Delayed IPEX Syndrome with a Rare Mutation

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ABSTRACT

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare, life-threatening X-linked recessive disorder caused by *FOXP3* gene mutations, with an incidence of less than one in a million. It typically presents in infancy, with half of the cases manifesting within the first month, and is characterised by severe enteropathy, Type I diabetes, and recurrent infections. Here, the authors report a rare case of late-onset IPEX in a five-year boy with acute disease onset, multiple organ involvement, recurrent diarrhoea, diabetes, and infections. Genetic testing identified a novel c. 210 + 1G >C mutation in *FOXP3* which was not previously reported. The patient underwent a successful haematopoietic stem cell transplantation (HSCT) and remained relapse-free during a one-year follow-up. This case highlights the potential for late-onset IPEX, the importance of genetic testing in atypical cases, and the efficacy of HSCT as a curative treatment. Further research is needed to explore the long-term outcomes of HSCT and the genotype-phenotype correlations in IPEX syndrome.

Key Words: *IPEX, Haematopoietic stem cell transplantation, Forkhead box protein 3, Diarrhoea*.

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INTRODUCTION

Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome the syndrome is an X-linked recessive genetic disorder that was first reported in 1982. The pathogenic gene, *FOXP3* (*forkhead box protein 3*), was identified in 2001.[1] The typical clinical manifestations of IPEX syndrome usually include enteropathy, Type I diabetes, and eczema. Regarding treatment, immunosuppressive therapy and allogeneic haematopoietic stem cell transplantation (HSCT) represent the main approaches. The patient reported in this article presented with recurrent diarrhoea and multi-organ involvement. He was diagnosed with IPEX syndrome through genetic testing, and treatment with HSCT achieved remarkable results.

CASE REPORT

A male child was five years and two months of age when he developed diarrhoea without any obvious cause. He experienced 3-4 times/day with dilute watery stools and undigested food residues, occasionally with abdominal pain around the umbilicus, which could be relieved within half an hour.

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This condition was also accompanied by abdominal distension and nausea. After one month of treatment, the diarrhoea worsened to 2-10 times/day, with a large number of watery stools. The diarrhoea improved with symptomatic treatment but recurred after half a month.

Upon physical examination, the breath sounds of both lungs were slightly coarse, and no other obvious abnormalities were observed. The auxiliary test results indicated the presence of diabetes, dyslipidaemia, and hypothyroidism. The immunological test results demonstrated the presence of immunoglobulin M at a concentration of 0.25 g/L, glutamate decarboxylase antibody at a titre of >2000.00 IU/ml, islet cell antibody at a concentration of 37.30 cut-off index (COI), and insulin autoantibody at a concentration of 0.10 COI. Histopathological examination of the bowel showed more eosino- philic infiltration locally in the mucosa of the transverse colon; the disappearance of goblet cells in the mucosa of the sigmoid colon did not exclude the possibility of very early-onset inflammatory bowel disease.

The results of the completed genetic tests are presented in Figure 1. A hemizygous variation in the *FOXP3* gene, c. 210 + 1G >C (the nucleotide guanine in the adjacent region of coding region No. 210 was mutated to cytosine), was identified. This novel pathogenic mutation has not been previously reported. The family validation analysis demonstrated that the submitted sample met the criteria for pathogenic moderate 6 (PM6). Additionally, the parents of the proband did not carry this variation. This variation may be novel, and there was no relevant family history of the disease. The diagnosis was that of IPEX syndrome, and the recommendation was for an HSCT.

After thorough infection prevention treatment and exclusion of contraindications, pre-treatment was carried out prior to the infusion of umbilical cord blood haematopoietic stem cells (UCB HLA 8/10). The first transplant failed to establish haematopoiesis. A second transplant was planned. After pre-treatment, umbilical cord blood was infused, followed by peripheral blood haematopoietic stem cells on the second day. On the 12th day, the child's peripheral blood short tandem repeat (STR)-PCR showed 99.39%, and on the 14th day, myeloid haematopoiesis was re-established, indicating a successful transplant. However, the child experienced recurrent diarrhoea accompanied by fever, which improved after treatment. Regular follow-ups were conducted for over a year, with no adverse reactions reported, stable blood sugar levels, and no further episodes of diarrhoea or infections.

DISCUSSION

IPEX syndrome is an extremely rare X-linked genetic disorder with an incidence of less than one in a million. According to a study by Bacchetta and Roncarolo its clinical manifestations typically appear within the first year of life, with approximately half of the affected infants developing symptoms within the first month.[2] Currently, the treatment of IPEX syndrome primarily includes supportive therapy and alternative therapy. Supportive therapy involves total parenteral nutrition (TPN), electrolyte imbalance correction, and infection control, while alternative therapy mainly consists of immunosuppression and HSCT.[3] HSCT is the only potentially curative treatment for IPEX syndrome; however, its success rate is limited by various factors.[4] A study by Barzaghi *et al*. reported that the overall survival rate of IPEX patients after HSCT is 73% (n = 58), but due to graft failure (7%) and disease recurrence (33%), the final survival rate drops to 60%.[5] Additionally, the severity of organ damage before transplantation is a key factor affecting HSCT success, whereas age, donor type, and conditioning regimen have relatively minor impacts.[6]

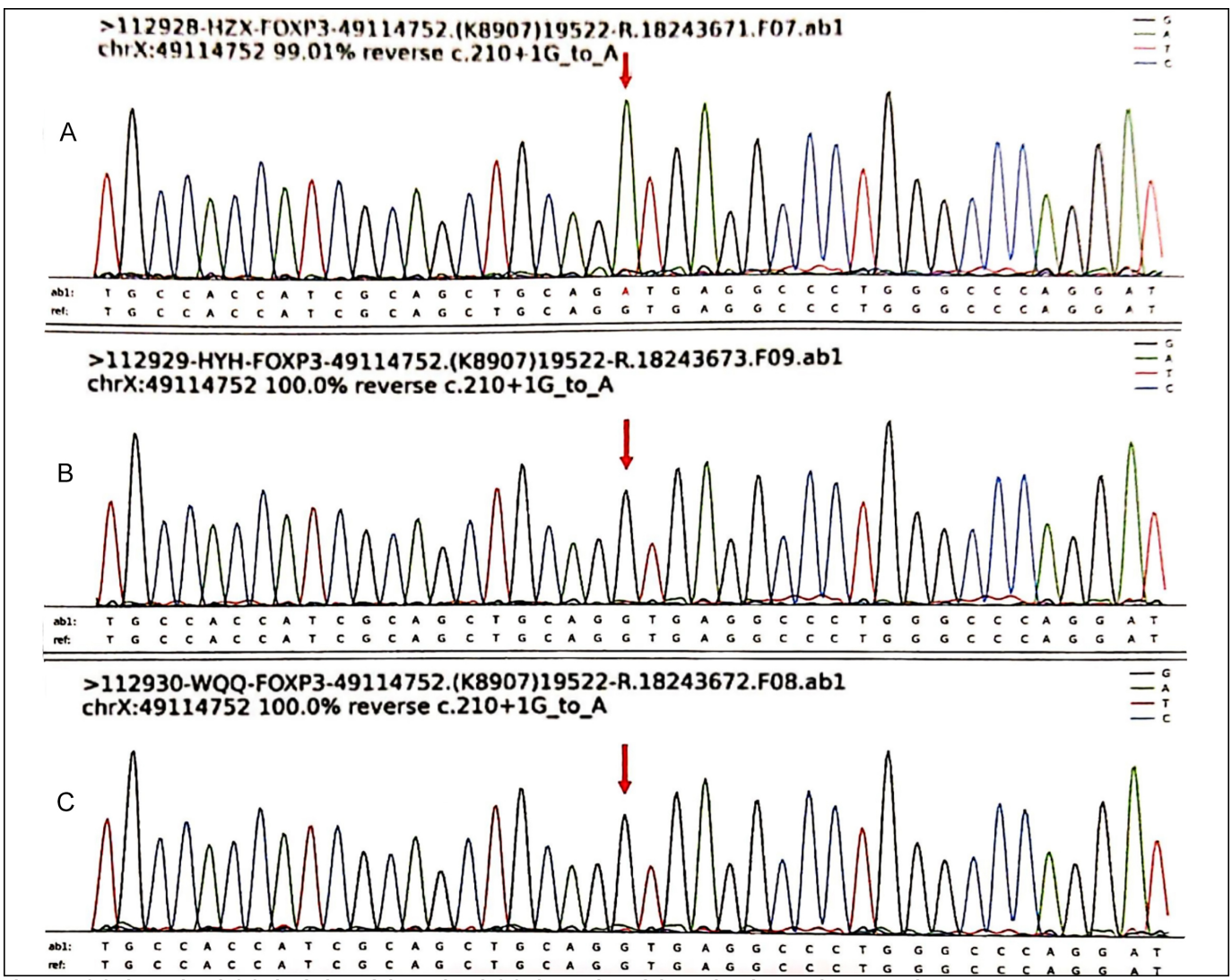

Figure 1: (A) The proband, (B) The father of the proband, (C) The mother of the proband. *Genetic test results; c. 210 + 1G >C.*

The major limiting factors for HSCT success include autoimmune complications, donor availability, and graft-*versus*-host disease (GVHD). Patients with severe enteropathy, pancreatic dysfunction, or renal impairment before transplantation have a significantly higher risk of transplant failure. Furthermore, low donor compatibility increases the incidence of GVHD, further compromising long-term survival. However, previous studies have reported that IPEX patients who develop stable mixed chimerism after HSCT can survive up to 10 years.[7] Early detection, diagnosis, and treatment are crucial for IPEX patients. Despite the high early mortality rate of HSCT, advancements in donor selection, conditioning regimens, and GVHD prevention strategies continue to improve outcomes, making HSCT a viable hope for long-term survival and potential cure in some patients.

The unique characteristics of this case are summarised as follows: First, the patient had an onset at the age of five years, which is relatively later compared to the children reported in previous literature. Second, the variant site c. 210 + 1G >C detected by genetic testing is a novel pathogenic mutation that has not been reported before. Third, the patient's symptoms were controlled after treatment with HSCT, with a good prognosis and no recurrence after a one-year follow-up.

In conclusion, this case report aimed to provide a reference for the diagnosis and treatment of similar cases, to draw clinical attention, avoid misdiagnosis, and missed diagnosis, so that more patients can receive timely and effective treatment.

PATIENT'S CONSENT:
Informed written consent was obtained from the patient.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
WTX: Design of the study, data collection, analysis, and the drafting of the manuscript.
TF, YZX: Reviewing and editing.
SFZ: Drafting, review, and editing.
All authors approved the final version of the manuscript to be published.

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