Case Report

Childhood myelodysplastic syndrome with increased fibrosis in association with neurofibromatosis 1: A case report

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ABSTRACT

Childhood myelodysplastic syndromes (MDSs) are rarely seen and their association with neurofibromatosis 1 (NF1) is also rare. Monosomy 7 predisposition syndrome can arise in NF1 patients. MDS with increased fibrosis carries a poor prognosis. We are reporting the case of a 7-year-old boy who presented with fever and on routine evaluation, pancytopenia was found. He had multiple café-au-lait spots. Further testing revealed dysplastic megakaryocytes along with increased marrow fibrosis. This case contributes further to the knowledge of childhood MDS and NF1.

Key words: Bone marrow fibrosis, Childhood myelodysplastic syndrome, Monosomy 7, Myelodysplastic syndrome, Neurofibromatosis 1

CASE REPORT

A 7-year-old boy presented to the pediatric outpatient department with a history of fever for 5 days which was undocumented and associated with dry cough and watery stools. There was a history of multiple hospital admissions for recurrent infections and anemia in the past 6 months and he had received a blood and platelet transfusion once. His birth and development were normal, and he was immunized for his age.

On examination, there was moderate pallor, without icterus, lymphadenopathy, or petechiae. His vitals were stable and weight was 20 kg. He had multiple café-au-lait macules (>10 mm and >10 in number) over the face, trunk, and limbs (Fig. 1a). Multiple café-au-lait macules and papulonodular lesions (neurofibromas) were also noted in the child’s mother (Fig. 1b). On per abdomen examination, the liver was palpable 4 cm below the right costal margin, firm in consistency, with a span of 13 cm, suggesting hepatomegaly. Spleen, however, was not palpable. Rest systemic examination was normal.

On investigations, a hemogram revealed pancytopenia, with hemoglobin 5.7 g/dL, total leukocyte count of 2.63×10³/µL (absolute neutrophil count: 315/µL), and platelet count of 22,000/µL. A peripheral blood smear revealed macrocytic anemia, leukopenia, and thrombocytopenia. Liver and renal function tests were normal. Serum folic acid was 8.10 ng/mL and Vitamin B12 was 673 pg/mL.

Bone marrow (BM) aspiration revealed a dry tap. BM biopsy was performed, and paraffin-embedded sections were processed. Hematoxylin and eosin and reticulin stain were done. Microscopic examination of the BM biopsy sections revealed cells representative of all three lineages with a preponderance of megakaryocytes which were present in clusters. The megakaryocytes displayed dysplasia in the form of nuclear hyperchromasia, hypolobation, separate nuclear lobes, and micro megakaryocytes were also seen. Myeloid precursors were relatively more than erythroid precursors (Fig. 2a). Reticulin stain revealed increased fibrosis (World Health Organization grade MF 2) (Fig. 2b). A possibility of myelofibrosis was kept and the patient was referred to the higher institute where fluorescent in situ hybridization was done. It revealed the abnormal presence of monosomy 7 (Table 1).
MONOSOMY 7 account for 25–30% of such cases [1]. BM fibrosis is diagnosed based on increased reticulin fibrosis. Increased narrow fibrosis is considered a poor prognostic factor in MDS. Studies have shown that TP53 mutations are closely related to marrow fibrosis in MDS and it can further lead to resistance to conventional therapeutic agents [5,6].

Our case had MDS with increased fibrosis in association with NF1 and monosomy 7. NF1 is an autosomal dominant neurocutaneous disorder. He had multiple café-au-lait macules and his mother had neurofibromas and multiple café-au-lait macules. Hence, the child was diagnosed with NF1 as per the revised diagnostic criteria [7]. NF1 was the first human condition mapped to the RAS pathway which is implicated in the development of juvenile myelomonocytic leukemia. It is a negative regulator of the RAS pathway, and its deficiency leads to increased cellular proliferation [8]. Monosomy 7 predisposition syndromes are characterized by childhood or young-adult onset of BM insufficiency in association with severe cytopenias, variable adaptive immune deficiency, BM aplasia, MDS, and/or AML. NF1 gene is one of the causative factors of this predisposition syndrome [9].

Patients with monosomy 7 predisposition syndrome can initially have normal karyotype and treatment with steroids can also mask its cytogenic identification. Once this monosomy occurs, the progression of the disease is rapid; however, studies have shown the resolution of monosomy 7 in children without advanced MDS [10].

A study conducted by Maris et al. has shown monosomy 7 MDS as the second most common myeloid malignancy in children with NF1 [11]. However, cases reported by Maris et al. developed MDS after chemotherapy for a primary neoplasm. There was no history of any therapy in our case. Monosomy 7 usually occurs as an additional cytogenetic event in patients with a predisposing condition [12]. Here, in this case, monosomy 7 has led to the development of MDS. However, increased reticulin fibrosis is usually not seen in children and this can also imply poor prognosis.

Alogeneic hematopoietic stem cell transplantation is advocated in the treatment of childhood MDS to prevent recurrent
infections and transfusion dependence. Our case contributes to the awareness that childhood MDS with increased reticulin fibrosis can develop in NF1. Hence, such patients should be kept on regular follow-up so that the morbidity is minimal and hematopoietic stem cell transplantation can be timely planned. Genetic counseling and timely diagnosis of the predisposition syndromes can play a major role in reducing further complications.

CONCLUSION

MDS with increased fibrosis is rare in children and their association with NF1 is also very less seen. Children with NF1 should be regularly followed up for the development of the same.

REFERENCES


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