

CASE REPORT

Cow's milk allergy non-responsive to amino acid-based formula? A successful transplanted patient with immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome

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Abstract

The wide variety of IPEX symptoms leads to diagnosis and treatment delay with fatal outcomes if left untreated before two first years of life. Cow's milk allergy non-responsive to amino acid-based formula must raise suspicion of this syndrome.

KEYWORDS

allergy and immunology, gastroenterology and hepatology, genetics, haematology, paediatrics and adolescent medicine

1 | INTRODUCTION

The Immune dysregulation, Polyendocrinopathy, Enteropathy, and X-linked (IPEX) syndrome is a rare primary immune regulatory disorder (PIRD). It is mainly characterized by severe enteropathy, polyendocrinopathy (most commonly early-onset insulin-dependent diabetes mellitus), and eczematous dermatitis. The IPEX syndrome (OMIM304790) is caused by hemizygous mutations in the Forkhead Box Protein 3 (FOXP3) gene.^{1,2}

FOXP3 is a master member of the forkhead transcription factor family expressed in CD4⁺ regulatory T cells (Tregs), a cell subset that plays an essential role in self-tolerance and immunological homeostasis.^{3,4}

Clinical manifestations typically begin in the first year of life with a broad clinical spectrum, including autoimmune cytopenia, hepatitis, glomerulonephritis, lymphadenopathy, splenomegaly, alopecia, arthritis, and lung disease. Cow's milk allergy (CMA) presenting as watery diarrhea is a major differential diagnosis of IPEX-associated

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enteropathy. Overlapping clinical manifestations between IPEX and CMA include eczema, failure to thrive, and high level of immunoglobulin E (IgE).⁵

Thus, the wide variety of IPEX symptoms leads to diagnosis and treatment delay with fatal outcomes if left untreated before two first years of life.⁶ Currently, the only curative therapy is allogeneic hematopoietic stem cell transplantation (HSCT).⁷ We aimed to present the first Peruvian case diagnosed with IPEX syndrome who received a successful HSCT.

2 | CASE REPORT

A two-month-old boy was admitted to the Emergency room with chronic diarrhea, failure to thrive, and sepsis. He was born healthy at term from non-consanguineous parents. No family history of primary immunodeficiency was reported, and he had an apparently healthy older sister. He underwent neonatal immunization according to the national program (Bacillus Calmette-Guerin and Anti-Hepatitis B) without adverse reactions. He received mixed feeding.

During the second week of life, he initiated vomits and watery diarrhea that progressively worsened. Then,

he presented with fever and diarrhea turned to up to 20 episodes per day. He was initially treated at a local hospital, where he received broad-spectrum antibiotics without improvement. Watery diarrhea turned to mucus without blood, fever persisted, and skin lesions appeared compatible with eczema.

Three weeks later, he was admitted to our hospital. Symptoms persisted, and he showed worsened eczema in the perioral region, hand palms, and back (Figure 1A). With the differential diagnosis of CMA, a hydrolysate formula was initiated (Aminomed[®]) due to high levels of IgE and positive specific IgE for milk protein (Table 1). However, diarrhea remained with the same characteristics after two weeks of enteral nutrition. Consequently, parenteral nutrition was started due to malnutrition and failure to thrive. Antibiotics course started again due to central catheter-related *Staphylococcus aureus* sepsis.

Other causes of chronic diarrhea were ruled out, including drug-induced, infectious, and metabolic. Upon laboratory investigations (Table 1), complete blood count, and differentials initially revealed moderate anemia, complicated with thrombocytopenia. Liver tests confirmed malnutrition with severely diminished albumin levels (1.73 g/dl), Enzymatic liver tests and kidney function tests were within normal ranges.

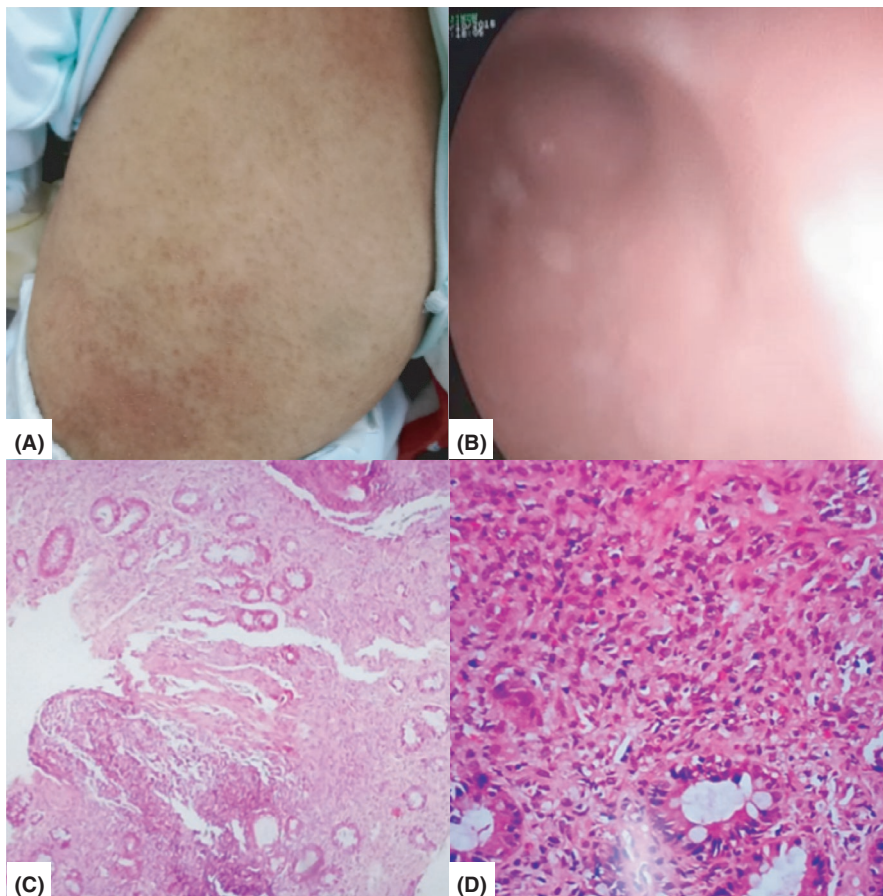


FIGURE 1 (A) Skin lesions at admission consisting of eczema in the patient's back. (B) Colonoscopy showed rectosigmoid mucosa without folds, atrophic, and edematous with mucoid secretion. (C) Small bowel through microscope 100X revealed severe architectural alteration, mild-to-moderate lymphoplasmacytic infiltrate and mild cryptitis. (D) and intraepithelial lymphocytes, 100 eosinophils per High Power Field and fibrosis of lamina propria

TABLE 1 Laboratory parameters of the patient

	Admission	Follow-up	After HSCT	Normal range (2–5 months)
Hematology				
White blood cells (10 ⁶ /ml)	5.760	7.550	5.380	6–17.5
Neutrophils (10 ⁶ /ml)	1.71	2.98	2.030	1–8.5
Lymphocytes (10 ⁶ /ml)	3.06	3.04	2.77	4–13.5
Monocytes (10 ⁶ /ml)	0.96	1.36	0.23	0.2–1.0
Eosinophils (10 ⁶ /ml)	0.01	0.16	0.15	<0.5
Hemoglobin (mmol/l)	9.4	7.6	12.8	10.1–12.9
Platelets (10 ⁶ /ml)	325	10	136	150–300
Immunology, humoral				
IgG (g/L)	9.03	–	5.92	3.3–6.98
IgA (g/L)	0.68	–	0.45	4–27
IgM (g/L)	0.16	–	1	25–52
IgE (g/L)	>2000	–	–	0–49
Lymphocyte counts (cells/μl)				
CD3 ⁺ T cells	3160	–	2216	2300–6500
CD3 ⁺ CD4 ⁺ T cells	841	–	1412	1500–5000
CD3 ⁺ CD8 ⁺ T cells	2449	–	662	500–1600
CD4/CD8 ratio	2.91	–	2.13	1.7–3.9
CD3 [−] CD16 ⁺ CD56 ⁺	924	–	74.79	200–1400
CD19 ⁺ B cells	202	–	445	600–1900

Abbreviations: hematopoietic stem cell transplantation; HSCT; Ig, immunoglobulin.

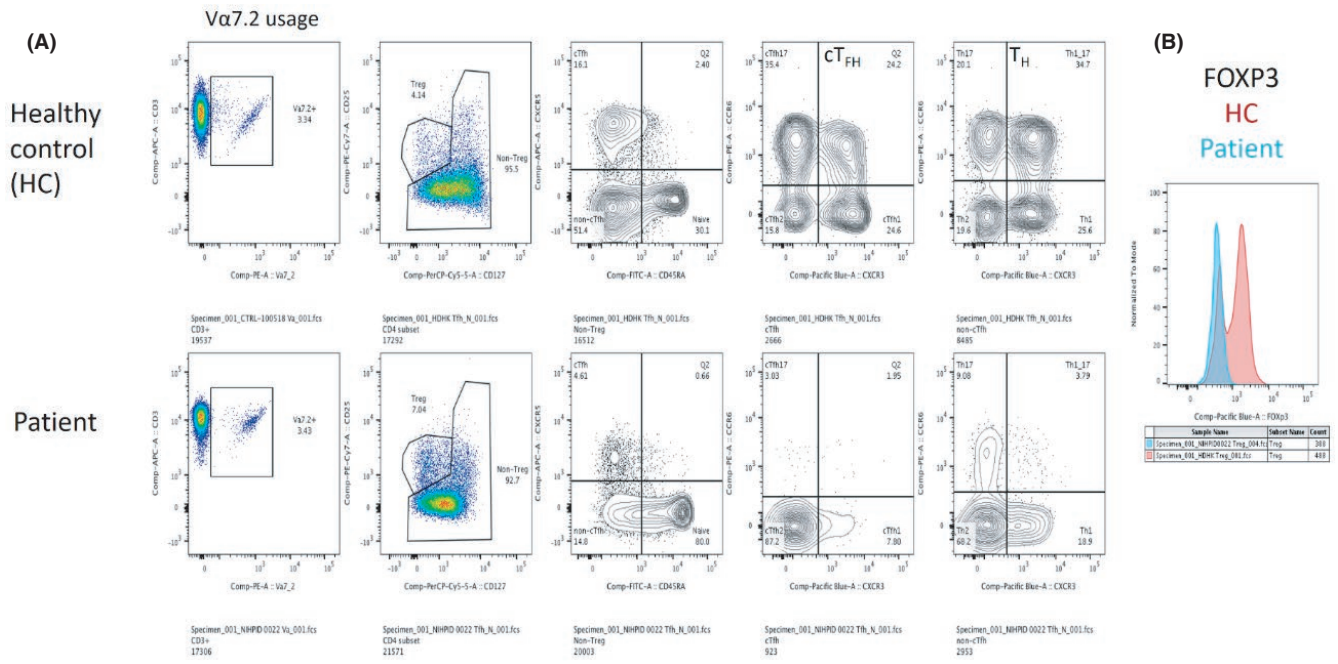


FIGURE 2 (A) Immunophenotyping of T-lymphocyte subsets of the patient (upper panel) compared to a healthy control (lower panel) showing Th2 predominance. (B) Assessment of expression of intracellular forkhead box protein 3 (FOXP3) showing absent of expression in the patient compared with the control

The immunological tests showed normal serum IgG, IgA, and IgM and extremely high IgE levels, including specific IgE for cow's milk (18.2 KUI/L - class IV by chemiluminescence) and sensitized to several allergens like egg, chocolate, orange, strawberry, and others (class I). Hormonal tests showed normal function of the pancreas, diminished TSH and elevated anti peroxidase antibody. Furthermore, he showed diminished C4. Functional and microbiological stool tests (bacterial, viral, and parasitic) were repeatedly normal. Basic lymphocyte population analysis by flow cytometry, available at our hospital, showed low numbers of B (CD19+) with normal T (CD3+) cell and NK (CD56+CD16+) cell numbers.

Unfortunately, additional testing such as anti-enterocyte autoantibodies (anti-villin or anti-harmonin) and autoantibodies associated with diabetes are not available in our hospital. Neither functional tests were performed.

When the required equipment was available at the age of four months, a combined gastro-duodenoscopy and colonoscopy were performed (Figure 1B-D). Duodenal mucosa showed severe architectural alteration, mild-to-moderate lymphoplasmacytic infiltrate and mild cryptitis. There were also observed intraepithelial lymphocytes, 100 eosinophils per High Power Field (HPF) and fibrosis of lamina propria. 2. Stomach presented mild chronic gastritis with mild focal activity, no intestinal metaplasia, or glandular atrophy, presence of up to 5 eosinophils per HPF and lymphoid accumulation. Colonic mucosa showed distortion of the architecture, mucinous damage,

and glandular atrophy. Furthermore, there were fibrosis associated with chronic inflammation and presence of 10–30 eosinophils per HPF. Immunohistochemical study evidenced that the lymphocytic infiltrate was predominantly TCD3+. Lymphocyte TCD4+ and TCD8+ had a similar distribution. Scattered plasma cells CD38+ were shown.

We had high suspicion on a primary immunodeficiency that could explain patient features summarized in early-onset diarrhea, fever, autoimmune features, and moderate eczema. Consequently, a blood sample was sent to the National Institute of Health (NIH) at Maryland (USA) for detailed immunophenotyping of the T-cells subsets. It revealed a predominantly Th2 population compared with healthy control. The percentage of Treg cells determined by CD25 and CD127 was normal, but the intracellular FOXP3 expression was absent compared to healthy control (Figure 2). FOXP3 full gene (NM_014009) sequencing performed by Sanger technique showed a hemizygous mutation c.1038C>G, p.I346 M (Figure 3) predicted to disrupt the Forkhead DNA-binding domain. His mother was found heterozygous for the mutation. Interestingly, this variant has not been reported previously.

Upon confirmation of IPEX syndrome, the patient received immunosuppressive therapy, consisting of corticosteroids (methylprednisolone pulses 18mg/m²/day per three days and continue with 3.18 mg/m²/day per three months while tapering) and oral tacrolimus (0.5 mg twice/day). He remained stable without resolution of symptoms until he was admitted for a humanitarian program to receive HSCT at Ospedale Pediatrico Bambino Gesù (Rome,

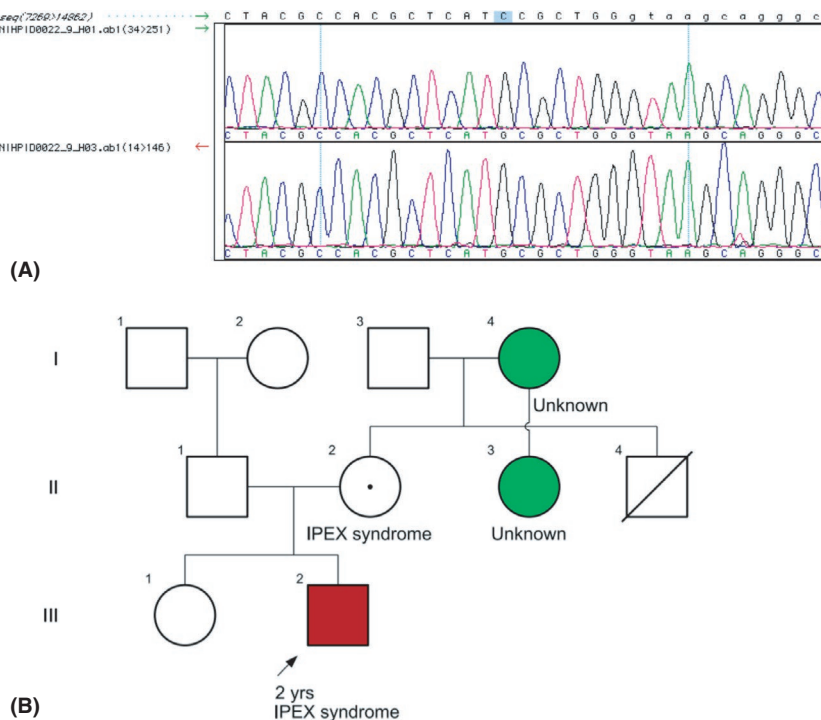


FIGURE 3 (A) Mutation c.1038C>G, p.I346 M in the forkhead box protein 3 (FOXP3) gene identified using Sanger sequencing. The index patient is hemizygous, and the mother is a heterozygous carrier (not shown). (B) Family pedigree, the mutation might have occurred as de novo change in the mother of the patient. However, she had a brother who died at birth without an explained reason. Consequently, the grandmother could also be a carrier. Arrow indicates index patient

Italy). At one year of age, the boy received bone marrow stem cells from her full-HLA-matched older sister. The transplant procedure was well tolerated without serious adverse reactions or graft-versus-host disease (GVHD).

Our patient is currently two years old without additional medication and resolution of diarrhea, eczema, and laboratory alterations (Table 1). He gained adequate weight and height without food restrictions. He was discharged with mixed chimerism of 48% cells of the donor (evaluated by 12 regions of short repeated tandem STR). Chimerism in subpopulations was 79% of CD3+ cells, 28% of CD14+ cells, 70% of CD56+ cells, and 50% CD19+ cells from the donor. He and his family are currently in Peru, patient is detailed evaluated periodically with close coordination between our hospital and Bambino Gesù Hospital.

3 | DISCUSSION

We present a Peruvian boy diagnosed with IPEX syndrome who received a successful HSCT. Our patient developed early-onset severe, intractable enteropathy manifesting as his main feature.

Since the first IPEX syndrome patient was described in 1981,⁸ nearly 300 individuals have been already diagnosed, and its prevalence has been estimated in 1 in 1.6 million people.^{9,10} IPEX syndrome belongs to the Primary Immunodeficiency Disease (PID) group of Diseases of Immune dysregulation.¹¹ It is caused by mutations in any of the four functional domains of the protein FOXP3, which affect the ability of the transcription factor to regulate gene expression in Treg cells,¹² including IL2RA (CD25) and CTLA4, and by acting as a transcriptional repressor.^{13,14} IPEX syndrome presents an X-linked recessive inheritance. It has been described previously that the clinical manifestations at onset are independent of the site of the mutations.¹⁵ Although only our patient and his mother were genetically studied, it remains suspicious about his maternal uncle, who died at birth without an explanation. Non-immune fetal hydrops has been described as a cause of early death in IPEX patients.¹⁶

Symptoms classically manifest with a triad of enteropathy, cutaneous involvement, and autoimmune disease. However, they can vary from one patient to another.¹⁷ The onset of clinical syndrome usually occurs during the first months of life, being the most common feature of watery diarrhea that could be mucoid or bloody, which histologically is characterized by villous atrophy and inflammation.¹⁸ This intractable diarrhea leads to severe malabsorption and failure to thrive, requiring nutritional support with total parenteral nutrition.⁷

Intractable diarrhea of Infancy (IDI) is a term used for patients with diarrhea longer than two weeks in the first two years of life and may require parenteral nutrition. IDI has a wide range of differential diagnoses considering different types of diarrhea, such as osmotic, fatty, watery, or secretory. The initial characteristics of diarrhea in our patient were classified in the secretory group.¹⁹ First, it was necessary to rule out infections. However, during the disease, diarrhea turned to bloody and mucoid supporting evidence of early-onset inflammatory bowel disease that includes autoimmune enteropathies caused by IPEX syndrome.²⁰ The differential diagnosis of IDI also includes eosinophilic gastroenteritis (EGE), a chronic gastrointestinal (GI) disease, which diagnosis is based in the presence of GI symptoms, histological demonstration of eosinophilic infiltration into the GI tract, and exclusion of other causes of tissue eosinophilia.²¹

The biopsy was fundamental to distinguish between normal histology (congenital lactase deficiency, congenital sodium diarrhea, neuroendocrine tumors), structural abnormalities (microvillus inclusion disease, integrin deficiency, and immunodeficiencies like IPEX syndrome) and eosinophilic enteropathies.^{19,21} Finally, our patient developed severe malnutrition fulfilling the criteria for diagnosis of Intestinal Failure of non-digestive etiology.²²

In this case, the association of IDI and skin lesion in a patient that had only fed with breast milk, and milk formula made considered the possibility of a food-sensitive enteropathy. Being classified as a case of CMA, our patient started elemental formula with initially partial response. The literature describes that IPEX syndrome diarrhea markedly worsens after switching from being breast-fed to regular formula and typically persists despite dietary exclusion.^{5,23}

Concerning other features, cutaneous manifestations usually consist of eczema, psoriasis, atopic or exfoliative dermatitis, which typically do not improve with usual medication and could facilitate bacterial entry contributing to severe infection that can exacerbate or complicate the existing clinical symptoms. Sepsis is considered one of the leading causes of death in this syndrome, and the most common organisms described are *Enterococcus* and *Staphylococcus* species.^{24,25} The endocrinopathies in IPEX are usually limited to the thyroid and pancreas. Thyroid compromise includes autoimmune thyroiditis that can lead to a hyperthyroid or hypothyroid state.²⁴ Our case showed low thyroid hormone levels without altering peripheral thyroid hormones.

The clinical features of our patient also resemble similar PIDs without Foxp3 abnormality. These are called IPEX-like syndromes that also belong to the Diseases of Immune dysregulation.¹¹ In IPEX-like individuals, autoimmunity results from various underlying monogenic

defects, including CD25/IL2RA, STAT5B, LRBA, and CTLA4. However, each defect is characterized by specific associated features, and respiratory tract infections, bronchiectasis, and organomegaly are more common.²⁵

Therapeutic approaches of IPEX syndrome are broad-spectrum supportive care, immunosuppressive therapy, and HSCT. Immunosuppressive treatment (eg, glucocorticoids, cyclosporine, rapamycin, rituximab, tacrolimus, azathioprine, and others) has been reported to only partially control the autoimmune manifestations.^{1,26} HSCT is currently the sole curative option for IPEX. However, severe comorbidities, including failure to thrive, repetitive infections, and organ damage, can complicate the outcomes. Thus, pretreatment organ impairment score in IPEX best predicts overall survival after HSCT.¹⁵

In the described case, immunosuppressive therapy consisted initially of corticosteroid that decreased the frequency and amount of diarrhea. We added tacrolimus as a combination therapy based on the use of Calcineurin inhibitors described in the literature and its availability in our hospital. However, the patient persistent severe malnourished and dependent on parenteral nutrition. We did not add other immunosuppressive agents to avoid adverse effects in our patient, weighing 3.5 Kg. Only after HSCT and a lengthy recovery period in Ospedale Pediatrico Bambino Gesù, he was able to eat, and his nutritional state has normalized.

Although the percentage of donor cells necessary to establish an adequate number of Treg cells is not firmly established, the post-HSCT patient can be cured with mixed chimerism due to the establishment of donor Treg cells are able to restore the immunological homeostasis.²⁷ At present, a new strategy for autologous HSCT and gene therapy utilizing a lentiviral vector to restore FoxP3 expression in murine transplant models and humanized mice engrafted has demonstrated preclinical efficacy.²⁸

Finally, this case gives us essential lessons according to early suspicious and timely management of PID. Severe diarrhea can start early in life in patients with severe combined immunodeficiency or IPEX; both of these PIDs are considered pediatric emergencies.²⁹ Food allergy suspicion leads to diagnosis delay in our case. However, we must be aware that allergic diseases can be a common component of a primary immune deficiency and can even be the presenting sign of certain specific PIDs. In other cases, it may have a syndromic association and comorbidities independent of PIDs.^{30,31}

In Peru, PID diagnosis and therapy are still challenging with limited laboratory resources and awareness. Consequently, we need multidisciplinary focus and international support to provide alternatives for good outcomes as in the reported patient.

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CONFLICTS OF INTEREST

The authors declare that this case report was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

LVE, CRV, RDS, JAB, and GAL have been involved in patient care regarding the initial diagnosis and follow-up after the HSCT. MB and FL performed the HSCT and its follow-up. All the authors have contributed to the draft of the manuscript and have approved the final version.

ETHICAL STATEMENT

Patient anonymity has been preserved in accordance with the principle of confidentiality.


CONSENT

The authors confirmed that patient consent has been signed and collected in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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