

CASE REPORT

Idiopathic hypereosinophilic syndrome: A rare diagnosis in children

Kristine Appel Uldall Pallesen¹  | Troels Herlin² | Mette Holm² | Christian Høst² | Mette Christiansen³ | Mette Ramsing⁴ | Mads Kirchheiner Rasmussen¹ | Mette Sommerlund¹

¹Department of Dermatology, Aarhus University Hospital, Aarhus N, Denmark

²Department of Paediatrics, Aarhus University Hospital, Aarhus N, Denmark

³Department of Molecular Medicine, Aarhus University Hospital, Aarhus N, Denmark

⁴Department of Pathology, Regionshospitalet Randers, Randers, Denmark

Correspondence

Kristine Appel Uldall Pallesen, Department of Dermatology, Aarhus University Hospital, 99 Palle Juul-Jensens Boulevard, DK-8200 Aarhus N, Denmark.
Email: KRPALL@rm.dk

Abstract

Idiopathic hypereosinophilic syndrome (IHES) is one of numerous hypereosinophilic syndromes. The incidence of IHES among children is unknown, but it is considered a rare disease. We report a pediatric case of IHES and the challenges to finding an effective treatment. The patient described here was responsive to prednisolone and thalidomide.

KEYWORDS

hypereosinophilia, idiopathic hypereosinophilic syndrome, prednisolone, thalidomide

1 | INTRODUCTION

Hypereosinophilic syndrome (HES) was first described in 1968 by Hardy and Anderson.¹ According to the World Health Organization (WHO), IHES is characterized by eosinophilia greater than $1.5 \times 10^9/L$ for at least 6 months and the presence of end-organ damage. In children, hypereosinophilia often occurs secondary to parasitic infections, medications, atopic dermatitis, and primary immunodeficiency like hyper-IgE syndrome, and rarely occurs due to graft-versus-host disease and neoplastic disease.² The prevalence and incidence of IHES are unknown, but it is considered a rare disease in children and mainly affected adults between 20 and 50 years old with a 9:1 male-female ratio.^{3,4} Hypereosinophilia can lead to cell damage and organ dysfunction due to the release of granule proteins.⁵ Here, we report a pediatric case of IHES with severe

eosinophilia, intense pruritus, and a generalized papulonodular skin rash.

2 | CASE REPORT

A 10-year-old boy with parents of Kurdish origin presented with a generalized, itchy, papulonodular skin rash at the outpatient clinic of dermatology and pediatrics at Aarhus University Hospital. The patient had allergic rhinitis with type 1 allergies to birch, cats, peanuts, and dust mites. There was no family history of atopy or eosinophilia. The parents were nonconsanguineous, and the two older siblings were healthy.

At birth, a pustular rash was observed on the face and back, which was diagnosed as erythema toxicum neonatorum.

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The exanthema, however, persisted and spread to the extremities during the first 6 weeks of life, especially the hands and feet. Later, it involved the extensor side of the extremities, trunk, and face (Figure 1). At 10 years of age, the patient presented with multiple hyperkeratotic papules located on the face, body, hands, and feet, with oedematous palms and soles (Figure 1). He showed no dysmorphic features, although his fingers appeared shortened. He suffered from asthma, but did not experience any gastrointestinal symptoms. Clinical examination showed no enlargement of the liver or spleen and no lymphadenopathy.

Laboratory tests revealed persistent eosinophilia for more than 5 years, with peripheral blood eosinophil levels ranging between 20×10^9 and $36 \times 10^9/L$, increased leukocyte count from 12×10^9 to $56 \times 10^9/L$ and elevated IgE > 5000 kU/L. The lymphocyte count was between 4.7 – $6.2 \times 10^9/L$ and with

normal platelet and hemoglobin level. Serum cobalamin, tryptase, and IL-5 levels were normal. Exome sequencing for pathogenic variants in the *STAT1*, *STAT3*, *DOCK8*, *PGM3*, and *TYK2* genes was negative. Variants in a list of 92 genes related to HES were also assessed, but none were predicted to be pathogenic. Whole-genome sequencing identified no further pathogenic variants but confirmed a variant in the *TRAP1* gene of unknown significance. This variant has been reported in relation to autoinflammatory diseases (HGMD accession CM1712682). A stool sample tested negative for parasites. Chest X-ray and ultrasonography of the abdominal organs were normal.

Skin biopsies from the palms and backs of the hands showed keratoderma-like epidermal hyperplasia and hyperkeratosis, as well as limited dermal eosinophilia (not shown). A biopsy from an active lesion of the abdominal skin showed



FIGURE 1 A, Generalized dermatitis with papulonodular skin rash on the extensor side of extremities and trunk. B, Dermatitis with papulonodular skin rash on the hands and feet. C, Punch biopsy from lateral abdominal skin showing epidermal irregular acanthosis with superficial incrustation and a dermal perivascular and an interstitial mixed inflammatory infiltrate with lymphocytes, histiocytes, and eosinophils (HE $\times 400$). Insert: Close-up from mid dermis showing massive eosinophilia (HE $\times 4000$)

severe perivascular and sparse interstitial dermal inflammation dominated by lymphocytes and severe eosinophilia (Figure 1). Bone marrow examination revealed eosinophilia without any signs of malignancy. Molecular analysis did not reveal Fip 1-like 1-platelet-derived growth factor receptor alpha (FIP1L1-PDGFR α) chain fusion. A standard cytogenetic examination of the bone marrow showed no clonal changes.

The patient was diagnosed with IHES and initially treated with oral prednisolone at a dose of 25 mg/day (0.9 mg/kg bodyweight) for 10 days, which was gradually reduced thereafter. The clinical response was rapid, with almost complete remission of the skin rash and blood eosinophilia, which decreased from 23.6×10^9 to 1.27×10^9 /L. However, the patient experienced numerous flares on tapering, which led to consistent maintenance on prednisolone for several years, associated with considerable growth retardation and pubertal delay. Additional treatment attempts with immunosuppressants, including azathioprine, ciclosporin, intravenous immunoglobulin, methotrexate, mepolizumab, rituximab, omalizumab, and hydroxyurea, did not have a sufficient effect. Finally, thalidomide given as an oral daily dose of 100 mg (2.2 mg/kg bodyweight) resulted in long-lasting complete resolution of the skin rash, including normalization of the skin and cessation of the pruritus, enabling the complete tapering of prednisolone. Our patient has now been in remission without flares or side effects to thalidomide for more than 18 months, and he has maintained a relatively low level of blood eosinophils.

3 | DISCUSSION

Six clinical variants of hypereosinophilic syndrome have been proposed: a myeloproliferative, lymphoproliferative, overlapping, idiopathic, associated, and familial variant.⁶ The diagnosis can be difficult because the symptoms and clinical presentation vary depending on the affected organs. In this case report, the patient's primary symptoms were intense itching and a generalized papulonodular skin rash. This is in accordance with the literature, as the majority of IHES patients have cutaneous manifestations, followed by pulmonary and gastrointestinal involvement.⁷

Hyper-IgE syndrome was initially suspected in our patient because of the very high IgE level, atopy, and dermatitis; however, this syndrome was ruled out when exome and genome sequencing for variants in relevant genes came back negative.⁸ Moreover, the child did not show increased susceptibility to cutaneous infections or episodes of invasive infections. There were also no skeletal abnormalities and no characteristic facial features of hyper-IgE syndrome.

In the current case, peripheral blood hypereosinophilia returned to a low level (1.27×10^9 /L) after initiation of oral

prednisolone at a dose of 25 mg/day for 10 days. However, the cutaneous symptoms and eosinophilia returned upon tapering, thus supporting the use of supplementary immunosuppressants. The early diagnosis and treatment of hypereosinophilia are of great importance because long-term hypereosinophilia can affect the skin, kidneys, lungs, heart, muscles, and nervous system.

There are currently no treatment guidelines for pediatric patients, but the standard treatment for adult FIP1L1-PDGFR α -negative HES patients is prednisolone. Other treatment options include hydroxyurea, interferon alpha, ciclosporin, and anti-IL-5 antibodies. Imatinib is an effective treatment in patients with FIP1L1-PDGFR α -positive HES.^{6,9} However, this treatment was not considered in our case as the patient was FIP1L1-PDGFR α -negative and had severe corticosteroid-induced growth retardation. The treatment goal for IHES is the normalization of blood eosinophil levels and control of the disease. Thalidomide treatment resulted in the achievement of long-term remission in our patient. It has been well tolerated, and no subjective side effects are reported. Although the precise mechanism of action is unknown, thalidomide is a unique immunomodulator agent with an antiangiogenic effect, which also inhibits TNF- α and IL-6.¹⁰ The use of thalidomide has previously been reported to improve several cutaneous diseases.¹¹ To our knowledge, this is the first report of a patient with IHES showing a clinically significant response to thalidomide treatment.

4 | CONCLUSION

We report a rare case of idiopathic hypereosinophilic syndrome with a neonatal onset which was successfully treated with thalidomide. IHES is a challenging diagnosis with a high mortality rate when left untreated, emphasizing the importance of awareness. This case illustrates the benefit of close cooperation between dermatologists and pediatricians in the diagnosis and treatment of HES patients.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

AUTHORS CONTRIBUTION

KP: contributed writing the manuscript, conducted literature review, and final approval of the version to publish. TH: contributed writing the manuscript and final approval of the version to publish. MC, MH, CH, and MR: Contributed writing case report, corrected part of the paper, and final approval of the version to publish. MR: contributed with figure and writing case report, corrected part of the paper, and final approval

of the version to publish. MS: contributed writing the manuscript, conducted literature review, and final approval of the version to publish.

ORCID

Kristine Appel Uldall Pallesen  <https://orcid.org/0000-0003-4570-600X>

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