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Exceptional Case

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Serum amyloid A-type amyloidosis of the kidney and immune complex-mediated glomerulopathy in the setting of hyperimmunoglobulin E (Job's) syndrome

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ABSTRACT

Hyperimmunoglobulin E syndrome (HIES) is a rare immunodeficiency syndrome with characteristic features of pulmonary infections, eczema, recurrent skin abscesses and elevated serum IgE. We present a case of an HIES patient referred for nephrology consultation with elevated serum creatinine and nephrotic-range proteinuria. The subsequent kidney biopsy revealed AA-type amyloidosis and a separate and distinct inactive immune complex-mediated glomerulopathy with frequent glomerular capillary wall and mesangial polyclonal deposits. Potential kidney pathology in the setting of HIES has not been well described previously, and this case provides insight into associated renal comorbidities faced by patients with this rare syndrome.

Keywords: AA-type amyloidosis, hyperimmunoglobulin E syndrome, immune complex-mediated glomerulopathy, Job's syndrome, proteinuria

BACKGROUND

Hyperimmunoglobulin E syndrome (HIES), also known as Job's syndrome, constitutes an immunodeficiency syndrome with elevated serum immunoglobulin E (IgE) levels and characterized by pulmonary infections, eczema and recurrent skin abscesses [1, 2]. Herein, we present the case of a patient with HIES and history of associated infections with elevated serum creatinine and proteinuria. A subsequent kidney biopsy revealed extensive serum amyloid A (AA) and an inactive immune complex-mediated glomerulopathy, providing unique insight into renal pathology afflicting HIES patients.

CASE REPORT

Clinical history and initial laboratory data

A 50-year-old Caucasian man with HIES [reportedly with signal transducer and activator of transcription 3 (STAT3) mutation] was referred after detection of elevated serum creatinine and

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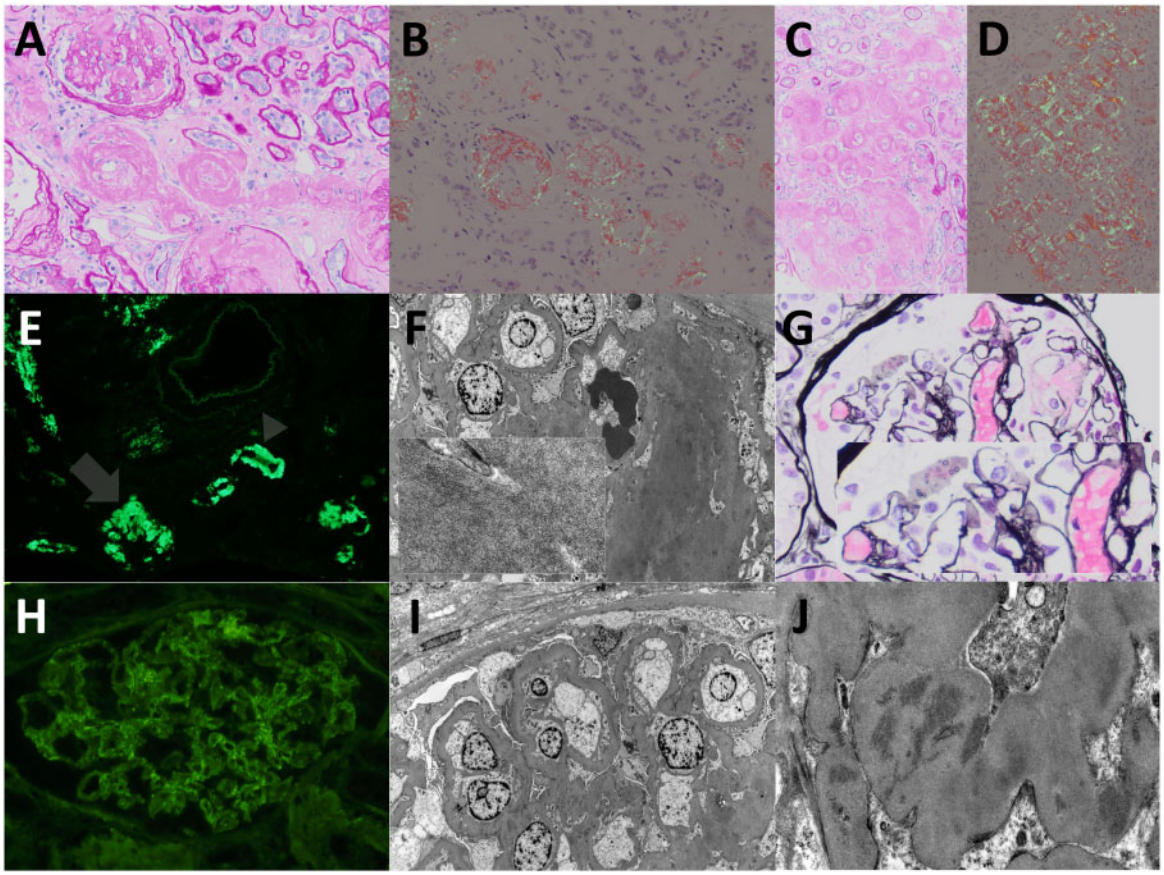

FIGURE 1: By light microscopy, periodic acid-Schiff (PAS)-negative amorphous material was deposited along arterial vessel walls and segmentally within glomeruli (**A**) and positive by Congo red staining (**B**). The amyloidogenic deposits notably showed extensive mural deposition along the vasa recta (**C** and **D**). By immunofluorescence, the amyloid deposits showed strong expression of protein A (**E**) in glomeruli (arrow) and along arterioles (arrowhead), and did not show reactivity for other tested reactants including immunoglobulin heavy or light chains (those studies not shown). Electron microscopy showed the typical ultrastructural appearance of the amyloid deposits with randomly arranged fibrils (**F**). In addition to the AA-type amyloidosis, the glomeruli also showed evidence of a separate and discrete inactive immune complex-mediated glomerulopathy. With Jones silver stain, the glomerular basement membranes revealed numerous, variably sized crater-like defects (**G**); on higher power and closer inspection the craters are more conspicuous (G, inset). By immunofluorescence microscopy, the glomeruli showed granular staining for IgG predominately along capillary loops (**H**) and equally intense staining for kappa and lambda light chains (immunoglobulin light chain and other heavy chain studies not shown). By electron microscopy, glomerular capillary loops revealed numerous electron-dense deposits, predominately subepithelial, but also intramembranous and within the mesangium (**I**), and the fine granular immune complexes were ultrastructurally distinct from the fibrillary amyloid deposits (**J**). Original magnifications for A, B and E at ×200; for C, D, G and H at ×400; G inset at ×600; F and I at ×2900; F inset at ×30 000; J at ×23 000.

nephrotic-range proteinuria. HIES was managed with immunoglobulin replacement therapy, ipratropium bromide, albuterol and posaconazole (history of aspergilloma). Medical history was further notable for osteomyelitis and computed tomography of the chest revealed extensive/diffuse bronchiectatic changes with multiple air-fluid levels and possible fungal balls. Pertinent laboratory values included serum creatinine of 1.86 mg/dL (estimated glomerular filtration rate: 39 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease equation), blood urea nitrogen of 26 mg/dL, serum albumin of 2.8 g/dL, total urine protein-to-creatinine ratio of 4.58 mg/mg, and a complete blood count showed a normocytic anemia. There were normal serum C3 and C4 levels, and serum protein electrophoresis was negative for a monoclonal protein. Testing was negative for anti-nuclear antibodies, antineutrophil cytoplasmic antibodies (ANCA), viral hepatitis B and C, and human immunodeficiency virus (HIV). Prior laboratory testing showed an elevated serum IgE level of 282 IU/mL. There was no edema noted on examination.

A kidney biopsy was obtained and reviewed at our institution.

Kidney biopsy

A total of 25 glomeruli were present, 9 of which were globally sclerosed. The glomerular capillary loops are irregularly thickened, with occasional craters by Jones silver stain (Figure 1). Endocapillary proliferation or cellular crescents were not present. The mesangium was expanded in a segmental-nodular manner by amorphous Congo red-positive material. Congo red-positive material was also very focally present in the interstitium. Approximately 50% of the renal cortex showed tubular atrophy and interstitial fibrosis, and arteries/arterioles showed sclerosis and prominent mural deposition of amyloid.

Immunofluorescence microscopy performed on frozen sections showed fine granular reactivity for IgG (3+), and kappa (3+) and lambda (3+) light chains predominately along the glomerular capillary loops but also within the mesangium, and staining for phospholipase A2 receptor showed only trace positivity. The amorphous material in the glomeruli, along vessel walls, and in the interstitium only showed reactivity for protein A (3+). There was no difference in reactivity between kappa and lambda light chains in the tissue.

Electron microscopy showed segmental mesangial and partial glomerular capillary wall deposition of straight nonbranching fibrils (9.7 nm in average diameter). The podocytes revealed extensive effacement of their foot processes. Distinct from the fibrillary deposits were finely granular electron-dense deposits frequently present along the glomerular capillary walls (subepithelial and intramembranous) and within the mesangium. Fibrillary deposits were also seen extensively along arteriolar vessel walls.

Diagnoses

AA-type amyloidosis of the kidney, and an inactive immune complex-mediated glomerulopathy with glomerular capillary wall and mesangial deposits.

DISCUSSION

HIES is an immunodeficiency syndrome with associated recurrent infections, with autosomal dominant (associated with mutations in STAT3) and autosomal recessive [most commonly associated with mutations in dedicator of cytokinesis 8, (DOCK8)] forms of the disorder recognized [1]. STAT3 is a signal transduction protein involved in secretion or signaling of numerous pro- and anti-inflammatory cytokines accounting for both the augmentation and lack of inflammation seen, while DOCK8 is involved in cytoskeletal modulation related to cellular migration, adhesion and growth [1]. Reflecting the low incidence of disease—estimated at ~1 in 1 000 000—characterization of these patients' renal function and potential associated underlying pathologies have been described in a limited manner [1, 2]. Hypertension is commonly observed in HIES, although related renal pathophysiology is not well-understood [1]. Two prior cases of patients with HIES have reported renal involvement by amyloidosis, albeit without detailing the histopathologic findings [3, 4]. Gonzalez Sanchidrian *et al.* described a patient with nephrotic-range proteinuria and a kidney biopsy revealed AA-type amyloidosis, while L'Huillier *et al.* reported that a patient developed renal amyloidosis, the type not being specified [3, 4].

Renal pathology of patients with HIES has not been described previously in detail, although the findings are not entirely surprising as AA-type amyloidosis (also referred to as secondary or reactive amyloidosis) affecting the kidney has been observed in patients with similar syndromes of the immune system. AA-type amyloidosis has been described to complicate heritable disorders including familial Mediterranean fever, cryopyrin-associated periodic syndrome and hyperimmunoglobulin D syndrome [5]. The precursor protein in AA-type amyloidosis is serum protein A, which as an acute-phase reactant elaborated by the liver can, with longstanding inflammation, form amyloidogenic deposit in tissues including the kidney [6]. As such, AA-type amyloidosis can develop in the setting of the aforementioned disorders as well as chronic infections and autoimmune disease.

The presented patient's immune complex-mediated glomerulopathy could be in part be contributed to by a history of recurrent infections (both pulmonary and osteomyelitis) or even systemic autoimmune disease, although the patient has no clinical or laboratory data to support the latter. That said, patients with HIES have been described to have systemic lupus erythematosus and autoimmune vasculitis [2]. A prior case report described a set of twin HIES patients who underwent kidney biopsies, both of which revealed involvement by an underlying active crescentic immune complex-mediated glomerulonephritis with glomerular capillary wall and mesangial deposits [7]. These cases are similar to the presented case with there being an immune complex-mediated glomerulopathy; however, our case did not have evidence of endocapillary proliferation/hypercellularity or crescent formation. Unfortunately, the cases reported by Ahmed *et al.* [7] are the rare examples providing insight into the renal pathology afflicting patients with HIES.

CONFLICT OF INTEREST STATEMENT

None declared.

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