Diagnostic approach to eosinophilia in children

Raghba Shasho

Correspondence:
Dr. Raghba Shasho
Specialist Paediatrician
PHCC - Muaither health center
Doha, Qatar
Email: dr.raghebashasho@gmail.com

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Abstract

Hematopoiesis is the process which maintains life-long production of haemopoietic (blood) cells from bone marrow. Blood consists of three types of cells (Erythrocyte – Leukocytes - palates), and plasma. Leukocytes are divided into 2 types of granulocytes (including neutrophils, eosinophils and basophils); and agranulocytes (including lymphocytes and monocytes). Eosinophil attack and kill parasites and cancer cells, and help with allergic responses, so their role is to protect the body from bacteria and parasites. They are found in the peripheral blood and also tissue, so they are closer to where the site of infection may occur.

The eosinophil is a much-overlooked cell, more usually considered as a curious form of phagocytic leucocyte with functions similar to its more numerous cousins, the neutrophil. However, a dramatic blood and tissue eosinophilia is an important part of adaptive immunity to parasitic helminthic infections, whilst more detrimentally, the eosinophil is thought to make a major contribution to the inflammation underlying the pathogenesis of disorders such as asthma, allergic rhinitis and atopic dermatitis .[1].

Eosinophilia is a common finding in clinical practice and presented in a broad spectrum of diseases, some of them hematologic disorders and others non – hematologic (infection disease – allergic disease – medication reaction, and autoimmune disease).

Key words: eosinophilia, children, diagnostic approach

Definition

Eosinophilia is defined as an elevated absolute number of eosinophilic leukocytes in peripheral blood or tissue. The first step in elucidating the cause is to determine the absolute eosinophil count (AEC)[2], which is calculated from multiplying the percentage of eosinophils by the total white blood cell count,. using the following formula: Absolute Eosinophil Count = WBC * Eosinophils / 100

Eosinophilia is classified into three degrees:[3]
●**Eosinophilia – AEC ≥500 eosinophils/microL** in most clinical laboratories. Eosinophilia is not defined by the percentage of eosinophils (typically <5 percent in healthy individuals), because the percentage varies with the total WBC count and the proportion of other WBC lineages (eg, neutrophils, lymphocytes).

●**Hyper eosinophilia – ≥1500 eosinophils/microL** (with or without end-organ damage).

●**Hyper eosinophilic syndromes (HES)** – AEC ≥1500/microL (on two occasions ≥1 month apart) **plus** organ dysfunction attributable to eosinophilia.

THE IDIOPATHIC hyper eosinophilic syndrome (HES) is a leukoproliferative disorder, or more likely disorders, marked by a sustained overproduction of eosinophils. The distinctiveness of the syndrome, in addition to its eosinophilia, is its marked predilection to damage specific organs, including the heart. Such cardiac pathology is not unique to the idiopathic HES, because it may develop with eosinophilia associated with other diseases with identifiable etiologies. Conversely, yet enigmatically, not all patients with hyper eosinophilia develop the organ damage characteristic of the HES [4].

Tissue HE can be defined as a percentage of eosinophils that exceeds 20% of all nucleated cells in the bone marrow or tissue infiltration that is deemed extensive by a pathologist [5].

Physiology

Eosinophils are bone marrow–derived cells of the granulocyte lineage. They have an approximate half-life of 8 to 18 hours in the bloodstream, and mostly reside in tissues where they can persist for at least several weeks. Their functional roles are multifaceted and include antigen presentation; the release of lipid-derived, peptide, and cytokine mediators for acute and chronic inflammation; responses to helminth and parasite clearance through degranulation; and ongoing homeostatic immune responses. They can be part of the overall cellular milieu in malignant neoplasms and autoimmune conditions, and connective tissue disorders [6].

In normal tissue and organs, eosinophils are either absent or scattered, depending on the sites. Tissue eosinophilia is defined as increased eosinophils or signs of eosinophil degranulation in extramedullary sites such as the gastrointestinal tract, lung, thymus, spleen or lymph nodes. Eosinophils are normally controlled by cytokines interleukin (IL)-5, GM-CSF, and IL-3 produced by T-lymphocytes, mast cells, and stromal cells. Upon activation, eosinophils release their granules, such as eosinophil peroxidase, eosinophil cationic protein, major basic protein, and cytokines like TGF-β that may lead to thrombosis and tissue fibrosis and injury [7].

Eosinophils have been implicated in the pathogenesis of tissue fibrosis, thrombosis, vasculitis, and allergic inflammation. The propensity of eosinophils to cause these effects depends on a number of factors, including the number of eosinophils, their location, and degree of activation. Although these factors may be influenced by the underlying etiology of the eosinophilia, the consequences of eosinophilic inflammation can be identical despite markedly different clinical diagnoses [8].

Activated eosinophils contribute to disease pathogenesis both through direct cytotoxic effects and by recruitment and activation of other inflammatory cells. Tissue deposition of eosinophil granule proteins (major basic protein, eosinophil-derived neurotoxin, eosinophil cationic protein, and eosinophil peroxidase) contained in the characteristic secondary granules of eosinophils plays a major role in direct tissue damage. Granule proteins can be released from intact eosinophils through a process called piecemeal degranulation, whereby selective secretion of individual granule components occurs without disruption of the cell membrane, or from “cell-free” granules liberated by exocytosis or during extracellular DNA trap cell death (ETosis). In addition to the granule proteins, a wide array of cytokines and chemokines are stored preformed in the secondary granules and can be secreted in response to specific signals, leading to the recruitment and activation of other cells involved in the inflammatory response, including lymphocytes, mast cells, and fibroblasts. Eosinophil activation also leads to secretion of reactive oxygen intermediates and the formation of increased numbers of lipid bodies, the primary site of synthesis of eicosanoids, inflammatory mediators that include leukotriene C4 and 5-lipoxygenase [8].

Normal eosinophils are round to oval, 10 to 15 μm in diameter, and have a nucleus cytoplasmic ratio of 1:3; they are identified via their characteristic refractile, coarse, orange-red granules, which are typically uniform in size and generally evenly fill the cytoplasm. Eosinophils exhibit the same stages of development as neutrophils. In the most mature eosinophil form, the nucleus segments into two or more lobes connected by thin filaments with approximately 80% of segmented eosinophils containing a two-lobed nucleus with lobes of equal size and ovoid shape with dense chromatin. The remainder of segmented eosinophils will typically have three lobes, and occasionally, an eosinophil can have up to four or five lobes. Immature eosinophils are rarely seen in the blood, but can be seen in bone marrow smears, and may have fewer granules than the more mature forms. The eosinophilic

myelocyte is the earliest recognizable eosinophilic form on light microscopy. Eosinophilic myelocytes typically contain orange-red secondary granules with rare primary granules. Sometimes irregular eosinophilic cytoplasmic granulation or abnormal nuclear lobulation can alert one to a clonal eosinophilic abnormality or neoplastic process. For example, eosinophils can present with atypical/basophilic granules at any stage of maturation, but this is most often seen at the myelocyte stage. The abnormal granules resemble basophilic granules but lack myeloperoxidase and toluidine blue reactivity. These cells are referred to as harlequin cells and are associated with clonal myeloid disorders, typically a specific type of acute myeloid leukemia (AML) [9].

Causes of eosinophilia

Peripheral eosinophilia can be divided into categories of primary, secondary and idiopathic. Primary eosinophilia usually occurs in the context of hematologic malignancies and myeloproliferative disorders, including acute or chronic myeloid leukemia, and a variety of other proliferative conditions with eosinophil counts usually greater that 5000/ul. Secondary eosinophilia is associated with many other conditions. Many infectious agents can cause secondary eosinophilia that can be of moderate to severe level. In addition, a variety of diseases including most prominently allergic disorders, drug allergy, autoimmune diseases, endocrine disorders such as Addison's disease, and many different cancers can be associated with eosinophilia [10].

*Acute eosinophilia: which is associated with Allergic rhinitis – asthma – hypersensitivity reaction to drugs and foods and parasitic diseases.

*Chronic eosinophilia: Eosinophils can be inappropriately stimulated by activated T cells releasing both IL-3 and IL-5. The eosinophil granule contents irritate and deform the normal structures they come in contact with, including vascular walls, endo-cardial surfaces and mesenchymal tissues. Because of these effects, persistent eosinophilia signifies a serious parasitic infection or other serious disorders that stimulate eosinophilia through generalized T cell activation [11].

The most common cause of eosinophilia is related to socioeconomic factors. In developing world countries, the most common cause is parasitic infection, otherwise in the developed world countries it is allergy.

The causes of eosinophilia are various and can be summarized by the acronym "APLV" which refers to Allergic disorders, Parasitic infections, Leukemia/Lymphomas (and solid tumours) and Vasculitis-Immunodeficiency diseases, with allergic disorders and parasitic infections representing the most commonly identified causes. Allergic disorders are usually associated with mild eosinophilia, whereas values >20.000 cell/µl are highly suggestive for myeloproliferative disorders [12].

A Allergic disorders

Asthma: Infiltration of the bronchial mucosa by often large numbers of eosinophils is one of the consistent features of asthma. The ability of eosinophils to generate an array of pro-inflammatory mediators, in particular the cytotoxic granule proteins such as eosinophil major basic protein (MBP), has led to the hypothesis that asthma is an on-going mucosal inflammatory disease, a major component of which is the tissue damage mediated by eosinophil-derived mediators. Eosinophils are present even in mild asthma and their numbers correlate with disease severity [1].

Atopic dermatitis may produce a more significant eosinophilia if affecting a large part of the body and if associated with significant atopy. Eosinophilic esophagitis as well as other eosinophilic gastrointestinal diseases can cause a mild peripheral eosinophilia [13].

Chronic sinusitis, especially of the polypoid variety seen in aspirin-exacerbated respiratory disease, produces a more robust eosinophilic response that can be in the mild to moderate range. Often these patients start with nasal allergies and asthma, but then develop abnormal arachidonic acid metabolizing cascades and hence have a more dramatic presentation both of their disease entity and of the eosinophilia [13].

Allergic bronchopulmonary aspergillosis, related both to a fungus (Aspergillus) and to sensitization in an allergic/asthmatic host, can also produce varied and sometimes significant degrees of eosinophilia and also elevated total immunoglobulin (Ig)E [13].

Chronic eosinophilic pneumonia often starts in a sensitized, asthmatic host. Although these patients may have milder peripheral eosinophilia at disease onset, they often have more moderate range eosinophilia later in the course. They also have bronchoalveolar lavage fluid that contains at least 40% eosinophils in up to 80% of cases. This form of eosinophilic pneumonia can be premonitory to the later development of the eosinophilic vasculitis, eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss vasculitis [13] .

Drug allergy can cause anywhere from mild to severe eosinophilia and often waxes quickly and wanes in a slower fashion; it can take months for eosinophilia from drug allergy to clear. There is usually, although not always, an associated drug rash of the diffuse/maculopapular variety. Patients can also present with asymptomatic eosinophilia owing to drugs, especially penicillins, cephalosporins, or quinolones. Pulmonary infiltrates and peripheral eosinophilia have been associated with varied medications, including nonsteroidal anti-inflammatory drugs, sulfa drugs, and nitrofurantoin. Drug-induced diseases of other organs can also elicit tissue and blood eosinophilia (e.g. drug-induced interstitial nephritis) [6].

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a life-threatening adverse drug reaction that is distinct from other drug-related reactions.

Patients with DRESS present with generalized rash, fever and internal organ involvement weeks to months after initiation of several known medications. Characteristic laboratory findings include eosinophilia and/or atypical lymphocytes, in addition to evidence of organ dysfunction. Prompt recognition of this disorder is important because the mortality is 10% but can be up to 40% if organ failure is present [14].

DRESS syndrome usually presents within 8 weeks of initiation of the causative medication. Aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine) are the most common cause of DRESS, but a variety of other drugs, such as allopurinol, minocycline, dapsone, sulfasalazine, and mexiletine, have also been associated with DRESS. The estimated occurrence of the syndrome is between 1 in 1,000 and 1 in 10,000 exposures to antiepileptic drugs. There is a 10% mortality rate from DRESS, mostly due to liver damage thought to be secondary to eosinophilic infiltration. The diagnostic criteria for DRESS syndrome include (a) widespread cutaneous eruption; (b) fever; (c) systemic involvement, including lymphadenopathy and/or 1 or more internal organ involvements (for example, interstitial nephritis, myocarditis, pericarditis, pneumonitis, hepatitis); and (d) 1 or more biologic abnormalities (for example, eosinophilia >1,500/mm3, mononucleosis-like atypical lymphocytosis) [14].

A wide variety of parasites can elicit eosinophilia, even if only relatively few of them can be responsible for such a marked increase in eosinophil levels. The pattern and degree of eosinophilia in parasitic infections result from the development, migration, and distribution of the parasite within the host, as well as from the host's immune response. Parasites tend to elicit marked eosinophilia when they or their products come into contact with immune effector cells in tissues, particularly during migration. When mechanical barriers separate the parasite from the host, or when parasites no longer invade tissues, the stimulus to eosinophilia is usually absent. Therefore, eosinophilia is highest in infections with a phase of parasite development that involves migration through tissues (eg, trichinosis, ascariasis, gnathostomiasis, strongyloidiasis, schistosomiasis, and filariasis). Detection of eggs, larvae or adult worms in faeces is necessary to make a diagnosis. However, being very difficult to obtain, a negative examination does not allow to exclude a parasitic infection with certainty. The rapid increase in eosinophil count, the potential risk of evolution to the hypereosinophilic syndrome or to organ damage, and the history suggestive of a parasite infection prompted us to undertake an albendazole-based empiric therapy [15].

A variety of infections may be associated with eosinophilia; these include helminths (worms), fungi, protozoa, bacteria, the retroviruses HIV and human T cell lymphotropic virus type 1 (HTLV-1), and scabies (a mite infestation). Most acute bacterial infections and viral infections are not associated with eosinophilia[16].

Gastrointestinal disorders: Eosinophilic gastroenteritis, ulcerative colitis and regional enteritis are often associated with blood eosinophilia. Chronic active hepatitis, milk precipitin disease, and radiation therapy for intra-abdominal neoplasia can engender blood eosinophilia[11].

Eosinophilic esophagitis (EoE) is also a common cause of HE in the pediatric age group. This diagnosis can often be missed if an appropriate history is not obtained. The primary symptoms of EoE vary with age, with younger patients presenting with feeding difficulties, frequent vomiting, food refusal/selective eating, and failure to thrive. As these children increase in age, complaints of abdominal pain and dysphagia increase, and adolescents can develop food impactions. Other primary gastrointestinal eosinophilic disorders (eosinophilic gastrointestinal disease) can also cause HE in children, although these disorders are less common than EoE. Additionally, inflammatory bowel disease can be associated with a peripheral eosinophilia[5].

Eosinophilic gastroenteritis: is a rare condition defined by eosinophilic infiltration of the intestinal wall, especially at stomach and duodenum levels. Clinical manifestations are abdominal pain and cramps, growth retardation, diarrhea, vomiting, failure to thrive, malabsorption syndrome. Diagnosis requires presence of symptoms, eosinophilic infiltration on biopsy specimens and the absence of a known cause of eosinophilia [17].

Additionally, inflammatory bowel disease can be associated with a peripheral eosinophilia.

Rheumatologic disease is the less common etiology of HE in children. Notably, eosinophilic granulomatosis with polyangiitis (EGPA, previously called Churg-Strauss syndrome) is a potentially life-threatening vasculitis rarely seen in the pediatric population and is commonly associated with moderate-to-severe peripheral blood eosinophilia, allergic rhinitis, and asthma. The most commonly involved organs include the lung and skin, although this disease can affect virtually any organ system, including the cardiovascular, gastrointestinal, renal, and central nervous systems. Other autoimmune diseases associated with HE in children include systemic lupus erythematosus, dermatomyositis, and inflammatory arthritis[5].

Approximately 10% of patients with rheumatoid arthritis will develop a mild eosinophilia.
Immune deficiency syndromes: Such as Wiskott – Aldrich syndrome, Job's Syndrome, hyperimmunoglobulin E Syndrome, Severe combined immune deficiency due to adenosine deaminase deficiency and Omenn's Syndrome.[11]

Eosinophilia is frequently present in the thrombocytopenia with absent radii (TAR) and familial reticule endotheliosis with eosinophilia syndromes. Hodgkin disease and non-Hodgkin lymphoma are frequently associated with eosinophilia. Brain tumors and myeloproliferative disorders are also associated with blood eosinophilia. Hyper eosinophilic syndrome is very rare in children. It is associated with various systemic symptoms and

a diversity of potential organ involvement. Eosinophil counts are usually > 5,000/µl. One of the most serious and more frequent complications in this disorder is cardiac disease secondary to endomyocardial thrombosis and fibrosis. Mortality is very high with a mean survival of 9 months[11].

Neoplasms: Before the recognition that most patients with hyper eosinophilia did not have a truly malignant disease, patients with HES were reported as having eosinophilia leukemia. The distinction between these disease processes, the truly malignant and the more usual nonmalignant HES, can be difficult in some patients who present with acute HES. Acute eosinophilic leukemia can be distinguished from HES when there is a marked increase in the number of immature eosinophils in the blood and/or marrow, with more than 10% blast forms in the marrow, infiltration of tissues with immature cells of predominantly eosinophilic type, and a clinical course similar to other acute leukemias. including pronounced anemia and thrombocytopenia and susceptibility to infections[5].

Lymphocytic variant HE/HES (L-HE or L-HES) is a category of disorders characterized by a clonal or aberrant lymphocyte population that produces cytokines that propagate eosinophil production and survival. Included within this category are lymphoid neoplasms, some of which are more common in children (ex. pre-B cell acute lymphoblastic leukemia [ALL]). ALL can present with HE in children, in some cases months before the underlying malignancy is detected. In these situations, eosinophils are not part of the neoplastic clone and represent a secondary response to the malignancy[5].

Adrenal insufficiency has been associated with eosinophilia, possibly due to the loss of endogenous glucocorticoids [5].

Hypoadrenalism associated with Addison disease and adrenal hemorrhage are associated with blood eosinophilia[11].

Other secondary causes of HE to consider in certain clinical situations include graft-vs.-host disease following hematopoietic stem cell transplantation, solid-organ transplant rejection, and sickle cell disease[5].

A systematic approach to the evaluation and management of eosinophilia

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History:

Clinical history is the key to identify the potential causes of eosinophilia and should first involve evaluation of the presenting complaint, followed by a systemic review.

Patients should be questioned about the following symptoms:

● Allergy: a history of fever, eczema, asthma, pruritus, urticaria, angioedema, rash and ulcers.

● History of traveling or residence in an area where parasitic infection is pandemic, or if the patient is living in a tropical region to rule out exposure to soil or freshwater which suggest parasitic disease.

● History of diet to rule out risk for ingestion of raw or undercooked meat, particularly wild game meat that can increase risk for Trichinosis. Ingestion of fruits, vegetables, or soil (i.e., a child with pica) possibly contaminated by dog or cat feces can be a risk factor for Toxocariasis.

●HIV positive patients are more likely to have disseminated parasitic or fungal infections that promote eosinophilia.

●History of medication especially non – prescription drugs or newly-given drugs (usually started 2 – 6 weeks previously) and immunosuppressive drugs. Some drugs (ex: sulfonamides, cephalosporins, penicillin, nitrofurantoin, carbamazepine, allopurinol, phenytoin or gold).

Presenting with fever, rash, lymphadenopathy and impaired liver function may indicate an adverse drug reaction.

●History of rash or lymphadenopathy is not related only to drug reaction. Leukemia, lymphoma, or systemic Masto cytosis can all cause both a rash and lymphadenopathy.

●Respiratory: Nasal/sinus symptoms, wheezing, cough, chest congestion

●Gastrointestinal: Weight loss, dysphagia (eosinophilic esophagitis), nausea, vomiting, diarrhea and abdominal pain (eosinophilic gastroenteritis), food intolerance, changes in stools

●Cardiac history: Dyspnea, chest pain, palpitations, symptoms of heart failure in a patient with marked eosinophilia, and this case considered a clinically urgent situation.

●Nervous system: Transient ischemic attack, cerebrovascular accident, behavioral changes, confusion, balance problems, memory loss, change in vision, numbness, weakness, pain

●Other: Including symptoms attributable to lymphadenopathy or hepatosplenomegaly (i.e. new abdominal or chest discomfort, early satiety), ocular findings, genitourinary complaints, myalgia, arthralgia, and anaphylaxis.

●Galich's Syndrome: rare condition of recurrent angioedema with eosinophilia and increased IgM levels.

Physical exam:

Physical examination is still the cornerstone to evaluate the presenting complaint. A careful physical exam should be completed at every visit, noting any fever, skin rashes, lymphadenopathy, nasal obstruction, abnormal or decreased lung sounds, abdominal tenderness, hepatosplenomegaly, cardiac failure, neuropathy or joint redness/swelling.

***Temperature:** should be checked and documented. Presenting with fever may indicate parasitic or fungal infection or drug reaction.

***Skin:** should be inspected for erythema, eczematous, rash, oedema, urticaria or skin infiltration.

***Vasculitis signs** should be examined to rule out a primary vasculitis condition such as eosinophilic granulomatosis with polyangiitis (Churg – Strauss Syndrome)

***Lymph node:** in case of lymphadenopathy the lymph nodes should be assessed from the size – texture looking for a possible neoplasm (EX: lymphoma – lymphoid or myeloid leukemia).

Hard – fixed and non – tender nodes are more likely to associated with malignancy.
***Bronchospasm** should be checked to rule out asthma, allergic bronchopulmonary aspergillosis or a severe drug reaction. Presenting of cough, dyspnea or wheeze may indicate a lifecycle – related pulmonary migration of parasites, a drug reaction or eosinophilic leukemia. Schistosomiasis can cause pulmonary hypertension, and eosinophilic granulomatosis with polyangiitis can cause pulmonary infiltrates.

***Hepatomegaly and splenomegaly** should be checked looking for lymphoma or eosinophilic leukemia
***Cardiomegaly,** arrhythmia or heart failure may be features of cardiac damage by eosinophilia

Eosinophils can accumulate in multiple organs, most commonly involving the heart, skin, lungs, spleen and liver. Neurological end-organ complications in hyper eosinophilic syndrome are unusual and have been established to be of three types: brain infarction, encephalopathy and sensory polyneuropathy. It is important to consider HES as an etiology for stroke and a high eosinophil count is an initial diagnostic clue[18].
Diagnostic evaluation: At the first step we should consider the severity of eosinophilia.

All children who meet diagnostic criteria for HE (i.e., blood AEC ≥1,500 cells/microL on at least 2 separate occasions [interval ≥1 month] or marked tissue eosinophilia) or moderate-to-severe eosinophilia with illness symptoms should undergo an initial diagnostic evaluation to try to determine the underlying etiology. Laboratory evaluation should include complete blood count with differential to evaluate for abnormalities in the other blood cell lines[19]. The CBC and blood film should also be used to look for the following findings: *Cytopenia, which may be found in hematological malignancy.

*Thrombocytosis which may occur secondary to infection, inflammation, hemorrhage, or malignancy as well as in certain hematological disorders (such as chronic myeloid leukemia, essential thrombocythemia, and polycythemia vera).

*Lymphocytosis which can present in many hematological neoplasms
*Malignant cells
*Filariae

Patients who present with acute eosinophilia need to be evaluated for the two most common causes, i.e. atopic and related diseases and parasitic infections. Atopic disease is the most common cause of eosinophilia in industrialized countries while parasitic disorders are more common elsewhere [10].

The first step in an evaluation of a chronic hyper eosinophilia syndrome would be to repeat the eosinophil count within at least two, and up to four weeks after initial observation in those whose eosinophilia is persistent and not easily explained. Attention needs to be paid to all of the diseases mentioned above and their potential associations with mild, moderate or severe eosinophilia. Under certain circumstances more intense evaluation, including chromosomal evaluation for the underlying disease needs to be aggressively pursued [10].

A peripheral blood smear should be reviewed to evaluate for white blood cell blasts or other blood dyscrasias that could suggest a primary hematologic disorder. If blasts are noted, LDH, uric acid and hematology/oncology consultation is indicated. Bone marrow examination (aspiration and biopsy) should be considered for any child whose initial evaluation demonstrates no clear secondary etiology and a primary hematologic cause of the eosinophilia remains possible. In addition, bone marrow examination is appropriate for any acutely ill child with specific organ involvement and no clear underlying diagnosis, children with an eosinophil count >100,000 eosinophils/microL, or children with abnormal features on their peripheral blood smear (immature or dysplastic white blood cells, thrombocytopenia, or unexplained anemia). Serum chemistries, creatinine, and urinalysis should be completed to evaluate for evidence of renal or bladder involvement. Abnormal serum chemistries could also suggest underlying adrenal insufficiency. Liver function tests (to determine hepatic involvement) and cardiac troponin levels (for evidence of subclinical myocardial disease) should also be obtained. Patients with an elevated troponin level should be further evaluated with electrocardiography and echocardiography. Serum B12 level should be obtained as a screening marker for myeloproliferative neoplasms and autoimmune lymphoproliferative syndrome (ALPS). Serum tryptase can be obtained to screen for systemic Masto cytosis. Stool testing for ova and parasites and serologic testing for endemic parasites should also be routinely completed (Strongyloides, Toxocara, Trichenella). The indication for additional parasite testing is typically determined by exposure (diet, travel). Chest radiography should be completed to evaluate pulmonary involvement. Finally, in patients with a history of recurrent infections, lymphadenopathy, and/or hepatosplenomegaly, flow cytometry to evaluate lymphocyte subsets and immunoglobulin levels can be sent to screen for lymphocyte clonality and selective lymphocyte and immunoglobulin deficiencies. Additionally, T-cell receptor rearrangement studies can be useful to provide evidence of oligoclonality in the lymphocyte compartment. Finally, depending on risk factors, HIV testing may be indicated [5]. If the patient is unwell or the count of eosinophil is markedly elevated and the cause is not obvious, further investigation is indicated. Sometimes such investigation is urgent (EX: in cardiac failure or if the eosinophil count is considerably high).

Treatment of eosinophilia :
Evaluation and treatment of pediatric patients with hyper eosinophilia is challenging, as the etiology is often difficult to discern. The differential diagnosis is broad, and work-up can ultimately be extensive and costly; thus, it is important to identify underlying conditions at which treatment can be directed rather than directing treatment at the eosinophilia itself [20].

Most cases of secondary eosinophilia are treated on the basis of their underlying causes. Allergic and connective tissue disorders may be amenable to corticosteroid treatment. Parasitic and fungal infections can be worsened or disseminated by use of steroids and should be ruled out if they are indicated by patient history[21].

In patients with primary eosinophilia without organ involvement, no treatment may be necessary. Cardiac function should be evaluated at regular intervals, however, as peripheral eosinophilia does not necessarily correlate with organ involvement. Steroid responsiveness should be evaluated, both for prognosis (steroid-responsive patients do better) and to guide treatment when needed [21].

Choices for systemic treatment of primary eosinophilia with organ involvement initially include corticosteroids, and interferon (IFN)-alpha for steroid-resistant disease. Other agents for steroid-resistant disease, which are usually given as long-term maintenance regimens to control organ involvement, include the following:

Hydroxyurea – Chlorambucil – Vincristine -Cytarabine - 2-Chlorodeoxyadenosine (2-CdA) -Etoposide Cyclosporine. [21]

Treatment decisions are determined based on suspected etiology and level of eosinophilia. The level of intervention involves the correct treatment of the underlying disorder. If an autoimmune disease is identified, appropriate treatment for the primary autoimmune disease should be undertaken. The same would hold for immunodeficiency or infection. For patients with HES with the **FIP1L1 genetic*** translocation, treatment with imatinib should be initially considered. For those without the translocation, steroids are the mainstay of therapy. Interferon alpha as well as other potential cytotoxic drugs such as hydroxyurea are necessary under some circumstances with severe hyper eosinophilia [10].

Hyper eosinophilic syndromes are a heterogeneous group of disorders that may be associated with life-threatening organ injury as a result of tissues infiltration by eosinophils. The main goal of therapy is to mitigate eosinophil-mediated organ damage. When possible, therapy should be directed at the underlying etiology. However, even in the absence of any known cause, when organ damage is present, hyper eosinophilia must be treated promptly and aggressively to reduce potential morbidity and mortality. Areas covered: Conventional therapies, including corticosteroids, hydroxyurea (hydroxycarbamide) and interferon-alpha, have shown variable efficacy and a non-negligible toxicity emphasizing the need of new therapeutic strategies based on drugs with different mechanisms of action. Expert opinion: Tyrosine kinase inhibitors have a central role among targeted therapies of hyper eosinophilic syndromes. Imatinib, initially empirically used based on its activity in chronic myeloid leukemia, achieved preliminary excellent results further confirmed in a large series of patients. Third-generation tyrosine kinase inhibitors such as ponatinib, while active in vitro and in vivo in animals, still deserve confirmation in properly designed clinical trials. In addition, clinical investigation on monoclonal antibodies against interleukin-5, interleukin-5Rα, IgE, and CD52 represents a promising area of research.[22] Finally, experimental treatment with anti-IL 5 has been considered in a variety of eosinophil associated secondary diseases including asthma, as well as in the treatment of primary hyper eosinophilia. This has resulted in significant success in terms of prevention of exacerbations of the underlying disease, as well as reduction in steroid dose required for the treatment of the primary and/or secondary cause of eosinophilia [10]. Management of medical emergencies should not be delayed by the diagnostic evaluation of eosinophilia. Patients with an acute illness due to leukocytosis or organ dysfunction from eosinophil infiltration may require urgent treatment with high dose steroids, leukapheresis, and/or cytoreduction as described separately[3].

Summary

Eosinophilia is defined as increase in peripheral blood eosinophil count Eosinophilia (≥500 eosinophils/microL) and hyper eosinophilia (≥1500 eosinophils/microL). Eosinophilia is a common finding in children. Allergic disease (eczema, allergic rhinitis, asthma) is a common cause of mild-to-moderate eosinophilia in the pediatric population and a minority of these patients can meet criteria for HE disease. Atopic disease is the most common underlying cause of eosinophilia in industrialized countries while parasitic disorders are more common elsewhere. To approach patients with eosinophilia we should follow the traditional model of clinical history, physical examination, laboratory, and other investigations, considering the likely causes in the individual patient. Ask for new exposures, including dietary changes and new medications, obtain a travel history, looking for focal symptoms, including rash, cough, shortness of breath, fever, connective tissue complaints, and GI symptoms, all may help clinically focus the evaluation.

Laboratory investigations including stool examination to rule out parasitic infections - Peripheral blood smear may help identify specific pathogens (e.g., microfilariae) or may identify an acute or chronic leukemia associated with eosinophilia. Other laboratory assessments to consider are complete blood count, serum immunoglobulins (including IgE), serum tryptase, and bone marrow biopsy. Treatment should be directed to treat underlying cause of eosinophilia rather than treat eosinophilia itself.

Corticosteroids have been used as first-line treatment. However, mucosal ulcers do not respond to corticosteroids. Other immunosuppresants and immunomodulating agents have been used as detailed in the medication section. These include hydroxyurea, vincristine, cyclophosphamide, busulfan, methotrexate, chlambucil, etoposide, cyclosproin, and alemtuzumab.

***FIP1L1 genetic: FIP1L1; factor interacting with PAPOLA and CPSF1**

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