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CASO CLÍNICO

Immune Dysregulation, Polyendocrinopathy and Enteropathy X-Linked Syndrome with Neonatal Onset: A Case Report

Síndrome de Disfunção Imune, Poliendocrinopatia e Enteropatia Ligada ao X com Início Neonatal: Descrição de Caso

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ABSTRACT

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare monogenic autoimmune disorder caused by mutations in the *FOXP3* gene. It typically presents in early infancy with severe multisystem autoimmunity. We report the case of a male preterm infant, born at 30 weeks' gestation, who developed enteropathy, eczema, eosinophilia, and transfusion-dependent cytopenias. Recurrent infections and a desquamative rash raised suspicion of an inborn error of immunity. Immunological studies revealed absent *FOXP3* expression, and genetic testing confirmed a hemizygous pathogenic variant in *FOXP3* (c.1076C>T), establishing the diagnosis. Immunosuppressive therapy with corticosteroids and sirolimus was initiated, and the patient was referred for hematopoietic stem cell transplantation. From the cases reported in the literature, this is the first neonatal onset case of IPEX reported in Portugal. This case highlights the importance of suspecting IPEX syndrome in infants with early-onset autoimmunity and immunodeficiency, enabling timely diagnosis and improved outcomes in this life-threatening condition.
Keywords: Genetic Diseases, X-Linked/genetics; Immune System Diseases/congenital; Immune System Diseases/genetics; Infant, Newborn; Polyendocrinopathies, Autoimmune/genetics

RESUMO

A síndrome desregulação imunológica, poliendocrinopatia e enteropatia ligada ao X (IPEX) é uma doença autoimune monogénica rara, causada por mutações no gene *FOXP3*. Apresenta-se tipicamente na infância precoce com autoimunidade multissistémica grave. Descrevemos o caso de um recém-nascido pré-termo do sexo masculino, nascido às 30 semanas de gestação, com enteropatia, eczema, eosinofilia e citopenias dependentes de transfusão. Infeções recorrentes e um exantema descamativo levaram à suspeita de uma imunodeficiência. Os estudos imunológicos revelaram ausência de expressão *FOXP3* e o estudo genético revelou uma variante patogénica hemizigótica no gene *FOXP3* (c.1076C>T), estabelecendo o diagnóstico. Iniciou-se imunossupressão com corticoterapia e sirolimus, e o doente foi referenciado para transplante hematopoiético. Que saibamos, este é o primeiro caso de síndrome IPEX com início tão precoce descrito em Portugal. Este caso reforça a importância de uma suspeita precoce da síndrome IPEX em lactentes com autoimunidade precoce e sinais de imunodeficiência, permitindo diagnóstico atempado e melhor prognóstico.
Palavras-chave: Doenças Genéticas Ligadas ao Cromossomo X; Doenças do Sistema Imunitário/congénito; Doenças do Sistema Imunitário/genética; Poliendocrinopatias Autoimunes/genética; Recém-Nascido

INTRODUCTION

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare monogenic autoimmune disorder first described by Powell *et al* in 1982, with fewer than 400 cases reported worldwide.[1,2] Neonatal-onset presentations are exceptional.[2] Beyond the classical triad of enteropathy, endocrinopathy, and dermatitis, IPEX may present with incomplete or atypical phenotypes, which can be isolated or of later onset.[3] The differential diagnosis includes combined immunodeficiencies and autoimmune polyglandular syndromes, underscoring its clinical heterogeneity.[3]

It results from mutations in the *FOXP3* gene on the X chromosome, which encodes a transcription factor essential for regulatory T-cell (Treg) function.[1-4] Treg maintain immune tolerance to self-antigens, and their dysfunction in IPEX leads to immune dysregulation and uncontrolled autoimmunity.[3] It should be considered in male infants with early-onset autoimmune manifestations.[4]

Laboratory findings often include peripheral eosinophilia, elevated serum IgE and IgA, and autoantibodies, although these features are nonspecific.[2] Flow cytometry may reveal reduced or absent *FOXP3* expression and the diagnosis is confirmed by identifying a pathogenic *FOXP3* variant.[2] Timely recognition is crucial, as hematopoietic stem cell transplantation (HSCT) remains the only curative treatment.[2] Immunosuppressive therapy can be used to control autoimmune manifestations and stabilize the patient as a bridge to HSCT, although efficacy is often partial and limited by infectious complications.[5] Gene therapy is an emerging field with promising early data.[2]

We report, to the best of our knowledge, the earliest-onset case of IPEX described in Portugal, emphasizing diagnostic challenges and the importance of timely recognition.

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CASE REPORT

A male preterm infant was born at 30 + 6 weeks of gestation by emergency cesarean section due to placental abruption. Birth weight was 1665 g, length 38.4 cm, and head circumference 28.6 cm (68th, 16th and 54th of Fenton curves, respectively). He was the third child of a non-consanguineous couple, with two healthy sisters. The maternal history included two spontaneous abortions and multiple miscarriages of male fetuses in the extended family.

At 16 days of life, he was transferred to a tertiary center after three days of worsening bloody diarrhea, metabolic acidosis, dehydration, and poor weight gain. Since birth, he had been receiving fortified breast milk. Cow's milk protein allergy was suspected, supported by marked eosinophilia (4480/µL), elevated total IgE (6538 U/mL), and positive specific IgE to milk proteins. Infectious causes were excluded (negative stool and blood cultures and stool *Clostridium difficile* toxin tests). Despite nutritional interventions (semi-elemental, elemental formulas, and exclusive parenteral nutrition), diarrhea and failure to thrive persisted.

Laboratory studies showed anemia with a positive direct Coombs test and thrombocytopenia, requiring multiple erythrocyte and platelet transfusions. Given maternal A Rh-positive and infant AB Rh-positive status, hemolytic disease due to blood group incompatibility was excluded. Despite confirmed cow's milk protein allergy, the severity of enteropathy, marked eosinophilia, elevated IgE, and transfusion-dependent cytopenias raised suspicion of an inborn error of immunity, particularly combined T- and/or B-cell immunodeficiencies or other IPEX-like disorders.

At 28 days of life, immunological studies showed normal lymphocyte subset counts and mildly elevated immunoglobulins [IgA 39 mg/dL (1 - 29), IgM 97 mg/dL (12 - 86), IgG 1305 mg/dL (108 - 702)], prompting whole exome sequencing (WES) to be performed.

On day 40, the patient developed a generalized desquamative exanthem and alopecia (Fig. 1), partially responsive to antihistamines, topical corticosteroids, and systemic prednisolone (1 mg/kg/day). He also experienced three episodes of sepsis—β-lactamase-producing *Klebsiella pneumoniae* (day 31, 69) and methicillin-sensitive *Staphylococcus aureus* (day 56).

He required invasive ventilation (FiO_2 up to 100%) and vasoactive support during sepsis episodes. Acute kidney injury and hypoalbuminemia secondary to enteropathy were resolved with fluids and albumin. Neurological assessment, including cranial ultrasound, was normal.

On day 55, flow cytometry revealed markedly reduced *FOXP3* expression, and WES confirmed a hemizygous missense *FOXP3* variant (c.1076C>T), establishing the diagnosis of IPEX. Endocrinological evaluation was unremarkable, with normal thyroid function, fasting glucose, HbA1c, and negative anti-thyroid and anti-pancreatic autoantibodies.

Following the diagnosis, intravenous prednisolone (1 mg/kg/day) was initiated, leading to improvement of enteropathy and dermatitis. Due to infectious complications, corticosteroids were paused for six days and restarted with sirolimus (1 mg/m^2), achieving sustained response. After identification of a fully HLA-matched sibling donor (12/12), he was transferred on day 85 to an international HSCT unit.

DISCUSSION

The IPEX syndrome presents with broad phenotypic variability beyond the classical triad, including hematologic, hepatic, renal, and dermatologic autoimmune manifestations,[3,4] with Coombs-positive anemia and neonatal-onset desquamative rash with alopecia increasingly recognized among its features.[2,4] In this case, prematurity was not considered causal, as IPEX does not predispose to preterm birth. Rather, the neonatal presentation of enteropathy, eosinophilia, hyper IgE, eczema, alopecia, and autoimmune cytopenias reflected early immune dysregulation. While this variant has been linked to classic presentations, genotype-phenotype correlation remains variable, reinforcing the need of a comprehensive clinical assessment.

The differential diagnosis included severe food protein-induced enteropathy, autoimmune cytopenias, and combined immunodeficiencies or other IPEX-like disorders, given the association of enteropathy, eosinophilia, hyper-IgE, and Coombs-positive anemia. This case illustrates the diagnostic approach to severe neonatal enteropathy: after exclusion of infectious causes and common causes, targeted immunologic studies were performed. Flow cytometry assessing Treg and *FOXP3* sequencing were decisive, and the maternal history of recurrent male miscarriages further supported an X-linked inherited pattern. While endoscopy or intestinal biopsies may assist in excluding other etiologies, early genetic testing should be prioritized when systemic autoimmunity is present.

Without treatment, IPEX often results in death within the first two years of life.[5] Corticosteroids and mTOR inhibitors – particularly sirolimus, due to its greater efficacy – are commonly used to control symptoms and stabilize patients as a bridge to HSCT.[5] Despite these measures, the patient developed multiple complications requiring intensive supportive

care. Even though the post-transplant result is not yet available, these interventions were crucial for stabilization and improved HSCT outcomes, as the extent of organ involvement at transplantation is a key prognostic factor, with better survival in patients achieving stabilization before HSCT.[2] Prompt recognition and coordinated multidisciplinary management are therefore essential to optimize outcomes.

According to published reports, this represents, to the best of our knowledge, the earliest neonatal-onset IPEX case reported in Portugal, underscoring the importance of considering IPEX in male infants with severe neonatal enteropathy and immune dysregulation.

PREVIOUS AWARDS AND PRESENTATIONS

Part of this work was previously presented as a poster at the "*3.ª Reunião da Sociedade Portuguesa de Imunodeficiências Primárias – A Interface Imuno-Neurológica*".

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The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

JB: Literature review and writing of the manuscript.
MC, ADC, IG: Writing and critical review of the manuscript.
IE, SV: Critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Parental consent was obtained.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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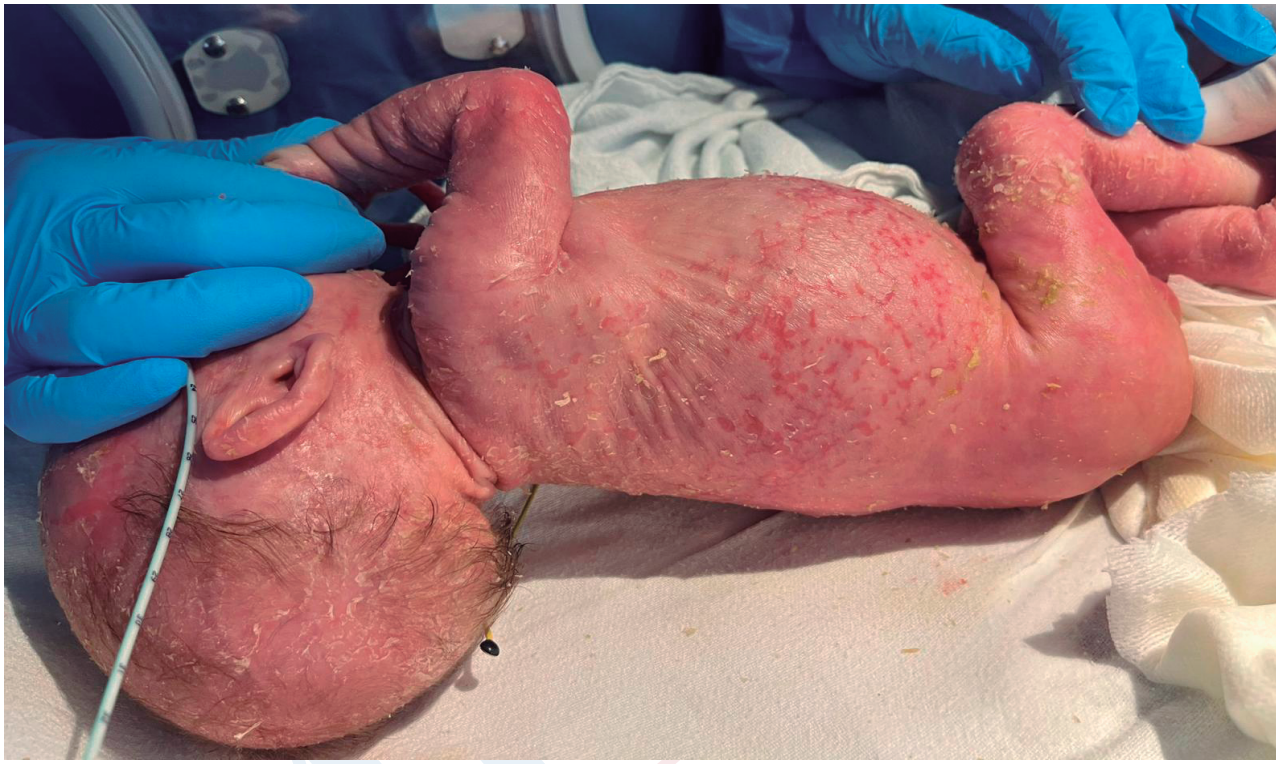

Figure 1 – Generalized desquamative exanthem and alopecia with onset on day 40 of life