

Rheumatoid Nodule Formation in the Kidney: A Diagnosis of Exclusion and a Rare Manifestation of Rheumatoid Arthritis Involving the Kidney



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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by an inflammatory poly-articular arthritis as well as extra-articular manifestations. Although renal involvement of the kidney by RA most often is expressed as an immune complex-mediated glomerulopathy or AA amyloidosis, rheumatoid nodule formation has been rarely described.¹ A rheumatoid nodule is characterized by necrotizing granulomatous inflammation, and can be found most commonly subcutaneously in patients with RA over sites prone to pressure or repetitive irritation, but also have been described to involve the deeper connective tissue, lungs, heart, and other tissue sites.² As the etiology of a necrotizing granuloma can be of an infectious process, this possibility must be excluded particularly for patients with RA.

We present a case in which a patient with long-standing RA is found by radiologic imaging to have a kidney mass. Histopathologic review of the subsequent partial nephrectomy revealed a necrotizing granuloma and an immune complex-mediated glomerulopathy predominately with a membranous pattern of injury. After histopathologic, molecular, further laboratory, and clinical evaluation, it was felt that the necrotizing granuloma was not of an infectious etiology and represented a rheumatoid nodule.

CASE PRESENTATION

Clinical History and Initial Laboratory Data

The patient was a 65-year-old woman undergoing a partial nephrectomy for a right kidney mass. Seven

months prior, she had presented to an outside hospital with fever, and in the course of the workup, radiologic imaging studies showed a right lower pole kidney mass (3.9 cm) with heterogeneous enhancement, an atrophic left kidney, and splenomegaly. Blood and urine cultures were negative at that time, and a complete blood cell count initially showed pancytopenia; however, with normal cell counts a week later. Radiologic imaging in 2005 reportedly showed normal kidneys. More recently performed preoperative laboratory testing showed a serum creatinine of 1.14 mg/dl (estimated glomerular filtration rate using the isotope dilution mass spectrometry-traceable Modification of Diet in Renal Disease Study equation of 48 ml/min per 1.73 m²), blood urea nitrogen of 29 mg/dl, serum albumin of 4 g/dl, and a complete blood cell count showed a normocytic anemia and thrombocytopenia. Recent urine protein quantification data were not available, aside from analysis 6 years before surgery for which proteinuria was not detected. Medical history was notable for RA (28-year history), secondary Sjögren's syndrome, hypertension, hyperlipidemia, coronary artery disease, hypothyroidism, gonorrhea, pelvic inflammatory disease, status-post salpingo-oophorectomy, and the patient was a former smoker. Fifteen years before the surgery she developed group A *Streptococcus* toxic shock syndrome while on methotrexate and etanercept. The patient was also status-post right hand and left elbow arthroplasty, and left hip and bilateral total knee replacement. Medication list at the time of surgery included etanercept (was held 1 week before the procedure), levothyroxine, simvastatin, and intermittent piroxicam. The patient had in the past been managed with gold sodium thiomalate, but developed

thrombocytopenia. Hepatitis C testing was negative 2 years prior. RA had resulted in second through fifth metacarpophalangeal synovial thickening with lax joints of the left hand without squeeze tenderness. There had been structural damage of both wrists and feet, right elbow flexion contracture, and C1-C2 subluxation. The patient had subcutaneous nodules on her hands, elbows, and feet.

The partial nephrectomy was completed without complication and the patient was discharged the next day after an uneventful postoperative course.

Partial Nephrectomy

The sample consisted of kidney cortex and medulla, with a prominent and well-circumscribed necrotizing granuloma. Four of 161 glomeruli were globally sclerosed (Figures 1 and 2). The viable glomeruli showed mesangium that was expanded mildly by extracellular matrix. Several craters were seen in the glomerular basement

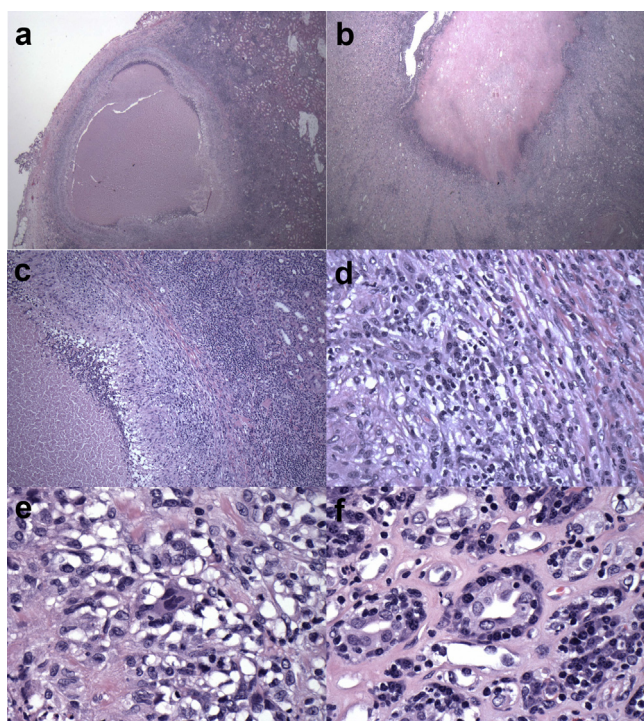


Figure 1. The partial nephrectomy revealed a tumefactive necrotizing granuloma that extended from the cortex (a) deeply to involve the medullary papilla (b). The necrotizing granuloma contains a central necrotic region, bounded by a granulomatous inflammation (c). The granulomatous inflammation is composed of a rim of palisading epithelioid histiocytes adjacent to the central necrotic core (c), and peripheral to the epithelioid histiocytes are admixed plasma cells and lymphocytes (d); rare multinucleated giant cells are present as a constituent of the granulomatous inflammation (e). Sampling of the medulla also revealed the presence of a focal tubulitis predominantly composed of mononuclear inflammatory cells, which is plasma cell rich. All images taken from paraffin sections were stained with hematoxylin and eosin. Original magnifications (a,b) $\times 20$; (c) $\times 100$; (d) $\times 400$; and (e,f) $\times 600$.

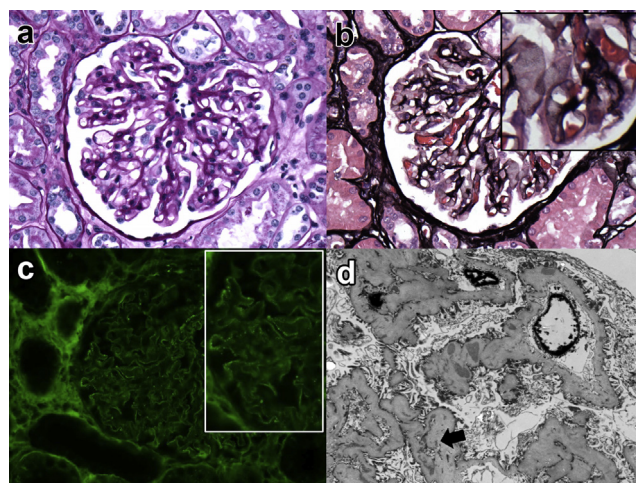


Figure 2. By light microscopy, the glomeruli show mild mesangial matrix expansion without evidence of an active glomerulitis (periodic acid–Schiff) (a); however, the glomerular basement membranes contain numerous crater-like defects by Jones silver stain (b); on higher power and closer inspection the craters are more conspicuous (b, inset). By immunofluorescence microscopy performed on protease-treated paraffin sections, the glomeruli showed granular staining for IgG predominately along capillary loops (c, and inset taken at same magnification and expanded), and with trace reactivity for IgA, and equally intense staining for kappa and lambda light chains (Ig light chain and other heavy chain studies not shown). By electron microscopy, glomerular capillary loops revealed numerous finely granular electron-dense deposits, predominately subepithelial, and with the mesangium also containing similar deposits (d, and arrow toward mesangial electron-dense deposits). Original magnifications (a,b) $\times 400$; (b, inset) $\times 600$; (c) $\times 400$; and (d) $\times 6000$.

membranes on silver stains. Signs of active glomerulitis were not present. Approximately 30% to 40% of the cortical parenchyma showed tubular atrophy and interstitial fibrosis, and there was mild medullary fibrosis. The medulla also showed a focal plasma cell-rich tubulitis. Arteries showed moderate sclerosis, and arterioles showed mild sclerosis; there was no evidence of an active vasculitis. The prominent necrotizing granuloma contained a central core of necrotic debris that extended from the cortex to the medullary papilla. Gram, Ziehl-Neelsen (acid-fast) stain, Warthin-Starry, and methenamine silver stains were negative for organisms. Immunohistochemical staining for mycobacteria and spirochetes were likewise negative.

Paraffin sections were pretreated with protease solutions for antigen retrieval and incubated with antibodies specific for the heavy chains of IgG, IgA, and IgM, for kappa and lambda light chains, C3, C1q, albumin, and fibrin-related antigens. Immunofluorescence staining for IgG subtypes 1 to 4 and phospholipase A2 receptor was also performed. There was fine-granular reactivity for IgG (1+), IgA (trace), kappa light chain (trace), and lambda light chain (trace), mostly along the capillaries and less so in the mesangium. Reactivity for IgG

subtypes was as follows: IgG1 (1+), IgG2 (negative), IgG3 (trace), and IgG4 (negative). Phospholipase A2 receptor was trace positive. The interstitium revealed no immune deposits. There was no difference in reactivity of kappa and lambda light chains in the tissue.

Electron microscopy showed that the glomerular visceral epithelial cells had mild segmental effacement of their foot processes. Glomerular capillary loops revealed finely granular subepithelial and few intramembranous and subendothelial electron-dense deposits. The glomerular basement membranes showed "spikes" along the sides of few subepithelial deposits. The mesangium revealed normal cellular elements and a mildly increased amount of matrix that contained fine-granular electron-dense deposits.

Polymerase chain reaction amplification of the 16S ribosomal RNA, hsp65, and IS6110 mycobacterial genes was performed (with the human beta-globulin gene used as an assay performance control) from sections of paraffin-embedded tissue, with the aforementioned mycobacterial genes not detected.

Diagnoses

Chronic-active interstitial nephritis with a necrotizing granuloma, and an immune complex-mediated glomerulopathy predominantly with a membranous pattern of injury. Special histologic stains and immunoperoxidase staining for infectious agents and polymerase chain reaction amplification of mycobacterial-specific genes were negative. The necrotizing granuloma could be considered to represent a rheumatoid nodule only after further exclusion (*via* laboratory and clinical investigation) of an infectious process.

Clinical Follow-up

Nineteen days postoperatively, the patient re-presented with bilateral lower extremity edema. Laboratory testing at this time showed a serum creatinine of 1.2 mg/dl (estimated glomerular filtration rate of 45 ml/min per 1.73 m²), blood urea nitrogen of 40 mg/dl, and serum albumin of 4 g/dl. Urinalysis at this time revealed a urine protein-to-creatinine ratio of 0.42, microalbumin-to-creatinine ratio of 149.5 mg/g, 5 to 10 red blood cells per high power field, and 10 to 20 white blood cells per high power field. An interferon-gamma release assay for *Mycobacterium tuberculosis* (T-SPOT TB test) was negative. After an infectious disease consultation, the patient was not favored to have an underlying infectious process.

DISCUSSION

The presented case illustrates 2 forms by which the kidney can be injured in the setting of RA. The necrotizing granuloma, as is in any tissue site, requires

thorough exclusion of an infectious etiology in a patient with RA and associated immunosuppressive therapy. Only after exclusion of an infectious process can the lesion be favored to represent a rheumatoid nodule. The kidney in this case also revealed an immune complex-mediated glomerulopathy, predominately with a membranous pattern of glomerular injury.

Necrotizing granulomatous inflammation involving the kidney that had been deemed to represent a rheumatoid nodule has been described sparingly in the literature. A patient with longstanding RA and numerous subcutaneous nodules was found at autopsy to have several cortical necrotizing granulomas (up to 2 mm in diameter).³ Although the patient had a history of cellulitis and pyelonephritis, special stains for acid-fast and fungal organisms were negative. Culture from the lungs and spleen did not reveal growth of bacteria organisms; however, cultures for fungi and *Mycobacterium* were not performed. Aside from the subcutaneous and renal lesions, necrotizing granulomas were not described to have been found elsewhere at the time of autopsy. Another case described a patient with longstanding RA presenting with painless hematuria and radiologic imaging revealing a tumefactive lesion involving the kidney.⁴ A subsequent nephrectomy revealed a 0.8-cm, predominately cortical, necrotizing granuloma. In that case, urine cultures (including acid-fast bacillus) cultures were negative. Bevens *et al.*⁵ described a patient with RA who at the time of autopsy was found with granulomatous inflammation, either necrotizing or non-necrotizing, involving numerous tissue sites including occasional small granulomatous lesions in the renal cortex; however, these were not described as being necrotizing. Granulomatous interstitial nephritis is a histologic finding that is nonspecific, and can be associated with medications (e.g., antibiotics, analgesics), infections, and inflammatory/autoimmune processes: necrotizing lesions can be seen in the setting of the latter two.^{6,7}

Kidney biopsies from patients with RA have been described to show immune complex-mediated glomerulopathies. Helin *et al.*¹ showed in a review of biopsies from Finland that mesangial glomerulonephritis was the most common lesion found, followed by amyloid A amyloidosis and membranous glomerulonephritis. The finding of membranous glomerulonephritis is also associated with patients managed with gold and/or penicillamine.^{1,8} Not only are the autoimmune disease processes of RA and related therapy associated with the development of an immune complex-mediated glomerulopathy, but these same immunosuppressed patients must be considered to have a current or previously active infection that could be implicated in the development and deposition of the immune complexes. The presented patient's immune complex-mediated

Table 1. Teaching points regarding renal manifestations of rheumatoid arthritis

1. Kidney biopsies of patients with rheumatoid arthritis can reveal immune complex-mediated glomerulopathies, including membranous glomerulonephritis and amyloid A amyloidosis
2. Necrotizing granulomas of any site should be evaluated for a possible infectious etiology
3. A membranous glomerulonephritis in patients with rheumatoid arthritis may also be associated with gold and/or penicillamine therapy
4. Rheumatoid nodule formation in the kidney has been rarely described in patients with rheumatoid arthritis

glomerulopathy could be in part contributed to by longstanding RA, previously administered gold sodium thiomalate, and/or previous infections (documented group A *Streptococcus* and gonorrhea).

Although the rheumatoid nodule is a common extra-articular manifestation of RA, diligence must be taken to exclude an infectious etiology in these immunosuppressed patients (Table 1). Consideration for an infectious etiology should be heightened when a necrotizing granuloma is found in atypical sites, as in the presented case. Only after considerable efforts are made should a necrotizing granuloma in the kidney in the setting of RA be deemed to represent a rheumatoid nodule.

DISCLOSURE

All the authors declared no competing interests.

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