Eczema and Urticaria as Manifestations of Undiagnosed and Rare Diseases

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KEYWORDS

• Eczema • Urticaria • Nutritional deficiencies • Immunodeficiency syndromes
• Autoinflammatory syndromes • Mycosis fungoides

KEY POINTS

- Autoinflammatory syndromes should be suspected in a child with recurrent bouts of urticaria associated with other symptoms of inflammation (fever, arthritis, serositis, hepatosplenomegaly, ocular, and/or neurologic involvement).
- Immunodeficiency syndromes often present with a neonatal eczematous eruption along with recurrent infections, chronic lymphadenopathy, and/or failure to thrive.
- In a child with a chronic dermatitis that is unresponsive to treatment, biopsy may be warranted to rule out mycosis fungoides (MF).
- Nutritional deficiencies are important to consider in children presenting with recalcitrant dermatitis, often with characteristic locations and/or other clinical features.

INTRODUCTION

Eczema and urticaria are common cutaneous eruptions seen in children. In the vast majority of cases, they are skin-limited disorders that run a benign course. In rare instances, they may signify a more serious underlying disease such as an immunodeficiency or an autoinflammatory syndrome. This review highlights the signs and symptoms that should alert the clinician to suspect something more concerning.

ECZEMA

Eczematous eruptions are characterized by scaly pink papules and plaques, often with associated pruritus. The most common eczematous eruption of childhood is

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atopic dermatitis, which affects nearly 13% of children in the United States.[1] Nearly two-thirds of children with atopic dermatitis have onset of skin manifestations before 1 year of age but typically after 2 months of age.[2] Atopic dermatitis has a predilection for the face, scalp, and extensor extremities in infants and young children, whereas flexural sites are more common in older children and adults. A personal or family history of atopy is also a clue for the diagnosis. Although eczema is often equated with atopic dermatitis, there are several other eczematous eruptions of the skin.

Because atopic dermatitis is such a common condition in childhood, it is important to recognize unusual clinical presentations that may indicate the need for further investigation. Many of the childhood diseases associated with eczematous eruptions benefit tremendously from early diagnosis. Some unusual, but very important, causes of eczema in childhood include:

- Primary immunodeficiencies:
  - Autosomal-dominant hyper-IgE syndrome (AD-HIES),
  - Dedicator of cytokinesis 8 gene (DOCK8) deficiency,
  - Phosphoglucomutase 3 (PGM3) deficiency,
  - Wiskott–Aldrich syndrome (WAS),
  - Severe combined immunodeficiency (SCID),
  - IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), and
  - Netherton syndrome (NS).
- MF.
- Nutritional deficiencies:
  - Pellagra,
  - Kwashiorkor,
  - Zinc deficiency, and
  - Biotin deficiency.

Primary Immunodeficiencies

Eczematous dermatitis is a significant clinical feature of many primary immunodeficiency disorders. When severe and widespread eczema develops at birth or in the early neonatal period and is associated with recurrent or severe infections, chronic lymphadenopathy, significantly increased IgE levels, persistent eosinophilia, recalcitrant oral thrush, or failure to thrive, an evaluation for an underlying immunodeficiency may be warranted.[3] The specific clinical manifestations of primary immunodeficiencies with associated eczematous dermatitis are listed in **Table 1**. For many of these conditions, hematopoietic stem cell transplantation is the treatment of choice, although gene therapy and enzyme replacement are novel treatments under development for some immunodeficiency disorders.

Autosomal-dominant hyperimmunoglobulin E syndrome

AD-HIES is an immunodeficiency syndrome caused by dominant negative mutations in the signal transducer and activator of transcription 3 (STAT3) gene. STAT3 regulates processes involving cell growth and inflammation, with mutations in STAT3 leading to failure of T helper 17 cell differentiation and reduced IL-17 production.[4,5] AD-HIES is characterized by eczematous eruptions, skin abscesses, recurrent sinopulmonary infections, mucocutaneous candidiasis, and malignancies. The rash commonly presents within the first few weeks of life, which is earlier onset than is typical for atopic dermatitis. The eruption tends to start on the face and scalp. It may be papulopustular at onset but within the first year of life, an eczematous dermatitis develops