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Chapter

Eosinophilic Disorders: Extrinsic and Intrinsic Immune Response, New Diagnostic Perspectives, and Therapeutic Alternatives

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Abstract

Eosinophils are immune response cells located in the peripheral blood, bone marrow, and lymph nodes, among others; an increase in the number of eosinophils in the peripheral blood above 5000/mm^3 is associated with conditions ranging from infections (bacterial and parasitic) and allergy (asthma, rhinitis, or drugs), even neoplasms. Various study groups have classified them according to their etiology, thus facilitating their diagnosis and treatment. The WHO divides them as primary and secondary and also considers the number of eosinophils/mm^3 and the involvement of white organs, while others have divided them into intrinsic and extrinsic. The former include mutations in the pluripotential hematopoietic cells, which lead to chronic myeloid leukemias with clonal expansion of eosinophils and extrinsic ones where the changes are related to a TH2 response activated by different cytosines such as IL-5. Current treatments are specifically aimed at modifying the clonal expansion of eosinophils with corticosteroids, hydroxyurea, interferon (peg) alpha, imatinib, among others, and bone marrow transplantation, while in extrinsic alterations corticosteroids and IL inhibitors are used –5 (mepolizumab).

Keywords: eosinophilia, hypereosinophilic syndrome, interleukin-5, diagnosis, treatment

1. Introduction

1.1 Characteristics: morphological, physiological, origin, immunological regulation, and distribution of eosinophil

Eosinophils are leukocytes (white cells) found in the peripheral blood, hematopoietic, lymphatic organs, the bone marrow, spleen, and thymus, and can migrate to connective tissues and digestive tract; they are part of the group of leukocytes called granulocytes, along with basophils and neutrophils. They were described

by P. Ehrlich in 1879 calling them eosinophils because their acidic granules in the cytoplasm were stained by their affinity dye aniline-eosin giving them the form of red-orange ammunition observed by optical microscopy: They are rounded cells from 8 to 15 μm in diameter, with a bilobed core with a fine nuclear bridge joining both lobes [1].

Identification and quantification.

Methodology: Manual count in Neubauer chamber and automatic hematology analyzer using impedance and colorimetry and flow cytometry CD16 (FcγRIII-CD16). Under normal conditions peripheral blood eosinophils represent 1–5% of total leukocytes, with an upper limit of 0.4 × 109 L,, the absolute eosinophilic count (AEC) of 350–500/mm^3 and in children is greater than 0.75 × 109 L, increasing the number of eosinophils (eosinophilia) to more than 3–5 times which is indicative of an activity of infectious, parasitic, allergic, and eosinophilic and hypereosinophilic disorders [1–5].

They originate in the bone marrow, by a process of maturation and differentiation that lasts approximately 8 days (hematopoiesis) from a pluripotential precursor cell (stem cell) differentiating itself as myeloid granulocytic line, under the influence of IL-3, IL-4 - granulocytic colony stimulation factor (GM-CSF) of eotaxin; evolving toward a mixed eosinophil-basophilic precursor and then differentiating toward eosinophils by action of IL-3, GM-CSF, and especially IL-5, they have a survival of 6–12 hours before moving to tissues where they remain between 2 and 5 days; once there is a stimulus, they respond by exercising their multiple functions regulated by T lymphocytes (**Figure 1**) [1, 2, 6].

The text begins with: Its main functions are the defense against parasites, helminths, nematodes, participate in allergic responses, inflammatory processes, restoration, and tissue repair; since they have specific chemotactic receptors on their membrane, eotaxin, cytokines (IL-3 -IL-5 and GM-CSF), eosinophil chemotactic factor of anaphylaxis (ECF-A); and nonspecific such as f MLP (from the wall of bacteria), complement activation products (C3a, C5a, C6, and C7), platelet-activating factor (PAF), leukotrienes (LTB 4 and LTD 4), histamine and IL-8. Diapedesis is mainly performed by integrins to adhere to the vascular endothelium

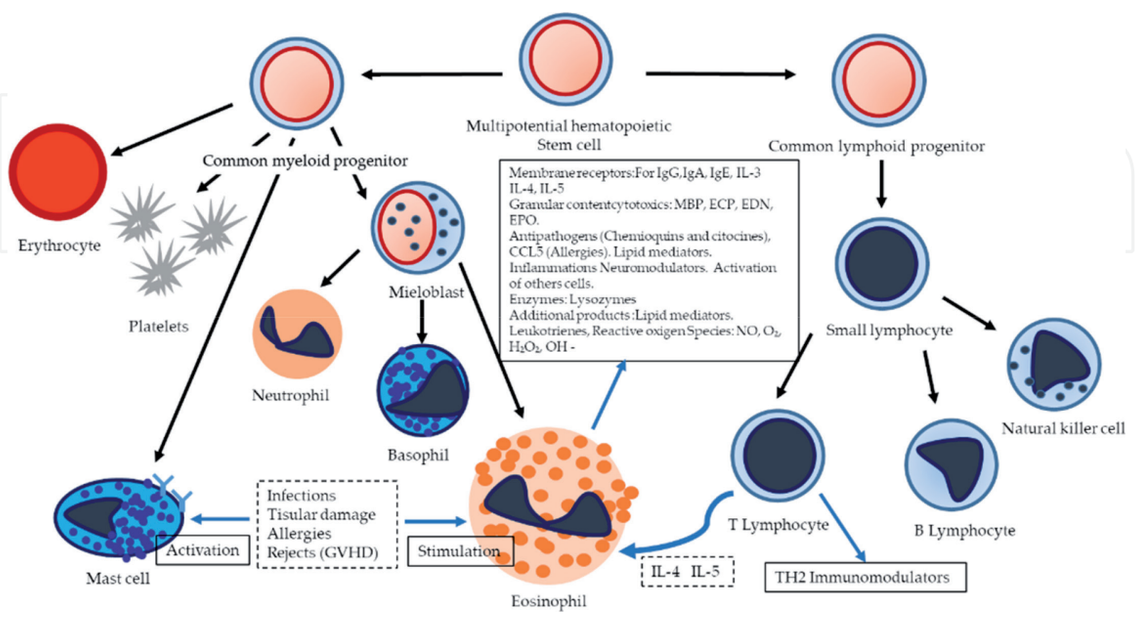


Figure 1.
Scheme representing hematopoiesis, origin of eosinophil and its main functions associated with eosinophilic disorders. Molecules expressed on its surface (FcεRI-CD23-IgE). CCR4, CD88,H4R. Adhesion molecules: CD11b, CD11c, CD62L, and chemokines that attract eosinophils from blood to tissues [3, 7].

(e.g., LFA-1-ICAM-1, the VLA-VCAM-1) and other multiple antibody receptors: IgA (Fc α R1-CD89), (FcεRIII-CD23-IgE), (FcYεRI-degranulation), (FcYRI-CD64-IgG1, IgG3 respiratory burst induction of microbial death), (FcYA-CD32-Ig G1-degranulation), (FcYRIIB-CD32-IgG1-No Phagocytosis, inhibition of cellular activity) (**Figure 1**) [2, 6, 8].

Granular content: Eosinophil mature contains in its cytoplasm primary granules rich in phospholipase A, rich in crystalline proteins of Charcot-Leyden-specific secondary granules containing the major or main basic protein (MBP), the eosinophilic peroxidase (EPO), eosinophilic protein (ECP)), and eosinophil-derived neurotoxin (EDN) that also appears in basophils and neutrophils; its response capacity is less than 1 hour, small granules containing arylsulfatase B and acid phosphatase and five lipid bodies main source of arachidonic acid, can be presenting cells, proliferation of T lymphocytes and basophils are capable of deliberating more than 35 cytokines, chemokines, and growth factors (**Figure 1**) [5, 9].

2. Diseases and classification

The severity of eosinophilia has been arbitrarily divided into mild (AEC from the upper limit of normal to 1500/mm^3), moderate (AEC 1500–5000/mm^3), and severe (AEC >5000/mm^3).

The classification of eosinophilic diseases was revised in 2008 and reaffirmed in 2016. In 2017 its diagnosis, risk stratification (prognosis), and management (treatment) proposed by the World Health Organization were covered [10].

Eosinophilic diseases can be classified in two types: primary, intrinsic hematology due to clonal disorders, and secondary, extrinsic or reactive disorders to an external cause that cause damage to different organs. Primary eosinophilias or clonal disorders can be diagnosed by studying the blood and bone marrow by the following methods: standard cytogenetics, molecular biology with monoclonal antibodies, flow cytometry, in situ hybridization, and evaluation of T cell clonality.

The major category of primary diseases corresponds to myeloid/lymphoid neoplasms with eosinophilia and rearrangements PDGFRA, PDGFRB, or FGR1; with PCMiJAK2 and MPN, a subtype of chronic eosinophilic leukemia or not specified by CEL-NOS, there is another lymphoid-eosinophilic variant of aberrant T cell clone.

The modern definition of hypereosinophilic syndrome (HES) is a vestige of the historical criteria outlined by Chusid and colleagues in 1975: The absolute eosinophil count is >1500/mm^3 for more than 6 months, and tissue damage is present [10, 11].

The Working Conference on Eosinophil Disorders and Syndromes proposed a new terminology for eosinophilic syndromes. Hypereosinophilia (HE) for persistent and marked eosinophilia (AEC >1500/mm^3) in turn, HE subtypes were divided into a hereditary (familiar) variant (HEfa); HE of undetermined significance (HEus), primary (clonal-neoplastic), HE produced by clonal/neoplastic eosinophils (HEn), and secondary (reactive) (HEr) can be considered a provisional diagnosis until a primary or secondary cause of eosinophilia is ascertained [12].

To have to a better understanding of the pathogenetic aspects of eosinophilia, other classifications of eosinophilic diseases were generated according to the site of eosinophilic infiltration associated with organ damage and dysfunction. The primary cause of eosinophilia located within the eosinophils (and/or eosinophil precursors) themselves or in other cells, similar to allergic diseases, can be divided in IgE-mediated (extrinsic) and non-IgE-mediated (intrinsic) diseases; the terms extrinsic and intrinsic eosinophilic disorders indicate whether the primary cause of eosinophilia is inside or outside the eosinophil lineage [11].

2.1 Eosinophilic intrinsic disorders

Chronic eosinophilic leukemias belong to a special group of chronic myeloid leukemias, in which eosinophil differentiation is dominant, resulting in blood eosinophil counts of greater than 1500/mm^3. However, other lineages are also affected, because the disease is the result of a mutation in a pluripotent hematopoietic stem cell. The chromosomal translocations related to breakpoints on chromosome 8p11 result in fibroblast growth factor receptor 1 fusion genes with increased kinase activity causing the so-called 8p11 syndrome. The increase in tyrosine kinase activity is caused by gene 1 and the growth factor, and this leukemia has a worse prognosis, which transforms chronic leukemia to an acute, 1–2 years. Another type of cause may be the increase in tyrosine kinase by fusion of the platelet growth factor alpha receptor genes (PDGFRA). PDGFRA is fused by the Fip1-like 1 (FIP1L1) gene as a result of a 4q12.9 chromosome damage. This is both in eosinophils and in other hematopoietic lineages such as neutrophils, monocytes, lymphocytes, and mast cells. This type of leukemia is pluripotent hematopoietic stem cell which responds to the tyrosine kinase inhibitor (imatinib) [10, 11].

Mutations in multipotent myeloid stem cells: In the chronic myeloid leukemias with eosinophilia, eosinophils are part of the clone. This is because eosinophil differentiation is often not as prominent as other myeloid cells, such as monocytes, which also show increased differentiation. Chromosomal translocations related to breakpoints on chromosome 5q33 are common and represent the basis for the formation of platelet-derived growth factor receptor b (PDGFRB) fusion genes; this result increases the tyrosine kinase activity. There are patients with positive Philadelphia chromosome who can develop chronic leukemia with eosinophilia due to two factors: fusion by breakpoint cluster region-Abelson (ABL) and fusion of transcription gene 6 (ETV6). Marked eosinophilia often associated with a cytogenetic evolution and other accelerated phases of ABL can occur during an acute transformation; ABL may be fused with the transcription factor E26 by means of variant ETV6 triggering chronic leukemia [10].

Myelodysplastic syndromes: During hematopoiesis there may be an inefficient process in the differentiation of stem cell by mutations, malignant clones producing myelodysplastic syndromes that lead to myeloproliferative diseases such as polycythemia vera, essential thrombocythemia, and agnogenic myeloid metaplasia. The exact molecular genetic abnormalities resulting in eosinophilia in these disorders remain to be determined [10, 11].

2.2 Eosinophilic extrinsic disorders

T cell-mediated eosinophilias: The common diseases are allergic rhinoconjunctivitis, bronchial asthma, drug allergic, eosinophilic esophagitis, and atopic dermatitis. Eosinophilia and IgE production due to the polarization of TH2 cells whose causes are extrinsic or external by stimulation of environmental immunogens or chemical compounds, which are presented by APC-MHC, stimulating the release of pro-inflammatory cytokines (IL4, IL5, and IL13), induce the increase in eosinophils of IgE survival, high affinity receptors with PKC activation, cross-linking and signaling for histamine release, as well as vasoactive amines that produce inflammatory processes and organ damage [10, 11].

Infectious diseases: TH2 inflammatory responses are induced by helminths; these responses are characterized by IgE antibody production and eosinophilia; both have been implicated in mediating protective immunity to the parasites. In contrast, there is little doubt that eosinophils contribute to tissue damage and therefore to the pathogenesis of these infections.

Viral infections are not common; however, when virus-specific T cells are generated in a TH2 environment, they can also release IL-5 and therefore trigger eosinophilia. In chronic rhinosinusitis, eosinophilia is related to fungal infections with certain molds (e.g., Alternaria) which is present in the nasal and paranasal cavities [5, 10, 11].

Autoimmune diseases: Because these diseases are often associated with a TH1-associated inflammatory response, eosinophilia is not frequent, but in systemic sclerosis, levels of major basic protein and extracellular major basic protein depositions were observed in skin and lung tissues. In primary biliary cirrhosis, eosinophilia is a distinctive feature that might be useful in the diagnosis of the disease [10, 11, 13].

Graft-versus-host diseases: When an allogeneic bone marrow transplant is carried out and there are differences in MHC molecule polymorphism, these can be recognized by the immune system, and responses can be made against the alloantigens, producing graft-versus- host-disease (GVHDs), carrying out a reaction antigen antibody, cellular or cytotoxic that produces lysis and destruction in specific organs (skin, liver, and gastrointestinal tract mainly).

Drug-induced diseases: Hypersensitivity drug reactions may present in some cases increased eosinophils. The manifestations range from maculopapular rashes of the skin to severe life-threatening drug reactions with eosinophilia and systemic symptoms (DRESS). Drugs and their metabolites can produce hypersensitivity by means of mechanisms mediated by APC-MHC TCR pi concept, generating TH2 polarity or TH1 with memory T cells [10, 11, 13].

There are other subgroups of this syndrome as episodic angioedema and hereditary eosinophilia. Where there is evidence of mechanism mediated by IL-5-producing T cells [5].

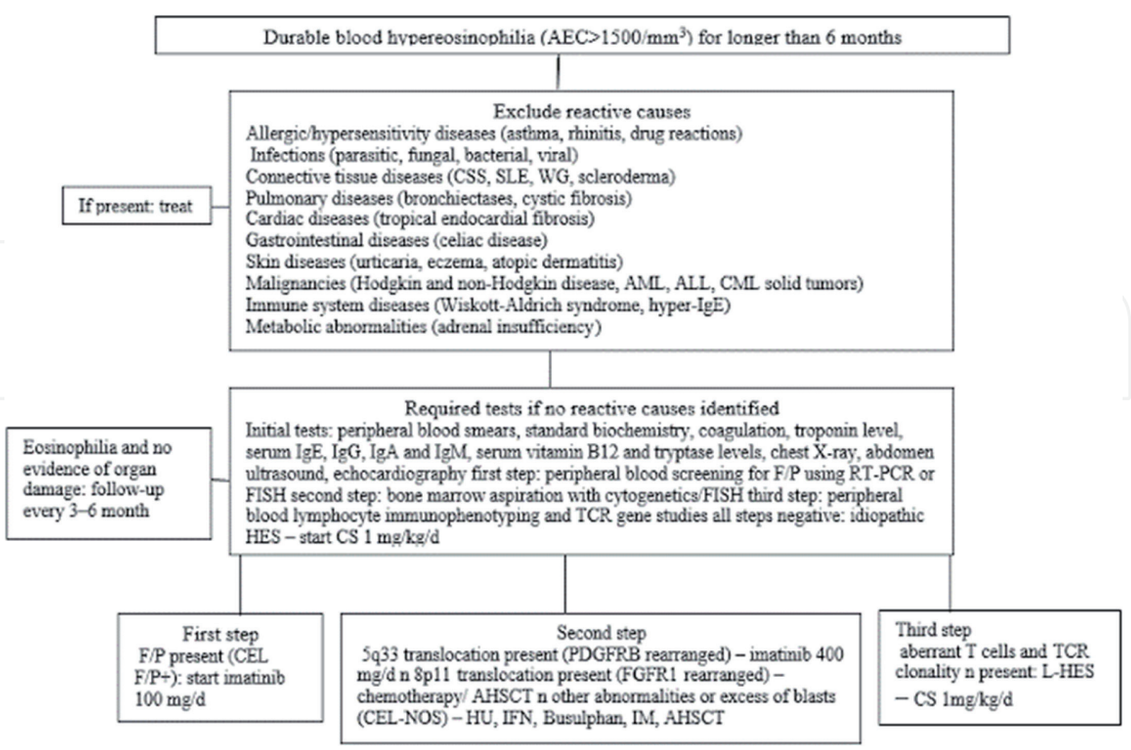


Figure 2.
Diagnostic algorithm for patients with hypereosinophilia. Due to the fact that eosinophilia can occur in different pathologies, an exclusion of the unlikely causes for hypereosinophilia is performed, in addition to a three-step follow-up treatment with imatinib due to mutation processes that is considered. Laboratory tests would be at the discretion of the doctor according to the medical history and the search according to the type of response to the genes involved [12].

Severe primary (IL-5) and secondary immunodeficiencies (HIV) are associated with eosinophilia when there is polarization of TH2 by the immunogen (allergen) or drug (antiretroviral); infections such as tuberculosis are the cause of infections and resistance to treatment (**Figure 2**) [11].

2.3 Treatment of HES and CEL-NOS

Corticosteroids should be considered a first-line treatment, which are potent anti-eosinophil agents, effective in producing rapid reductions. Maximal dose was 1 mg × kg 2 months, with symptom control and reduction of the eosinophil count to below 1500/mm^3 after 1 month of treatment.

Hydroxyurea is an effective first-line agent for HES which may be used in conjunction with corticosteroids or in steroid nonresponders. A typical starting dose is 500–1000 mg daily which can serve as effective palliative to control leukocytosis and eosinophilia but with no proven role in favorably altering the natural history of HES or CEL-NOS (**Figure 2**) [10, 12, 14].

IFN-a has demonstrated hematologic responses and reversion of organ injury in patients with HES and CEL-NOS refractory to therapies including prednisone and/or hydroxyurea. Remissions have been associated with improvement in clinical symptoms and organ disease, including hepatosplenomegaly, cardiac and thromboembolic complications, mucosal ulcers, and skin involvement [5, 10–12].

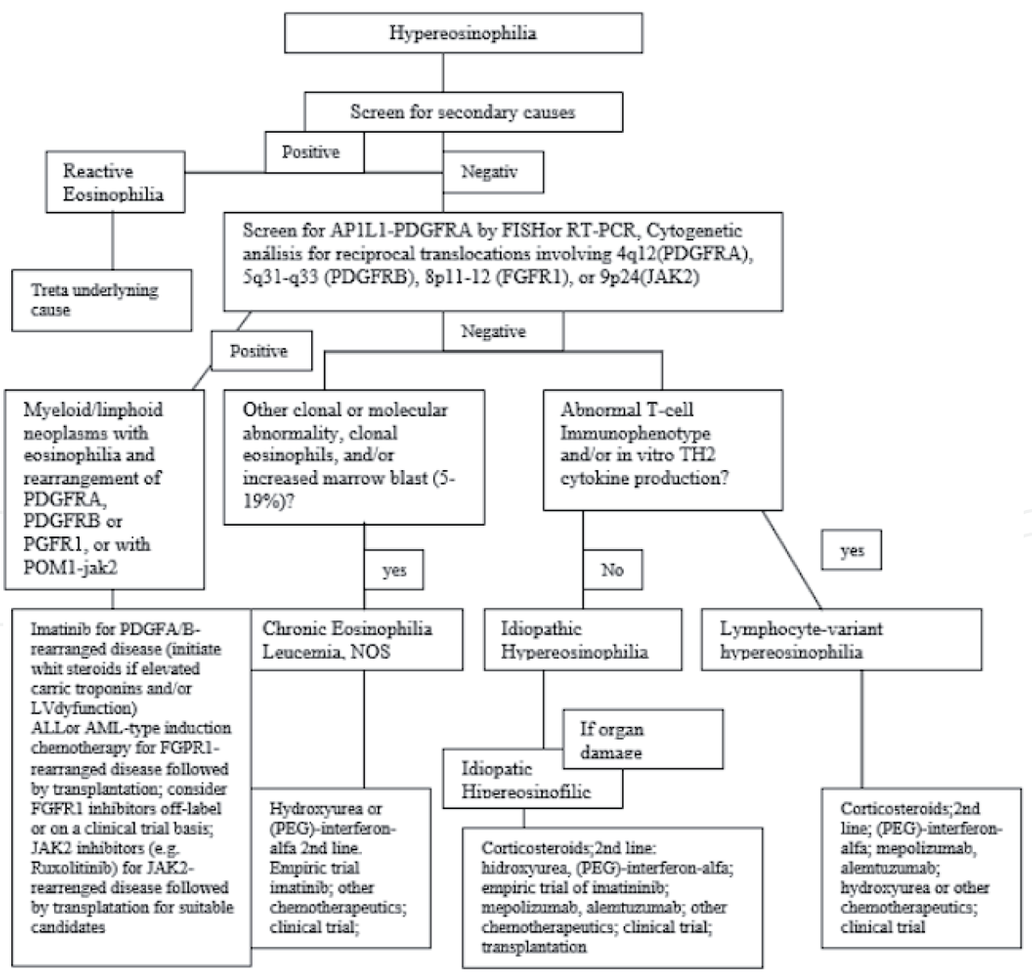


Figure 3.
Diagnostic and treatment algorithm based on revised 2016 WHO classification of eosinophilic disorders. According to the algorithm, the type of eosinophilia can be monitored according to the cases where other drugs other than imatinib should be used, with three pathological options being present: chronic leukemia with eosinophilia, idiopathic hypereosinophilia, and lymphocyte variant, all share the administration of imatinib and corticosteroids (idiopathic hypereosinophilia and lymphocyte variant) [10].

Mepolizumab anti-IL-5 antibody is a fully monoclonal IgG antibody that inhibits binding of IL-5 chain of the IL-5 receptor expressed on eosinophils [5, 14].

Alemtuzumab is an anti-CD52 monoclonal antibody that has been evaluated in idiopathic HES based on expression of the CD52 antigen on eosinophils. In patients with refractory HES, alemtuzumab was administered intravenously at a dose of 5–30 mg once to thrice weekly.

Bone marrow/peripheral blood stem cell allogeneic transplantation has been attempted in patients with aggressive disease; a disease-free survival ranging from 8 months to 5 years has been reported.

Imatinib is a small-molecule tyrosine kinase inhibitor 100 mg per day; it also shows activity against platelet-derived growth factor receptor (PDGF-R), c-Kit, Abl-related gene (ARG), and their fusion proteins while sparing other kinases (**Figure 3**) [10].

3. Hematologic and neoplastic diseases

Mastocytosis: Develops from a neoplastic proliferation of mast cells. It develops from a neoplastic clonal proliferation of mastocytes that accumulate in one or more organ systems and are organize as compact cohesive aggregate groups or multifocal groups of abnormal mastocytes. This disorder is diverse; it can be found as cutaneous lesions that may naturally recede, to highly aggressive neoplasias related with multiple organ failure and short outliving. Mastocytosis subtypes are principally characterized by the clinical manifestations and the spread of the disease. When cutaneous mastocytosis (CM) occurs, mastocyte infiltration is restricted to the skin, whereas systemic mastocytosis (SM) includes at least one extracutaneous organ, with or without skin lesions. Mastocytosis must be distinguished from mastocyte hyperplasia or from the mastocyte activation states, without the morphological or molecular abnormalities that characterize neoplastic proliferation [15]. The WHO classification includes seven types:

a. Cutaneous mastocytosis

b. Indolent systemic mastocytosis (ISM)

c. Systemic mastocytosis with associated clonal, hematologic non-mast cell lineage disease (SM-AHNMD)

d. Aggressive systemic mastocytosis (ASM)

e. Mast cell leukemia (MCL)

f. Mast cell sarcoma (MCS)

g. Extracutaneous mastocytoma

Hypereosinophilic syndrome (HES): It has been described as a condition associated with persistent eosinophilia in the peripheral blood, organ damage, and exclusion of any other underlying disease or condition that may explain eosinophilia or organ damage [4, 16–18]. The diagnostic algorithm must begin with the evaluation of peripheral blood hypereosinophilia (HE), defined as a persistent increase of blood eosinophils, above 1.5 X 109/L blood [4, 16–18]. The term "tissue HE" has also been proposed, and it may be useful in the evaluation and the classification of the disorders related to HES [16, 19]. The establishment of an HES diagnosis must be

considered: (a) the existence of an underlying disease or condition and (b) the presence of clinical signs and symptoms or laboratory abnormalities that show organ damage induced by HE (HES) [19]. There are four important groups of underlying disorders in patients with documented HES:

1. Hematopoietic neoplasias

2. Other neoplasias (non-hematopoietic) (paraneoplastic HE)

3. Common allergic, reactive, or immunological conditions

4. Infrequent clinical syndromes that present HE, including rare hereditary disorders [19]

Lymphoid and myeloid leukemias: Many hematologic disorders may present eosinophilia, but only a few present clonal (primary) neoplasias, and just a small number of neoplasms present HE and organ damage. Myeloid neoplasias that present HE include rare acute eosinophilic leukemia types. The most common type of chronic leukemia is chronic eosinophilic leukemia (CEL), which is frequently associated with the FIP1L1-PDGFRA rearrangement in endomyocardial fibrosis/thrombosis and other myeloid neoplasias with rearrangements, such as the 8p11 syndrome [19, 20]. Clonal eosinophilia is frequently observed in advanced cases of systemic mastocytosis [19, 21, 22].

Lymphoid neoplasms may present HE, and in most cases, a T cell lymphoma is diagnosed. Nevertheless, in such patients with 8p11 syndrome and other rare entities, both eosinophils and lymphocytes may be involved in the neoplastic clonal processes [19, 21].

Paraneoplastic conditions associated with hypereosinophilia. Different types of cancers may be preceded or accompanied by eosinophilia. Cancers associated with HE include lung, gastrointestinal tract, pancreas, and thyroid adenocarcinomas, gynecologic tumors, and skin cancer. Although pathogenesis is unclear, there is a widely accepted hypothesis stating that carcinogenic cells or cancer or the cancer microenvironment around fibroblasts produce eosinophilopoietic cytokines [19, 23].

Identification and quantification.

Classic methodology: Clinical manifestations and diagnosis depend on the type of disease and other factors, where different organs may be involved in patients with HES, for example, skin, gastrointestinal tract, heart, and central nervous system.

In order to establish an HES diagnosis, it is recommended to include clinical and laboratory parameters, such as:

a. Physical exam of organs and body systems

b. Laboratory exams: white blood cell count (eosinophils, basophils, neutrophils), hemoglobin, platelet count, B12 vitamin, hepatic enzymes, kidney function tests, and urinalysis

c. Organic functional tests: electrocardiogram, echocardiogram, pulmonary function tests, chest computed tomography and radiography, abdominal ultrasound, and normal endoscopic study [19]

d. Molecular detection of some translocations, such as TCR, BCR/ABL1, JAK2 V617F, KITD816V, PDGFRA/PDGFRB, and FGR1

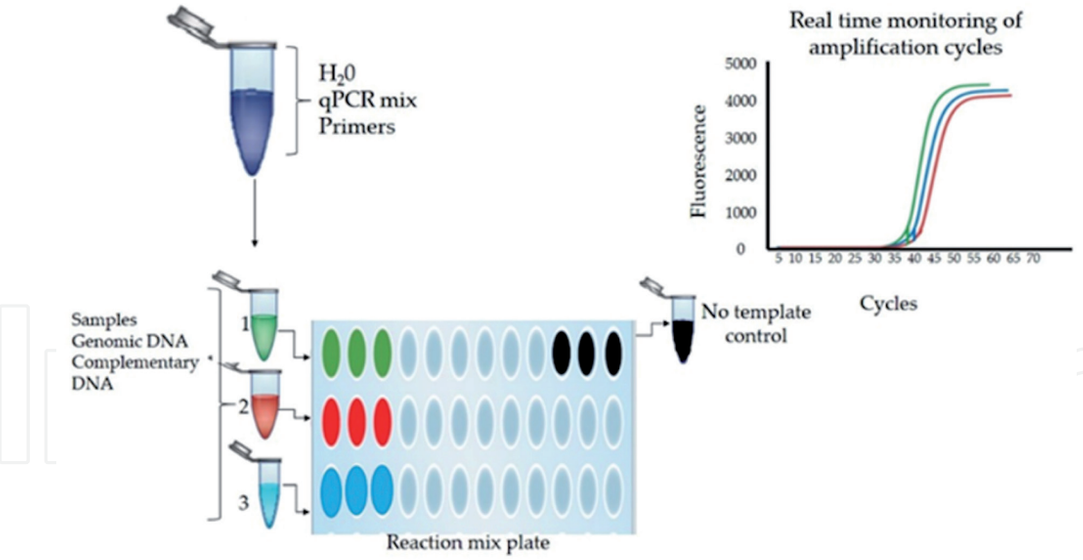


Figure 4.
Flow diagram to perform real-time PCR. In a simplified way, the preparation of the sample with its corresponding primer and the distribution of the samples for its reaction are shown, which can be seen in real time by monitoring the amplification as the cycles in the thermal cycler pass.

3.1 Laboratory diagnosis by molecular parameters

Immunoglobulins rearrangements are detected by real-time polymerase chain reaction with TaqMan molecular probes, such as TCR, BCR/ABL1, JAK2 V617F, KITD816V, PDGFRA/PDGFRB, and FGR1. The most recommended bone marrow exams are cytogenetic assays and fluorescence in situ hybridization (FISH)—other studies which do not include molecular detection are tissue immunohistochemistry and histology (**Figure 4**) [16].

4. Allergy and hypersensitivity to drugs (DHRs)

The WHO defines an ADR to any predictable noxious reaction that appears at therapeutic doses, depends on the doses, and is related to pharmacological actions. Other unpredictable reactions: hypersensitivity or allergic (DHRs) associated with immunological mechanisms, susceptibility (atopy), and polymorphism (pharmacogenetic, MHC-HLA) [24–27].

It is considered as a public health problem due to its high morbidity and mortality being 20%; hence, the importance of its clinical diagnosis and laboratory tests is being considered at all stages of life (prenatal, postnatal, childhood, adolescence, adult, and older adult).

4.1 Immune response to drugs in DHRs: haptens, pro-haptens, and TCR pi

Medications are usually non-immunogenic haptens of different types:

Pro-haptens. Drugs are generally non-immunogenic haptens of different types: Pro-haptens (non-active reagents) low molecular weight chemicals of less than 1000 D; examples aromatic, heterocyclic, sulfonamides, OH, halogens, resonance, and beta-lactam are processed and presented in the CPA-MHC context and produce a humoral response, IgE, IgG and IgM or cellular.

Active reagents: aromatic, polar, with nitrogen, to induce an immune response CPA-MHC.

Inert TCR pi (pharmacological interaction with immune receptors): Some drugs are able to bind non-covalently to TCR pi receptors pre-developed by a previous immune response to a non-covalently reversible drug and signaling toward a response of hypersensitivity and explain the rapid appearance of symptoms, some cross reactions to the drug, or its metabolites.

Pi concept and HLA restriction in hypersensitivity: In the pi concept, drugs primarily activate TCR, for example, abacavir associated with the HLA-B * 5701 allele in whites, Stevens-Johnson syndrome (SJS) with carbamazepine treatment in Chinese associated in patients with the HLA-B * 1502, and HLA-B * 5801 allele in allopurinol-induced adverse reactions such as SJS and toxic epidermal necrolysis (TEN) [28–31].

4.2 Hypersensitivity and diagnosis

Hypersensitivity is an exacerbated immune response, which produces a clinical picture with dermal, systemic disorders, and sometimes sudden death. In 1930 Coombs systematized these reactions according to the period of time in which the symptoms appear, and the dose of challenge has been fundamental to guide the diagnosis, treatment, and monitoring. It has many points in common with autoimmunity, where the antigens are their own; in the case of allergies to medications, the antigens are allergens: drugs or metabolic derivatives. Hypersensitivity reactions require that the individual has been previously sensitized or exposed to at least the antigens in question. The classification of allergic or hypersensitivity reactions into four types (I, II, III, and IV) and subsequently Pichler in 2003 proposed the subdivision of type IV into IVa, IVb, IVc, and IVd (**Table 1**) [28, 29].

4.3 In vitro tests associated with drug and drug eosinophilia: antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) anticonvulsants, and antidiuretics

Modified basophil degranulation (MBD): The test is a basophil activation test (BAT) which consists of incubating the basophils in vitro with the suspected drug to be carried out: epitope-paratope binding, activating the basophils and causing degranulation and release of the aforementioned content (specificity 100%, sensitivity 84.0%) [28, 29].

CD63 flow cytometry: Basophils with specific IgE when incubated with the suspected drug are activated by Fcε I receptors; high affinity and low affinity cause cross-linking and protein kinase signal transduction (MAP, PKC) that stimulate expression of the receptor (CD63) -gp53 (lysosomal-transmembrane protein tetraspanin LAMP-31) on the surface of the basophil while the eosinophilic expresses CD23 [30].

Modified leukocyte migration inhibition factor (MLIF) type IV a, b, and c. Associated with anaphylactic degranulation: It has been reported that leukocytes including basophils (BAT-Chemotaxis) also play a role in directional chemotaxis; therefore, when microhematocrits are incubated in Bloom chambers with medications in two dilutions (1 and 0.1 mg/mL) in an RPMI medium, with negative and positive controls, at 37°C, the first (20 min at 2 hours) and delayed migration can be measured (4, 6, and 18 hours); the % of MLIF can also be calculated against the negative control, as well as the reference values (RV) for MLIF (0–25% inhibition of leukocyte migration) [29].

Eosinophilia in the peripheral blood is a common cause in patients who consume medications, especially in developed countries, who are monitored and can restrict their consumption without changes. However, for the doctor, concern may arise in cases of impending hypersensitivity reaction (HSR). Severe HSRs associated with peripheral blood may include specific reactions of organs (heart, kidney, liver,

lungs, joints, central nervous system, and skin) and adverse skin reactions (SCAR) where SJS, TEN, and DRESS are included [32, 33].

Type	Type of immune response	Clinical symptoms	In vitro diagnostics	In vivo diagnostics
I	Measured by IgE eosinophils, mast cells, and basophils (immediate)	Urticaria Angioedema Rhinitis Bronchospasm Anaphylaxis	IgE specific Serum tryptase Cell stimulation test (CAST) BAT(MDB, CD63)	Cutaneous tests (prick, intradermal) Challenge tests Proving tests [Coombs]
II	Cytotoxicity dependent on IgG and IGM antibodies (not immediate) and complement	Hemolytic Anemia Thrombocytopenia Neutropenia Autoimmunity	Coombs test Ab vs. platelets Ab vs. neutrophils	Only challenges to the drug can make diagnosis but are high risk [Coombs]
III	Deposit of immunocomplexes [IgG and IgM] (not immediate) Complement or FcR	Serum disease Vasculitis, LES-like by medications Glomerulonephritis drug	C3, C4, ANA, ANCA, CCP, antithyroid, etc. Liver and kidney function tests Pathological anatomy	Biopsies with immunofluorescence [Coombs]
IVa	TH1 (IFNγ), TNFα, IL12, and macrophages (late)	Contact dermatitis	Lymphocyte transformation test (LT or BT), MLIF, cytotoxic T lymphocyte precursors (CTLp), cytokines (ELISA, PCR)	Patch tests [Pichler]
IVb	TH2 (IL-4, IL5, IL13) eosinophils	Maculopapular eruptions (MPE) with eosinophilia (DRESS)	CBC with check eosinophil cellularity, atypical lymphocytes MLIF, BT, LT	Patch tests [Pichler]
IVc	CLT, CD4/ CD8 (perforin, granzyme B, Fas L)	Contact dermatitis, maculopapular, and bullous diseases(SJS), TEN	MLIF, liver function tests, CD4/CD8 (death keratinocytes) Activity of IgM vs. herpes virus, Epstein-Barr, and cytomegalovirus (CMV)	Patch tests [Pichler]
IVd	T cells, IL8, CXCL8 cells Neutrophils Inflammation	Acute generalized exanthemic pustulosis (AGEP) pharmacodermias associated with neutrophilia	CBC T cells CD4/ CD8	Patch tests [Pichler]

Hypersensitivity reactions require that the individual has been previously sensitized or exposed at least once to the antigens in question. The classification of allergic or hypersensitivity reactions into four types (I, II, III, and IV) and subsequently Pichler in 2003 proposed the subdivision of type IV into IVa, IVb, IVc, and IVd [27–29].

Table 1.
Hypersensitivity classification according to the Gell and Coombs modified by Sell, Pichler, and ICON.

The prolongation of eosinophilia can cause tissue damage, although without being clarified specifically, adding to the condition infections as another factor that preserves eosinophilia (parasitic and fungal infestations) or decreases (eosinopenia due to bacterial and viral infections). The diagnosis can be complicated because of the presence of the drug which worsens a preexisting eosinophilia, particularly in atopic patients [33].

DRESS is more common in adult patients than in children, with approximately 50 drugs being described, highlighting anticonvulsants (phenytoin, phenobarbital, and carbamazepine) and antibiotics as the main causes of the syndrome and, to a lesser extent, sulfate derivatives, antidepressants, NSAIDs, and antidiuretics [34]. There is no clear association between variability of the type of drug and the affected organ with the degree of eosinophilia, which can be mild or self-limited and severe when multisystemic complications are generated due to the presence of symptoms that are not appreciated in the mild form [32, 33].

Other proposals that lead to the pathogenesis of DRESS include detoxification defects at the time of the formation of reactive metabolites, slow acetylation, and reactivation of the human herpes virus (HHV-6-7) or EBV [34].

In general, the diagnostic algorithm for eosinophilia linked to SCAR can be visualized as a hypersensitivity response type IVb (SJS and NET) and type IVc (DRESS), which in some way can highlight the pathogenesis proposals previously mentioned not only by DRESS but identify an atopic patient (**Table 1**).

5. Conclusions

Eosinophils are leukocytes (white blood cells) found in the peripheral blood, hematopoietic, lymphatic organs, thymus, connective tissue, and digestive tract. They are identified and quantified by manual counting (Neubauer chamber), automated count with autoanalyzer hemocytometers (impedance, colorimetry, and differential in optical microscope), flow cytometry after the advent of monoclonal antibodies, currently the most used to identify surface markers and immunoenzymatic methods (ELISA, RAST, IMMUNOCAP) for cytoplasmic granules.

The classification of eosinophilic diseases "eosinophilic disorders" was revised in 2008 and confirmed in 2016; its study focused on external (extrinsic) and internal (intrinsic) causes (optimized) and optimized and failed diagnosis by precise and timely diagnosis. The algorithms are used and started with the main pillar: The clinical history (clinical criteria, anamnesis, and exploitative maneuvers leading to clinical laboratory algorithms, with initial, basic, and special tests including imaging, tomography, and X-rays to finally improve the prognosis and modify the natural history. The intrinsic and extrinsic disorder algorithm planting is different; this is due to the recognition of molecular altered T cell clones, bone marrow studies, and markers of apoptotic genes, PCM1-JAK2, Fas L, and bcl2.

Some allergies to medications with symptomatology related to specific organ and severe cutaneous against antiepileptics (phenytoin, phenobarbital, carbamazepine) as well as other medications (antibiotics, NSAIDs, antidiuretics) can be related, which rethinks the proposed immunological response algorithm not only in basophil evaluation but also the search for eosinophils in flow cytometry or optical microscopy to assess not only damage but neutralization (eosinophil histaminase).

Corticosteroids are considered the first line of treatment because of their potent anti-eosinophilic effect for disease control, prognosis, and prevention. So the new

treatment alternatives could displace steroids with monoclonal antibodies such as the IL-5 inhibitor that show less long-term toxicity.

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Conflict of interest

There is no conflict of interest.

Appendices and nomenclature

AEC	absolute eosinophil count
HSR	hypersensitivity reaction
SCAR	severe cutaneous adverse reaction
SJS	Stevens-Johnson's syndrome
TEN	toxic epidermal necrolysis
DRESS	drug rash eosinophilia and systemic symptoms
CBC	complete blood count
DHRs	drug hypersensitivity reaction

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