PATHOLOGICA 2025;117:156-161;
DOI: 10.32074/1591-951X-975

Case report

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusion: report of two cases with different clinical presentation

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Summary

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (M/LN-eo-TK) such as PDGFRA, PDGFRB, FGFR1, JAK2, FLT3 rearrangement and ETV6::ABL1 fusion include rare and heterogeneous clinical-pathological entities with some similarities, not always associated with peripheral eosinophilia. Accurate diagnosis and demonstration of the specific genetic substrate have important implications since target therapy is possibly available. Herein we report two cases showing different bone marrow features and clinical presentation. Recognition of eosinophilic granuloblasts prompted genetic analysis that showed PDGFRB (case 1) and PDGFRA (case 2) gene rearrangement. Diagnosis of M/LN-eo-TK may be challenging. Pathologists may be the first professionals to suspect the disorder and should be aware of the therapeutic implication. Accurate BOM marrow evaluation with a panel of immunohistochemical reactions, and specific molecular analyses are required for proper diagnosis.

Key words: Myeloid/lymphoid neoplasms, Hypereosinophilia, TKI, PDGFRA, PDGFRB

Received: January 28, 2024
Accepted: February 5, 2025

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How to cite this article: Merenda E, Paciaroni K, Scalzulli E, et al. Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusion: report of two cases with different clinical presentation. Pathologica 2025;117:156-161. https://doi.org/10.32074/1591-951X-975

Introduction

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (M/LN-eo-TK) are a family of diseases caused by abnormal fusion genes that encode constitutively activated tyrosine kinases (TK) [1,2]. Despite the definition, eosinophilia is not always present. Clinical presentation is extremely heterogeneous partly due to different partner genes involved in the fusion rearrangement and, accordingly, diagnosis may be challenging for both clinician and pathologist [3]. Epidemiologic data show that overall M/LN-eo-TK are rare, show male prevalence and median age of onset in the fifth decade. Main presentations include features of myeloproliferative neoplasms (MPN), myelodysplastic neoplasms (MDS), myelodysplastic/myeloproliferative neoplasms (MDS/MPNs), systemic mastocytosis, or de novo or secondary acute leukaemias/lymphomas of mixed or ambiguous phenotype; and symptomatology related to eosinophils tissue infiltration, such as restrictive pulmonary fibrosis [4], restrictive cardiomyopathy due to endomyocardial fibrosis, eosinophilic gastritis or dermatitis. Pediatric cases are reported in the literature [5].

Genes that are more commonly rearranged are PDGFRA, PDGFRB,

FGFR1, and less commonly JAK2 and FLT3. In addition, ETV6::ABL1 and other more rare fusions are described [1]. The correct diagnosis of a M/LN-eo-TK has significant therapeutic implications given extraordinary sensitivity to imatinib (PDGFRA and PDGFRB fusions) and ruxolitinib (JAK2 fusions) bringing in some cases to complete clinical and molecular remission [6]. Histopathologically, the bone marrow is often abnormal showing panmyelosis, myelofibrosis and variable features including increased eosinophils, mast cells, and prominent dyserythropoiesis. Morphologic changes vary from case to case contributing to the challenging diagnosis [7].
Here we report two cases showing eosinophilic cells in different maturational stages in the bone marrow and different clinical presentation.

Clinical presentations case 1

A 56-year-old man was admitted to the hematology department presenting with mild anemia and mild splenomegaly (longitudinal diameter: cm 19).
A blood count performed in suspicion of a myeloproliferative disease gave the following results: total white blood cells: 9900/mm3; neutrophils: 6740/mm3, lymphocytes: 1750/mm3, eosinophils: 690/mm3), hemoglobin (Hb): 12 g/dL, platelets (PLT): 270,000/mm3.
Bone marrow aspirate smear was hypocellular and characterized by hyperplasia of the granuloblastic series present with notes of dysgranulopoiesis (numerous degranulated neutrophils). An increase in eosinophils was observed, some with morphological atypia and the presence of rare osteoclasts. Uric acid level was normal (14 mg/dl) and so were LDH (228 UI/L) and B12 (> 2000 pg/mL). The serological exams for viruses (HIV, HBV, HCV and EBV) were negative. The patient had ischemic stroke intermittent fever and gastric perforation in his past clinical history.

Clinical presentation case 2

A 65-year-old male presented with weakness, soaking sweats, 5 kg weight loss during the last two months. A recent blood count test documented leukocytosis with eosinophilia. Physical examination showed liver enlargement (liver could be detected 3 cm beyond the rib arch) and splenomegaly. Laboratory tests revealed a white blood cells count: 20.500/$mm^{3;}$ neutrophils: 1800/mm^3, lymphocytes: 2300/mm^3, eosinophils: 15.800/mm^3), haemoglobin (Hb): 16.3 g/dL, platelets (PLT): 215,000/mm^3. Uric acid was normal (7,6 mg/dl) and so were LDH (268 IU/L) and B12 (> 2000 pg/mL). Serological exams for viruses (HIV, HBV, HCV and EBV) were all negative. The patient had no relevant diseases in his past clinical history. Peripheral blood smear was characterized by massive presence of eosinophils, including band eosinophils and some other showing hypersegmented nuclear forms.

Bone Marrow Histology

Bone marrow biopsy from the two patients showed marked hypercellularity as expected for age (90%). In case 1 proliferation of immature myeloid cells with round shaped nuclei, inconspicuous nucleoli and abundant eosinophilic granules was the most striking feature, pointing to eosinophil precursors (Fig. 1). In case 2 a proliferation of both precursors and mature eosinophils was evident (Fig. 2). In both cases cells showed scattered MPO and CD15 positivity and were CD34 negative. Erythropoietic lineage was decreased and showed dyserythropoiesis. Megakaryocytes were decreased, slightly dysmorphic or presented as micromegakaryocytes, regularly distributed throughout the specimen. Mast cells, identified by antibodies against KIT receptor (CD117) and tryptase, were increased accounting for about 15% of the bone marrow cellularity. They were often spindle shaped, mostly isolated or in small loosely cohesive groups of less than 15 elements. Blast count [performed through CD34 and KIT receptor (CD117) immunostains] was < 4%.
Numerous small interstitial lymphocytes, most with T phenotype (CD3+), and to a lesser extent with B phenotype (CD20+), were distributed in nodular aggregates (case 1) and in single elements (8% of the total cellularity). Perisinusoidal plasma cells, isolated (case 1) and in small clusters, were also observed. Finally, vascular's density increase with sinus dilatation was observed. Reticulin fibers were diffusely increased throughout the sample and fibrosis grading was assigned MF-3 (case 1) and MF-2 (case 2) according to the WHO 2022 scoring system [1].
Altogether, clinical and histologic features suggested a diagnosis of myeloid neoplasm with eosinophilia and prompted genetic analysis that showed ETV6::PDGFRB fusion (case 1) and FIP1L1::PDGFRA fusion (case 2) (nested RT PCR). Genetic screening of JAK-2, BCR-ABL, and KIT was negative in both cases. Based on such findings patients underwent therapy with TK inhibitors (Imatinib) and corticosteroids. After a year of treatment, patients are in clinical remission.

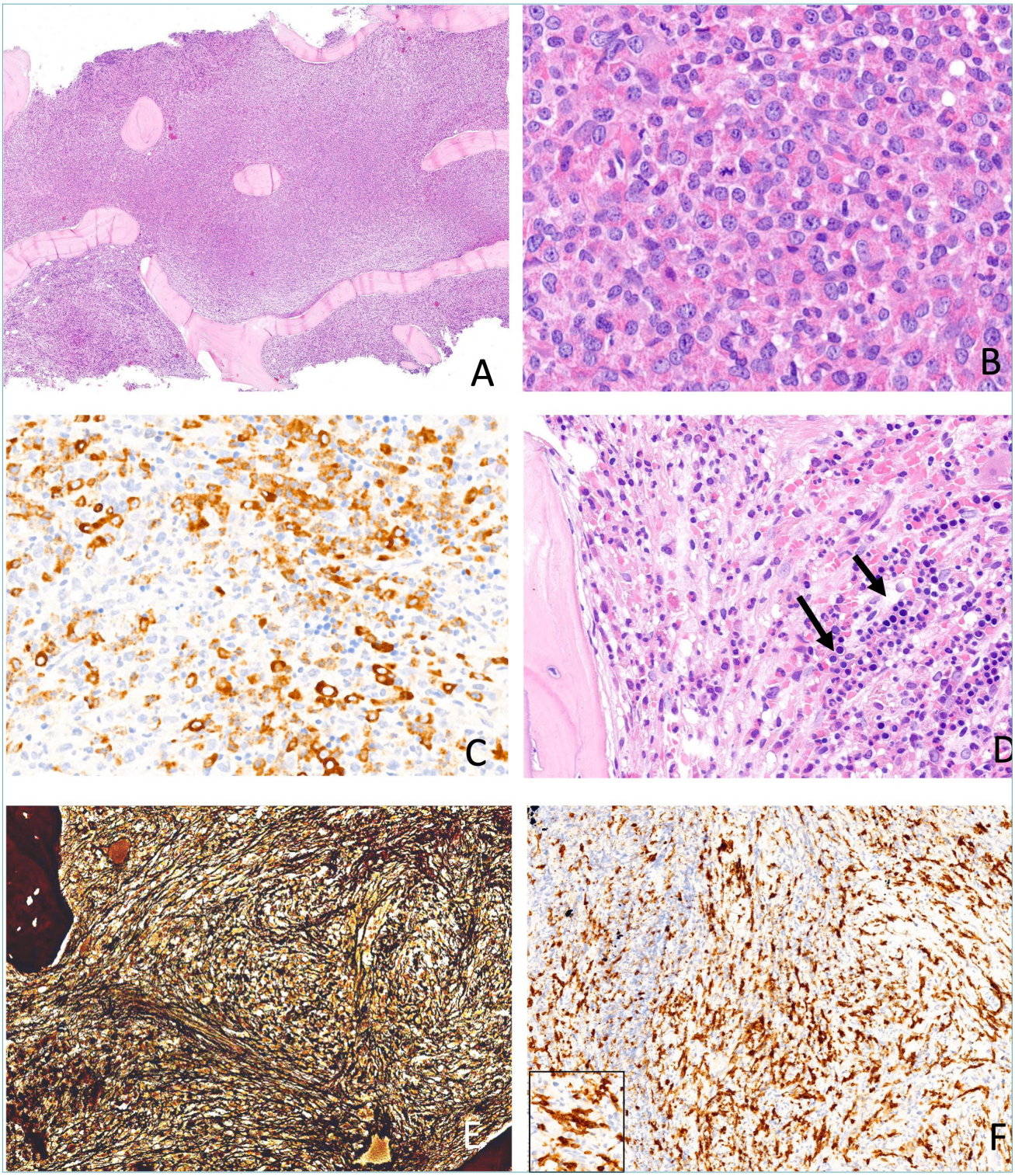

Figure 1. (A) Hypercellular bone marrow. Normal hematopoiesis is replaced by a monomorphic proliferation of eosinophil precursors (hematoxylin and eosin stain, original magnification 2X). (B) High power view shows eosinophil precursors as large oval cells with moderate cytoplasm containing cytoplasmic pink-reddish granules and a nucleus with coarse chromatin and indistinct nucleoli. No mature eosinophils are evident (hematoxylin and eosin stain, original magnification 60X). (C) Anti-myeloperoxidase (MPO) immunohistochemical stain is negative in neoplastic eosinophilic precursors. (original magnification 20X). (D) A few enlarged erythroid islands are highlighted in the para-trabecular space (arrow) (hematoxylin and eosin stain, original magnification 20X). (E) Reticulin fiber network is increased (silver stain, original magnification 20X). (F) Expansion of spindle-shaped mast cells which do not form highly cohesive groups. (Anti-tryptase antibody, original magnification 20X).

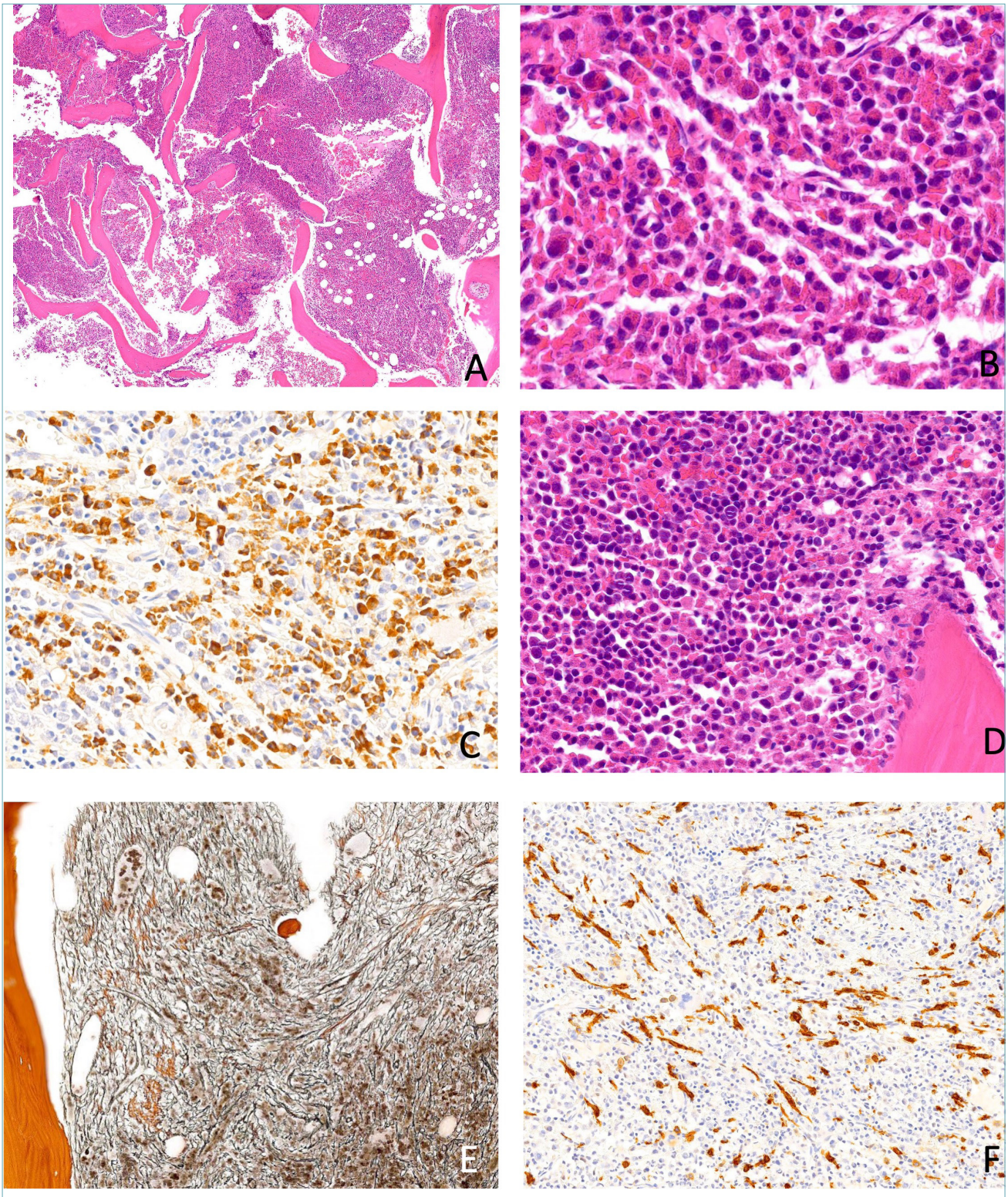

Figure 2. (A) Hypercellular bone marrow. Normal hematopoiesis is replaced by a monomorphic proliferation of eosinophilic myelocytes (hematoxylin and eosin stain, original magnification 2X). (B) High power view shows eosinophilic myelocytes as large oval cells with moderate cytoplasm containing cytoplasmic pink-reddish granules and a nucleus with coarse chromatin and indistinct nucleoli (hematoxylin and eosin stain, original magnification 60X). (C) Anti-myeloperoxidase (MPO) immunohistochemical stain (original magnification 20X). (D) Enlarged erythroid islands (arrow) (hematoxylin and eosin stain, original magnification 20X). (E) Reticulin fiber network is increased (silver stain, original magnification 20X). (F) Expansion of spindle-shaped mast cells which do not form highly cohesive groups. (Anti-tryptase antibody, original magnification 20X).

Discussion and conclusion

Since the discovery of the first ETV6-PDGFR fusion associated with eosinophilia, much progress has been made [8]. Hypereosinophilia has been historically defined as a persistent blood eosinophil count of at least 1.5x109/L. In 2001, the WHO proposed criteria to differentiate chronic eosinophilic leukemia (CEL) from lymphocyte variant hypereosinophilia and idiopathic hypereosinophilic syndrome (iHES). Diagnosis of CEL was made by the presence of increased blasts (peripheral blood and/or bone marrow) or cytogenetic/molecular evidence of clonality. In the absence of these two criteria, diagnosis of CEL could be suggested by clinical and laboratory features in common with chronic myeloid leukemia (CML) or myeloproliferative disease (MPDs) (such as hepato-splenomegaly, dysplasia in any lineages, myeloid immaturity, bone marrow fibrosis, elevated serum vitamin B12 or tryptase levels [9].

In the same year, Schaller and Burkland published the first empirical and successful imatinib treatment in a patient with hypereosinophilic syndrome (iHES) [10]. This case report was the turning point that addressed many researchers to better define the molecular basis of clonal eosinophilia. Imatinib sensitivity in patients with chronic myeloproliferative disorders associated with eosinophilia and PDGFRB rearrangements and identification of FIPILI-PDGRFA fusion as molecular basis for therapeutic response to imatinib were highlighted respectively in 2002 and 2003 placing the basis for new recategorization of disorders associated with eosinophilia [11,12].

Starting from evidence that some cases of eosinophilia are caused by genetic abnormalities and responded to imatinib, in 2008 WHO classification [13] introduced a new subgroup of MPN named ‘’Myeloid/lymphoid neoplasms with eosinophilia associated with rearrangements of PDGFRA, PDGFRB, or FGFR1” [9]. This semi-molecular classification underlined the importance of integration of clinical, molecular, genetic and immunophenotypic data. Importantly, in this new subcategory eosinophilia was not always present hence the necessity in 2016 to modify the criteria of this group that was re-named ‘’Myeloid/lymphoid neoplasm with eosinophilia (M/LN-eo) and gene rearrangement”, which included also a new provisional entity (i.e. myeloid/lymphoid neoplasms with PCM1:: JAK2 fusion) [14].

Two new classifications of myeloid and lymphoid neoplasms have recently been published: the 5th edition of WHO classification and the International Consensus Classification. In both of these classifications the category name changed again from the prior to M/LN-eo with tyrosine kinase (TK) gene fusions, expanding the number of genes involved and reiterating the notion that eosinophilia is a common, but not invariable, feature [1,15]. Both classifications include several specific disease group (PDGFRA, PDGFRB and FGFR1 rearrangement), recently expanded with FLT3 rearrangement, ETV6::ABL fusion and promoting PCM1::JAK2 (JAK2 rearrangement) and its genetic variants ETV6::JAK2 and BCR::JAK2 as formal entities from their provisional state in the 2016 WHO classification.

According to this molecular-based classification, eosinophilia can be considered a consequence of the rearrangement or fusion of TK genes, and this family of genes is the target of TKI such as imatinib [12]. PDGFRA- and PDGFRB-rearranged neoplasms show an excellent response to imatinib and other tyrosine kinase inhbitor (TKI) therapy. Resistance to imatinib is rare and is due to T674I mutation within the ATP-binding domain of PDGFRA which confers pan-resistance to multiple TKIs, except ponatinib [15]. In contrast, patients with FGFR1, JAK2, FLT3 rearrangement and ETV6::ABL1 fusion exhibit more aggressive behavior and variable sensitivity to TKI.

Starting from this brief recap it is clear that bone marrow biopsies may play an important role in diagnosing these rare neoplasms. Pathologists may be the first professionals to suspect the disorder and should be aware of the therapeutic implication. Accurate BOM marrow evaluation with a panel of immunohistochemical reactions are required for proper diagnosis. Generally, bone marrow biopsy is hypercellular with numerous eosinophils and precursors. Sometimes, as in our case 1, mature eosinophils may be scarce and precursors predominate. The latter finding may explain the absence of peripheral blood hypereosinophilia. An increased number of spindled, atypical mast cells eventually organized in loose clusters is common and might help towards the correct diagnosis, thus immunostaining for CD117 and/or tryptase are strongly recommended in the routine immunohistochemical BOM panel, eventually followed by molecular analysis of KIT D816V. Of note, aberrant expression of mast cells of CD25 has been reported in M/LN-eo, while CD2 is usually negative. In some cases, the mast cell proliferation may form dense clusters, showing histopathological features of systemic mastocytosis (SM) [17] but lack the KIT D816V mutation. In the current ICC, such cases are classified under M/LN-eo if one of the TK gene fusions is detected[2]. Reticulin fibrosis is almost a constant finding. When the described morphological features are present, it is mandatory to perform cytogenetic and molecular analyses such as array-comparative genomic hybridization (CGH) and RNA-se-

quencing and/or whole transcriptome sequencing to define the diagnosis. Conventional karyotyping allows the detection of the majority of rearrangement involving PDGFRB and FGFR1, however, to identify the specific fusion partner or to detect cryptic alteration (such as FIP1L1::PDGFRA fusion) fluorescence in situ hybridization (FISH) and/or molecular studies are required.

In conclusion, this heterogeneous group of neoplasms is tricky to diagnose and only a multidisciplinary workup can bring to correct diagnosis. The interest of our two cases resides mainly in similar bone marrow histology with totally different clinical presentations.

Conflicts of interest statement

The authors declare no conflicts of interest.

Funding

None.

Authors' contributions

All authors gave their approval for publications of the final version of the manuscript.

Ethical consideration

The present study complied with the Ethical Principles for Medical Research Involving Human Subjects according to the World Medical Association Declaration of Helsinki; all samples were anonymized before histology and immunohistochemistry; no futher ethical approval was necessary to perform this study.

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