

# Cardiopulmonary arrest in a patient with delayed diagnosis of immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

Louanne M. Tourangeau, M.D., and Taylor A. Doherty, M.D.

## ABSTRACT

We present the case of a 21-year-old male patient with a history of autoimmune nephritis, peripheral eosinophilia, eosinophilic esophagitis, and enteropathy who developed subacute worsening cardiomyopathy with systolic dysfunction. Diagnostic studies revealed a one-codon deletion in the FoxP3 gene, which led to the diagnosis of immune dysregulation polyendocrinopathy, enteropathy X-linked syndrome. Unfortunately, this patient suffered from cardiopulmonary arrest with resulting anoxic encephalopathy before diagnosis confirmation. Here, we discuss the key issues surrounding the diagnostic and therapeutic approaches to this patient's condition.

(Allergy Asthma Proc 32:74–78, 2011; doi: 10.2500/aap.2011.32.3378)

## CASE PRESENTATION

### Reason for Consult

New-onset cardiomyopathy in a patient with an undefined autoimmune disorder and long-standing peripheral eosinophilia.

### History of Present Illness

We report a 21-year-old white male patient with a 3-month history of progressive dyspnea, ascites, and chest discomfort who presented to the University of California, San Diego, Medical Center. Transthoracic echocardiogram revealed an ejection fraction of 33% with left ventricular dilation, moderate decreased systolic function, and global left ventricular hypokinesis. chest radiograph showed pulmonary edema and cardiac catheterization revealed normal coronary arteries. The Department of Allergy and Immunology was consulted because of long-standing eosinophilia and history of previously undiagnosed autoimmune disease.

### Medical History

The patient was reportedly healthy until 6 months of age, when he developed lymphadenopathy and eczema

followed by cellulitis and sinusitis at 9 months. At 2 years of age, he was evaluated for Fanconi syndrome and a renal biopsy revealed interstitial nephritis with lymphocytic infiltration and fibrosis; a diagnosis of autoimmune nephritis was made. At the age of 3 years, he developed Coombs positive autoimmune hemolytic anemia. At the age of 4 years, he suffered from chronic diarrhea; jejunal biopsy specimens revealed severe villous atrophy.

Renal transplant was performed at the age of 4 years for progressively worsening renal insufficiency. After transplant, he was started on cyclosporine. Five months after transplant his diarrhea improved and a repeat jejunal biopsy was normal.

At the age of 18 years, he experienced acute rejection of his transplanted kidney resulting in transplant nephrectomy. At the age of 19 years, he underwent a second renal transplant only to experience rejection <2 years later. At the age of 21 years, he underwent transplant nephrectomy and was taken off immunosuppression and placed on hemodialysis. This was 4 months before the patient's presentation at University of California, San Diego. Of note, he had no previous history of lung disease or recurrent pneumonias.

### Social History

Previously, he was a nationally ranked competitive gymnast in good physical condition. He had no history of alcohol, tobacco, or drug use.

### Family History

There was no family history of autoimmunity, recurrent infections, atopy, or consanguinity. There were no early deaths in the family. This patient has one sister

From the Department of Medicine, Division of Rheumatology, Allergy and Immunology, University of California, San Diego, La Jolla, California

There are no pertinent disclosures for this case report; L. Tourangeau's fellowship is supported through an NIH T32 grant AI 07469

The authors had no conflicts of interest

Address correspondence and reprint requests to Louanne M. Tourangeau, M.D., 9500 Gilman Drive, MC 0732, La Jolla, CA 92093-0732

E-mail address: ltourangeau@ucsd.edu

Copyright © 2011, OceanSide Publications, Inc., U.S.A.

Table 1 Differential diagnosis

| Immunodeficiencies with Elevated IgE                                         | Disorders with Elevated IgE and Peripheral Eosinophilia | Disorders with Autoimmunity and Elevated IgE | Other Considerations                             |
|------------------------------------------------------------------------------|---------------------------------------------------------|----------------------------------------------|--------------------------------------------------|
| Wiskott-Aldrich syndrome<br>Omenn syndrome                                   | Allergic conditions<br>ABPA                             | CVID<br>HES with autoimmunity                | Malignancy<br>Myelodysplastic syndrome           |
| Atypical complete DiGeorge syndrome<br>Comel-Netherson<br>Hyper-IgE syndrome | Strongyloides<br>HES<br>IPEX                            | Wiskott-Aldrich syndrome<br>IPEX             | Parasitic disease<br>Mastocytosis<br>Medications |

HES = hypereosinophilic syndrome; WAS = Wiskott-Aldrich syndrome; ABPA = allergic bronchopulmonary aspergillosis; CVID = common variable immunodeficiency; IPEX = immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome.

who is healthy and nulliparous, one maternal uncle who is healthy and without children, and one maternal aunt who has three children including a boy who is healthy. Biological father is assumed to be healthy but he is no longer involved with the patient and his family pedigree is unknown.

### Physical Examination

Examination revealed a man with short stature. Oropharyngeal exam was normal without retention of primary teeth. Chest auscultation revealed bibasilar crackles. Cardiac exam revealed a normal heart rate rhythm and no murmurs. Abdominal exam was remarkable for moderate abdominal distension, ascites, and well-healed abdominal scars. There were hyperpigmented macules scattered on bilateral lower extremities.

### Laboratory and Other Diagnostic Findings

Laboratory studies revealed a white blood cell count of  $10,900/\text{mm}^3$  (reference range, 4000–11,000  $\text{mm}^3$ ) with 25% eosinophils (reference range, 1–3%), hemoglobin of 9.4 (reference range, 14–17 gm/dL), and platelet count of  $343,000/\text{mm}^3$  (reference range, 130,000–400,000/ $\text{mm}^3$ ).

Total IgE was 11,444 IU/mL (reference, <100 IU/mL), tryptase was 25.6  $\mu\text{g/L}$  (reference range, 0.4–10.9  $\mu\text{g/L}$ ), and brain natriuretic peptide was >5000 pg/mL (<100 pg/mL). Thyroid stimulating hormone was 13.5 IU/mL and T4 was 0.078 IU/mL (reference range, 0.93–1.70 ng/dL) (previously undiagnosed hypothyroidism). The serum protein electrophoresis showed low albumin. Parietal cell antibody, anticardiolipin antibody, antimitochondrial antibody, antinuclear cytoplasmic antibody, and antinuclear antibody, were negative. Antismooth muscle antibody was positive with a titer of 1:160 (reference, <1:40 titer). Creatine kinase (CPK) was normal. Stool for ova and parasites was negative  $\times 3$ . Blood cultures were negative  $\times 3$ . T cell

subsets were normal. Glucose level was 88 mg/dL (reference range, 65–110 mg/dL).

Right thigh biopsy specimen showed irregular acanthosis and parakeratosis with minimal inflammation, superficial parakeratosis, and scattered eosinophils. Chest CT showed diffuse ground glass opacities with bibasilar edema consistent with congestive heart failure exacerbation. CT of the abdomen and pelvis revealed ascites with retromesenteric lymphadenopathy and splenomegaly.

## QUESTIONS

### What is the Differential Diagnosis?

The differential diagnosis for cardiomyopathy with hypereosinophilia and history of autoimmunity includes hypereosinophilic syndrome as a highly likely consideration. Additional considerations include immune deficiencies with elevated IgE levels, disorders causing elevated IgE and peripheral eosinophilia, and disorders with autoimmunity and elevated IgE such as immune dysregulation polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome and hyper-IgE syndrome. A more complete differential diagnosis is summarized in Table 1.

### What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

Hypereosinophilic syndrome causes end-organ damage and is associated with a restrictive or, less commonly, a dilated cardiomyopathy, caused by eosinophil invasion of the myocardium.<sup>1–3</sup> To investigate this possibility, a myocardial biopsy or a cardiac MRI is necessary. Recent developments in cardiac MRI modalities provide superior detection of eosinophilic endomyocardial disease and may be preferred over right ventricular biopsy.<sup>4,5</sup> Additionally, a bone marrow bi-

opsy should be undertaken to evaluate the presence of FIP1L1-PDGFR $\alpha$  fusion gene and clonal lymphocytic populations. The FIP1L1-PDGFR $\alpha$  mutation has therapeutic implications because it indicates responsiveness to Imatinib.<sup>6</sup> Bone marrow biopsy is also obligatory to investigate malignancy, mastocytosis, and myelodysplastic syndrome.

In terms of hyper-IgE syndrome, it is imperative to assess the presence of eczema-like rashes, recurrent staphylococcal infections, and pneumatocoles.<sup>7</sup> Our patient had an elevated total IgE level and the presence of atopic dermatitis. We, however, failed to identify retention of primary teeth, pneumatocoles, or staphylococcal infections. Because the patient had a significant history of autoimmunity, IPEX syndrome was a consideration, requiring assays for FoxP3 mutational analysis and protein expression.

### Clinical Course

The patient underwent a cardiac MRI, which did not show infiltrative disease or endomyocardial disease. Bone marrow biopsy revealed 20% eosinophils with a normal karyotype, cytogenetics, immunostaining, and mast cells. FIP1L1-PDGFR $\alpha$  fusion gene analysis was negative.

To investigate the possibility of IPEX, FoxP3 mutational analysis and FoxP3 protein expression was performed. He was subsequently discharged but suffered a cardiopulmonary arrest within 24 hours. Despite successful resuscitation, he suffered from anoxic encephalopathy and is currently in a persistent vegetative state.

Two weeks later, FoxP3 studies returned revealing a one-codon deletion in the leucine zipper domain of FoxP3. The deletion was located at 748\_750 del AAG (K250 del; Fig. 1) and is associated with IPEX syndrome in the hemizygous state.<sup>8–10</sup> FoxP3 protein expression was only modestly decreased at 80% (reference range, 84–95). Flow cytometry of peripheral CD4<sup>+</sup> cells is shown in Fig. 2.

### DISCUSSION

In this patient with a history of autoimmune nephritis, enteropathy, hemolytic anemia, hypothyroidism, elevated total IgE, and peripheral eosinophilia, the FoxP3 mutational analysis confirms the diagnosis of IPEX syndrome. IPEX syndrome is a rare entity that causes life-threatening systemic autoimmunity from underlying immune dysregulation. This condition was first described in 1982 in one Northern European family where 17 male infants died in the 1st years of life.<sup>11</sup> Interestingly, the gene itself was not mapped until 18 years later when it was found on the short (p) arm of the X chromosome at position 11.23.<sup>12</sup> Several studies have found that FoxP3 is expressed at high levels in thymic-

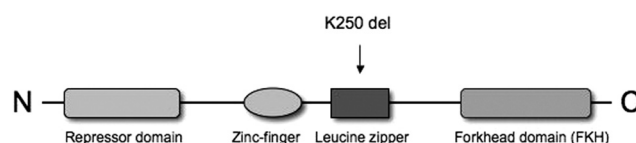


**Figure 1.** Organization of FoxP3 protein. K250 deletion in leucine zipper shown (arrow) and it is known to impair oligomerization.

derived naturally occurring Treg cells (nTreg) and CD4<sup>+</sup>CD25<sup>hi</sup> adaptive Treg (aTreg) cells. Recent work suggests that cells identified as CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>lo</sup> correlate well with the CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup> population.<sup>13</sup>

Studies using the FoxP3-deficient scurfy mouse have provided insight into the pathogenesis of this syndrome. The scurfy mouse resembles IPEX syndrome because it shows X-linked inheritance of scaly skin, runting, hematologic abnormalities, lymphadenopathy, diarrhea, and death by 3–4 weeks of age. The mutated gene in scurfy mice was obtained by positional cloning and named “FoxP3.” Mutated FoxP3 results in a complete lack of CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells.<sup>3</sup> After identifying the FoxP3 mutation in murine models, the human FoxP3 was sequenced in several IPEX families and found to be mutated.<sup>14–16</sup>

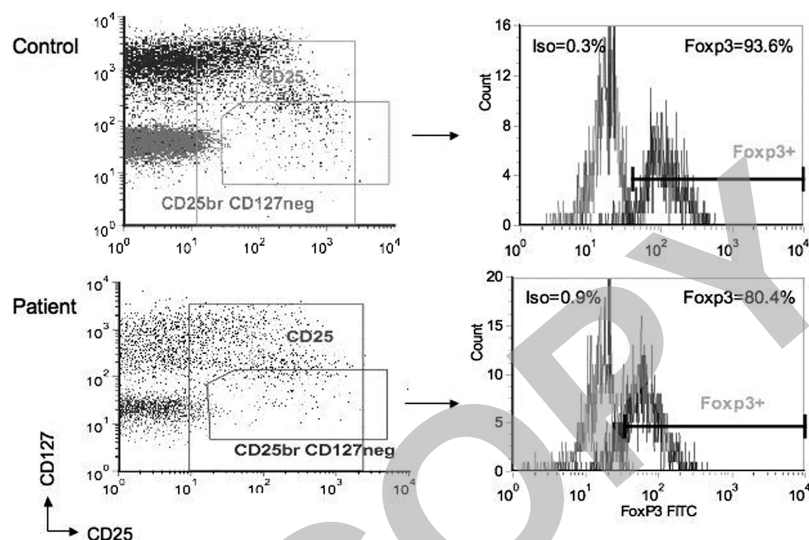
Structurally, FoxP3 protein encodes a forkhead DNA-binding domain, a N-terminus domain that regulates transcription, a zinc-finger domain that functions in protein–DNA interactions and a leucine zipper domain that functions in dimerization.<sup>17</sup> The leucine zipper domain was the affected portion of the protein in the patient presented here (Fig. 1). The K250 deletion in IPEX syndrome is known to eliminate FoxP3 homooligomerization.<sup>18</sup>

In regard to clinical studies, the largest study to date investigated 105 IPEX syndrome and IPEX-like syndrome patients. They found that genotypes do not necessarily correspond to the expressed phenotype and that FoxP3 mutations may not always result in protein abrogation.<sup>19,20</sup> This is consistent with the case presented, because the FoxP3 expression was only modestly reduced compared with IPEX phenotypes where almost no FoxP3 protein is detected.

In our patient’s case, he was treated with cyclosporine and prednisone from the age of 4 years as part of his antirejection regimen after renal transplant. Of interest, our patient worsened after his second transplant nephrectomy, when his immunosuppression was discontinued. It is likely that his immunosuppressive transplant regimen was inadvertently treating his undiagnosed IPEX syndrome and cessation of therapy worsened his condition. Therapeutic options for IPEX syndrome include immunosuppression with corticosteroids, calcineurin inhibitors, and, possibly, bone marrow transplantation.

It is unclear what relationship IPEX syndrome had in the pathogenesis of this patient’s cardiomyopathy and

**Figure 2.** Flow cytometry to evaluate Foxp3 protein expression. CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>—</sup> cells (left) were evaluated for Foxp3 expression (right). Control sample run the same day (top row) as well as the patient's sample (bottom row) are shown.



cardiac arrest, especially given the MRI without evidence of an infiltrative process. Although the symptoms reported for IPEX syndrome are diverse, we do not find any report of cardiomyopathy or cardiac arrest in IPEX syndrome patients. It is difficult to predict if ongoing immunosuppression would have led to a better outcome, especially given the severity of his cardiac dysfunction at the time of consultation.

## Final Diagnosis

Final diagnosis was IPEX syndrome.

## SUMMARY AND CONCLUSIONS

IPEX syndrome should be considered in any male patient with diarrhea, failure to thrive, eczema, and the presence of autoimmune disease or endocrine abnormalities. Clinicians should be aware that phenotypic expression varies greatly; as a result, a high degree of suspicion is necessary to make the diagnosis of IPEX syndrome. When establishing the diagnosis, investigation should include FoxP3 mutational analysis, as well as, FoxP3 protein expression. If diagnosed, genetic testing is recommended to identify if the condition is caused by an X-linked inherited mutation or a *de novo* mutation. If it is found to be X-linked, genetic counseling should be provided for all carriers. This case illustrates the heterogeneous nature of IPEX syndrome and the need for awareness of this disease.

## ACKNOWLEDGMENTS

The authors thank the participating family members and the presented patient, as well as, Cincinnati Children's Hospital Diagnostic Center for Heritable Immunodeficiencies for performing the FoxP3 mutational analysis and protein expression.

## REFERENCES

1. Christen R, Morant R, Schneider J, et al. Progressive dilated cardiomyopathy in a patient with longstanding and complete prednisone-induced hematological remission of idiopathic hypereosinophilic syndrome. *Klin Wochenschr* 67:358–365, 1989.
2. DePace NL, Nestico PF, Morganroth J, et al. Dilated cardiomyopathy in the idiopathic hypereosinophilic syndrome. *Am J Cardiol* 52:1359–1360, 1983.
3. Subhash HS, George P, Sowmya G, et al. Progressive dilated cardiomyopathy in a patient with hypereosinophilic syndrome despite prednisone induced hematological remission. *J Assoc Physicians India* 49:944–945, 2001.
4. Syed IS, Martinez MW, Feng DL, and Glockner JF. Cardiac magnetic resonance imaging of eosinophilic endomyocardial disease. *Int J Cardiol* 126:e50–e52, 2008.
5. Ogbogu PU, Rosing DR, and Horne MK III. Cardiovascular manifestations of hypereosinophilic syndromes. *Immunol Allergy Clin North Am* 27:457–475, 2007.
6. Scheinfeld N. A comprehensive review of imatinib mesylate (Gleevec) for dermatological diseases. *J Drugs Dermatol* 5:117–122, 2006.
7. Grimbacher B, Holland SM, Gallin JJ, et al. Hyper-IgE syndrome with recurrent infections—An autosomal dominant multisystem disorder. *N Engl J Med* 340:692–702, 1999.
8. Kobayashi I, Shiari R, Yamada M, et al. Novel mutations of FOXP3 in two Japanese patients with immune dysregulation, polyendocrinopathy, enteropathy, X linked syndrome (IPEX). *J Med Genet* 38:874–876, 2001.
9. Owen CJ, Jennings CE, Imrie H, et al. Mutational analysis of the FOXP3 gene and evidence for genetic heterogeneity in the immunodysregulation, polyendocrinopathy, enteropathy syndrome. *J Clin Endocrinol Metab* 88:6034–6039, 2003.
10. Wildin RS, Smyk-Pearson S, and Filipovich AH. Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. *J Med Genet* 39:537–545, 2002.
11. Powell BR, Buist NR, and Stenzel P. An X-linked syndrome of diarrhea, polyendocrinopathy, and fatal infection in infancy. *J Pediatr* 100:731–737, 1982.
12. Bennett CL, Yoshioka R, Kiyosawa H, et al. X-Linked syndrome of polyendocrinopathy, immune dysfunction, and diarrhea maps to Xp11.23–Xq13.3. *Am J Hum Genet* 66:461–468, 2000.
13. Hannibal MC and Torgerson T. IPEX Syndrome. *Gene Rev NIH*, Dec. 2007.
14. Bennett CL, Christie J, Ramsdell F, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet* 27:20–21, 2001.

15. Chatila TA, Blaeser F, Ho N, et al. JM2, encoding a fork head-related protein, is mutated in X-linked autoimmunity-allergic dysregulation syndrome. *J Clin Invest* 106:R75–R81, 2000.
16. Wildin RS, Ramsdell F, Peake J, et al. X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. *Nat Genet* 27:18–20, 2001.
17. Campbell DJ, and Ziegler SF. FOXP3 modifies the phenotypic and functional properties of regulatory T cells. *Nat Rev Immunol* 7:305–310, 2007.
18. Li B, Samanta A, Song X, et al. FOXP3 is a homo-oligomer and a component of a supramolecular regulatory complex disabled in the human XLAAD/IPEX autoimmune disease. *Int Immunol* 19:825–835, 2007.
19. Gambineri E, Perroni L, Passerini L, et al. Clinical and molecular profile of a new series of patients with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome: Inconsistent correlation between forkhead box protein 3 expression and disease severity. *J Allergy Clin Immunol* 122:1105–1112 e1, 2008.
20. Gambineri E, Hackett M, Añover S, et al. Clinical, Laboratory, and molecular evaluation of 105 patients with a phenotype of immune dysregulation, polyendocrinopathy, x-linked (IPEX) syndrome. *J Allergy Clin Immunol*, 2009. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.