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Case Report: Eosinophilic gastritis with pyloric stenosis in immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

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Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare X-linked recessive immunodeficiency caused by mutations in the forkhead box protein 3 (*FOXP3*) gene. IPEX is characterized by the onset of intractable diarrhea, type 1 diabetes mellitus (T1DM), and eczema in the early stages of life. The typical clinic triad for IPEX is not always seen. Here, we report a 15-year-old male patient with atypical IPEX syndrome complicated with severe eosinophilic gastritis (EG) and pyloric stenosis. The patient had noticeable eczema during the first year of life and had a history of food allergies. At the age of 3 years, the patient was diagnosed with EG, *Helicobacter pylori* (HP) infection, pyloric stenosis with recurrent vomiting, and failure to thrive. The patient did not respond to long-term symptomatic treatments in the following years, including methylprednisolone, proton pump inhibitors (PPI), L-glutamine and sodium gualenate granules, anti-HP therapy, and balloon dilation. At the age of 12 years, the patient received surgical interventions, including a laparoscopic jejunostomy feeding tube placement, gastrojejunal anastomosis bypass, and jejunal-jejunal end-to-side anastomosis. Intractable diarrhea and T1DM were not present in the patient. At the age of 14 years, the patient was diagnosed with IPEX syndrome due to a c.748–750del (p.Lys250del) mutation in the leucine zipper domain of the FOXP3 protein. The patient underwent matched sibling peripheral blood hematopoietic stem cell transplantation (HSCT) and showed good evolution after 3 months of HSCT. In summary, this case report provides information of unusual gastrointestinal findings in

Abbreviations

IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; T1DM, type 1 diabetes mellitus; FOXP3, forkhead box protein 3; Treg, regulatory T; NGS, next-generation sequencing; EG, eosinophilic gastritis; HP, *Helicobacter pylori*; EGD, esophagogastrroduodenoscopy; IgG, immunoglobulin G; PPI, proton pump inhibitors; CD, Crohn's disease; HSCT, hematopoietic stem cell transplantation; WES, whole-exome sequencing; GvHD, graft-versus-host disease; STR, short tandem repeat; BMI, body mass index; HPF, high power field.

IPEX syndrome and highlights the need for increased awareness and early diagnosis of IPEX syndrome, which is vital for improving the patient's outcome.

KEYWORDS

IPEX, FOXP3, eosinophilic gastritis, pyloric stenosis, HSCT

Introduction

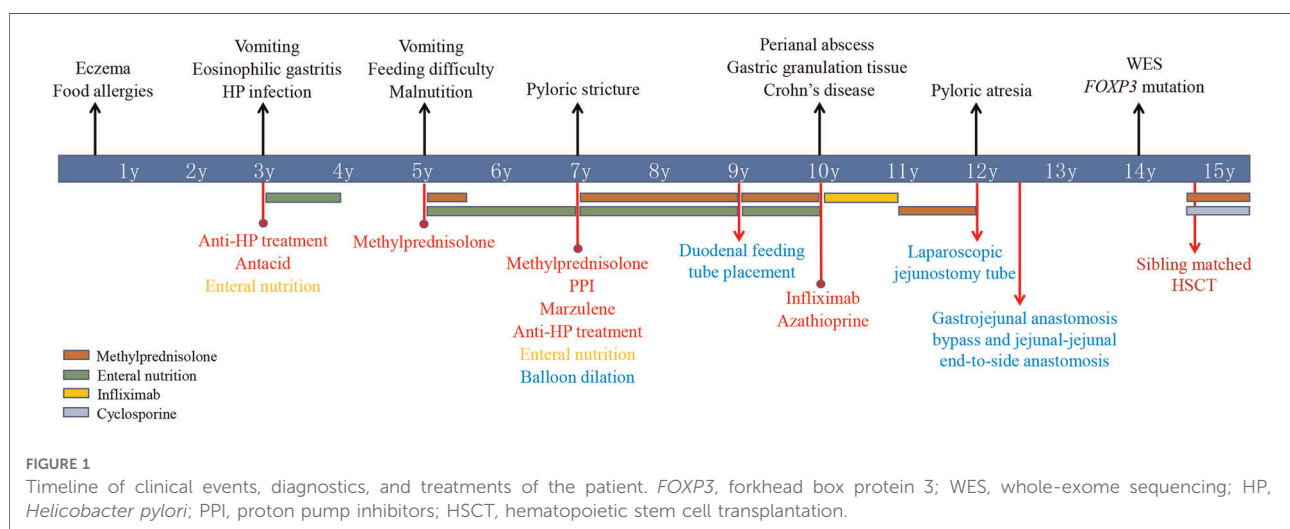
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare X-linked recessive immunodeficiency characterized by the onset of intractable diarrhea, type 1 diabetes mellitus (T1DM), and eczema in the early stages of life. IPEX syndrome was first reported by Powell et al. in 1982 (1), and subsequent studies identified mutations in the forkhead box protein 3 (*FOXP3*) gene located in the centromeric region of the X chromosome as the genetic etiology (2, 3). Loss-of-function mutations in *FOXP3* lead to a defect of CD4⁺ CD25⁺ regulatory T (Treg) cell development, which impairs immune homeostasis and acts against autoimmunity (4, 5). IPEX syndrome is a fatal condition in which untreated affected individuals with typical clinical manifestations usually die within the first 2 years of life. IPEX syndrome may encompass other variables and distinct clinical manifestations that complicate the clinical diagnosis (6). The typical clinical triad for IPEX is not always seen. Many atypical cases, including late-onset symptoms, mild condition phenotypes, and other predominant clinical features, were diagnosed with the advent of next-generation sequencing (NGS) in recent decades, which indicates the variable expressivity of IPEX (6). Therefore, an early diagnosis is vital for patients with atypical IPEX syndrome receiving the appropriate treatments to achieve optimal outcomes.

Eosinophilic gastritis (EG) is a rare disorder characterized by marked eosinophilia and tissue damage in the stomach (7). The known etiologies of EG include infections of specific pathogens [such as *Helicobacter pylori* (HP)], drugs, connective tissue

disorders, hematopoietic disorders, and food allergies (8). Eosinophilic infiltration occurs predominantly at different gastric wall layers, leading to diverse clinical manifestations (9). EG involving the muscle layer typically presents with symptoms of gastric outlet obstruction due to an increased thickness of the wall caused by eosinophil infiltration (10, 11). Here, we report a case with atypical IPEX syndrome complicated with severe EG and pyloric stenosis diagnosed by genetic testing at the age of 14 years.

Case presentation

The patient was a 15-year-old boy with a genetic diagnosis of IPEX syndrome at the age of 14 years (Figure 1). The patient was born full-term by cesarean section with a birth weight of 4,200 g after an uneventful pregnancy. The patient is the fifth child of a healthy non-consanguineous couple of Chinese Han ethnicity. The patient's three old sisters are healthy. However, the patient's brother experienced intractable diarrhea, recurrent fever, and severe malnutrition, and died at the age of 2 years. The patient had noticeable eczema during his first year of life and had a history of food allergies in childhood. At the age of 3 years, he presented with recurrent vomiting and was treated with conventional antibiotics and symptomatic therapies in a local hospital for suspected acute gastroenteritis, but the symptoms did not improve. An esophagogastroduodenoscopy (EGD) showed multiple gastric ulcers, and a gastric biopsy revealed a marked infiltration of eosinophils and HP positivity. The colonoscopy was unremarkable. The patient was diagnosed with



EG and HP infection and successively received anti-HP treatment, antacid medication, and nutritious formula feeding, but the patient's vomiting did not improve in the following 2 years. At the age of 5 years, the patient experienced frequent vomiting, an EGD showed multiple gastric ulcers, and a biopsy revealed eosinophil infiltration. No presence of duodenal villous blunting was observed. Although vomiting and gastric ulcers improved after 5 months of oral methylprednisolone, the patient started to present with feeding difficulties and malnutrition. The patient could not eat meat or rice because it caused vomiting. The symptom did not improve by symptomatic therapies and nutritional support in the following years.

At the age of 7 years, the patient was admitted to our hospital for further evaluation. Physical examinations revealed severe failure to thrive (height, 107 cm, Z-score, -3.12 ; weight, 15.2 kg, Z-score, -4.22 ; BMI, 13.13 kg/m^2 , Z-score, -2.42) (**Supplementary Figure S1**). An EGD showed redness, erosion, and edema throughout the stomach. Pyloric stricture and stiffness were observed, and the endoscope could not enter the duodenal bulb (**Figure 2A**). Upper gastrointestinal radiography revealed pyloric stenosis with a slow barium passage

(**Figure 2B**). A biopsy of the antrum suggested moderate non-atrophic gastritis, infiltration of eosinophils (10–30 eosinophils/HPF), and HP infection. The colonoscopy was normal, and no presence of villous blunting was observed in the terminal ileum. The laboratory blood tests were unremarkable, including normal eosinophil counts, complement, immunoglobulin G (IgG), IgA, IgM, and IgE levels. The serum tests of antineutrophil cytoplasmic and other autoantibodies, including antinuclear, antidiabetes-related (anti-insulin and anti-islet cell antibodies), and antithyroglobulin autoantibodies, were all negative. Balloon dilation was applied to treat the pyloric stenosis. The patient received oral methylprednisolone (4 mg per day), proton pump inhibitors (PPI), L-glutamine and sodium gualenate granules, and anti-HP treatment. However, the vomiting reoccurred after improvement, and the pyloric stenosis did not improve. In the following years, the patient was repeatedly admitted to our department. The patient was managed with a series of symptomatic and supportive treatments, including multiple balloon dilations, enteral nutrition, and oral methylprednisolone. At the age of 9 years, an EGD showed that the pyloric stenosis was aggravated. Endoscopically assisted duodenal feeding tubes

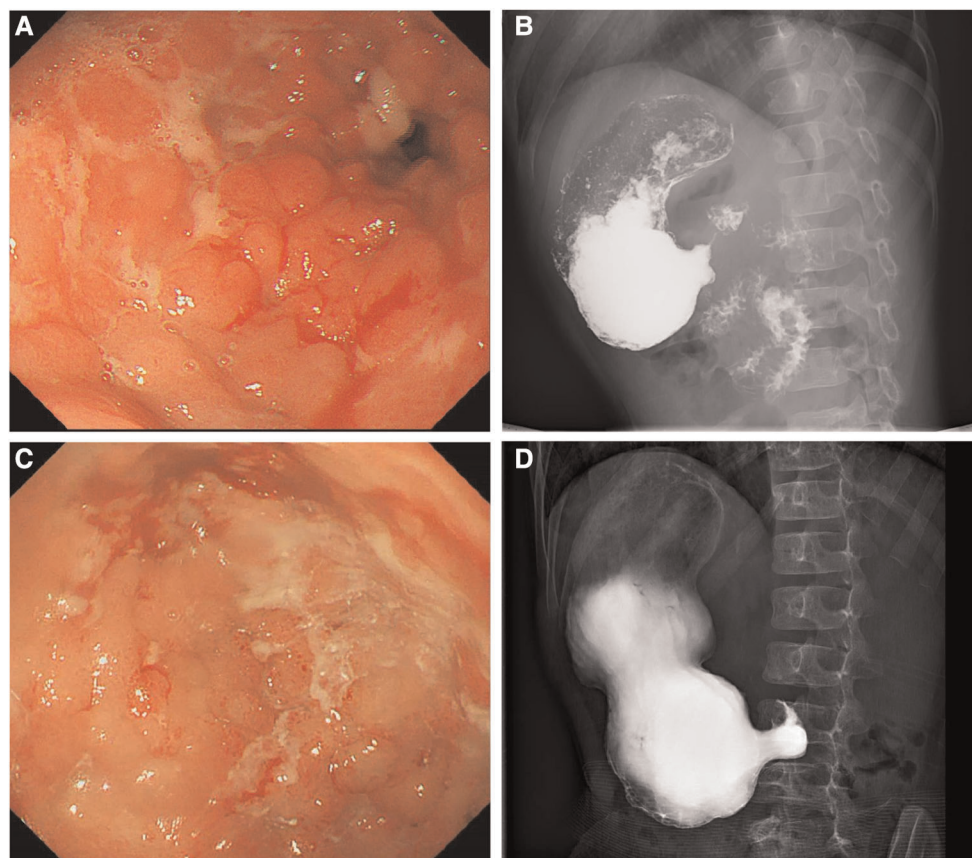


FIGURE 2

Esophagogastroduodenoscopy (EGD) showing edema, erosion, multiple ulcers, and pyloric stenosis of the stomach at 7 (A) and 12 (C) years old. Upper gastrointestinal radiography showing gastric retention and pyloric stenosis at 7 (B) and 12 (D) years old.

beyond the second portion of the duodenum were placed for enteral nutrition and liquid food. At the age of 10 years, due to the appearance of a perianal abscess and gastric non-necrotizing

granulomas with inflammatory cell infiltration (**Figure 3A**), the patient was diagnosed with Crohn's disease (CD). He received infliximab (eight times) and azathioprine treatments for CD in

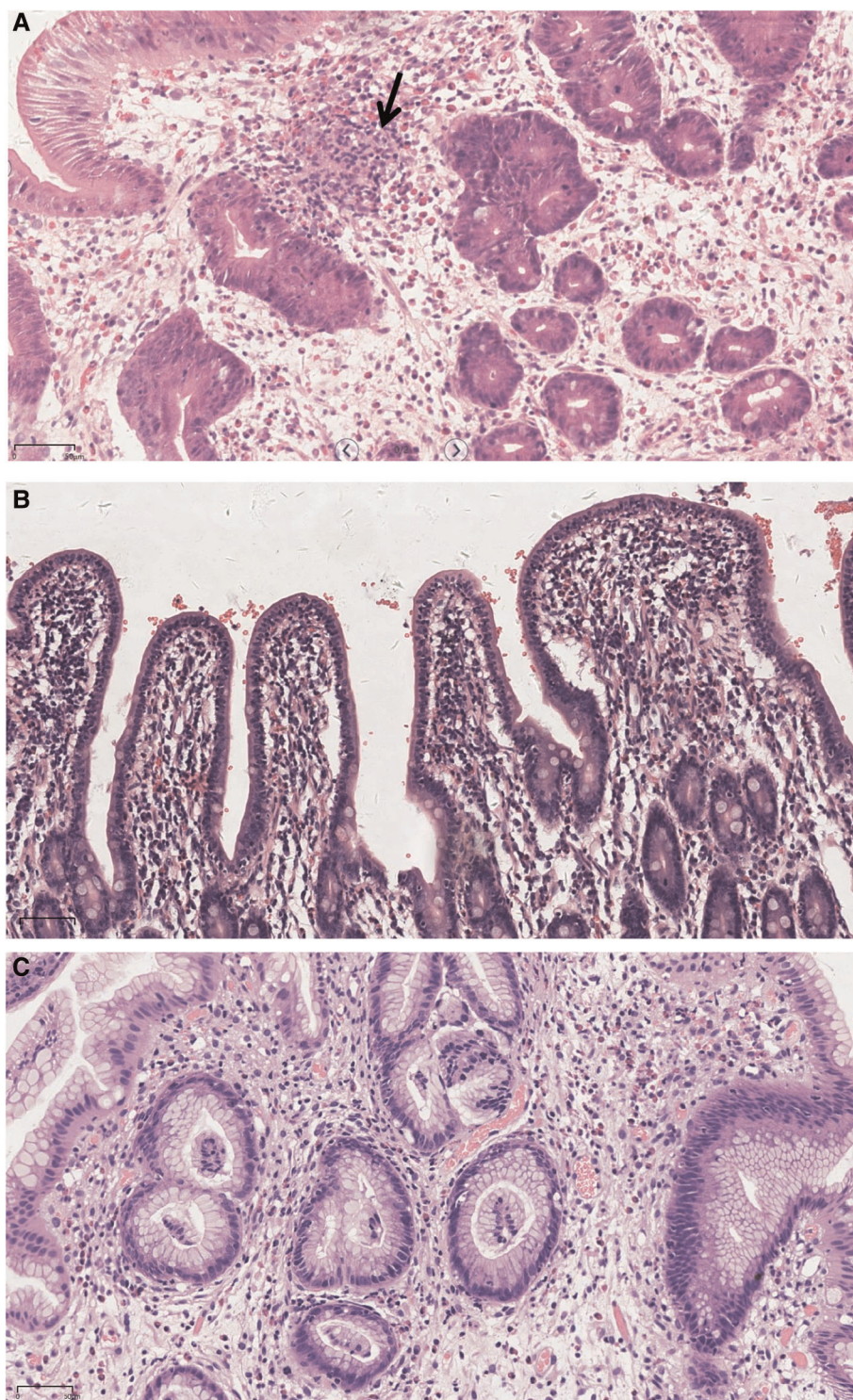


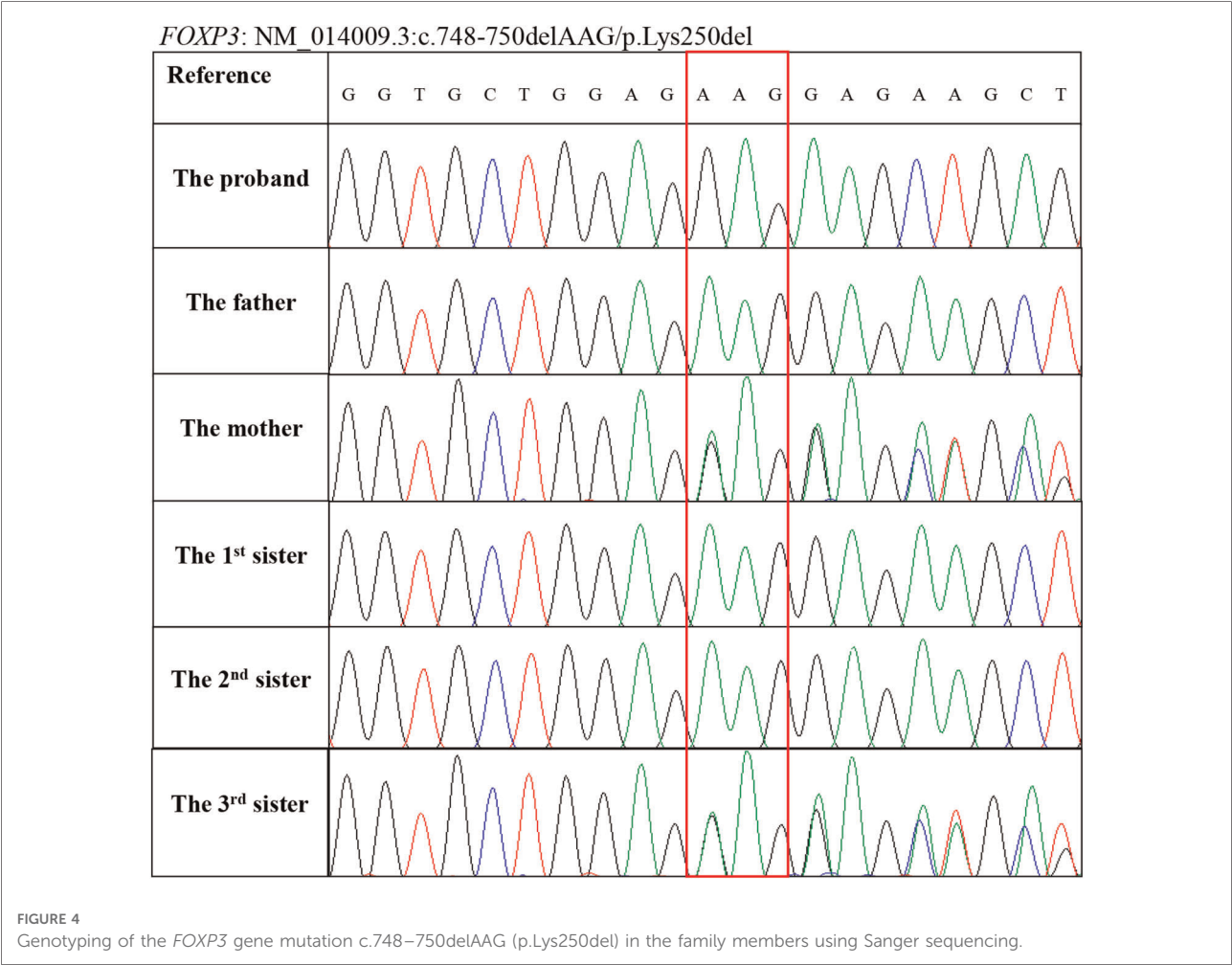
FIGURE 3

Representative histological images showing the infiltration of eosinophils, plasmacytes, and neutrophils in the upper gastrointestinal tract. (A) Gastric nonnecrotizing granulomas (arrow). (B) Small intestinal villi. (C) Gastric antrum (H&E, $\times 200$; scale: 50 μm).

the following year. The level of serum infliximab did not achieve an adequate concentration (1 µg/ml) after three instances of intravenous infusions at a dose of 5 mg/kg. Then, the infliximab dose increased to 8 mg/kg, and the serum infliximab level increased to 3.5 µg/ml. The serum anti-infliximab antibody concentration was below 4 ng/ml. However, the infliximab infusion remained sub-therapeutic despite a dose escalation. The gastric lesions persisted, and the perianal abscess recurred after a partial improvement during the treatment. At the age of 12 years, upper gastrointestinal radiography showed gastric retention and severe pyloric stenosis (Figure 2C). The barium did not pass through the pylorus after 6 h (Figure 2D). A laparoscopic jejunostomy feeding tube placement was performed after 1 month of treatment with intravenous methylprednisolone. An EGD was placed through the surgical incision, and an intestinal biopsy showed normal intestinal villi without villous blunting or atrophy (Figure 3B). A gastrojejunal anastomosis bypass and jejunal-jejunal end-to-side anastomosis were performed 5 months later. The patient's vomiting improved; the patient was able to eat and this resulted in a significant weight gain after the surgery. At the age of 13 years,

the patient had a height of 125 cm (Z-score, −4.21), weight of 29 kg (Z-score, −2.99), and BMI of 18.56 kg/m² (Z-score, −0.06) (Supplementary Figure S1). Although the patient had a steady increase in height with age, his body weight fluctuated along with the recurrent symptoms and changes in nutrient intake. The patient's weight increased to 31.5 kg at the age of 13.5 years but dropped to 28.4 kg over the next 6 months due to the loss of appetite. At the age of 14 years, an EGD revealed persistent erosive gastritis with gastric ulcers, and a biopsy of the antrum showed significant eosinophil infiltration (40–65 eosinophils/HPF) (Figure 3C).

At this point, whole-exome sequencing (WES) was performed on a HiseqX10 (Illumina, USA) platform using genomic DNA extracted from the patient's peripheral blood. A 3 bp deletion in exon 7 of the *FOXP3* gene, c.748–750del (p.Lys250del), was identified and further confirmed by Sanger DNA sequencing. Genotyping of the unaffected family members by Sanger sequencing showed that his mother and third sister carry this mutation, and his father and two other sisters are normal (Figure 4). The c.748–750del (p.Lys250del) mutation is located in the leucine zipper domain of the



FOXP3 protein, which is critical for dimerization and DNA binding, and a previous study demonstrated that the developments of the CD4⁺ CD25⁺ FOXP3⁺ T cell are significantly impaired in patients with this mutation (12). To date, intractable diarrhea and T1DM have not been observed.

The patient underwent matched sibling (his first sister) peripheral blood hematopoietic stem cell transplantation (HSCT) using reduced-intensity conditioning with busulfan, fludarabine, cyclophosphamide, and anti-thymocyte globulin 8 months after his genetic diagnosis. The CD34 cell dose was $0.37 \times 10^6/\text{kg}$, the number of neutrophils was $0.75 \times 10^9/\text{L}$, and the number of platelets was $300 \times 10^9/\text{L}$. He received sustained cyclosporine (35 mg per day) and methylprednisolone (2 mg/kg per day) to prevent graft-versus-host disease (GvHD) 7 days before the HSCT. At day +17 after the HSCT, the short tandem repeat (STR) test showed that the patient was engrafted with 100% of donor cells. The patient started to experience a skin rash and diarrhea on day 26 after the HSCT. He was diagnosed with acute GvHD (grade 2) and treated with methylprednisolone and ruxolitinib. The skin rash disappeared, and the diarrhea recovered after 2 weeks of therapy. In addition, symptomatic treatments and antibiotics were applied to treat several episodes of oral, lung, and intestinal infections after the HSCT. The patient's weight decreased from 31 kg to 28 kg in 2 months after the HSCT. At the time of this writing, the patient is 15 years old and remains stable after 3 months of HSCT. The patient is managed with sustained cyclosporine (100 mg per day) and methylprednisolone (0.5 mg/kg per day). The patient takes food orally with a normal diet, and no feeding tube is needed. However, the patient continues to present with severe failure to thrive (height, 137 cm, Z-score, -4.01 ; weight, 28 kg, Z-score, -5.53 ; BMI, 14.88 kg/m^2 , Z-score, -3.16) (Supplementary Figure S1). Structuring and eosinophilic GI diseases should be re-evaluated shortly.

Discussion

Classical IPEX syndrome caused by mutations in *FOXP3* is characterized by the triad of early-onset intractable diarrhea, type T1DM, and eczema (6). Emerging reported atypical cases in the last two decades, including late-onset symptoms, mild phenotypes, single system involvement, or rare clinical features, extend the clinical spectrum of IPEX syndrome (13). As an autoimmune disorder, symptoms other than the classical triad have been described, such as thyroiditis, thrombocytopenia, arthritis, neutropenia, nephropathy, and hepatitis (13). In this report, we described a case of atypical IPEX syndrome featuring eczema, food allergies, severe EG, and pyloric stenosis. The patient presented with early-onset eczema as an initial symptom in the first year of life. Food allergies were observed after the introduction of solid food.

Vomiting, EG, pyloric stenosis, and failure to thrive developed at the age of 3 years. The patient's condition did not respond to long-term symptomatic therapies and nutritional support. Identical to several patients with reported atypical IPEX (14–17), the patient was suspected of having CD, but infliximab therapy was ineffective in improving the symptoms. The pyloric stenosis was further aggravated, and he had to receive a gastrojejunal anastomosis bypass. Finally, the patient was diagnosed with IPEX syndrome due to a 3 bp deletion in exon 7 of *FOXP3*, c.748–750del (p.Lys250del). This mutation is located in the leucine zipper domain of the FOXP3 protein and has been demonstrated to impair the development of the CD4⁺ CD25⁺ FOXP3⁺ T cell (12). The main reasons for the delayed genetic diagnosis of IPEX syndrome are due to the atypical clinical presentations and the parents' reluctance for genetic testing. The patient was considered to have EG and CD-related pyloric stenosis. His brother's presentation of life-threatening diarrhea resulting in death at the age of 2 years elicited a possible family history of monogenic inborn immunity error. Genetic testing with WES was strongly recommended during his first hospitalization in our department at the age of 7 years. However, the patient's parents refused because he has three healthy sisters. Thus, physicians should be aware of the variable phenotypes of atypical IPEX syndrome. Early genetic testing is necessary to achieve an accurate diagnosis in cases of atypical IPEX, particularly in patients with a high degree of suspicion of family history. If a proband has healthy sisters, X-link defects must be considered in clinical practice.

Although enteropathy in IPEX syndrome can present different histopathologic phenotypes, such as GvHD-like changes, celiac disease-like pattern, and depletion of goblet cells (18), gastritis is rarely reported. Scaillon et al. reported a case of IPEX that developed with extensive exfoliative gastritis (19). Luo et al. reported a case of IPEX carrying the same mutation that presented with metaplastic atrophic gastritis and villus atrophy in the descending part of the duodenum (20). There have been several cases of eosinophilic esophagitis reported in IPEX syndrome (21) as well as at least two patients with pyloric stenosis described by Fang et al. (22), but it is rare to see chronic gastritis with eosinophilic infiltration (23). In this report, we described an atypical IPEX case presenting with severe gastritis and pyloric stenosis. The common histopathological finding of these IPEX cases with gastritis is remarkable eosinophil infiltration. Neither genotype-phenotype correlations nor phenotype associations have been observed in IPEX patients with gastritis. Four different mutations in *FOXP3*, c.1040G>A (R347H) (19), c.748–750del (p.Lys250del) (20), c.1280dupC (p.P427fs) (22), and c.766A>G (p.M256V) (22), have been identified in IPEX patients with gastritis. They can present simultaneously with either T1DM or other autoimmune manifestations. In addition, patients carrying the c.748–750del (p.Lys250del)

mutation present with different clinical manifestations, such as nephrotic syndrome and autoimmune hepatitis (12, 20, 24). Therefore, further studies are needed to explore the genotype-phenotype correlations of IPEX syndrome. Nevertheless, a lack of enteropathy in atypical IPEX syndrome has been well reported in the literature (13). A recent review conducted by Consonni et al. showed that no enteropathy was described in 15 of 59 cases in a series of cases of atypical IPEX syndrome, reflecting approximately 25% (13).

The current therapeutic approaches for IPEX syndrome are immunosuppressive treatment and HSCT (6). Immunosuppression strategies can be effective, particularly in atypical IPEX cases with mild disease. HSCT is a curative therapy for IPEX syndrome, and the outcome depends on it being performed in the early stages of the disease (25). Thus, a prompt diagnosis is critical for managing patients with IPEX syndrome. Gastritis is an unusual gastrointestinal finding in IPEX syndrome, often leading to a delayed diagnosis of IPEX syndrome. Indeed, most of the reported IPEX cases with gastritis were diagnosed in adolescents by a confirmation of the *FOXP3* mutation by genetic testing (22). The delayed diagnosis of IPEX syndrome can lead to inappropriate therapy and an impaired quality of life in the patient. Pediatricians should raise awareness of IPEX syndrome and improve the diagnosis and intervention strategy.

In summary, this case report further highlights the unusual gastrointestinal findings in IPEX syndrome as well as the need for increased awareness as an early diagnosis of IPEX syndrome is vital for improving the patient's outcome.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: <https://www.ncbi.nlm.nih.gov/>, SRA/PRJNA888449.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Review Board of Shanghai Children's Hospital. Written informed consent to participate in this study was provided by the participant's legal guardian/next of kin.

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Author contributions

TZ and YW contributed to the study conception and design. RY, YX, and HH acquired, analyzed, and interpreted the clinical data. WX performed the genetic testing and analysis. RY and YW drafted the manuscript. TZ and YW edited and revised the manuscript. All authors agreed to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fped.2022.1039341/full#supplementary-material>.

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