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CASE REPORT

Isolated renal sarcoidosis: a rare presentation of a rare disease treated with infliximab

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Abstract Sarcoidosis is a multisystem disease characterized by noncaseating granulomatous reaction frequently involving the lymph nodes, lungs, liver, skin, and eyes. Acute renal failure (ARF) as an isolated manifestation of sarcoidosis is rare. We describe a case of sarcoidosis presenting as transient polyarthritis and ARF due to isolated granulomatous infiltration of the renal parenchyma. Renal biopsy showed granulomatous interstitial nephritis with noncaseating granulomas consistent with sarcoidosis. Bacterial, fungal, and mycobacterial infections were excluded. There was no evidence of extrarenal sarcoid involvement. Prednisone of 60 mg daily resulted in significant improvement in renal function. Because of recurrent flares on steroid taper and steroid toxicity, treatment with infliximab, an anti-tumor necrosis factor-α (TNF-α) antibody, was instituted and resulted in stabilization of renal function despite steroid taper. Although uncommon, renal sarcoidosis should be considered in the differential diagnosis of acute or chronic renal failure of uncertain etiology, as early diagnosis and treatment can lead to recovery of renal function and prevent interstitial fibrosis. Corticosteroids are mainstay of therapy. Steroid-dependant or refractory cases may respond to other immunosuppressants including anti-TNF-α agents.

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Sarcoidosis is a chronic, multisystem disease of uncertain etiology, which is characterized by an increased cellular immune response to an unknown antigen and noncaseating granulomatous reaction involving almost any tissue but frequently the lymph nodes, lungs, liver, skin, and eyes [1]. Recent studies have suggested a prominent role for tumor necrosis factor alpha (TNF-α) in the inflammatory process seen in sarcoidosis [2]. Renal impairment in sarcoidosis is usually due to hypercalcemia and nephrocalcinosis, but can be due to glomerulonephritis, or interstitial nephritis with or without granuloma. Renal failure as an isolated manifestation of sarcoidosis is an uncommon occurrence. We describe a rare case of sarcoidosis presenting as transient polyarthritis and acute renal failure (ARF) due to isolated granulomatous infiltration. An initial good response to corticosteroids was followed by recurrent flares on steroid taper. Treatment with infliximab, an anti-TNF-α monoclonal antibody, resulted in improvement and stabilization of renal function and successful steroid taper.

Case report

A 57-year-old white male was admitted with 1 week history of myalgias, additive polyarthritis, and ARF in August 2004. Eight days before the admission, he woke up with pain in the left arm and elbow, and over the next several days, he developed pain in the right elbow, hips, thighs, and both knee joints. On the day of admission, he developed chills, dysuria, headache, and neck pain which were relieved with acetaminophen. He denied any fever, weight loss, or rash. He reported chronic loose stools since the

intestinal bypass surgery for morbid obesity 30 years before the admission. Fifteen years before the admission, he had symptomatic cholelithiasis requiring cholecystectomy and recurrent left-sided calcium oxalate nephrolithiasis requiring multiple lithotripsies. He was diagnosed with hypertension few years before the admission. His home medications included nifedipine, acetaminophen, and multivitamins. Four weeks before the admission, he was prescribed with celecoxib 200 mg daily for a painful wart on the plantar surface of the left foot, which he stopped taking about 1 week before the admission. He was a pastor by profession and denied smoking, drinking alcohol, illicit drug, or use of herbal medicine.

The patient was a well-developed male who appeared ill. On physical examination, his temperature was 99.1°F, heart rate was 104/min, respirations were 20/min, and blood pressure was 139/76 mmHg. There were no palpable lymph nodes in the cervical, axillary, or inguinal regions. There were no signs of meningeal irritation, retinal exudates, or rash. His lung, cardiovascular, abdominal, and neurological examinations were normal. Musculoskeletal examination showed synovitis at left elbow, tenderness at metacarpophalengeal joints, left trochanteric bursitis, and bilateral knee effusion.

His laboratory data on admission included: a hemoglobin of 11.9 g/dl (normal range 11.3–15.4 g/dl), white blood cell (WBC) count of 9,480/mm^3 (normal range 3,400–9,200), platelet count of 315,000/mm^3 (normal range 142,000–405,000), blood urea nitrogen of 37 mg/dl (normal range 8–25 mg/dl), serum creatinine of 2.9 mg/dl (normal range 0.7–1.3 mg/dl) elevated from a baseline of 1.0 mg/dl in April 2003 and 2.1 mg/dl five weeks before the admission, erythrocyte sedimentation rate of 27 mm/h (normal range 0–15 mm/h), albumin level of 2.8 g/dl (normal range 3.5–5.0 g/dl), C-reactive protein of 3.32 mg/dl (normal range 0.0–0.5 mg/dl), and creatine phosphokinase of 40 U/l (normal range 30–200 U/l). Urinalysis contained 10 to 20 white cells and 0 to 2 red cells, and urine cultures grew *Pseudomonas aeruginosa*. Synovial fluid from left knee revealed WBC count of 3,675/μl. Other laboratory findings included: serum calcium of 9.0 mg/dl (normal range 8.9–10 mg/dl), 24-h urine protein and calcium of 1.4 g and 81 mg, respectively, 24-h urine oxalate 55 mg (normal range 7–44 mg/24 h), and creatinine clearance of 21 ml/min. Liver function tests, serum complements, serum and urine electrophoresis, and 1,25-dihydroxyvitamin D were normal. Hepatitis B surface antigen, hepatitis C, and antinuclear and antinuetrophilic cytoplasmic antibodies were absent. Angiotensin-converting enzyme level was elevated at 88 U/l (normal range 8–52 U/l).

Chest radiograph, renal ultrasound, and pulmonary function tests were normal. He was treated with ceftazidime for urinary tract infection. His constitutional and arthritic symptoms resolved spontaneously within few days. His renal functions continued to decline, and serum creatinine peaked at 3.6 mg/dl on the sixth hospital day. A renal biopsy was performed which showed granulomatous interstitial nephritis (GIN) with prominent noncaseating epithelioid granulomatous inflammation occupying at least 50% of the tubulointerstitial compartment consistent with sarcoidosis. Bacterial, fungal, and mycobacterial infections were excluded. There was no evidence of nephrocalcinosis. Calcium oxalate crystals were not seen. Prednisone of 60 mg daily resulted in significant improvement in renal function in 1 month with a decrease in serum creatinine to 1.8 mg/dl (Table 1). Prednisone was gradually tapered. Three months after decreasing the prednisone dose to 20 mg/day, he developed erythema nodosum on his legs and creatinine increased to 2.8 mg/dl. Skin lesions improved and creatinine decreased to 1.9 mg/dl within 1 week of increasing the prednisone to 40 mg/day. After creatinine remained stable for several weeks, another attempt was made to decrease the steroids, and the prednisone dose was tapered slowly to 20 mg/day. He was admitted again in August 2005 with a relapse manifested by fevers, chills, night sweats, nausea, fatigue, and increased serum creatinine of 2.9 mg/dl. He was treated with intravenous methylprednisolone 1 g daily for 3 days followed by increased prednisone to 100 mg daily. This again resulted in resolution of his constitutional symptoms and decrease in serum creatinine to 2.0 mg/dl within few days. Because of recurrent flares requiring high-dose steroids which resulted in significant weight gain and worsening hypertension, infliximab of 3 mg/kg/month was added in October 2005. His renal function had been stable, and the prednisone dose had been decreased to 10 mg/day without further relapse.

Discussions

Extrapulmonary forms of sarcoidosis may go unrecognized leading to the delay in diagnosis and treatment. The frequency of renal involvement in sarcoid had been reported to range between 7 and 27% [3, 4]. General consensus is that while the histologic evidence of renal involvement is not uncommon in patients with multisystem involvement; the frequency of clinically apparent primary renal involvement is considerably low.

Impairment of renal function in sarcoidosis is most commonly due to hypercalcemia, hypercalciuria, and nephrocalcinosis; however, nephrolithiasis, glomerulopathies, interstitial nephritis without sarcoid granuloma, and sarcoid granulomatous infiltration of the kidney may also occur. Hypercalcemia in sarcoidosis occurs in 20% of cases. The enhanced production of the enzyme 1-α-hydroxylase by

Table 1 Changes in renal function with disease activity and response to therapy

	July 04	Aug. 04	Sep. 04	Oct. 04	Nov. 04	Dec. 04	Jan. 05	Feb. 05	Mar. 05	Apr. 05	May 05	June 05	July 05	Aug. 05	Sep. 05	Nov. 05	Jan. 06
BUN	26	37	36	23	23	25	28	29	34	23	27	22	29	28	28	25	23
S. Cr	2.1	3.6	2.2	1.8	1.7	1.7	1.7	2.5	2.8	1.9	1.7	1.7	1.9	2.9	1.9	1.8	1.8
U. P/Cr		75/89							8/18		17/34				10/30		
Pred	–	–	60	40	20	20	20	20	40	30	30	30	20	100	40	10	10
Infliximab																	3 m/kg/month
24HUPR		1416	899				732										

BUN Blood urea nitrogen (mg/dl), *S. Cr* serum creatinine (mg/dl), *U. P/Cr*, urine protein and creatinine (mg/dl); *Pred* prednisone (mg); 24HUPR, 24-h urine protein (mg/24 h)

activated monocytes in sarcoid granulomas converts 25-hydroxyvitamin D to calcitriol which is the most active metabolite of vitamin D. The increased intestinal absorption of calcium leads to hypercalcemia, hypercalciuria, polyuria, nephrolithiasis, nephrocalcinosis, and renal insufficiency. Primary glomerular diseases are well described in sarcoidosis but more commonly cause proteinuria ranging to a full-blown nephrotic syndrome than ARF [5]. There was no evidence of calculi, hypercalcemia, nephrocalcinosis, or glomerular disease in our patient. Renal granulomas may occur in up to 40% of cases of sarcoidosis (found in autoptic or bioptic circumstances) [6], but these seldom cause renal impairment, particularly in the absence of other organ involvement [7–9]. An isolated renal failure as a presenting feature of GIN in the absence of widespread involvement of other organs with sarcoidosis is rare and must be distinguished from other causes of GIN (Table 2).

GIN and renal failure have been reported to occur rarely after jejunoileal bypass surgery. The histological changes on renal biopsy in such cases show interstitial nephritis, oxalate crystal deposition, and aggregates of multinucleated giant cells related to the crystal material (granulomatous reaction). Ultrastructural and histochemical studies in one such case demonstrated mitochondrial alterations in the tubular epithelial cells suggesting proximal tubular origin of the giant cells [10]. The association of the oxalate crystals with damaged tubules and giant cells suggested that the oxalate crystals were responsible for these alterations. It is interesting to note that our patient also had intestinal bypass surgery for morbid obesity 30 years before the admission; however, calcium oxalate crystals were not seen on renal biopsy in our patient.

Our patient had a prompt response to treatment with corticosteroids resulting in improvement in creatinine; however, each time steroids were tapered, he experienced a relapse. Previous studies have suggested a prominent role for TNF-α in the inflammatory process seen in sarcoidosis. The chemokine and cytokine pathways that regulate granuloma formation are not well understood, but TNF-α is known to play a key role [2]. TNF-α and interleukin-1 are released by alveolar macrophages in patients with active lung disease. Moreover, there are several case reports of refractory extrarenal sarcoidosis treated successfully with infliximab [11]. Infliximab is a chimeric, monoclonal antibody that specifically binds to human TNF-α. Our patient's disease has been stable since the institution of infliximab, and no further relapse was seen despite continued steroid taper.

Conclusions

We report a rare case of sarcoidosis presenting as transient polyarthritis and ARF from isolated granulomatous infiltration of the renal parenchyma. Although uncommon, renal sarcoidosis should be considered in the differential diagnosis of acute or chronic renal failure of uncertain

Table 2 Causes of granulomatous interstitial nephritis

Infections
Tuberculosis
Histoplasmosis
Leprosy
Malacoplakia
Xanthogranulomatous pyelonephritis
Echinococcus disease
Vasculitis
Wegener's granulomatosis
Microscopic polyangiitis
Churg–Straus Syndrome
Sarcoidosis
Jejunoileal Bypass
Drug-induced
Ampicillin, penicillin, aztreonam
Cephalosporins, sulphonamides
Erythromycin, fluoroquinolones
Griseofulvin, diuretics, omeprazole
Allopurinol, aspirin, captopril, azathioprine,
Carbamazepine, cimetidine, gamma-interferon, lamotrigine
Levodopa, lithium and other heavy metals, alendronate sodium
Nonsteroidal anti-inflammatory drugs, etc.

etiology. A prompt diagnosis and early treatment with steroids can lead to recovery of renal function and prevent interstitial fibrosis. Prolonged treatment with steroids for up to 1–2 years may be required. Steroid-dependant or refractory cases may respond to other immunosuppressants including anti-TNF-α agents. Close follow-up is necessary to monitor for a relapse. Additional studies are needed to evaluate the role of TNF inhibition in sarcoidosis.

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