Fraternal twins with job's syndrome and immune complex nephritis

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Abstract Job's syndrome or autosomal dominant hyperimmunoglobulin E syndrome (Hyper-IgE) is a rare disorder that results from a STAT3 gene mutation, which results in the absence of T-helper 17 (Th17) cells and manifests as a severe immunodeficiency. Affected individuals suffer recurrent soft tissue and pulmonary infections among other manifestations, and the spectrum of the disease is still being characterized. We describe 2 sisters with Job's syndrome each with variable expressivity. However, both patients developed proteinuric kidney disease and had biopsies confirming the presence of immune complex glomerulonephritis with staining for immunoglobulins and complement components. Previous reports link Job's syndrome and the development of systemic lupus erythematosus (SLE), but proliferative immune complex glomerulonephritis has not been described. We speculate that continual internal and external antigen exposure may induce an autoimmune process similar to SLE, which in turn may account for the immune complex disease in the kidney.

Keywords Job's syndrome · Hyperimmunoglobulin E syndrome · Immune complex glomerulonephritis · Lupus nephritis

Abbreviations

AKI	Acute kidney injury
ANA	Anti-nuclear antibody
Anti-Sm	Anti-smith antibody
SLE	Systemic lupus erythematosus
STAT-3	Signal transducer and activator of transcription 3
Th17	T-helper 17 cell

Introduction

Job's syndrome, named after the Biblical figure who suffered greatly from cutaneous afflictions, is a primary immunodeficiency syndrome affecting T cell and myeloid cells first described by Davis et al. in 1966 [1]. The genetic basis for the disease was unknown until a pair of reports by Holland et al. and Menegishi et al. published their findings nearly 40 years later in 2007 [2, 3]. The syndrome is characterized clinically by eczema and recurrent pyogenic skin, sinus and pulmonary infections. The syndrome is also known as hyperimmunoglobulin E syndrome (HIES) because eosinophilia and elevated IgE levels are hallmark findings of the disease [4]. Other manifestations include several soft tissue abnormalities such as retained primary teeth, scoliosis, hyperextensibility, arched palate and frontal bossing. Patients are also at significant life-long risk for developing lymphoma. We present the cases of African-American fraternal twins with Job's syndrome who

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developed a distinct pattern of renal injury that has not been reported.

Case report

Twin A

A 23-year-old African-American female with a childhood history significant for severe eczema, severe persistent asthma, scoliosis s/p repair at age 16, and Arnold–Chiari malformation corrected at age 11, who presented for evaluation of recurrent soft tissue infections and abscesses. She developed multiple cold abscesses (often without fever) that were large and invasive due to delayed detection. Her severe atopy extended to several food allergies with wide reactivity on her allergy panel. She had frequent asthma exacerbations and required chronic bronchodilator and chronic steroid therapy to manage symptoms. As a teenager, she developed recurrent staphylococcal cellulitis and deep tissue abscesses that often required prolonged hospitalizations for intravenous antibiotics and surgical drainage. She did not have a history of fungal, viral, or parasitic infections. She did not have any unusual occupational, animal, or travel exposure and reported no tobacco, alcohol, or illicit drug use. She had no known family history of rheumatologic or immunologic disorders. At age 18, she developed a large pneumatocele and underwent resection and partial pneumonectomy. During the hospitalization for the lung abscess, she required temporary hemodialysis for acute kidney injury (AKI), which was only partially recovered. A kidney biopsy was performed several weeks later because of the presence of persistently elevated serum creatinine (SCr), proteinuria and hematuria.

At the time of her kidney biopsy, her physical examination revealed a normal blood pressure that averaged in 120/70 mmHg. She was well-developed young woman with mild frontal bossing, arched palate and mild left-leaning scoliosis; otherwise, she is normal in appearance. Her exam revealed mild bilateral wheezing related to her asthma. She did not have abdominal tenderness, masses and did not have any edema. Her skin had multiple well-healed scars from various prior infections. Her laboratory results at the time of her first biopsy and serologies obtained shortly afterwards indicate profoundly elevated IgE levels and proteinuric renal disease, but further testing is notably required for negative ANA, Anti-DS DNA and Anti-Sm. Gene mutation testing revealed that the patient was heterozygous for a c.1962_1964delCAT Mutation in the STAT3 gene. Confirmed by genetic testing, neither of her parents carries the gene mutation and has no other siblings other than her sister.

Her kidney biopsy (Fig. 1) showed the following: out of 12 glomeruli, 1 was globally sclerotic and 5 showed segmental lesions, which were composed of both cell proliferation and sclerotic components, including small fibrous crescents. The remaining glomeruli were open and showed global diffuse moderate mesangial sclerosis and hypercellularity. There was mild interstitial fibrosis and tubular atrophy. Immunofluorescent studies showed IgG (2+), C3 (2+) involving predominantly mesangial areas, with a few areas of peripheral staining also (Fig. 2). There was no significant staining for the other immunoglobulins and complement components. Electron microscopic study showed many electron-dense deposits (Fig. 3). These deposits were seen mostly in mesangial areas, but a few intramembranous, subepithelial and subendothelial electron-dense deposits were also noted.

Since her kidney biopsy showed active immune complex nephritis and was proteinuric, she was given a trial of prednisone and low-dose mycophenolate mofetil. Over the next several months improved from 5.3 to 3 g/day. However, over the course of the next year, her serum creatinine continued to rise and a repeat kidney biopsy was performed in 12/2011 revealing severe interstitial fibrosis and global sclerosis of the majority of her glomeruli. Since she continued to have skin boils during this period and her renal biopsy showed significant fibrosis, a decision was made to discontinue her immunosuppression. She had progressive decline in renal function and eventually required dialysis 3 years removed from her first kidney biopsy.

Twin B

Twin B much like her sister suffered from severe childhood eczema and recurrent cellulitis. Her social history did not reveal any illicit or unusual exposures and did not drink alcohol or smoke tobacco. Unlike her sister, she does not have frontal bossing, asthma, scoliosis or an Arnold–Chiari malformation. However, similar to her sister she suffered from recurrent skin abscesses through her teen years to the present. These infections were milder, rarely requiring hospitalization or surgical incision and drainage. She sought medical attention for approximately 15 recurrent skin infection episodes since the age of 12 years until the time of kidney biopsy. Approximately 1 year preceding her kidney biopsy, she developed a cold abscess over her axillary region associated with bacteremia, which required hospitalization for IV antibiotics and successfully recovered. She never developed AKI nor did she have a significant rise in her serum creatinine. She also developed a skin rash around this time, which was biopsied and was diagnosed with discoid lupus. Because of her persistent proteinuria, which reached 1.1 grams/day she was referred for nephrologic evaluation.

Fig. 1 Twin A. **a** A glomerulus showing segmental endocapillary cell proliferation with fibrinoid change (left). **b** Glomerulus with segmental sclerosis (ss), together with a fibrous crescent (fc). **c** There is a background of mesangial hypercellularity in open glomeruli ($\times 40$ for all panels, Hematoxylin&eosin stain for **a**, periodic acid-Schiff stain for **b** and **c**)

Fig. 2 Twin A. There is global mesangial and segmental peripheral staining for IgG and C3 (Immunofluorescence $\times 40$ for both panels)

Her physical exam the visit prior to her renal biopsy revealed a blood pressure of 118/74 mmHg, she was normal in appearance without frontal bossing. Her oral exam was normal and did not have arched palate. Her lung and heart exam were unremarkable. Her abdomen revealed no tenderness or organ enlargement and she had no edema. A few scars were noted over her arms and back at the sites of previous infections.

Her laboratory findings revealed a positive ANA and Anti-Sm. Although she had a normal SCr of 1.0 mg/dL, she had increasing proteinuria up to 1 gram per day. In light of her sister's history, which had become apparent at the time, a decision was made to pursue a kidney biopsy. Gene testing also confirmed that she was heterozygous for the identical STAT 3 gene mutation as her sister.

Fig. 3 Twin A. **a** Several mesangial electron-dense deposits (*arrows*) are noted. **b** There are a few subepithelial electron-dense deposits (*arrows*). **c** There are rare subendothelial deposits (*arrows*) (electron microscopy; $\times 3000$ for **a**, $\times 8000$ for **b** and **c**)

Fig. 4 Twin B. **a** A glomerulus with segmental sclerosis (*ss*) associated with a fibrocellular crescent (*fcc*). **b** Global mesangial IgG deposits. **c** Segmental mesangial C3 deposits. **d** Mesangial electron-dense deposits (*arrows*) (Periodic acid-Schiff stain, $\times 40$ for **a**; immunofluorescence, $\times 40$ for **b** and **c**; electron microscopy $\times 3000$ for **d**)

The kidney biopsy (Fig. 4) showed segmental lesions, which were composed of both cell proliferation and sclerotic components. These lesions are associated with small fibrocellular crescents. The remaining glomeruli are open and showed global diffuse, moderate mesangial sclerosis and hypercellularity. There was also moderate chronic tubulointerstitial injury. By immunofluorescence, there is staining for IgG, IgA, IgM, C3 (1–2+) involving

predominantly mesangial areas. Small, patchy peripheral staining for these molecules was also noted. Electron microscopic study showed electron-dense deposits. These are mostly in mesangial areas. Intramembranous, subepithelial and subendothelial deposits were also seen.

Prior to the renal biopsy being performed, she was on low-dose prednisone, and afterwards was started on mycophenolate mofetil 500 mg every morning and 250 mg

at night. Treatment has resulted in stabilization of proteinuria and renal function.

Discussion

Patients with Job's syndrome lack a subclass of CD4+ cells called T-helper 17 (Th17). Normally, STAT3 binds to phosphorylated cytosolic Janus kinases (JAK) complex, which leads to nuclear translocation and subsequent expression of the th17 signature transcription factor ROR γ T. The absence of Th17 cells results in dysregulation of immune response against extracellular pathogens that result in frequent skin and mucosal infections in Job's syndrome. Furthermore, Th17 cells also produce IL-17, which is involved in the development of multiple cell types including neutrophils and keratinocytes and other functions. Because there is global inhibition of STAT3, a key mediator for many pathways including those of the immune system, cell growth, wound healing, vascular remodeling is expressed widely in most tissue types, patients with Job's Syndrome have variegated phenotypic expression, illustrated by the present report and prior accounts [5]. The elevated IgE level seen in Job's syndrome, however, represents an appropriate response to ineffective cell-mediated immunity.

The cases we describe raise the specter of autoimmune features associated with Job's syndrome. The first published clinical description of systemic lupus erythematosus (SLE) complicating Job's syndrome was in 1983. The report by Schopfer et al. described a 20-year-old man with life-long staphylococcal infections who developed symptoms and signs of SLE, including strongly positive lupus serologic tests [6]. However, the clinical description did not include renal involvement. Leyh et al. in 1986 described a 9-year-old girl, who developed hyper-IgE and SLE associated with membranous glomerulonephritis [7]. However, it was not clear whether she had a primary immunodeficiency. A report by Burgnoni et al. involved a set of monogenic twins who were discordant for SLE and Job's syndrome suggesting that Job's syndrome can present along a spectrum that includes classic autoimmune disease exclusive of repeated infections [8]. Still it is conceivable and an interesting line of thoughts that impaired Treg function in the absence of Stat3 signaling increases the likelihood of developing glomerulonephritis.

The kidney biopsies from Twin A showed features of segmental proliferative glomerulonephritis with both cell proliferation and sclerotic component. They are seen in a background of marked mesangial sclerosis and hypercellularity. The glomerulonephritis is immune-mediated, as evidenced by the presence of immunoglobulins and

complement components by immunofluorescence and electron-dense deposits by electron microscopy. Although the glomerulonephritis is definitively immune-mediated, whether it is related to systemic lupus is debatable, especially since her serologies were negative. Aside from systemic lupus, other diseases including infection or other types of immune abnormalities can be associated with this type of glomerulonephritis. Interestingly, the kidney biopsy in Twin B showed identical segmental proliferative glomerulonephritis with both sclerotic and active components. The morphological spectrum is similar to that identified in Twin A, but in her case, she did have classic autoimmune markers (i.e., ANA, Anti-Sm) classically associated with SLE.

An explanation for an association between Job's syndrome and SLE (or lupus-like syndrome) could be that the increased number of infections increases the likelihood of cross-reactions occurring between foreign and self-antigens or the impaired antibody responses generate insoluble immune complexes. The molecular link between Job's syndrome and SLE has not been elucidated, but are beginning to be uncovered. A recent report found that global inhibition of STAT3 or reduced Th17 cells resulted in crescentic glomerulonephritis in animal models of nephrotoxic nephritis [9]. We speculate that corruption of STAT3, which is involved in a number of signaling pathways involving immune surveillance and cell regulation, can result in autoimmune manifestations, which is evident from previously published reports.

Conclusion

In summary, the cases we report of dizygotic twins with Job's syndrome complicated by lupus nephritis are novel. The 'great masquerader' has long been a title associated with lupus, but the spectrum of disease associated with Job's syndrome may rival it. The strength of the present report is the genetic and pathologic characterization that is available for the two cases. Furthermore, we have documented pathologically in the first case that this entity can result in progressive renal disease and ESRD. The limitation is that more cases of this rare disease are not available to us to better establish a stronger nexus between Job's syndrome and nephritis. We suspect that further study of patients with Job's syndrome will reveal renal involvement, perhaps to varying degrees.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interests, financial or otherwise, regarding content of this manuscript.

Informed consent Written informed consent was obtained from two patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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