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Eosinophilia associated with disorders of immune deficiency or immune dysregulation

Kelli W. Williams, MD, MPH¹, Joshua D. Milner, MD², and Alexandra F. Freeman, MD¹

¹Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland ²Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Synopsis

Elevated serum eosinophil levels have been associated with multiple disorders of immune deficiency or immune dysregulation. Although primary immunodeficiency diseases (PIDD) are rare, it is important to consider these in the differential diagnosis of patients with eosinophilia. This review discusses the clinical features, laboratory findings, diagnosis, and genetic basis of disease of several disorders of immune deficiency or dysregulation – all which have documented eosinophilia as part of the syndrome. The article includes autosomal dominant hyper IgE syndrome, DOCK8 deficiency, PGM3 deficiency, ADA-SCID, Omenn syndrome, Wiskott-Aldrich syndrome, Loeys-Dietz syndrome, autoimmune lymphoproliferative syndrome, immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, Comel-Netherton syndrome, and severe dermatitis, multiple allergies, and metabolic wasting syndrome (SAM).

Keywords

eosinophilia; immune; deficiency; dysregulation

1 Introduction

While elevated peripheral eosinophilia can be found in patients with parasitic infection, significant atopic disease, drug hypersensitivity reactions, connective tissue disorders,

Corresponding Author: Alexandra F. Freeman, MD, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10 Center Drive, Building 10/CRC, Room 12C103, Bethesda, MD 20892, Telephone: 301-594-9045, Fax: 301-496-0773, freemaal@mail.nih.gov.

Co-author: Kelli W. Williams, MD, MPH, Allergy and Immunology Clinical Fellow, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 33 North Drive, Building 33, Room 2W10A, Bethesda, MD 20892, Telephone: 301-443-5769, Fax: 301-480-5705, kelli.williams@nih.gov

Co-author: Joshua D. Milner, MD, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10 Center Drive, Building 10/CRC, Room 5-3950, Bethesda, MD 20892, Telephone: 301-827-3662, Fax: 301-480-8384, jdmilner@mail.nih.gov

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malignancy, and rare hypereosinophilic syndromes, monogenic disorders of immune deficiency or dysregulation should be considered, particularly in the pediatric age group. Some of these syndromes include clinical manifestations of atopy, such as atopic dermatitis or food allergy, which may contribute to the eosinophilia; however the mechanism driving the eosinophilia is not well understood. Many of these monogenic diseases are characterized by increased production of Th2 cytokines, such as IL-5, which is an essential promoter of eosinophil differentiation, maturation and survival [1].

This article reviews several disorders of immune deficiency or dysregulation that have documented eosinophilia as part of the syndrome (Figure 1). The clinical features, common infections, laboratory findings, diagnostic methods, and genetic basis of disease of each syndrome will be discussed.

2 Syndromic causes of elevated IgE and eosinophilia

2.1 Autosomal dominant HIES

Job's syndrome was first described in 1966 with two patients who had recurrent staphylococcal abscesses, similar to the boils borne by the prophet Job in the Bible [2]. This clinical syndrome, which was first characterized as a triad of recurrent staphylococcal abscesses, pulmonary infections, and an eczematous dermatitis, was later found to be associated with elevated serum IgE levels leading to the name autosomal dominant Hyper IgE syndrome (AD-HIES) [3].

2.1.1 Clinical features, infections, and management—AD-HIES typically presents within the first few days of life as neonatal acne or erythema toxicum neonatorum secondary to the pustular rash that often encompasses the face, scalp, and upper body [4, 5]. Histologically, the skin infiltration is predominantly eosinophils [6]. The rash usually evolves to resemble an eczematous dermatitis, which is papular, pruritic, lichenified, and typically driven by *Staphylococcus aureus* colonization and superinfection [7].

Patients with AD-HIES classically have recurrent, “cold” *S. aureus* abscesses, which have frank pus when excised despite their lack of dolor, rubor, and calor [2]. Recurrent sinopulmonary infections generally start in the first several years of life with *S. aureus* being the most common pathogen implicated in the pneumonias. *Streptococcus pneumoniae* and *Haemophilus influenzae* also occur frequently, and the first presentation of pneumonia in infancy may be caused by *Pneumocystis jirovecii* [8, 9]. As with the cold abscesses, AD-HIES patients with pneumonia lack systemic signs of inflammation, including fever, frequently delaying diagnosis leading to parenchymal lung damage (Figure 2). Pneumatocoles and bronchiectasis increase the patients' susceptibility to difficult to treat microbes, like *Aspergillus*, *Scedosporium*, *Pseudomonas*, and nontuberculous mycobacteria, which contribute significantly to their morbidity and mortality [9–11].

Fungal susceptibility is apparent with more than 80% of patients having chronic mucocutaneous candidiasis [12] (Figure 3). Unlike patients with DOCK8 deficiency, those with AD-HIES do not commonly have severe viral infections (Table 1) [13, 14].

Despite the very elevated levels of serum IgE characteristic of these patients, allergy and asthma are not typically severe or difficult to manage in AD-HIES. Siegel et al. reported a diminished allergic phenotype in patients with AD-HIES compared to other patients with a comparably elevated IgE and atopic dermatitis, although allergies are more frequent than those with normal IgE levels [15].

AD-HIES is a multi-system disease with many non-immunologic abnormalities. A characteristic facial appearance usually emerges during adolescence with porous skin, a prominent forehead, deep-set eyes, and a bulbous and broad nose (Figure 3). Most patients fail to shed their primary teeth, requiring medical removal to allow the secondary teeth to emerge normally. Patients also have a high-arched hard palate and palatal and lingual ridges or grooves [8, 10, 16].

Extensive musculoskeletal abnormalities include scoliosis, osteopenia or osteoporosis, minimal trauma fractures, craniosynostosis, and joint hyperextensibility [8, 17] (Figure 3). Joint hyperextensibility occurs in more than two-thirds of AD-HIES patient and may contribute to the high frequency of degenerative bone disease [12].

Recently, manifestations of gastrointestinal disease in AD-HIES patients have been described. In a cohort of 70 individuals, nearly two-thirds of those with AD-HIES who underwent gastrointestinal endoscopy had eosinophilic esophagitis as defined by the updated consensus guidelines [18, 19]. Food allergy was not as common as in DOCK8 deficiency [18].

As with several other primary immunodeficiency diseases, patients with AD-HIES are at increased risk of developing malignancy, particularly non-Hodgkin's lymphoma [13, 20].

Because the clinical impact of recurrent infections can be profound, the primary focus in management is treatment of infections and prophylaxis to prevent future infections, especially with *S. aureus*. Suppression of skin colonization with *S. aureus* through antiseptics, such as dilute bleach baths and chlorhexidine washes, frequently leads to minimal dermatitis. Patients with chronic mucocutaneous candidiasis, or in areas endemic for *Coccidioides* or histoplasmosis, may also benefit from antifungal prophylaxis.

Parenchymal lung disease and subsequent chronic infection with molds, such as *Aspergillus*, and Gram-negative bacteria, such as *Pseudomonas*, contribute to most cases of death in AD-HIES [11]. Because of this, pyogenic pneumonias should be aggressively diagnosed and treated to minimize parenchymal damage.

Immunoglobulin replacement should be considered in those patients with impaired specific antibody responses, bronchiectasis and breakthrough infections while on prophylaxis. Hematopoietic stem cell transplant (HSCT) has been performed infrequently as a possible curative treatment for AD-HIES with varying clinical results [21–23].

2.1.2 Clinical laboratory findings—In addition to the hallmark laboratory finding of elevated serum IgE levels, most patients with AD-HIES have peripheral eosinophilia. IgE levels are often greater than 2000 IU/mL, although may decrease and even normalize as

adults, and absolute eosinophil counts are quite variable but frequently greater than 700 cells/ μ L. Despite this, the underlying etiology of these elevations is still unclear, and the serum eosinophil levels have not correlated with serum IgE level or clinical phenotype. In addition to the peripheral eosinophilia, increased eosinophils have been identified in sputum and abscesses.

Generally, patients with AD-HIES have normal white blood cell counts, although absolute mild neutropenia and leukopenia are fairly common. Serum IgG and IgM levels are often normal, whereas serum IgA may be normal or low. Specific antibody responses to vaccines are variable among patients with AD-HIES, with some patients producing little or no response [12, 24, 25].

2.1.3 Genetics and pathogenesis—Dominant-negative mutations in STAT3 cause AD-HIES. These mutations are primarily missense or single-codon in-frame deletions that result in single amino acid changes [24, 26].

Identifying the genetic mutation in STAT3 has offered important insight on the clinical phenotype. STAT3 is a transcription factor that plays an essential role in the signal transduction of many cytokines, including IL-6, IL-10, IL-21, IL-22, and IL-23. STAT3 is activated by Janus kinase 2 and phosphorylated in order to dimerize and translocate into the nucleus to initiate targeted gene transcription [27, 28]. Because of its involvement with many cytokines, STAT3 plays a crucial role in immunity, inflammation, wound healing, cell survival, embryogenesis, and oncogenesis, with disruption leading to the multisystem nature of AD-HIES.

The most consistent immunologic finding in these patients is a lack of CD4⁺ Th17 cell differentiation [29–32]. The importance of IL-17 in the clearance of *Candida*, *Klebsiella*, and *Staphylococcus aureus* has been established in mice, and in humans disruption of the IL-17 and IL-22 pathway leading to mucocutaneous candida susceptibility is evident through several PIDD [33–38].

AD-HIES is also associated with diminished memory T and B lymphocytes. Decreased central memory CD4⁺ and CD8⁺ T lymphocytes are clinically evident by the reactivation of latent viral infections, resulting in an increased incidence of zoster and asymptomatic EBV viremia. Decreased memory and class switched B cell is frequently seen as well [3, 25, 39].

2.2 DOCK8 deficiency

2.2.1 Clinical features, infections, and management—DOCK8 mutations were described in 2009 in a subset of patients with an autosomal recessive inheritance pattern of many features of AD-HIES, although lacking most of the skeletal and connective tissue abnormalities [40]. The many clinical characteristics of DOCK8 deficiency include atopic dermatitis, food or environmental allergies, marked IgE and eosinophil elevations, recurrent sinopulmonary infections, recurrent *Staphylococcal* skin infections or abscesses, mucocutaneous candidiasis, and, distinctly, a breadth of disseminated cutaneous viral infections. Additionally, a significant portion of patients with DOCK8 deficiency went on to

develop malignancies, some fatal, likely resulting from the oncogenic properties of the cutaneous viruses and a dysfunction in tumor surveillance [41, 42].

Many patients with DOCK8 deficiency have an exaggerated atopic phenotype when compared to those with AD-HIES, and anaphylaxis and food allergy are more common [15, 41, 43, 44]. Nearly all patients with DOCK8 deficiency (99%) have an eczematous dermatitis that begins in infancy, but less commonly a newborn rash [13, 45, 46]. The immunologic mechanism driving their atopy and eosinophilia is unclear, but is associated with a predominance of Th2 cytokine production and regulatory T lymphocyte deficiency [45, 47].

Nearly 90% of affected patients have recurrent and even concurrent cutaneous viral infections, namely with human papillomavirus, herpes simplex virus, molluscum contagiosum virus, and varicella zoster virus (Figure 4) [41, 43, 44, 48]. Severe systemic viral infections are less frequent [44, 49].

The majority of patients with DOCK8 deficiency (>90%) have recurrent upper respiratory tract infections, pneumonias, sinusitis, and otitis media. Pulmonary pathogens include the more common *Streptococcus pneumoniae* and *Haemophilus influenzae*, but the spectrum broadens when bronchiectasis is present [13, 41, 43, 44]. Fungal infections include mucocutaneous candidiasis, cryptococcal meningitis, disseminated histoplasmosis, and *Pneumocystis jirovecii* [41, 44, 49]. Eosinophilic pneumonias have also been seen in DOCK8 deficiency. Autoimmunity in DOCK8 deficiency has included difficult to treat autoimmune hemolytic anemia, hypothyroidism, and vasculitis [49].

DOCK8 deficiency has a worse prognosis than AD-HIES, with most patients dying in the 2nd and 3rd decade of life. To date, the only curative treatment for DOCK8 deficiency is HSCT, and this should be strongly considered for these patients. Those who have been transplanted had near or complete resolution of their cutaneous viral infections and improvement in their T lymphocyte populations and function, eczema, and recurrent sinopulmonary within a year of transplantation [43, 50–58].

Management of DOCK8 deficiency focuses on treating and preventing infections in a manner similar to those with AD-HIES. Immunoglobulin replacement therapy is frequently indicated due to poor specific antibody production [41, 59]. Acyclovir or valacyclovir should be considered for prophylaxis to prevent recurrent HSV and VZV infections. Warts and molluscum are difficult to treat in this population, and standard therapies tend to be ineffective; interferon- α has had variable benefit [6, 13, 60].

2.2.2 Clinical laboratory findings—Peripheral eosinophilia, typically greater than 1000 cells/ μ L is common, as is elevated serum IgE. The etiology of the eosinophilia and elevated IgE levels is not well understood. Serum levels of IgM are classically very low or even undetectable [41, 43, 44, 49]. Serum IgG levels are often normal or slightly elevated, whereas serum IgA levels are variable with typically poor specific antibody responses [41].

The combined immune deficiency in DOCK8 patients is apparent with CD4⁺ and CD8⁺ T cell lymphopenia that often worsens with age, and variability in NK cell and B lymphocyte

deficiency [41, 42]. Additionally, T lymphocyte activation and proliferation are diminished, particularly in the CD8+ population, thus contributing their increased viral susceptibility [41, 44]. Diagnosis is confirmed with DOCK8 sequencing, and can be strongly suggested by absence of expression on flow cytometry [41, 61].

2.2.3 Genetics and pathogenesis—Mutations in DOCK8 render most patients protein negative [41, 44, 49]. Recently revertant mutations have been shown, but the clinical significance remains unknown [62]. DOCK8 belongs to the DOCK180 superfamily of guanine nucleotide exchange factors [63]. These guanine nucleotide exchange factors are known to interact with the Rho family of GTPases, which can be found in all eukaryotic cells and have an important role in organelle and cytoskeletal development, cell migration, phagocytosis, and wound healing [64, 65]. We now know that DOCK8 plays a critical immunologic role, specifically in T, B lymphocyte, and natural killer T cell survival, migration, and synapse formation [42, 66, 67].

2.3 PGM3 deficiency

2.3.1 Clinical features, infections, and management—Mutations in Phosphoglucosyltransferase 3 (PGM3) were recently defined leading to a multisystem disease sharing some clinical features with AD-HIES and DOCK8 deficiency. The initial clinical description of patients with this disease was the report of an autosomal recessive vasculitis-myoclonus syndrome associated with infection and severe atopy in a family with five affected children [68, 69]. The clinical phenotype of PGM3 deficiency is still being defined, but cutaneous leukocytoclastic vasculitis, eczema-like rash, cognitive impairment and myoclonus, and delayed visual and sensory evoked potentials have all been present, as well as severe bronchiectasis [69, 70].

Poor control of viruses has presented as widespread molluscum contagiosum in one affected individual and poor control of EBV, with persistent EBV viremia and EBV associated Hodgkin's lymphoma in two individuals [69, 70]. Clinical variability is evident by the cohort with B and T lymphopenia similar to that seen in severe combined immunodeficiency (SCID), neutropenia and progression to bone marrow failure [71]. Autoimmune and immune-mediated diseases have included membranoproliferative glomerulonephritis, autoimmune neutropenia, psoriasis and vasculitis. Skeletal abnormalities have manifested as scoliosis, facial dysmorphism, and hyperextensibility. Cognitive impairment appears common and demyelination has been observed on brain MRI for several patients [69–71].

Treatment of PGM3 deficiency is currently supportive. Prophylactic or suppressive antimicrobials should be considered based on clinical presentation. Immunoglobulin replacement may be considered if poor specific antibodies are present, however anecdotal reports of improvement have been mixed. Transplant improved the bone marrow failure and immunologic phenotype in two patients, but the impact on the neurologic and skeletal phenotype is unclear [71]. Dietary supplementation has been used in other congenital disorders of glycosylation, but has not yet been established for this defect [72].

2.3.2 Clinical laboratory findings—Most individuals identified with PGM3 deficiency have had significantly elevated serum IgE, variable eosinophilia and immune abnormalities.

Leukopenia appears common with both lymphopenia and neutropenia. The lymphopenia is predominantly from decreased CD8⁺ T cells and low memory B cells. IgG, IgE and IgA have all been increased, and specific antibodies have been present but less robust than frequently seen in healthy controls. Consistent with the atopic clinical phenotype, the T cell cytokine responses have a Th2 skew with increased secretion ex vivo of IL-4, IL-5 and IL-13. Compared to DOCK8 deficiency and AD-HIES, the T lymphocyte production of IL-17 appears increased, which may explain some of the autoimmunity features and the lack of candidiasis [63, 70].

PGM3 deficiency should be suspected in an individual with an exaggerated allergic phenotype, recurrent infections and neurologic deficits. Glycosylation defects can also be suggested by glycan profiling of urine and serum. In PGM3 deficiency, both O and N-linked glycans are abnormal. Sequencing of PGM3 is key to the diagnosis.

2.3.3 Genetics and pathogenesis—PGM3 is an enzyme responsible for the conversion of GlcNAc-6-phosphate to GlcNAc-1-phosphate, which then converts to UDP-GlcNAc. This is a key early step in multiple glycosylation pathways, and thus essential to allow normal activity of many diverse proteins. As the majority of proteins require glycosylation, absence of activity would not be compatible with life and is embryonic lethal in mice. The disease is autosomal recessive, and all mutations found have been hypomorphic, allowing diminished but present activity. A mouse model of PGM3 deficiency caused by hypomorphic point mutations led to lymphopenia with T lymphocytes predominantly affected, anemia and thrombocytopenia [73].

2.4 Wiskott-Aldrich syndrome

2.4.1 Clinical features, infections, and management—Peripheral and tissue eosinophilia (e.g. in lymph nodes and spleen) are characteristic of Wiskott-Aldrich syndrome (WAS) [74, 75]. WAS was first described in 1954 with its X-linked inheritance pattern of severe eczema, thrombocytopenia with small platelets, and recurrent infections [76]. A wide variety of infections have been reported in WAS and include *Pneumocystis jirovecii* pneumonia, severe and/or disseminated HSV and varicella, and invasive fungal infections [77]. Because of the significant thrombocytopenia, patients can present with bleeding, petechiae or ecchymoses. Autoimmunity (e.g. autoimmune cytopenias, inflammatory bowel disease, renal disease) and malignancy (notably lymphoma) are seen as well [78]. Similar to those with DOCK8 deficiency, vasculitis and aortic aneurysm have also been described [79, 80].

Morbidity and mortality related to WAS are high if not properly treated. Death is usually secondary to infection, bleeding or malignancy [77]. Because of the poor antibody responses, immunoglobulin replacement therapy is often helpful in reducing serious infections. The immunoglobulin therapy has not shown appreciable impact on the thrombocytopenia, although splenectomy has led to normalization of platelet counts [81, 82]. Those who are status-post splenectomy should receive appropriate prophylaxis with vaccination and penicillin. HSCT or gene therapy should be considered [83, 84].

2.4.2 Clinical laboratory findings—Complete blood counts almost always reveal thrombocytopenia with microthrombocytes on peripheral smear. Peripheral eosinophilia and anemia are often observed, and as with other PIDD, the mechanism driving the eosinophilia is unclear. Typically, serum IgM is decreased, serum IgG and IgA are variable, and serum IgE is elevated. Poor polysaccharide vaccine responses are characteristic [74, 77, 83, 85].

Flow cytometry typically reveals mild T cell lymphopenia, normal circulating B lymphocytes, and normal or increased NK cells. Poor lymphocyte proliferation and NK cytotoxicity is characteristic as WASp (WAS protein) is essential for colocalizing with actin to NK cell activating synapses [83, 85]. In addition to sequencing, flow cytometry is also used to evaluate WASp expression in suspected cases of WAS [83].

2.4.3 Genetics and pathogenesis—Mutations in the gene WAS, located on the X-chromosome, have been identified as causing deficiency in WASp. WASp is a crucial regulator of platelet and lymphocyte development and is critical for cytoskeletal and immunologic synapse formation and regulatory T-cell function [86–88]. Genotype-phenotype correlations have been described with those having X-linked thrombocytopenia and X-linked neutropenia having distinct and often milder phenotypes [89].

3 Severe combined immunodeficiency and related disorders associated with eosinophilia

3.1 ADA-SCID

3.1.1 Clinical features, infections, and management—While eosinophilia is not a prominent feature in all variants of SCID, peripheral eosinophilia is a commonly encountered clinical manifestation seen in ADA-SCID. Because of the profound T, B, and NK cell lymphopenia seen in ADA-SCID, affected individuals typically present in infancy with severe opportunistic infections, such as with *Pneumocystis jirovecii* pneumonia. Recurrent and/or severe respiratory infections typically occur within the first few months of life, along with failure to thrive, frequent thrush, and chronic diarrhea [85, 90, 91]. Partial ADA deficiency has been described in a subset of patients who typically present later in life, such as in late infancy or early childhood, with a milder phenotype that may include autoimmune manifestations [92].

Atopy is a common feature found in ADA-SCID, found in about half of those with early onset disease. Of the atopic manifestations, allergic rhinitis, asthma, food allergy, mild atopic dermatitis, and urticaria were the most common identified in this population [93].

Given the ubiquitous nature of ADA expression and the profound impacts of deoxyadenosine, S-adenosylhomocysteine, and deoxyadenosinetriphosphate accumulation within the tissues, patients with ADA deficiency often present with other systemic manifestations, such as hepatic degeneration and dysfunction, costochondral abnormalities, and skeletal dysplasia [90, 94]. Neurologic motor and hearing impairments (i.e. bilateral sensorineuronal deafness) have also been associated with ADA deficiency, and patients may have cognitive and behavioral deficits [95, 96].

Without early recognition and treatment, ADA-SCID is often fatal within the first year of life [90, 97]. To date, the treatment options for ADA deficiency include allogeneic hematopoietic stem cell therapy, enzyme replacement therapy with pegylated bovine ADA, and gene therapy [98].

3.1.2 Clinical laboratory findings—Patients with ADA-SCID have a severe combined immunodeficiency with a profound deficiency of circulating T lymphocytes, B lymphocytes, and NK cells, more so than any other form of SCID [90, 97]. Serum IgG is usually normal at presentation due to maternal transfer of IgG, but decreases soon after. Serum IgA and IgM levels are variable, although more commonly IgM is low in this population [97]. Serum eosinophilia and IgE levels are also variable but frequently elevated among both those with early and delayed onset, presumably due to their increased CD4+ Th2 cytokine production and their clinical features of atopy [91, 93, 99].

When ADA-SCID is suspected, ADA activity should be assessed and will be low or absent. Additionally, levels of S-adenosylhomocysteine and deoxyadenosinetriphosphate will be elevated in ADA-SCID. Newborn screening for SCID through a quantitative evaluation of T-cell receptor excision circles (TREC) is helpful in identifying infants with SCID that can be further screened for ADA and other etiologies [100, 101].

3.1.3 Genetics and pathogenesis—Accounting for 10–20% of all SCID cases, ADA-SCID results from autosomal recessive mutations in the ADA gene [97, 102]. ADA is an enzyme that is crucial in the purine salvage pathway, catalyzing the deamination of deoxyadenosine and adenosine to deoxyinosine and inosine. In an ADA-deficient state, there is build up of deoxyadenosine, S-adenosylhomocysteine, and deoxyadenosinetriphosphate in the intra- and extracellular compartments, ultimately leading to impaired T and B lymphocyte development. In addition to inducing thymocyte apoptosis, deoxyadenosinetriphosphate interferes with terminal deoxynucleotidyl transferase activity and restricts V(D)J recombination [97, 103, 104].

3.2 Omenn syndrome

3.2.1 Clinical features, infections, and management—Similar to early-onset ADA-SCID, Omenn syndrome presents in infancy with peripheral eosinophilia, high serum IgE and rash. The rash is typically a generalized and often exfoliative erythroderma in contrast to the pustular or erythema toxicum neonatorum rash seen in AD-HIES [105]. Impairment of V(D)J recombination leads to abnormally expanded T lymphocytes. Affected infants commonly present with recurrent and severe infection, chronic diarrhea, lymphadenopathy, hepatosplenomegaly, and failure to thrive [47].

HSCT can be curative in Omenn syndrome, and without early transplant the disease is often fatal; however, in addition to pre-transplant supportive care with immunoglobulin replacement therapy and prophylactic antimicrobials, these patients also require systemic immunosuppression for their marked lymphoproliferation and inflammation [84, 100, 106–108].

3.2.2 Clinical laboratory findings—Patients with Omenn syndrome have elevated serum IgE and profound eosinophilia, likely resulting from Th2 skewing, despite the low or absent circulating B lymphocytes, decreased IgG, decreased IgM, and decreased IgA [105]. In contrast to classical SCID, patients have normal or even markedly increased circulating activated T lymphocytes; however they are oligoclonal and associated with poor antigenic responses [109–111].

3.2.3 Genetics and pathogenesis—Omenn Syndrome appears to be caused by hypomorphic mutations in genes associated with SCID. These have included include RAG1/2, Artemis, IL-7R α , DNA ligase IV, RNA-processing endoribonuclease, ADA, and γ c [85, 111]. Patients with atypical DiGeorge syndrome (due to a microdeletion at chromosome 22q11.2) may also present with a clinical phenotype that resembles Omenn syndrome [112–114].

4 Immune dysregulatory syndromes associated with eosinophilia

4.1 Autoimmune lymphoproliferative syndrome

4.1.1 Clinical features, infections, and management—While eosinophilia is often not the clinical feature driving presentation of patients with autoimmune lymphoproliferative syndrome (ALPS), eosinophilia is a common manifestation. ALPS typically presents in childhood with marked splenomegaly, generalized lymphadenopathy, and chronic cytopenias. Autoimmune hemolytic anemia, neutropenia and thrombocytopenia are typical. Patients with ALPS are at increased risk for developing B and T cell lymphomas due to the marked lymphoproliferation. In a recent natural history of ALPS study done at the NIH, 12% of the cohort developed either Hodgkin's or non-Hodgkin's lymphoma [115, 116].

The management of ALPS focuses on three main aspects of the syndrome: controlling the cytopenias, preventing infection, and malignancy surveillance. Additionally, spleen guards should be worn to protect against rupture and splenectomy should be avoided [117].

4.1.2 Clinical laboratory findings—The unique laboratory finding, which is required for and ALPS diagnosis, is elevated CD3+ $\alpha\beta$ CD4-CD8- double negative T lymphocytes (>1.5% of total lymphocytes or >2.5% of CD3+ lymphocytes). Total lymphocyte counts will also be normal or elevated [115, 116]. Serum vitamin B12 levels are elevated in ALPS and have proven to be a reliable biomarker for lymphoproliferation. Patients with ALPS often have elevated serum immunoglobulins (namely IgG, IgA, and IgM) [115]. Anemia, neutropenia or thrombocytopenia are common due to the autoimmunity associated with the syndrome. Autoantibodies are frequently positive, including rheumatoid factor, direct antiglobulin test, anticardiolipin antibody, antithyroid antibodies, and antinuclear antibodies.

Approximately 25% of ALPS patients will have peripheral eosinophilia (>750 cells/ μ L) [115, 116]. The cause of the eosinophilia is likely a result of Th2 skewing that produces an increase in IL-5. Fas-mediated apoptosis of eosinophils (as assessed *in vitro*) is impaired in patients with ALPS, with and without eosinophilia, suggesting this is not the cause of the observed eosinophilia [118]. Patients with eosinophilic ALPS also have more profound

cytopenias and are at significantly increased risk for death due to infectious complications from their immunosuppression [118].

4.1.3 Genetics and pathogenesis—The majority of ALPS cases are due to heterozygous mutations in the FAS gene, which encodes the tumor necrosis factor receptor superfamily-6 protein (TNFRSF6; Fas). Somatic or germline mutations in FAS-ligand, FAS-associated death domain, caspase 8, and caspase 10 have also been identified to cause ALPS. These mutations lead to defective lymphocyte apoptosis and thus lymphoproliferation [115, 119]. An ALPS-like phenotype can also be caused by germline gain-of-function STAT3 mutations [120].

4.2 Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

4.2.1 Clinical features, infections, and management—Patients with immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome frequently present with eosinophilia and severe atopy [121]. In addition, the classic triad of enteropathy, endocrinopathy, and dermatitis is observed [122]. Most commonly these patients present with early onset severe and watery diarrhea, type 1 diabetes mellitus, and failure to thrive [123]. Endoscopic biopsies of the gastrointestinal tract reveal villous blunting and lymphocytic infiltration, similar to that described in celiac disease and graft versus host disease [124]. The dermatitis resembles that of eczema and may vary in severity. IPEX patients have frequent autoimmunity, recurrent infections largely from immunosuppression, and may have food allergy [123, 125].

4.2.2 Clinical laboratory findings—Many of these patients have elevated serum IgE, elevated serum IgA, peripheral eosinophilia, and normal T and B lymphocyte subsets; however, they lack the essential CD4⁺CD25⁺ FOXP3⁺ regulatory T lymphocytes. Regulatory T lymphocytes have been shown to secrete IL-10 and TGF- β , and lead to suppression of serum IgE [126]. Presumably the deficiency in regulatory T lymphocytes contributes to the elevated IgE levels.

4.2.3 Genetics and pathogenesis—Mutations in both the coding and non-coding regions of FOXP3 have been identified in the majority of patients with IPEX. FOXP3 encodes the protein scurfin, a transcription factor which is the master regulator in the development and functioning of regulatory T lymphocytes [127, 128]. Mice lacking FOXP3 (scurfy mice) share many characteristics of patients with IPEX [127]. The lack of regulatory T lymphocytes leads to the loss of peripheral tolerance and marked cytokine overproduction in effector T lymphocytes.

In addition to sequencing, flow cytometry is often used as a clinical tool to evaluate FOXP3 protein expression in suspected cases of IPEX [123]. IPEX-like phenotypes including eosinophilia can also be seen in patients with CD25 deficiency and gain-of-function mutations in STAT1 or STAT3 [120, 129, 130].

4.3 Loeys-Dietz syndrome

4.3.1 Clinical features, infections, and management—Loeys-Dietz syndrome (LDS) is a connective tissue disorder with multisystem involvement, a large segment of which develops significant atopy, and eosinophilia. There is a great deal of clinical overlap between AD-HIES and LDS. Musculoskeletal abnormalities are variable and can include craniosynostosis, retained primary dentition, facial asymmetry, pectus deformity, scoliosis, flat feet, and joint hyperextensibility. Additionally, patients may have a high arched or cleft palate, an abnormal uvula, and hypertelorism. Their skin is classically thin and translucent, and easy bruising and poor wound healing are not uncommon [131, 132]. Vascular anomalies are a prominent feature of LDS. Diffuse arterial abnormalities, such as aneurysms and tortuosity, put patients at great risk for dissection and/or hemorrhages [131, 133].

LDS patients have an exaggerated allergic phenotype, which can include asthma, food allergy, atopic dermatitis, and allergic rhinitis. Gastrointestinal complaints, such as chronic abdominal pain, poor growth, constipation, and vomiting, are common among patients with LDS. Eosinophilic gastrointestinal disease (e.g. eosinophilic esophagitis, colitis, and/or gastritis) is often diagnosed pathologically. Targeted elimination diets appear to be beneficial in reducing clinical symptoms [132, 134].

4.3.2 Clinical laboratory findings—Elevated serum IgE and absolute eosinophil counts are prevalent laboratory findings in patients with LDS. These findings may be in part due to the Th2 skewing that is apparent in this population. The Th2 cytokine production is associated with an increased CD4+CD25+ FOXP3+ regulatory T lymphocyte population, which abnormally produces Th2 cytokines [134].

4.3.3 Genetics and pathogenesis—To date, four genetic mutations have been identified in LDS. These include heterozygous mutations in TGFBR1, TGFBR2, SMAD3, and TGFB2. Each mutation results in altered TGF- β signaling, yielding abnormal collagen and connective tissue growth, and effects on lymphocyte differentiation [131–134]. Despite the genetic and phenotypic variation seen in the LDS types, medical management is similar [132].

5 Dermatologic syndromes with immunodysregulation associated with eosinophilia

5.1 Comel-Netherton syndrome

5.1.1 Clinical features, infections, and management—Comel-Netherton syndrome is a dermatologic condition associated with an exaggerated allergic phenotype including severe atopic dermatitis, allergic rhinitis, peripheral eosinophilia and elevated serum IgE. The hallmark clinical features of Comel-Netherton syndrome are severe congenital ichthyosis and the pathognomonic bamboo hairs, known as trichorrhexis invaginata. The extent of skin involvement varies and may include an erythroderma or migrating and scaly plaques [135–137]. The skin lesions are usually quite pruritic secondary to the profound skin barrier defect and enhanced inflammation. *S. aureus* skin infections are frequent. Additional

findings associated with Comel-Netherton syndrome include failure to thrive, sparse or absent hair, eyebrows and eye lashes at birth, and chronic diarrhea [136, 137].

Mortality is highest in the neonatal period from sepsis, dehydration or malnutrition [136]. Management is aimed at systemic and cutaneous symptom management. Emollients are essential for their skin, and adequate nutrition and hydration is critical. Intravenous immunoglobulin and anti-TNF- α monoclonal antibodies have been effective in reducing skin inflammation [137, 138].

5.1.2 Clinical laboratory findings—Elevated serum IgE and absolute eosinophil counts are common and lymphocyte phenotyping may reveal increased NK cells and decreased switched and unswitched memory B cells found [136, 137, 139]. Poor NK cell cytotoxicity has also been identified [137]. Histopathology of skin biopsy reveals epidermal hyperplasia, minimal granular layer, and typically stratum corneum detachment [136].

5.1.3 Genetics and pathogenesis—Comel-Netherton syndrome stems from loss-of-function mutations in SPINK5, which encodes the serine protease inhibitor LEKTI [136, 140, 141]. LEKTI is expressed in both the epithelia and the thymus. Murine models have shown that LEKTI deficiency leads to unopposed kallikrein-related peptidase activity, ultimately causing impaired epidermal differentiation, defective cornification and poor skin barrier formation [136, 142, 143].

5.2 Severe dermatitis, multiple allergies, and metabolic wasting syndrome

5.2.1 Clinical features, infections, and management—SAM syndrome closely resembles that of Comel-Netherton syndrome with congenital ichthyosis, erythroderma, severe atopic dermatitis, peripheral eosinophilia and elevated serum IgE. The dermatitis has been described as papular, scaly and with plaque formation. Like Comel-Netherton syndrome, hair is absent or sparse [143, 144]. Unique to SAM syndrome is the early and severe development of food allergies and prominent metabolic wasting. Malabsorption and failure to thrive are also common, and eosinophilic esophagitis was identified in one patient. Recurrent infections, developmental delay, and minor cardiac defects, such as ventricular septal defects, have also been described [143, 144].

5.2.2 Clinical laboratory findings—Elevated serum IgE and absolute eosinophil counts are found in SAM syndrome. Keratinocytes from those with SAM syndrome showed upregulation of proinflammatory cytokine genes, such as IL5, which likely contributes to the eosinophilia. Other laboratory immune defects have not been described to date. Skin biopsy pathology reveals abnormally formed desmosomes and loss of cell-cell adhesion [144].

5.2.3 Genetics and pathogenesis—Homozygous loss-of-function mutations in DSG-1 were identified in two consanguineous families with SAM syndrome [144]. As with the other desmogleins, DSG-1 plays a crucial role in cell-cell adhesion in keratinocytes, as well as myocardial cells [145]. DSG-1 deficiency leads to absent cell-cell adhesion and abnormally formed epidermal desmosomes [144]. Without adequate cell-cell adhesion, the epidermal barrier dysfunction results.

6 Conclusions

The differential diagnosis of eosinophilia is broad and includes disorders of immune deficiency or dysfunction, especially those with prominent atopy as a clinical manifestation. There is a great deal of overlap in many of these disorders, thus a thorough clinical and laboratory evaluation is warranted.

Abbreviations

AEC	Absolute eosinophil count
AD-HIES	Autosomal dominant Hyper IgE syndrome
ADA	Adenosine deaminase
ALPS	Autoimmune lymphoproliferative syndrome
AR-HIES	Autosomal recessive Hyper IgE syndrome
DOCK8	Dedicator of cytokinesis 8
DSG-1	Desmoglein-1
FOXP3	Forkhead box protein P3
G-CSF	Granulocyte-colony stimulating factor
HIES	Hyper IgE syndrome
HPV	Human papillomavirus
HSCT	Hematopoietic stem cell therapy
HSV	Herpes simplex virus
IPEX	Immunodysregulation, polyendocrinopathy, enteropathy, X-linked
LDS	Loeys-Dietz syndrome
LEKTI	Lymphoepithelial Kazal-type related inhibitor
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
PGM3	Phosphoglucomutase 3
PIDD	Primary immunodeficiency diseases
SAM	Severe dermatitis, multiple allergies, and metabolic wasting
SCID	Severe combined immunodeficiency
SMAD3	Decapentaplegic homolog 3
SPINK5	Serine protease inhibitor Kazal-type 5
STAT3	Signal transducer and activator of transcription 3
TGFB2	Transforming growth factor- β 2 ligand
TGFBR	Transforming growth factor- β receptor

TNFRSF6	Tumor necrosis factor receptor superfamily member 6
TREC	T-cell receptor excision circles
VZV	Varicella zoster virus
WAS	Wiskott-Aldrich syndrome
WASp	Wiskott-Aldrich syndrome protein

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Key Points

- Eosinophilia can be seen in many disorders of immune deficiency or immune dysregulation; however, there are a few key syndromes that have eosinophilia as a consistent clinical feature.
- In these monogenic diseases of immune deficiency or immune dysregulation, peripheral and tissue eosinophil counts are variable and do not correlate with severity of disease.
- Ultimately, a marginal number of patients with eosinophilia have an underlying immune defect, but given the profound impact these diseases can have on morbidity and mortality, all cases of eosinophilia warrant a thorough clinical evaluation.

Figure 1.

Flow diagram showing disorders of immune deficiency or dysregulation with variable levels of peripheral and tissue eosinophilia. Characteristics of each disorder are listed once under the most prevalently featured category. AD-HIES: autosomal dominant hyper IgE syndrome, DOCK8: Dedicator of cytokinesis 8, PGM3: Phosphoglucomutase 3, ADA-SCID: Adenosine deaminase-severe combined immunodeficiency, ALPS: autoimmune lymphoproliferative syndrome, IPEX: Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, LDS: Loeys-Dietz syndrome, SAM: severe dermatitis, multiple allergies, and metabolic wasting, WAS: Wiskott-Aldrich syndrome

Figure 2. Parenchymal lung findings and complications in AD-HIES. Chest CT from a 43-year-old woman with AD-HIES, multiple pneumatoceles and an evident aspergilloma (arrows).

Figure 3. Characteristic clinical features found in AD-HIES. From left to right: characteristic facies, chronic mucocutaneous candidiasis, and severe scoliosis.

Figure 4. Cutaneous viral infections seen in DOCK8 deficiency. From left to right: disseminated *Molluscum contagiosum* due to molluscum contagiosum virus and verrucous and flat warts due to human papillomavirus.

Table 1

Comparison of the clinical features among the key syndromes of elevated IgE: STAT3, DOCK8, and PGM3

	STAT3	DOCK8	PGM3
Elevated serum IgE level	+++	+++	+++
Peripheral eosinophilia	+++	+++	+
Low CD4+ Th17 cells	+++	++	–
Newborn rash	+++	+	+
Eczematous dermatitis	+++	+++	+++
Recurrent skin abscesses	+++	++	++
Recurrent pneumonias	+++	++	+++
Mucocutaneous candidiasis	+++	++	–
Cutaneous viral infections	+	+++	+
Parenchymal lung changes	+++	+	++
Asthma	–	++	++
Food allergies	+	+++	++
Eosinophilic GI disease	++	++	+
Characteristic facies	+++	–	+
Retained primary teeth	+++	–	–
Scoliosis	+++	–	++
Minimal trauma fractures	+++	–	–
Hyperextensibility	+++	–	+
Vascular abnormalities	++	–	–
Autoimmunity	+	++	++
Malignancy	++	+++	++