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CASE SERIES

Juvenile myelomonocytic leukaemia: a case series

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Abstract

Juvenile myelomonocytic leukaemia (JMML), previously known as juvenile chronic myeloid leukaemia (JCML) is a rare, myelodysplastic – myeloproliferative disease typically presenting in early childhood. This disorder is difficult to distinguish from other myeloproliferative syndrome such as chronic myeloid leukaemia (CML) because of the similarities in their clinical and bone marrow findings. However, because of its unique biological characteristics such as absolute monocytosis with dysplasia, absence of Philadelphia chromosome or BCR-ABL fusion protein, hypergammaglobulinaemia and raised fetal haemoglobin level, this disorder does not satisfy the criteria for inclusion in the CML or chronic myelomonocytic leukaemia (CMML) group, as seen in adult patients. We describe a series of three patients with JMML, who had almost similar clinical and laboratory findings, and discuss the difficulty in the classification and treatment of the disease.

Keywords: Juvenile myelomonocytic leukaemia, myelodysplastic – myeloproliferative disease

INTRODUCTION

Juvenile myelomonocytic leukaemia (JMML) is characterized by excessive growth of exclusively myelomonocytic cells in both mature and immature forms. Patients with JMML usually present before the age of 2 years with hepatosplenomegaly, lymphadenopathy, infection and skin disease. The diagnosis requires the absence of the Philadelphia chromosome or BCR-ABL fusion protein, monocytosis of more than 1 x 10^9/l on peripheral blood and bone marrow blast count of less than 20%. Further evidence includes an elevated fetal haemoglobin level, white cell count of more than 10 x 10^9/l, myeloid precursors on peripheral blood, hypergammaglobulinaemia, detection of clonal abnormality and *in vivo* hypersensitivity to granulocyte colony stimulating factor (GM-CSF).[1] Other pathological findings include infiltration of various non-haemopoietic organs (skin, lungs, intestines) with leukaemic monocytic cells. There is also increased incidence of monosomy 7 as well as neurofibromatosis type 1 abnormalities. Cytogenetic abnormalities have been detected in patients with JMML of which monosomy 7 is the most frequent abnormality.[1]

JMML constitutes less than 2% of childhood leukaemias and conventional chemotherapy rarely results in durable responses, with a median survival of less than 2 years.[2] Long term survival, however has been reported after allogeneic bone marrow transplantation.

JMML patients rarely undergo transformation to a blast crisis, and death is usually a result of infection or organ failure due to infiltration by monocytes and macrophages.[3] The worst prognosis group is those patients over the age of 2 years, with a low platelet count and a high fetal haemoglobin level.[2,4]

CASE REPORT

Patient 1: An 8-year-old boy presented with recurrent diarrhoea, abdominal pain and leucocytosis. He was diagnosed to have CML and referred for further management. Clinically he had generalized lymphadenopathy and hepatosplenomegaly. Full blood count on admission showed leucocytosis (32.3 x 10^9/l) with thrombocytopenia (31 x 10^9/l). His peripheral blood smear showed a left shift with monocytosis and presence of 3% blast

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cells. NAP score was raised (150/100). Lactate dehydrogenase (LDH) was significantly high (1571 μ/L). Haemoglobin F was normal: 0.9%; unfortunately, the immunoglobulin levels were not determined. The bone marrow aspiration showed hypercellular marrow with dyserythropoietic and dysmegakaryocytic changes. The granulocytic series showed marked hyperplasia. Cytogenetic analysis showed presence of trisomy 8. DNA analysis for BCR-ABL gene was negative. The patient was given intravenous fluids at double his maintenance requirement and allopurinol. He was planned for chemotherapy with the AML BFM 87 protocol. Unfortunately the parents requested for supportive treatment at their local hospital.

Patient 2: This 3-year-old boy had a history of recurrent upper respiratory tract infection for 4 months associated with loss of appetite and loss of weight. Physical examination on admission showed that he was febrile, pale with hepatosplenomegaly. His full blood count showed anaemia (6g/dl), leucocytosis (30 x 10^9/l) with thrombocytopenia (59 x 10^9/l). His peripheral blood smear also showed a left shift with monocytosis and 15% blast cells (Figures 1 and 2). NAP score was normal. Both LDH and Haemoglobin F were elevated: 1812 μ/L and 60.4% respectively. The patient also had hypergammaglobulinaemia: IgG 4960 mg/dl (550-1000), IgM 161 mg/dl (40 – 80) and IgA 247 mg/dl (35 – 75). A bone marrow aspirate biopsy revealed hypercellular marrow with granulocytic hyperplasia (Figures 3 and 4). The erythropoiesis and megakaryopoiesis was depressed with marked dysplastic features. The differential count were: erythroid precursors 10%, neutrophils 19%, promyelocytes 17%, myelocytes 26%, metamyelocytes 18% and blast cells 10%. Cytogenetic analysis showed presence of trisomy 8 (Figure 5). DNA analysis for BCR-ABL gene was negative.

Chemotherapy (AML BFM 87 protocol) was started but the patient had to receive two courses of induction chemotherapy before achieving morphology remission. His sibling was HLA – identical but both parents were not keen for allogenic bone marrow transplantation (BMT). He relapsed after completion of consolidation. He was reinduced with a course of mitoxantrone and attained remission again but transformed into AML during maintenance chemotherapy. The patient was subsequently given chemotherapy

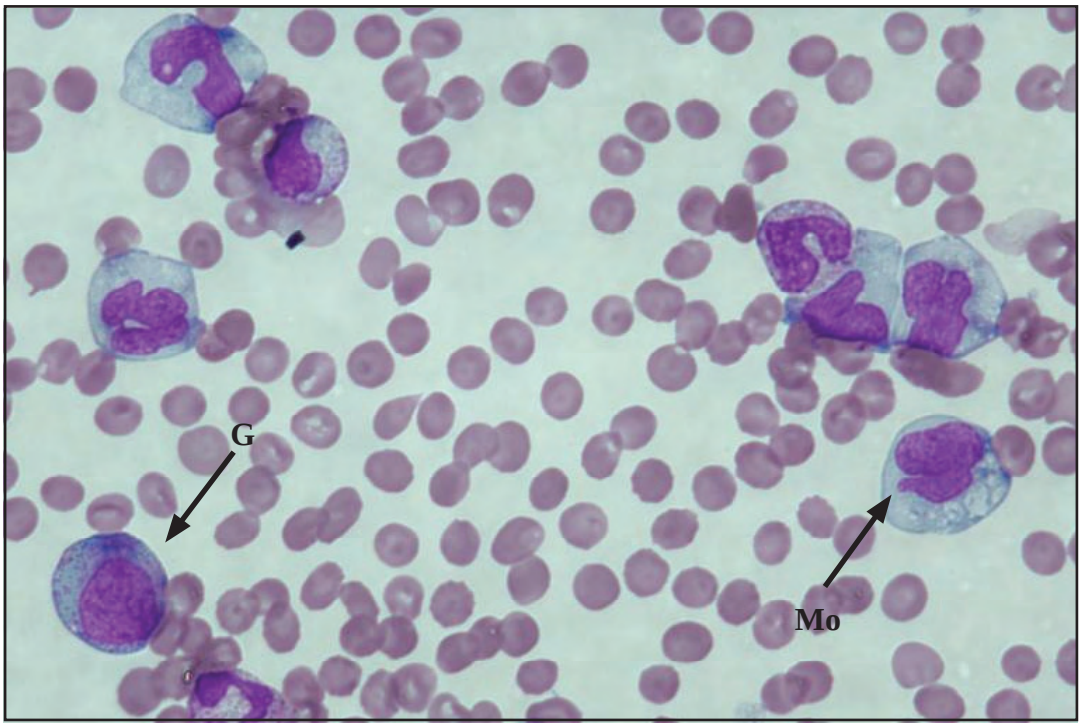

FIG. 1: Peripheral blood film of patient 2 showing immature granulocytes (G) and monocytes (Mo). Wright stain X 400

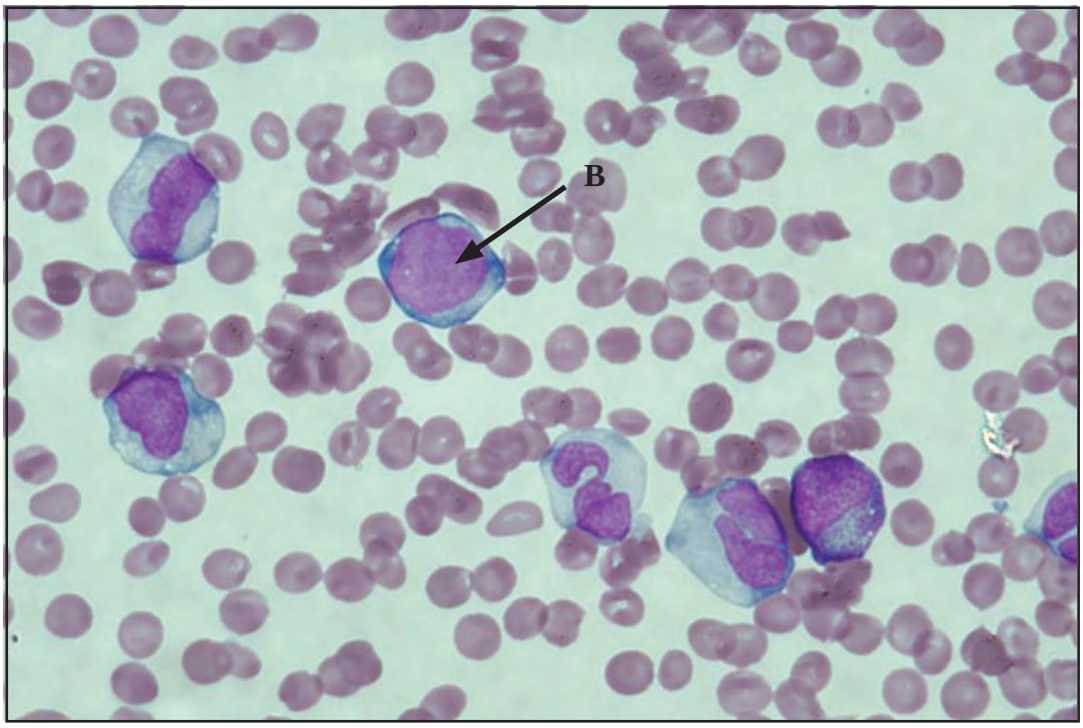

FIG. 2: Another field of the same film showing presence of blast cells (B). Wright stain X 400

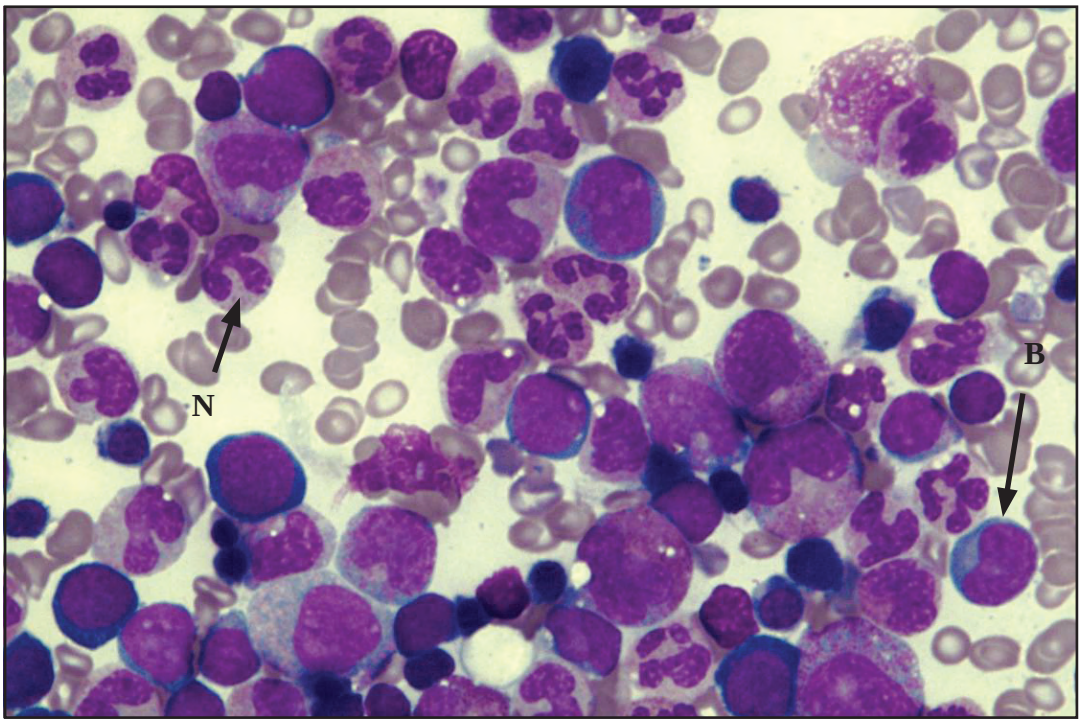

FIG. 3: Bone marrow aspiration of patient 2 showing granulocytic hyperplasia with dysplastic neutrophils (N) and presence of blast cells (B). MGG x 400

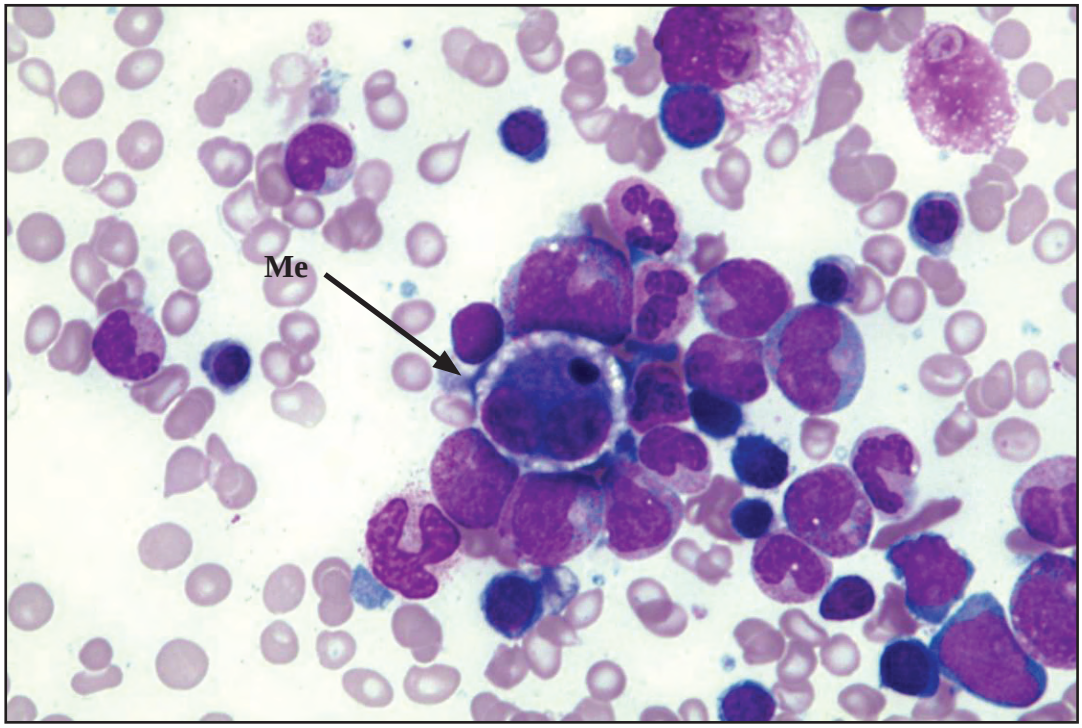

FIG. 4: Another field of the same marrow smear showing presence of dysplastic megakaryocytes (Me). MGG X 40

comprising fludarabine and cytarabine (FLAG regime) and he achieved morphological remission for the third time. At that point of time, the parents consented to the option of BMT. Unfortunately, he developed an episode of febrile neutropenia and finally succumbed.

Patient 3: A 4-year-old boy presented with recurrent suppurative cervical lymphadenopathy associated with petechiae and leucocytosis. Physical examination showed that he was pale, had generalized petechiael rash with generalized lymphadenopathy and hepatosplenomegaly.

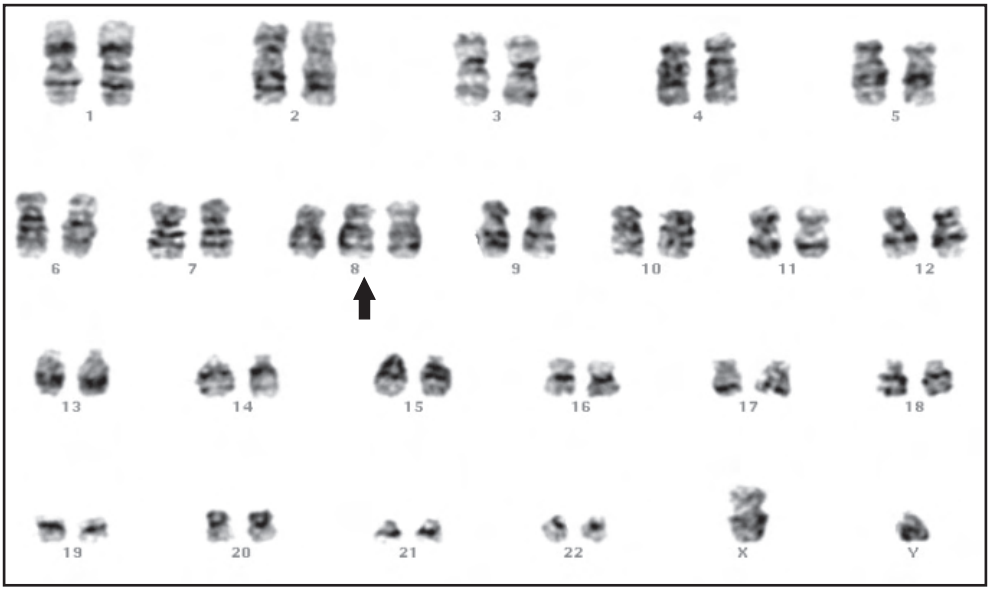

FIG. 5: Giemsa-banded chromosomes showing the karyotype of patient 2 with trisomy 8.

His full blood count on admission showed anaemia (9.1g/dl), thrombocytopenia (75 x 10^9/l) and hyperleucocytosis (128 x 10^9/l). The peripheral blood smears showed neutrophilia and monocytosis with a left shift, and 9% blast cells. His serum LDH was increased (732 μ/L) but Haemoglobin F was normal (1.2%). The patient also had hypergammaglobulinaemia: IgM 226 mg/dl (40 – 80), IgA 296 mg/dl (35 – 75) and IgG 1660 mg/dl (550-1000).

His bone marrow aspirate biopsy revealed marked granulocytic hyperplasia, monocytosis and presence of 17% blast cells. Erythropoeisis was markedly depressed with dysplasia of all three cell lines. Unfortunately cytogenetic analysis was not determined. DNA analysis for BCR-ABL gene was negative.

The patient was managed supportively with intravenous fluids and alkalization. Exchange transfusion was also done three times to reduce the white cell counts. Chemotherapy (AML BFM 97 protocol) was started on the sixth day following admission. A repeat bone marrow aspiration done a month later showed remission and consolidation phase of chemotherapy was started. Four months later, his white cell count started to increase again. A repeat bone marrow aspiration showed features of relapse JMML. He was planned for palliative chemotherapy. Unfortunately, he succumbed to overwhelming septicaemia and disseminated intravascular coagulopathy.

DISCUSSION

Myelodysplastic syndromes (MDS) and myeloproliferative disorders (MPD) of childhood are a heterogenous group of clonal disorders of haematopoiesis with overlapping clinical features and inconsistent nomenclature.[1] The classification of MDS in childhood has been a subject of controversy. The use of the French-American-British (FAB) classification system has traditionally been accepted for adults with

TABLE 1: Diagnostic features on presentation in 3 children with JMML

Case no.	1	2	3
Age (yr) /Sex at diagnosis	8/male	3/male	4/male
Liver (cm)	3	9	5
Spleen (cm)	8	14	1
WBC (10^9/L)	32.3	30	128
Platelets (10^9/L)	31	59	75
Absolute monocyte (peripheral)	8,398	3,000	7,680
Blasts in bone marrow (%)	3%	15%	9%
NAP score	150	normal	192
Serum Immunoglobulin (mg/dl)	Not determined	Hypergammaglobulinaemia IgG 4960 IgM161 IgA247	Hypergammaglobulinaemia IgG 1660 IgM 226 IgA 296
Hb F (%)	0.9	60.4	1.2
Cytogenetics	Trisomy 8	Trisomy 8	Not determined
BCR-ABL	Negative	Negative	Negative

MDS, but the classification for children has been inconsistent and imprecise. Previously this disorder has also been referred to as CMML.[2] However, the classification of CMML in both adults and children into either the MDS category or MPD category has been particularly problematic. As the FAB classification has gained acceptance, several groups have attempted to apply these criteria to paediatric disorders, usually by placing the disorder JCML within the FAB category of CMML.[2] Patients who present with peripheral blood monocytosis and bone marrow dysplasia (often in association with monosomy 7) with a morphological picture of CMML in the absence of the t(9;22) translocation are generally considered to have the juvenile form of CMML. In December 1996, the International Working Group proposed that the term juvenile myelomonocytic leukaemia (JMML) be added to the FAB MDS system to accommodate children previously classified as having JCML or infantile monosomy 7 syndrome,[5] but the FAB classification has no prognostic relevance in children.

An expert group convened by the WHO has proposed a classification of the MPD, MDS and of the overlap MDS/MPD as shown in table 2. The important features of this classification are the recognition of a group of conditions in which there are features of both myelodysplasia and myeloproliferation and the assignment of JMML and CMML to this group rather than to the MDS.[6,7] Hasle *et al* have proposed a new classification for paediatric MDS and myeloproliferative diseases (Table 3). The classification recognizes three major diagnostic groups: (1) Myelodysplastic/Myeloproliferative disease; (2) myeloid leukaemia of Down syndrome, a disease with distinct clinical and biological features, encompassing both MDS and AML occurring in Down syndrome; and (3) MDS occurring both *de novo* and as a complication of previous therapy or pre-existing bone marrow disorder (secondary MDS).[8] However, the most recent WHO classification on paediatric MDS did not address this matter.[7]

Most patients with JMML are between the ages of 3 to 24 months at diagnosis, though it is seen in patients up to 8 years of age as described in this report. It is rarely seen in the neonatal period and thus is not considered as a congenital disease. CML rarely occurs in this age group, thus it is inappropriate to classify our patient under the CML classification group.

A number of conditions have been identified as predisposing factors for JMML. These include: Down syndrome, Kostmann syndrome, Noonan syndrome, Fanconi anaemia, trisomy 8 mosaicism, neurofibromatosis, Schwachmann syndrome, immunodeficiency and familial

TABLE 2: The WHO classification of the myelodysplastic syndromes and myelodysplastic/ myeloproliferative diseases.[7]

Myelodysplastic/myeloproliferative disorders
Chronic myelomonocytic leukaemia
Atypical chronic myelogenous leukaemia, *BCR-ABL1* negative
Juvenile myelomonocytic leukaemia
Myelodysplastic / myeloproliferative disorders, unclassifiable
Refractory anaemia with ring sideroblasts associated with marked thrombocytosis
Myelodysplastic syndromes
Refractory cytopenia with unilineage dysplasia
Refractory anaemia
Refractory neutropenia
Refractory thrombocytopenia
Refractory anaemia with ringed sideroblasts
Refractory cytopenia with multilineage dysplasia
Refractory anaemia with excess blasts
Myelodysplastic syndrome associated with isolated del(5q)
Myelodysplastic syndrome, unclassifiable
Childhood myelodysplastic syndromes,
Refractory cytopenia of childhood

TABLE 3: Classification of paediatric MDS[8]

I.	Myelodysplastic/Myeloproliferative disease
	Juvenile myelomonocytic leukaemia (JMML)
	Chronic myelomonocytic leukaemia (CMML) (secondary only)
	BCR-ABL-negative chronic myeloid leukaemia (Ph^- CML)
II.	Down syndrome (DS)
	Transient abnormal myelopoiesis (TAM)
	Myeloid leukaemia of DS
III.	Myelodysplastic syndromes
	Refractory cytopenia
	Refractory cytopenia with excess blasts
	RAEB in transformation

leukaemia.[9] In addition, previous chemotherapy administered to children for other disorders can also be a predisposing factor for the subsequent development of childhood MDS and MPDs. In this case series, there was no risk factor identified.

Early phase JMML can clinically resemble infection such as Epstein-Barr virus, cytomegalovirus, or other agents. As described in patients 2 and 3, these patients present with features of infection. Patient 2 had recurrent upper respiratory tract infection while patient 3, recurrent cervical node abscess. Most JMML patients have hepatosplenomegaly and lymphadenopathy, as seen in this case series. Busque L *et al* showed that most cases had a leucocyte count of less than 50 x 10^9/l; less than 8% of cases have counts greater than 100 x 10^9/l which is seen in patient 3.[10] Monocytosis exceeding 5 x 10^9/l with circulating immature myeloid cells, erythroblasts, and minimal blasts are typical findings. The haemoglobin level is usually low. Bone marrow analysis shows increase in cellularity, with the majority of cells belonging to the myeloid series in all stages of maturation. Monocytes account for 5 – 10% of all myeloid cells. There is also an alteration in the haemoglobin pattern in patients with JMML: Hb A2 concentration is reduced, whereas Hb F level is greater than 10% at diagnosis.[11] However, in our case series, only one patient had elevated Hb F. Activation or suppression of alpha or beta genes, reactivation of gamma genes or activation and proliferation of dormant precursor cells with fetal characteristics were possible genetic mechanisms responsible for the elevation of Hb F.[12] Polyclonal hypergammaglobulinaemia is also common, which was seen in the second and third case; its significance remains unclear.

In general, JMML has a lack in cytogenetics abnormalities; 40 – 67% of patients will have normal cytogenetic analysis, 25 – 33% will have monosomy 7 and only 10 – 25% will have other chromosomal aberrations.[11] Both patients 1 and 2 have trisomy 8, an uncommon chromosomal abnormality which is seen in only 4% of patients in the study done by Passmore SJ *et al*[4]. Most of the patients in this study had normal karyotype. The commonest abnormality is monosomy 7 (17%). To date, there has been no case report of JMML with t(9;22) translocation and BCR-ABL rearrangement. The BCR-ABL fusion gene, the main product of the t(9;22) translocation, is found in at least 95% of CML cases and 5% of children with acute lymphoblastic leukaemia (ALL) cases. The absence of the t(9;22) translocation and BCR-ABL rearrangement is actually one of the laboratory criteria for the diagnosis of JMML according to the International Juvenile Myelomonocytic Leukaemia Working group[1]. As seen in this case series, the patients were all negative for BCR-ABL gene by molecular DNA analysis.

JMML is typically more fulminant than most other chronic myeloproliferative disorders with a median survival of less than 10 months.[2] The initial course of JMML is varied with approximately one third of patients developing a rapidly progressive course leading to early death. Morbidity and mortality often occur due to bleeding, infection or non-haematopoietic organ failure due to monocytic infiltration. The worst prognosis are those patients over the age of 2 years, with a low platelet count and a high fetal haemoglobin level. As in this

case series, all of them were more than 2 years old at diagnosis. All presented with a low platelet count but only patient 2 had a high haemoglobin F level. The treatment of JMML continues to generate controversy. Intensive AML-type chemotherapy has been used to induce complete remission (CR), similar to its use in AML or in MDS patients with RAEB or RAEB-t. In contrast to AML and the other MDS patients, JMML patients rarely achieve a remission with intensive chemotherapy regimens alone, and if they do achieve a remission it is short-lived.[2] This clinical course is similarly reflected in all our patients; the second patient could only sustain remission for a month before he relapsed. Following that, he transformed into acute myeloid leukaemia whilst on maintenance chemotherapy. Our third patient survived for 8 months from the time of diagnosis. He also received an intensive AML-based regimen. The total white cell count significantly dropped after the treatment was started and a repeat bone marrow one month later showed that he was in marrow remission. Unfortunately he had defaulted during consolidation phase, relapsed and died due to the complications of the disease. Currently, stem cell transplantation is the only therapy that clearly improves outcome in the clinical management of JMML.

In conclusion, JMML is a unique but very aggressive disease. Early diagnosis of JMML can be difficult because of the overlap in some of the clinical and laboratory features with other types of myelodysplasia or myeloproliferative disease. A correct diagnosis is however important since intensive chemotherapy and early stem cell transplantation will help improve the survival of these patients.

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