Med & Health Aug 2024; 19(2): 671-677 https://doi.org/10.17576/MH.2024.1902.26

CASE REPORT

Marrow Fibrosis in Epstein-Barr Virus Infection, Masking Preleukaemic Phase of Acute Lymphoblastic Leukaemia: A Case Report

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Received: 29 Dec 2023 / Accepted: 23 Jan 2024

ABSTRAK

Fasa pre-leukemia bagi penyakit leukemia limfoblastik akut (ALL) ialah satu kejadian yang jarang dan boleh berlaku pada kanak-kanak serta remaja. Biasanya, fasa ini dicirikan dengan keadaan pansitopenia dan hipoplasia sumsum tulang, diikuti dengan fasa leukaemik dalam peredaran darah periferi dalam masa 2 tahun. Kami melaporkan satu kes fibrosis sumsum tulang yang berlaku pada seorang pesakit berumur 25 tahun dengan jangkitan virus Epstein-Barr (EBV). Pesakit ini mula-mula hadir ke hospital kerana demam dan mempunyai pansitopenia semasa pemeriksaan awal. Tiga bulan kemudian, dia disahkan menghidap ALL apabila filem darah periferinya menunjukkan neutropenia dengan kehadiran 59% sel leukemia. Kes ini menekankan kepentingan pemantauan rapi dalam kes pansitopenia yang menunjukkan penemuan yang tidak spesifik dalam pemeriksaan sumsum tulang. Pemeriksaan sumsum tulang berulang harus dipertimbangkan untuk kes pansitopenia yang berlanjutan dan tidak dapat dijelaskan, untuk membolehkan pengesanan awal ALL dengan cepat.

Kata kunci: Fibrosis dalam sumsum tulang; jangkitan virusEpstein-Barr; leukemia limfoblastik akut

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ABSTRACT

Preleukaemic phase of acute lymphoblastic leukaemia (ALL) is a rare occurrence that might affect children and adolescent. Typically, it is characterised by pancytopenia and bone marrow hypoplasia, followed by a leukaemic phase in peripheral circulation within 2 years' time. We herein reported a case of marrow fibrosis in a 25-year-old patient with Epstein-Barr Virus (EBV) infection, whom presented with fever and incidental findings of pancytopenia. He was later found to have ALL when his peripheral blood findings showed neutropenia with presence of 59% blasts after 3 months of presentation. This case highlighted the importance of close monitoring of pancytopenia cases with non-specific findings in bone marrow examination. A repeat bone marrow examination should always be considered for cases with persistent unexplained pancytopenia, to allow early detection of overt ALL without delay.

Keywords: Acute lymphoblastic leukaemia; Epstein-Barr virus infection; myelofibrosis

INTRODUCTION

Preleukaemia is described as a condition which the bone marrow does not produce enough blood cells, and this bone marrow dysfunction eventually progresses to the development of acute leukemia. This condition is typically characterised by a transient period of pancytopenia, which persists for few weeks to several months, followed by spontaneous recovery or corticosteroid induced recovery of the blood counts (Liang et al. 2015).

Traditionally, the term preleukaemia is commonly associated with myeloid neoplasm in the past. It was first used to describe the myelodysplastic syndrome which is prone to progress to acute myeloid leukaemia. Following the advancement in molecular genetics, preleukaemic was also used to describe individuals with germline mutation (such as *RUNX1*, *CEBPA* or *GATA2*) or some clonal haematopoietic mutations (such as *DNMT3A*, *TET2* or *IDH1/2* mutations) which have been identified to have a higher risk of developing frank acute myeloid leukaemia (Koeffler & Leong 2017).

On the other hand, literature on preleukaemia in lymphoid leukaemia is rather less. Preleukemic acute lymphoblastic leukaemia (pre-ALL) is observed in about 2% of acute lymphoblastic leukaemia (ALL) cases. It is a rare occurrence that usually affects children and adolescence. These cases are preceded by fever, infections, transient non-specific anaemia and resembling aplastic anaemia. Bone marrow examination is usually required in these cases to establish the causes of pancytopenia (Zimmermannova et al. 2017).

The pathogenesis of pre-ALL and

mechanism of temporary remission of pancytopenia are not well understood. In more recent years, it was postulated that the pre-ALL stage is a time window when the covert preleukaemic clones in ALL, usually of prenatal origin, convert to ALL leukaemic cells via acquisition of additional genetic events or infection (Hein et al. 2020). From eight ALL cases analysed by Zimmermannova et al. (2017), this preleukaemic period can last from 6 weeks to 17 months, before the patient is diagnosed with acute leukaemia.

Secondary marrow fibrosis refers to marrow fibrosis that is associated with underlying neoplastic or non-neoplastic condition such as myeloid or lymphoid haematological malignancy, autoimmune diseases or infections (Khatuni et al. 2021). It results from diseases that stimulate fibroblastic activity in the marrow and it can be reversible once the stimulant is withdrawn. It is not uncommon to see the suppression of normal haematopoiesis following this kind of fibroblastic/scarring response in the marrow (Cain 2018).

We herein reported a case of marrow fibrosis in patient with Epstein-Barr Virus (EBV) infection, whom developed ALL three months after presentation.

CASE REPORT

A 25-year-old Bidayuh man, not known to have any medical illness, presented with 6 days history of sore throat, fever and odynophagia. On physical examination, there was mild conjunctival pallor and bilateral tonsillar enlargement (grade III) with exudate. There was no lymphadenopathy or hepatosplenomegaly. He was treated for acute exudative tonsillitis. Full blood count showed pancytopenia with haemoglobin (Hb) 9.8g/dL, total white cell count (TWC) 1.9 $x10^9$/L, absolute neutrophil count (ANC) of 0.06 x 10^9/L, and platelet count of 109 $x10^9$/L. Reticulocytopenia was noted with reticulocytes count of 0.6 x 10^4/L. Peripheral blood film verified the pancytopenia with no blast or abnormal lymphoid cells seen. Infective screening for Hepatitis B, Hepatitis C, human immunodeficiency virus (HIV) and syphilis were negative. EBV serology sent during admission was positive for both Immunoglobulin (Ig) G and IgM. Bone marrow aspiration was a dry tap with very few haematopoietic cells were seen. Trephine biopsy revealed cellular marrow with fibrosis (Figure 1a) and reactive features (increased in T cells and plasma cells). There was

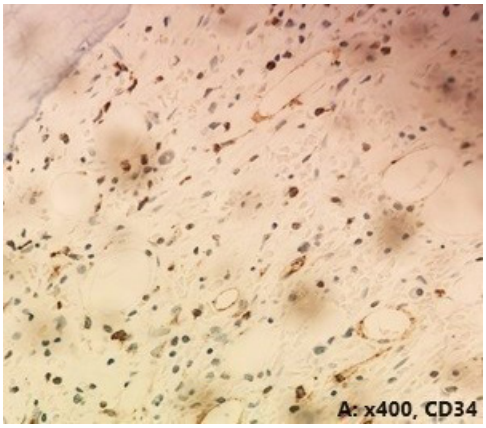

FIGURE 1a: Trephine section during initial presentation. Slight increase in CD34 positive cells as shown by CD34 immunohistochemical stain

no evidence of marrow infiltration. Nevertheless, a slight increase in CD34 positive cells (<10%) was observed (Figure 1b).

Cytogenetic and molecular study by a mutltiplex RT-PCR assay (HemaVision 28N, DNA Diagnostic, Denmark) were not helpful due to inadequate analysable spreads for analysis and low concentration of nucleated cells. In the ward, patient was treated as neutropenic sepsis and was given two weeks of antibiotic, one

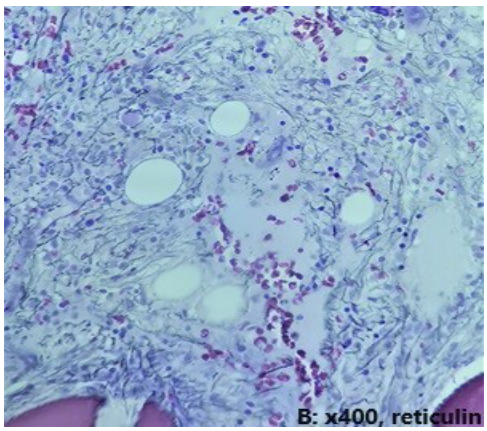

FIGURE 1b: Trephine section during initial presentation. WHO Grade 1 fibrosis as highlighted by reticulin stain

week of antifungal and antiviral. Upon discharge, his blood counts improved. Two months later during follow up, patient's Hb and platelet counts had normalised to Hb of 13.8g/dL and platelet 312 x 10^9/L. However, there was still neutropenia (0.33 x 10^9/L) with lymphocytosis (5.93 x 10^9/L). Peripheral blood film at that time showed leucoerythroblastic picture with many reactive lymphocytes. One month later, patient presented to a private center for gastritis. Full blood count showed neutropenia (ANC 1.77 x 10^9/L, Hb 14.0g/dL and platelet 164 x 10^9/L). Peripheral blood film revealed 59% of blasts which were small in size and had high nuclear to cytoplasmic ratio (Figure 2).

Immunophenotyping performed on the peripheral blood showed presence of 50.3% blast population gated at CD19 positive and low side scatter. The blast cells expressed cTdT, CD34, CD10, CD38, CD58 and

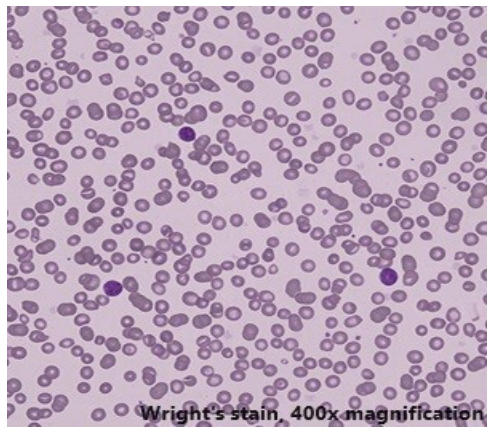

FIGURE 2: Lymphoblast seen in the peripheral blood film

aberrant marker CD13, consistent with Precursor B-cell ALL (common ALL). Patient was then transferred to another centre for further management. Bone marrow examination confirmed the diagnosis of B-lymphoblastic leukemia with presence of 36% blasts in bone marrow aspirate (Figure 3A & B). Patient was started on chemotherapy. However, he succumbed to disease complication two months later.

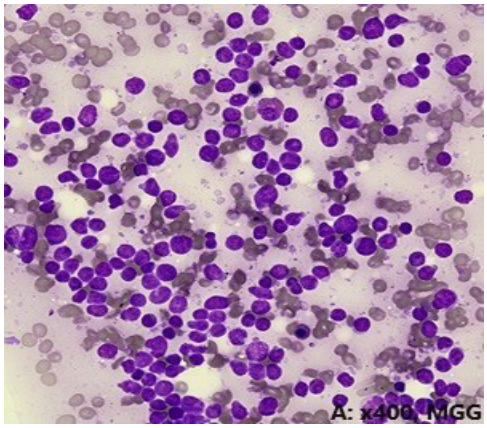

FIGURE 3a: During the diagnosis of acute leukaemia. Trephine imprint showed many blastic looking cells

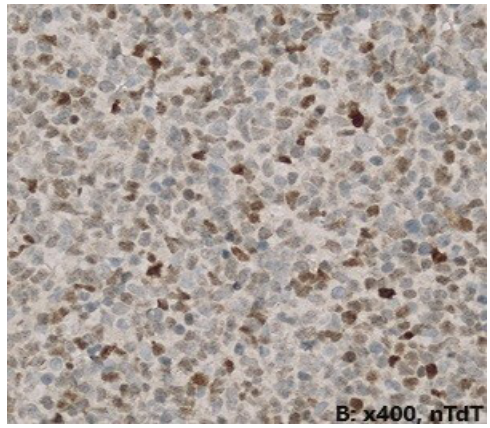

FIGURE 3b: During the diagnosis of acute leukaemia. Trephine section showed proliferation of blasts as demonstrated by nTDT immunohistochemical stain

DISCUSSION

Preleukemia is a haematologic condition which occurs prior to the development of acute leukemia. This condition is commonly associated with acute non-lymphoblastic leukemia. Historically, this term was first used to describe the myelodysplastic syndrome which have a tendency to progress to acute myeloid leukemia (Koeffler & Leong 2017). However, few studies have revealed that certain cases of ALL may manifest preceding symptoms of haematopoietic disorders (Liang et al. 2015). Pre-ALL is also known as preleukemic ALL, aleukemic prodrome of ALL, aplastic presentation of ALL or hypoplastic preleukemia in other names, were reported mostly in children and only a few cases among adults since 80s (Boonchalermvichian et al. 2012).

The prevalence of pre-ALL is low, which accounts for 1.3-2.2% of ALL cases in paediatric patient (Liang et al. 2015). This rare event usually affects children and adolescents, although there are few reports documented in adults, there are no documented prevalence of pre-ALL in adult population. This condition was previously described to be commonly occur in those children under the age of 10, have a female predominance, clinical features of fever, transient pancytopenia and responding to corticosteroid therapy, laboratory findings of normo- or hypoplastic marrow with fibrosis, and have a similar prognosis as compared to *de novo* ALL (Li et al. 2008). Typically, patient presents with pancytopenia which lasting for weeks or months, followed by a transient recovery of peripheral blood counts spontaneously or after active treatment, before they enter the acute leukemia phase (usually within 6 months) (Boonchalermvichian et al. 2012). Besides the gender predominance and age, this case shared a similar clinical progress as described in the literature, which is

pancytopenia and hypoplastic marrow with fibrosis, followed by a transient recovery of blood counts before progression to leukemic phase.

EBV is one of human herpesviruses that infects B-lymphocytes and epithelial cells. EBV infection is usually asymptomatic and has viral latency. It is known to cause infectious mononucleosis, and is strongly associated with lymphoma, as well as gastric and nasopharyngeal carcinomas (Mrozek-Gorska et al. 2019; Poulson et al. 2020). Occasionally, this viral infection may be complicated by transient cytopenia (Khan et al. 2013) or even rarely, myelofibrosis (Politano et al. 2008).

A study published by Ahmed et al. (2012) from Sudan in year 2012 described that significant number of patients (41.5%) with ALL showed evidence of active EBV replication, although the positivity rate is far below the 80% for Hodgkin lymphoma in developing world. On the other hand, in a case report published in year 2007, Karapinar et al. (2007) reported a 12-year-old girl with EBV infection, presented with pancytopenia and her bone marrow examination revealed haemophagocytosis and myelofibrosis with grade 4 reticulin fibrosis. Politano et al. (2008) also described in a case report published in year 2008, a 21-year-old lady with pancytopenia and EBV infection, her bone marrow biopsy showed scattered areas of gelatinous atrophy and diffuse reticulin fibrosis consistent with grade 2 myelofibrosis. These case studies share the similarities of cytopenia associated with EBV infection and myelofibrosis as in this case.

Preleukemia in ALL is difficult to diagnose early, and maybe easily neglected or misdiagnosed when complicated with infection. Bone marrow features may be masked by reactive features from the overwhelming infection. In this case, the pancytopenia during initial presentation could be the prodrome of ALL. However, due to the active EBV infection and no notable morphological abnormalities on the peripheral blood film, the pancytopenia was attributed to the EBV infection and the myelofibrosis from the EBV infection.

CONCLUSION

In summary, this case highlighted the importance of close monitoring particularly in pancytopenia cases with non-specific findings, for example slightly raised blasts or marrow fibrosis, as seen in this case. Close monitoring and follow up with repeat bone marrow examination should always be considered for cases with persistent unexplained pancytopenia, to allow early detection of overt ALL without delay.

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