

CASE REPORT

Autosomal recessive hyper-IgE syndrome successfully treated with hematopoietic stem cell transplantation

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Abstract

Autosomal recessive hyper-IgE syndrome is a primary immunodeficiency that results from a mutation in the *DOCK8* gene. We report a case of a patient presenting with severe eczema, atopy, and recurrent skin infections since the first months of life. The diagnosis of autosomal recessive hyper-IgE syndrome was made at the age of 7 by a positive *DOCK8* genetic test. The patient underwent hematopoietic stem cell transplantation, with complete remission of the various manifestations.

KEYWORDS

eczema, genodermatoses, immunodeficiency

1 | INTRODUCTION

Autosomal recessive hyper-IgE syndrome (AR-HIES) is a primary immunodeficiency that results from a mutation in the *DOCK8* gene. It is characterized by the high incidence of cutaneous infections, eczema from an early age, atopy, and sustained elevation of serum IgE. Treatment is generally unsatisfactory, with the exception of hematopoietic stem cell transplantation (HSCT), which may be curative.

2 | CASE REPORT

We report the case of a 9-year-old girl who presented with a history of ichthyosiform erythroderma, evolving from the first month of life. She first presented at age 9 months with erythematous, scaling, exudative patches, initially on the chest, with rapid generalization (Figure 1). In addition, she had a history of multiple food sensitivities (egg, wheat, cow's milk proteins, soy, and banana), confirmed by elevated food allergen-specific IgE. Other abnormalities, such as facial dysmorphism, skeletal, ocular, or cardiac changes were absent. Family history was not relevant, except for her father's allergic rhinitis. She had a healthy sister, 2 years older. There was a distant history of consanguinity (maternal great-grandmother was first cousin

of paternal great-grandfather). Pregnancy and delivery were without complications.

The patient had previously been evaluated elsewhere at age 5 months and had tried multiple treatments, such as topical therapies (emollients, antiseptics, corticosteroids, and antibiotics), several cycles of systemic corticosteroids, antihistamines, antifungals, and oral antibiotics, all without significant improvement.

By the end of the first year of life, she started to develop recurrent skin infections (candidal intertrigo, impetigo, and scabies). Initially considered as atopic dermatitis, due to the persistence of the lesions and resistance to therapy, a cutaneous biopsy was performed, revealing parakeratotic hyperkeratosis, spongiosis, and very mild lymphocytic exocytosis. In the dermis, a discrete lymphohistiocytic infiltrate with some eosinophils was observed. The blood tests, including a complete blood count and lymphocyte subset analysis, revealed lymphopenia with predominantly T CD8⁺ lymphocytes, eosinophilia (maximum 15 000/μL), and persistently elevated levels of IgE (maximum 13 320/μL). Given this picture, the diagnostic hypotheses formulated were autosomal dominant hyper-IgE syndrome (AD-HIES), Netherton syndrome, and peeling skin syndrome. These diagnoses were excluded as no mutations were found in *STAT3*, *SPINK5*, and *CDSN* mutations, respectively.

Over the following years, she had growth delay, with weight and height in the 10th percentile, and developed abnormalities such as



FIGURE 1 Photographs of the patient by the age of 2 y and 9 mo. Multiple erythematous patches can be seen

generalized lymphadenopathy and dental caries. She was repeatedly hospitalized due to infections, such as bacterial pneumonia, pyelonephritis, and varicella. At age 7, she presented to the emergency department with a sudden onset of right hemiparesis and gait imbalance. She was diagnosed with left lenticulocapsular ischemic stroke in the context of varicella-zoster virus induced vasculopathy, after isolation of the agent in the cerebrospinal fluid by polymerase chain reaction. Recovery was complete, with no permanent neurologic sequelae.

During these years, many treatments were tried, such as acitretin (0.5 mg/kg/d, stopped after 7 months due to gastrointestinal intolerance), narrowband UVB phototherapy (12 sessions with marginal improvement), cyclosporine 3 mg/kg/d (for 4 months, without benefit), and IV immunoglobulin (2 g/kg every 3 weeks), with a slight clinical benefit and maintained until the age of 8.

Given the strong clinical suspicion of hyper-IgE syndrome, due to persistently elevated IgE levels, mutations in the *DOCK8* gene were searched, which revealing a homozygous deletion in exons 1 to 4 [c.(?-112)(404+1_405-1)del(p.?)], diagnostic of AR-HIES.

At age 8, she was submitted to a haploidentical hematopoietic stem cell transplant from the mother, depleted in alpha/beta and CD19 T cells, after a conditioning regimen with treosulfan, fludarabine, thiotepa, antithymocyte globulin, and rituximab. The procedure went without complications, and the patient had an excellent recovery both clinically and analytically (Table 1), with complete donor chimerism 6 months after the transplant.

Two years after transplantation, the patient remains stable without immunosuppressive medications, without relevant systemic infections, with complete remission of the cutaneous manifestations, and with resumption of normal growth (Figure 2).

TABLE 1 Laboratory values, before and 6 months after transplant

	Pre-transplant	Post-transplant
Leukocytes ($\times 10^3/\mu\text{L}$)	16.11	4.8
Neutrophils (%)	29.0	78.2
Lymphocytes (%)	12.0	13.1
Monocytes (%)	6.0	5.6
Eosinophils (%)	53.0	2.7
Basophils (%)	0.0	0.3
T-cell immunophenotype		
CD3 (%)	46.99	58.64
CD3 ($/\text{mm}^3$)	908	370
CD4 (%)	30.73	30.43
CD4 ($/\text{mm}^3$)	594	192
CD8 (%)	14.09	26.85
CD8 ($/\text{mm}^3$)	272	269
B-cell immunophenotype		
CD19 (%)	28.13	25.78
CD19 ($/\text{mm}^3$)	156	163
IgE (KU/L)	8030	1063

3 | DISCUSSION

DOCK8 is a 190 kDa protein expressed primarily in hematopoietic tissue, where it plays a key role in the innate and adaptive immune response through the reorganization of the actin cytoskeleton. This reorganization is necessary for processes such as mobilization and

FIGURE 2 Photographs of the patient by the age of 9 (9 mo after the transplant). Complete remission of skin findings



homing of hematopoietic cells and activation of lymphocytes. It participates in the migration of dendritic cells from the skin to the lymph nodes and in the accumulation of adhesion molecules and cytotoxic granules in the immunologic synapses. Its deficit contributes to the decrease in survival of B, T, and NK cells (which may explain the lymphopenia of the patient) and the production of antibodies. DOCK8 mediates the translocation of STAT3 to the nucleus and the transcription of STAT3-dependent genes, which may explain the clinical overlap between AD-HIES and AR-HIES.¹

AR-HIES results from a homozygous mutation in the DOCK8 gene, located on chromosome 9. It usually presents in the first months of life with eczema, recurrent infections, atopy, and marked and persistent IgE elevation. The most distinctive manifestation is the predisposition to viral skin infections, which are usually extensive, recurrent, and refractory to therapy. The viruses most often implicated are herpes simplex virus, human papillomavirus, molluscum contagiosum virus, and varicella-zoster virus.² In our case, the viral manifestations were limited to an episode of varicella, complicated by central nervous system vasculitis manifested in the form of a stroke. AR-HIES is also associated with other infections, such as upper and lower respiratory infections, otitis, mastoiditis, and sinusitis. Unlike AD-HIES, pneumonias are not often caused by *Staphylococcus aureus*, but rather by a broad spectrum of gram-positive and gram-negative bacteria and fungi.³ *Candida* infections are common in both syndromes, but more in AD-HIES, due to the more marked defect in Th17 response.⁴ AR-HIES is also associated with gastrointestinal tract infections, such as *Salmonella* and giardiasis.³

Atopy usually manifests in the form of asthma and food and environmental allergies, which are often severe, and sometimes in the form of anaphylaxis. It results from a shift to a Th2 response, which can explain the eosinophilia and IgE elevation.⁵ In addition to atopy and susceptibility to infections, AR-HIES is also associated with a higher incidence of neoplasms in childhood and adolescence, such as human papillomavirus-induced squamous cell carcinomas, and

Epstein-Barr virus-induced cutaneous lymphomas. Together with systemic infections, these manifestations contribute to a significant reduction in the survival of these patients, with a survival of only 37% by the age of 30.⁶ Other than this typical clinical phenotype, DOCK8-deficient patients can also present in other ways such as recurrent infections with mild eczema, severe molluscum contagiosum infection, epidermodysplasia verruciformis, and Epstein-Barr virus-positive lymphomatoid granulomatosis. Intrafamilial variability has occasionally been reported.⁷ The diagnosis of AR-HIES can be easily missed in the presence of severe atopic dermatitis. Susceptibility to infections, extremely high levels of IgE, and lymphopenia should lead to the search for alternative diagnoses.⁴ In AD-HIES (Job's syndrome), the phenotype may be slightly different. In AD-HIES, facial dysmorphism, skeletal and dental abnormalities, and pneumatocoles are usually present, eczema, and atopic manifestations are less frequent, as are recurrent viral infections. The increased incidence of cutaneous malignant neoplasms is also absent in AD-HIES.⁵

Treatment is difficult and often unsatisfactory. The use of antiseptics and antibiotics can reduce the colonization of *S aureus* and reduce the severity of eczema. Topical corticosteroids and calcineurin inhibitors may also be useful to improve the dermatitis but may exacerbate skin infections. The use of antivirals may be useful in cases of herpes virus or varicella virus infections. The treatment of molluscum contagiosum and viral warts is difficult, given the extent of disease and high rate of relapse. Some patients may benefit from IV immunoglobulin, which reduces the incidence of sinopulmonary infections. Phototherapy may be attempted, but the results are unsatisfactory and may further increase the risk of cutaneous neoplasms. Photoprotection measures should be encouraged, as should regular full body examination.⁴ Hematopoietic stem cell transplantation is the only potentially curative treatment. The first reports of successful transplantation were published in 2010⁸ and since then a few others have been described, with variable success.⁶ The largest cohort of transplanted DOCK8-deficient patients to date was recently published

by Aydin et al.⁹ It included 81 patients from 22 centers, with a median age of 9.7 years. The procedure was generally well tolerated. Severe acute or chronic graft-vs-host disease developed in 11% and 10% of the patients, respectively. After a median follow-up of 26 months, 68 (84%) patients were alive. Causes of death were infections (n = 5), graft-vs-host disease (5), multiorgan failure (2), and preexistent lymphoma (1). After HSCT, there is often a complete resolution of eczema and recalcitrant viral infections. Bacterial infections including skin boils, pneumonia, and otitis media may continue to develop, although less frequently. Food allergies resolve post-HSCT in the vast majority of patients. While elevated eosinophil counts consistently decline post-HSCT, total serum IgE may remain elevated in some patients, despite complete donor chimerism.¹⁰ It remains to be clarified whether the transplantation prevents the appearance of neoplasms, given the expression of the mutated protein in tissues other than the hematopoietic² and whether HSCT is the recommended treatment for all patients, regardless of clinical presentation.

The association of refractory skin lesions and allergic manifestations should raise concerns and lead to further investigation, as multiple conditions may present with these findings. The approach to the patient should be carried out by a multidisciplinary team, where the dermatologist plays a fundamental role in the diagnosis and management of this condition.

INFORMED CONSENT

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images. A copy of the written consent is available for review on request.

ETHICAL APPROVAL

The case is exempt from ethical approval in this institution.

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