Paediatric Idiopathic Myelofibrosis

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Abstract Pediatric myelofibrosis is a rare disorder. It is usually secondary to other diseases. Rarely, when no underlying cause is found, it is termed idiopathic. We present here, a rare case of idiopathic myelofibrosis in a 10 year old male child. Bone marrow aspirate was dilute. Bone biopsy showed marrow fibrosis, with grade 2–3 reticulin fibres, with no evidence of granuloma, parasite or infiltrative disorder. Acid fast bacillus stain was negative. Iliac lymph node biopsy showed reactive sinus histiocytosis with extramedullary hematopoiesis. Thus, diagnosis of pediatric idiopathic primary myelofibrosis was made. Idiopathic pediatric myelofibrosis should be suspected in a child with progressive pallor, hepatosplenomegaly and dry tap on bone marrow aspiration and marrow fibrosis on bone biopsy, after exclusion of secondary causes.

Keywords Pediatric · Idiopathic · Myelofibrosis

Introduction

Pediatric myelofibrosis is a rare disorder [1, 2] It is usually secondary to hematologic malignancies, metabolic disorders and infections [1]. Rarely, when no underlying cause is found, it is termed idiopathic. We present here, a rare case of idiopathic myelofibrosis in a 10 year old male child.

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Case

A 10 year old male, resident of Delhi, was admitted with complaints of fever, off and on, for past 3 months. Fever was mild to moderate, with evening rise and relieved by oral medications. Progressive pallor insidious in onset with increased fatigability were present for past 1 ½ months. Patient also complained of pain in lower limbs, leading to decreased activity. There was no history of petechiae, bruise or bleeding from any site. There was past history of pulmonary tuberculosis 4 years back based on X-ray finding and sputum examination for AFB, which responded to antitubercular treatment (ATT). Physical examination revealed presence of pallor. There was no icterus, rash or clubbing. Cervical, axillary and inguinal lymph nodes were palpable. They were 1 × 1 cm, discrete, mobile and non tender. There was bony tenderness in both lower limbs. Abdominal examination revealed enlargement of liver 2 cm below costal margin (BCM), soft, non tender with rounded border and spleen 3.5 cms along splenic axis BCM, firm and non tender. Chest, cardiovascular and central nervous systems were within normal limits. Thus, since this patient had fever, anemia, hepatosplenomegaly and lymphadenopathy, his differential diagnosis included tuberculosis, enteric fever, malaria, kala-azar, HIV, megaloblastic anaemia and lymphoreticular malignancy.

Investigations revealed Chest X-ray to be normal. X-ray of both legs did not show any lytic lesions. Ultrasound of abdomen revealed liver 16 cm craniocaudal and spleen 14 cm craniocaudal, both having normal echotexture. There was also presence of multiple lymph nodes in para aortic, mesenteric & retroperitoneum, CECT abdomen showed multiple enlarged retroperitoneal lymph nodes along the great vessels. Other detailed investigations are given in Table 1.

Table 1 Table showing the investigations done and their result in the patient

		Test results
Hematological tests	Hb	4.1 gm/dl
	TLC	$3.6 \times 10^9/l$
	Platelet count	$64 \times 10^9/l$
	DLC	Myelocyte 4 %, metamyelocyte 5 %, polymorphonuclear cells 34 %, lymphocyte 54 %, monocyte 2 %, eosinophils 1 %
	Peripheral smear	Normocytic, normochromic RBC, Tear drop red cells, 2 nucleated RBC/100 WBC, no malarial parasite
	Reticulocyte count	1 %
	ESR	10 mm in 1st hour
	Direct Coomb's test	Negative
	PNH (CD55, CD59 by gel card)	Negative
	Serum B12 & folic acid	Normal
	Neutrophil alkaline phosphatase score	250
Biochemical tests	Parathormone levels	Normal
	Serum calcium	9.5 mg/dl
	Serum phosphate	5.3 mg/dl
	Serum alkaline phosphatase	197 units/l
	Anti nuclear antibody	Negative
Microbiology	RK39 Ag	Negative
	Widal	Negative
	Serum Optimal test for malaria	Negative
	HIV serology	Negative
	Gastric aspirate for AFB	Negative

Bone marrow aspirate showed a dry tap. Bone marrow biopsy showed fibrosis of marrow spaces, which were replaced by spindle shaped fibroblasts with streaming of hematopoietic precursors (Fig. 1). Erythroid precursors showed normoblastic reaction with few macronormoblasts. Myeloid precursors were unremarkable with mild increase in eosinophilic precursors. Megakaryocytes were unremarkable. There were increased lymphocytes and plasma cells and occasional histiocyte. No well formed granuloma,

Fig. 1 Bone marrow biopsy showing marrow fibrosis (H&E × 40×) **Fig. 2** Bone marrow biopsy showing grade 3 reticulin fibres on reticulin stain

parasite or infiltrative disorder was identified. Reticulin stain showed Grade 2–3 reticulin fibres (Fig. 2). AFB stain was negative. On immunohistochemistry, markers for B cells (CD 19 and 20), CD61, CD30 were negative and T cell marker (CD3) was positive in some cells. Bone marrow biopsy was reported as myelofibrosis and lymph node biopsy was advised to exclude TB/Hodgkin's disease. Lymph node biopsy of right & left iliac lymph nodes revealed reactive sinus histiocytosis with evidence of extramedullary haematopoiesis (Fig. 3). Thus a final diagnosis of idiopathic pediatric myelofibrosis was made.

Fig. 3 Lymph Node biopsy showing extramedullary hematopoiesis (H & E $\times 400\times$)

Discussion

Pediatric myelofibrosis is rare and is reported in 100 cases worldwide. It is usually secondary to malignancies such as AML (M6,M7), NHL, ALL, Hodgkin's disease, metabolic disorders like rickets, renal osteodystrophy, osteopetrosis and hyperparathyroidism, infections such as tuberculosis etc. [3, 4]. When no cause is found, it is termed Idiopathic [5]. Idiopathic paediatric myelofibrosis has been described in only 46 patients till date. It usually occurs in patients below 3 years of age and females predominate (female: male-2:1). These younger patients are more likely to have Down's syndrome, rickets, or a familial (possibly autosomal recessive) form of myelofibrosis. Among older patients, AML, systemic lupus erythematosus, and tuberculosis are the most common associations. The present case was interesting as it occurred in a male of 10 years age and no underlying cause could be identified.

The bone marrow examination showed presence of unremarkable megakaryocytes. This is at variance from adult myelofibrosis where hyperchromatic, smudgy, "cloud-like" nuclei of megakaryocyte are described. In pediatric cases, megakaryocytes may be normal looking or have micromegakaryocytes, hypolobation, and separation of nuclear lobes [6]. JAK mutation was not looked for in the present case as the facility was not available. However, unlike adult myelofibrosis where JAK2V617F or MPLW515 K/L

mutations are present in about 50 % cases, absence of these mutations has been described in pediatric cases, suggesting a different clonal change in pediatric myelofibrosis. This hypothesis is also strengthened by presence of different cytogenetic abnormalities like trisomy 21 in pediatric myelofibrosis [1], versus trisomies in chromosomes 8 or 9, deletions in the long arm of chromosomes 20 or 13, and abnormalities in chromosome 1 in adults [7].

Unlike adult myelofibrosis, pediatric myelofibrosis cases have a benign course with spontaneous resolution, although some children with more severe disease may need stem cell transplantation. Disease evolution into acute myeloid leukemia, a major concern in adults with primary myelofibrosis is unusual in children. However, a close hematological follow up is often advised.

It is concluded that Idiopathic paediatric myelofibrosis should be suspected in a child who presents with progressive pallor, hepatosplenomegaly, dry tap on bone marrow aspiration after exclusion of secondary causes and confirmed on BM biopsy [8]. It is important to diagnose this disease since haematopoietic stem cell transplant may be a therapeutic option [2].

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