A delayed diagnosis of atypical immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome

A case report
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Abstract
Introduction: Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome is a rare monogenic autoimmune disease, which is caused by mutations in the forkhead box protein 3 gene, can affect various systems. The typical clinical manifestations of IPEX are enteropathy, type 1 diabetes mellitus, and skin diseases. However, some atypical phenotypes can easily be misdiagnosed clinically.

Patient concerns: A 9-year-and-7-month old patient suffered from recurrent wheezing, hematochezia, and eczematous dermatitis at the age of six months, but did not have any manifestations of autoimmune endocrinopathy. The patient was treated with glucocorticoids for more than six years, and he developed bronchiectasis.

Diagnosis: Whole exome sequencing revealed a hemizygous pathogenic mutation c.1010G>A, p. (Arg337Gln) in Forkhead box protein 3 gene (NM_014009.3).

Interventions: The patient was treated with oral mycophenolate mofetil combined with inhaled budesonide formoterol for six months after diagnosis.

Outcomes: The respiratory symptoms of the patient seemed to be controlled but eczematous dermatitis progressed, which led the patient to give up the treatment.

Conclusion: Early diagnosis and treatment of IPEX are crucial. Lung injury may be a major problem in the later stages of atypical IPEX, and mycophenolate mofetil seems to control the respiratory symptoms, but could induce significant skin side effects.

Abbreviations: FOXP3 = forkhead box protein 3, FOXP3 = forkhead box protein 3 gene, FVC = forced vital capacity, HSCT = hematopoietic stem cell transplantation, IPEX = immune dysregulation, polyendocrinopathy, enteropathy, X-linked, Treg = regulatory T cell.

Keywords: forkhead box protein 3, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

1. Introduction
Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome is a rare, often fatal, monogenic autoimmune disease that affects various systems. IPEX is caused by mutations in forkhead box protein 3 gene (FOXP3), which was first identified in 2000. Over 70 FOXP3 mutations have been identified in patients with IPEX.[1] Forkhead box protein 3 (FOXP3) has emerged as a key regulator of immune tolerance by...
diabetes mellitus, and skin diseases. However, there are many different clinical manifestations of IPEX, and there is no clear genotype-phenotype correlation.\(^3\)

2. Patient concerns

The patient was referred to the hospital at the age of 9 years and 7 months due to a 3-month history of cough with sputum and wheezing, which was more obvious at night and resulted in sleeplessness and hypoxia. The patient was born at term with a birth weight of 3300g after an uneventful pregnancy and had no special family history. He developed recurrent wheezing from the age of six months and was diagnosed with asthma and started regular treatment at the age of 3 years. However, his condition was not controlled even with a high dose of inhaled corticosteroids.

Meanwhile, the patient began to experience recurrent hematochezia at the age of six months after introducing formula milk, accompanied by intermittent abdominal pain and vomiting. At the age of 4 years, he was diagnosed with allergic enteritis. Following a short period of remission after taking low-dose prednisone (1–2 mg/kg/day), the patient’s illness recurred, and he was diagnosed with ulcerative colitis and food protein-mediated enterocolitis at seven years of age and started taking mesalazine, 5-ASA, and mesalamine with little effect. He was then treated with corticosteroids and immunosuppressants, and the patient’s condition was stabilized.

On admission, he was afebrile and had a normal heart rate, blood pressure, and oxygen saturation in ambient air. However, he was shorter (124.0cm, below the second percentile for age) and lighter (25.0 kg, below the 5th percentile of height and 10th percentile of weight) than normal. His routine blood test results were normal, except for the eosinophil count and proportion, which could be masked by eosinophilic leukocytosis. The patient’s stool and urine test results were normal, except for C-reactive protein (CRP) of 25.0 (reference range 0–10 mg/L).

3. Clinic findings

On admission, his body temperature was 38.9°C, blood pressure was 110/60 mmHg, heart rate was 100 bpm, respiratory rate was 20/min, and oxygen saturation in ambient air was 95%. On physical examination, his body weight was 25.0 kg, height was 124.0 cm, and head circumference was 52 cm. His weight and height were both below the 5th percentile for age. He had bilateral hip tenderness and epigastric tenderness. He had a cough with productive sputum, which was yellowish-white in color. His oral cavity was normal, and his tongue was slightly red with a yellowish-white coating. His pharynx was normal, and his trachea was midline. His heart sounds were clear, and his lungs were clear on auscultation. His abdomen was soft, and his liver and spleen were not palpable. His peripheral lymph nodes were not significantly enlarged. His peripheral pulses were normal, and his skin was not significantly flushed. His extremities were normal, with no clubbing or cyanosis.

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The patient also developed allergic rhinitis, allergic conjunctivitis, and eczema symptoms within the first year of life, which are still ongoing. He did not receive the vaccine as planned, and had chicken pox and hand, foot, and mouth disease in infancy. He was allergic to cefotixin, piperacillin sulbactam, cefotaxime, and cefoperazone sulbactam, all of which presented as immediate generalized urticaria many days or course after the first infusion.

Table 1

| Date      | WBC (G/L) | Neutrophil (%) | Eosinophil (%) | Hemoglobin (g/L) | Thrombocyte (G/L) | CRP (mg/L) |
|-----------|-----------|----------------|----------------|------------------|-------------------|------------|
| 2019-09-20| 15.3 (9.6–9.7) | 75.7 (23.6–75.0) | 1.4 (0.0–6.8) | 150 (110–146) | 180 (100–450) | 11 (0–10) |
| 2019-10-02| 38.11 (3.6–9.7) | 85.5 (23.6–75.0) | 0.5 (0–6.8) | 148 (110–146) | 193 (100–450) | 39 (0–10) |
| 2020-03-23| 11.02 (3.6–9.7) | 58.5 (23.6–75.0) | 10.3 (0.0–6.8) | 128 (110–146) | 249 (100–450) | 1 (0–10) |

CRP = C-reactive protein, WBC = white blood cell.

Table 2

| Date      | IgG (g/L) | IgM (g/L) | IgA (g/L) | C3 (g/L) | C4 (g/L) |
|-----------|-----------|-----------|-----------|----------|----------|
| 2011-8-14 | 10.67 (8–16) | 0.96 (0.5–2.2) | 0.23 (0.7–3.3) | 0.99 (0.8–1.6) | 0.14 (0.15–0.4) |
| 2017-7-17 | 13.20 (8–16) | 0.57 (0.5–2.2) | 0.32 (0.7–3.3) | 1.27 (0.8–1.6) | 0.30 (0.15–0.4) |
| 2020-3-23 | 10.33 (8–16) | 0.51 (0.5–2.2) | 0.20 (0.7–3.3) | 1.19 (0.8–1.6) | 0.17 (0.15–0.4) |
chronic inflammation of the mucosa with erosion, and a small amount of eosinophil infiltration in the stroma (<10/high-power field) of the duodenal bulb. Light to moderate chronic inflammation with erosion and much greater eosinophil infiltration in the stroma (50–100/ high power field) were observed in the descending duodenum (Fig. 1).

The patient’s pulmonary imaging findings showed gradually worsening bronchiectasis (Fig. 2), and the forced vital capacity (FVC), forced expiratory volume in one second, Forced expiratory volume in 1 second/FVC, forced expiratory flow at 50% and 75% of FVC, and maximum mid-expiratory flow of forced ventilation were significantly lower than normal (Table 3), indicating severe mixed ventilation dysfunction. The detection of pulmonary diffusing function demonstrated that the diffusion capacity for carbon monoxide in the lung was 83.1%, total lung capacity was 80.8%, residual volume was 168.25%, and residual volume/total lung capacity was 45.47%, which suggested that the pulmonary diffusing capacity was normal.

4. Diagnosis
Whole-exome sequencing was performed using a tri-diagnostic approach (patient and both parents). The results revealed a hemizygous pathogenic mutation c.1010G>A, p. (Arg337Gln) in FOXP3 (NM_014009.3) (Institute of Birth Cohort, Beijing Children’s Hospital, Capital Medical University) in the patient, which was not found in his parents.

5. Intervention and outcome
The patient chose oral mycophenolate mofetil (0.5 g/day) with budesonide formoterol inhalation therapy after diagnosis. The patient experienced temporary herpes zoster and aggravated eczematous dermatitis with an unbearable itchy sensation during the treatment period. Although the patient had only 1 episode of mild wheezing in the 6 months of treatment, he eventually discontinued treatment with mycophenolate mofetil and refused other immunosuppressants.

6. Discussion
FOXP3 is a member of the forkhead box protein family of transcription factors, and its stable expression is crucial for the development, maturation, and maintenance of CD4+ regulatory Tregs. Functional mutations of FOXP3 result in a decrease in Tregs or defects and fall within the category of diseases of immune dysregulation. FOXP3 is located in the centromeric region of the X chromosome (Xq11.3-q13.3). Mutations in both coding and non-coding regions can cause IPEX, and the most frequent mutations occur in the FKH domain.
Patient’s mutation [c.1010G>A, p. (Arg337Gln)] is located in the common site of the FKH domain and exon 10, but it is sporadic and different from other genealogical cases.\textsuperscript{7–9}

FOXP3 plays a direct role in suppressing Th2-like Tregs,\textsuperscript{10} and the uncontrolled Th2 immune responses of IPEX not only dominate the autoimmune responses in the target tissues, but also hinder the host from mounting effective and appropriate immune responses to invading microorganisms and exogenous antigens,\textsuperscript{11,12} which lead to autoimmune diseases, allergies, and recurrent infections. Although the typical clinical manifestations of IPEX are early onset enteropathy, type 1 diabetes mellitus, and skin diseases, almost every system can be involved.\textsuperscript{13–17} Our patient’s lesions began appearing at six months of age, and were located in the respiratory tract, gastrointestinal tract, and skin, presenting with refractory asthma, recurrent serious respiratory infections, controlled enteropathy, and chronic eczematous dermatitis but without any manifestation of autoimmune endocrinopathy. Therefore, except for male sex, the onset age, affected organs, lesion type, and prognosis can vary, even with the same mutation.\textsuperscript{3,7,9,18–21}

The patient’s respiratory symptoms seemed to be a major problem in the later stages. Lung diseases, including bronchiectasis, emphysema changes, and pulmonary fibrosis, are the most common clinical features of primary immunodeficiency disease.\textsuperscript{22} However, lung diseases are not common in patients with typical IPEX,\textsuperscript{4} which may be because the lung damage process is a consequence of chronic and recurrent infections paired with inflammatory or autoimmune diseases.\textsuperscript{22} Therefore, only patients with atypical and mild disease, like our patient, may develop lung disease. However, it is interesting to note that not all mild cases will cause lung damage,\textsuperscript{9} which supports the hypothesis that the epigenetic regulation of FOXP3 expression plays an important role in the development of IPEX.\textsuperscript{23,24} Chronic lung diseases can lead to decreased exercise tolerance,

### Table 3

| Date       | FVC (%pre) | FEV1 (%pre) | FEV1/FVC (%pre) | FEF50 (%pre) | FEF75 (%pre) | MMEF (%pre) |
|------------|------------|-------------|-----------------|--------------|--------------|-------------|
| 2016-04-07 | 66.4       | 57.9        | 86.2            | 31.5         | 20.6         | 25.8        |
| 2017-10-26 | 66.1       | 57.7        | 86.3            | 33.3         | 29.3         | 32.2        |
| 2018-09-07 | 61.1       | 43.2        | 69.7            | 21.0         | 12.5         | 14.1        |
| 2020-03-24 | 59.6       | 38.3        | 63.5            | 16.0         | 11.6         | 14.7        |

FEF50 and FEF75 = forced expiratory flow at 50% and 75% of the FVC, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, MMEF = maximum mid-expiratory flow of forced ventilation, pre = prediction.
The mTOR pathway compared to Tregs. However, immune suppressor, as a primary drug (alone or in combination with non-calcineurin inhibitors such as rapamycin, cyclophosphamide, azathioprine, and mycophenolate mofetil) are often used to control T cell activation during the remission period. Oral mycophenolate mofetil combined with inhaled budesonide formoterol seemed to control respiratory symptoms well, but induced aggravated eczematous dermatitis with an unbearable itchy sensation, which led the patient to give up treatment. Increasing evidence supports rapamycin, an mTOR inhibitor, as a primary drug (alone or in combination with corticosteroids) because effective T cells are more dependent on the mTOR pathway compared to Tregs. However, immune suppression can be effective in improving the symptoms of autoimmune and allergic diseases, but it does not appear to halt disease progression and may induce severe side effects, such as osteoporosis, dyslipidemia, and chronic renal dysfunction. The only potentially curative therapy for IPEX syndrome is HSCT, the less organ damage, the better the prognosis. The clinical manifestations of IPEX are variable and laboratory test results including the number of CD4+ FOXP3+ Tregs, serum immunoglobulin levels, and types of autoantibodies are nonspecific; therefore, we have summarized some diagnostic clues from this case and previous literature:

1. Inflammatory bowel-like disease is 1 of the most prominent overlapping clinical disease features caused by Tregs impairment;
2. Early-onset autoimmune diseases;
3. Males simultaneously suffers atopic and autoimmune diseases;
4. Early-onset inflammatory skin diseases, which rapidly develop and are resistant to strong corticosteroids; and
5. Refractory allergic asthma complicated with recurrent serious respiratory tract infections and ventilation function damage.

If the possibility of primary immunodeficiency is considered, genetic testing should be improved as soon as possible.

7. Conclusion

The clinical manifestations of IPEX vary. Early diagnosis and treatment are crucial even in cases without endocrine gland injury or those who have atypical presentations and mild courses. Lung injury may be a major problem in the later stages of atypical IPEX, and mycophenolate mofetil seem to be effective for respiratory symptoms, but could induce significant skin side effects.

Author contributions

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Formal analysis: Tao Ai and Hanmin Liu.
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