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Case Report

A Mild Presentation of Immune Dysregulation Polyendocrinopathy Enteropathy X-linked Syndrome

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Abstract

Patients with Immune Dysregulation Polyendocrinopathy Enteropathy X-linked Syndrome classically present in infancy with intractable diarrhea, chronic dermatitis and autoimmune disorders. However, its presentation can be variable and often very mild. We present an atypically mild case of IPEX demonstrating the importance of genetic workup and high index of suspicion. Laboratory evaluation was performed including T, B, and NK cells, immunoglobulin levels, autoantibodies, lymphocyte mitogen proliferation assay, as well as neutrophil oxidative burst assay. FOXP3 flow cytometry was performed on peripheral blood mononuclear cells and the FOXP3 gene was sequenced. Patient was found to have normal T and B cells, elevated IgE and low IgA. His initial foxp3 flow cytometry was normal but a repeat flow cytometry showed a mild decreased percentage of CD4+CD25+FOXP3+ T cells compared to normal control. FOXP3 mutation identified: Hemizygous c.454+4A>G. The patient's very mild presentation of IPEX may be secondary to the fact that he is able to produce a small percentage of normal FOXP3 protein. This is the mildest clinical presentation of IPEX reported. However, it is expected that he will ultimately have significant clinical problems making his early diagnosis very important.

Abbreviations

IPEX: Immune Dysregulation Polyendocrinopathy Enteropathy X-Linked Syndrome

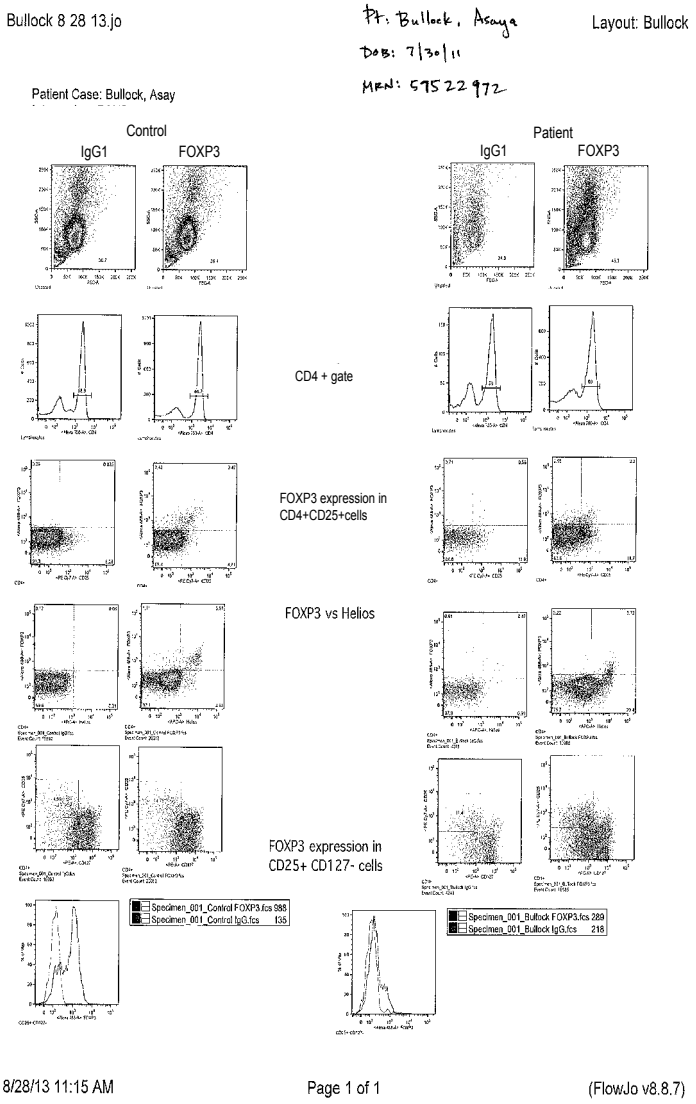
Introduction

Immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome is a rare x-linked inherited condition. Various mutations in the transcription factor *forkhead box protein 3 gene* (FOXP3) [1], the major regulator of T regulatory cells located on chromosome Xp11.23, cause IPEX. Patients classically present in infancy with intractable diarrhea often requiring total parental nutrition, chronic dermatitis and autoimmune disorders such as insulin- dependent diabetes mellitus. Affected males may die before one year of age if the disease is not diagnosed early. However, recent reports suggest that IPEX may present with less severe manifestations such as mild to moderate arthritis or enteropathy [2]. We present the mildest case of IPEX syndrome reported in a 23 month old boy with normal FOXP3 flow cytometry but with the genetic mutation.

Case Report

The patient is an active African American boy with sickle cell trait, urticaria related milk allergy and blaschkitis with non-significant family history who initially presented at 16 months old to the gastroenterologist with a history of painless hematochezia and frequent soft stools. The patient was in the 86th and 33rd percentile for height and weight respectively. An infectious workup, complete blood count, comprehensive metabolic panel, and inflammatory markers

were all unremarkable except mild eosinophilia of 9% (0.80 x10(9)/L). At follow up one month later, the patient continued to experience hematochezia and a decrease to 79th and 24th percentile for height and weight respectively. He was diagnosed with C. difficile colitis that was initially treated with Metronidazole followed by Vancomycin when his symptoms worsened. After treatment, repeat C. difficile polymerase chain reaction was negative but he was admitted to the hospital for intravenous hydration secondary to continued emesis, bloody diarrhea and minimal oral intake. An endoscopy and colonoscopy were performed that grossly showed an erythematous stomach with snakeskin appearance, and diffuse severe inflammation characterized by erythema, friability, loss of vascularity and pus from rectum to transverse colon. Pathologic evaluation showed small intestinal mucosa with focal partial villous atrophy and crypt hyperplasia. The entire colon and rectal mucosa showed acute and chronic inflammation with acute cryptitis and crypt abscesses. He was diagnosed with presumed inflammatory bowel disease and started on sulfasalazine. Repeat colonoscopy two months later showed worsening of his pathological findings despite improved clinical symptoms. At the age of 19 months, he was seen by Allergy and Immunology for possible immunodeficiency. Clinically, he was well appearing with weight in the 56th percentile. His diarrhea had resolved and he had a good appetite eating a variety of foods despite his persistent pathological findings. Autoimmune work-up included negative anti-thyroid antibodies and anti- islet cell antibodies. His immunoglobulins were notable for IgM 50.1 mg/dl, elevated IgG 1850 mg/dl, elevated IgE 339 IU/ml and low IgA<6mg/dl; T/B/NK cell subsets revealed CD3: 77% (2130 cells/uL); CD4: 51% (1424 cells/uL); CD8: 21% (584 cells/uL); CD19: 17% (482 cells/uL); CD16/56: 4% (122 cells/uL). Both mitogen lymphocyte proliferation and neutrophil oxidative burst assay were normal. CD18 (95%) and CD15s (100%) expression were normal. Initial FOXP3 flow cytometry was normal but genetic testing revealed an intron mutation of 454+4A>G. We then sent blood specimen to another lab where the patient's FOXP3 flow cytometry showed 2.2% CD4+CD25+FOXP3+ T cells compared to the normal control (3.5%) (Figure 1) and that these cells were FOXP3 dim based on mean fluorescence intensity. They also confirmed the same mutation (Troy Torgerson, MD, PhD, Immunology Diagnostic Laboratory, Seattle, WA). FOXP3 cDNA demonstrated that the predominant spliced mRNA transcript lacked both exons 2 and 3, causing a frameshift and significantly truncated FOXP3 protein. Less than 10% of transcripts were full length, thereby producing only a small amount of normal protein. (Dr. Troy Torgerson, MD, PhD, Immunology Diagnostic Laboratory, Seattle, WA). The patient's mother and sister were also tested and found to be carriers of the same foxp3 mutation.



Discussion

This case of the mildest phenotype reported of IPEX adds to the growing literature of varying phenotype and genotype presentations of this syndrome [1]. Although there are no clear indications as to when to suspect IPEX, this patient had some consistent clinical features including enteropathy, eosinophilia and elevated IgE [3]. His histopathology also showed partial villous atrophy of the small intestine, which is seen in IPEX patients. Other immunological conditions that are part of the differential include Common Variable Immunodeficiency, Chronic Granulomatous Disease, and Leukocyte Adhesion Deficiency for which we ruled out. The patient's mild clinical presentation may be attributed to the small amount of normal mRNA transcript and presumably protein production present. This case demonstrates the importance of obtaining genetic mutation analysis in addition to flow cytometry. Flow cytometry alone may have delayed diagnosis or led to misdiagnosis in this patient. It is important to note that even with this milder presen-

tation, the patient is at increased risk for significant problems later in life as evidenced by an adult patient reported in the literature who was determined to have the same mutation with persistent enteropathy who developed multiple severe chronic diseases over time [2]. Interestingly, the adult patient also had a brother who had died at one month old from intractable diarrhea. Compared to him, our patient is doing remarkably well, currently without significant gastrointestinal symptoms, never requiring chronic steroids, and without any manifestations of other autoimmune disorders at 3 years old. However, as only one other patient was reported to have this same mutation in the literature and knowing the potential morbidity and mortality of IPEX, our patient's prognosis is uncertain. There are currently no standardized treatment guidelines but bone marrow transplant (BMT) is known to be potentially curative. Various immunosuppressive medications have been tried such as high dose steroids, cyclosporine, tacrolimus, methotrexate, infliximab, and rituximab but are usually only temporarily effective and have significant side effects [4]. Recently in two small studies, sirolimus was found to be helpful in controlling gastrointestinal symptoms but potential for long term remission is still unknown [5,6]. Our patient is awaiting BMT given the high likelihood of disease progression and morbidity. When considering the differential of early onset enteropathy or autoimmune endocrinopathy it is important to consider IPEX even when the symptoms may not be severe or life threatening, especially with accompanying clinical features such as eosinophilia, elevated IgE, or characteristic small bowel pathology.

Conflict of interest: There are no conflicts of interests to disclose.

Contributors' Statement

Dr. Spalding, Dr. Klevner, and Dr. Kim directly takes care of the patient and wrote the various sections of the case report together.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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