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

Childhood myelodysplastic syndrome (MDS) is a clonal disorder with an annual incidence of 1–4 cases per million and accounts for <5% of pediatric malignancies [1]. Germline predisposition is being recognized as the etiology in pediatric patients [2]. Neurofibromatosis 1 (NF1) is an autosomal-dominant neurocutaneous disorder [3]. It is associated with an increased risk of developing monosomy 7 syndrome and the incidence is higher in young boys [4].

Here, we report the case of a 7-year-old boy diagnosed with childhood MDS with increased fibrosis associated in association with NF1.

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 $2.63\times10^3/\mu L$ (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).

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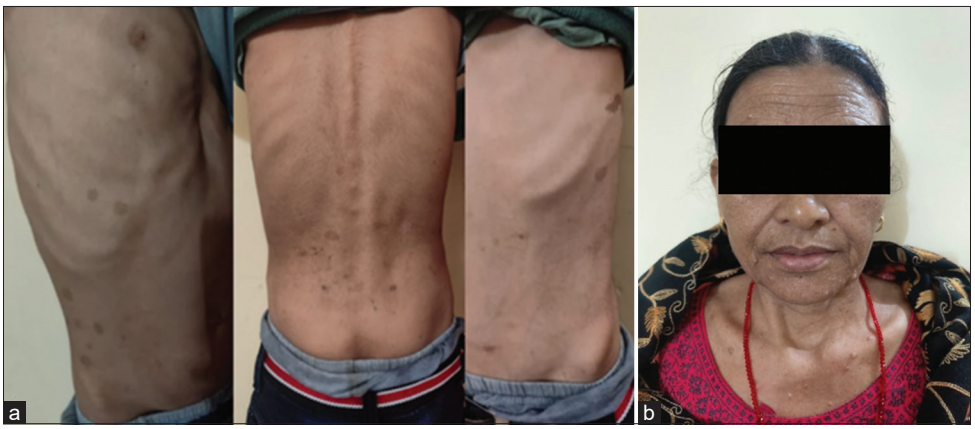

Figure 1: (a) Multiple café-au-lait macules on patient's trunk; (b) Patient's mother has multiple café-au-lait macules and papulonodular lesions (neurofibromas)

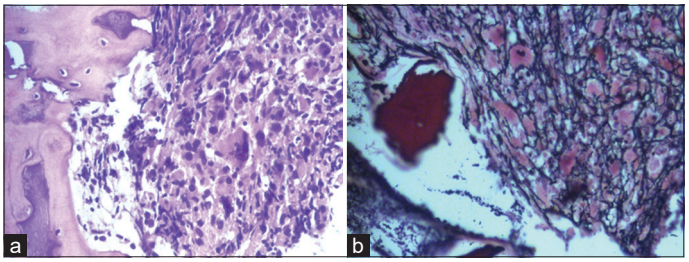

Figure 2: (a) Bone marrow biopsy (H and E stain, ×400) revealing dysplastic megakaryocytes; (b) Bone marrow biopsy (reticulin stain, ×400) showing diffuse and dense increase in reticulin with extensive intersections (World Health Organization Grade MF 2)

Table 1: Investigations of the patient

Investigation	Result
Hemoglobin	5.7 g/dL
Total leukocyte count	$2.63\times10^3/mm^3$
Platelet count	$22000/mm^3$
Serum folic acid	8.10 ng/mL
Serum vitamin B12	673 pg/mL
Peripheral smear	Macrocytic red blood cells with leukopenia and thrombocytopenia
Bone marrow Aspiration	Dry tap
Bone marrow biopsy	Dysplastic megakaryocytes reticulin stain: World Health Organization MF-2
Fish	Monosomy 7

Hence, the case was diagnosed as childhood MDS with increased fibrosis, with monosomy 7 and NF1.

DISCUSSION

MDS is a rare clonal disorder seen in children leading to ineffective hematopoiesis, cytopenias, and risk of progression to acute myeloid leukemia (AML). Primary MDS in children differs from secondary MDS which occurs due to congenital or acquired BM failure syndromes and therapy-related MDS. Childhood MDS is often associated with inherited BM failure syndromes or genetic predisposition syndromes. Chromosomal aberrations like monosomy 7 account for 25–30% of such cases [1]. BM fibrosis is diagnosed based on increased reticulin fibrosis. Increased marrow 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.

Allogeneic 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.

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