

Favourable response to splenectomy in familial myelodysplastic syndrome

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ABSTRACT

Familial myelodysplastic syndrome occurring at a young age is a very rare childhood haematological malignancy. Two siblings, aged three and 18 years, from a consanguineous marriage, presented with pancytopenia and was subsequently diagnosed to have myelodysplastic syndrome. Both remained clinically stable throughout the illness. Splenectomy appeared to have fully corrected the cytopenia in one of them.

Keywords: myelodysplastic syndrome, pancytopenia, splenectomy

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INTRODUCTION

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal stem cell disorders characterised by ineffective haematopoiesis, morphological abnormalities in the bone marrow and the probability of evolution to acute myeloid leukaemia. MDS occurs predominantly in the elderly. Although several series of MDS in childhood have been reported,⁽¹⁻³⁾ epidemiological data are very limited in part because paediatric MDS is relatively rare.^(1,2) This may be partly due to difficulties in its diagnosis and classification.^(3,4) Report on familial childhood MDS is even rarer, and most cases of familial MDS are often cited occurring in late adulthood.^(5,6) In this report, we describe two siblings from a consanguineous marriage who presented to our institution with MDS at an early age.

CASE REPORTS

Case 1

The younger of the two siblings, presently 13 years of age, was referred to us at the age of three years for pancytopenia. There was no history of petechiae, bruises or other associated physical abnormalities. The parents were first cousins and the four other siblings were essentially normal at that point in time. On examination, he was not dysmorphic. He was markedly pale and there were no petechiae or bruises. There were also no lymphadenopathy and hepatosplenomegaly.

Laboratory investigations revealed haemoglobin level of 3.4 g/dL, white cell count of $2.7 \times 10^9/L$, and platelets of $62 \times 10^9/L$. The peripheral blood film showed hypochromic microcytic anaemia with moderate anisopoikilocytosis. There was leucopenia. No blasts cells or dysplastic cells were seen. Serum iron, serum ferritin and total iron binding capacity were within the normal range for his age. The haemoglobin electrophoresis was normal. Viral screening studies were negative. Bone marrow aspiration and trephine biopsy were consistent with myelodysplastic features. The marrow was hypercellular. Dysplastic features were observed in all blood cell series. The blast cells were not increased (< 5%). No ring sideroblasts were seen.

The patient was not started on any chemotherapy nor planned for bone marrow transplantation. He was managed conservatively with packed red cell transfusions as he was considered to have low-grade myelodysplastic syndrome. Cytogenetic analysis was not performed since the bone marrow sampling was repeatedly inadequate for the study. Following the first transfusion, the haemoglobin level fell to below 7 g/dL in about three months. A three-monthly transfusion regime was therefore planned for him, or earlier, when the level of haemoglobin fell below 7.0 g/dL. He continued to be managed on this regime for approximately three years. He later developed hypersplenism and his transfusion requirement gradually became more frequent, to almost monthly. Although he was documented to have iron overload, chelation therapy could not be offered to the patient then.

Fortunately, he did not develop any life-threatening events throughout his illness. At the age of 12 years, his parents finally agreed to splenectomy. The spleen was more than 20 cm below the subcostal margin. It weighed 2 kg postoperatively. The splenic histopathological report was consistent with extramedullary haemopoiesis. He showed good response to splenectomy. Both the haemoglobin concentration and platelet count increased and remained within normal values. At one year post-splenectomy, he does not seem to require any transfusion.

Case 2

The elder sister, aged 20 years, was referred for pancytopenia two years ago. There was no history of

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petechiae or bruises. She was not dysmorphic. She was pale but not jaundiced. There was no lymphadenopathy or hepatosplenomegaly. Other systems were essentially normal. The haemoglobin level was 6.9 g/dL, white cell count $3.5 \times 10^9/L$ and platelets $98 \times 10^9/L$. Her peripheral blood film showed hypochromic microcytic anaemia and leucopenia. No immature and dysplastic cells were seen. Screening tests for connective tissue disease were negative. Iron studies were within normal. The haemoglobin electrophoresis finding was normal. The bone marrow examination showed mixed area of hypercellularity and hypocellularity with increased granulopoiesis. Though the megakaryocytes were adequate in number, some exhibited dysplastic features. Iron store was adequate and no ring sideroblasts were seen. The management instituted was similar to her younger brother. No chemotherapy was started. Cytogenetic analysis was also not performed for the same reason.

DISCUSSION

Myelodysplastic and myeloproliferative disorders are rare in childhood, with each representing less than 5% of all haematological malignancies.⁽¹⁻⁴⁾ Most of the reported cases occur sporadically while familial MDS occurring during childhood or adolescence is even rarer.^(5,6) A characteristic feature of childhood MDS is its frequent association with other conditions such as Down's syndrome and neurofibromatosis type 1.⁽⁷⁾

The paediatric and adult MDSs are subjected to ongoing debates regarding the optimum diagnostic classification and treatment. The French-American-British classification for MDS, though widely accepted when applied to general paediatric MDS, may need to be modified as children with constitutional predispositions are a distinct group.⁽¹⁾ The classification for adults does not adequately address all syndromes that occur in children. According to this classification, both patients fall into the refractory anaemia (RA) subtype. Based on the recently-proposed WHO classification for paediatric MDS, our first patient is in the refractory cytopenia (RC) subtype. RA (with or without ring sideroblast) is rare in children.⁽³⁾ MDS in childhood tends to present as RA with excess blasts, or RA with excess blasts in transformation.

The diagnosis of myelodysplasia was made in both patients based on the clinical presentations, persistent pancytopenia and bone marrow findings, which exhibited dysplastic features. At the point of presentation, acute leukaemia, aplastic anaemia and infection with probable concomitant iron deficiency or underlying thalassaemia trait, were considered. Sideroblastic anaemia was also a differential diagnosis in view

of the pancytopenia with hypochromic microcytic red blood cells. Since MDSs display remarkable clinical, pathological and cytogenetic heterogeneity, a careful study of prognostic features, to guide the treatment decision, is important. There have been few systematic attempts to define a prognostic score in MDS in the paediatric age group, one of which is the FPC (foetal haemoglobin, platelets and cytogenetic) score.⁽⁷⁾ The International Prognostic Scoring System (IPSS), published in 1997 and developed for adult MDS, was also applied to children. However, the value of this prognostic scoring system in children is less clear than in adults. Both of the patients could not be categorised under the IPSS, as cytogenetic analysis was not carried out. However, since our paediatric patients had a blast count of less than 5% (RA/RC) and may pursue an indolent course, a decision to manage both patients conservatively was made. The therapeutic goal was to ameliorate the haematological deficiency.

The outcome in most childhood MDS is poor, though some showed prolonged and stable clinical course without treatment,^(8,9) as with our patients. Choices for treatment include cytokines, immunosuppressive therapy, chemotherapy, and haematopoietic stem cell transplantation (HSCT). To date, no treatment other than HSCT offers significant curative potential, though the outcome following HSCT is jeopardised if disease progression has occurred.^(10,11) On hindsight, the choice of not to commence any treatment except for supportive therapy in the first patient is appropriate, since the clinical course of the disease remained stable over the past nine years. Similarly, chemotherapy was not started in his elder sister, and she was only transfused with packed red cells when her haemoglobin level dropped below 7.0 g/dL.

Very few cases of splenectomy in MDS have been reported.⁽¹⁰⁻¹³⁾ In most cases, it is performed because of splenomegaly or cytopenia, especially in those with severe thrombocytopenia leading to life-threatening events. The expected improvement in the cytopenia is unpredictable. Bourgeois et al postulated that thrombocytopenia in MDS is due to peripheral destruction similar to other childhood thrombocytopenias.⁽¹⁰⁾ Others have suggested that splenectomy could accelerate the myeloid transformation.^(11,12)

Splenectomy was indicated in the first case because of hypersplenism and the discomfort caused by the massive spleen size. There was a delay in deciding for splenectomy because of the uncertainty of the success in improving the cytopenia. However, the procedure appeared to have corrected both the anaemia and the severe thrombocytopenia. The full blood count remained within the normal reference range following

the surgery. We anticipate that the elder sister would eventually require splenectomy should hypersplenism occur. A report by Kraus et al, where 13 cases of MDS underwent splenectomy, showed that the splenic histopathological findings were dominated by erythrophagocytosis and extramedullary haematopoiesis.⁽¹³⁾ They concluded that these findings were sequelae of dyspoiesis rather than due to the proliferative phase. In our first patient, the findings were similar to that reported by Kraus et al.

In summary, familial myelodysplastic syndrome in a young age group is a very rare haematological disease. Splenectomy does help in correcting the anaemia and thrombocytopenia in patients with MDS. However, careful patient selection is mandatory to ensure the success of correcting the cytopenia.

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