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Review article

Eczema the hidden face of primary immunodeficiency diseases

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Primary immunodeficiency diseases (PIDs) are a group of more than 130 disorders caused by genetic defects of the immune system. Most of these disorders are caused by single gene defects, but the variable penetrance of these mutations results in heterogeneous phenotypes which lead to a delay in the diagnosis.[1] In the USA, the prevalence of all PIDs per 100,000 has increased over the last decade from 66.6 in 2003 to 126.8 in 2012[2] and this could reflect the rise in the disease awareness. The classical clinical presentation of PIDs includes recurrent or unusual infections, however, new presentations are now coming to attention such as autoimmune diseases, malignancy and cutaneous manifestations.[3]

Cutaneous manifestation in PIDs affects around 40 % to 70 % of patients and they include various presentation as eczema, cutaneous granulomas, recurrent abscesses, dysplasia of skin, hair, and nails, autoimmune conditions, and others.[4] Dhouib et al found that the incidence of cutaneous manifestation among 200 children with PIDs to be 56%[5], whereas Al-Herz[6] et al and Moin et al[7] found it to be 48% and 32% respectively. Cutaneous manifestations could be the first presenting symptoms and faulty presenting to dermatologist. In a series of 75 patients with severe dermatitis with no known underlying primary immunodeficiency, Aghamohammadi et al identified 5 patients with hyperimmunoglobulin E syndrome (HIES) and one patient with Wiskott Aldreich syndrome (WAS).[8] This raises the awareness to suspect an underlying PID in patients presenting with severe and non-resolving cutaneous manifestation.

Eczema (Atopic dermatitis "AD") is an inflammatory, chronically relapsing, non-contagious and extremely pruritic skin disease.[9] It is commonly associated with an elevation in total immunoglobulin E, which sometimes correlates with disease severity.[10,11] The prevalence of childhood AD ranges from 15% to 30%. AD is one of the commonest cutaneous manifestations for some PID diseases[12] and sometime used as one of the disease diagnostic critieria[13] of HIES, WAS, and others (Table). It is characterized by being severe, resistant to treatment and associated by chronic or recurrent viral or bacterial infections.[14] Such condition confirms the importance of eliciting history of recurrent infections in affected patients or history of infection in any of their family members .

Table 1. Primary immunodeficiency diseases associated with eczema[15]

Wiskott-Aldrich syndrome[a]
Hyper-IgE syndrome[a]
Selective IgM deficiency[b]
X-linked agammaglobulinemia[b]
X-linked immunodeficiency with hyper-IgM[b]
Ataxia telangiectasia
Selective IgA deficiency[a]
Severe combined immunodeficiency
Primary neutropenia
Schwachman Diamond syndrome[b]
Chronic granulomatous disease[b]

[a] Associated with atopic eczema
[b] Occasional association with atopic eczema claimed in some reports

Hyper-IgE syndrome (HIES)

The first HIES was described in 1996 (Job's syndrome). The syndrome includes a combination of recurrent cold abscesses, eczematous dermatitis and lung disease and elevated IgE>2000 IU/ µL.[16] It is also known as autosomal dominant HIES (AD-HIES). It shares several clinical features with dedicator of cytokinesis 8 (DOCK8) deficiency, known as autosomal recessive (AR)-HIES. In addition, there are two other rare autosomal recessive diseases associated with HIES. The first is caused by mutations in phosphoglucomutase-3 (PGM3) and the second is associated with a mutation in tyrosine kinase 2 (Tyk2). Both could also share some features with AD-HIES.[14]

AD-HIES

AD-HIES was found to be caused by a mutation in the signal transducer and activator of transcription 3 (STAT3).[17,18] STAT3 is important in wound healing, angiogenesis, cancer and immune function[19,20]. It is integral for T helper 17 (Th 17)

cell differentiation and interleukin 17 (IL-17) production.[21,22] Th17 is needed for neutrophil recruitment[23] and defense against Staphylococcus aureus infection which is considered the main infectious pathogens present in such patients.[19] Accordingly, patients usually present in the neonatal period with papulopustular eruption that changes into eczema[24], recurrent sinopulmonary infections ending into abscess formation and pneumatocele which predispose patients to subsequent Pseudomonas, Aspergillus, or atypical mycobacterial infections and additional morbidity.[14]

Eczema in AD-HIES which starts at the neonatal period in 78% of cases. It usually begins as pink to red papules that become pustules, exude pus, and turn into a crusted form. Lichenification, xerosis and scales are either absent or mild. The rash is distributed on the scalp, face, neck, axillae, and diaper area. In older cases, eczema is seen in 100% of HIES patients and it is usually moderate to severe eczema in 71% of cases. The main clinical clues that differentiate it from atopic dermatitis include; a severe prolonged clinical course, beginning at an earlier age, atypical distribution on axillae, groin and perineum, chronicity of dermatitis, recurrent staphylococcal skin infections, cold abscesses and resistance to conventional therapy, and responsiveness to anti-staphylococcal antibiotics.[16,25]

AD-HIES is a multisystem disease that also affects the connective tissue causing various skeletal and vascular disorders.[23,26] Somatic features include facial asymmetry broad nose, high arched palate and porous skin. Skeletal manifestation includes osteopenia, increase liability of fracture to minimal trauma and hyperextensibility of joints. Vascular abnormalities may include coronary aneurysm and lacunar brain infarction.[23,26] AD-HIES is also associated with an increased risk of malignancy, most commonly non-Hodgkin's lymphoma.[27] The life expectancy of patients ranges from the fifth to the sixth decade. Mortality is most commonly from infection.[28] The National Institute of Health (NIH) scoring system was developed for diagnosis due to phenotype variability. It uses both clinical and laboratory findings such as eczema, presence of facies, retained primary, serum IgE level and others. A total-point score of 15 points, makes the subject likely to carry an HIES genotype; at 10–14 points, the presence of an HIES genotype is indeterminate; and at <10 points, the subject is unlikely to have an HIES genotype.[29] Treatment is supportive during infections and in between prophylactic treatment against Staphylococcal aureus using topical and systemic antiseptic.[19] Hematopoietic stem cell transplantation (HSCT) has been done in a small number of cases, with mixed outcomes.[30]

AR-HIES

DOCK8 deficiency

DOCK8 deficiency is an AR-HIES, first described in 2009.[14] DOCK8 protein is normally expressed in mature peripheral T cells, hematopoietic stem cells, and thymocytes[31]. This protein mediates the cytoskeleton reorganization needed for hematopoietic stem cell homing and mobilization as well as T-cell polarization.[32,33] DOCK8 deficiency is characterized by elevation of IgE, recurrent sinopulmonary infections, severe eczema with on top resistant staphylococcal aureus infection and finally multiple food allergies similar to AD-HIES. But unlike AD-HIES, it has increase liability to viral infection on top of eczema commonly by human papilloma virus and herpes virus14 that could lead to disfiguring scars and may predispose to malignancy. This could be due to associated impaired natural killer (NK) cell development and survival, which likely contributes to the profound susceptibility to cutaneous viral infections.[34] Early bronchiectasis occurs in life.[35] It has a higher mortality rate due to sepsis and higher risk of malignancy in the second and third decade of life.36 The diagnosis is somehow difficult due to the wide range of clinical phenotype.[36]

Laboratory findings includes low numbers of or dysfunctional B cells and NK cells[35,36] along with low CD4+ cells and CD8+ cells[37] and low T cell receptor excision circles (TRECs).[36,38] Some studies reported low IgM level.[32] Treatment of eczema is difficult due to concomitant viral and bacterial infection.[14] Patients with extensive viral skin infection should be treated with systemic antiviral as acyclovir or valacyclovir. Giving the risk of malignancy, HSCT represents a promising therapeutic option for DOCK8-deficient patients[32] as it ameliorates the infectious and atopic symptoms within the first 6 months.[14]

PGM3 deficiency

It is an autosomal recessive disease first described in 2014.[39] PGM3 is a critical component of glycosylation pathway as it catalyzes the conversion of N-acetlyglucosamine-6-phosphate (GlcNAc-6-P) into GlcNAc-1-P in the synthesis of uridine diphosphate (UDP)-GlcNAc, thereby affecting a wide range of diverse proteins.[40] It is considered to be a variant of HIES where patients usually present with atopic dermatitis, asthma and other allergies, in addition to recurrent

sinopulmonary infections ending with bronchiectasis, skin and soft tissue bacterial infections. In contrast to HIES patients presents with various neurological symptoms such developmental delay, ataxia, sensorineural hearing loss and abnormal EEG findings. Uniquely, it was found that numerous patients have leukocytoclastic vasculitis and hematologic manifestations such as cytopenia, namely lymphopenia and neutropenia.[40]

Immune dysregulation, polyendocrinopathy and enteropathy, X-linked syndrome (IPEX)

IPEX is an X-linked disease that is generally considered as a syndrome of neonatal enteropathy[41,42] and polyendocrinopathy.[41,43] It is due a mutation in FOXP3 gene[44] which causes a decrease or absence in CD4+CD25+Treg cells and eventually loss of self-tolerance.[43] There is a considerable variation in the clinical phenotype, but the awareness of the disease allowed picking atypical cases.[44] The typical presentation usually starts in the first year of life with a triad of watery diarrhea, eczematoid dermatitis and type 1 diabetes mellitus[45], which is considered the most common and early manifestation of endocrinopathy, followed by thyroiditis.[41] There are other autoimmune manifestations as autoimmune cytopenia, hepatitis and nephritis. Alopecia has been reported in some cases.[46] More than 50% of patients suffer from invasive sepsis, meningitis, osteomyelitis.[47] Carrier females are generally healthy.45 Most patients have normal level of CD3+CD4+ and CD8+T-cells, with normal proliferative assay to mitogens. However, there is depletion of naïve T cell and increase in memory Tcell.[48] Symptomatic treatment includes transfusion of necessary blood elements, immunosuppressive drugs and total parental nutrition.[44] The only definitive cure is bone marrow transplantation [49], however, it will not cure the endocrinological disorders[44,50] and the results in some studies were not permanent.[51]

HSCT is curative now and gene therapy has been tried.[14]

Omenn's syndrome

Omenn syndrome is an autosomal recessive disease of combined immunodeficiency[52,53] and was first reported in 1985.[54] It usually presents in early infancy with recurrent severe and serious infections as severe combined immunodeficiency (SCID), generalized rash usually exfoliative erythroderma, chronic diarrhea, generalized lymphadenopathy, hepatosplenomegaly and failure to thrive.[14,55] The main pathology underlying its clinical picture is impairment of V(D)J recombination[55] leading to abnormally expanded activated oligoclonal T lymphocytes predominantly Th2 type which will infiltrate the skin and gastrointestinal tract.[52] Such abnormal T cells, working unopposed by other components of the immune system, will secrete cytokines promoting autoimmune and allergic inflammation.[56] It results from hypomorphic mutations of genes associated with SCID which includes RAG1/2, Artemis, IL-7Rα, DNA ligase IV, RNA-processing endoribonuclease, ADA, and γc.[57] In addition, it was found that some patients with atypical DiGeorge syndrome may present with a clinical phenotype resembling Omenn syndrome.[58] A similar clinical picture occurs in SCID with materofetal engraftment indicating molecular genetic studies to differentiate the origin of the abnormal Tcell.[59] Laboratory finding includes an elevation of serum IgE along with eosinophilia, despite having low or absent circulating B lymphocytes, decreased IgG, IgM, and IgA.[59] T lymphocytes are normal or increased. Treatment is usually supportive in the form of immunoglobulin replacement therapy, prophylactic antimicrobials, and in some cases systemic immunosuppression till doing HSCT. Early HSCT is important as the disease is fetal.[59]

Wiskott -Aldrich syndrome (WAS)

WAS is an X-linked life threatening PID presenting with a triad of eczema and recurrent serious infections, micro-thrombocytopenia and is associated with high incidence of autoimmune diseases and malignancy.[60] Its incidence is one to four cases per 1,000,000 live male births, with an average age at diagnosis of 24 months in families without a previously affected family member.[61] WAS is due to a defect in the WAS protein (WASP), which is a member of a family of proteins involved in signaling and actin cytoskeletal organization.[62] Actin cytoskeleton is important for vital cells function as growth, endocytosis, exocytosis and cytokinesesis.[63] Accordingly, mutation in this protein will affect the proper signaling and growth of different haemopoietic lineage and abnormal migration[64] and motility of many immune cellular components especially dendritic cells, myeloid cells ,macrophages ,natural killers and T and B cells.[65,66] The responsible gene was identified in 1994 and since then clinical and basic researches has started[67] which lead to more understanding of the protein function and its expression and its correlation with different clinical and phenotypic spectrum .

The other two different phenotypes are the X-linked thrombocytopenia (XLT) and X-linked neutropenia (XLN).[68] Reversion to normal of inherited mutation had been reported in some cases of WAS leading to a somatic mosaicism and mild clinical phenotype. Classical WAS usually presents early in life with the triad. The most common organisms are Pneumocystis jirovecii, HSV and varicella, and invasive fungal infections.[56] Thrombocytopenia causes bleeding tendency with variable severity and sometimes misdiagnosed as ITP due to presence anti-platelet antibody.[66] Eczema develops in 80% of WAS patients[69] and varies in its severity and response to the standard therapy. It has no distinct features from atopic dermatitis. Autoimmune manifestations occur in 40-70% of patients[60] and usually presents in the first two years of life.[70] It is due to the defect in the peripheral tolerance due to defective T regulatory cells (Tregs) due to abnormal WASP.[71] Malignancy occurs in 10-20% of patients and mainly it is lymphoreticular as lymphoma.[69]

A scoring system is used to define the variable phenotype of WAS (0-5) and to predict patients' prognosis. The clinical scoring system is derived from a variety of clinical parameters, including the presence of thrombocytopenia, eczema, immunodeficiency, autoimmunity, and malignancy. A WAS score greater than or equal to 3 is considered "classic" WAS. These patients have thrombocytopenia, eczema, immunodeficiency, and infectious. The presence of autoimmunity and/or malignancy is consistent with a WAS score of 5. Transient eczema, immunodeficiency, and mild infectious complications may also occur and may not portend a bad prognosis. These patients may be classified as XLT and will have a WAS score of 2. A WAS score of 0 is reserved for those patients with gain-of-function mutations associated with XLN and/or myelodysplasia. Patients may change from a lower WAS score to a higher WAS score.[72,73,74]

The characteristic laboratory finding is micro-thrombocytopenia and eosinophilia in the peripheral blood. Serum immunoglobulin levels show low IgM, high IgE and variable IgA and IgG. Flow cytometry reveals mild T cell lymphopenia, normal B cell, and normal or increased NK cells. The evaluation of WASP expression is important for diagnosis.[75] Poor response to polysaccharide vaccine are noted along with poor lymphocyte proliferation and NK cytotoxicity.[75] Treatment of WAS patients includes supportive treatment for active infections and autoimmune diseases and prophylactic antibiotics to guard against infection. The curative treatment is achieved by HSCT with better results if done at younger age.[61] The new recommended treatment now is gene therapy which was found to cause improvement at 24 months in eczema, the frequency and severity of infections, bleeding tendency, autoimmunity, reduction in disease-related days of hospitalization, and improvement in immunological and hematological parameters.[76]

Other PIDs rarely present with eczema

Selective IgA deficiency

Selective IgA deficiency is the most common PID syndrome in humans. It is more common in females than males. Symptoms usually includes recurrent, sometimes severe infections, particularly of the upper and lower respiratory and gastrointestinal tract. The most common offending pathogens are Gram-positive cocci, H. influenzae, and E. coli. Giardiasis, celiac disease, and malignancies have been described. There is an increased incidence of autoimmune diseases and lymphoreticular neoplasms.[77] A major feature of selective IgA-deficiency is the high incidence of atopic diseases. In a large series of IgA-deficient children, Plebani et al. found clinical manifestations of atopic symptoms in 25 % of patients. Atopic manifestations included allergic rhinitis, asthma, urticaria, and AD. Eczema was much less frequently found than rhinitis and asthma. Association with atopic symptoms was clearly linked to the presence of elevated IgE in more than 50 % of patients.[78] The underlying pathogenesis is attributed to failure of B cells to differentiate into IgA-secreting plasma cells. Severe and partial forms of the disease are distinguished, the former being defined as IgA levels below 7 mg/dl plus absence of secretory IgA. IgG and IgM as well as specific antibody production following immunization are usually normal, but IgG subclasses (IgG2, IgG4) may be deficient.[77] Moreover, serum IgE is elevated in 30 %, as are eosinophils. B and T lymphocytes are normal in number and function. IgA B cells, however, are arrested at an early stage of maturation and fail to differentiate further.[78] Although no consistent T cell defect has been demonstrated, subtly defective immunoregulation by T cells appears to be a major pathogenic feature.[79]

Selective IgM deficiency

Selective IgM deficiency is another very rare PID syndrome found in some patients with autoimmune diseases, characterized by the partial absence of IgM while the levels of other immunoglobulins are

normal. It is likely to be an X-linked disorder, its pathogenesis and relationship with autoimmunity remain unclear. Reduction or absence of secreted IgM may correlate with the progression of autoimmune diseases in humans.[80] In milder forms of IgM deficiency, recurrent Gram- positive infections predominate; severe deficiency often leads to fatal meningococcal septicemia and may be associated with AD according to some reports.[15]

Mammalian sterile 20-like 1(MST-1)

Mammalian sterile 20-like 1(MST-1) deficiency, also known as serine/threonine protein kinase 4 (STK4) deficiency, is an autosomal recessive disorder characterized by recurrent bacterial, viral and candida cutaneous infection along with structural cardiac anomalies. It rarely presents with eczema.[14] but is usually associated with bacterial and viral infections (HSV, HPV, MCV, EBV) as well as mucocutaneous candidiasis. The disease was first reported in 2012, when four consanguineous affected families with MST-1 deficiency have been described.[81,82] Systemic findings include structural cardiac anomalies (atrial septal defects and patent foramen ovale) and valvular disease.[83] Eczematous dermatitis has been reported, but is poorly characterized.[83] Affected patients have a peripheral neutropenia with normal bone marrow maturation, as well as T and B cell lymphopenia. The primary therapeutic intervention for this condition is infection control. Three patients with MST-1 deficiency have undergone HSCT, but two died within six months due to graft-versus-host disease and infectious complications.[14]

Shwachman- Diamond syndrome

Shwachman-Diamond syndrome is an autosomal recessive multisystem disorder involving an insufficiency of the exocrine pancreas and hematological problems as main symptoms. Frequently, ichthyosiform skin lesions are described but are usually not the leading symptom of the disease. It may present with skin eruptions as main symptom. A mixed clinical picture with an atopic dermatitis may occur and can aggravate skin symptoms. Additional medical problems like failure to thrive or neutropenia should lead to further diagnostic procedures to exclude Shwachman-Diamond syndrome.[84]

Conclusion

Dermatological disorders should be considered as one of the main clinical manifestation of PID especially eczema. It might be the first and only presenting symptoms. Eczema in early age is an alerting sign. Eczema resistant to treatment, recurrent and/or in unusual sites is another altering sign. Accordingly, dermatologist should be vigilant to suspect PID in any case presenting with recurrent and/or persistent skin diseases.

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