INTRODUCTION

When renal biopsy reveals crescentic glomerulonephritis, differential diagnosis is wide and includes 3 immunopathologic categories of disease: immune-complex–mediated glomerulonephritis (such as IgA nephropathy, lupus nephritis, and bacterial infection–associated glomerulonephritis, particularly infectious endocarditis-associated glomerulonephritis), anti–glomerular basement membrane nephritis, and pauci-immune crescentic glomerulonephritis (associated with antineutrophil cytoplasmic antibody seropositivity in most patients). Careful integration of immunofluorescence and ultrastructural findings with the serologic tests and medical history is essential to determine the underlying cause. Rarely, crescentic glomerulonephritis occurs concomitantly with granulomatous interstitial nephritis, and the differential diagnosis in this scenario includes granulomatosis with polyangiitis and sarcoidosis. Here we report an unusual case of pauci-immune crescentic and necrotizing glomerulonephritis concurrent with granulomatous interstitial nephritis due to disseminated histoplasmosis.

CASE PRESENTATION

A 65-year-old woman from Missouri presented with progressive weakness, myalgia, and gastrointestinal symptoms. As she was being worked up, she was found to have pancytopenia and acute kidney injury. She had a history of mixed connective tissue disease with manifestations of Raynaud’s phenomenon and CREST syndrome diagnosed 13 years prior and was treated with methotrexate in the past and was on hydroxychloroquine, prednisone, and mycophenolate mofetil at presentation. She had intermittent fevers for 8 months. On physical examination, her blood pressure was 112/80, temperature 37.8, and heart rate 90. She appeared cachectic (weight 45 kg), without skin rash or peripheral edema.

Laboratory data were as follows: hematocrit, 20.5%; hemoglobin, 6.9 g/dl; white blood count, 2100/μl, with lymphopenia (200/μl); platelet count, 119,000/μl; serum albumin, 2.8 g/dl; serum calcium, 7.2 mg/dl; and serum creatinine, 2.8 mg/dl, which was increased from 0.6 mg/dl 4 months prior. Urine protein-to-creatinine ratio was 3. Urinalysis showed 0 to 5 white blood cells per high-power field and 0 to 2 red blood cells per high-power field. Antinuclear antibodies were positive (titer 1:1280 with a speckled pattern) and ribonucleoprotein was positive (>643 relative luminescence units). All other serologies were negative, including anti–double-stranded DNA, Smith, Sjögren syndrome A, Sjögren syndrome B, scleroderma 70, HIV, and antineutrophil cytoplasmic antibodies. C3 and C4 complement levels were normal. A liver profile was normal. Quantitative Igs were normal. Monoclonal protein studies were unrevealing, including negative serum protein immunofixation for monoclonal protein and normal serum-free kappa to lambda ratio at 1.1. A chest radiograph showed no acute lung process. Computed tomography scan of the chest showed chronic interstitial lung disease and calcified mediastinal lymph nodes consistent with prior granulomatous disease but without mediastinal or hilar adenopathy. Computed tomography scan of the abdomen and pelvis showed splenic and hepatic granulomatous disease. Renal ultrasonography was negative for obstruction or masses. The patient empirically received methylprednisolone 250 mg/d i.v. for 3 days pending the results of kidney biopsy.

Pathologic Findings

Renal Biopsy Findings

Light microscopic examination revealed renal cortex and medulla. Thirty-nine glomeruli were sampled, 2 of which were globally sclerotic. Twenty (51%) glomeruli
showed segmental to circumferential cellular crescents (Figure 1a and Supplementary Figure S1A), some of which were associated with peri-glomerular granulomatous reaction. Eleven of these glomeruli exhibited fibrinoid necrosis with karyorrhexis, rupture of the glomerular basement membranes, and intracapillary and extracapillary fibrin deposition. The remaining glomeruli appeared unremarkable, without mesangial or endocapillary hypercellularity (Supplementary Figure S1B). There was severe diffuse interstitial inflammation composed of mainly lymphocytes, monocytes, and histiocytes, with multifocal lymphocytic tubulitis. Many large interstitial noncaseating epithelioid granulomas associated with giant cells were seen (Supplementary Figure S1B). There was mild tubular atrophy and interstitial fibrosis with patchy acute tubular injury. One arteriole showed fibrinoid necrosis with intimal and medial fibrin deposition and rupture of the elastica interna and elastica externa, consistent with arteriolitis (Supplementary Figure S1C).

On periodic acid–Schiff and Gomori methenamine silver stains, small rounded *Histoplasma* spp. microorganisms were seen focally within glomerular capillaries and crescents and within the interstitial granulomas (Figure 1b and c). No glomerular electron-dense immune-complex–type deposits were seen on electron microscopy and no glomerular staining for IgG, C3, or C1q were seen on immunofluorescence, which provided evidence against immune-complex–type glomerulonephritis. Few *Histoplasma* yeasts were sampled for electron microscopy and exhibited the typical clear, peripheral cytoplasmic halo and membrane-bound organelles (Figure 1d).

**Bone Marrow Biopsy Findings**
Bone marrow biopsy showed multiple non-necrotizing granulomas with giant cells (Supplementary Figure S1D). Rare *Histoplasma* yeasts similar to those seen in the kidney were present in these granulomas.

**Follow-up**
Serum *Histoplasma* antibody test was weakly positive, whereas serum and urine *Histoplasma* antigen tests were negative. Based on the kidney biopsy findings, mycophenolate mofetil were discontinued and the

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**Figure 1.** Kidney biopsy findings. (a) A glomerulus showing a circumferential cellular crescent and fibrinoid necrosis associated with rupture of Bowman’s capsule. A multinucleated giant cell is seen in the interstitium (arrow) (Jones methenamine silver, original magnification ×200). (b) Several small oval *Histoplasma* yeasts are seen within a glomerular capillary (arrow), associated with rupture of the glomerular basement membrane and an overlying cellular crescent (periodic acid–Schiff, original magnification ×1000). (c) Small oval *Histoplasma* yeasts are seen within a glomerular crescent (arrows), one of which shows narrow budding (Gomori methenamine silver, original magnification ×400). (d) An electron microscopic figure showing a yeast cell of *Histoplasma* within a cellular crescent. A clear, peripheral cytoplasmic halo and membrane-bound organelles are evident (original magnification ×4800).
patient was treated with amphotericin B and then switched to itraconazole. Four months following the kidney biopsy, serum creatinine improved to 1.5 mg/dl and proteinuria improved to 1.27 g/dl. Repeat biopsy was not performed.

**DISCUSSION**

Histoplasmosis is an invasive mycosis caused by inhalation of spores of the dimorphic fungus *Histoplasma capsulatum*. It is found worldwide, but is particularly common in the Ohio and Mississippi River valleys of the central United States. Acute pulmonary histoplasmosis, the most common form, is the initial pulmonary response to inhalation of *Histoplasma* spores and is usually a self-limited disease. Less commonly, it causes chronic cavitory lung disease or manifests as disseminated disease affecting many organs. Disseminated histoplasmosis occurs predominantly in elderly persons, infants, and immunocompromised persons, including those with hematologic malignancies, solid organ transplantation, or AIDS. The disseminated disease may show a rapidly progressive, potentially fatal course with generalized involvement of the reticuloendothelial system, typically seen in immunocompromised individuals, or subacute or chronic course with more restricted organ involvement, more commonly seen in immunocompetent patients. The most common symptoms of disseminated histoplasmosis are fever, fatigue, weight loss, anorexia, lymphadenopathy, pancytopenia, and elevated liver enzymes. Rarely, histoplasmosis can cause vasculitis, including pulmonary and skin vasculitides.

Kidney involvement in disseminated histoplasmosis in the form of parasitized macrophages in the glomerular capillaries or the interstitium is common, reported in up to 40% of patients at autopsy, usually not associated with impairment of kidney function. However, chronic recurrent abscesses of the interstitium and urogenital tracts or granulomatous acute interstitial nephritis leading to acute renal failure have been described. Glomerulonephritis in the setting of disseminated histoplasmosis is very rare. Bullock et al. described a patient with disseminated histoplasmosis and circulating immune complexes who developed hematuria and proteinuria leading to kidney biopsy that showed mild IgA nephropathy. No renal *Histoplasma* fungi or granulomas were seen in this patient. Papo et al. reported a patient who presented with oral granulomatous ulceration due to histoplasmosis and pauci-immune crescentic glomerulonephritis, mimicking granulomatosis with polyangiitis. Because no renal *Histoplasma* fungi or granulomas were seen in the kidney biopsy in this patient, and because antineutrophil cytoplasmic antibody testing was not done, a causative link between histoplasmosis and pauci-immune crescentic glomerulonephritis is not proven.

The combination of pauci-immune crescentic glomerulonephritis and granulomatous interstitial nephritis is rarely seen in renal biopsies, and when it occurs the differential diagnosis includes granulomatosis with polyangiitis and sarcoidosis. Granulomatosis with polyangiitis is unlikely in our patient based on the negative antineutrophil cytoplasmic antibody serology and absence of upper airway disease. Sarcoidosis is also unlikely due to the absence of mediastinal lymphadenopathy or hypercalcemia. To our knowledge, this is the first proven case of pauci-immune crescentic and necrotizing glomerulonephritis due to disseminated histoplasmosis. The presence of *Histoplasma* microorganisms within glomerular crescents and capillary lumina, the presence of concurrent fungal granulomatous interstitial nephritis, and the renal response to antifungal medications and discontinuation of immunosuppressive medications favor that the crescentic glomerulonephritis in this patient is driven by a direct glomerular invasion by *Histoplasma* fungi, rather than coincidental occurrence of pauci-immune crescentic glomerulonephritis with fungal granulomatous interstitial nephritis. Antifungal therapy alone in our patient led to significant but not complete improvement of kidney dysfunction. The residual mild proteinuria and renal insufficiency could be secondary to irreversible glomerular scars/fibrous crescents and/or interstitial fibrosis following the very active crescentic glomerulonephritis and granulomatous interstitial nephritis.

The mechanism by which *Histoplasma* caused crescentic glomerulonephritis in this patient is unclear. It could be due to extension of granulomatous inflammation from the surrounding interstitium. Alternatively, it may be due to hematogenous spread of *Histoplasma* microorganisms to glomeruli, evoking an *in situ* inflammatory response and cytokine release, ultimately leading to rupture of the glomerular basement membrane and crescent formation. The absence of glomerular electron deposits by electron microscopy, the negative glomerular staining for Igs, C3, and C1q on immunofluorescence, and the normal serum complement argue against an immune reaction due to *Histoplasma* antigen(s)-driven immune complex formation and complement activation.

Of note, *Histoplasma* immunodiffusion and complement fixation antibody tests can be falsely negative, particularly in immunocompromised patients due the suppressive effects of the underlying condition or immunosuppressive medications. Furthermore, as is
the case in our patient, *Histoplasma* antigen detection in the serum and urine by the commercially available enzyme immunoassays can be negative in 7% to 27% of patients, and false-positive results can occur in blastomycosis and other fungal infections.8

### CONCLUSION

In conclusion, fungal infections should be included in the differential diagnosis of pauci-immune crescentic glomerulonephritis concomitant with granulomatous interstitial nephritis, and fungal histochemical stains should be performed, regardless of the results of fungal antibody and antigen tests (Table 1). Fungal infection–associated crescentic glomerulonephritis may respond to antifungal agents.

### DISCLOSURE

All the authors declared no competing interests.

### SUPPLEMENTARY MATERIAL

**Figure S1.** Kidney biopsy and bone marrow biopsy findings. (A) Two glomeruli showing cellular crescents with periglomerular granulomatous inflammation (Jones methenamine silver, original magnification ×200). (B) The glomeruli without crescents appear normocellular. Periglomerular granulomas with several multinucleated giant cells are seen (trichrome stain, original magnification ×200). (C) An arteriole showing transmural fibrinoid necrosis with karyorrhexis and disruption of elastic interna, consistent with necrotizing arteriolitis (Jones methenamine silver, original magnification ×400). (D) A bone marrow biopsy image showing an epithelioid granuloma with multinucleated giant cells (hematoxylin and eosin, original magnification ×200). Few *Histoplasma* yeasts were present in these granulomas (not shown). Supplementary material is linked to the online version of the paper at www.kireports.org.

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