In the light of recent advances: eosinophil, eosinophilia and idiopathic hypereosinophilic syndrome

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INTRODUCTION

Eosinophil is a different cell containing highly toxic substances the functions of which are still incompletely understood. Eosinophilia is a condition where the eosinophil concentrations in the blood and some tissues increase to unusual high levels in some abnormal conditions and disease states. Being a common finding in clinical practice, in the majority of cases, it can be ascribed to an underlying disease[1]. The role of interleukin-5 (IL-5) in the induction of hypereosinophilia in allergic diseases and parasitosis has been established recently[2]. It is an important task for clinicians to distinguish these conditions from the very rare, but more serious idiopathic hypereosinophilic syndrome (IHES), characterized by persistent eosinophilia in peripheral blood, bone marrow and eosinophilic infiltration of multiple organs leading to severe organ dysfunction[3]. Recently, with the discovery of different well-characterized underlying molecular defects that ultimately lead to eosinophil expansion in some patients, the term "idiopathic" has become outdated in many cases[1].

In the light of recent advances, we made an attempt to review the eosinophil, eosinophilia, IHES and the evaluation and management of the latter.

THE EOSINOPHIL

The eosinophil was first recognized 125 years ago as a distinct cellular element through the pioneering work of Paul Erlich. The ruddy dye, eosin, was named after the Greek goddess of the morning sun, for use in histologic staining by Erlich[4].

Eosinophils are derived from myeloid progenitors (GEMM-CFU) in bone marrow[1]. Eosinophil production, maturation and survival are under the control of some cytokines and growth factors, including IL-2, IL-3, IL-5, IL-13 and granulocyte macropha-

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ge colony stimulating factor (GM-CSF)[5]. IL-5 is the major growth factor for eosinophils. Morphologically, eosinophils in the peripheral blood are approximately the same size as polymorphonuclear leukocytes (PMNLs), 12 to 15 μm in diameter, having mostly bilobed nuclei. The cytoplasm is normally filled with approximately 200 large, eosin-staining unique granules containing a central crystalloid core and high concentrations of hydrolases, cationic and basic proteins. There are also several smaller, enzyme-rich non-eosinophilic granules present in the cytoplasm. With an appropriate stimulus, the number of specific granules in the average eosinophil significantly declines, and the cell often becomes vacuolized[4]. They are primarily a tissue cell, with only 1-2% of them found in the circulation. They have a life span of 8 to 12 hours in circulation and then remain another 1 to 2 weeks in destination tissues[6].

Normal functions of eosinophils resemble to those of other circulatory phagocytes (such as PMNLs and monocytes): chemotaxis, chemokinesis, phagocytosis, cytotoxicity, antiparasitic activity, bactericidal activity, effector of immediate hypersensitivity, modulation of inflammatory response. Unlike PMNLs, when stimulated, they also possess the capacity to elaborate substances that are toxic to a wide variety of multicellular parasites. Eosinophils also act as immunomodulators, particularly in their ability to dampen the host's immediate allergic response[7]. Although, it is unclear whether they are innocent bystanders or agents adding to tissue injury, in other disease states, they are involved directly with critical pathologic events. Their most virulent effects are seen in conditions like Loeffler disease (eosinophilic fibroplastic endocarditis) and the IHES in which permanent deleterious tissue injuries is due to their presence[8].

EOSINOPHILIA

The normal absolute eosinophil count for both adults and children is ≤ 350/μL. A level of 500 to 1500/μL is considered as mild; 1500 to 5000/μL as moderate; and > 5000/μL as severe eosinophilia. Eosinophils are cells that mainly reside in tissues. For every one blood eosinophil, there are 100 tissue eosinophils[9]. In the normal individual, a circadian rhythm can be noted in peripheral blood absolute eosinophil count due to normal fluctuation in glucocorticoids seen during the day. Besides, relative eosinophilia is often noted during the convalescent phase of a variety of systemic infectious processes[4].

There is an association in children between total eosinophil counts in the peripheral blood, and age. Eosinophil concentrations are elevated at birth; continue to rise subsequently for several weeks. Then, by 8 weeks of age, eosinophil counts begin to decline to the levels at which they are normally seen throughout the rest of life[10]. As many as 70%, of premature babies may show at least mild eosinophilia. Infants with high eosinophil counts (> 700/μL) at 3 months of age and beyond are at risk of developing atopic diseases[11].

Mature eosinophils are released into the bloodstream and rapidly migrate to peripheral tissues, namely gut and bronchial mucosa and skin, where they soon undergo apoptosis and are cleared by macrophages, unless survival factors such as IL-3, IL-5 and/or GM-CSF are present. Thus, overproduction of one or more of these cytokines is sufficient to induce normal or abnormal blood or tissue eosinophilia, which accounts for hypereosinophilia in various disorders[12].

Mild and Moderate Eosinophilia

There are many conditions associated with mild to moderate eosinophilia (500 to 5000/μL) (Table 1). Moreover, a wide variety of pharmaceutical agents are associated with mild or moderate, sometimes profound eosinophilia in children.

The most common cause of eosinophilia worldwide is helminthic infection and, in industrialized countries, atopic disease[13,14].

Table 1. Causes of mild to moderate eosinophilia in children[4]

Nonpathologic	**Gastrointestinal**
Prematurity	Milk protein allergy
Neonatal rapid growth	Inflammatory bowel disease
Hyperalimentation	Eosinophilic gastroenteritis
Familial	**Endocrine**
Dermatologic	Postadrenalectomy
Eczema	Addison's disease
Pemphigus	Panhypopituitarism
Dermatitis herpetiformis	**Cardiovascular**
Infantile eosinophilic pustular folliculitis	Loeffler's disease (fibroplastic endocarditis)
Gleich syndrome	Congenital heart disease
Eosinophilic fasciitis (Schulman syndrome)	Hypersensitivity vasculitis
Urticaria	**Infectious**
Eosinophilic cellulitis (Well's syndrome)	Parasitic (trichinosis, strongyloidiasis, pneumocystosis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis)
Kimura disease	Bacterial (brucellosis, tularemia, cat-scratch disease, chlamydia, group A *Streptococcus*)
Pulmonary	Fungal (histoplasmosis, blastomycosis, coccidiomycosis, bronchopulmonary aspergillosis)
Allergic (rhinitis, asthma)	Mycobacterial (tuberculosis, leprosy)
Loeffler's syndrome	Viral (hepatitis A, B, C, Ebstein-Barr, HIV, HTLV-II)
Hypersensitivity pneumonitis	**Immunologic**
Eosinophilic pneumonia	IgA deficiency
Pulmonary interstitial eosinophilia syndromes	Hyper IgE (Job's) syndrome
Oncologic	Wiscott-Aldrich syndrome
Neoplasm (lung, gastrointestinal, uterine)	Graft versus Host Disease
Hodgkin's disease	Drug hypersensitivity
Leukemia	Postirradiation
Myelofibrosis	Postsplenectomy
Drugs	
Antibiotics	
Antimycobacterials	

In general, gastrointestinal parasites lacking a tissue-invasive phase tend to produce only mild eosinophilia. On the other hand, tissue-invasive parasites often produce severe eosinophilia like toxocara[15]. Nonparasitic infections capable of producing a granulomatous tissue reaction such as mycobacterial or fungal infections (including histoplasmosis, blastomycosis, and coccidiomycosis) or chronic bacterial infections (brucellosis, tularemia) can be associated with eosinophilia[16].

Loeffler syndrome, in distinction to the fibroplastic endocarditis termed Loeffler disease, refers to a rather common condition characterized by eosinophilia associated with cough and transient pulmonary infiltrates. The most common cause of the syndrome is migration through the lungs of the larval stages of certain intestinal parasites like ascaris. Occasionally, some children may develop this picture without evidence of parasitic infection. One such entity is allergic bronchopulmonary aspergillosis. Another similar condition can be seen after the inhalation of certain foreign antigens by a sensitized individual. Such antigens may be household environmental substances; chemicals encoun-

tered occupationally, animal products, or plant materials. The patient develops diffuse pulmonary infiltrations with alveolar-capillary block resulting in hypoxia[17].

Asthma, an atopic condition, is well-known to be associated with mild or moderate peripheral eosinophilia. Eosinophilia is commonly seen in young infants who have milk intolerance caused by either milk protein allergy or disaccaharidase deficiency[4]. Any condition with low levels of functional corticosteroids is associated with a degree of eosinophilia[4].

The study of Mehrizi suggested that children who have some congenital heart defects, such as coarctation of aorta, ventricular septal defect, frequently demonstrate unexplained mild to moderate eosinophilia[18]. There is also a well-known relation between eosinophilia and postpericardiotomy syndrome. But, the most serious cardiac condition associated with eosinophilia is Loeffler disease (eosinophilic endocardial fibroelastosis). Eosinophilic endocardial fibroelastosis has been observed in children who have a wide variety of underlying eosinophilic conditions, including severe asthma, eosinophilic leukemia, acute lymphocytic leukemia (ALL), and acute myeloid leukemia (AML), as well as a complication of the IHES[8].

Profound Eosinophilia

Profound (> 5000/μL) eosinophilia is a rarely encountered condition. Visceral larva migrans, AML, ALL, eosinophilic leukemia, toxic oil syndrome, ingestion of L-tryptophan byproduct, IHES, periarteritis nodosa and other conditions may be associated with profound eosinophilia.

Visceral larva migrans is caused by infection with the larval stages of the common pet nematode *Toxocara canis* and *catii*. Patients have cough, prominent organomegaly, generalized lymphadenopathy, rash, hypergammaglobulinemia, hypoalbuminemia and sometimes extremely high levels of isohemagglutinins[4].

Eosinophilic leukemia is exceedingly rare in children. The patients may develop rapid loss of cardiac functions. Profound eosinophilia may be seen rarely in ALL and AML, confusing identification of the truly malignant cell line[19]. As much as one quarter of patients who have Hodgkin disease have profound eosinophilia[20].

Patients who have periarteritis nodosa usually present with nonlocalizing systemic symptoms, including fever of unknown origin, abdominal pain, arthritis, rash, leukocytosis, hematuria and eosinophilia. Definitive diagnosis can only be made by muscular artery biopsy[21].

Two major epidemics of profound eosinophilia have occurred in the past. People who ingested olive oil mixed rapeseed oil suffered toxic oil syndrome, and those who ingested an undetermined toxin in an adulterated product contaminated with L-tryptophan suffered eosinophilia-myalgia syndrome[22,23].

Some dermatologic conditions are also associated with severe eosinophilia in children and adults. Gleich syndrome is a distinct patient subpopulation of IHES, many of whom are children, have extremely high eosinophil counts, and additionally suffer frequent episodes of severe angioedema associated with weight gain, hypotension and shock[4].

Eosinophilic End-Organ Damage

Sustained hypereosinophilia, whether reactive or clonal, can lead to eosinophilic end-organ damage, but does not always do so, even after many years. Therefore, other factors, possibly cytokines, genetic propensity, T-cell clones, neutrophil and eosinophil activation, and tyrosine kinases, may be necessary to cause the end-organ damage. Regardless of the cause of activation, eosinophilia generates cytokines which in turn produce an autocrine IL-2/IL-2R loop which further activates Th2 type cells, leading to continued eosinophil degranulation and activation[24].

Cardiac involvement is the most important cause of morbidity and mortality due to end-organ damage of eosinophilia. This condition generally evolves in three stages. The early necrotic stage, rarely symptomatic, is followed by a thrombotic stage in which intracavitary thrombi develop along the damaged endocardium. In the final fibrotic stage, endomyocardial fibrosis and damage to atrioventricular valves result in congestive heart failure[12]. Since, cardiac involvement does not correlate with the level of blood eosinophilia, careful follow-up is essential. Measurement of serum concentrations of cardiac troponin T is thought to be a sensitive non-invasive marker of involvement[25].

Evaluating an Eosinophilic Patient

When dealing with a child who has eosinophilia, the actual presence of eosinophilia needs to be confirmed with repeated counts. If the eosinophil counts remain elevated, a focused history and physical examination should be performed (Table 2).

In their study, Bridgen et al showed that eosinophilia noted on a single complete blood cell count (CBC) is common and should be no cause for alarm[26]. A CBC was performed in 195.000 outpatients, 225 (0.1%) were found to have an absolute eosinophil count > 700/μL. Less than 9% of them had a serious systemic problem (parasitemia, collagen vascular disease, malignancy) as the cause of their eosinophilia[25].

IDIOPATHIC HYPEREOSINOPHILIC SYNDROME (IHES)

Although increased peripheral blood and bone marrow eosinophilia is the hallmark of IHES, the clinical presentations are extremely varied, ranging from asymptomatic eosinophilia to life-threatening organ damage. Recent studies clearly indicate that many patients fulfilling the diagnostic criteria of this syndrome can now be classified as presenting one of two major disease variants: the myeloproliferative or the lymphocytic variant[1]. To understand the clinical heterogeneity of IHES, one should review chronologic advances in definition and pathogenesis.

Chronologic Advances in Definition and Pathogenesis of IHES

In 1912, the idiopathic proliferation of eosinophils was initially recognized by Stillman. Since then, designations as eosinophilic leukemia, disseminated eosinophilic collagen disease, endomyocardial disease and eosinophilia have been used to describe this disorder[27]. Hardy and Anderson draw attention to the interrelationships among these disorders in 1969[28]. Some authors have considered the syndrome as a form of leukemia, while others doubted that the syndrome was a neoplastic proliferation[27]. In 1975, Chusid et al established the three empirical diagnostic criteria of IHES that are still in use today: (1) blood eosinophilia exceeding 1500/μL for more than six consecutive months; (2) absence of an underlying cause of hypereosinophilia despite extensive diagnostic evaluations; and (3) presence of organ damage or dysfunction related to hypereosinophilia[29]. Flaum et al reported elevation of serum vitamin B12 levels in 1981[27]. The prognosis of the patients has been poor in the literature prior to 1976, and then a more favourable course has been noted with a regimen of Parillo and Fauci that includes prednisone or hydroxyurea[30]. Because of the expanded eosinophilic and neutrophilic pool and the absence of an identifiable cause in IHES; Zittoun suggested including this syndrome in myeloproliferative disorders[31].

Clinical heterogeneity of IHES has complicated the understanding of its etiology and pathogenesis even in 1994[12]. In 1994, Cogan et al showed a T-cell population able to produce IL-5 and IL-4, and bearing a unique CD3-CD4(+) surface phenotype[32]. Simon et al reported an alternative mechanism of hypereosinophilia in

Table 2. Evaluation of eosinophilic patient[4]

History
- Asthma
- Allergies
- Atopy
- Travel
- Environmental exposure
- Diet
- Medications
- Pet, animal exposure
- Radiation
- Systemic symptoms (weight loss, fever, lethargy, and so forth)

Physical examination
- Lymphadenopathy
- Rash, fibrosis
- Cardiac function, murmur
- Organomegaly
- Muscular and neurologic abnormalities

Initial laboratory evaluation
- Complete blood count
- Absolute eosinophil count
- Stool ova and parasites
- Erythrocyte sedimentation rate
- Serum total protein, albumin

Further evaluation based on suspected cause

Atopy
- Nasal smear
- Skin tests
- Pulmonary function tests
- Chest X-ray
- IgE

Drug hypersensitivity
- Discontinue suspected drug
- Rechallenge

Parasites
- Stool ova and parasites
- Chest X-ray
- Serologic tests

Malignancy
- Lactic dehydrogenase
- Bone marrow aspiration
- Chest and abdomen tomography
- Lymph node biopsy

Gastrointestinal
- Upper gastrointestinal series
- Barium enema
- Endoscopy

Infection
- Streptococcal serologies
- Tuberculosis skin test
- Fungal serologies (histoplasmosis, blastomycosis, coccidiomycsis)
- Cat-scratch disease
- Blood culture

1996, via failure of apoptosis of Fas-deficient T-cells or secretion of soluble Fas receptor on a population of CD4-CD8(-) T-cells in two patients[33].

Emerging evidence is suggesting that IHES may be either a reactive condition or a chronic myeloproliferative disorder[29]. Bain signalled the relationship among tyrosine kinase gene and myelodsyplastic syndrome in the study of Wlodarska and postulated that the location of genes including IL-3, IL-4, IL-5 and GM-CSF in chromosome 5 is relevant in the pathogenesis of IHES[34]. Then, De Vries et al presented two patients with rapidly evolving cardiac and respiratory failure, moreover, some patients experience normalization of eosinophil levels before the defined six month interval is completed, and thus do not fulfil Chusid' criteria although they clearly present IHES. This means that there were some clinical pitfalls in the diagnosis of IHES based on Chusid criteria[35]. This condition has led several authors to suggest that these criteria be revised to include such patients. In the same year, the increasing availability of detecting techniques of clonality led to think that IHES could be a T-cell disorder secreting eosinokines or failure of eosinophil

apoptosis[24]. Thus, in 1999, Simon et al reported that clonal populations of T-cells with an abnormal immunophenotype (such as CD3+, CD4-, CD8-) that secrete IL-5 are present in some patients with IHES. These subsets generally display an activated (HLA-DR+ and/or CD25+) memory (CD45RO+) phenotype[33]. They could not demonstrate clonality by conventional techniques but, the presence of a uniform population of T-cells expressing an aberrant phenotype suggested clonality. Therefore, the diagnosis of IHES requires the exclusion of occult cytokine-secreting T-cell clones.

However, pathogenic diversity of the striking clinical heterogeneity of patients and occasional development of malignancy involving either the myeloid or the lymphoid lineage was still a problem. Cools et al demonstrated that many patients who would previously have been categorized as having IHES actually have chronic eosinophilic leukemia since they can be demonstrated to have a clonal molecular genetic abnormality, specifically a FIP1L1-PDGFRA fusion gene resulting from a cryptic deletion of part of the long arm of chromosome 4[36]. Other groups confirmed this fusion gene both on patient samples and EOL-1 cell line[37,38]. The central role of this fusion gene in IHES pathogenesis is supported by its disappearance in most patients successfully treated with imatinib mesylate[39].

Therefore, accumulation of eosinophils in peripheral blood and tissues can either be the result of an acquired abnormality involving the myeloid lineage (myeloproliferative variant), or be due to the production of eosinophilopoietic cytokines by nonmyeloid cells (lymphocytic variant). In primary eosinophilia, clonal eosinophil expansion may occur late in the process of differentiation, in which case the rare diagnosis of “eosinophilic leukemia” is currently thought to be appropriate. Secondary eosinophilia is a reactive cytokine-driven process with the accumulation of polyclonal eosinophils.

Pediatric IHES

Pediatric IHES has only a slight male predominance whereas adult IHES is reported to be more common among males than females, at a ratio of 9 to 1. Katz et al reported an IHES patient and reviewed long-term prognosis of pediatric cases in the literature; 15 patients were reported to be alive at that time their cases were published, whereas 21 have expired[40]. In this recent review, there were 38 pediatric IHES cases; 17 female and 21 male. Their ages were ranged between 1 to 16 years, with a mean of 8.2. Presenting symptoms of them [n, (%)] were fever in 20 (58.8), arthralgias in 8 (23.5), fatigue in 8 (23.5), rash in 8 (23.5), cough in 7 (20.6), neurologic symptoms in 6 (17.6), dyspnea in 6 (17.6), diarrhoea in 5 (14.7), abdominal pain in 4 (11.8), vomiting in 4 (11.8), headache in 4 (11.8), sore throat in 4 (11.8). Involved organs were heart in 27 (71.0), lungs in 21 (55.3), skin in 13 (34.2), nervous system in 10 (26.3), gastrointestinal in 8 (21.0) cases. Pediatric IHES associated with ALL in 14 (36.8) of them. Of 28 pediatric IHES patients, 11 responded to corticosteroids. FIP1L1-PDGFRA fusion gene has not been reported to date in pediatric cases.

Management of Patients with IHES

Patients diagnosed as IHES should be referred to experienced teams as; optimal management depends on the ability to classify the disease variant both technically and clinically. Distinction of myeloid vs. lymphoid variants is the critical first step (Table 3). Identification of patients with l-IHES is based on showing aberrant T-cell population and analysis of TCR gene rearrangement patterns using Southern Blot and PCR amplification[1]. Negative findings may reflect true absence of clonality, or clonality may be undetected[33]. Analysis of cytokine profiles must be performed for assessment of underlying T-cell disorder. Cytokine concentrations can be measured in supernatants of cultured pe-

Table 3. Investigation steps for IHES[1]*

Chest X-ray
Electrocardiogram
Echocardiography MRI
IgGAM
Vitamin B12
ALP
Bone marrow smear (tryptase and reticulin stain)
Lymphocyte phenotyping
Abdominal ultrasound (measurement of liver and spleen)
TCR** gene rearrangement analysis (Southern blot or PCR)
Conventional cytogenetic analysis on peripheral blood and bone marrow
Investigations referred to qualified laboratories
Serum tryptase
Serum TARC***
FIP1L1-PDGFRA fusion (RT-PCR, FISH)
Lymphocyte phenotyping****
Including CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD25, CD27, CD45RO, TCRα/β, TCRγ/δ, HLA-DR, CD95
TCR gene rearrangement analysis****
Eventually on a FACS-sorted phenotypically aberrant population
Conventional cytogenetic analysis****
In the presence of rIL-2 in addition to usual mitogens
Cytokine profile of T cell populations
IL-4, IL-5, IL-13, IL-3, GM-CSF, IL-2, IFNα
Intracellular cytokines at the single cell level by flow cytometry
Cytokines in culture supernatants of phenotypically suspect T-cell populations

* IHES: Idiopathic hypereosinophilic syndrome.
** TCR: T-cell receptor.
*** TARC: Thymus and activation regulatory chemokine.
**** When found normal in routine investigations.

ripheral blood mononuclear cells or purified aberrant lymphocyte subsets by enzyme-linked immuno-sorbant assay, in the absence or presence of T-cell stimulating agents, or by determining the proportion of cytokine-positive cells within a given lymphocyte subset by flow-cytometry[1]. Conventional cytogenetic analysis and detection of F/P must be performed systematically in IHES patients. Certain translocations [i.e. t (5;12) (q33;q13) or t (8;13)] or chromosomal abnormalities may actually change the diagnosis from IHES to eosinophilic leukemia[1,41]. Also, CHIC2 deletion could serve as a surrogate marker for F/P[39]. Bone marrow sampling will disclose existence of an underlying lymphoma in a patient with hypereosinophilia. Tryptase staining may reveal the presence of increased numbers of dysplastic spindle-shaped mast cells and reticulin staining may show degrees of myelofibrosis in m-IHES[37]. Following the diagnostic workup, classification of an IHES patient can be made (Table 3)[1]. In the lack of a primitive myeloid or lymphoid disorder, a third truly 'idiopathic' HES group could be defined. Instead of these difficult and expensive techniques, diagnostic markers to distinguish variants of IHES are being explored. Increased serum tryptase appears to be a good marker for m-IHES associated with the F/P[1,3]. Increased serum TARC levels may represent a highly discriminative diagnostic test for l-IHES[42]. In the follow-up of IHES patients, clinicians should expect development of peripheral T-cell lymphoma in lymphocytic variant and AML in myeloid variant. As expected, therapeutic perspectives have radically changed in the past several years with the description of aberrant lymphocyte subsets and F/P. The new therapeutic strategies in IHES variants are shown in Table 4. It should not be forgotten that congestive heart failure, even relapse may develop while receiving imatinib therapy[38,43].

Table 4. Therapeutic strategies in IHES variants[1]

Myeloproliferative variant
Imatinib mesylate (Gleevec)
First choice if F/P present (or therapeutic trial in presence of features of MP disease)
Hydroxyurea
Interferon-α
In presence of signs of malignant transformation
Chemotherapy
Bone marrow or stem cell transplantation
Lymphocytic variant
Glucocorticoids
Interferon-α (associated with glucocorticoid)
Cyclosporine A
Anti IL-5 monoclonal antibodies (remains to be assessed)
In presence of signs of malignant transformation
Fludarabine, 2-chlorodeoxyadenosine
Chemotherapy (CHOP-like regimens)
Bone marrow or stem cell transplantation

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