Malaysian J Pathol 2007; 29(2) : 113 – 117

CASE REPORT

Bone marrow necrosis preceding infantile acute lymphoblastic leukaemia

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Abstract

We report a case of bone marrow necrosis preceding infantile acute lymphoblastic leukaemia (ALL). Bone marrow necrosis is a rare antemortem event and has been known to be present in many conditions, notably in haematological malignancies like acute lymphoblastic leukaemia. This case was a 6-month-old Chinese boy who was referred to Hospital Universiti Kebangsaan Malaysia for further investigation of pancytopaenia, high-grade fever, bloody diarrhoea and petechial rashes for one week. His first bone marrow aspirate revealed bone marrow necrosis. His clinical condition improved after ten days. However, his full blood picture then revealed the presence of 5% blast cells. His subsequent marrow 2 weeks later revealed acute lymphoblastic leukaemia (FAB-L1) and immunophenotyping showed precursor B acute lymphoblastic leukaemia-null type. He was started on United Kingdom Acute Lymphoblastic leukaemia (UK ALL) Infantile Leukaemia protocol, however, he defaulted treatment after 3 days. Mode of presentation, mechanism of disease and laboratory investigations and outline of treatment will be discussed.

Key words: infantile leukaemia, bone marrow necrosis, acute lymphoblastic leukaemia.

INTRODUCTION

Bone marrow necrosis is a rare event in the antemortem period. There are multiple causative factors. It is usually associated with haematological malignancies (leukaemia, lymphoma), infections and sickle cell crises. Other causative factors are autoimmune disorders and disseminated carcinoma. The presence of bone marrow necrosis in leukaemia usually confers a poor prognosis but this observation has been contradicted in several other reports.[1,2]

Acute lymphoblastic leukaemia (ALL) is among the hematological malignancies commonly associated with bone marrow necrosis. Few reports from other investigators have seen this association in childhood acute lymphoblastic leukaemia and although it is related to poor prognosis, some authors reported survival of these patients following chemotherapy.[1,2] We report here an unusual case of bone marrow necrosis preceding infantile acute lymphoblastic leukaemia in a 6-month-old child.

CASE REPORT

MTJ, a 6-month-old Chinese boy was referred from a private hospital in Malacca for further investigation of pancytopaenia. He presented initially as an outpatient in Malacca with vomiting, diarrhoea and high-grade fever of one week duration. Subsequently, petechial rashes were noted in the lower limbs, which spread to other areas of the body.

Physical examination revealed an infant who appeared to be irritable and always crying when handled. Petechial rashes were noted over both lower limbs and trunk. He was febrile with a temperature of 39°C. Blood pressure was 104/46 mm Hg. Multiple shotty cervical and inguinal lymph nodes were felt bilaterally. Abdominal examination revealed hepatosplenomegaly of 5cm each below the right and left subcostals respectively. Cardiovascular and respiratory examinations were unremarkable.

Initial laboratory investigations showed pancytopaenia, with a haemoglobin level of

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32g/L (140-170g/L). The white blood cell count was 2.0 x 10^9/L (4-11.0 x 10^9/L) and the platelet count was 76 x 10^9/L (150-400 X 10^9/L). The peripheral blood film showed atypical lymphocytes and thrombocytopaenia (Figure 1). The level of lactate dehydrogenase (LDH) was 371 U/L (reference range: 211-423 U/L) and alanine transaminase level was 53 U/L (less than 44 U/L). The alkaline phosphatase level was elevated to 122 U/L (32-104 U/L) and the serum protein was 73 g/L (67-88 g/L). His initial corrected calcium was 2.57 mmol/L (2.14-2.54 mmol/L). A bone marrow aspirate and trephine biopsy was performed from three different sites at the left and right tibia**,** and revealed necrotic marrow fragments and cells with bare nuclei (Figure 2). Within a week, the full blood count showed improvement of his haemoglobin to 116g/L, the white cell count to 27.3 X 10^9/L and the platelet count to 503 X 10^9/L. However, the peripheral blood film showed the presence of 5% blast cells**,** which morphologically appeared to be lymphoblasts. Two days later, the total white cell count was 127 X 10^9/L and the peripheral blood film showed 67% blast cells. The lactate dehydrogenase level was raised to 979 U/L. His calcium and alkaline phosphatase levels were elevated to 2.84 U/L and 227 U/L respectively.

A repeat bone marrow aspiration revealed more than 90% blast cells and morphologically, a diagnosis of infantile acute lymphoblastic leukaemia (FAB classification – L1) was reached. (Figures 3 & 4). Immunophenotyping showed precursor B- acute lymphoblastic leukaemia with CD 10 (CALLA) negativity (Null ALL) (Figure 5). The cytogenetic analysis revealed 46XY and there was no chromosomal abnormality detected. The molecular study demonstrated a negative bcr-abl mRNA transcript. He was started on UK ALL protocol for Infantile Leukaemia. He defaulted treatment after 3 days of starting the chemotherapy.

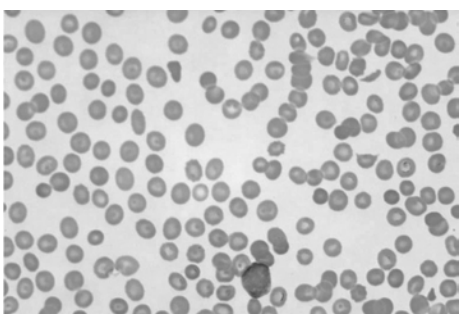

FIG. 1: The initial peripheral blood film, which shows pancytopenia and presence of atypical lymphoid cells. (MGG X 40)

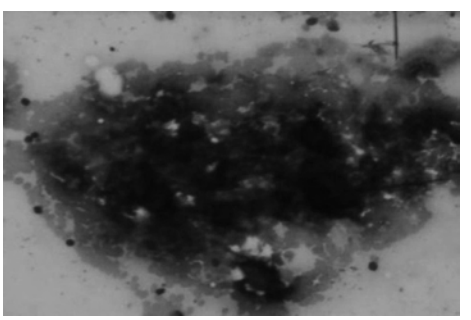

FIG. 2: The initial bone marrow aspirate, which shows a necrotic marrow fragment, devoid of hemopoietic cells (MGG X 20)

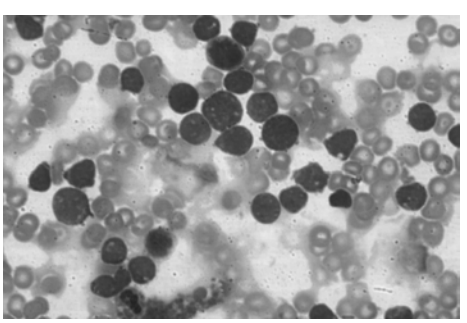

FIG. 3: Peripheral blood film showing presence of lymphoid blast cells with high nucleocytoplasmic ratio and multiple nucleoli. (MGG X 40)

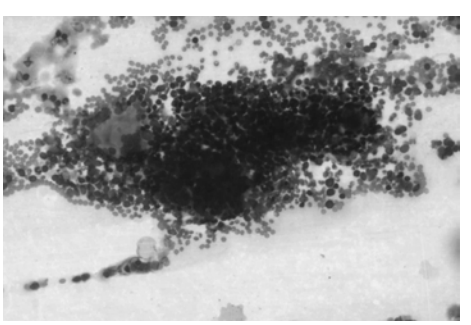

FIG. 4: Hypercellular bone marrow aspirate infiltrated by lymphoid blasts.(MGG X10)

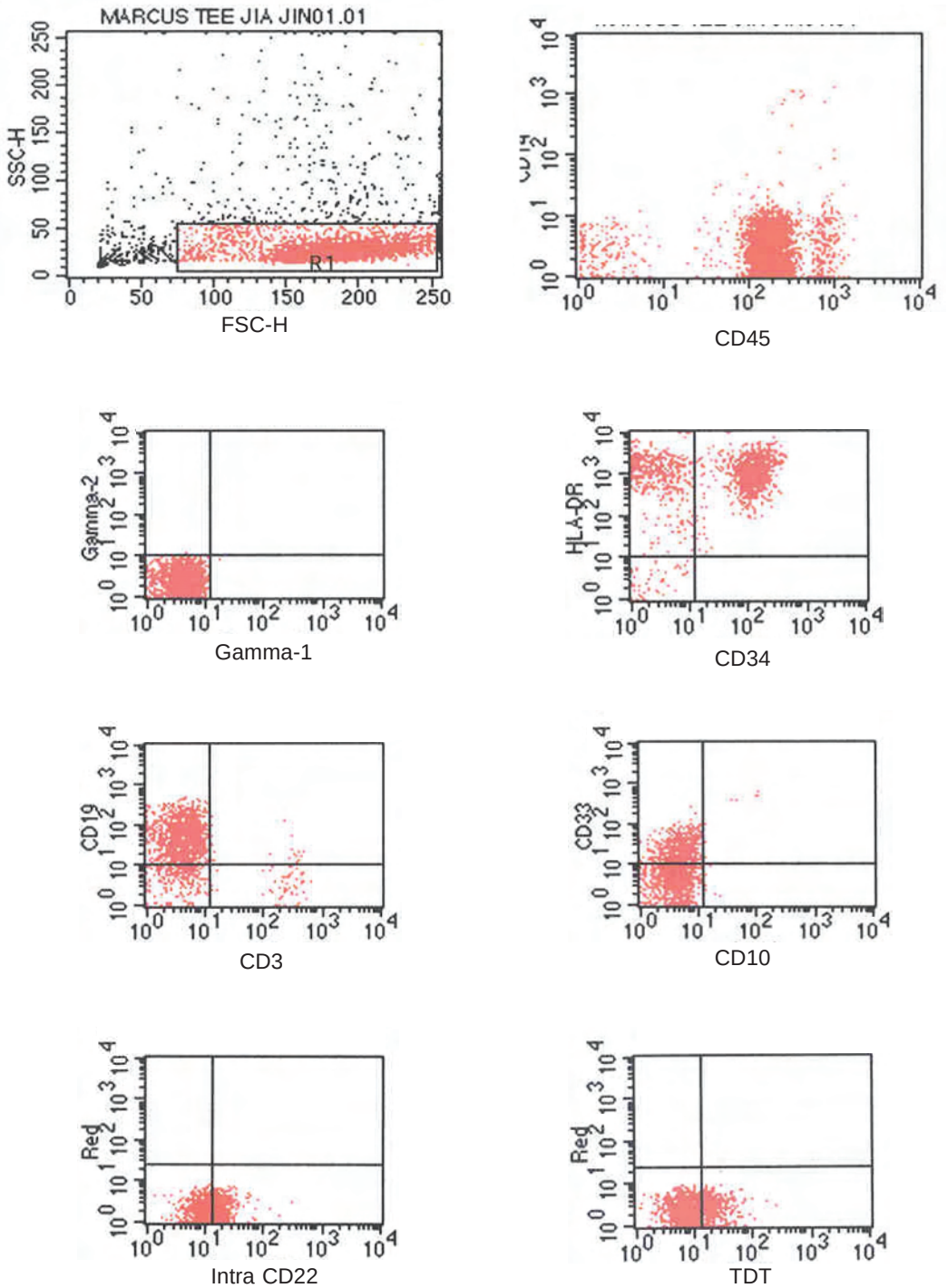

FIG. 5: Dual coloured immunophenotyping shows the gated cells express positivity towards CD19, HLA DR, CD34, intra CD22 and TdT. The gated cells do not express CD10. The immunophenotyping is consistent with B-precursor acute lymphoblastic leukaemia (Null type).

DISCUSSION

Antemortem bone marrow necrosis (BMN), a rare event in childhood, is even rarer in infancy. Many conditions can cause bone marrow necrosis. The incidence of BMN is variable (0.5%-3**%).** Mostly, it is associated with sickle cell anaemia, severe infections or malignancy, notably haematological malignancies such as acute leukaemia and lymphoproliferative diseases.[3]

Layla *et al* reported that BMN occurs most commonly in Hodgkin's disease, followed by metastatic carcinoma, acute lymphocytic leukaemia, acute myelocytic leukaemia and non-Hodgkin lymphoma.[3] A few cases have been reported in association with positive antiphospholipid antibody syndrome, systemic lupus erythematosis, previous irradiation, anti-neoplastic therapy and non-malignant conditions such as disseminated intravascular coagulation and anorexia nervosa. [3]

The common symptoms of BMN reported in a review were: bone pain (80% of cases), fever (70% of cases) and fatigue which were associated with anaemia and thrombocytopaenia.[4]

In children, acute lymphoblastic leukaemia has been the major causative factor for bone marrow necrosis and it is regarded as a preleukaemic phase.[5] In adults, it has been associated with a wider variety of conditions, from infection to malignancy. However, unlike in children, BMN usually occurs at the terminal phase in adult ALL.

Bone marrow necrosis is described as necrosis of the haemopoietic cells or necrosis of the neoplastic cells that have replaced normal marrow cells. The stromal elements of the bone marrow can also be necrotic. Bone marrow necrosis usually results from microvascular failure, often in association with a hypercellular marrow. When the microvasculature has been restored, there is removal of necrotic material by phagocytosis, followed by reconstitution of the bone marrow with proliferating capillaries and fibroblasts. Repopulation of the marrow by normal haematopoietic tissue is the rule.[4] The chemical mediators that are associated with bone marrow necrosis are tumour necrosis factor (TNF) and C-reactive protein. A high concentration of TNF in the blood may act as a mediator of necrosis.[6] Knupp *et al* reported two cases of cancer with extensive marrow necrosis and these cases revealed high levels of TNF measured by plasma cytotoxicity assay, which is comparable to levels of TNF in lethal sepsis. Thus TNF may be used as a marker to help in establishing diagnoses or monitoring cases of bone marrow necrosis in the future. The rise in C-reactive protein levels can also serve as a marker in bone marrow necrosis.[7] Hypercalcaemea has been seen in association with marrow necrosis as has also been demonstrated in our case.[8,9]

Two cases of acute lymphoblastic leukaemia with bone marrow necrosis had been reported, which showed complex translocation involving chromosomes 2, 6, 8, 14 and 9.[10] Chromosome 2 translocation is consistently seen in ALL FAB-L3 in the variant of the Burkitt associated translocation. Few authors have also reported the presence of bone marrow necrosis in Philadelphia chromosome positive acute lymphoblastic leukaemia.[11]

The bone marrow aspirate in BMN is usually abnormal as seen in this case. Microscopically, there is amorphous eosinophilic material, and the cells lose their normal staining characteristics.[4] In other reviews, the trephine is usually more helpful in determining the diagnosis of bone marrow necrosis, since a larger volume is sampled and the architecture of the bone marrow is preserved. However it is the reverse in this case, where aspirate was more helpful. Reports from other investigators showed that the appearances in the trephine biopsies were dependent on the underlying causative factor. In the trephine biopsy, bone marrow necrosis is characterized by gelatinous transformation and necrosis of myeloid tissue, focal hypoplasia, and a background of amorphous eosinophilic material. [4] The BMN is graded based on the percentage of the diameter of the biopsy showing necrosis. [4] However, in our case, the trephine was inconclusive and did not show of any of the above features, which could be due to sampling or technical error. The bone marrow aspirate, cytochemistry and immunophenotyping results proved the causative factor of the bone marrow necrosis was infantile B- precursor acute lymphoblastic leukaemia, CD10 (CALLA) negative- null ALL.

The occurrence of bone marrow necrosis in infantile acute lymphoblastic leukaemia is rare. There is no report available from other investigators that describe the association of bone marrow necrosis and infantile leukaemia. The youngest case reported is an 18-month-old girl.[12] Generally the presence of bone marrow necrosis has always been regarded as a poor prognostic index, but some researchers think

otherwise. Macfarlane *et al* (1986) reported four cases of ALL preceded by BMN which went into remission following standard chemotherapy treatment and with complete marrow healing.[2] Niebrugge *et al* (1983) reported two similar cases and the patients also went into remission following chemotherapy.[1] Infantile leukaemia itself in comparison with childhood acute lymphoblastic leukaemia carries a poorer prognosis, even with adequate treatment.

Infantile leukaemia display unique biological and clinical features that provide important insights into the mechanisms governing normal and aberrant haemopoiesis in the fetus and young children, as well as reasons for the increased rate of treatment failure compared with older children.

Infantile acute lymphoblastic leukaemia is usually associated with high leukocyte count at presentation, hepatosplenomegaly and central nervous system involvement.[13] The immunophenotype is usually that of immature B- lineage precursors and is characterized by the lack of CD10 expression, and the co-expression of myeloid associated antigens[13] as is seen in our case**.** Infantile ALL is also usually associated with a high frequency of myeloperoxidase gene expression, which actually signifies that the classic form of infantile ALL originates in a stem cell that is not fully committed to lymphoid differentiation.[13] Molecular studies show the frequency of ALL1/MLL/HRX gene rearrangements is very high, as predicted by the high frequency of t (4,11), the translocation involved where the fusion gene is situated.[13]

Among infants, the occurrence of CD10 negativity, co-expression of myeloid markers, ALL1/MLL/HRX rearrangement and an age of less than 6 months are all associated with poor prognosis.[13]

We believed that our case is among one of the rare cases of infantile leukaemia preceded by bone marrow necrosis. Further study into the chemical mediators, mechanism and pathophysiology governing bone marrow necrosis and its relationship with infantile leukaemia is indicated.

REFERENCES

1. Niebrugge DJ, Benjamin DR. Bone marrow necrosis preceding acute lymphoblastic leukaemia in childhood. Cancer 1983; 52: 2162-4.
2. Macfarlane SD, Tauro GP. Acute lymphoblastic leukaemia in children presenting with bone marrow necrosis. Am J Hematol 1986, 22:341-6.
3. Layla B, Mohammed BS. Bone marrow necrosis-report of five cases and review of the literature. Ann Saudi Med 2000; 20:78-82.
4. Semra P, Melek E, Fikri B, Sinan Y, Suzan Z, Berksoy S,Filiz AB. Bone marrow necrosis : Clinicopathologic analysis of 20 cases and review of the literature. Am J Hematol 2002;70: 300-5.
5. Sills RH,Stockman JA III. Preleukaemic states in children with acute lymphocytic leukaemia. Cancer 1981, 48: 110-2.
6. Knupp C, Pekala H. Extensive bone marrow necrosis in acute leukaemia. Am J Hematol 1988, 29: 215-21.
7. Grutzmeier S, Malm C. CRP concentration in patient with acute leukaemia and bone marrow infarction. Med Oncol Tumor Pharmacotherapy 1988; 5(3):199-200.
8. Ranaghan L, Morris TCM, Desai ZR, Markey GM. Bone marrow necrosis. Am J Pathol 1994; 47:225-8.
9. Ranaghan L, Morris TC. Bone marrow necrosis. Am J Hematol 1994;.47:225-8.
10. Terpos E, Konstantinopoulos K. A new complex translocation (2; 19; 6) (q13; p13; p12) in a case of de novo acute lymphoblastic leukaemia with t (8; 14) (q24; q32) and bone marrow necrosis. J Hellenic Soc Haematol 2000; 2: 104-6.
11. Kwong YL, Pollock A, Wei D, Lie AKW. Philadelphia chromosome positive acute lymphoblastic leukaemia masquerading as asymptomatic bone marrow necrosis. Pathology 1994; 22:183-5.
12. Bevilacgua G, Abdessa A. Bone marrow necrosis foreshadowing acute lymphoid leukaemia. Am J Hematol 1985; 7 (3): 228-33.
13. Andrea B, Giuseppe C. Biological and therapeutic aspect of infant leukaemia. Blood 2000; 96: 24-30.