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Mini Review

Pediatric Bone Marrow Myelofibrosis: A Heterogeneous "Entity" Requiring Refined Classification to Guide Therapy

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Abstract

Diagnosing and treating cytopenic myelofibrosis in children is challenging due to the wide spectrum of clinical and pathological features, underlying etiologies, and variable therapeutic responses. In this review, we summarize the related literature and present our diagnostic algorithm to differentiate pediatric myelofibrosis and guide therapy. In brief, primary myelofibrosis is extremely rare in children, while myelofibrosis secondary to non-neoplastic or neoplastic disorders should be thoroughly ruled out in ambiguous cases. Moreover, it is reasonable to closely follow up patients and repeat bone marrow biopsy before reaching a definitive diagnosis.

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Introduction

Cytopenic myelofibrosis (MF), characterized by low blood counts, bone marrow fibrosis, and other systemic symptoms (e.g., bone pain, fever), has a wide spectrum of etiology and variable therapeutic success and outcomes. In clinical practice, pediatric MF typically falls into three categories: MF secondary to either non-neoplastic or neoplastic disorders, primary myelofibrosis (PMF) (often requiring evidence of genetic abnormalities), and idiopathic MF (exclusive of the other two categories).[1] For instance, a study of fourteen consecutive pediatric cases of myelofibrosis revealed four with PMF; seven with immune-related MF in patients presenting with autoimmune-related syndromes or autoantibodies without defined disorders; and three with idiopathic MF in those not fulfilling the criteria for PMF and with no secondary etiologies.[1] Clinical evidence and genetic test-based guidelines for investigating patients with chronic cytopenia have been well illustrated in large registries and multi-institutional networks.[2] However, there is a lack of consensus and guidelines for patients with cytopenic myelofibrosis in the literature. Moreover, new classifications of hematolymphoid tumors have recently been published.[3,4] Therefore, we briefly summarize our diagnostic workup algorithm for myelofibrosis in children (Fig. 1), which may contribute to guide therapy.

Keywords: Myelofibrosis; Cytopenia; Myeloproliferative neoplasm; Meylodysplastic syndrome; Autoimmune myelofibrosis; Idiopathic myelofibrosis.

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Diagnostic workup of PMF

PMF, a chronic myeloproliferative neoplasm characterized by cytopenia, hepatosplenomegaly, bone marrow fibrosis, and other systemic symptoms (e.g., bone pain), is extremely rare in children.[3–7] Cytopenia is rare in patients with an initial diagnosis of essential thrombocythemia or polycythemia vera, and the clinical history is critical for establishing a diagnosis of post-essential thrombocythemia or polycythemia vera myelofibrosis.[3,4] In a study of fifty children with Philadelphia-negative myeloproliferative neoplasms, only one case of PMF was reported.[8] Although the genetics and pathobiology of adult PMF have been extensively studied, there is limited data on childhood PMF.[9] In one study, children with PMF had a male-to-female ratio of 2:1 and a median age at diagnosis of 3.4 years (range: 0.1–17.7).[10]

Three pediatric PMF cases were submitted to the bone marrow workshop of the European Association of Haematopathology 2020 Virtual Meeting.[11] The histopathological features of these three pediatric PMF cases were similar to those of adult PMF,[5,11] and molecular studies revealed a CALR type 1 mutation, an MPL in-frame insertion, or no somatic mutation in each case.[11] A separate study reports the presence of *CALR* type 2 mutations in up to 50% of pediatric patients with PMF.[12] These findings suggest that morphological and molecular criteria for PMF might be applicable for diagnosing PMF in children. Therefore, the revised World Health Organization and International Consensus Classification have not characterized pediatric PMF separately from adult PMF.[3,4,13,14] Nevertheless, due to the limited number of reported pediatric PMF cases, more data is certainly needed in the future. Moreover, diagnosing PMF in children can be challenging, especially when negative for *JAK2, CALR,* and *MPL* mutations.[11,12,15–18]

Diagnostic workup of myelofibrosis secondary to non-neoplastic or neoplastic disorders

Among all the secondary non-neoplastic etiologies of mye-

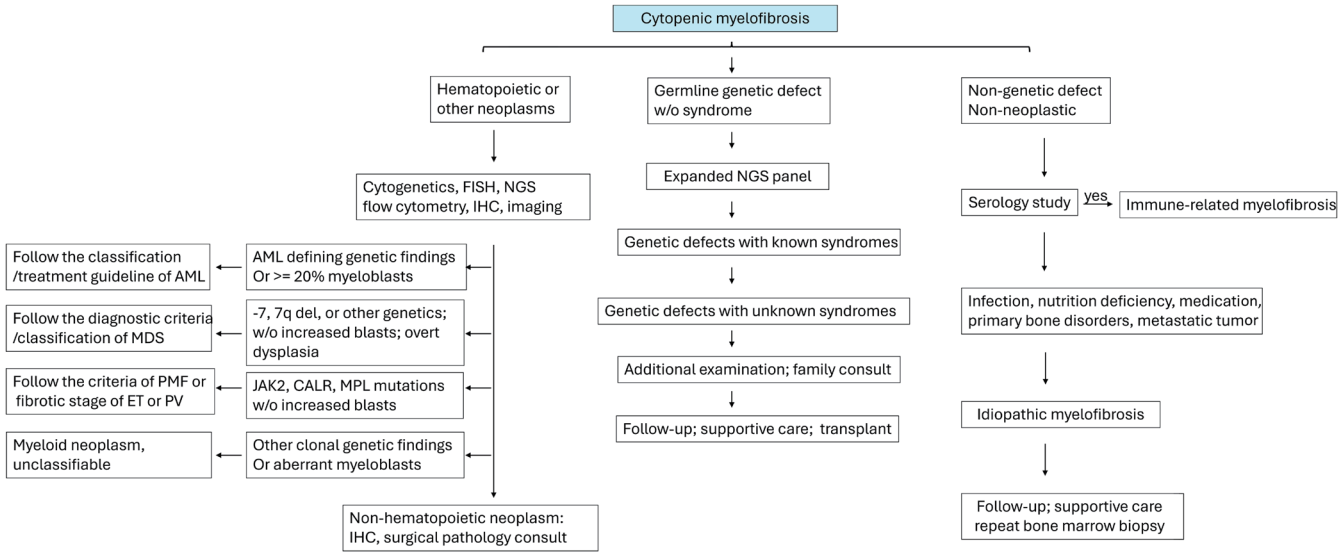

Fig. 1. An integrated diagnostic algorithm for pediatric myelofibrosis. AML, acute myeloid leukemia; ET, essential thrombocythemia; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry staining; MDS, myelodysplastic syndrome; NGS, next-generation sequencing; PMF, primary myelofibrosis; PV, polycythemia vera.

lofibrosis, autoimmune myelofibrosis (AIMF), a rare cause of bone marrow fibrosis occurring with or without a defined autoimmune disease, is probably the most common etiology. It is characterized by bone marrow fibrosis, pancytopenia, with or without bone pain, and other features resembling PMF in both children and adults. Children with AIMF may experience spontaneous resolution or respond to immunomodulatory treatment.[9] For instance, a cohort of nineteen pediatric AIMF patients showed a male-to-female ratio of 1.7:1, frequent hepatosplenomegaly, cytopenia, and occasional infections. The histologic, clinical, and molecular features differ from those in adults. None of the AIMF patients had somatic mutations in JAK2 or MPL or developed malignant transformations. However, some children with AIMF may have a poor outcome if they do not receive prompt workup and treatment.[9]

Several pathological features help differentiate AIMF from PMF. Morphologically, bone marrow biopsy from patients with AIMF often shows hypercellularity with variable erythroid and megakaryocytic hyperplasia, variable reticulin fibrosis, presence of lymphoid aggregates (mixture of T and B lymphocytes), and variable polytypic plasmacytosis.[9,19,20] The myelofibrosis in AIMF appears to be mild to moderate (reticulin fibrosis grade 1–2 out of 3), with the absence of osteosclerosis. Splenomegaly, if present, is usually mild. Cytogenetic abnormalities and somatic mutations should be negative in patients with AIMF.[19,21] However, atypical or dysplastic megakaryocytes can be seen in AIMF, likely caused by the fibrosis effect.[19] In persistent AIMF refractory to treatment, next-generation sequencing (NGS) with a larger gene panel should be attempted to identify less common genetic defects and further rule out rare diseases, such as inborn errors of immunity and congenital bone marrow failure disorders.[1,18,20,22–25] A careful clinical examination of the skin, cardiac, and other organ systems can help identify congenital disorders, with or without a hereditary familial history.

The secondary causes of myelofibrosis also include hematopoietic (e.g., acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), lymphoma) and non-hematopoietic neoplasms.[26] For instance, patients with bone marrow involvement in classic Hodgkin lymphoma and other B or T cell lymphomas often present with myelofibrosis and cytopenia.[27] The reticulin fibrosis may range from mild (grade 1 out of 3) to severe (grade 3 out of 3) in these patients. Similarly, moderate to severe myelofibrosis can be seen in acute megakaryoblastic leukemia, which may contain a low percentage of blasts in the bone marrow biopsy and aspirate. Identification of recurrent genomic abnormalities is helpful for establishing the diagnosis of AML. Additionally, primary bone disorders may present with significant fibrosis, cytopenia, and hepatosplenomegaly. A consultation with surgical pathologists, a careful physical and laboratory examination, and cross-sectional imaging studies with contrast-enhanced computed tomography and/or positron emission tomography are required to avoid diagnostic delays.

Lastly, the most challenging differential diagnosis of myelofibrosis is MDS with fibrosis. When assessing bone marrow pathology in primary or secondary myelofibrosis in both children and adults, atypical or dysplastic megakaryocytes are frequently seen on the bone marrow biopsy, which makes MDS, a rare disease in children, a differential diagnosis.[28] The bone marrow workup at the European Association of Haematopathology 2020 Virtual Meeting showed five pediatric MDS cases with variable fibrosis, all containing chromosomal abnormalities.[11] Therefore, the presence of clonal chromosomal abnormalities or somatic mutations is critical to distinguishing MDS from AIMF. However, it can be challenging to distinguish *JAK2*, *MPL,* and *CALR* triple-negative PMF from MDS with fibrosis due to the lack of specific molecular markers or clinical presentations.[29] Nevertheless, most pediatric patients with either PMF or MDS with fibrosis would eventually receive a hematopoietic stem cell transplant, with or without bridging therapy.[10]

Diagnostic workup of idiopathic MF

The diagnosis of idiopathic MF is based on the exclusion of PMF or any secondary MF. In a series of one hundred and twenty-two consecutive patients with bone marrow fibrosis initially categorized as idiopathic MF, a rigorous clinical and

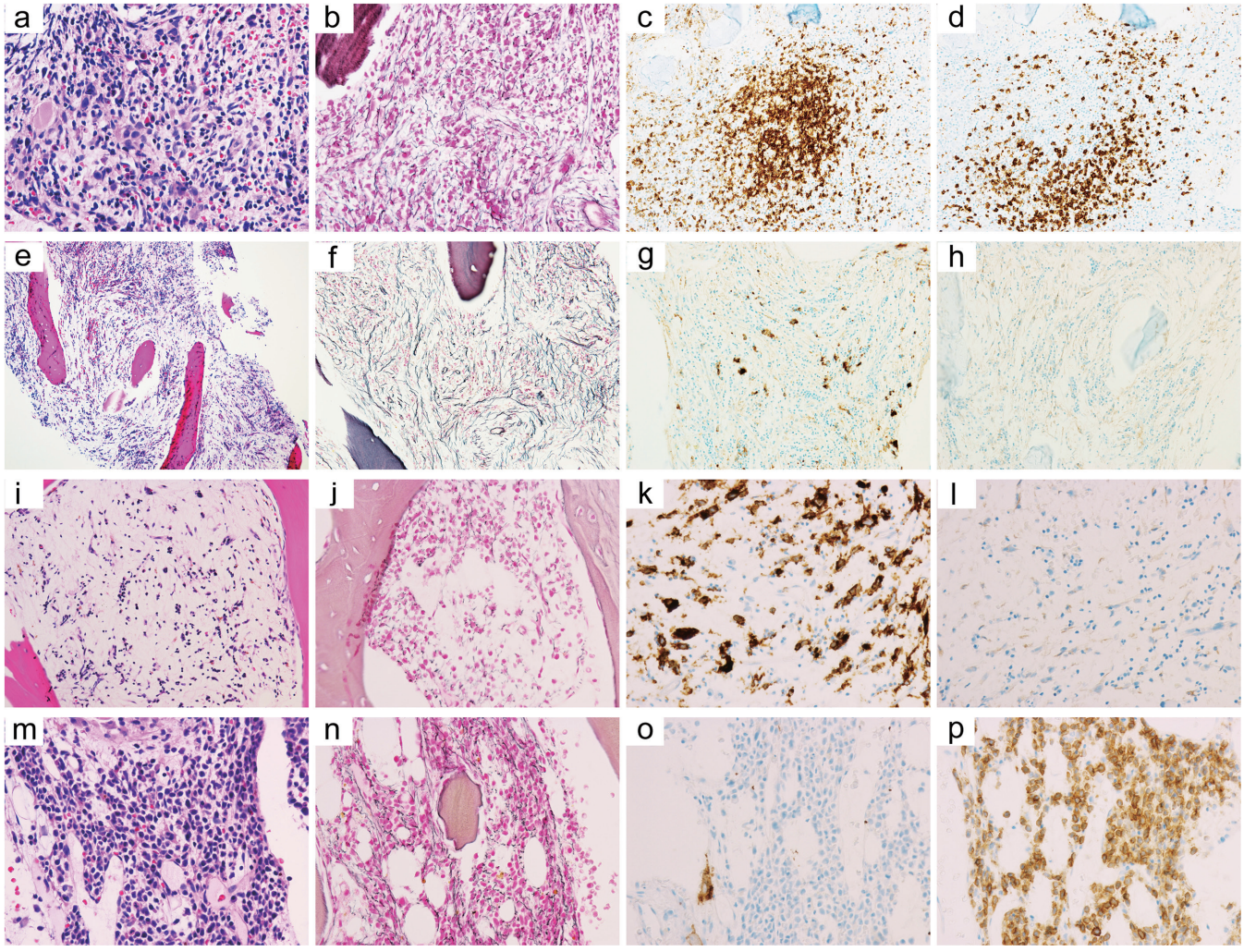

Fig. 2. Acute myeloid leukemia was established after multiple bone marrow biopsies in a child with cytopenia and bone marrow fibrosis. (a)-(d): The bone marrow biopsy shows mild hypercellularity (a, H&E 200×) and mild to moderate fibrosis (b, Reticulin stain, 200×). CD79a (c, 200×) and CD3 (d, 200×) immunostains highlight lymphoid aggregates with B and T lymphocytes. (e)-(h): The second bone marrow biopsy shows patchy cellularity (e, H&E 200×) and severe fibrosis (f, Reticulin stain, 200×). CD61 (g, 200×) immunostain highlights scattered megakaryocytes, including rare small ones; CD117 (h, 200×) immunostain is mostly negative. CD34 was negative (not shown). (i)-(l): The third bone marrow biopsy shows patchy low cellularity (i, H&E 200×) and mild to moderate fibrosis (j, Reticulin stain, 200×). CD61 (k, 200×) immunostain highlights many megakaryocytes, including small ones; CD117 (l, 200×) immunostain is mostly negative. CD34 was negative (not shown). The patient then received chemotherapy. (m)-(p): The fourth bone marrow biopsy shows patchy hypercellularity (m, H&E 200×) and moderate fibrosis (n, Reticulin stain, 200×). CD61 (o, 200×) immunostain highlights very rare megakaryocytes; CD117 (p, 200×) immunostain highlights numerous blasts. CD34 was negative (not shown). H&E, hematoxylin and eosin.

pathological review revealed fourteen cases of post-polycythemia myelofibrosis, seven cases of transitional myeloproliferative disorder, thirteen cases of hairy cell leukemia, three cases of malignant lymphoma, two cases of malignant histiocytosis, and one case of systemic lupus erythematosus.[30] Of note, infectious, cardiovascular, thromboembolic, and hemorrhagic complications were reported in 63%, 50%, 40%, and 33% of the patients, respectively.[30]

Follow-up and repeated bone marrow biopsies with ancillary molecular studies are required for patients with idiopathic MF. For example, as shown in Figure 2, this patient initially presented with cytopenia, fever, and bone pain, along with a diffuse bone marrow infiltrate on imaging. The extensive workup for infectious diseases and immunology was negative. The first bone marrow biopsy showed mild to moderate myelofibrosis (MF1-2) with no overt dysplasia or increased blasts; cytogenetics and FISH for the MDS panel were negative. CD79a and CD3 immunostains highlighted numerous B and T lymphocytes, which can be seen in AIMF. The patient was closely monitored, and a second bone marrow biopsy was performed two months later, which showed marked progression of myelofibrosis (MF3). However, there was no increase in blasts by flow cytometry and CD34 and CD117 immunostaining. An NGS panel containing approximately 50 common myeloid genes, as well as a germline bone marrow failure NGS panel, were negative for somatic or germline mutations. However, cytogenetics identified copy gains of chromosomes 19 and 21 in 3 out of 20 metaphase cells. In the presence of clonal chromosomal abnormalities, a myeloid neoplasm was suggested. A third bone marrow biopsy was performed one month later, which revealed moderate myelofibrosis (MF2) and 1.3% aberrant myeloblasts detected by flow cytometry. The same chromosomal gains were present in 17 out of 20 metaphase cells. A large NGS panel contain-

ing 500 genes identified a low level of *KMT2A* fusion gene but no other somatic mutations. Therefore, a diagnosis of AML was suggested, and the patient received chemotherapy per the Children's Oncology Group AML protocol.[3,4,31] However, the patient's symptoms did not improve, and a fourth biopsy performed six weeks after chemotherapy revealed a marked increase in blasts.

Conclusions

Myelofibrosis in pediatric patients shows a wide spectrum of clinical and pathological features, depending on the underlying etiology and genetics. In our practice, we carefully integrate clinical presentation, laboratory workup, bone marrow pathology, and extensive genetic studies, and follow the diagnostic algorithm to make an accurate diagnosis and guide therapy. However, there is still a lot of diagnostic or therapeutic uncertainty in cytopenic myelofibrosis due to its rarity in children. We anticipate multi-institutional collaborations to establish evidence- and consensus-based guidelines for widespread clinical use in the future.

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Conflict of interest

The author declares that there is no conflicts of interest.

Author contributions

JC is the sole author of the manuscript.

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