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CASE REPORT

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Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked: IPEX syndrome in pediatrics

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ABSTRACT

Immune dysregulation, polyendocrinopathy, X-linked enteropathy (IPEX) is a rare genodermatosis associating dermatitis, enteropathy, type 1 diabetes, thyroiditis, hemolytic anemia and thrombocytopenia. It is an X-linked recessive disease affecting regulatory T lymphocytes. It is diagnosed in early childhood and can be quickly fatal. Malabsorption and associated problems cause affected individuals to die early in their lives. IPEX is caused by mutations in the FOXP3 gene on X chromosome, which encodes a DNA-binding protein required for regulatory T cell development. Treatment choices are restricted and primarily rely on the combination of immunosuppressive medicines such as prednisolone, tacrolimus, or sirolimus, or, when possible, hematopoietic stem cell transplantation. Here we present this pathology in a 3-year-old boy who received an allogeneic bone marrow transplant from an HLA-identical family member.

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1. INTRODUCTION

IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) is a recessive early childhood illness. Symptoms of the condition typically show in early childhood and include persistent diarrhea, ichthyosiform dermatitis, insulin-dependent diabetes, thyroiditis, and hemolytic anemia [1,2].

More than 70 FOXP3 mutations related with IPEX syndrome have been identified in the literature ; however, the association between genotype and phenotype remains unclear. Similar genetics can produce distinct phenotypes; severe and mild versions of IPEX syndrome have been reported in children from the same family. IPEX syndrome symptoms are associated with FOXP3 genetic alterations, including nonsense variations, missense variants, minor in-frame deletions or insertions of amino acids, and splicing site variants [3,4].

Skin manifestations are common in IPEX. Patients experienced mild enteropathy and most cases are associated with other autoimmune diseases - autoimmune hemolytic anemia, neutropenia and/or tubular nephropathy [5].

2. CASE REPORT

We present this case of a three-year-old child admitted for the management and investigation of refractory anemia. He was born into a second degree consanguineous marriage; we find two deaths for the same symptoms: a sister died at the age of twenty months from anemia and ichthyosis, and a brother died at the age of eleven months. This infant is being monitored for insulin-dependent diabetes, which was discovered at the age of 2.5 months and was associated with a skin rash described as generalized eczema. He has been on corticosteroids, topicals,

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and emollients from the age of two months, and he is intolerant to protein cow's milk under an exclusive regime. The child was pale, without hemorrhagic syndrome, and presented a generalized exfoliative skin rash with bubbles of different ages, most of which were ruptured (Figures 1,2) stage I mucositis lesions, multiple cervical, axillary and inguinal lymphadenopathy between 1.5 and 2 cm in diameter, and delayed growth with a weight of 8 kg (< - 2 SD) and a height of 73 cm (< - 3 SD).

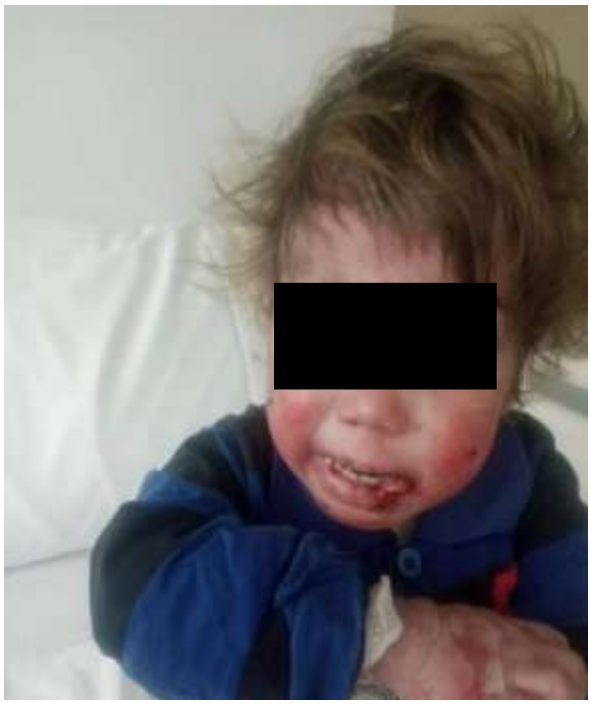

Figure 1. Lesions of the face and mucous membranes before bone marrow transplantation

A biological evaluation reveals a normocytic normochromic anemia at 5g/dL with a reticulocyte level of 300,000/mm^3, a leukocytosis of 16,000/mm^3 with a neutrophil predominance, an LDH level of 1641, a ferritinemia of 721, and a haptoglobin level of 0.20 g/L. The blood smear showed polynucleosis hyperleukocytosis with dacrocytes and shredded red blood cells, but no suspicious cells.

Given these clinical symptoms, which included generalized exfoliative skin damage, hemolytic anemia, insulin-dependent diabetes, obvious low body weight, and allergy symptoms, the diagnosis of primary immunodeficiency was made, and an immunological study was conducted in this direction. TCD 4+ lymphopenia without reversal of the CDU/CDP ratio, decrease in naïve T lymphocytes, and expansion of memory clones with moderate increase in LTCD 3+ TCR 2 α B+ CDU- CD8-. There was also hyper IgE with hypereosinophilia, a significant increase in IgG and IgA, particularly anti-red blood cell IgG and a slight BCD19T lymphopenia, as well as an increase in B-switched lymphocytes (CD27+IgD-) and plasma blasts (IGM-CD38++). The direct coombs was positive, and this relationship corresponded to an IPEX or IPEX-like. Given the frequent association with enteropathy, we performed an esophagogastroduodenal fibroscopy with biopsies, which revealed no abnormalities.

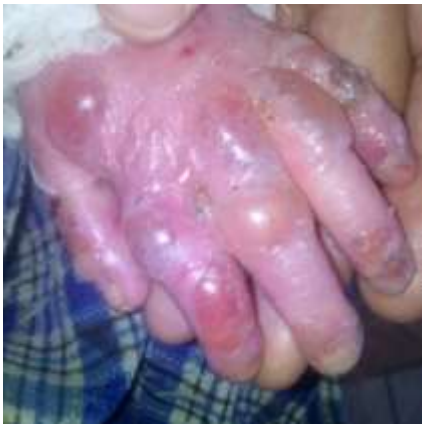

Figure 2. bullous lesions

Unfortunately, genetic testing could not be performed in this case, but the patient's phenotype, which included autoimmune disorders, abnormal laboratory tests, and a family history, strongly supported the diagnosis of IPEX syndrome.

The child was placed on corticosteroid therapy in accordance with the High Authority of Health's (HAS 2017) scheme for his autoimmune hemolytic anemia. It was difficult for us to control his diabetes due to his pathology, corticosteroid therapy, and the food allergy that he presented; however, consulting with a dietician was extremely beneficial in managing this imbalance with the exclusion of gluten and potentially food allergens. The second therapeutic aspect concerned the skin damage caused by the shredded losses. We used topical vaseline and emollients in conjunction with local corticosteroid therapy and mummification. The results were better than his condition at admission, but not spectacular, so we had to add an immunosuppressant like methotrexate.

He responded well hematologically, with an increase in hemoglobin and a decrease in reticulocytes. He was discharged after a month and a half of admission, and he later received a bone marrow transplant.

After one year on immunosuppressants, the child is doing well; he no longer has hemolytic anemia or skin damage (figure 3), and his diabetes is under control.

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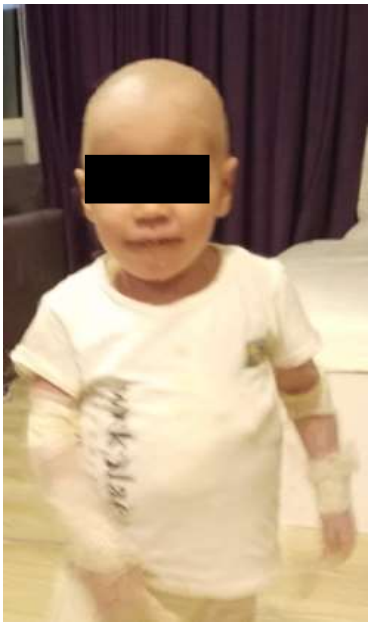

Figure 3. Lesions disappear after bone marrow transplantation.

3. DISCUSSION

IPEX syndrome was first described in the early 1980s as a life-threatening systemic autoimmunity disease in male children [6]. Approximately 50% of patients with an IPEX-like clinical phenotype have mutations in FOXP3 [7]. Atypical clinical manifestations of IPEX may imply an underestimation of the actual morbidity. Similar genetics do not always result in similar phenotypes for disease presentation [8]. IPEX syndrome has a poor prognosis without adequate immunosuppression and intense supportive care. Haematopoietic stem cell transplantation is the only possible cure. It appears that the earlier the HSCT is performed, the greater the chance of treatment before long-term end organ damage has occurred. Our patient had a severe presentation on the skin (frequent superinfections) and on the hematological level, as well as the balance of his diabetes and food sensitivities.

Other atypical and uncommon symptoms may appear during IPEX syndrome [9-11]. Certain tests are routinely requested when there is a suspicion of an IPEX; these include a blood count with phenotype and weight dosage of immunoglobulin (Ig), glycated hemoglobin, fasting blood sugar, and renal and hepatic function. The mentioned laboratory tests may initially appear normal in IPEX patients. Serum IgG and IgM levels are typically normal or lower in cases of protein-losing enteropathy. [12] IPEX patients frequently exhibit eosinophilia, cytopenias, or an increase in IgE and IgA levels [13]. Our patient had hyper eosinophilia and hyper IgE, which explained his polysensitivity to several foods.

Tissue infiltration by lymphocytes, serum autoantibodies, and FOXP3 mutations expressed in lymphocytes in IPEX patients strongly suggest that the pathogenesis of the disease involves the immune system, prompting the use of "an immunosuppressive treatment for this condition." Without bone marrow transplantation (BMT), the prognosis is poor because IPEX is usually fatal within the first two years of life. BMT appears to be the only curative treatment for this disease. The estimated overall survival rate for transplant patients after 15 years is 73.2% [14]. Our patient's bone marrow transplant was followed by complete remission. Surprisingly, the conditioning regimen effectively controlled the majority of the disease's clinical and biological manifestations, including hyperglycemia and dermatitis. The transplant most likely facilitated a prolonged remission, and the patient remained in clinical and biological remission for a year after the bone marrow transplant, without inducing the irreversibility of his insulin-dependent diabetes; this is significant because a lack of Pancreatic islets has been discovered at autopsy in several patients with IPEX [14,15].

4. CONCLUSION

IPEX syndrome is a rare but often fatal multisystemic autoimmune disease with a variety of phenotypes. It is critical to consider it as a diagnosis in patients suffering from multiple autoimmune/inflammatory phenomena, regardless of whether these manifestations go beyond the classic clinical description of the syndrome or how they appear.

Conflict of interest statement: None to declare

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