To the editor:

Bone marrow histology for the diagnosis of essential thrombocytethemia in children: a multicenter Italian study

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Essential thrombocytthemia (ET) is a myeloproliferative neoplasm (MPN) that mainly affects middle-aged patients. Although pediatric cases occur, they are rare, and their molecular features considerably differ from the adult counterparts: JAK2V617F mutation occurs in only 25% of cases,1 CALR mutations are found in <10% of patients,2 and the MPLW515L mutation is anecdotal.3 Overall, <40% of children with unexplained, long-lasting thrombocytosis have a clonal marker of ET.2

After the release of the 2001 World Health Organization (WHO) classification,4 bone marrow (BM) evaluation has become a cornerstone of ET diagnosis. However, the majority of studies has focused on adults, and little is known about the role of BM biopsy in pediatric ET. In fact, BM biopsy is seldom performed in children with a clinical picture of ET due to the invasiveness of the procedure. The main objective of this study was to explore the relevance of BM histology in children with high platelet counts in order to identify possible differences in: (1) primary vs reactive/secondary thrombocytosis (PedST) of childhood; and (2) pediatric (PedET) vs adult (AdET) cases of ET.

Treatment-naive diagnostic BM samples were collected from 21 pediatric patients clinically diagnosed with ET according to the 2008 WHO diagnostic criteria in 7 Italian pediatric centers (2011-2016). All cases were reviewed (separately and in joint sessions) by 2 hematopathologists (M.P., E.S.) who were blind to any clinical and/or molecular information. Six BM samples of PedST were used as controls, 5 of which had lymphoma and 1 prolonged spontaneously remitted thrombocytosis. The histological features were compared with those of 36 consecutive AdET cases, which were strictly diagnosed according to the 2008 WHO criteria in 7 Italian pediatric centers (2011-2016). The histological features were compared with those of 36 consecutive AdET cases, which were strictly diagnosed according to the 2008 WHO criteria in 7 Italian pediatric centers (2011-2016). The remaining 4 mutated cases exhibited a BM picture consistent with ET. Re-evaluation of the 12 triple negative (3NEG) cases revealed features consistent with ET in 9 cases, 2 cases compatible with pre-PMF (Figure 1 A-C), and 1 case with characteristics of secondary thrombocytosis (ST).

These results provide insight into the complex scenario of high platelet counts in childhood. Thrombocytosis is indeed a common
finding in children. Most cases are secondary/reactive forms, which spontaneously normalize over time. Rare hereditary thrombocytosis has also been documented. Primary thrombocytosis is extremely rare, with an estimated incidence of ~1 per 10 million annually.

The differential diagnosis of pediatric thrombocytosis may be challenging in clinical practice, and, unlike in adults, molecular biology is of limited value. Children with suspected ET have indeed low rates of driver mutations with a lower allele burden than adults.

Consequently, molecular studies cannot definitively identify the nature of several putative pediatric ET cases. Histological evaluation may prove to be of greater value, but little has been reported in the literature so far. The only few available studies have either examined single cases or small series of pediatric ET and have reported variable results.

Moreover, another large study about pediatric ET did not specifically address BM importance.

Our study is seemingly the largest published study on BM histology in pediatric patients with clinically diagnosed ET to date. Among 21 children, 20 cases had BM findings consistent with MPN (ET: n = 16; PV: n = 1; pre-PMF: n = 3) and 1 3NEG case had a histological picture of ST. The findings of histologically confirmed ET were distinct from those of PedST, and are thus consistent with the data status. Furthermore, the interpathologist agreement regarding the PedET were similar to those of AdET, irrespective of the mutational

Presence of BM reticulin fibrosis, n (%) 6 (28.5)* 0 6 (16.7)

MKD, megakaryocytes density; NA, not available.

*Two of these cases had histological features consistent with pre-PMF, 1 had masked PV, and 3 had ET.

In conclusion, the data presented in this study clearly show that BM evaluation is pivotal for ET diagnosis among the pediatric population, as it is for adults. BM assessment proves particularly helpful in the differential diagnosis between ET and its clinical mimickers (ie, PMF, PV, and ST) and should be part of the diagnostic workup of children with long-lasting unexplained thrombocytosis, together with several other clinical, laboratory, and molecular parameters.

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