of peritoneal fluid, which was positive for CD34, CD33 and CD38 (heterogeneous).

febrile neutropenia, massive pleural effusion with invasive fungal pneumonia and pulmonary tuberculosis (TB). He was unable to receive full anti-TB treatment due to the deranged liver function tests and instead received bridging therapy consisted of Streptomycin, Erythromycin and Ciprofloxacin instead. Isoniazid was later introduced after ALT improved.

A bone marrow biopsy re-assessment showed morphological remission with Grade 2 fibrosis. Due to poor platelet recovery and intercurrent infections, the consolidation chemotherapy could not be delivered timely. Unfortunately, the leukaemia relapsed after 42 days post induction with peripheral leukocytosis of 93 x 10^9/L and increased blasts seen on CD34 and CD117 stain on trephine. He opted for palliative therapy and succumbed to the illness after a month later.

DISCUSSION

CML is a myeloproliferative disorder characterized by Philadelphia chromosome that is detected in up to 95% of newly diagnosed cases. In addition more than 80% of cases were detected during chronic phase in which 25% remained asymptomatic.[1] There are three phases of CML, chronic, accelerated and blast phase but commonly characterized with biphasic course as most of patients were diagnosed either at chronic or blast phase.[1] Even though chronic phase CML is associated with good prognosis, Antin documented that a median survival for blast phase is only three to six months.[4]

The transition of CML from chronic to blast phase is contributed by few factors such as clonal evolution, new mutations and gene amplification with most of the disease progression is associated with clonal evolution by 40%.[1] Even though the Philadelphia chromosome is the hallmark of CML, Arion et al. outlined on few alterations of this unique marker that leads to blast phase such as variant of t(9;22), trisomy 8, anomalies on chromosome 17 and occurrence of second Philadelphia chromosome. Moreover, a regulatory gene such as p53, which plays a major role with apoptosis of cells, may be inactivated and hence lead to faulty cellular progression and thus blast phase.[1]

Extramedullary manifestation of chronic myeloid leukaemia in blast phase had been reported such as in lymph nodes, bones and central nervous system.[3,5] However, infiltration to gastrointestinal system e.g. liver and peritoneal fluid such as in our patient was rare. Below is a summary of case reports for CML with extramedullary leukaemic infiltration.

In addition, Kim *et al.* outlined the spectrum of extramedullary disease established on cytomorphologic features that are based on proportion of blast to granulocytic mature cells. As for our patient, his trephine biopsy revealed granulocytic maturation ranging from blast to mature cells and hence pointing towards mature category.[3] Other categories are blastic in which the cytomorphologic features are predominate of blasts and considered immature when there are presence of non-blastic myeloid precursors.[3]

CONCLUSION

In conclusion, this case illustrates the challenges in managing leukaemic ascites in the presence of liver infiltration, severe thrombocytopenia and coagulopathy. Insertion of a pigtail catheter for continuous ascetic drain was difficult due to the bleeding risks. Furthermore, the chemotherapy dose had to be modified to limit the hepatotoxicity in an already infiltrated liver. In depth counselling in young CML patients should take place regularly to guide them through therapeutic directions.

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