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REVIEW

Pathogenesis, classification, and therapy of eosinophilia and eosinophil disorders

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ABSTRACT

Eosinophilia is a recurrent feature and diagnostic clue in several hematologic malignancies. In stem cell- and myelopoietic neoplasms, eosinophils are derived from the malignant clone, whereas in lymphoid neoplasms and reactive states, eosinophilia is usually triggered by eosinopoietic cytokines. Myeloid neoplasms typically presenting with eosinophilia include chronic myeloid leukemia, chronic eosinophilic leukemia (CEL), other myeloproliferative neoplasms, some acute leukemias, advanced mast cell disorders, and rare forms of myelodysplastic syndromes. Diagnostic evaluations in unexplained eosinophilia have to take these diagnoses into account. In such patients, a thorough hematologic work-up including bone marrow histology and immunohistochemistry, cytogenetics, molecular markers, and a complete staging of potentially affected organ systems has to be initiated. Endomyocardial fibrosis, the most dangerous cardiovascular complication of the hypereosinophilic state, is frequently detected in PDGFR-mutated neoplasms, specifically in FIP1L1/PDGFRA+ CEL, but is usually not seen in other myeloid neoplasms or reactive eosinophilia, even if eosinophilia is recorded for many years. Treatment of hypereosinophilic patients depends on the variant of disease, presence of end organ damage, molecular targets, and the overall situation in each case. In a group of patients, oncogenic tyrosine kinases (TK) such as FIP1L1/PDGFRA, can be employed as therapeutic targets by using imatinib or other TK-blocking agents.

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Biology of eosinophils and reactive eosinophilia

Eosinophils are myelopoietic effector cells that produce and store a number of biologically active molecules, including eosinophil cationic protein (ECP), major basic protein (MBP), eosinophil neurotoxin, lipid mediators (prostaglandins, leukotriens, and thromboxan A2), and cytokines such as tumor necrosis factor (TNF) alpha.[1–3] Once activated, eosinophils release their mediators and cytokines, thereby influencing homeostasis and tissue integrity.[3] In case of massive and permanent activation, eosinophils can induce or trigger inflammatory processes and cause changes in the microenvironment, sometimes resulting in fibrosis or/and thrombosis, and thus in severe or even life-threatening end organ damage.[3–6]

In common with other leukocytes, eosinophils originate from multipotent and lineage-committed CD34+ hematopoietic precursor cells (Fig. 1).[7–10] Precommitted progenitors often are bipotent and give rise to eosinophils and basophils when exposed to eosinophil growth factors (Fig. 1).[7,8] These cells (CFU-eo/ba) are detectable in the bone marrow and peripheral blood in healthy subjects as well as in various pathologic conditions.[7,8,11,12] The most potent growth factors for eosinophils are interleukin(IL)-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-3 (Fig. 1).[13–15] These regulators are primarily produced by activated T lymphocytes, mast cells, and tissue stroma cells.[16–19] Eosinopoietic cytokines act on progenitor cells and mature eosinophils via specific receptors.[20] An interesting fact is that the receptors for IL-3, IL-5, and GM-CSF display ligand-specific alpha chains, but share a common beta subunit.[20,21] Another important aspect is that eosinopoietic cytokines can trigger not only growth but also activation of normal and neoplastic eosinophils.[19,20] Apart from the above mentioned (classical) growth regulators, other cytokines can also trigger eosinophil functions. Among these are chemokines, platelet derived growth factor (PDGF), and fibroblast growth factors (FGFs) (Fig. 1). Reactive eosinophilia is usually caused by eosinopoietic cytokines, mostly IL-5 and GM-CSF, whereas clonal eosinophils usually are triggered by mutated and thus constitutively activated cytokine receptors or/and by disease-specific oncoproteins.

In general, eosinophilia can be divided into idiopathic eosinophilia, reactive eosinophilia, idiopathic hypereosinophilic syndrome (HES), chronic eosinophilic leukemia (CEL), and other hematopoietic (myeloid, lymphatic, or mast cell) neoplasms accompanied by eosinophilia (Table 1).[22–25] Reactive eosinophilia is either a transient or a chronic blood count abnormality. Transient eosinophilia is frequently seen in acute reactive

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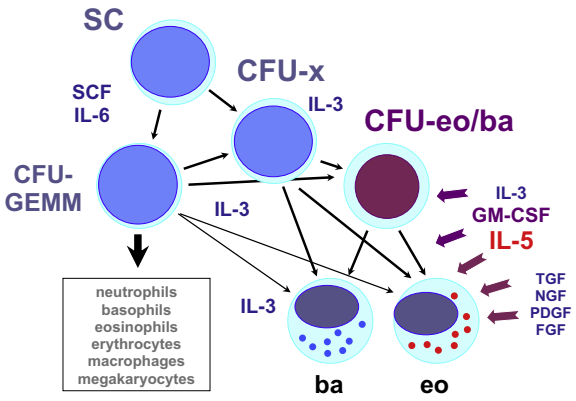

Fig. 1. Development of eosinophilic cells from stem cells as well as uncommitted (multi-potent) and eosinophil-committed progenitor cells. A frequently detectable bipotent progenitor cell (CFU-eo/baso) gives rise to basophils and eosinophils regardless what multilineage growth factors are applied (are present). This cell is detectable in the bone marrow and peripheral blood in healthy subjects as well as in patients with myeloproliferative neoplasms. SC, stem cell; CFU, colony-forming unit (progenitor cell); IL-3, interleukin-3; IL-5, interleukin-5; GM-CSF, granulocyte-macrophage colony-stimulating factor; TGF, transforming growth factor; NGF, nerve growth factor; PDGF, platelet derived growth factor; FGF, fibroblast growth factor.

processes such as non-specific inflammation, allergic reactions, drug reactions, or infections with viruses or with bacteria (recovery phase of an infection).[22–25] Chronic reactive eosinophilia is found in patients with persistent chronic infections (viral, fungal, bacterial, parasitic), autoimmune disorders, atopic diseases, distinct endocrinologic disorders, and certain tumors (Table 1).[25–30] A major cause of persistent eosinophilia are chronic helminth infections (nematodes, cestodes, or tremadodes).[22,25,26] In all these cases, reactive eosinophilia supposedly results from progenitor cell stimulation by eosinopoietic growth factors.[25–30] Reactive eosinophilia usually presents as an isolated blood finding, but may (less frequently) also be accompanied by other blood count abnormalities. Sometimes, an excessive increase in eosinophils is seen. If no cause for a reactive eosinophilia is found, an underlying hematopoietic disease must be considered (Fig. 2).

Diagnostic algorithm and initial investigations

Several different pathologic conditions may lead to an increased production and/or accumulation of reactive/non-neoplastic eosinophils. In most instances, an underlying cause is known or is revealed after initial investigations. Such investigations include a detailed case history, thorough physical examination, X-ray of chest (and lung function test if necessary), electrocardiogram and echocardiogram, ultrasound of abdomen, a complete blood count with microscopic differential count, and a complete serum chemistry with immunoglobulins (including IgE), C reactive protein, fibrinogen, and serum tryptase (Fig. 2). In addition, stool specimens are examined to exclude or reveal a worm (helminth) infection. Depending on findings, an extended search for non-hematologic disorders including autoimmune disorders and cancer, is initiated. The measurement of eosinopoietic cytokines (e.g. IL-5 and GM-CSF) may be helpful to confirm the presence of a reactive form of eosinophilia, but these tests (ELISA) are usually not available in routine laboratories. Sometimes, a lung or heart disease is diagnosed, but it remains unclear whether the patient is suffering from secondary eosinophilia or from an underlying hypereosinophilic syndrome (HES).

A number of clinically defined rare syndromes such as the Churg-Strauss syndrome or Kimura's disease are accompanied by eosinophilia, which is often a diagnostic clue in such patients.[23,25,29,30] Table 2 shows a summary of these conditions, together with major clinical features. In some cases, eosinophilia persists over months but neither an underlying (hematopoietic or non-hematopoietic) disease or molecular marker, nor organopathy or a rare syndrome is found, and the clinical course is stable. These cases are classified as 'chronic idiopathic eosinophilia' (Table 1, Fig. 2).

The hypereosinophilic syndrome (HES)

Major diagnostic criteria for the so called hypereosinophilic syndrome are (i) a permanent eosinophil count of >1500/μL (for at least 6 months) and (ii) the typical end organ damage.[29–34] In addition, unrelated disorders and transient eosinophilia have to be excluded. Patients with HES may suffer from multiorgan involvement or from isolated end organ damage. In many cases, lung- or endomyocardial fibrosis is seen. In other patients, thrombosis, neurologic symptoms, mucosal ulcera, or skin involvement is found.[29–34] HES can present as a primary idiopathic disease (idiopathic HES), but may also develop on the basis of a defined hematopoietic malignancy (Fig. 2).[31–33] Based on a literature search and review of our case series, most patients with secondary HES and typical cardiac damage (endomyocardial fibrosis) are suffering from a FIP1L1/PDGFRA+ CEL as underlying disease. Other organ manifestations (skin, lung, neurologic) are unusual in these patients – such manifestations are more frequently recorded in patients with idiopathic HES. Sometimes, HES is diagnosed in patients with myeloid neoplasms other than CEL or even in lymphoid neoplasms.[30–34] However, the disease-related organ damage in most myeloid neoplasms (presenting with or without eosinophilia) is quite different from that seen in patients with typical CEL. Notably, in these patients, no cardiopathy is found even if eosinophilia is recorded over many years. Also, in advanced mast cell disease with eosinophilia, end organ damage, e.g. hepatopathy or osteolysis, is distinctively different from organopathies recorded in patients with CEL/HES, unless a FIP1L1/PDGFRA+ CEL coexists with mastocytosis (SM–CEL).

Diagnostic approach in patients with suspected hematologic neoplasm

In patients in whom eosinophilia is unlikely to be reactive and/or is accompanied by other blood count abnormalities or by typical end organ damage (HES), specific blood tests are performed, and the bone marrow is examined. Fig. 2 provides a diagnostic algorithm for these patients. Most molecular studies can be performed using peripheral blood and thus yield rapid diagnostic results.[25,34,35] Depending on clinical and blood findings, initial tests include markers indicative of (a) a stem cell- or myeloproliferative neoplasm (in those with signs of myeloproliferation), (b) a primary eosinophil neoplasm, i.e. CEL (isolated marked eosinophilia±HES), (c) a lymphoid neoplasm (lymphomas, lymphocytosis), or (d) a mast cell neoplasm (skin lesions, highly elevated serum tryptase). Molecular markers indicative for a primary eosinophil disease (CEL) include oncogenic variants of the PDGFRA, and less frequently, an oncogenic PDGFRB or FGFR1.[31,32,34,35] The KIT mutant D816V is typically found in systemic mastocytosis (SM), but the test may be false-negative in the blood, and thus should be performed using bone marrow cells.[36,37] In addition, not all patients with SM harbour KIT D816V.[36,37] Table 3 shows a summary of markers indicative of hematopoietic neoplasms frequently presenting with eosinophilia. Bone marrow studies include a biopsy with immunohistochemistry, using B cell- and T cell markers, CD34, KIT, tryptase and CD25 as well as a platelet marker (e.g.

Table 1
Disorders and conditions associated with eosinophilia.

Disorder/condition	Variant of disease	Mechanism (eosinophilia)
Idiopathic eosinophilia	–	Unknown
Reactive eosinophilia	Transient	Cytokines (IL-5, others)
	Infections	
	Allergic reactions	
	Drug reactions	
	Chronic/Persistent	Cytokines (IL-5, others)
	Chronic helminth infections	
	Other chronic infections	
	Autoimmune diseases	
	cGvHD	
	Atopic diseases	
	Endocrinopathies	
	Solid tumors/cancer	
	B cell lymphoma/leukemia	
	T cell clones	
	T cell lymphoma/leukemia	
	Eosinophil syndromes – see Table 2	
Idiopathic hypereosinophilic syndrome (HES[a])	–	Unknown
Chronic eosinophilic leukemia (CEL)	With FIP1L1/PDGFRA (+/−HES[a])	PDGFRA[b]
	With other PDGFRA-fusion genes	PDGFRA
	With other oncogenic mutants	PDGFRB, FGFR1[b]
	Without known defect	Unknown
Classical MPN with eosinophilia (MPN-eo)	CML	BCR/ABL[c]
	JAK2 V617F+ MPN (ET, PV, PMF)	Unknown
Atypical MPN with eosinophilia (aMPN-eo)	With oncogenic PDGFR mutants	PDGFRA/B
	With other oncogenic TKs	PDGFRB, FGFR1
	Without known defect	Unknown
MDS/MPN overlap syndromes with eosinophilia	CMML, rarely others with oncogenic PDGFRB mutants	PDGFRB
	With other oncogenic TKs	PDGFRA, FGFR1
	Without known defect	Unknown
Stem cell leukemia/lymphoma syndrome	8p11 syndrome	Oncogenic FGFR1
MDS with eosinophilia (MDS-eo)	Diverse subvariants	Unknown
Unclassifiable MDN, MPN, or MDN/MPN with eosinophilia	With oncogenic PDGFR mutants	PDGFRA/B
	With oncogenic FGFR1 mutants	FGFR1
	Without known defect	Unknown
Systemic mastocytosis with eosinophilia (SM-eo)	Smouldering SM (SSM-eo)	Unknown
	Aggressive SM (ASM-eo)	Unknown
	Mast cell leukemia (MCL-eo)	Unknown
	SM-eo with AHNMD: SM–CEL, SM–CML, etc.	AHNMD-related defects

IL-5, interleukin-5; cGvHD, chronic graft versus host disease; PDGFR, platelet derived growth factor receptor; MPN, myeloproliferative neoplasm; CML, chronic myeloid leukemia; aMPN-eo, atypical MPN with eosinophilia; ET, essential thrombocythemia; PV, polycythemia vera; PMF, primary myelofibrosis; FGFR, fibroblast growth factor receptor; SM, systemic mastocytosis; AHNMD, associated clonal hematologic non-mast cell lineage disease.

[a] HES can develop as an unexplained idiopathic condition (disease) or as secondary HES, e.g. in patients with CEL.

[b] The PDGFRs and the FGFR tyrosine kinase activity are considered to be involved in clonal eosinophil differentiation, but the exact mechanisms remain unknown.

[c] The BCR/ABL tyrosine kinase is considered to be involved in clonal eosinophil differentiation, presumably via IL-3R-like signalling networks.

CD42 or CD61). In addition, an aspirate is obtained for morphologic assessment, flow cytometry analysis, cytogenetics, and molecular studies, including *KIT* mutations. Chromosome analysis should be performed on bone marrow cells and includes conventional karyotyping as well as fluorescence in situ hybridization (FISH) with probes specific for CHIC2 (4q12) and other aberrations, depending on laboratory and clinical findings.[33–35,38] It is important to note that the CHIC2 deletion (associated with FIP1L1/PDGFRA) is only detectable by FISH but not by conventional cytogenetics. Another caveat in the diagnosis of CEL is that depending on the sensitivity of the assay and percentage of clonal cells (eosinophils), the FIP1L1/PDGFRA mutant may not be detectable in the peripheral blood. Therefore, the diagnostic work-up in suspected CEL should always include bone marrow studies and FISH.[33–35] When all laboratory tests are negative, and there is no indication for an underlying eosinophil (or other hematopoietic) disease, the condition is monitored in the follow up. In some patients, organopathy or/and a frank hematologic disease is detected after a certain latency period.

Chronic eosinophilic leukemia (CEL)

Chronic eosinophilic leukemia (CEL) is a myeloproliferative neoplasm defined by the following criteria: persistent eosinophilia (>1500/μL for at least 6 months) and molecular or/and cytogenetic evidence of monoclonal eosinophils, and/or presence of blast cells in the peripheral blood (>2%) or bone marrow (5–19%), and exclusion of all other hematologic and non-hematologic causes of eosinophilia, with recognition of the principle possibility of coexistence of two separate disorders (e.g. co-existing helminth infection or a lymphoma can as per definition *not* exclude the presence of a CEL).[38–40] In most patients with CEL (about 60%), eosinophils display *PDGFRA*-fusion genes and related cytogenetic defects.[25,38–41] The most commonly detected oncoprotein is FIP1L1/PDGFRA. As mentioned above, the related chromosome defect, a deletion of CHIC2 at 4q12, is demonstrable by FISH.[39–42] Other less commonly detected fusion partners for *PDGFRA* in CEL are *BCR*, *KIF5B*, and *CDKRAP2* (Table 3).[25,38–40] Chromosome defects creating these fusion genes are detectable by conventional karyotyping.[38–40]

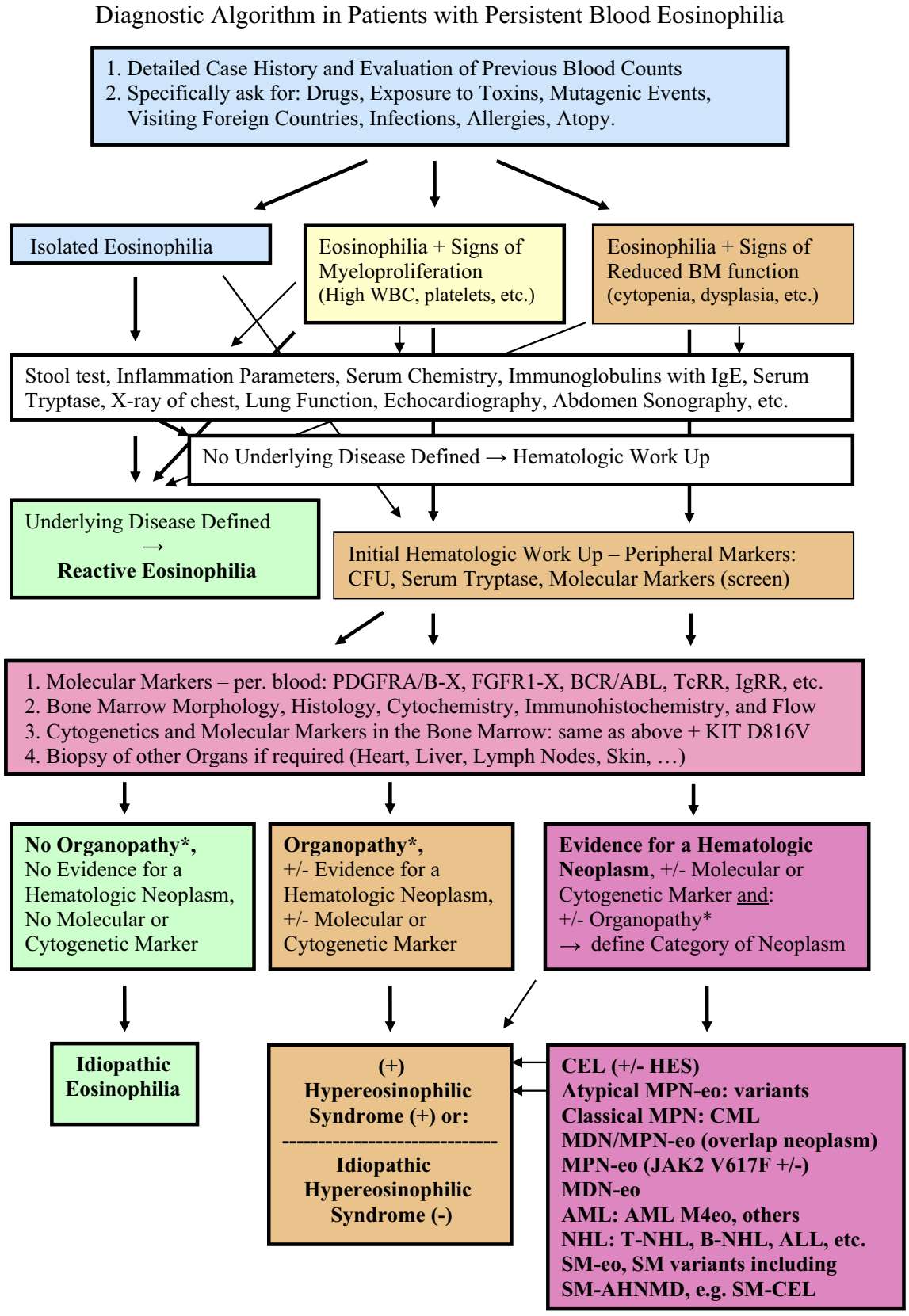

Fig. 2. Diagnostic algorithm for patients with eosinophilia. Diagnostic studies are initiated in a step-wise approach: first, the patient is examined for causes of reactive eosinophilia. If reactive eosinophilia is unlikely (has been excluded), the second step is to investigate the hematopoietic organ system in detail and to clarify whether the patient suffers from a hematologic neoplasm. In addition, the patient is examined carefully for the presence of HES-related organopathy. In those without any marker or underlying disease and without any organopathy, the diagnosis chronic idiopathic eosinophilia is established after 6 months. Molecular markers are helpful screen tests and assist in reaching the final diagnosis.

Table 2
Overview of clinical syndromes associated with eosinophilia.

Disease/syndrome	Typical findings
Systemic	
Kimura's disease	Large subcutaneous masses in the head and neck, mostly seen in the asian population, smaller lesions also in other races (angiolymphoid hyperplasia with eosinophilia = AHE)
Shulman's syndrome	Eosinophil fasciitis, erythema and swelling of skin, induration of skin (scleroderma-like) with major pathologies found in the subcutaneous tissue
Churg-Strauss syndrome (CSS)	Necrotizing vasculitis with eosinophilia (ANCA+ and ANCA− subvariant)
Eosinophil-myalgia syndrome	Polymyalgia syndrome plus eosinophilia
DRESS syndrome	Drug rash with eosinophilia and systemic symptoms
Omenn syndrome	Severe combined immunodeficiency + eosinophilia
Hyper IgE syndrome	Severe combined immunodeficiency + elevated levels of IgE + eosinophilia
Organ-restricted	
Eosinophil esophagitis (EE)	Prominent eosinophilic infiltrate
Eosinophil gastritis	Prominent eosinophilic infiltrate
Eosinophilic panniculitis	Eosinophilic infiltration of subcutaneous fat
Well's syndrome	Eosinophilic cellulitis with recurrent swelling of extremities (resistant to antibiotic therapy)
Acute eosinophilic pneumonia	Prominent eosinophilic infiltrate
Chronic eosinophilic pneumonia	Prominent eosinophilic infiltrate
Löffler's endocarditis	HES-related endomyocardial fibrosis (+/− CEL)

IgE, immunoglobulin E; HES, hypereosinophilic syndrome; CEL, chronic eosinophilic leukemia.

Table 3
Molecular markers and related cytogenetic defects occurring in myeloid neoplasms presenting with eosinophilia[a].

Molecular defect oncoprotein	Cytogenetic defect	Disorder/diagnosis
BCR/ABLp210	t(9;22)	CML
CBFβ/MYH11	inv(16)	AML M4-eo
FIP1L1/PDGFRA	del(4q12)	CEL, SM–CEL, CMML-eo, atypical/unclassifiable MPN-eo
BCR/PDGFRA	t(4;22)(q12;q11)	CEL, unclassifiable MPN-eo
KIF5B/PDGFRA	t(4;10)(q12;p11)	CEL
CDK5RAP2/PDGFRA	ins(9;4)(q33;q12q25)	CEL
ETV6/PDGFRB	t(5;12)(q33;p13)	CMML-eo, atypical MPN-eo, CEL
BABAPTIN5/PDGFRB	t(5;17)(q33;p13)	CMML-eo
HCMOGT1/PDGFRB	t(5;17)(q33;p11.2)	JMML-eo
CEV14/PDGFRB	t(5;14)(q33;q32)	AML-eo
NIN/PDGFRB	t(5;14)(q33;q24)	Atypical/unclassifiable MPN-eo
KIAA1509/PDGFRB	t(5;14)(q31;q32)	CMML-eo
TP53BP1/PDGFRB	t(5;15)(q33;q22)	Atypical/unclassifiable MPN-eo
PDE4DIP/PDGFRB	t(1;5)(q23;q33)	Atypical/unclassifiable MPN-eo
HIP1/PDGFRB	t(5;7)(q33;q11.2)	CMML-eo
H4/PDGFRB	t(5;10)(q33;q22)	Atypcial/unclassifiable MPN-eo
ZNF198/FGFR1	t(8;13)(p11;q12)	SCLL, atypical MPN-eo, CEL
FOP/FGFR1	t(6;8)(p27;p11)	SCLL
TIF1/FGFR1	t(7;8)(q34;p11)	SCLL
MYO18A/FGFR1	t(8;17)(p11;q23)	SCLL
HERVK/FGFR1	t(8;19)(p12;q13.3)	SCLL
BCR/FGFR1	t(8;22)(p11;q11)	Atypical MPN-eo (CML-like)
CEP110/FGFR1	t(8;9)(p12;q23)	SCLL
FGFR1OP2/PDGFRA	ins(12;8)(p11;p11p22)	SCLL
KIT D816V	–	SM-eo: (ISM-eo, SSM/ASM-eo) MCL-eo, SM–AHNMD
JAK2 V617F	–	Classical MPN: PV, ET, PMF

Abbreviations: CML, chronic myeloid leukemia; AML, acute myeloid leukemia; CEL, chronic eosinophilic leukemia; MPN, myeloproliferative neoplasm; CMML, chronic myelomonocytic leukemia; JMML, juvenile myelomonocytic leukemia; SCLL, stem cell leukemia/lymphoma syndrome; SM, systemic mastocytosis; ISM, indolent SM; SSM, smouldering SM; PDGFR, platelet derived growth factor receptor; FGFR, fibroblast growth factor receptor; ASM, aggressive SM; MCL, mast cell leukemia; AHNMD, associated clonal hematologic non-mast cell lineage disorder. PV, polycythemia vera; ET, essential thrombocytosis; PMF, primary myelofibrosis.

[a] Molecular defects refer to data reported in the available literature.[25,34,35,38–40]

Oncogenic *PDGFRB* fusion gene products may also be detected in CEL, although in most cases, these patients are classified as atypical MPN or chronic myelomonocytic leukemia (CMML), but not as CEL (Table 3).[25,38–40] The most frequent oncoprotein is ETV6-PDGFRB associated with the t(5;12)(q33;p13). Oncogenic PDGFR variants detectable in CEL usually represent targets for imatinib.[41–45] A very few patients presenting with CEL have defects in the *FGFR1* gene or a related defect involving 8p11.[25,39] Here, the most common translocation is t(8;13)(p11;q12) that is related to the ZNF198-FGFR1 oncoprotein.[25,39] However, most of these patients have multilineage involvement, and thus no typical CEL. Table 3 shows a summary of fusion genes and related chromosome defects detectable in CEL and other myeloid neoplasms presenting with eosinophilia. In a few patients with CEL, no specific chromosome abnormality or molecular marker is found. In some of these cases, eosinophils display activated or/and overexpressed PDGFRA, PDGFRB, or FGFR1, suggesting the presence of further, as yet unknown, defects in these genes.

In a majority of all patients with typical CEL and FIP1L1/PDGFRA, endomyocardial fibrosis (HES) is diagnosed or will develop over time.[38–42] However, in a few cases, no cardiopathy is detectable in the follow up. In other patients, the disease progresses into an acute leukemia.[38–42] So far, little is known about factors contributing to end organ damage or progression in CEL. An attractive hypothesis is that additional gene aberrations and defects (oncogenic hits) contribute to disease progression.[46] Alternatively, inherited genetic factors (germ line polymorphisms) may play a certain role in the pathogenesis of CEL. Likewise, it has been described that the severity of FIP1L1-PDGFRA-positive CEL is predetermined by a polymorphism in the *IL5RA* gene locus.[47] Other studies have shown that IL-5 cooperates with FIP1L1-PDGFRA in inducing a CEL-like disease in mice.[48] These data suggest that several different factors including cytokines and cytokine receptors, may contribute to disease manifestation and progression in patients with FIP1L1-PDGFRA+ disease (CEL).

Myeloproliferative and stem cell neoplasms, myelodysplastic syndromes (MDS), and overlap syndromes

Eosinophilia is typically found in various myeloproliferative neoplasms (MPN). In Philadelphia chromosome positive (Ph+) CML, eosinophilia and basophilia are almost always present at diagnosis, and often also when the disease progresses. In patients with typical JAK2 V617F+ MPN, eosinophilia is less frequently detected, but may also occur.[25] However, in distinct variants of (atypical) MPN, namely those that develop on the basis of (in association with) an oncogenic form of PDGFRA, PDGFRB, or FGFR1, eosinophilia is a common finding.[25,33–35,38–40] This holds true also for myeloid neoplasms classified as MDS/MPN overlap disease, such as CMML (CMML-eo), and for atypical variants of MDS (MDS-eo). However, not all patients with MPN-eo, MDS-eo, or MDS/MPN-eo present with such cytogenetic abnormalities. The new WHO classification separates classical MPN-eo without a clonal marker from cytogenetically (molecular) defined subvariants, i.e. those with oncogenic variants of PDGFRA, PDGFRB, or FGFR1.[40] A special multilineage neoplasm is the '8p11 syndrome', also referred to as 'stem cell leukemia/lymphoma syndrome'.[25,39,40] These patients have multilineage involvement, monoclonal eosinophils, and a mutated variant of the *FGFR1* gene. As mentioned above, the most frequent translocation is t(8;13)(p11;q12).[25,39] Many patients with 8p11 syndrome present with a T cell lymphoma, and several of them develop AML or progress into a myelosarcoma-like disease in their terminal phase.[25,39,40] The prognosis is grave in these patients.

In patients with MPN, MDS, or MDS/MPN, eosinophilia can also develop during the course of disease. In particular, about 10% of all patients with MDS develop massive eosinophilia (>10% in blood) in the follow up.[49] In some of these cases, the occurrence of eosinophilia is associated with disease progression. Moreover, in MDS, eosinophilia at diagnosis is of prognostic significance.[50] These patients apparently have an increased risk to develop secondary AML and a reduced survival.[50] Clinically, it is also important to note that patients with CML, MDS/MPN, or MDS who have permanent eosinophilia (>1500 for at least 6 months) usually do not develop endomyocardial fibrosis (and no other HES-like end organ damage) even when eosinophilia persists for years, contrasting the course in FIP1L1/PDGFRA+ CEL.

Mast cell disorders – systemic mastocytosis (SM) and mast cell leukemia

Although indolent and aggressive variants of SM may be accompanied by eosinophilia (SM-eo), an increase in eosinophils is more frequently observed in advanced forms of the disease, i.e. smoldering SM (SSM-eo), aggressive SM (ASM-eo), and mast cell leukemia (MCL-eo).[51,52] Moreover, eosinophilia in SM is of prognostic significance.[52] A subvariant of ASM-eo is lymphadenopathic SM with eosinophilia.[36,53] In advanced SM and some patients with ISM, eosinophils are considered to belong to the neoplastic clone.[54,55] Rarely, eosinophils even represent the predominant cell type in the bone marrow and blood, which may be a diagnostic challenge. The situation is complicated by the fact that SM can be accompanied by an associated clonal hematologic non-mast cell disorder (AHNMD), including CEL.[36,37,52] Thus, in SM, eosinophilia must be considered as a 'pre-diagnostic' checkpoint (SM-eo) at which molecular markers need to be applied, but is not a final diagnosis.[36,37,52,56] Rather, only a complete staging and grading and search for disease-specific markers can provide the information necessary for a correct final diagnosis.[36,37] Clinically, it is important to note that in most patients with SM-eo, no AHNMD (no CEL/HES) is found.[51,52] Notably, these patients usually do not develop CEL or a HES, even if eosinophilia persists for many years or even decades.[51,52] On the other hand, an increase in atypical CD25+ mast cells is often seen in patients with CEL without SM, i.e. when by morphology and phenotype mast cells are abnormal, but criteria for SM are not met.[25,37–40] This may sometimes be because (diagnostic) mast cell infiltrates are distorted by the co-existing eosinophil infiltrate and thus remain subdiagnostic (occult SM). Similarly, while most cases of CEL with an increase in mast cells are described to be KIT D816V-negative, it remains unclear whether this is because neoplastic mast cells are outnumbered by eosinophils in the test tube, bear other *KIT* mutations or are non-neoplastic but still CD25+ cells. The possibility that FIP1L1/PDGFRA (per se) is a trigger of mast cell differentiation would be another alternative. Whatever the explanation is, it should be emphasized that FIP1L1/PDGFRA remains a molecular marker of CEL, but is not a marker of SM.[37–40,56,57] On the other hand, diagnostic criteria for SM are sometimes fulfilled in patients with CEL, and then the final diagnosis should be SM–AHNMD/CEL.[36,37,51,52]

Malignant lymphomas and other lymphoid neoplasms

A number of lymphoid neoplasms may be accompanied by eosinophilia. Such neoplasms include T cell lymphomas, Hodgkin's disease, and less frequently B cell Non Hodgkin's lymphomas (NHL), NK cell neoplasms, acute lymphoblastic leukemia (ALL), and other B cell malignancies.[25,33,38,39] In an early phase of disease, eosinophilia may be the only sign for a (T cell) lymphoma. In other patients, a monoclonal T cell population (clone) is detected by PCR or immunophenotyping, but does not develop into an overt lymphoma.[58,59] In most lymphoma patients, eosinophils may be reactive (non-neoplastic) in nature. In fact, neoplastic (T) lymphocytes are considered to produce eosinopoietic growth factors, such as IL-5 or GM-CSF.[58,59] In other cases, however, eosinophilia may arise on the basis of a co-existing myeloid neoplasm or a stem cell disease, like the 8p11 syndrome.[25,39,40] It should be noted here that the co-existence of two myeloid disorders, of a myeloid and a lymphoid neoplasm (or of a multilineage malignancy with distinct clinical features produced by lineage-related subclones) in one patient may be a more frequent phenomenon than has so far been assumed. Therefore, it is important to evaluate all these patients carefully and to apply all appropriate histopathologic, cytogenetic, and molecular markers.

The WHO classification of eosinophil disorders

The WHO classification 2008 defines two groups of patients with neoplastic eosinophils.[60,61] One group of patients is suffering from a "myeloid or lymphoid (or stem cell) neoplasm with eosinophilia

and abnormalities in *PDGFRA*, *PDGFRB*, or *FGFR1* genes".[60] The second group, integrated in a subchapter as MPN category, is termed "chronic eosinophilic leukemia, not otherwise specified".[61] The advantage of the WHO classification is that it is based on potential targets, and therefore is in support of therapy-related algorithms that will facilitate the management and treatment of patients and will increase the awareness for cytogenetic and molecular markers in various centers. A disadvantage of the classification may be that eosinophil neoplasms are split into two categories, and that one category consists of a mixture of myeloid and lymphoid neoplasms. Here, it seems as if single molecular markers were introduced as primary diagnostic criteria without bringing them in a closer context with well established major histopathological and clinical criteria of CEL or other lymphohematopoietic disorders. Therefore, from reading the WHO book it seems as if two classifications coexist, one based on histopathological criteria and a second one that is based on molecular markers. Likewise, in each of the three groups defined by *PDGFRA*, *PDGFRB*, and *FGFR1*, the first criterion listed is an established hematopoietic (myeloid or lymphoid) neoplasm.[60,61]

We believe that all these new markers and potential co-criteria for eosinophil-related disorders have to be further validated and weighed against already existing histopathological and clinical criteria of CEL and of other hematopoietic disorders. It seems also clear that more molecular defects will be detected in the future, and that in many patients with eosinophil disorders, more than one or two markers may be detected, which points to the need to integrate all these co-criteria in a unifying classification that adheres (leads back) to basic histopathological and clinical criteria.

Therapy of patients with hypereosinophilic disorders

A number of molecular targets related to CEL or to other hematopoietic malignancies presenting with eosinophilia have been defined recently.[25,38–44,62] A summary of potential targets is shown in Table 3. In the individual patient, it is of importance to define the nature of eosinophilia by application of such markers, but also to define the clinical impact of eosinophilia by appropriate staging and assessment of organ infiltration and organ damage, i.e. by applying also clinical and histopathological criteria. Only after having reached the correct final diagnosis and having documented disease-severity by appropriate staging and grading, a treatment plan should be established. By contrast, it is not appropriate to establish a diagnosis or even a treatment plan based on the presence of eosinophilia alone, or only based on the presence of a certain target or marker. Some of these patients harbour such marker or have eosinophilia, but may not develop a progressive neoplasm requiring therapy.

The most frequent mutant and target detectable in patients with CEL is FIP1L1/PDGFRA.[25,38–44] This fusion gene product is a target of imatinib and several other TK inhibitors such as nilotinib, dasatinib, or sorafenib (Table 4).[41–44,63–69] Based on evidence from multiple clinical trials, imatinib is considered standard first line therapy, the starting dose being 100 mg per os daily.[41–45] Whereas most patients show a long lasting response to this standard dose, a few patients require dose-escalation (to 400 mg daily) or are resistant, which is mainly caused by rare FIP1L1/PDGFRA point mutations associated with decreased (or loss of) drug-binding capacity. One of these mutants is the T674I variant of FIP1L1/PDGFRA.[66–69] For these patients, novel TK inhibitors, shown in Table 4, may be considered.[66–69] Another approach is to apply alternative cytoreductive agents, interferon-alpha, hydroxyurea, or experimental drugs such as new antileukemic agents or targeted antibodies.[62,70,71] In patients who progress to leukemia, high dose chemotherapy ± stem cell transplantation has to be considered.

On the other hand, there are patients with FIP1L1/PDGFRA+ CEL who are not suffering from end organ damage or progression for years, so that no therapy is required. In these cases, especially when eosinophil counts remain low, it may be possible to wait and watch until first signs of progression or end organ involvement, occur. On the other hand, there are no predictive markers that can by employed to define groups of patients who are at risk to progress. The dilemma here is that it remains also unknown what strategy would more likely facilitate disease progression in these patients: (a) therapy with a TK inhibitor or other potentially mutagenic drug or (b) uncontrolled proliferation of neoplastic stem cells with accumulation of further hits that might be prevented by early intervention with TK inhibitors.

For monitoring CEL during therapy, serial determination of eosinophil counts is usually sufficient, i.e. to document responses to a TK inhibitor or other drug.[42–44] In those in whom an elevated serum tryptase or elevated ECP level is recorded before treatment, these markers can also be employed as follow up parameters. To document a cytogenetic or a molecular response, FISH analysis and quantitative PCR (qPCR) have to be performed in the follow up.[69,72,73] Whereas FISH is a generally available test, qPCR for FIP1L1/PDGFRA or other fusion gene products is usually not available in routine laboratories, but is only available in specialized reference centers.

Table 4
Kinase inhibitors recognizing PDGFRs or FGFR1.

Substance	Drug name	Major drug targets	Inhibits growth of neoplastic eosinophils
STI571	Imatinib/Gleevec	ABL, KIT, PDGFRs	+
AMN107	Nilotinib/Tasigna	Multiple kinase targets including: ABL, KIT, PDGFRs FIP1L1/PDGFRA T674I	+
BMS354825	Dasatinib/Sprycel	Multiple kinase targets including: ABL, KIT, PDGFRs, BTK, LYN	+
PKC412	Midostaurin	Multiple kinase targets including: PKC, VEGFR, FLT3, PDGFRs, KIT FIP1L1/PDGFRA T674I	+
BAY 43-9006	Sorafenib/Nexavar	Multiple kinase targets including: RAF, FLT3, PDGFRs, KIT, VEGFR FIP1L1/PDGFRA T674I	+
SU11248	Sunitinib	Multiple kinase targets including: FLT3, PDGFRs, KIT, VEGFR	n.k.
GW786034	Pazopanib	PDGFR, VEGFR, KIT	n.k.
BMS-540215	–	FGFR1, VEGFR	n.k.
TKI258	–	Multiple Kinase Targets including: FGFR1, VEGFR, PDGFR, FLT3, KIT	+
PD 173074		FGFR1, other FGFRs, VEGFR	n.k.
SU 5402		FGFR1, other FGFRs	n.k.

PDGFR, platelet derived growth factor receptor; FGFR, fibroblast growth factor receptor; VEGFR, vacular endothelial growth factor receptor; PKC, protein kinase C. n.k., not known.

The reactive form of hypereosinophilia (including patients with lymphomas) should be managed by treating the underlying disease if possible and if necessary. In many cases, symptomatic therapy is sufficient to control symptoms related to eosinophil activation in these patients. However, it is not appropriate to treat hypereosinophilia per se in these patients, i.e. when no severe and clearly eosinophil-related organopathy (e.g. HES) develops. If the underlying disease is accompanied by a HES and cannot be treated with conventional (symptomatic) therapy or is resistant, the eosinophil count can usually be kept under control using glucocorticosteroids, hydroxyurea, or interferon-alpha. Another interesting option for these patients is to apply (additional) anti-IL-5 antibodies.[71,74] In all patients, the risk and side effects of anti-eosinophil therapies have to be weighed against the potential benefit and the real need to treat.

Summary and future perspectives

Eosinophilia is an important diagnostic and/or prognostic feature in various myeloid neoplasms. We recommend the use of the appendix 'eo' (e.g. MPN-eo, SM-eo) for patients in whom this important diagnostic checkpoint has been reached. Cytogenetic and molecular markers are then applied, and are helpful for determining the final diagnosis. In addition, several of these markers also represent important therapeutic targets. Patients with oncogenic variants of the PDGFR are candidates for treatment with imatinib. In reactive hypereosinophilia, the condition is best controlled by treating the underlying disease. If this is not possible and eosinophilia causes clinical problems, eosinophil counts may be kept under control using glucocorticosteroids, cytoreductive agents, or experimental drugs. Our increasing knowledge about the nature of eosinophilia and development of more specific therapeutic approaches should improve treatment and prognosis in eosinophil disorders in the future.

Conflict of interest statement

The author has no conflict of interest.

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