

The Many Faces of Renal Sarcoidosis - Minireview and Case Presentation

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ABSTRACT

Sarcoidosis is a multisystemic immune-mediated inflammatory disease characterized by the development of non-caseating epithelioid granulomas in different organs. Sarcoidosis can affect all tissues and organs in the human body but most commonly involves the lungs, lymphoid organs (lymph nodes and spleen), skin, liver, central nervous system, and kidneys. The authors discuss the different types of renal involvement in sarcoidosis and present typical ultrasound and X-ray images of patients with sarcoidosis.

Key words: Glomerulonephritis, renal failure, renal involvement, sarcoidosis, tubulointerstitial nephritis

INTRODUCTION

Sarcoidosis is a multisystemic immune-mediated granulomatous inflammatory disorder of unknown origin.^[1-4] Its name is related to the typical histological changes resembling sarcomatous tissue. Sarcoidosis is also known as Boeck's disease, Besnier-Boeck-Schaumann disease, and lupus pernio. The hallmark of sarcoidosis is the typical non-caseating epithelioid cell granulomas that can develop in every tissue and organ of the human body but is usually found in the reticuloendothelial structures and lungs.^[2] The intrathoracic structures - mediastinal and hilar lymph nodes and lungs - are the most commonly affected organs. Sarcoidosis can affect the skin, eyes, joints, central nervous system, liver, and kidneys.^[2,3] The disease can develop in all age groups but young females, especially of African descent, are more commonly affected.^[2,3] The disease shows positive association with HLA A1, B8, and DR3, the association with HLA B27 correlates with the presence of lung involvement, and HLA B12 and DR4 seem to correlate negatively with the development of sarcoidosis.^[2]

Over 95% of the patients show intrathoracic and lung involvement^[2,3] that is classified in four major

clinicoradiological stages: I - bilateral hilar lymphadenopathy; II - bilateral hilar lymphadenopathy plus renal parenchymal involvement (reticulonodular parenchymal infiltrates); III - interstitial lung disease (pulmonary infiltrates); and IV - advanced lung fibrosis.

The etiology of sarcoidosis remains unclear. Certain bacterial agents have been suspected to induce granuloma formation, including mycobacteria, mycoplasma, and propionibacteria.^[2,3] The progression of the disease is thought to be influenced by changes in CD4+ cells and interleukin (IL) 2 and 12 expression (with proliferation and activation of T-cells), IL6 and IL8, and IL15 (produced by macrophageal cells and stimulating T- and B-cells). Increased IL4 secretion (with subsequent production of matrix proteins), IL5 and IL13 (with increase in Immunoglobulin E synthesis), and chemotaxin secretion have been described. Alterations of the dendritic cells have also been described, and approximately 10% of the patients with sarcoidosis develop common variable immunodeficiency.^[2]

Clinically significant renal involvement can develop in less than half of sarcoidosis patients and is associated with:^[1-3,5-19,20-28]

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- Changes in calcium-phosphate metabolism - hypercalcemia and hypercalciuria due to increased macrophage expression of 1-alpha-hydroxylase in the granulomatous tissue with increased synthesis of dihydroxy Vitamin D [(OH)2D] and the development of nephrolithiasis, nephrocalcinosis, and interstitial nephritis (acute or chronic);
- Granulomatous interstitial nephritis;
- Glomerular involvement - IgA, membranous, mesangiocapillary/membranoproliferative, crescenting, antineutrophil cytoplasmic antibodies (ANCA)-associated glomerulonephritis, focal and segmental glomerular sclerosis, etc.;
- Obstructive uropathy - obstruction of the urinary flow due to the migration of renal stones, retroperitoneal lymphadenopathy, retroperitoneal fibrosis, or granulomatous infiltration of the ureters;
- Renal failure - acute (hypercalcemic crisis, extreme dehydration, and obstructive uropathy) or chronic (as a consequence of persistent hypercalcemia and hypercalciuria, tubulointerstitial nephritis, glomerulonephritis, and obstructive uropathy with recurrent urinary tract infections, etc.);
- Association with urogenital neoplasms: Papillary adenocarcinoma of the kidney, hypernephroma, transient-cell cancer of the renal pelvis/urinary bladder, etc.

The prevalence of clinically significant renal disease in sarcoidosis is unknown.^[5,24,29,30] In the systemic search of renal changes in such patients (including histological verification of granulomatous renal lesions, tubulointerstitial or glomerular alterations, and/or progressive decrease of renal function in the absence of renal biopsy), kidney involvement can be detected in up to 35–50% of the cases.^[24] Nephrolithiasis can be detected in 1–14%,^[4,14,16,23] nephrocalcinosis – in approximately 5%,^[30] granulomatous interstitial nephritis (with or without renal functional changes) – in 20%,^[16] glomerular involvement and obstructive uropathy are rare. In some patients, more than one type of renal involvement can be found.^[2,7,24] Acute renal failure is rare, usually associated with acute hypercalcemia, proliferative glomerulonephritis, or bilateral obstructive uropathy, and the development of chronic renal failure is not common.

Nephrolithiasis and nephrocalcinosis

The increased synthesis of (OH)2D in sarcoidosis leads to persistent hypercalcemia and hypercalciuria^[1,2,4,7,10,17,22,24] with subsequent formation of calcium-containing renal stones and parenchymal calcifications (nephrocalcinosis). Persistent hypercalcemia may lead to impaired vasopressin response and polyuria that further increases the risk of stone formation.^[31] Nephrocalcinosis and nephrolithiasis may be the first symptoms of sarcoidosis, and the typical intrathoracic changes may develop later in the course of the disease.^[25] The treatment of nephrolithiasis is aimed at suppression of disease activity of sarcoidosis (corticosteroids

and cytotoxic medications), treatment of renal colic/desobstruction, and urinary tract infections. In patients with nephrocalcinosis, the main goal of the treatment is inhibition of the underlying inflammation and granuloma formation to prevent hypercalcemia/hypercalciuria and the deposition of calcium within the renal parenchyma.

Interstitial nephritis

The development of interstitial nephritis in sarcoidosis is due to two major types of changes:

- Formation of sarcoid granulomas within the renal parenchyma - perivascular, peritubular, and interstitial, with subsequent fibrogenesis,^[2,7,24] and
- Hypercalcemia/hypercalciuria-induced tubulointerstitial changes without granuloma formation^[2,24] - usually in long-standing sarcoidosis.^[19]

Sarcoidosis patients with interstitial nephritis usually have lung and/or lymphonodular changes and present with non-specific and constitutional symptoms: fatigue, weight loss, low-grade fever.^[19] Non-specific urinary changes can be detected - sterile leukocyturia, low-grade proteinuria, erythrocyturia, glucosuria, hypercalciuria, changes in urine concentration and acidification, decreased renal functional capacity.^[2,24] This condition should be differentiated from other granulomatous disorders, including infections with granuloma formation (tuberculosis, brucellosis, histoplasmosis, etc.), vasculitis and inflammatory bowel disease, tubulo-interstitial nephritis+uveitis syndrome, etc., and other organ involvement characteristic for sarcoidosis (especially intrathoracic) should be sought.^[2,3,7,24,32-34]

The treatment of renal tubulointerstitial changes in sarcoidosis is aimed at suppression of inflammation and granuloma formation (glucocorticosteroids, antimalarial and cytotoxic agents, antitumor-necrosis factor alpha, etc.) and correction of metabolic disturbances.

Glomerular involvement

Different types of glomerular lesions have been described in sarcoidosis, including immunoglobulin A (IgA), membranous, mesangiocapillary/membranoproliferative, crescenting (mainly ANCA-associated), and focal and segmental glomerulosclerosis, with or without granuloma formation and calcium deposition within the glomerular structures.^[2,7,9,11,24,28,35] The glomerular changes may remain undiagnosed or manifest clinically with nephrotic syndrome with massive proteinuria and edema or as acute nephritic syndrome with hematuria, moderate proteinuria, edema, renal failure, and arterial hypertension. Sarcoidosis may coexist with Wegener's granulomatosis.^[3] The treatment of the glomerular involvement does not differ from that of the underlying condition, glucocorticosteroids and cytotoxic agents.

Obstructive uropathy

In sarcoidosis, the migration of kidney stones, retroperitoneal lymphadenopathy and/or fibrosis, and the ureteral engagement with sarcoid granulomatous inflammation may lead to urinary flow obstruction^[2,8,20,24,36,37] with recurrent urinary tract infections and progressive deterioration of renal function. The treatment is aimed at ureteral desobstruction (double J stents, ureteral liberation, implantation of nephrostomic catheters, lithotripsy, etc.), anti-inflammatory/immunosuppressive treatment, and treatment and prophylaxis of urinary tract infections.

Organ transplantation

The presence of sarcoidosis is not a medical contraindication for renal or other organ transplantation^[2,38,39] and the graft (kidneys, lungs, and heart), and patient survival is comparable with those of non-sarcoidosis patients.^[8,24,35,39] After the transplantation, the disease may recur in the graft - lung, heart, kidney, etc. After successful renal transplantation, recurrence of IgA nephropathy and sarcoid granulomas within the graft has been described.^[2,24,38,39] The risk for sarcoidosis and glomerulonephritis recurrence within the graft after renal transplantation requires close follow-up and aggressive treatment.

CASE REPORT

Clinical case 1

A 40-year-old male patient was admitted to the Clinic of Dermatology in March 2005 for diagnostic evaluation of facial granulomatous lesion. During the hospital stay, he was found erythrocyturia (6-8 leukocytes/power field) and low-grade proteinuria of 480 mg/24 h with normal renal function (serum creatinine of 76 $\mu\text{mol/l}$) and normal erythrocyte sedimentation rate (ESR) (6 mm/h) and serum calcium levels (2.46 mmol/l). The patient reported having erythema nodosum attack 4 years earlier. The chest X-ray revealed bibasal fibrosis and hilar lymphadenopathy [Figure 1], and the lung function tests revealed mild restrictive plus obstructive changes (forced vital capacity of 66% of the predicted and forced expiratory volume for 1 s of 74% and peak expiratory flow of 79–80%). The skin biopsy and lung biopsy both revealed that the presence of non-caseating granulomas and sarcoidosis was diagnosed. The patient was referred to the clinic of nephrology for evaluation.

The ultrasound examination of the kidneys [Figure 2] revealed increased kidney size, increased parenchymal echogenicity with contrasting pyramids, and small parenchymal calcifications. Renal biopsy revealed mesangioproliferative IgA glomerulonephritis.

Lung sarcoidosis with IgA glomerulonephritis was diagnosed, and the patient was started in low-dose corticosteroids

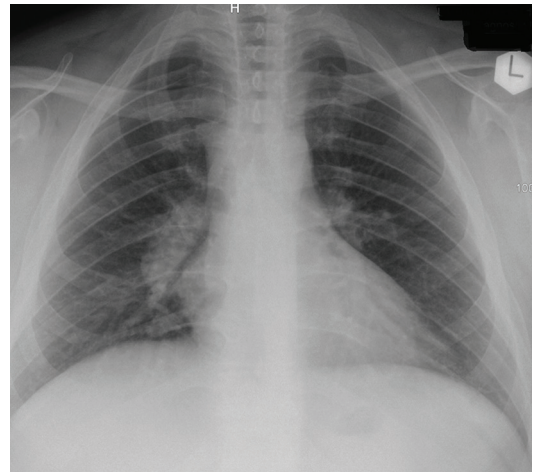


Figure 1: Chest X-ray examination of patient 1. Bibasal lung fibrosis and bilateral hilar lymphadenopathy (stage II)

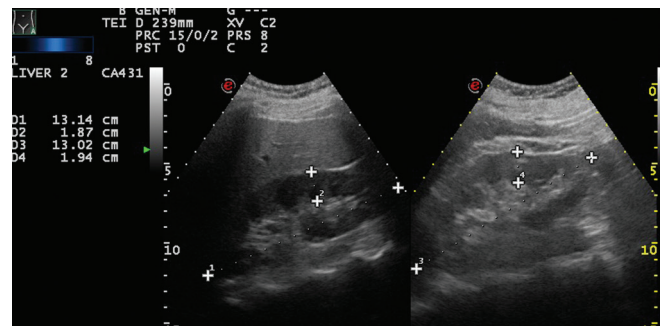


Figure 2: Ultrasound examination of the kidneys of patient 1. Increased kidney size and increased parenchymal echogenicity with contrasting pyramids and small parenchymal calcifications

(0.5 mg/kg/24 h.). In 8 weeks skin changes and lymphonodular changes, proteinuria and erythrocyturia subsided.

Clinical case 2

A 39-year-old female patient with 8 years' history of hepatolienal sarcoidosis was admitted to the Clinic of Nephrology in May 2005 for urinary tract infection. The patient was on treatment with prednisolone 10 mg a day. The clinical laboratory investigations revealed increased ESR (65 mm/h), increased leukocyte count (15.3 G/l), bacteria, leukocytes, and erythrocytes in the urinary sediment and acute urinary tract infection with *Escherichia coli*. Renal function was normal (serum creatinine of 65 $\mu\text{mol/l}$) and serum calcium was mildly increased (2.7 mmol/l). Abdominal ultrasound [Figure 3] revealed enlarged liver with increased parenchymal echogenicity, enlarged spleen, and a small calyceal stone in the right kidney. Antibiotic treatment was started and the corticosteroid dose was increased to 20 mg a day. Urinary tract infection subsided. Within 4 weeks, calcium levels have decreased to the normal limits (2.34 mmol/l).

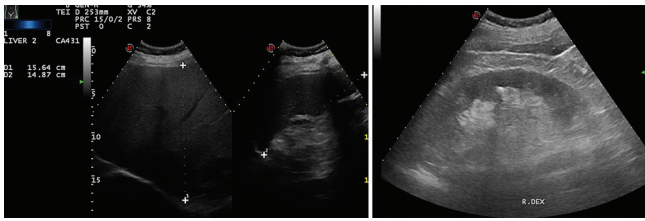


Figure 3: Abdominal ultrasound of the patient 2. Note enlargement of the spleen and liver (a) and small calyceal stone in the right kidney (b)

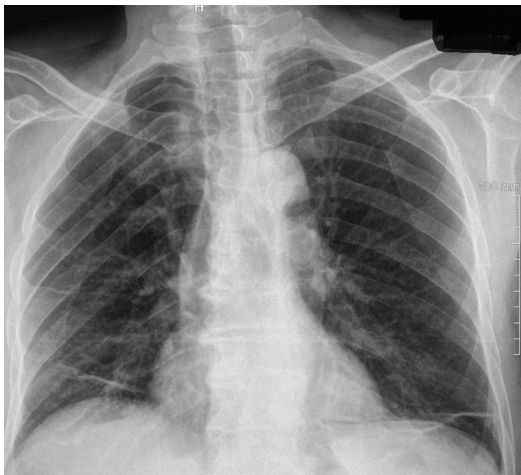


Figure 4: Chest X-ray examination of the patient 3 - lung fibrosis (stage IV)



Figure 5: Abdominal ultrasound of the patient 3 - renal parenchymal calcification (arrow)

Clinical case 3

A 45-year-old male patient with 6 years' history of lung sarcoidosis with erythema nodosum was admitted to the Clinic of Nephrology in September 2001 for urinary tract infection. The patient was on prednisolone 10 mg a day. The clinical laboratory investigations revealed increased ESR (46 mm/h.), increased leukocyte count (17.2 G/l), bacteria, leukocytes, and erythrocytes in the urinary sediment and acute urinary

tract infection with *Enterococcus faecalis*. Renal function was normal (serum creatinine of 77 $\mu\text{mol/l}$) and serum calcium was mildly increased (2.8 mmol/l). Chest X-ray revealed lung fibrosis [Figure 4]. Abdominal ultrasound revealed renal parenchymal calcifications (cortical nephrocalcinosis) [Figure 5]. The patient was started on antibiotic and the dose of prednisolone was increased to 20 mg a day. The urinary tract infection subsided, and in 4 weeks, serum calcium levels decreased to normal limits (2.28 mmol/l).

DISCUSSION AND CONCLUSION

Sarcoidosis is a rare immune-mediated granulomatous disorder, characterized by the development of non-caseating epithelioid-cell granulomas in different tissues and organs. It can affect every organ in the human but most commonly involves the lungs, lymph nodes, eyes, joints, skin, nervous system, liver, and kidneys.

The renal involvement may be primary - non-caseating granuloma formation within the renal tissue, or due to persistent hypercalcemia and/or hypercalciuria. Both glomerular and tubulointerstitial renal lesions with or without the development of renal failure have been described. Obstructive uropathy is rare. The presented cases illustrate the multiple clinical faces of sarcoidosis: Glomerular lesions at the background of lung, lymphonodular, skin, and articular involvement in the patient 1, hepatolienal sarcoidosis with nephrolithiasis in the patient 2, and lung, articular, and renal involvement with nephrocalcinosis in the patient 3. Two of the presented patients had hypercalcemia.

The presented clinical cases once again show the non-specific nature of renal changes in sarcoidosis and underline the importance of the teamwork in the evaluation and treatment of these patients.

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