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Renal-predominant FOXP3-related immune dysregulation with ALPS-like lymphoproliferation: a case report

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Abstract

Background

FOXP3 controls regulatory T-cell development and function. Pathogenic variants in X-linked FOXP3 cause IPEX syndrome. Classic IPEX includes early enteropathy, insulin-dependent diabetes, and eczema. Some patients show non-classic disease. These forms may involve the kidney, blood, or lymph nodes.

Method

We report a 3-year-old boy with a kidney-predominant presentation. He had periorbital edema, progressive pallor, cervical lymphadenopathy, proteinuria, and kidney dysfunction. He did not have the classic IPEX triad. Kidney biopsy showed mixed glomerular and tubulointerstitial injury. The biopsy showed glomerulosclerosis, capsular adhesions, podocyte foot-process effacement, immune deposits, and interstitial inflammation and fibrosis. Immune testing showed non-neoplastic lymphoproliferation. The findings resembled autoimmune lymphoproliferative syndrome (ALPS). They included lymphadenopathy, reactive lymphoid hyperplasia, and increased double-negative T cells. Next-generation sequencing found a hemizygous FOXP3 variant, NM_014009.4:c.746A > T (p.Glu249Val). The variant was absent from population databases. In silico tools predicted a harmful effect. Sanger sequencing confirmed the variant in the patient. His mother was a heterozygous carrier. His father tested negative. This pattern supported maternal transmission, not a de novo event.

Results

The patient received prednisone at 1 mg/kg/day at first. The dose was tapered after 1 month. Proteinuria decreased from 1328 mg/24 h to 871 mg/24 h. Kidney function did not worsen during available follow-up. The lymphoproliferative features improved clinically.

Conclusion

This case suggests that FOXP3-related immune dysregulation can present with kidney-predominant disease. It can also appear with ALPS-like lymphoproliferation. This may occur without the classic IPEX triad. FOXP3 testing may help selected boys with unexplained nephropathy and immune abnormalities. This is a single case without functional testing. For this reason, the link between the variant and the phenotype remains suggestive, not proven.

Introduction

Inherited disorders of immune regulation have broad clinical features. Patients may show autoimmunity, inflammation, infection, blood abnormalities, or lymph node enlargement. Next-generation sequencing

now helps identify single-gene immune disorders. This is useful when the phenotype does not match a classic diagnosis[1, 2].IPEX syndrome is caused by pathogenic variants in FOXP3[3–7]. FOXP3 is needed for the development and suppressive function of CD4 + CD25+FOXP3 + regulatory T cells[8–12]. Classic IPEX usually presents with early autoimmune enteropathy, insulin-dependent diabetes, and eczema[4, 6, 7, 13–15]. But FOXP3-related disease can be non-classic. Reported forms include late onset, incomplete triads, kidney disease, lung disease, and blood or lymphoproliferative features[16, 17]. Kidney involvement in FOXP3-related disease is still not fully defined. Reported patterns include tubulointerstitial nephritis, membranous glomerulopathy, minimal-change-like lesions, and other immune-mediated kidney injuries[18–21]. These findings show that FOXP3-related kidney disease is not one single pathology.Here, we describe a boy with a hemizygous FOXP3 c.746A > T (p.Glu249Val) variant. His main findings were nephropathy and ALPS-like lymphoproliferation. He did not show the classic IPEX triad. This case supports FOXP3 testing in selected boys with unexplained kidney disease and immune abnormalities.

Case presentation

Clinical presentation

The patient was a developmentally normal 3-year-old boy. He developed acute periorbital edema. He also had progressive facial pallor and cervical lymphadenopathy. Further evaluation found laterocervical, axillary, and abdominal lymphadenopathy. Cervical lymph-node biopsy showed reactive lymphoid hyperplasia. The available evaluation did not support malignancy.The patient later developed marked kidney involvement. Proteinuria was 1328 mg/24 h. The estimated glomerular filtration rate was about 49.4 ml/min/1.73 m2 at biopsy. He also had features of distal renal tubular acidosis. Kidney ultrasound was normal.Blood tests showed leukopenia, neutropenia, and anemia. Autoantibody screening was negative for antinuclear antibodies and antineutrophil cytoplasmic antibodies. Complement levels, including C3, C4, and CH50, were normal. These findings suggested immune disease without clear systemic autoantibody positivity.

Renal pathology

Kidney biopsy contained 39 glomeruli. Light microscopy showed 11 globally sclerosed glomeruli. Eight glomeruli had periglomerular fibrosis. Four glomeruli had capsular adhesions. Some glomeruli showed focal segmental mild mesangial proliferation. Most capillary loops remained open. Diffuse glomerular basement membrane thickening was not seen.The tubulointerstitial compartment showed important changes. Tubular atrophy involved about 1% of the cortex. Interstitial fibrosis was prominent. Patchy inflammatory infiltrates were mainly lymphocytes. Some lymphocytes were scattered, and some formed focal groups. Occasional eosinophils were present. Interstitial vessels were unremarkable.Immunofluorescence showed granular mesangial IgG deposition in 16 glomeruli. IgA, IgM, C3, C4, C1q, and fibrinogen were negative. Type IV collagen staining showed normal alpha-2 and alpha-5

chain distribution. These findings supported immune deposits without broad complement staining.Electron microscopy showed several linked changes. The glomerular basement membrane showed focal thickening of about 260–400 nm. Podocyte foot processes showed segmental effacement or fusion. Mesangial electron-dense deposits were present. Segmental subepithelial electron-dense deposits were also seen along capillary loops.

Overall, the biopsy showed mixed glomerular and tubulointerstitial injury. The pattern included glomerulosclerosis, segmental podocyte injury, immune deposits, and interstitial inflammation and fibrosis. This supports an immune-mediated component. It does not fit isolated primary focal segmental glomerulosclerosis alone.

Immunologic and lymphoproliferative evaluation

The patient had non-neoplastic lymphoproliferation with ALPS-like features. These features included lymphadenopathy, reactive lymphoid hyperplasia, and increased double-negative T cells. The DNT population was defined as CD3 + TCRalpha beta+CD4-CD8-. Immune phenotyping also showed fewer CD4 + FOXP3+CD25high Treg lymphocytes.These findings supported immune dysregulation. They also resembled ALPS. But the available data did not prove classic ALPS. Apoptosis assays were not fully documented. A complete ALPS biomarker panel was also unavailable. Full genetic testing of classic apoptosis-pathway genes was not documented. For this reason, we use the term ALPS-like lymphoproliferation.

Genetic analysis

Genetic testing was performed because the patient had nephropathy and immune dysregulation. Next-generation sequencing used phenotype-driven variant review. It identified a hemizygous FOXP3 variant, NM_014009.4:c.746A > T (p.Glu249Val). The variant was absent from gnomAD. In silico tools predicted a harmful effect. Sanger sequencing confirmed the variant in the patient. His mother was a heterozygous carrier. His father tested negative. This pattern supports maternal transmission rather than a de novo event. The healthy mother does not rule out pathogenicity in an X-linked disorder[13, 19–21]. Female carriers may remain asymptomatic because of X-chromosome inactivation. But X-chromosome inactivation was not tested here. So segregation alone cannot prove causality.

The FOXP3 variant and the Treg abnormality raised suspicion for FOXP3-related disease. The immune phenotype also supported this suspicion. But no functional test was available for p.Glu249Val. The genotype-phenotype link remains suggestive.

Treatment and follow-up

The patient received prednisone at an initial dose of 1 mg/kg/day. The dose was tapered after 1 month. During follow-up, proteinuria decreased from 1328 mg/24 h to 871 mg/24 h. Kidney function remained stable or improved in the available records. The lymphoproliferative features improved clinically.The partial fall in proteinuria is consistent with an immune-mediated component. It does not prove that the FOXP3 variant caused the kidney injury. Longer follow-up is needed to define kidney prognosis.

Discussion

This case shows a kidney-predominant and non-classic presentation of suspected FOXP3-related immune dysregulation. Classic IPEX often begins in infancy. It usually includes enteropathy, insulin-dependent diabetes, and eczema[4, 6, 7, 14, 15]. This patient first showed nephropathy, cytopenia, and lymphoproliferation. So the absence of the full classic triad should not exclude FOXP3-related disease[18, 22]. Kidney disease is now recognized within the FOXP3/IPEX spectrum. But reported pathology is variable. Prior studies described tubulointerstitial nephritis, membranous glomerulopathy, minimal-change-like disease, and other immune-mediated glomerular lesions[20, 21]. In this patient, the biopsy showed both glomerular and tubulointerstitial injury. Immune deposits and interstitial inflammation argue against a purely structural podocyte disease. These findings support an immune-mediated component.

The lymphoproliferative findings need cautious wording. Classic ALPS is linked to defective lymphocyte apoptosis. It is often associated with FAS, FASLG, CASP10, and related pathways[23–27]. This patient had lymphadenopathy, reactive lymphoid hyperplasia, and increased DNTs. But the available data were not enough for definitive ALPS. Renal disease has also been described in ALPS, but this association is uncommon[28]. We use ALPS-like lymphoproliferation to show similarity without overdiagnosis.

A simple mechanism can connect the observed findings. FOXP3-dependent Treg dysfunction can weaken immune tolerance[15]. This may allow humoral immune activation, renal immune deposits, and non-neoplastic lymphoproliferation. The reduced CD4 + FOXP3+CD25high Treg population fits altered Treg biology. But this mechanism is only inferred. FOXP3 activity, Treg suppressive function, cytokines, and specific autoantibodies were not tested in a systematic way.

The variant interpretation also needs care. The c.746A > T (p.Glu249Val) variant was absent from population databases. Prediction tools suggested a harmful effect. The patient phenotype fits FOXP3-related immune dysregulation[13, 14]. But the variant came from a clinically healthy mother. In X-linked disease, this pattern can occur[7, 13]. Still, segregation alone does not prove causality. Functional testing and similar cases would strengthen the evidence.

This report has clear limits. It describes one patient only. A complete ALPS diagnostic panel was not available. The kidney biopsy showed overlapping glomerular and tubulointerstitial features. More serum immunoglobulin subclass data could clarify the diagnosis. Validated immunostaining and representative electron-microscopy images would also help. No functional assay tested the effect of p.Glu249Val on FOXP3 expression, localization, DNA binding, or Treg suppression.

Even with these limits, the case has clinical value. FOXP3 testing may help selected boys with unexplained nephropathy and immune abnormalities. Useful clues may include immune deposits, tubulointerstitial inflammation, cytopenia, lymphadenopathy, or ALPS-like immune findings[18, 28]. This approach may be useful even when severe enteropathy, diabetes, and eczema are absent.

Declarations

Conflict of interest:

The authors declare no competing interests.

Consent for publication:

Written informed consent was obtained from the patient's legal guardians. The consent covered this case report and accompanying images. The patient was de-identified.

Ethics approval and consent to participate:

Not applicable for this case report, or approved or waived by the local institutional review board according to institutional policy.

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Authors' contributions

L.H. designed and supervised the study. L.H.drafted the first manuscript. Y.X. revised and edited the manuscript. Y.W. and H.F. analyzed the clinical, pathological, and genetic data. All authors reviewed and approved the final manuscript.

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None.

Availability of data and materials

The reference resources used for interpretation are available from public databases. These include NCBI, Monarch Initiative, RCSB Protein Data Bank, gnomAD, and VarSome. Patient-level data are available from the corresponding author on reasonable request. Access requires appropriate ethical approval.

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Tables

Table 1. Clinical, immunological, renal, and genetic findings of the patient

Category	Finding
Demographics	3-year-old boy; developmentally normal before disease onset.
Initial manifestations	Acute periorbital edema, progressive facial pallor, and cervical lymphadenopathy.
Lymphoproliferative findings	Laterocervical, axillary, and abdominal lymphadenopathy. Cervical lymph-node biopsy showed reactive lymphoid hyperplasia. The available evaluation did not support malignancy.
Hematologic findings	Leukopenia (2.21 x 10^9/L), anemia (hemoglobin 70 g/L), and neutropenia.
Immunologic findings	Increased DNTs (2.5%; reference <1.5%). Reduced CD4+FOXP3+CD25high Treg lymphocytes (0.06%; reference 1-5%). Treg suppressive function was not assessed.
Renal presentation	Proteinuria 1328 mg/24 h. eGFR was about 49.4 ml/min/1.73 m2 at biopsy. Features of distal renal tubular acidosis were present. Kidney ultrasound was normal.
Light microscopy	Thirty-nine glomeruli were obtained. Eleven were globally sclerosed. Eight had periglomerular fibrosis. Four had capsular adhesions. Focal segmental mild mesangial proliferation was present. Interstitial fibrosis and patchy lymphocytic infiltrates were prominent.
Immunofluorescence / IHC	Granular mesangial IgG deposition was seen in 16 glomeruli. IgA, IgM, C3, C4, C1q, and fibrinogen were negative. Type IV collagen alpha-2 and alpha-5 chains were normally distributed.
Electron microscopy	Focal GBM thickening (260-400 nm). Segmental podocyte foot-process effacement or fusion. Mesangial electron-dense deposits. Segmental subepithelial electron-dense deposits.
Genetic findings	Hemizygous FOXP3 NM_014009.4:c.746A>T (p.Glu249Val) variant. Absent from gnomAD. Predicted harmful by in silico tools. Mother was a heterozygous carrier. Father was negative.
Treatment and outcome	Prednisone 1 mg/kg/day at first. Dose tapered after 1 month. Proteinuria decreased to 871 mg/24 h. Kidney function did not worsen during available follow-up. Lymphoproliferative features improved clinically.

Figures

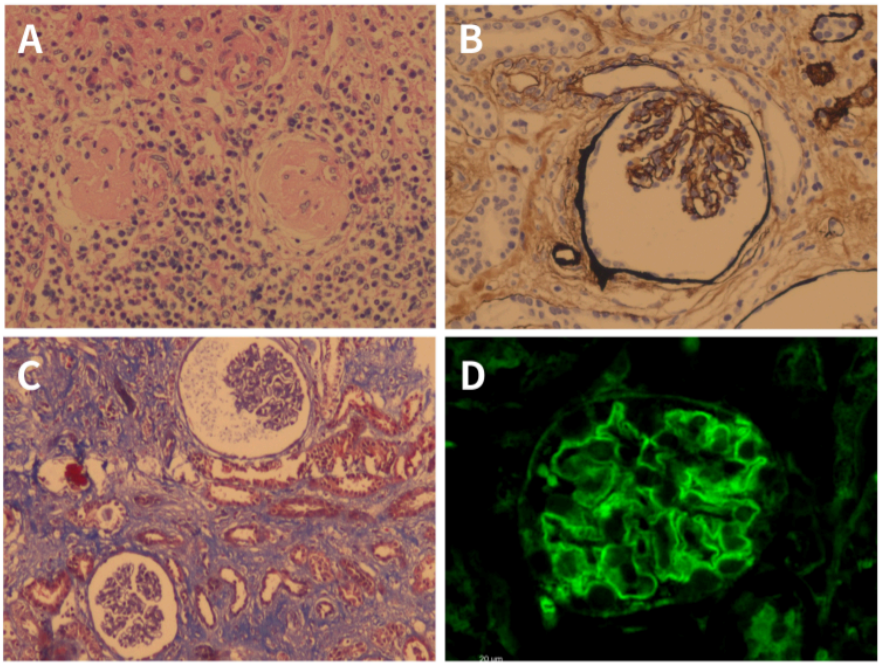


Figure 1

Renal histopathology of the patient. Representative kidney biopsy images show mixed glomerular and tubulointerstitial injury. (A) Periodic acid-Schiff staining shows globally sclerosed glomeruli and interstitial inflammation. (B) Periodic Schiff-methenamine silver staining shows capsular changes, segmental glomerular injury, and capillary-wall changes. (C) Immunofluorescence shows granular mesangial IgG deposition. (D) Electron microscopy shows segmental podocyte foot-process effacement or fusion and electron-dense deposits. Original magnifications and scale bars are shown in the figure panels.

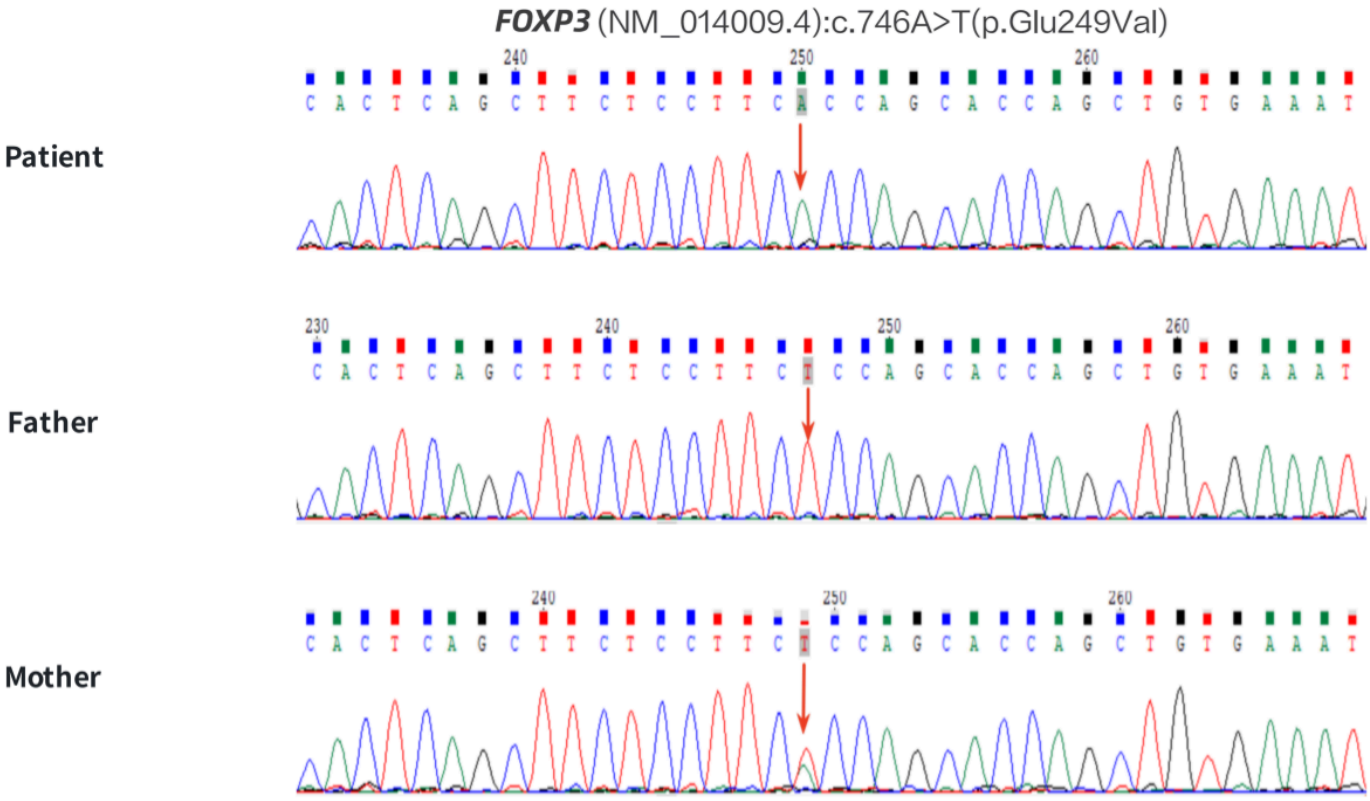


Figure 2

Segregation analysis of the FOXP3 variant. Sanger sequencing confirmed the hemizygous FOXP3 NM_014009.4:c.746A>T (p.Glu249Val) variant in the patient. The mother was a heterozygous carrier. The father tested negative. This result supports maternal transmission rather than a de novo event.