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REVIEW

Updates on eosinophilic disorders

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Abstract

This review addresses changes and updates in eosinophilic disorders under the International Consensus Classification (ICC). The previous category of myeloid/lymphoid neoplasm with eosinophilia (M/LN-eo) and a specific gene rearrangement is changed to *M/LN-eo with tyrosine kinase gene fusions* to reflect the underlying genetic lesions. Two new members, M/LN-eo with *ETV6::ABL1* fusion and M/LN-eo with various *FLT3* fusions, have been added to the category; and M/LN-eo with *PCM1::JAK2* and its genetic variants *ETV6::JAK2 and BCR::JAK2* are recognized as a formal entity from their former provisional status. The updated understanding of the clinical and molecular genetic features of *PDGFRA, PDGFRB* and *FGFR1* neoplasms is summarized. Clear guidance as to how to distinguish these fusion gene–associated disorders from the overlapping entities of Ph-like B-acute lymphoblastic leukemia (ALL), de novo T-ALL, and systemic mastocytosis is provided. Bone marrow morphology now constitutes one of the diagnostic criteria of chronic eosinophilic leukemia, NOS (CEL, NOS), and idiopathic hypereosinophilia/hypereosinophilic syndrome (HE/HES), facilitating the separation of a true myeloid neoplasm with characteristic eosinophilic proliferation from those of unknown etiology and not attributable to a myeloid neoplasm.

Keywords Myeloid/lymphoid neoplasm with eosinophilia · Tyrosine kinase gene fusion · *ETV6::ABL1*; *FLT3* rearrangement · Chronic eosinophilic leukemia · NOS · Idiopathic hypereosinophilic syndrome

Introduction

In adults, peripheral blood (PB) eosinophilia is defined by $\geq 0.5 \times 10^9$/L eosinophils and hypereosinophilia (HE) by $\geq 1.5 \times 10^9$/L. Tissue eosinophilia is defined by increased eosinophils or signs of eosinophil degranulation beyond the normal range for the particular sites [1]. A definition of BM eosinophilia has been proposed to require ≥ 20% eosinophils, with or without PB eosinophilia. Hypereosinophilic syndrome (HES) is defined as peripheral blood (PB) hypereosinophilia in association with tissue/organ damage [1]. The causes of eosinophilia are broad and can be reactive (majority), neoplastic, or idiopathic [2, 3]. In eosinophilia associated with a hematopoietic neoplasm, eosinophils often bear the same molecular genetic aberrations as their progenitors and/or other myeloid components [4]. These hematopoietic neoplasms can be further categorized into three large groups: (1) myeloid/lymphoid neoplasms with eosinophilia (M/LN-eo) and recurrent genetic rearrangements such as *PDGFRA, PDGFRB*, *FGFR1*, or *PCM1::JAK2* [5]; (2) eosinophilia associated with another well-defined myeloid neoplasm, such as chronic myeloid leukemia (CML) or acute myeloid leukemia (AML) with inversion of chromosome 16; and (3) chronic eosinophilic leukemia (CEL), not otherwise specified (NOS) [5]. This current review highlights the updates in the International Consensus Classification

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(ICC) [6] on eosinophilic disorders, mainly in the category of M/LN-eo and recurrent genetic rearrangements and the further refinement of the definitions for CEL, NOS, and idiopathic HE/HES.

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

M/LN-eo and rearrangements of *PDGFRA, PDGFRB*, and *FGFR1* were recognized as a standalone category in the 2008 WHO classification of myeloid neoplasms [7]. M/LN-eo with *PCM1::JAK2* fusion was added to this family as a provisional entity in the 2016 WHO classification. The common features shared among the members in this category include: (1) constitutive tyrosine kinase (TK) signaling as a result of a gene fusion; (2) origin from mutated pluripotent bone marrow (BM) stem cells that can differentiate into myeloid and/or lymphoid progenies, leading to clinically complex and heterogeneous manifestations; (3) frequent association with PB and/or tissue eosinophilia; and (4) excellent responses of some entities to specific TK inhibitors (TKI).

The category name is changed to *M/LN-eo with TK-gene fusions* (M/LN-eo-TK) in the ICC [6] and applies to instances bearing the respective genetic aberration at the initial presentation and not to other well-defined hematopoietic neoplasms that have acquired such abnormalities later in the course of disease. The name change emphasizes the molecular genetic changes underlying these hematopoietic neoplasms that lead to constitutive TK signaling amenable to targeted therapy [3, 8]. Additional important changes made in this disease category are the inclusion of M/LN with t(9;12)(q34;p13)/*ETV6::ABL1* and *FLT3*-rearrangements as new members and promoting *PCM1::JAK2* and its genetic variants *ETV6::JAK2* and *BCR::JAK2* as formal entities from their provisional state in the 2016 WHO classification. The update also provides clear guidance on how to distinguish M/LN-eo presenting as B- or T-acute lymphoblastic leukemia (ALL) from Philadelphia (Ph)-like B-ALL or de novo T-ALL, and M/LN-eo with mast cell proliferation from systemic mastocytosis.

Myeloid/lymphoid neoplasms with ETV6::ABL1/t(9;12)(q34.1;p13.2) fusion

ETV6::ABL1 fusions have been reported in various hematologic malignancies, including B- or T-ALL, AML, and chronic myeloid neoplasms (CMN) such as myeloproliferative neoplasm (MPN) and myelodysplastic/myeloproliferative neoplasm (MDS/MPN) [9–13]. In the 44 cases summarized by Zaliova and colleagues [12], half (22/44, 50%) were ALL (20 B-ALL and 2 T-ALL) and more than half occurred in infants or pediatric patients. Interestingly, although these ALL cases presented with high white blood cell counts (WBCs), eosinophilia was only reported in 3/13 patients. Of note, *ETV6::ABL1* fusion was reported to occur in 0.17% of pediatric B-ALL [14], and 0.38% of adult B-ALL, and comprised approximately 1–2% Ph-like B-ALL [12]. The two aforementioned T-ALL cases also occurred in pediatric patients as de novo disease. These cases should be categorized as Ph-like B-ALL and de novo T-ALL with *ETV6::ABL1* if there is not a prior, concurrent or post-treatment myeloid neoplasm, and not as M/LN-eo.

Cases that should be considered for categorization as M/LN-eo most often present as CMN and rarely as AML with *ETV6::ABL1*. CMN with *ETV6::ABL1* shows clinicopathological features reminiscent of chronic myeloid leukemia (CML) with eosinophilia; however, some cases may resemble atypical CML (aCML) or essential thrombocythemia [9]. Patients often present with an elevated WBC, eosinophilia (> 90% cases), and many also with increased basophils (> 1%, up to 10%). Eosinophilia may not be prominent at initial diagnosis but eventually emerges at relapse or disease progression. Common findings in the BM include hypercellularity, a markedly increased M:E ratio and increased eosinophils. Megakaryocyte morphology is highly variable and ranges from normal forms to small, large, or a mixture of small and large forms. Dysgranulopoiesis and dyserythropoiesis are uncommon, while increased fibrosis is quite common. Most patients present in chronic phase, and, to a much lesser extent, in myeloblastic or lymphoblastic phase. A few cases of AML or myeloid sarcoma (Fig. 1) with this fusion are reported, all associated with eosinophilia. However, it is unclear if these cases arose de novo or as a myeloblastic phase of myeloproliferative neoplasm (MPN).

ETV6::ABL1 fusion results from a complex rearrangement involving a translocation and inversion or an insertion of *ETV6* in 9q34 or *ABL1* in 12p13. The fusion is often cryptic; thus, fluorescence in situ hybridization (FISH) analysis using *ETV6* and *ABL1* break-apart probes and/or RNA-sequencing (RNA seq) technology are needed for detection. The alternative splicing generates two fusion transcripts—type A (without *ETV6* exon 5) and type B (with exon 5); the latter of which is significantly more common. Although both transcripts result in constitutive chimeric TK functionality, type B has higher kinase activity due to a direct SH2 domain of the GRB2 binding site on *ETV6* exon 5, enhancing the PI3-kinase and MAP-kinase pathways [15]. *ABL1* has also

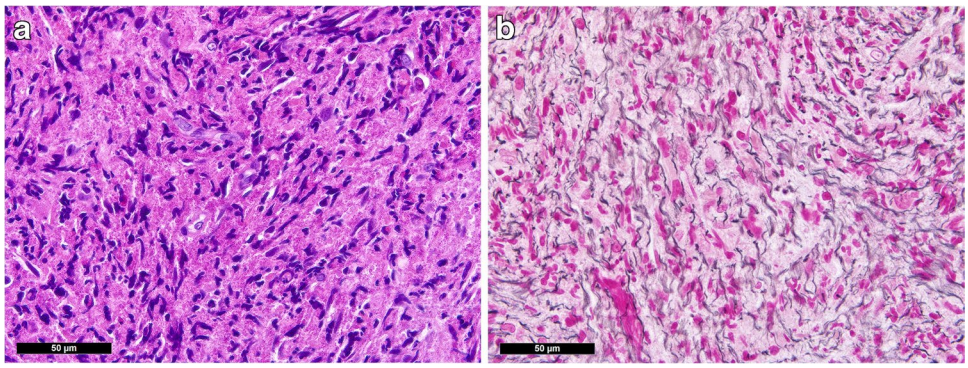

Fig. 1 **A** "Sarcomatous" appearing eosinophilic spindle-cell tumor destroying the tibia of a 61-year-old male patient that was diagnosed as an *ETV6::ABL1*-fused M/LN-eo (H&E stain, original magnification 600×. **B**: Diffuse MF1 fibrosis with woven pattern accompanying the case from Fig. 1A (Gömöri staining on an automated stainer, original magnification 600×)

been reported to fuse with alternate partners [16]; however, most of these cases present as Ph–like B-ALL [17] or de novo T-ALL [18]. Therefore, for the time being, only *ETV6::ABL1* M/LN-eo is included in this category. With the increased use of RNA seq in clinical samples, *ABL1* fusions with other partner genes (including cryptic lesions) with clinical features of M/LN-eo may be discovered.

Somatic mutations detected by next generation sequencing (NGS) are reported in approximately 50% of cases [9, 11, 19], including *ARID2, TP53, SETD2, CDKN1B, PTPN11,* and *SMC1A* genes. Due to the rarity of this disease and only a few cases being tested, the biological role of these mutations is unclear.

Patients with *ETV6::ABL1* have shown various responses to TKI targeted therapy [9–13]. *S*econd- or 3rd-generation TKI [10] appear to be superior to the first-generation imatinib. Durable hematological and molecular remissions have been observed in a significant number of patients presenting in chronic phase but not CMN in blast phase. Disease progression is reported in around 30% patients, which can progress to myeloblastic or lymphoblastic phase or myeloid sarcoma, and in such occasions, the prognosis is dismal despite the addition of TKI to the standard chemotherapy.

Myeloid/lymphoid neoplasms with FLT3/t(v;13q12) rearrangements

FLT3 is located on chromosome 13q12 and belongs to the receptor TK (RTK) subclass III family. *FLT3* rearrangement in hematolymphoid neoplasms is uncommon with around 30 cases reported [20–34]. The most common is *ETV6::FLT3*/t(12;13)(p13;q12), which is not cryptic if adequate metaphases are obtained for analysis. Other partner genes reported are *ZMYM2*/13q12 [25, 28], *TRIP11*/14q32 [24], *SPTBN1*/2p16 [30], *GOLGB1*/3q13 [23], *CCDC88C*/14q32 [31], *MYO18A*/17q12 [29], and *BCR*/22q11. There are a number of uncharacterized partner genes, for example, rearrangement t(13q12;v) (3q27, 5q15, 5q35, 7q36, 13q22) [32, 34]. Some of the fusions are cryptic, such as *ZMYM2::FLT3* [25, 28], and require FISH or RNA seq for identification.

FLT3-rearranged cases often present as MPN with eosinophilia, or as MDS/MPN resembling chronic myelomonocytic leukemia (CMML), a typical CML (aCML), juvenile myelomonocytic leukemia, or systemic mastocytosis associated with hematological malignancy. Extramedullary involvement is very frequent and includes diagnostic entities including T-ALL/LBL, mixed phenotype leukemia, myeloid sarcoma, and, rarely, T cell lymphoma or B-ALL/LBL.

Mutations detected by NGS have been assessed in a small number of cases. Such aberrations occur in approximately 40–50% of cases [34], including *ASXL1, PTPN11, RUNX1, SETBP1, SRSF2, STAT5B, TET2, TP53,* and *U2AF1* genes. The significance of these mutations is unknown.

Of the reported cases, 9 patients received a FLT3 inhibitor, sunitinib or sorafenib [21, 25, 26, 28, 31, 33, 34]. Rapid hematological improvements with or without complete cytogenetic response to sunitinib or sorafenib monotherapy have been observed. Some patients achieved a sustained remission; some lived with stable disease; and some received allogeneic hematopoietic cell transplant (HSCT). Loss of response may occur due to acquired *FLT3* N841K mutation in the activation loop of the TK domain [21].

Myeloid/lymphoid neoplasms with PCM1::JAK2/t(8;9)(p22;p24.1) fusion

M/LN-eo with *PCM1::JAK2* fusion [35-37] and its genetic variants was proposed as a provisional entity in the 2016 WHO classification. Subsequently, several studies have described the disease spectrum and histopathological and molecular genetic features of these disorders [10, 38–41]. Affected patients are mostly in the later 40s (years of age), exhibit a pronounced male predominance,

and approximately 60% present with MPN or MDS/MPN [42], which is commonly accompanied by eosinophilia, hepatosplenomegaly, and occasionally basophilia. Some cases may initially present as B-lymphoblastic crisis. Extramedullary disease involvement is common. It is known that *PCM1::JAK2* can be acquired at disease progression, such as an AML at relapse. Importantly, these should not be considered in the category of M/LN-eo [38, 39]. De novo AML is extremely rare. For patients presenting as CMN, the disease may be indolent, with a reported 5-year survival around 80% [36, 38, 39, 42]. However, for patients who present with increased blasts or blast phase or progress to acute leukemia, the prognosis is poor. Targeted therapy with JAK2 inhibitors such as ruxolitinib has produced clinical responses in patients presenting in chronic phase but the response may be short lived with limited survival benefit [10, 38, 43–45]. HSCT provides ultimate cure for these patients.

The BM of *PCM1::JAK2* is usually hypercellular with increased eosinophils, increased immature erythroid precursors (pronormoblasts) in aggregates or sheets, and increased fibrosis. The presence of "erythroid microtumors" accompanied by eosinophilia and increased fibrosis in a male patient presenting with a MPN or MDS/MPN-like disorder is virtually pathognomonic and should prompt a presumptive diagnosis of M/LN-eo with *JAK2*-fusion (Fig. 2). "Erythroid microtumors" are also frequently observed in extramedullary lesions, and some have been diagnosed as erythroblastic sarcoma [38–40].

M/LN-eo with alternate partners to *JAK2* such as t(9;12)(p24.1;p13.2)/*ETV6*::*JAK2* and t(9;22)(p24.1;q11.2)/*BCR::JAK2* [10, 38, 39, 41] show less distinctive histopathological features, such as the characteristic large immature erythroid islands. However, they demonstrate similar clinical and genetic features, and are considered as genetic variants of t(8;9)(p22;p24.1)/*PCM1::JAK2*. *JAK2* fusions with other partner genes, such as t(5;9)(q14.1;p24.1)/*STRN3::JAK2* [46], and *PAX5::JAK2* [47] are usually seen in Ph-like B-ALL; which are, per definition, not M/LN-eo.

Mutations detected by NGS in *PCM1::JAK2* M/LN-eo are reported to range from 14 to 50% of cases studied [38,

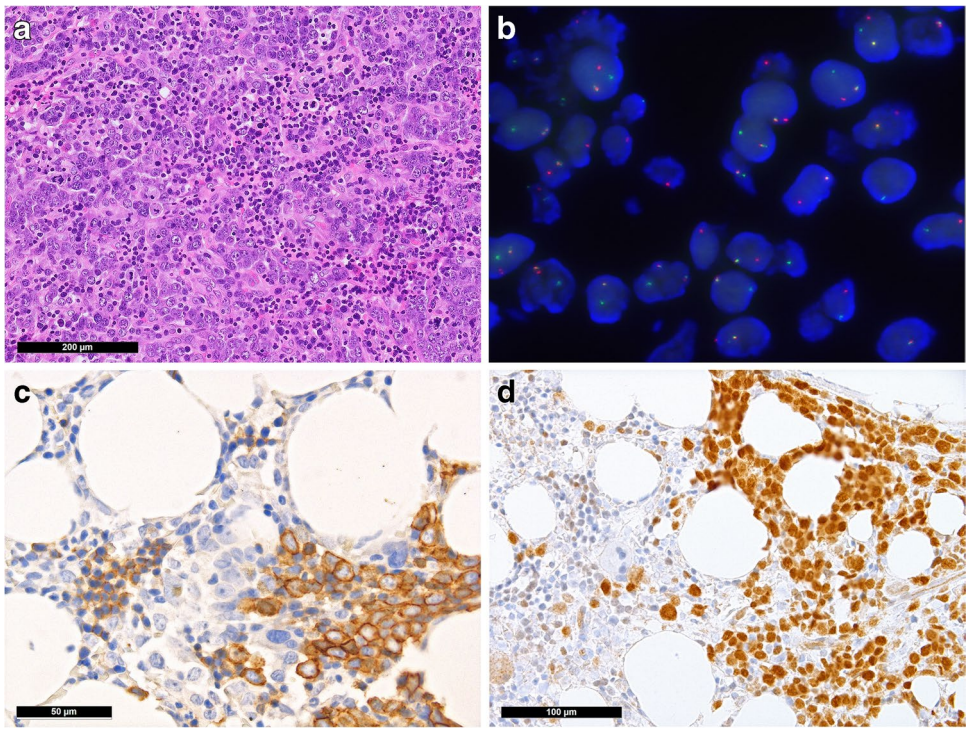

Fig. 2 **A** Erythroid microtumors in a lymph node of a 45-year-old male patient suffering from *PCM1::JAK2*-fused M/LN-eo image (H&E stain, original magnification 100×). **B** Split red and green fluorescent in situ hybridization (FISH) signals with the break-part probe for the *JAK2*-locus in cells from the case on Fig. 1A; note the fused yellow-orange signals of the non-rearranged allele (FISH with DAPI-counterstain; original magnification 1000). **C** Erythroid microtumor in a relapsing *PCM1::JAK2*-fused M/LN-eo after allogeneic hematopoietic cell transplantation in comparison to an normal erythroids on the left side of the image; note that the affected erythroid cells are at least four times larger than the normal counterparts (immunoperoxidase staining on an automated stainer with the antibody clone EP700Y against E-cadherin, original magnification 600×). **D** Pathologic overexpression of phosphorylated STAT5 in the erythroid microtumor shown on Fig. 2C compared to the weak expression in the background unaffected erythropoiesis (immunoperoxidase staining on an automated stainer with the antibody clone 8–5-2, original magnification 400×)

39, 48] and include *ASXL1, TET2,* and *BCOR* genes. Mutations appear to be lower in cases presenting as MPN and higher in cases presenting as acute leukemia.

M/LN-eo with t(8;9)(p22;p24.1)/*PCM1::JAK2* is now accepted as a formal entity under M/LN-eo with TK fusion by ICC, and t(9;12)(p24.1;p13.2)/*ETV6::JAK2* and t(9;22)(p24.1;q11.2)/*BCR::JAK2* are recognized as genetic variants.

M/LN-eo with PDGFRA, PBGFRB, and FGFR1 rearrangements

M/LN-eo with *PDGFRA, PBGFRB,* and *FGFR1* rearrangements represent the three original members in the category of M/LN-eo. Since their initial inclusion, there has been an expanded understanding of the clinical features and cytogenetic characteristics. *PDGFRA*-rearranged cases are by far the most common in this category of M/LN-eo and show a very striking male predominance (male-to-female ratio of 17:1). The usual age at onset is in the late 40s, but pediatric patients may be affected [49], and the disease may occur in the therapy-related setting. Eosinophilia is common, 70–90%, frequently with hypereosinophilia. High level of vitamin B12 is often observed, and serum tryptase may be elevated. BM is often hypercellular with eosinophilia. Megakaryocytes are often decreased, may or may not exhibit dyspoietic changes, and fibrosis is common (Fig. 3A and B). Splenomegaly occurs in approximately 60% patients, and extramedullary tumors in approximately 50%. The latter are mostly myeloid, either mature or immature (myeloid sarcoma), and occasional lymphoblastic, commonly involving epidural and paraspinal space or lymph nodes.

The disease-defining interstitial deletion of approximately 800 kb (including *CHIC2)* on chromosome 4q12 that leads to the *FIP1L1::PDGFRA* fusion is below the level of resolution of conventional cytogenetics (e.g., cryptic). Routine detection of the interstitial deletion is best achieved by FISH or RT-PCR. On the other hand, fusions with 6 other partner genes, including *CDK5RAP2::PDGFRA*, *ETV6::PDGFRA, FOXP1::PDGFRA, KIF5B::PDGFRA*, *STRN::PDGFRA*, and *TNKS2::PDGFRA*, are often not cryptic. *BCR::PDGFRA/* t(4;22)(q12;q11) cases may have a clinical presentation similar to CML or aCML with marked

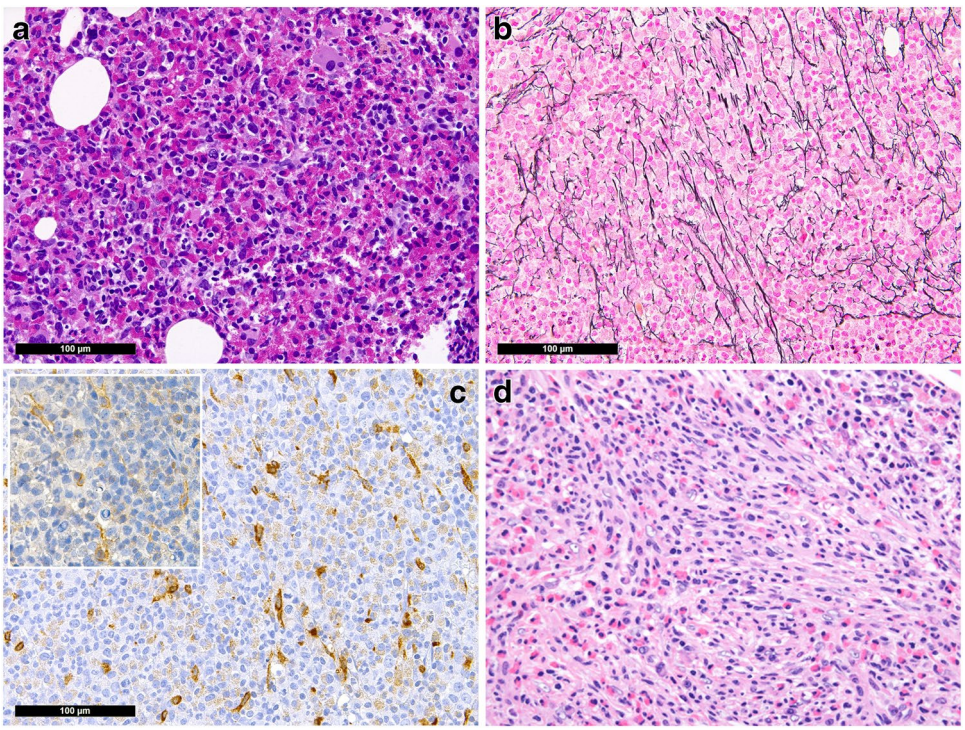

Fig. 3 **A** Typical morphological appearance of a myeloid/lymphoid neoplasms with eosinophilia (M/LN-eo) and *FIP1L1::PDGFRA*-fusion in a 48-year-old male patient; hypercellular bone marrow with myeloid hyperplasia and accompanying 40% eosinophilia as well as one dysplastic megakaryocyte with nuclear separation in the upper, right-middle part of the image (H&E stain, original magnification 200×). **B** Diffuse MF1 fibrosis that is common in M/LN-eo (same case as Fig. 1A) (Gömöri staining, original magnification 200×). **C** Increase of spindle-shaped atypical mast cells that weakly co-express CD25 (Insert) in a 52-year-old male patient suffering from *ETV6::PDGFRB*-fused M/LN-eo; note that there are no mast cell clusters. **D** In a case of *FIP1L1::PDGFRA*-fusion, the mast cell proliferation forms dense clusters mixed with many background eosinophils, which was initially thought as systemic mastocytosis until the demonstration of *FIP1L1::PDGFRA* fusion. *KIT* D816V mutation was negative

leukocytosis [50]. Cases with activating point mutations of *PDGFRA* have been reported [51]; however, it is unsure if all CMN with *PDGFRA* are within the spectrum of M/LN-eo.

Almost all patients with a *PDGFRA* fusion are sensitive to imatinib. Primary or secondary resistance is unusual, but if it occurs, it is linked to the T674I or D842V mutation within the ATP-binding domain of *PDGFRA* [52, 53]. Such patients have been shown to be responsive to 2nd- or 3rd- generation TKI [54] or FLT3 inhibitors [53].

Within the category of M/LN-eo, *PDGFRB* rearranged cases are the second most common. There is a male-to-female ratio of 2:1 with the usual age of onset also being in the late 40s (similar to *PDGFRA*). In addition, it also can occur in the therapy-related setting. In contrast to *PDGFRA*- rearranged cases, M/LN-eo with *PDGFRB* fusions may present with monocytosis, resembling CMML, and some may display a cytopenic presentation without eosinophilia, resembling MDS [39].

The *PDGFRB* gene is located at 5q31 ~ 33, and more than 30 partner fusion genes have been described to date [3]. Typically, *PDGFRB* rearranged M/LN-Eo should demonstrate a 5q32 abnormality by conventional cytogenetic analysis if 20 adequate metaphases are obtained for analysis. However, recent studies have shown that cryptic *PDGFRB* rearrangements are common [39, 55] and often occur in partner genes other than t(5;12)(q32;p13.2)/*ETV6::PDGFRB*, such as *DIAPH1::PDGFRB* [28], *BCR::PDGFRB* [56], *AFAP1L1::PDGFRB*, *SART3::PDGFRB* and *G3BP1::PDGFRB* [57]. Importantly, some of the fusions may not even be detected by FISH, and consequently RNA seq is required for identification. All reported *PDGFRB* rearranged cases, regardless of partner genes, are sensitive for TKI therapy.

M/LN-eo with *FGFR1* rearangement is very uncommon. The male-to-female ratio is 1.5:1. The usual age at onset is in the 30s [58, 59]. B-symptoms, lymphadenopathy, and hepatosplenomegaly are common, especially in patients with T-LBL/ALL. Accompanying eosinophilia is seen in 60–70% of cases, especially in patients with a MPN-like presentation. Cases with an acute leukemic presentation or extramedullary lesions may fulfill criteria of T-ALL, B-ALL, or mixed phenotype acute leukamia (MPAL). In such instances, the background features of MPN may be obscured by the blasts and become more obvious post myeloablative treatment. M/LN-eo associated with t(8;13)(p11;q12)/*ZMYM2::FGFR1* frequently presents with nodal (or extranodal) disease with a T-LBL component admixed with scattered or perivascular myeloid blasts, termed "bilineal lymphoma" [39, 60]; an eosinophilic infiltrate is frequently present and may provide a hint for the diagnosis.

Conventional cytogenetic analysis is reliable in demonstrating translocations at 8p11. The t(8;13) is the most common translocation, and, thus, *ZMYM2* is the most common fusion-partner of *FGFR1*, but there are 14 additional fusion partners. The clinicopathological manifestations may differ according to these; e.g., patients with t(8;22)(p11.2;q11.2)/*BCR::FGFR1* usually manifest with monocytosis and B-ALL (B-lymphoblastic phase) [61], while approximately half of the affected with t(8;9)(p12;q33)/*CEP110::FGFR1* display monocytosis and tonsil hypertrophy [62].

Unlike M/LN-eo with *PDGFRA* and *PDGFRB* fusions, *FGFR1*- rearranged neoplasms are usually not responsive to imatinib. Clinical trials with 3rd-generation TKI (ponatinib) and the FGFR inhibitor pemigatinib are promising [63], yet HSCT remains the only curative option [64].

Mutations detected by NGS are reported in 20–50% of cases with *PDGFRA* M/LN-eo [39, 48] including *ASXL1, BCOR, DNMT3A, ETV6, SRSF2,* and *RUNX1* genes. A similar mutation frequency is reported in *PDGFRB* M/LN-eo, 30–50%, involving *ASXL1, TET2, BCOR, ETV6, STAG2,* and *RUNX1* genes [39, 48, 65]. Mutations in *FGFR1* rearranged cases are highly frequent, detected in 70–80% of cases, and typically (80%) involve *RUNX1* [48, 66]. *RUNX1* mutations have been significantly associated with an acute leukemic presentation or progression [66]. The common clinical presentations, molecular genetic alternations, responses to TKI treatment of M/LN-eo are summarized in Table 1.

Addressing the overlap of M/LN-eo-TK with other entities

It is known that an abnormal mast cell proliferation can be seen in M/LN-eo with any of the recurrent fusion genes, particularly in *PDGFRA* fusion cases (Fig. 3C). In most instances, the mast cells are scattered, are spindle shaped, and show aberrant CD25 expression. In some cases, the mast cell proliferation may form dense clusters, showing histopathological features of systemic mastocytosis (SM) (Fig. 3D) [24, 34, 39, 67–69]. Pardanani and colleagues [69] studied 19 cases of SM with concomitant hypereosinophilia, and over 50% of cases (10/19, 56%) were found to have the *FIP1L1::PDGFRA* fusion. Importantly, these cases consistently lacked the *KIT* D816V mutation and did not behave or exhibit features of typical SM. Therefore, categorization of these rare cases as SM is problematic. In the current ICC, such cases are classified under M/LN-eo if one of the TK gene fusions is detected [6]. As such, it is highly recommended to test cases of mast cell disease for rearrangements of the TK genes when SM is associated with eosinophilia or the *KIT* D816V mutation is absent.

M/LN-eo also can overlap with Ph-like B-ALL/LBL or de novo T-ALL with rearrangements involving one of the TK genes. For example, while the most common genetic variant of *PDGFRB*, t(5;12)(q32;p13.2)/*ETV6::PDGFRB,*

Table 1 Genetic abnormalities, clinical presentations, and targeted therapy of myeloid/lymphoid neoplasms with eosinophilia (M/LN-eo) and tyrosine kinase (TK) gene fusions

TK gene	Most common fusion	Other Partner genes/variants	Typical clinical and bone marrow (BM) manifestations	Accompanying mutations	Targeted therapy
PDGFRA	Cryptic deletion 4q12/ *FIP1L1::PDGFRA**	*BCR; CDK5RAP2; ETV6; FOXP1; KIF5B; STRN; TNKS2*	Male-to-female ratio: 17:1 Age at presentation: late 40 s The most common among M/LN-eo-TK PB eosinophilia: > 95% Common: CEL-like with extramedullary** involvement; MPN-type megakaryocytes, MF, spindled $CD25^+$ mast cells Others: MDS/MPN, ***B-ALL/LBL, AML or mast cell proliferations	*ASXL1, BCOR, DNMT3A, RUNX1, SRSF2, TET2*	Excellent response to TKI, imatinib
PDGFRB	t(5;12)(q32;p13.2)/ *ETV6::PDGFRB*	> 30 partners, cryptic	Male-to-female ratio: 2:1 Age at presentation: late 40 s *PDGFRB* rearrangements in 3% of adults with unexplained eosinophilia PB eosinophilia: about 80% Common: CEL-like or CMML/aCML-like with eosinophilia; MF, spindled $CD25^+$ mast cells Others: ***ALL/LBL, AML or mast cell proliferations, occasionally MDS	*ASXL1, BCOR, DNMT3A, NRAS, STAG2, STAT5B, TET2, ZSRS2*	Excellent response to TKI, imatinib
FGFR1	t(8;13)(p11.1;q12.1)/ *ZMYM2::FGFR1*	15 other partners, including *BCR*	Male-to-female ratio: 1.5:1 Age at presentation: late 30 s PB eosinophilia: about 70% Common: nodal T-ALL/LBL (admixed with myeloid blasts and/or eosinophils) with MPN-like features or blast phase MPN in the BM; MF, often decreased megakaryocytes Others: ***B-ALL/LBL, AML or MPAL, myelosarcoma, monocytosis, polycythemia, tonsil hypertrophy, thrombopenia	*ASXL1, CSFR3, STAG2, RUNX1* (rather constant feature)	Responsive to FGFR1 inhibition by pemigatinib, 3rd generation TKI ponatinib, especially in chronic phase
JAK2	t(8;9)(p22;p24.1)/ *PCM1::JAK2*	*ETV6* and *BCR*	Male-to-female ratio: 5.5:1 Age at presentation: late 40 s PB eosinophilia: about 70–80% Common: MPN or MDN/MPN-like BM with eosinophilia; erythroid precursors in aggregates/ "erythroid microtumors", MF Others: ***B- and T-ALL/LBL with MPN-like BM features	*ASXL1, BCOR, BCORL1, CD36, EP300, ETV6, RUNX1, SRSF2, TET2, TP53*	Limited response to ruxolitinib, resistant to imatinib and dasatinib
FLT3	t(12;13)(p13.2;q12.2)/ *ETV6::FLT3*	*BCR; CCDC88C; GOLGB1; MYO18A; SPTBN1; TRIP11; ZMYM2*	Male-to-female ratio: 2.2:1 Age at presentation: mid 40 s PB eosinophilia: about 70–80% Common: ***T-ALL/LBL or myeloid sarcoma with CEL-, MPN- or MDS/MPN-like BM features	*ASXL1, RUNX1, STAT5B, SRSF2, TET2, TP53, U2AF1*	Various responses to specific FLT3 inhibitors
ETV6::ABL1	t(9;12)(q34.1;p13.2)/ *ETV6::ABL1*	Unknown	Male-to-female ratio: 3:1 Age at presentation: late 40 s PB eosinophilia: about 90–100% Common: CML-like with eosinophilia in chronic or blast phase	*ARID2, CDKN1B, TP53, SMC1A*	Various responses to 2nd or 3rd generation TKI

aCML/CML, atypical/chronic myeloid leukemia; *ALL/LBL* acute lymphoblastic leukemia/lymphoblastic lymphoma; *AML*, acute myeloid leukemia; *CEL* chronic eosinophilic leukemia; *CMML* chronic myelomonocytic leukemia; *MDS MPN* myelodysplastic syndrome/myeloproliferative neoplasm; *MF*, myelofibrosis; *MPAL* mixed phenotype acute leukemia; *TK/TKI*, tyrosine kinase/inhibitors. PB eosinophilia is defined as eosinophils > 6% and an absolute eosinophil count > 0.5×10^9/L. While most of the chronic myeloid neoplasms present with an absolute eosinophil count > 1×10^9/L, the cases presenting as lymphoblastic leukemia may not have significant eosinophilia.

*Cases with activating point mutations of *PDGFRA* have been reported and should, as an exception with the family of M/LN-eo, be considered within the spectrum of M/LN-eo.

**Epidural and paraspinal involvements are a particular feature of *PDGFRA* rearranged cases, frequently myeloid tumor with eosinophilia, either mature or immature, occasionally lymphoblastic.

***For cases presenting as B-ALL or T-ALL, an involvement of myeloid cells should be demonstrated in order to distinguish from Ph-like B-ALL and de novo T-ALL.

often manifests with multilineage involvement and features of M/LN-eo, *PDGFRB* rearrangements with alternate partners such as *EBF1*, *SSBP2*, *TNIP1*, *ZEB2,* and *ATF7IP* often present as de novo B-ALL, and are thus best classified as Ph-like B-ALL [70]. *ETV6::JAK2* is now formally accepted as a genetic variant of *PCM1::JAK2*, and the entity should be limited to cases with an involvement of myeloid cells. If a case with a lymphoblastic presentation, an underlying myeloid neoplasm needs to be demonstrated. In fact, of the reported cases of hematopoietic neoplasms with *ETV6::JAK2* fusion, more than half were de novo B-ALL or de novo T-ALL [36, 71] without an associated CMN, and such cases should be classified as Ph-like B-ALL or de novo T-ALL [70, 72]. As a rule, cases being classified as M/LN-eo-TK with presentation as B- or T-ALL, the TK fusion genes should involve the myeloid lineage in addition to lymphoblasts. Often, patients have a CMN that manifests either prior to, concomitantly, or post therapy for ALL. In performing FISH, the fusion signals are not only observed in blasts but also in segmented neutrophils, providing strong evidence of multilineage involvement [73]. A road map (Fig. 4) is provided to illustrate the basic principles in distinguishing these two categories of diseases.

Chronic eosinophilic leukemia, not otherwise specified and idiopathic hypereosinophilia/hypereosinophilic syndrome

CEL, NOS is a myeloid neoplasm included in the category of MPN. It is characterized by persistent eosinophilia not meeting the criteria for other genetically defined entities. Idiopathic hypereosinophilic syndrome (iHES) is defined as persistent HE (≥ 6 months) with associated tissue/organ damage/injury due directly to eosinophil-released cytokines or enzymes, and the underlying cause, either reactive or a distinct clonal myeloid process, cannot be identified. Idiopathic HE or HE of unknown significance (HEus) [74] is referred to as persistent HE of unknown etiology without related organ/tissue damage. In the 2008 WHO classification, CEL, NOS was distinguished from idiopathic HE/HES by the presence of increased blasts and/or the presence of clonal karyotypic abnormalities. With the advent of NGS in hematopoietic neoplasms, somatic mutations associated with myeloid neoplasms have been detected in 25–30% of patients who have persistent hypereosinophilia [75–78], a normal karyotype, and no increase in blasts, and who would be otherwise considered as "iHES." Mutations detected by NGS were found mostly in genes involved in DNA methylation and chromatin modification, such as *ASXL1, TET2, EZH2,* and *DNMT3A,* but also in other genes such as *SRSF2, TP53,* and *SETBP1* [75–77, 79]. *STAT5B* N642H [78] has been reported in some patients with a referral diagnosis of eosinophilia (1.6%), including patients who would be otherwise diagnosed with iHES. While *STAT5B* mutations can help to establish clonality and facilitate a diagnosis of CEL, NOS, *STAT5B* mutations can be seen in other myeloid neoplasms without a prominent eosinophilic proliferation and are felt not unique for CEL, NOS.

Overall, while a positive mutation by NGS provides evidence of clonality, such mutations have also been reported in aging individuals lacking evidence of a myeloid neoplasm. Indeed, some cases with a very typical

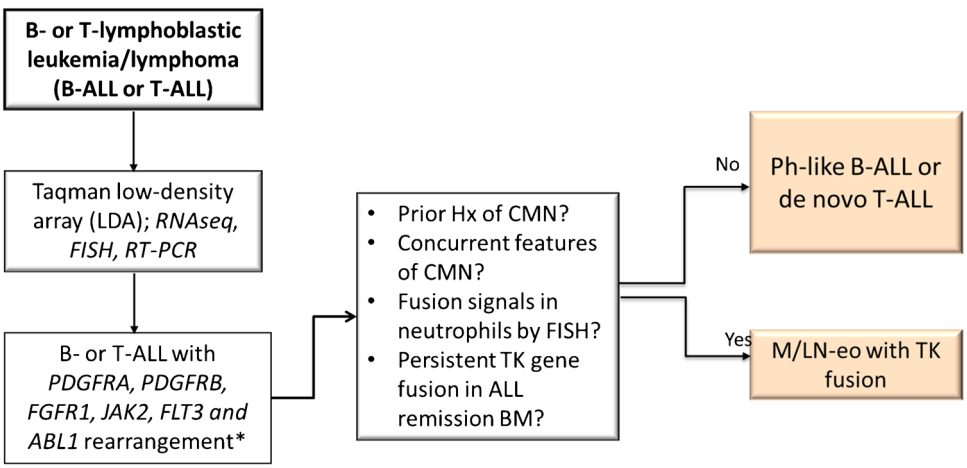

Fig. 4 How to differentiate myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase fusion from Ph-like B-lymphoblastic leukemia (Ph-like B-ALL) or de novo T-ALL. *It is known that certain partner genes, such as *EBF1, SSBP2, TNIP1, ZEB2*, and *ATF7IP* with *PDGFRB*, partner genes other than *PCM1, BCR, ETV6* with *JAK2*, and partner genes other than *ETV6* with *ABL1*, most likely occur in Ph-like B-ALL or de novo T-ALL. Abbrevations: CMN, chronic myeloid neoplasm; FISH, fluorescence in situ hybridization

clinical course of iHES/HEus and normal BM morphology have been reported to carry somatic mutations [79, 80]. On the other hand, some true CEL, NOS, even the ones with karyotypic abnormalities, may not show detectable mutation tested by the myeloid neoplasm-targeted NGS panels [2, 79, 80].

In CEL, NOS, the BM is usually markedly hypercellular due to a prominent proliferation of eosinophils and granulocytic cells. Megakaryocytes are almost always abnormal, frequently showing MDS-type small hypolobated forms or a mixture of MDS-like and MPN-like megakaryocytes (Fig. 5). Given that the eosinophil proliferation can be quite significant, it is critical to carefully search for abnormal megakaryocytes in such cases. Dysgranulopoiesis and/or dyserythropoiesis may be present in some cases. MF2 or MF3 fibrosis is seen in 20–30% patients. These features were similar to those seen in MDS or MDS/MPN. Although not entirely specific, significant cytologic abnormalities in eosinophils (≥ 20% of eosinophils) are frequently observed in CEL, NOS patients [79, 80], including abnormal granulation (hypogranular, uneven granulation), abnormal nuclear lobation (multilobation, hypolobation, nuclear branching), and large or markedly left-shifted forms (Fig. 5). Such BM features have been found extremely valuable in identifying cases with clinical and biological features, and the natural history of a myeloid neoplasm [80]. In contrast, the BM of iHES and HEus is, except for increased eosinophils, largely morphologically unremarkable (Fig. 6) [79–81]. A key update in the ICC is that abnormal BM histopathology is now incorporated into the diagnostic criteria for CEL, NOS Table 2). This allows for a more evidence-based support of the neoplastic nature of CEL, NOS [6], and a more definitive separation from

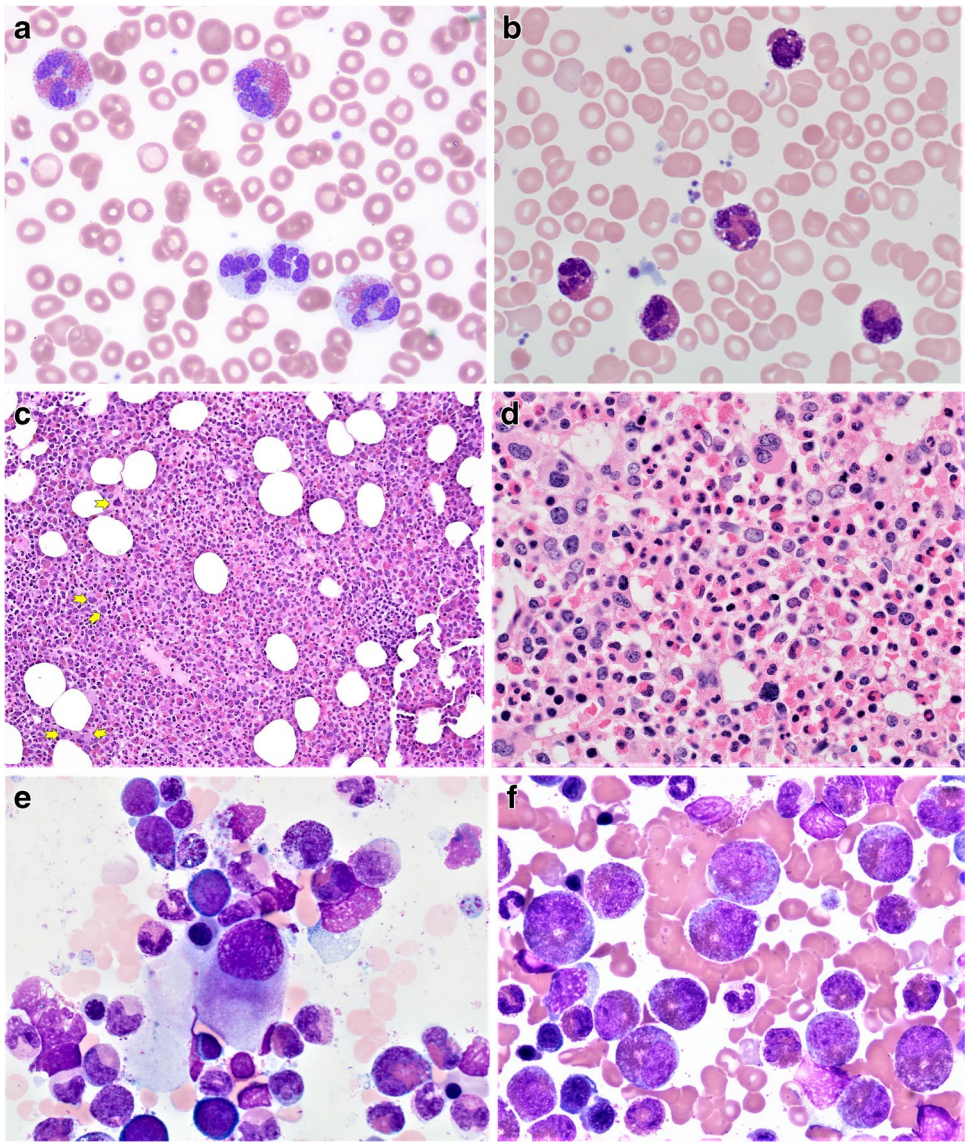

Fig. 5 Abnormal morphological features observed in chronic eosinophilic leukemia (CEL), NOS. Peripheral blood frequently show very abnormal eosinophils (**A** and **B**), with abnormal nuclei that can be hypolobated or hypersegmented (in the current two cases), abnormal granulation (hopogranular **A** and hypergranular **B**). Bone marrow is almost always hypercellular (**C** and **D**), megakaryocytes can be decreased (**C**), normal in numbers or occasionally increased, frequently dysplastic (MDS-like small megakaryocytes) (both cases **C** and **D**), occasionally can be mixed with small and large megakaryocytes. Bone marrow aspirate confirms the presence of a small monolobated megakaryocyte (**E**) and eosinophilia. In some cases, eosinophils are left-shifted with many eosinophilic myelocytes (**F**)

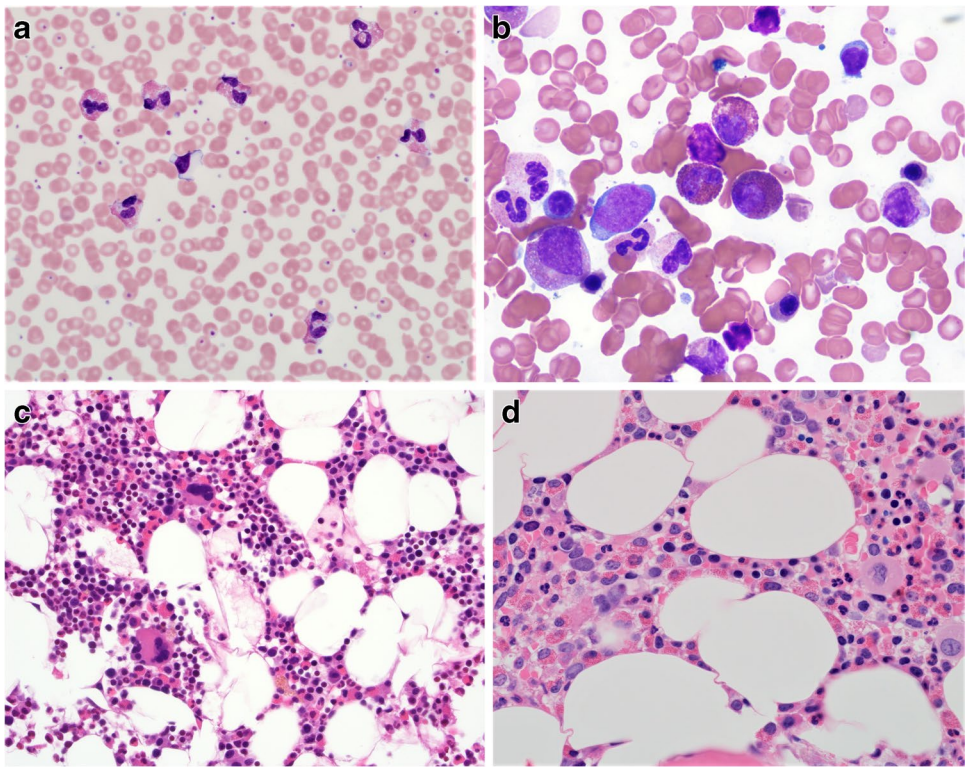

Fig. 6 Idiopathic hypereosinophilic syndrome (iHES). Peripheral blood smears show eosinophilia (**A**), most of the eosinophils are normally bilobated forms, with occasional eosinophils showing mild uneven granulation. Bone marrow aspirate smears show normal appearing eosinophils and precursors with no dysplasia in erythroids and myeloids (**B**). Bone marrow biopsies show increased eosinophils, but otherwise normal cellularity, normal appearing megakaryocytes and normal bone marrow topography (two different cases **C** and **D**)

iHES/HEus (Table 3). Of note, the somatic mutations in iHES/iHES are often present as either a single gene alteration (often involving the DTA genes *DNMT3A*, *TET2* and *ASXL1*) and/or at a relatively low variant allele frequency (VAF) [79, 80]. Clinical features may also help to distinguish CEL, NOS from iHES [75, 79, 80]: CEL, NOS patients are older, with higher WBCs and absolute eosinophil counts, often display cytopenia(s), exhibit frequent constitutional symptoms, hepatosplenomegaly, and high LDH. In contrast, iHES patients are significantly younger, with more allergic or rheumatoid symptoms, and skin rash, pulmonary, gastrointestinal, and /or endocrine involvement. Ideally, a diagnosis of CEL, NOS is supported by the presence of clonal molecular genetic abnormalities and abnormal BM findings or increased blasts. However, in some cases, clonal cytogenetic or molecular alterations may not be demonstrated with current testing methods. In such instances, after other causes of eosinophilia have been exhaustively excluded, abnormal BM findings reminiscent of MDS or MDS/MPN suffice to establish a diagnosis of CEL, NOS in the presence of persistent and unrelenting hypereosinophilia.

Table 2 Diagnostic criteria for chronic eosinophilic leukemia, not otherwise specified (CEL, NOS)

Peripheral blood hypereosinophilia (eosinophil count $\geq 1.5 \times 10^9$/L and eosinophils $\geq 10\%$ of white blood cells)
Blasts constitute $< 20\%$ cells in peripheral blood and bone marrow, not meeting any other diagnostic criteria for AML*
No tyrosine kinase gene fusion including *BCR::ABL1,* other *ABL1, PDGFRA, PDGFRB, FGFR1, JAK2*, *FLT3* fusions
Not meeting criteria for other well-defined MPN; chronic myelomonocytic leukemia, or systemic mastocytosis**
Bone marrow shows increased cellularity with dysplastic megakaryocytes with or without dysplastic features in other lineages and often significant fibrosis, associated with an eosinophilic infiltrate OR • There are increased blasts $\geq 5\%$ in the bone marrow and/or $\geq 2\%$ in the peripheral blood
Demonstration of a clonal cytogenetic abnormality and/or somatic mutation(s) ***

*AML with recurrent genetic abnormalities with $< 20\%$ blasts is excluded.

**CEL, NOS may occur as SM-AMN (systemic mastocytosis associated with myeloid malignancies).

***In the absence of a clonal cytogenetic abnormality and/or somatic mutation(s) or increased blasts, bone marrow findings supportive of the diagnosis will suffice in the presence of persistent eosinophilia, provided other causes of eosinophilia having been excluded.

Table 3 Diagnostic criteria for idiopathic hypereosinophilic syndrome

Persistent peripheral blood hypereosinophilia (eosinophil count $\geq 1.5 \times 10^9$/L and $\geq 10\%$ eosinophils)*
Organ damage and/or dysfunction attributable to tissue eosinophilic infiltrate**
No evidence of a reactive, well-defined autoimmune disease or neoplastic condition/disorder underlying the hypereosinophilia
Rule out lymphocyte variant hypereosinophilic syndrome***
Bone marrow morphologically within normal limits except for increased eosinophils
No molecular genetic clonal abnormality, with the caveat of clonal hematopoiesis of indeterminate potential (CHIP)

**Preferably a minimal duration of 6 months if documentation is available.

**Hypereosinophilia of uncertain significance has no tissue damage, otherwise, should follow the same diagnostic criteria.

***The abnormal T cell population needs to be detected immunophenotypically with or without TCR clonality by PCR.

There is a caveat when interpreting a "high" eosinophil count. When the WBC is high, a small percentage of eosinophils may, by default, amount to an absolute eosinophil count $\geq 1.5 \times 10^9$/L. In the ICC update, both CEL, NOS and iHES/HEus are now required not only to show an absolute eosinophil count $\geq 1.5 \times 10^9$/L, but also relative eosinophilia ($\geq 10\%$). This change emphasizes that there needs to be a characteristic feature of eosinophilic proliferation in such disorders. As a result, if a CMN shows a relative and absolute eosinophilia without defining genetic lesions, a diagnosis of CEL, NOS would supersede a diagnosis of aCML, MDS/MPN-U, or MPN-U.

In summary, the changes and updates related to eosinophilic disorders in the ICC are highlighted and elaborated with literature support in this review. The updates in M/LN-eo involve the following: (1) change of the category name from M/LN-eo with gene rearrangement to myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase gene fusion; (2) additions of *ETV6::ABLI* and *FLT3* fusions as new members; (3) recognition of *PCM1::JAK2* and its genetic variant *BCR::JAK2* and *ETV6::JAK2* as formal entity; and (4) provide guidance in distinguishing M/LN-eo from Ph-like B-ALL and de novo T-ALL, and address the issue of mast cell proliferation with TK fusions. The changes in CEL, NOS and iHES/HEus are to include BM morphology in the diagnostic criteria and require not only absolute but also relative eosinophilia in the definition. These changes are evidence based; reflect a consensus based on disease genetic, histopathological, and clinical features; and will impact the diagnosis and clinical management of patients (Table 2 and 3).

Author contribution AZ, RH, DA, AO, and SW participated in the discussion and formulation of the International Consensus Classification (ICC) on eosinophilic disorder. All authors participated in the writing, editing, and proofreading of the manuscript.

Declarations

The review follows the ethical standards.

Conflict of interest The authors declare no competing interests.

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