Review

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Review

Hematological Neoplasm with Eosinophilia

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Simple Summary: This should be written in one paragraph before the Abstract in layman's terms, to explain why the research is being suggested, what the authors aim to achieve, and how the findings from this research may impact the research community. Please use as few abbreviations as possible and do not cite references in the Simple Summary. The Simple Summary should not exceed 150 words. Submissions without a simple summary will be returned directly. An example can be found at https://www.mdpi.com/2072-6694/12/9/2424.

Abstract: Eosinophils in peripheral blood account for 0.3-5% of leukocytes, which is equivalent to 0.05-0.5 x 10^9/l. A count equal or above 0.5 x 10^9/l is considered eosinophilia, while a count equal or above 1.5 x 10^9/l is defined as hypereosinophilia. In bone marrow, eosinophilia is considered when eosinophils make up more than 6% of the total nuclear cells. In daily clinical practice, the most common causes of reactive eosinophilia are non- hematologic, whether non-neoplastic (allergic diseases, drugs, infections or immunological diseases) or neoplastic (solid tumors). Eosinophilia associated with a haematological malignancy may be reactive or secondary to the production of eosinophilopoietic cytokines, and this is mainly seen in lymphoid neoplasms (Hodgkin lymphoma, mature T-cell neoplasms, lymphoid variant of hypereosinophilic syndrome and B-acute lymphoblastic leukemia/lymphoma). Eosinophilia associated with a haematological malignancy may also be neoplastic or primary, derived from the malignant clone, usually in myeloid neoplasms or with origin in stem cell (myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions, acute myeloid leukemia with Core Binding Factor translocations, mastocytosis, myeloproliferative neoplasms, myelodysplastic/myeloproliferative neoplasms and myelodysplastic neoplasms). There are no concrete data in standardized cytological and cytometric procedures that could predict whether eosinophilia is reactive o clonal. The verification is usually indirect, based on the categorization of the accompanying hematologic malignancy. This review focuses on the broad differential diagnosis of haematological malignancies with eosinophilia.

Keywords: eosinophilia; hematological neoplasm; myeloid/lymphoid neoplasm with eosinophilia; tyrosine kinase fusion genes; acute leukemia.

1. Introduction

1.1. The eosinophil

Eosinophils are granular leukocytes originating in the bone marrow. The term "eosinophil" was coined by Paul Ehrlich in 1879 when he observed that the granules of these cells stained with acidic dyes, specifically with eosin Y (tetrabromofluorescein), producing a striking bright orange color [1]. However, it is highly likely that other researchers had observed this cell before Ehrlich [2].

Eosinophils should be considered tissue cells, with their presence in the blood being only circumstantial. They originate in the bone marrow from a pluripotent stem cell, which gives rise to a pluripotent myeloid progenitor cell, and this, in turn, to a specific or committed precursor in the

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genesis of the eosinophil granulocyte. Cytokines encoded by genes located proximally on 5q31, such as interleukin 3 (IL-3), interleukin 5 (IL-5) (the most specific to the eosinophil lineage), and granulocyte-macrophage colony-stimulating factor (GM-CSF), act on them, regulating their maturation and differentiation [3]. Similarly, IL-33 is also crucial for the basal homeostasis of eosinophils, involved in their differentiation and activation through its interaction with Interleukin 1 receptor-like 1 (IL1RL1), also known as the ST2 receptor [4]. After entering the bloodstream (hours), they migrate to various tissues. They are attracted in response to chemokines, primarily those of the eotaxin family: eotaxin-1/CCL11, eotaxin-2/CCL24, eotaxin-3/CCL26, RANTES/CCL5, which activate the CCR3 receptor (C-C motif chemokine receptor 3) expressed on eosinophils. These chemokines are produced by fibroblasts, epithelial cells, endothelial cells, smooth muscle cells, T lymphocytes, and macrophages [5]. In the same way, complement C5a and lipid mediators have been linked as chemotactic factors [6]. Once in the tissues, eosinophils can survive for several weeks. They are preferentially present in the mucosa of the respiratory, digestive, and genitourinary tracts.

1.2. Eosinophil biological activity

Eosinophils process a single type of granulation, with heterogeneous content in their primordial stage (pre-eosinophil), which later condenses and crystallizes into what is referred to as specific granulation [7]." In terms of ultrastructure, these granules possess a central electrondense crystalline core surrounded by a matrix, and they are rich in cationic proteins that are highly toxic to parasites (helminths), as well as to bacteria, fungi, and viruses. The "major basic protein" is concentrated in the central crystalline core, while the matrix contains the "eosinophil-derived neurotoxin" or ribonuclease 2, the "cationic protein of the eosinophil" or ribonuclease 3, and the "eosinophil peroxidase" that generates potent oxidants. They also contain galectin-10, or "Charcot-Leyden protein," which can be observed when crystallized in bone marrow aspirates and in tissues affected by eosinophilic infiltration [8]. In addition, mediators such as cytokines, chemokines, growth factors, lipid mediators, as well as multiple receptors for these, and enzymes are found. Thus, they play an immunomodulatory role in innate and adaptive immune responses, have anti-inflammatory and antitumor activity, and mediate in the repair, remodeling, and maintenance of tissues and their homeostasis [9].

However, when eosinophils undergo massive and persistent activation, they can damage the tissues and organs in which they operate due to the toxicity of their content. This is what happens in hypereosinophilic syndromes or immediate hypersensitivity reactions (type I). A proinflammatory and prothrombotic state is generated, and transforming growth factor-beta and interleukins are released, promoting the proliferation and activation of fibroblasts, leading to subsequent fibrosis at the expense of the parenchyma [9].

1.3. Normal and Pathological Morphology of Eosinophils

In blood smears fixed with methanol and stained with Romanowsky stains (based on methylene blue, eosin, and their derivatives), the normal mature eosinophil reaches a size between 14 and 16 μm. The nucleus is bilobed, classically described as eyeglass-shaped, and sometimes trilobed. The cytoplasm, which appears translucent, is almost entirely occupied by a relatively thick, dense, orange granulation (0.5-1.5 μm) that, unlike basophils, does not overlap the nucleus. Vacuoles are not typically observed (Figure 1A,B).

Regarding cytochemical aspects, the presence of myeloperoxidase in normal eosinophils is demonstrated through enzymatic cytochemistry and an appropriate substrate. Indirectly, the "content" of myeloperoxidase can be deduced (though not proven) through staining with Sudan Black B, which is particularly soluble in neutral fats (triglycerides) and phospholipids, both of which are abundant in the granulation of neutrophils and eosinophils. These cell types can be distinguished by the thicker granulation of eosinophils (Figure 1C,D). The eosinophil exhibits an absence of esterases and both acid and alkaline phosphatases. The Periodic Acid-Schiff (PAS) reaction is negative, or with weak intergranular positivity, in contrast to the marked positivity of segmented neutrophils.

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Additionally, metachromasia with Toluidine Blue, which is characteristic in basophilic granulocytes, is not observed [3].

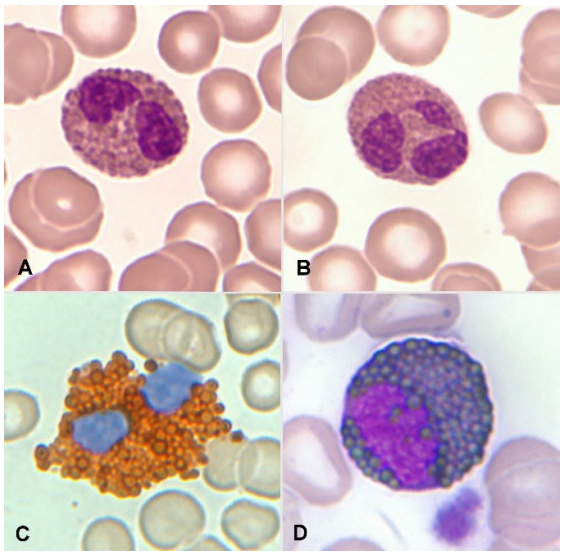

Figure 1. A. Bilobed eosinophil. B. Trilobed eosinophil. C. Eosinophil with high myeloperoxidase content. D. Eosinophil myelocyte which is Sudan Black B positive.

Morphological alterations of the eosinophil, regardless of whether eosinophilia is reactive or malignant, can include nuclear morphological abnormalities (absence of lobulation, hypersegmentation, or ring nuclei), defects in the cytoplasm (total or partial degranulation, vacuoles, persistent basophilia, visualization of pre-eosinophilic granulation, increased thickness of granules), size alteration (anisocytosis, gigantism, small forms), and maturation disharmonies, which encompass previous defects such as persistence of cytoplasmic basophilia in elements with advanced maturity [10] (Figure 2).

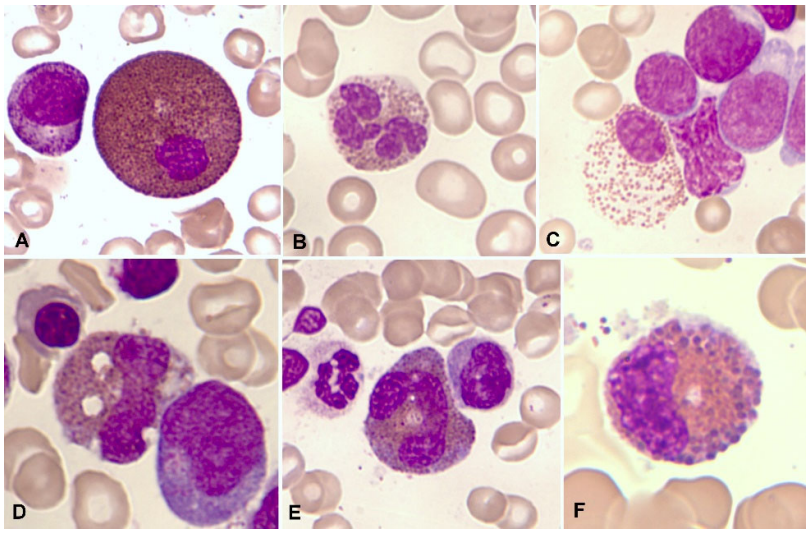

Figure 2. Bone marrow aspirate. May-Grünwald-Giemsa (MGG), x1.000. Dysplastic eosinophils. A. Giant form with a small non-lobulated nucleus. B. Nuclear hypersegmentation. C. Mature eosinophil with a round non-lobulated nucleus and hypogranularity. D. Vacuolar images. E. Persistence of cytoplasmic basophilia in a large band eosinophil, F. Metamyelocyte with thick pre-eosinophilic granulation arranged peripherally.

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1.4. Flow cytometry of the eosinophil

By immunophenotype, the normal eosinophil is characterized by a pattern of elevated size (FSC) and complexity (SSC), reflecting its cytomorphological features. They originate in the bone marrow from pluripotent hematopoietic stem cells CD34+ CD117+. They express the panleukocytic marker CD45, and with differentiation, they lose the expression of CD34, CD117, and HLADR, acquiring CD11b, CD15, CD65, and cytoplasmic eosinophilic peroxidase (CyEPO). Eosinophils produce this peroxidase, which shares some homology with the myeloperoxidase found in neutrophil and monocyte leukocytes [11]. Other markers present in these cells include CD13, CD33, CD193 (CCR3), and the alpha subunit of the High-affinity IgE receptor (FcεR1α) [4,12]. In contrast to neutrophils, they exhibit slightly weaker expression of CD15 in the absence of CD16 (Figure 3) [12].

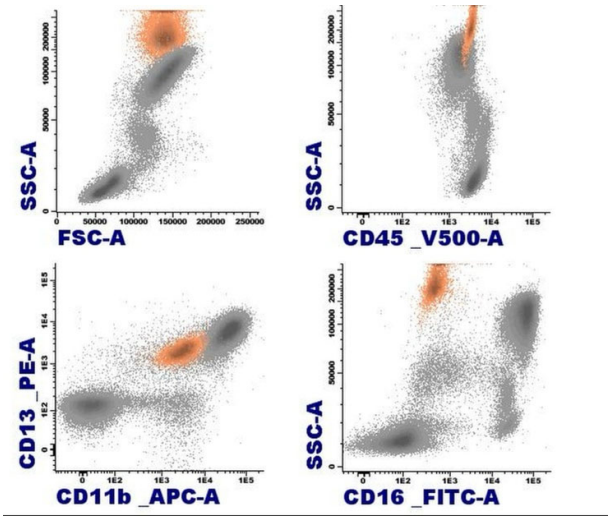

Figure 3. Representation of normal eosinophils (in orange) by flow cytometry in peripheral blood.

2. Eosinophilia

Eosinophils in peripheral blood constitute 0.3-5% of leukocytes, equivalent to 0.05-0.5 x 10^9/l. Eosinophilia is considered when their count is ≥ 0.5 x 10^9/l, and hypereosinophilia when it is ≥ 1.5 x 10^9/l. In a bone marrow aspirate, a normal rate is considered up to 6% and, in bone marrow biopsy, the definition of medullary eosinophilia has been proposed with ≥ 20% eosinophils [13,14].

Most cases of eosinophilia are not associated with hematologic diseases and are reactive. Among their causes are parasitic infections, allergies, medications, chronic inflammatory processes, etc. Solid tumors that can present with a leukemoid reaction featuring blood and/or bone marrow hypereosinophilia, mimicking a myeloproliferative neoplasm (MPN) (Figure 4), should also be included. Additionally, some of the new antitumor immunotherapies can cause eosinophilia with dysplasia [15,16].

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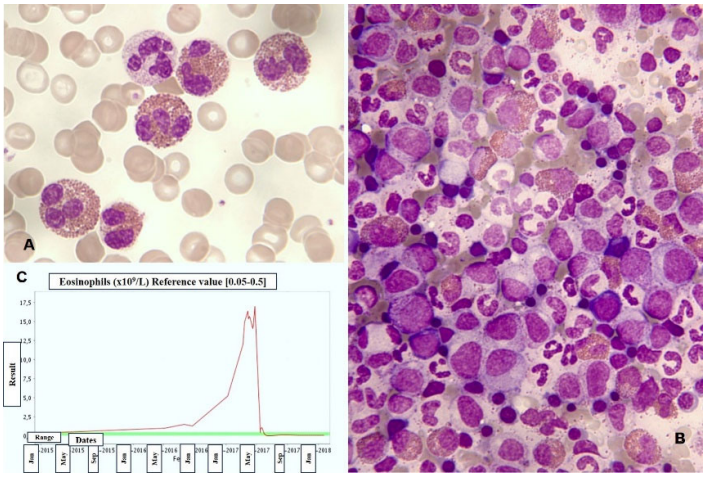

Figure 4. Leukemoid reaction with accompanying hypereosinophilia concurrently with the diagnosis and treatment of cervical cancer. A. Peripheral blood smear showing abundant eosinophils (MayGrünwald-Giemsa [MGG], x1.000). B. Hypercellular bone marrow aspirate with scattered eosinophils (MGG, x1.000). C. Chart displaying elevated eosinophil counts in the blood, which sharply decrease following tumor remission.

Persistent eosinophilia associated with a hematologic disease can be reactive to the release of eosinopoietic cytokines (polyclonal or benign) or neoplastic (belonging to the malignant clone) Table 1 [17]. In practice, clonality is not directly determined on purified eosinophils. Instead, the evidence is indirect and is based on the underlying pathology and identified markers of clonality.

Table 1.

Haematological neoplasm associated with eosinophilia
Haematological neoplasm associated with reactive or secondary eosinophilia* 1. Hodgkin lymphoma 2. Mature T-cell neoplasms 3. Lymphoid variant of hypereosinophilic syndrome 4. B-cell lymphoblastic leukemias/lymphomas 5. T-lymphoblastic leukemias/lymphomas
Haematological neoplasm associated with neoplastic or primary eosinophilia** 1. Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangements: 1.1. Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement 1.2. Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement 1.3. Myeloid/lymphoid neoplasms with *FGFR1* rearrangement 1.4. Myeloid/lymphoid neoplasms with *JAK2* rearrangement 1.5. Myeloid/lymphoid neoplasms with *FLT3* rearrangement 1.6. Myeloid/lymphoid neoplasms with *ETV6*::*ABL1* rearrangement 1.7. Myeloid/lymphoid neoplasms with other tyrosine kinase gene fusions 2. Core binding factor acute myeloid leukemia 2.1. Acute myeloid leukemia with *CBFB*::*MYH11* fusion 2.2. Acute myeloid leukemia with *RUNX1*::*RUNX1T1* 3. Mastocytosis 4. Myeloproliferative neoplasms 4.1. Chronic myeloid leukemia 4.2. Chronic eosinophilic leukemia 5. Myelodysplastic/Mieloproliferative neoplasms 6. Myelodysplastic neoplasms

*In these disorders, eosinophilia is usually reactive to the release of eosinopoietic cytokines (polyclonal or benign). **In these disorders, eosinophils are usually neoplastic (belonging to the malignant clone).

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3. Hematological neoplasms associated with eosinophilia

3.1. Hematological neoplasms associated with reactive eosinophilia

3.1.1. Classical Hodgkin Lymphoma

The observation of pronounced and persistent reactive eosinophilia is an unusual finding in patients with B-cell lymphomas, except for Hodgkin lymphoma. Approximately 15% of these patients exhibit it, typically in a mild form. Histologically, it is better distinguished in the inflammatory infiltrate surrounding Reed-Sternberg cells (Figure 5). Inside these cells, IL-5 mRNA has been demonstrated by *in situ* hybridization. It is unknown whether these cells or the abundant Th2 lymphocytes present are the main source of eosinopoietic cytokines [18,19].

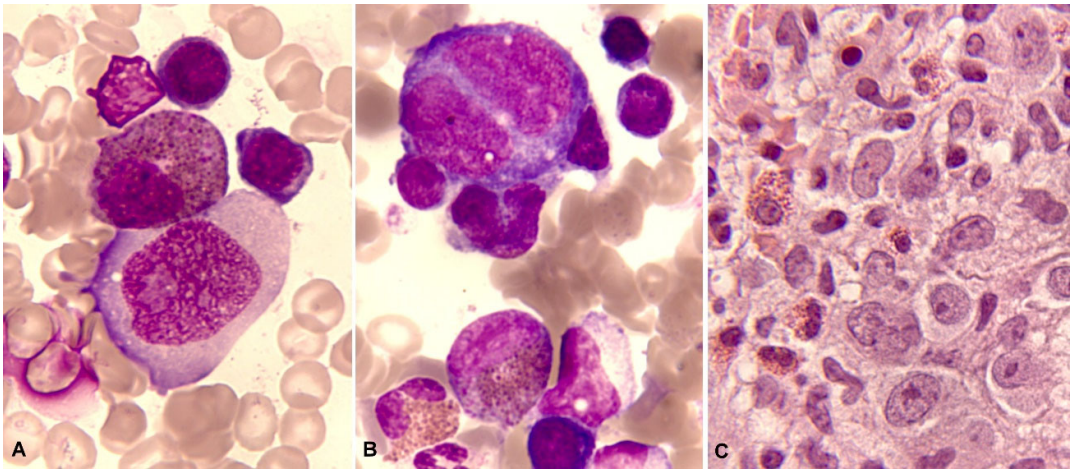

Figure 5. Bone marrow aspirate. May-Grünwald-Giemsa, x1.000. Patient with Hodgkin's lymphoma presenting infiltrative nodules in the bone marrow with an eosinophilic component. A. Hodgkin cell with a large irregular nucleolus. B. Reed-Sternberg-like cell with mirror nucleus. C. Bone marrow biopsy. Hematoxylin and eosin, x630. Mononuclear cells with prominent nucleoli and infiltration of eosinophils.

3.1.2. Mature T-cell neoplasms

Mature T-cell neoplasms associated with eosinophilia mostly derive from memory CD4+ T cells, which can produce eosinophilopoietic cytokines. Sometimes it is doubtful whether eosinophilia is due to the tumor cells themselves or to locally attracted reactive Th2 lymphocytes. In any case, proliferating eosinophils are not related to the malignant clone, and can be integrated into the inflammatory context that surrounds the tumor cells. In the setting of eosinophilia, the study of the immunophenotype of T lymphocytes is relevant, with the antibody against TRBC1 JOVI-1 having recently been incorporated and validated as a useful marker in the identification by flow cytometry of clonal T populations with a TCR alphaBeta [20].

The presence of eosinophilia is estimated in 17-25% of mycosis fungoides cases, and it is described with much higher frequency in Sezary syndrome, observed in 10 out of 13 patients (77%) [18,21]. In both mycosis fungoides and Sezary syndrome, clonal T lymphocytes commonly exhibit a CD4+ CD3+ phenotype in the absence of CD7 and CD26 expression. In the case of Sezary syndrome, a phenotype of central memory CD4 T lymphocytes (CD45RA- CD45RO+ CCR7+ CD27+ and CD62L+/-) is characteristic, unlike mycosis fungoides where its immunophenotype profile is that of an effector memory cell resident in the skin (CD45RA - CD45RO+, CCR7-, CD27- and CD62L-). Furthermore, it is accompanied by the expression of intense CD28+ and CD279 [22]. In nodal T-follicular helper cell lymphoma, angioimmunoblastic-type, eosinophilia is also common, in 32-50% of cases. This lymphoma originates from a follicular CD4 T cell with a phenotype that is characterized

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by weak or negative expression of CD3, with expression of CD10 and PD-1 (CD279) maintaining the expression of other pan-T markers such as CD5 (Figure 6) [23]. Adult T-cell leukemia/lymphoma follows in frequency with eosinophilia in 20% of cases. In this case, it is generally a CD4+CD8- T lymphocyte phenotype, although to a lesser extent they can be double positive (CD4+CD8+) or CD4-CD8+. Furthermore, the expression of CD25 and CCR4 is typical, the latter being essential as it is currently a therapeutic target [24]. More rarely, eosinophilia is found associated with other T lymphomas, although histologically it is frequently found with a peritumoral arrangement [18].

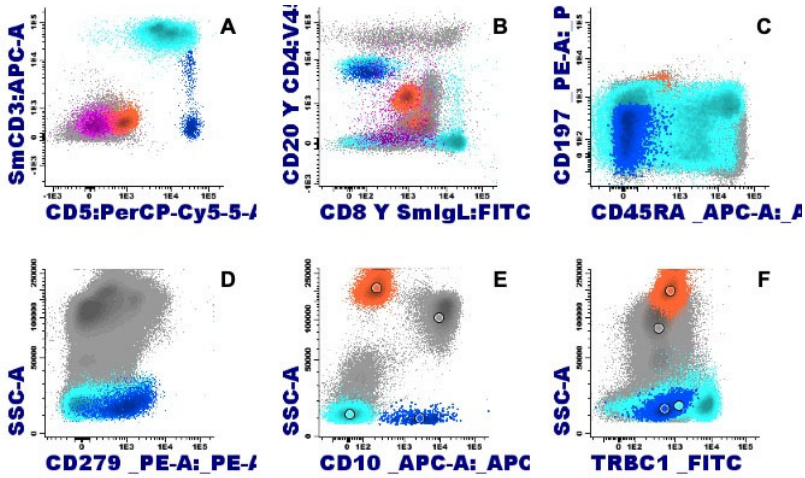

Figure 6. Characteristic immunophenotype of angioimmunoblastic T lymphoma (AITL) with eosinophilia is illustrated in a representative case: light blue, T cells; blue, abnormal T cells; orange, eosinophils; purple, plasma cells. A. Abnormal T cells express CD5 bright and lack CD3 or show dim expression. B. CD4+ CD3-/+ weak subset. C. Differentiation markers of T cells show effector memory phenotype (CD45RA- CD197-/+weak). D. Positive expression of CD279. E. CD10 specific pattern of AITL; abnormal T cells show a clonal pattern according to expression of TRBC1 (TRBC1 negative). .

3.1.3. Lymphocyte variant hypereosinophilic syndrome

This is a rare variant of hypereosinophilic syndrome (HES), with eosinophilia due to overproduction eosinophilopoeitic cytokines secreted by clonal T lymphocytes with an abnormal immunophenotype. Persistent blood hypereosinophilia is related to tissue infiltration and organ damage. In a large review of 148 cases, the median age at diagnosis was 46 years-old and there was no difference by gender. The most common clinical manifestations were cutaneous (81%), while cardiovascular manifestations occurred in 11.5% of cases. The most frequent immunophenotype of T cells was $CD3^{-}$ $CD4^{+}$. Although their behavior is indolent, they have an increased risk of transformation to T lymphoma (risk of transformation at 10-year: 19,9%) [25].

3.1.4. B Acute lymphoblastic leukemia/lymphoma

Significant eosinophilia during or prior to diagnosis is observed in less than 1% of B acute lymphoblastic leukemia/lymphoma (B-ALL). The expansion of eosinophils is considered reactive to the production of cytokines by lymphoblasts. Eosinophils can show dysplastic feature in morphology and by immunophenotype (Figures 7 and 8).

Eosinophilia is often associated with B-ALL with t(5;14)(q31.1;q32.1);*IGH*::*IL3*, an entity initially defined in the 2008 World Health Organization (WHO) Classification. Actually, this entity is named as B-ALL with t(5;14)(q31.1;q32.3)/*IL3*::*IGH* in accordance with International Consensus Classification (ICC) 2022. It is a very rare subtype of B-ALL. In a review of 24 patients, this leukemia mainly affects adolescent or young adult males who suffer frequent manifestations derived from eosinophilia (neurological, thromboembolic, pulmonary and cutaneous) [26]. The relevance of eosinophilia in the blood and bone marrow can relativizes the percentage of blasts, which can be less than 20%. In addition, eosinophilia and *PAX5* rearrangement (*PAX5*::*GSDMA* and *PAX5*::*ZCCHC7*)

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has also been found [27,28]; as well as the observation of a hyperdiploid karyotype with structural alteration [29].

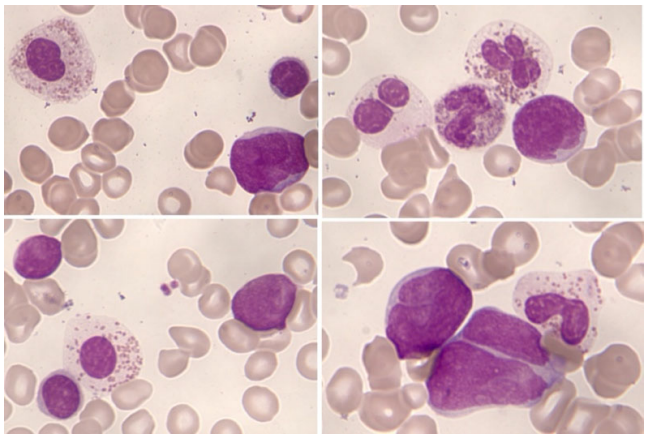

Figure 7. Bone marrow aspirate. May-Grünwald-Giemsa, x1.000. B-acute lymphoblastic leukemia. B. Blasts accompanied by dysplastic eosinophils characterized by their large size, hypogranularity, and nuclear immaturity.

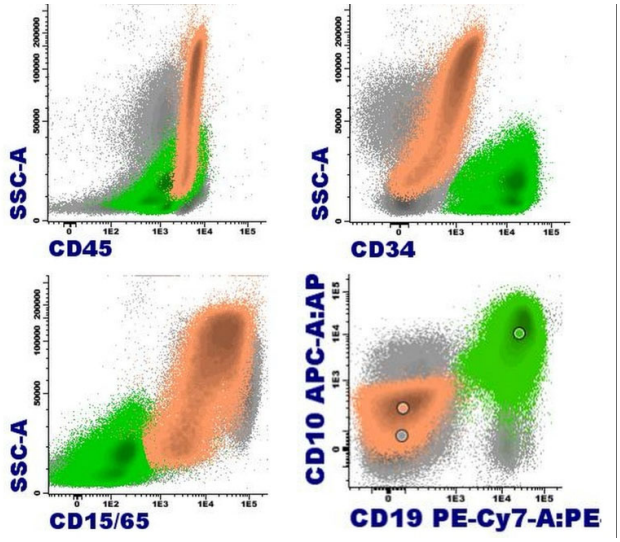

Figure 8. B acute lymphoblastic leukemia (B-ALL) with eosinophilia by Flow cytometry (bone marrow): In orange, eosinophils are represented with varying degrees of granulation, mostly hypogranular, making identification challenging (heterogeneous SSC, mostly low). Eosinophils are characterized by intense expression of CD45 and weakly positive for CD15; the immature B-cell population, highlighted in green, corresponds to a common B-cell acute lymphoblastic leukemia (ALL-B), characterized by weak expression of CD19, CD34, CD45, and positive for CD10, and negative for CD15/CD65.

3.1.5. T acute lymphoblastic leukemia/lymphoma

The appearance of eosinophilia in T acute lymphoblastic leukemia/lymphoma (T-ALL) is anecdotal, having been described in a case of near-early T precursor ALL with a t(5;7)(q31;q21)/*CDK6*::*IL3*, which may have a functional mechanism similar to the *IGH*::*IL3* rearrangement of B-ALL [30].

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3.2. Hematological malignancies associated with neoplastic or primary eosinophilia

3.2.1. Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangement.

The 2016 WHO classification recognized four entities with genetic rearrangements of *PDGFRA* (4q12), *PDGFRB* (5q32), *FGFR1* (8p11.2) and as a provisional entity *PCM1*::*JAK2* [t(8;9)(p22;p24.1)] [31]. These entities are recognized within the section of "Myeloid/lymphoid neoplasms with eosinophilia (M/LN-eo) and defining gene rearrangements" in the 5th edition 2022 WHO classification. While in the 2022 ICC the name of this section is "M/LN-eo and tyrosine kinase gene fusions" [32,33]. Both classifications include a modification in the *PCM1*::*JAK2* category that is now called *JAK2* rearrangement. Also, the latest classifications include three new entities: M/LN-eo with *FLT3* rearrangement, M/LN-eo with *ETV6*::*ABL1* fusion, and M/LN-eo with other tyrosine kinase gene fusions. They have in common a very low incidence, and the cell of origin is a pluripotent stem cell, hence the variability in the involvement of hematopoiesis. The most common presentation is as a chronic process resembling MPN or myeloproliferative/ myelodysplastic neoplasia (MDS/MPN). However, an aggressive presentation of disease can be observed at diagnosis or by progression, in the form of acute myeloid leukemia (AML), T-ALL and, more rarely, B-ALL or acute leukemia of ambiguous lineage. In some patients the same neoplasia occurs simultaneously chronically in the bone marrow and aggressively in the extramedullary involvement [34,35]. Currently, an association with a low-grade B lymphoid neoplasia has not been described. Singularly, when the clinical presentation is a B-ALL, the differential diagnosis must be made with B-ALL with *BCR*::*ABL1*-like features. In the latter case, the rearrangement is restricted to lymphoblasts, normally without eosinophilia, unlike an aggressive form of NLM-eo in which the rearrangement affects all hematopoietic lineages, with or without eosinophilia [35]. The pathophysiology of these diseases includes the expression of a fusion gene that involves *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *FLT3*, *ABL1* or other kinases giving rise to an aberrant constitutively activated tyrosine kinase.

The observation of eosinophilia in blood, bone marrow and, in certain cases, extramedullary involvement is usually a common sign that guides the diagnosis, although peripheral or tissue expression may be very mild or absent. When its presentation is as MPN or MDS/MPN, a certain degree of fibrosis in bone marrow frequently is observed. The vast majority of rearrangements can be diagnosed by fluorescence in situ hybridization (FISH) and suspected in cytogenetic study, except for *FIP1L1*::*PDGFRA,* which is cryptic. At diagnosis, reverse transcription polymerase chain reaction (RT-PCR) can also be used for the *FIP1L1*::*PDGFRA* rearrangement. Likewise, RT-PCR can be used to follow-up when the partner of any of them is identified. Exceptionally, in all groups there may be cryptic cases that require RNA sequencing for identification.

Significantly, the majority of patients are male, especially in *PDGFRA*, *PDGFRB* and, to a lesser extent, *JAK2* rearrangements and *FGFR1.* It occurs at any age of life with a peak between 45-50 years, being a little earlier in the *FGFR1* group [34–37]. The clinical manifestations and exploratory findings are diverse. In stable chronic forms, a constitutional syndrome can simply be seen, eventually with hepatosplenomegaly, and in case of morphology of chronic eosinophilic leukemia (CEL), organic involvement with fibrosis secondary to eosinophilic infiltration can be added. Obviously, the deterioration is more severe when it is AML or T-ALL, accompanied in this case by lymphadenopathy [34,35].

PDGFRA and *PDGFRB* rearrangements are very sensitive to first- and second-generation tyrosine kinase inhibitors (imatinib and dasatinib). Responses with these inhibitors are also described in the *ETV6*::*ABL1* fusion. Cases of *FLT3* rearrangement may be sensitive to *FLT3* inhibitors; while in those of *FGFR1* and *JAK2* the response to therapeutic targets is much lower, being the allogeneic transplantation of hematopoietic progenitors the curative option [38].

3.2.1.1. Myeloid/lymphoid neoplasm with PDGFRA rearrangement

This is the most frequent among M/LN-eo and defining gene rearrangement. The annual incidence has been estimated at around 0.18 cases per million inhabitants [39]. Within the rarity of these neoplasms, the most observed rearrangement is the *FIP1L1-PDGFRA* fusion, a cryptic

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translocation due to an interstitial deletion in 4q12. This category also includes variant translocations of *PDGFRA* with other genes such as *KIF5B* [40], *CDK5RAP2* [41], *STRN*, *ETV6* [42] *BCR* [43], *TNKS2* [44] and *FOXP1* [45].

At diagnosis, it is usual the presentation as MPN, almost always chronic eosinophilic leukemia, with the eosinophils frequently being dysmorphic, although they can be practically normal or with minimal dysplasia. Eosinophilia is a generalized trait (close to 100%), normally very high, although there may be a selection bias in some series that only included patients with eosinophilia. Isolated cases lacking relevant eosinophilia have been described [46]. Generally, the bone marrow is hypercellular, with an increase in eosinophils that can be normal or dysmorphic; there may also be an increase of blast (<20%), and an increase in dispersed mast cells is common or, more rarely, forming loose clusters, which may present atypical spindle-shaped morphology and usually express CD25. Histologically, the finding of moderate reticulin fibrosis is characteristic [39]. This presentation can occur with or without simultaneous extramedullary involvement by myeloid sarcoma, T-ALL, or rarely B lymphoblastic lymphoma [47]. Chronic forms (CEL or other MPN) can also progress to the blast phase, mainly to AML or to T-ALL. Progression to B-ALL is exceptional, with two cases having been described in adult subjects, one with *FIP1L1-PDGFRA* rearrangement and another with *BCR-PDGFRA*; the first of them presented during diagnosis with MPN with eosinophilia and T lymphoblastic lymphoma and a year later developed B-ALL [48]. The second case presented as MPN in the chronic phase, developing B-ALL a month later [49].

Other less common presentations may include systemic mastocytosis (SM) with eosinophilia, AML, T-ALL, or other MPN, often associated with peripheral eosinophilia. Its presentation as B-ALL is not described except for a single case, without specifying its characteristics, within a series of cases of Ph-like B-ALL [50]. Although infrequently, a subclass of cases could present with extramedullary involvement without concomitant bone marrow involvement [34]. Anecdotal presentations include a patient with three synchronous hematologic malignancies driven by the *FIP1L1*::*PDGFRA* rearrangement: cutaneous T lymphoma, lymphoblastic lymphoma in lymph node, and MPN in bone marrow [51]. Likewise, some association with papulosis lymphomatoid has been described [52].

In the context of *FIP1L1*::*PDGFRA* rearrangements, 2 series stand out with 151 and 78 patients, respectively [36,39]. In the largest series, a retrospective study of 151 patients in the chronic phase, the mean age at diagnosis was 49 years (±12) and 95% was male. Although a fraction of patients (17%) were asymptomatic, the remaining majority presented general symptoms such as asthenia, weight loss and persistent fever. Up to 72% of patients may manifest at least one symptom related to hypereosinophilia: skin manifestations (pruritus, dermal lesions), pulmonary (cough, restrictive disease related to fibrosis), cardiac (sometimes as severe as endomyocardial fibrosis, acute myocarditis, heart and mitral failure, or intracardiac thrombus formation), neurological (mainly ischemic stroke), gastrointestinal (eosinophilic gastroenteritis) and/or vascular (venous thromboembolism and arterial thrombosis). In approximately half of the cases, splenomegaly was demonstrated at diagnosis, which may be accompanied by hepatomegaly. All patients present eosinophilia and in up to 31% it is the only finding. Anemia (24%), mild thrombopenia (28%), and variable leukocytosis, often with neutrophilia (20%), but also with monocytosis (16%), basophilia (13%) or lymphopenia (12%), are also described. The observation of lymphocytosis is unusual. Serum levels of vitamin B_{12} and tryptase are regularly elevated, being much less common an increase in IgE [39].

German Registry for Disorders of Eosinophils and Mast Cells (GREM) described 78 patients with *FIP1L1*::*PDGFRA* gene fusion, 65 patients (83%) presenting in the chronic phase and 13 cases (17%) in the blast phase. In addition, 4 patients developed a blast phase during follow-up. Fourteen out of the 17 cases that developed acute leukemia were of the myeloid line (4 extramedullary cases) and the remaining 3 cases were of the lymphoid line (all of them extramedullary disease) [36].

In pediatric age, this rearrangement is extremely rare, with the male predominance being less pronounced. Five of the 11 cases described were girls. Nine cases were MPN with eosinophilia type CEL, one an T-ALL and the last one extramedullary B-ALL with MPN with eosinophilia in bone marrow [47].

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Virtually almost all patients with *PDGFRA* rearrangements respond to imatinib, with a sensitivity 100 times greater than *BCR::ABL1*, hence the importance of its early detection for the prevention of organ and tissue damage [53].

3.2.1.2. Myeloid/lymphoid neoplasm with PDGFRB rearrangement

PDGFRB rearrangement follow in order of frequency to the *PDGFRA* rearrangement. Both types of neoplasms share a marked parallelism in their pronounced dominance in men, median age of presentation in adults aged 49–53 years (range 20–80), clinical and cytological presentation, and in their excellent response to imatinib. The most expressive difference between the two neoplasms lies in the lower incidence and amount of eosinophilia in M/LN-eo with *PDGFRB* rearrangement, which was limited to 50–58% of cases, and even absent in up to 21–25% of cases [36,54]. Organic involvement is not significant, except for splenomegaly, which is described in up to 83% of affected patients and which may be accompanied by hepatomegaly [54].

More than 40 different partners of *PDGFRB* rearrangement have been described, with *ETV6* being the most frequent. In this case, the presentation as chronic myelomonocytic leukemia (CMML) with eosinophilia and t(5;12)(q32;p13.2)(22) is typical. Most of *PDGFRB* rearrangements are detected by alterations in the karyotype that affect 5q32 and by a break-apart FISH probe, although exceptionally this rearrangement can be cryptic and require RNA-sequencing for diagnosis. The high availability of partners seems to influence the heterogeneity of presentation in the chronic phase. This partner availability is greater than in individuals with *FIP1L1-PDGFRA* and may present as MPN or MDS/MPN (more like CMML and less like atypical chronic myeloid leukemia) (Figure 9). *PDGFRB* rearrangement can also present as acute leukemia, at diagnosis or in progression, typically as AML and rarely as T lymphoblastic lymphoma. In exceptional cases, progression as angioimmunoblastic T cell lymphoma has been described [54].

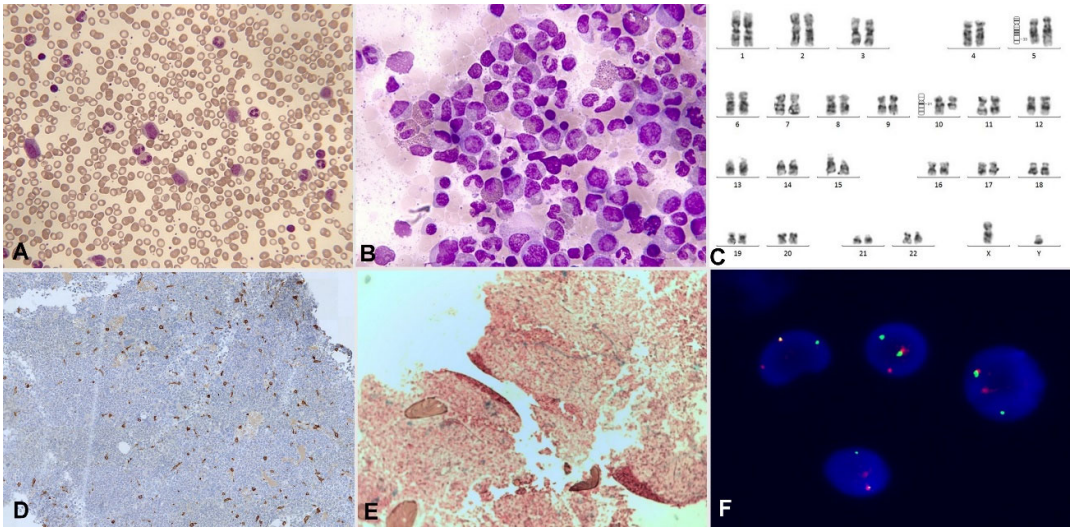

Figure 9. Patient with M/lN-eo with *PDGFRB* rearrangement (Courtesy or Dr. Marina Gómez Rosa, Virgen de Valme hospital, Seville). May-Grünwald-Giemsa. A. Peripheral blood: myelemia and left shift, B. Hypercellular bone marrow (aspirate) with eosinophilia. Bone marrow biopsy: D. Inmunohistochemistry with CD117 reveals an increase in scattered mast cells. E. Bone marrow biopsy showing Grade 1 reticulin fibrosis by the World Health Organization criteria. E. Bone marrow karyotype: 46,XY, t(5;10)(q32;q21)[20]. F. Break-apart probe for *PDGFRB* rearrangement: a rearrangement of *PDGFRB* is observed.

In a series of 135 adult patients with M /LN-eo), 26 cases corresponded to the subcategory of *PDGFRB* rearrangements. Of these cases, 22 (85%) presented as chronic phase, while four cases (15%) were in blast phase, with one patient developing a blast phase during follow-up. Of the five cases

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that developed acute leukemia, two were of myeloid lineage (one extramedullary case) and three cases of lymphoid lineage (two extramedullary, one a T-cell lymphoma) [36]. At least nine pediatric cases were reported [55–60], with no differences by gender.

Responses with durable remissions have been described to low doses of imatinib [54].

3.2.1.3. Myeloid/lymphoid neoplasm with FGFR1 rearrangement

The cases with this rearrangement are particularly rare, with around 100 cases having been reported. As with the previous subtypes, presentation is highly heterogeneous. However, the common link is the demonstration of the rearrangement of *FGFR1* (chromosome 8p11). These rearrangements are usually observed by cytogenetics, although at least three cases have been described with cytogenetically cryptic *FGFR1* detected by FISH or RNA sequencing [61]. At least 14 partner genes have been reported. The most frequently observed are *ZMYM2* in t(8;13)(p11;q12), followed by *BCR*, *CEP110*, and *FGFR1OP* (*FOP*). While a certain tendency for the "partner" to influence the phenotype of the disease has been observed, this is not always the case. Somatic mutations are common, especially in *RUNX1*. The age range of the patients is wide (1–87 years), with a median age in adults in the largest series between 46 and 51 years [62,63]. Unlike *PDGFRA* and *PDGFRB* rearrangements, men displayed only a slight predominance of *FGFR1* rearrangement – slightly above 50% [62,63].

M/LN-eo with *FGFR1* rearranged present most frequently as MPN with or without concomitant involvement by acute leukemia or lymphoblastic lymphoma. Blood eosinophilia is common, ranging from 50% to 80% (assessed in short series of patients) [35,36,63]. A high tendency towards blastic transformation, AML, B or T-ALL, or mixed phenotype leukemia was observed [64–66]. Presentations have been described as B-ALL with *BCR*::*FGFR1* rearrangement and additional cytogenetic alterations. When acute leukemia is treated and remitted, MPN appears with leukocytosis, splenomegaly, and isolated persistence of the *FGFR1* rearrangement [65].

About 27 cases are described with this rearrangement that present as acute leukemia of a mixed phenotype, ambiguous lineage or switching lineage in the evolution (eight cases), without eosinophilia in up to 21% of the cases [61], similar to the cases with *BCR*::*ABL* and *KMT2A* rearrangements. Occasionally, patients with M/LN-eo and *FGFR1* rearrangement associated with systemic mastocytosis were seen, although an activating mutation of *KIT* D816V was not always confirmed. These cases should be classified as systemic mastocytosis with an associated hematological malignancy [67].

In children, at least seven cases have been published [59,68–73].

A highly significant difference of this group of patients compared to *PDGFRA* and *PDGFRB* rearrangements is their lack of response to first- and second-generation tyrosine kinase inhibitors. The clinical course of the *FGFR1* rearrangement cases is usually aggressive, with rapid progression to blast crisis and a short period of patient survival. Aggressive chemotherapy and allogeneic transplantation of hematopoietic progenitors are considered the best curative option. In isolated cases, clinical trials with other therapeutic targets, such as pemigatinib, ponatinib, sorafenib or olverembatinib, have demonstrated some clinical efficacy [74].

3.2.1.4. Myeloid/lymphoid neoplasm with PCM1::JAK2 rearrangement

In addition to *PCM1*::*JAK2* o t(8;9)(p22;p24), *ETV6*::*JAK2* and *BCR*::*JAK2* stand out for their similar behavior. Thus, in the fifth edition of the WHO Classification and the ICC, this subtype has been redefined as NLM-eo with *JAK2* rearrangement [32,75]. To date, approximately 100 cases of M/LN-eo with *PCM1*::*JAK2* rearrangement or variants have been described. In a review of 66 cases with *PCM1*::*JAK2* rearrangement [76], the mean age of presentation was 47 years (range 6–86 years), with 77% being men. The most common presentation was chronic, as MPN or MDS/MPN, with eosinophilia in 75% of patients, and often with erythroid proliferation dysplastic. Other less frequent presentations were as acute leukemia (AML or B/T ALL), or blast crisis from a previous MPN, or a minority as cutaneous T-cell lymphoma. When this subtype presents as B-ALL, a differential diagnosis must be made with Ph-like B-ALL, although rearrangements with certain "partners"

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(*SSBP2*, *PAX5*, *RFX3*, *USP25* and *ZNF274*) are normally considered Ph-like B-ALL. Survival is highly variable, depending on presentation. Target therapy with *JAK2* inhibitors, such as ruxolitinib, may be of benefit [77] but allogeneic transplantation of hematopoietic progenitors is considered the only curative option [37].

3.2.1.5. Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangement: new entities

In 2022, both the fifth edition of the WHO Classification and the ICC recognized the following three new groups within the NLM-eo and tyrosine kinase (TK) fusion genes category:

Myeloid /lymphoid neoplasms with *FLT3*/t(v;13q1212) rearrangements

These neoplasms are rare, just over 30 cases have been described in the literature, including a multicenter study with 12 patients and case report descriptions, [78,79]. The most frequent fusion partner is *ETV6* (12p13), while the following have also been described: *ZMYM2*, *TRIP11*, *SPTBN1*, *GOLGB1*, *CCDC88C*, *MYO18A*, and *BCR*. This subtype predominates in men, although, with an M:F ratio (1.9:1), not as marked as in other types of M/LN-eo. The age at diagnosis is highly variable, with an age range from eight months to 80 years. Eosinophilia is frequent, although absent in some cases [78,80]. Regarding presentation, these patients often manifest as MPN-eo or MDS/NMP. Extramedullary involvement is common, including T-lymphoblastic lymphoma, mixed-phenotype acute leukemia, myeloid sarcoma, and, rarely, B-ALL. Coexistence of extramedullary disease and chronic form in the bone marrow have also been described [35]. Pediatric cases are anecdotal, but at least three cases have been described [78,81,82].

FLT3/t(v;13q1212) rearrangements are largely detectable by cytogenetics (chromosome 13q12) and FISH but can be cryptic (like *TRIP11*), which would require RNA-sequencing. The importance of their recognition lies in the fact that they respond to FLT3 inhibitors.

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

This category currently only includes one *ABL1* partner, which is *ETV6*. At least 13 other partners of *ABL1* have been described, but most cases present as Ph-like B-ALL or de novo T-ALL. These cases are therefore not included in this category [83,84].

Because the *ETV6*::*ABL1* rearrangement shares the constitutive activation of the same tyrosine kinase as the *BCR*::*ABL1* rearrangement, it has the peculiarity of being the one that most closely resembles chronic myeloid leukemia (CML), although it is much less frequent. The myeloid neoplasm with E*TV6*::*ABL1* rearrangement typically presents in chronic phase with a CML- like morphology. The presence of eosinophilia is almost constant and basophilia is common. As in CML, there may be progression to blast crisis (myeloid or lymphoid, mostly B lineage and a minority T) or rarely present as AML. When the *ETV6*::*ABL1* rearrangement presents as B-ALL, it most often corresponds to a Ph-like B-ALL, and eosinophilia is almost never present.

In the series by Zaliova and collaborators (own and a review of the literature) that includes 44 cases, up to 22 cases were ALL (21 being Ph-like ALL, 21 B-ALL and one T-ALL) and 22 myeloid neoplasms (18 MPN cases and four AML cases). The median age in the 18 cases described in the chronic phase is 51 (range 24–72 years), with a predominance in men: The male to female ratio is 2.4:1. In the same series, children and young adults with this rearrangement presented more like acute leukemias and older adults more like MPN [85].

Most of these rearrangements are produced by an insertion of either *ABL1* in *ETV6* or *ETV6* in *ABL1*. A translocation t(9;12) is less frequent since both genes would be transcribed in the opposite direction in this case, and an inversion of one of the two genes would also be required. Thus, its detection by cytogenetics is usually cryptic, and it is diagnosed by FISH with break-apart probes for *ABL1* (more useful when the insertion is of *ABL1* in *ETV6*) and for *ETV6* (more useful when the insertion is of *ETV6* in *ABL1*). This rearrangement can also be suspected when probes such as *BCR*::*ABL* or *ETV6*::*RUNX1* produce extra signals for *ABL1* or *ETV6*. RNA-sequencing can also confirm this rearrangement and provide a diagnosis if it had been previously overlooked.

In the chronic phase, these patients respond to tyrosine kinase inhibitors, such as imatinib, or second and third generation ones. Just like in CML, the response is poor in the blast phase.

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Myeloid/lymphoid neoplasms with other tyrosine kinase gene fusions

These gene fusions affect other tyrosine kinase genes not included in the previous categories, have hematopoietic lineage plasticity and eosinophilia, and present similarly. Some of these rearrangements are *ETV6*::*FGFR2* [86], *ETV6*::*LYN* [87], *ETV6*::*NTRK3* [88], *RANBP2*::*ALK* [89], *BCR*::*RET*, and *FGFR1OP*::*RET* [90].

3.2.2. Core Binding Factor acute myeloid leukemias

3.2.2.1. LMA with inv (16)(p13.1q22) o t(16;16)(p13.1;q22); CBFB::MYH11

The diversity of these leukemias presents a myelomonocytic cytology, sometimes purely monocytic. The percentage of eosinophils in the blood is usually normal – although eosinophilia may exist as these leukemias are usually hyperleukocytic – and eosinophils do not present relevant dysplasia. In the bone marrow examination, eosinophilia is usually frank, with unmature elements. Thick and dark violet-purple granules are characteristic (Figure 10) [91,92].

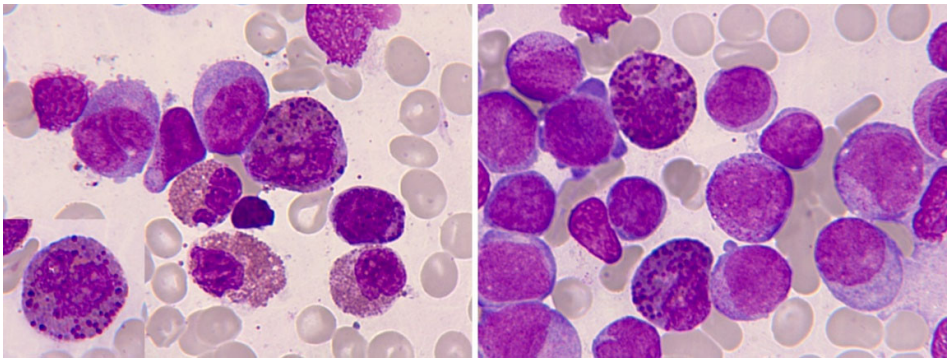

Figure 10. Bone marrow aspirate. May-Grünwald- Giemsa, x1.000. Acute myeloid leukemia with inv(16)(p13.1q22). In both images, dysmorphic eosinophils with thick reddish-violet granules are evident; the one on the left highlights the intensity of eosinophilia.

At times, the presence of eosinophils, less than 6%, is observed in a blastic hypercellularity environment. In our series of 13 cases, we observed blood eosinophilia in 6/13 (46%) and marrow eosinophilia in 10/13 (77%). In exceptional cases, bone marrow eosinophilia becomes massive, without expression in the blood (Figure 11).

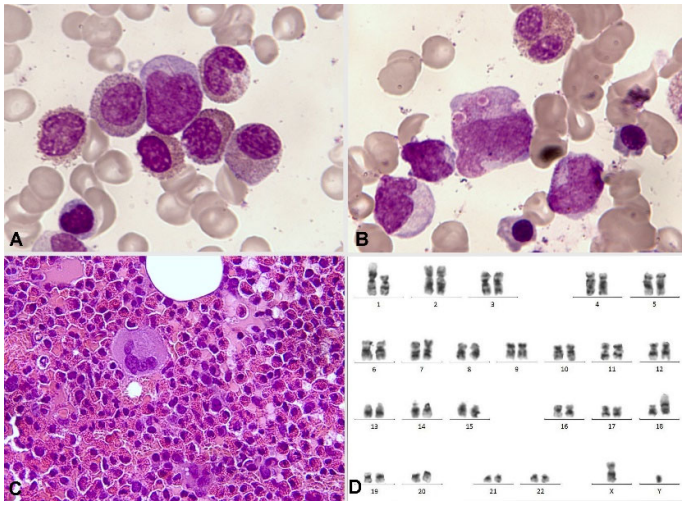

Figure 11. Bone marrow aspirate. May-Grünwald-Giemsa, x1.000. Oligoblastic acute myeloid leukemia with inv(16)(p13.1q22). A. Cytological image with a blast containing a long Auer rod, surrounded by eosinophils. B. Pseudo-Chédiak-Higashi inclusions. C. The histological image clearly

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shows massive medullary eosinophilia. D. Bone marrow karyotype: 46,XY,inv(16)(p13.1q22)[3]/46,idem,t(1;18)(p22;p11.2).

Cytochemically, positivity is typical both with the PAS reaction and in the enzymatic demonstration of chloracetate esterase (Figure 12). In the immunophenotypic pattern, the presence of blasts with myeloid differentiation is common, as is another subtype of blasts with commitment to monocytes according to their markers [93].

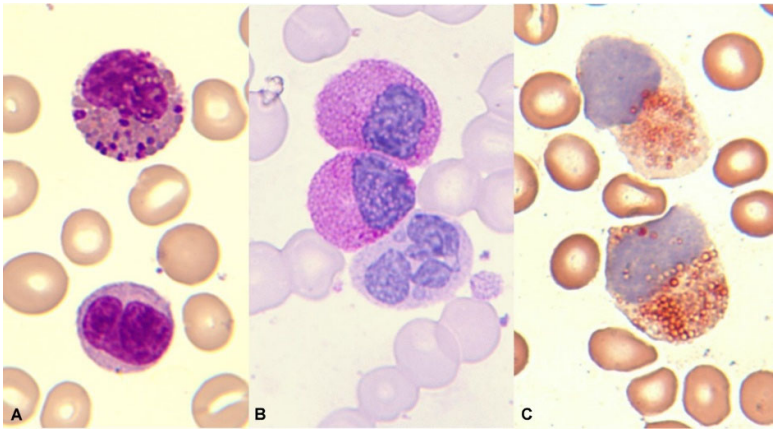

Figure 12. Bone marrow aspirate. May-Grünwald-Giemsa, x1.000. Acute myeloid leukemia with inv(16)(p13.1q22). A. Eosinophil with thick dark pre-eosinophilic granules. B. Positive periodic acid-Schiff (PAS) reaction in immature eosinophils, in contrast to the negativity in an immature segmented neutrophil. C. Two immature eosinophils showing marked chloroacetate esterase activity.

3.2.2.2. LMA with t(8; 21)(q22;q22.1); RUNX1::RUNX1T1

These leukemias are known for their peculiar morphology, with large Auer rods in the blasts and marked neutrophil dysgranulopoiesis. Eosinophilia, both in the blood and in the marrow, is much less evident than in the previous group. In a series of 165 patients collected by the Spanish Hematological Cytology Group [94], blood eosinophilia was observed in 7/148 cases (4.7%) and marrow eosinophilia in 22/137 (16%); (unpublished data). The eosinophils are less dysplastic and without thick and dark red-violet granulation (Figure 13). The chlorocetate esterase is negative, and the PAS reaction may be negative or positive [91,95,96]. In the immunophenotype, most common is the presence of immature blasts with expression of CD34 and CD117, with expression of myeloid markers, such as CD13, CD33 and lymphoid markers, especially CD19 and CD56 [93].

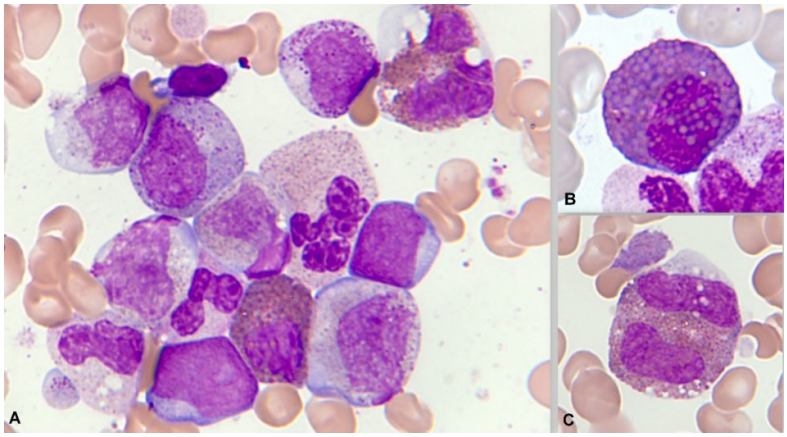

Figure 13. Bone marrow aspirate. May-Grünwald-Giemsa, x1.000. Acute myeloid myeloid with t(8;21)(q22;q22.1). A. Granulocytic dysplasia with peripheral basophilia reinforcement. B. Dysplastic eosinophils with increased granulation thickness. C. Eosinophils with mirror nuclei.

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3.2.3. Mastocytosis

In mastocytosis, a clonal proliferation of eosinophils can be observed that would have its origin in the same neoplastic precursor (multilineage involvement due to the *KIT* mutation).

The 2022 WHO classification includes peripheral and/or central eosinophilia among the signs of myeloproliferation and/or myelodysplasia that are part of the B findings of systemic mastocytosis (SM). However, this is only the case when no reactive cause is identified and criteria for associated hematological neoplasia are not met [32,97].

In a series of 2,350 patients with mastocytosis, eosinophilia was reported in 6.8% and hypereosinophilia in 3.1%, mainly associated with advanced forms. Eosinophilia is frequently seen in bone marrow aspirates and biopsies, even in cases without significant peripheral eosinophilia [98,99]. In exceptional cases, eosinophils can become phagocytosed by the mast cells of an MS, perhaps as a sign of malignancy [100].

In advanced MS with eosinophilia, a differential diagnosis must be made with M/LN- eo and defining gene rearrangements because the coexistence of both is exceptional [101]. It should be noted that in the M/LN- eo an increase in mast cells with aberrant expression of CD25 with or without expression of CD2 may occur. However, dense multifocal infiltrates do not form, and they do not present the *KIT* mutation [32]. Another frequently described marker (80%) in MS mast cells is CD30 [102,103], for which no conclusive descriptions currently exist in the M/ LN- eo. To diagnose the presence of both entities, it is necessary to demonstrate the rearrangement of an M/LN- eo and meet MS criteria.

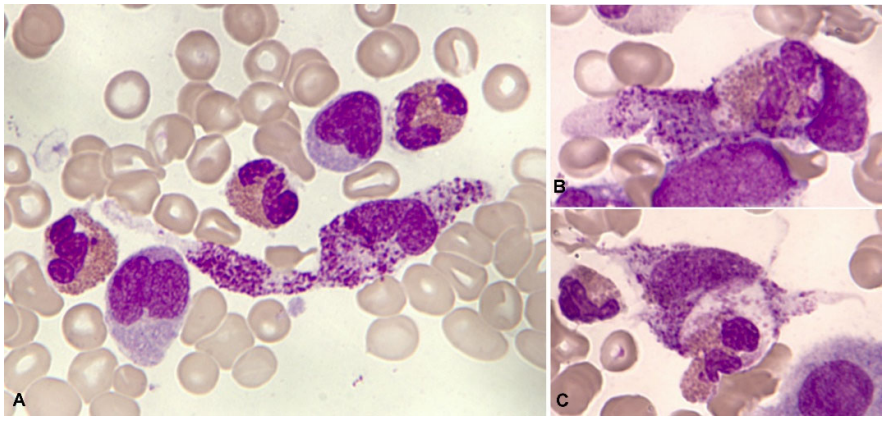

Figure 14. Bone marrow aspirate. May-Grünwald- Giemsa, x1.000. Systemic mastocytosis associated with chronic myelomonocytic leukemia with eosinophilia. A. Hypogranular spindle-shaped mast cell with bilobed nucleus, three eosinophils, and two promonocytic forms. B. Phagocytosis of eosinophil by mast cell, completed. C. Phagocytosis of eosinophil by mast cell, in progress.

3.2.4. Myeloproliferative neoplasms

MPN can present with eosinophilia that requires the ruling out of associated MS or M/LN-eo.

3.2.5. Chronic myeloid leukemia

In the chronic phase, eosinophilia may be present in peripheral blood and bone marrow. Unusual presentation forms have been identified, and they are recognized as “eosinophilic variants of CML” with intense eosinophilia similar to chronic eosinophilic leukemia (CEL). Approximately six cases have been described, with a median age lower than that of CML, most without splenomegaly, and with frequent cutaneous manifestations and vascular symptoms [104].

3.2.6. Chronic eosinophilic leukemia

CEL (2022 WHO), or CEL, not otherwise specified (ICC 2022) is an extremely rare disorder. CEL is accompanied by peripheral hypereosinophilia and significant infiltration of the marrow and

different organs. Cases with other MPN or MPN/MDS, NLM- eo, MDS, mastocytosis and AML with CBF translocations are excluded. The diagnostic criteria for CEL have been updated in 2022 WHO classification. In addition to eosinophilia (on at least two occasions over an interval of at least four weeks), the criteria include evidence of clonality and abnormal bone marrow morphology. The WHO has eliminated the increase in blasts (≥ 5% in the bones marrow and/ or ≥ 2% in the peripheral blood) as an alternative CEL criterion to clonality. This finding is maintained along with the rest of the criteria in the ICC 2022 [32,75].

Organic involvement due to eosinophil infiltration in the absence of abnormal bone marrow morphology, blastosis and/or genetic clonality points to idiopathic HES. In the same circumstances, if organic damage is absent, idiopathic hypereosinophilia would be considered.

One of the best studied series is from the Mayo Clinic, with 17 patients diagnosed according to 2016 WHO criteria (median 63 years, male 88%). Most patients presented with systemic symptoms due to digestive, cardiac, and pulmonary involvement, as well as splenomegaly and hepatomegaly. The blood count showed leukocytosis with eosinophilia (median 6.4 x 10^9/l) and moderate anemia. Eosinophils presented dysplasia in half of the cases. In bone marrow, an increase in the M:E ratio 5:1 (47%), eosinophilia (median 43%), dysmegakaryopoiesis (41.2%), fibrosis (17%), and one case with blasts (>5%) was described. Cytogenetic alterations were described in 15/17 patients and mutations in *ASXL1* in two patients. The prognosis was poor, with a median survival of 16 months and progression to acute leukemia in only three cases [105].

3.2.7. Myeloproliferative / myelodysplastic neoplasms

MDS/MPN can present with eosinophilia. In these cases, an associated systemic mastocytosis must be ruled out and/or, less frequently, a M/LN-eo.

3.2.8. Myelodysplastic neoplasms

The finding of eosinophilia in MDS is unusual and requires reactive causes to be ruled out. A retrospective series of 288 patients described marrow eosinophilia in 36 (12.5%) patients, of which only 18% had peripheral eosinophilia. The usual assumption is that eosinophilia is part of the neoplastic clone. The most common cytogenetic abnormalities are alterations of chromosome 7, complex karyotypes, and isochromosome 17q. A worse survival of these patients is reported, but it could be mediated by the underlying cytogenetics [106].

4. Conclusions

* Eosinophilia associated with a hematological malignancy can be reactive or secondary to the production of cytokines eosinophilopoietic. This type of eosinophilia is mainly observed in lymphoid neoplasms. Eosnophilia can also be neoplastic and primary derived from the malignant clone, usually in myeloid or stem cells neoplasms.

* No data collected in cytological and cytometric studies can predict whether eosinophilia is reactive or clonal. The verification is indirect and supported by the categorization of the accompanying hematological neoplasm.

* In the presence of eosinophilia, flow cytometry can identify a clonal T lymphoid population, mast cells with an aberrant phenotype, and blasts from an acute leukemia.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.X. and Y.Y.; methodology, X.X.; software, X.X.; validation, X.X., Y.Y. and Z.Z.; formal analysis, X.X.; investigation, X.X.; resources, X.X.; data curation, X.X.; writing—original draft preparation, X.X.; writing—review and editing, X.X.; visualization, X.X.; supervision, X.X.; project administration, X.X.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript." Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

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