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The protean face of sarcoidosis revisited

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Introduction

Sarcoidosis is a multisystem disorder characterized by non-caseating, epithelioid granulomas. Sarcoidosis predominantly affects the lungs; however, almost every organ can be involved including the kidneys. In fact, the absense of pulmonary findings by no means excludes sarcoidosis. The aetiology of the disease is still not fully elucidated. On the one hand, we have strong evidence from various sources suggesting that increased macrophage and CD4 helper T-cell activity results in accelerated inflammation. This extensive local response ultimately causes the granuloma formation. On the other hand, sarcoidosis patients show suppressed immune responses to *in vivo* and *in vitro* antigen challenges, such as tuberculin. The latter state of affairs is in stark contrast to the accelarated inflammation hypothesis and suggests an anergic state. Anergy is believed to be responsible for the increased risk of sarcoidosis patients to aquire opportunistic infections and cancer.

Interesting new findings from affected patients show that expanded $CD4^{+}CD25^{bright}FoxP3^{+}$ accumulate in the periphery of sarcoid granulomas [1]. These cells represent regulatory T-lymphocytes with a strong anti-proliferative effect. However, this suppressive effect was not sufficient to completely inhibit tumour necrosis factor-α (TNF-α) secretion in autologous lymphocytes. This finding would probably explain why granulomas still occur, for TNF-α is central to granuloma formation. The regulatory T-cells were nonetheless sufficient to prevent lymphocyte interleukin-2 (IL-2) secretion. The latter fact may induce a state of anergy by preventing antigen-specific memory responses.

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A second novel finding in sarcoidosis patients involves a recently described polymorphism in the butyrophilin-like 2 (BTNL2) gene [2,3]. BTNL2 belongs to the immunoglobulin superfamily, shows homology to B7-1, and probably functions as a co-stimulatory molecule for T-cell activation. Mutation of the gene with a G to A transition leads to a truncated variant of BTNL2 and to a loss of down-regulatory T-cell functions [2]. A better understanding of the underlying disease mechanisms could help to generate new treatment protocols.

An infectious cause of sarcoidosis has been postulated since the disease was first described. Provocative data have been reported on extrapulmonary sensitization to *Propionibacterium acnes* [4]. Pulmonary Th-1 granulomas were successfully produced in mice, mainly in the subpleural and peribronchovascular regions by means of *P. acnes*-primed CD4+ T-cell transfer. In their model, the investigators also experimented with live *P. acnes* in their mice and were able to show an effect on pulmonary granuloma formation and amelioration with antibiotic treament.

Currently, steroids are widely used to treat sarcoidosis patients, although there is no consensus about when to initiate the treatment, how intense the immunosuppression should be, and how the treatment should be monitored [5]. The spectrum of renal manifestation of sarcoidosis is widespread. Since our last review of renal involvement [6], we have encountered additional sarcoidosis patients who underscore the protean manifestations of this disease. Each of these patients taught us a different lesson highlighting distinct aspects of renal involvement.

Patient 1

A 62-year-old woman was admitted because of progressive renal insufficiency. She had also developed two episodes of uveitis and shortness of breath for the last 6 months. Chest roentgenogram and computed tomography showed bihilar lymph node enlargement and reticular structures in both lungs. We noted a peculiar redness under her right eye. The skin had a doughy consistency. We performed a biopsy (Figure 1). On admission, creatinine had risen to 279 μmol/l, urinary calcium excretion was 7.1 mmol/24 h, serum calcium concentration was 2.52 mmol/l, while calcitriol and intact parathyroid hormone (PTH) values were normal. Angiotensin converting enzyme (ACE) activity was 3-fold and soluble IL-2 receptor (IL-2R) was elevated 3.5-fold. Her urinary sediment was unremarkable. Nevertheless, progressive renal insufficiency prompted us to perform a renal biopsy. We observed a non-specific interstitial nephritis, but were fortunate enough to find an epithelioid cell granuloma adjacent to the renal capsule (Figure 1).

Although by no means disease-specific, granulomatous interstitial nephritis is the most common renal manifestation of sarcoidosis. The only granuloma that we found was by chance adjacent to the renal capsule. The patient exhibited rapidly progressive renal insufficiency without hypercalcaemia. We administered prednisolone and azathioprine for 6 months. The renal function stabilized at a creatinine of 204 µmol/l, serum calcium was 2.2 mmol/l, the ACE activity normalized, while IL-2R levels remained 2-fold increased.

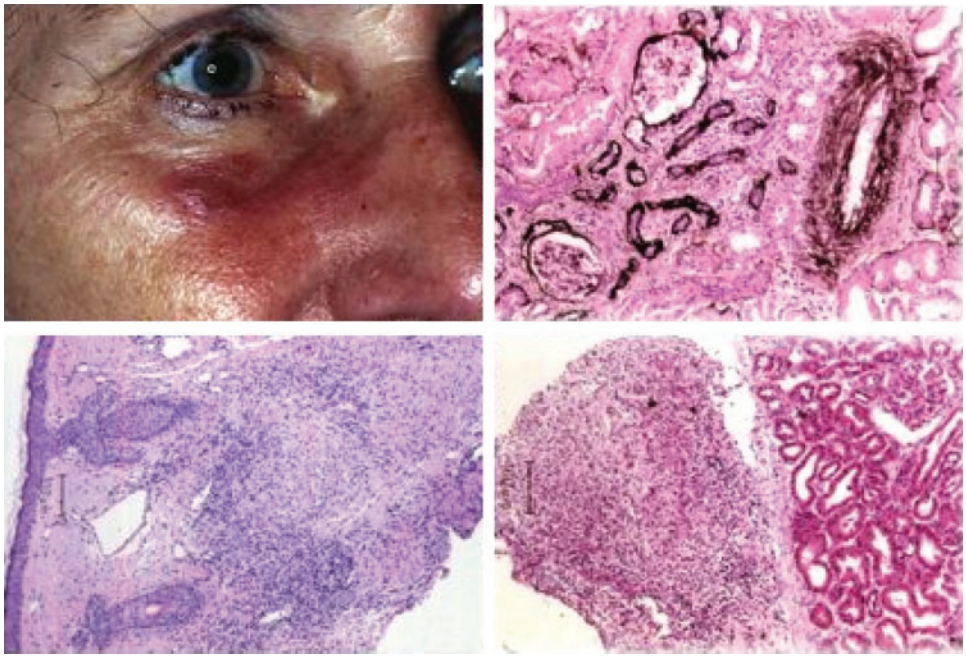

Fig. 1. Redness under the patient's eye with the corresponding biopsy showing granulomatous inflammation (lower left panel). Renal biopsy indicates an interstitial nephritis (upper right panel) and an epithelioid cell granuloma adjacent to the capsule (lower right panel).

Patient 2

A 58-year-old patient was admitted with acute renal failure. The serum creatinine was 536 μmol/l, but had been normal 8 months earlier. He complained of general malaise for the previous 2 months. His past medical history included coronary artery disease with a myocardial infarction, hypertension for 8 years and diabetes mellitus 4 years prior to admission. He had been a heavy smoker (50 pack years), but denied analgesic intake. On examination, the patient appeared anaemic and volume-expanded. He had severe hypertensive retinopathy. The haemoglobin was 10.4 mg/dl, the leucocytes were 5.5 Gpt/l, platelets were 238 Gpt/l, serum calcium 2.84 mmol/l, phosphorus 1.78 mmol/l, intact PTH was 0.14 pmol/l and the C-reactive protein was 6.5 mg/l. The complement system was activated with C3 0.27 g/l, C4 0.044 g/l and C1q 58 mg/l. Antinuclear antibodies (ANA) and anticytoplasmic neutrophil antibodies (ANCA) were not detected. Cryoglobulins, serology for hepatitis and HIV were negative. There were dysmorphic erythocytes, abundant hyaline and some granular cylinder in the urinary sediment. The protein was +1. Immunofixation of urine and plasma was negative. Renal biopsy showed a granulomatous interstitial nephritis including typical multinucleated giant cells (Figure 2). Tubular and glomerular tissue was replaced by the granulomas. There were no immunoglobulins or complement deposition detected in the glomeruli.

Low levels of complement C3 and C4 are commonly found in patients with several forms of glomerulonephritis, in haemolytic uraemic syndrome and in rare cases of immunotactoid glomerulonephritis [7–10]. Hypocomplementaemia in sarcoidosis appears to be an exception; we are aware of only very few additional case reports [11]. The report by Hagiwara *et al.* [11] is of special interest because the authors were able to demonstate *P. acnes* DNA in the glomeruli of their patient, giving support to the *P. acnes* granuloma model mentioned earlier. Of particular note is the fact that no complement deposition was detected in the renal tissue of our patient. Complement factors, such as C3 or C5 could stimulate macrophages that express the complementary surface receptors. Alveolar macrophages of sarcoidosis patients themselves produce higher amounts of complement factors, compared with healthy persons [12]. However, the complement system is probably less well investigated in sarcoidosis patients and its significance, if any, is not yet clear. Interestingly, low complement levels found in our patient normalized with corticosteroid treatment. He remains in remission for the second year on low-dose azathioprin. Creatinine was 116 μmol/l at the last follow-up.

Patient 3

A 64-year-old patient with mid back pain received a chest roentgenogram during his work up. The roentgenogram showed a broadened mediastinum

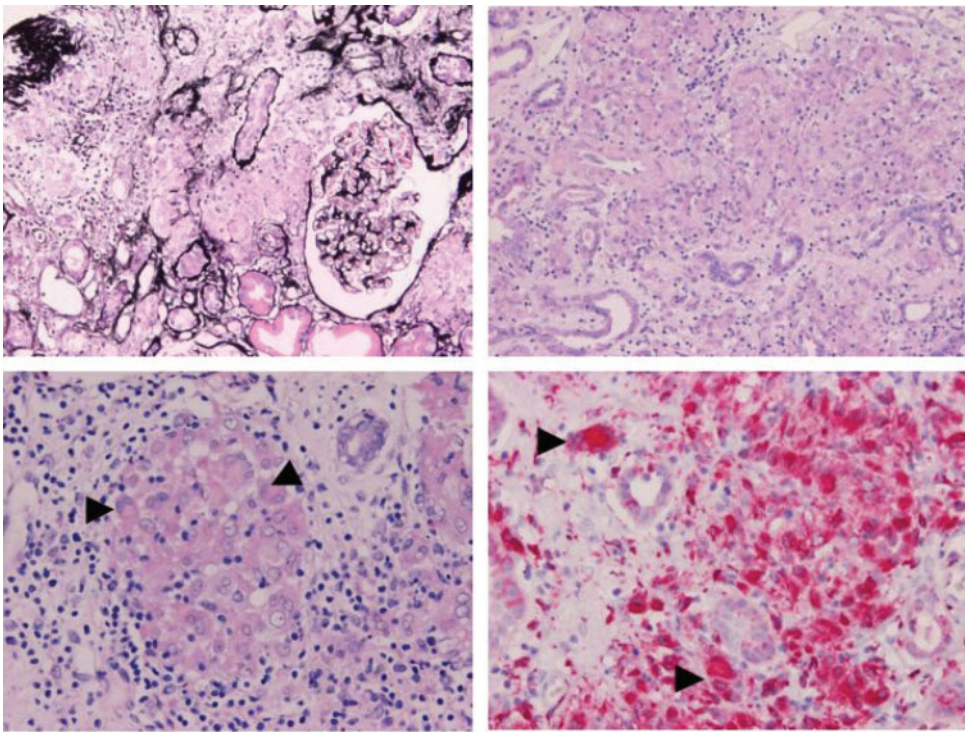

Fig. 2. Renal biopsy showed a granulomatous interstitial nephritis with a broadened interstitium, cellular infiltrates and granuloma with typical multinucleated giant cells (arrowheads). Tubular and glomerular tissue was replaced by the granulomas. Positive CD68 staining indicates numerous macrophages.

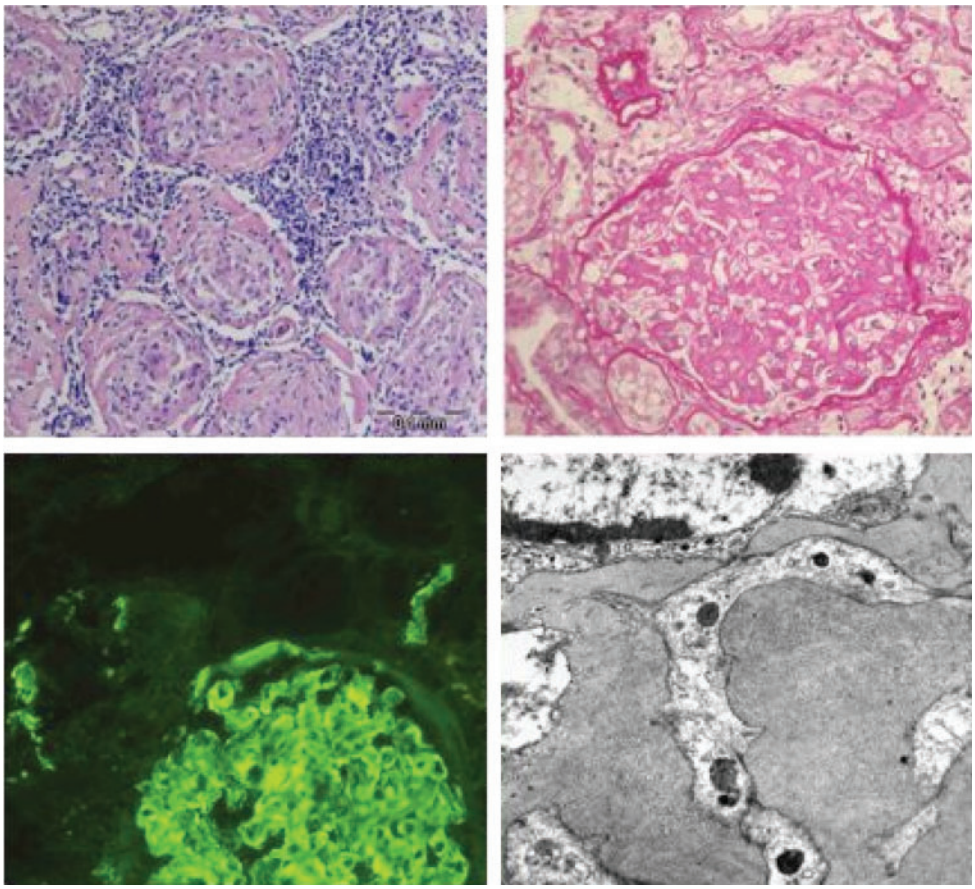

Fig. 3. The current lymph node biopsy showed granulomas consistent with sarcoidosis (upper left panel). The renal biopsy had been done 9 years earlier. In Periodic Acid Schiff (PAS) staining, glomerular mesaangial expansion is demonstrated (upper right panel) with mesangial staining for IgG (lower left panel). Electron microscopy shows mesangial and subendothelial deposition of parallel microfibrills with an outer diameter of 40 nm (lower right).

that prompted additional tests. Computed tomography revealed enlarged supra and infra-clavicular lymph nodes, as well as hepatic hilar nodes. In addition, the spleen showed a large hypodense lesion with calcification. Haemoglobin was 13.6 mg/dl. Leucocytes were 5.2 Gpt/l, platelets were 294 Gpt/l and the serum calcium concentration was 2.31 mmol/l. Soluble IL-2 Rlevels were elevated 4-fold, while ACE activity, complement, C-rective protein, ANA and ANCA were within the normal range. The patient excreted 1.2 g/day proteinuria and had a decreased, 75 ml/min creatinine clearance. His urinary sediment was unremarkable. He claimed to have undergone renal biopsy 9 years earlier because of 7 g/day proteinuria and hypertension. We performed biopsies of an enlarged lymph node and obtained the kidney sections (Figure 3).

Our patient had two histologically documented diseases, namely sarcoidosis and immunotactoid glomerulopathy (ITG). ITG is a rare condition comprising $\approx$0.06% of native kidney biopsies with a peak at age 60 years [13]. ITG is characterized by the deposition of Congo red-negative structures that contain immunoglobulins. These non-amyloid inmmunoglobulins form microtubular structures with a lumen and are arranged in parallel arrays. Whether or not ITG should be distinguished from fibrillary glomerulopathy is not yet clear. Most patients with ITG develop nephrotic syndrome. Frequently, some degree of renal insufficiency is detected at the time of diagnosis and the majority of patients will progress to end-stage renal disease without responding to immunosuppressive treatment. ITG may be associated with haematological disorders, hepatitis and HIV infection. However, to our knowledge, our report is the first description of an association of ITG with sarcoidosis. Our patient had a persistent leucopaenia, but no abnormalities in the differential. Five months after diagnozing sarcoidosis from the lymph node biopsy, the patient developed heavy arthalgias and uveitis. We initiated prednisolone treatment and the symptoms resolved. At the last follow-up, our patient's creatinine was 87 μmol/l with a creatinine clearence of 90 ml/min; the proteinuria was 2.3 g/day.

Conclusion

Renal sarcoidosis occurs in as many as 25% of sarcoidosis patients. The renal disease is commonly

related to elevated calcium levels with resultant nephrolithiasis and nephrocalcinosis. Other manifestations, including granulomatous interstitial nephritis, several forms of glomerulonephritis and even immunotactoid glomerulonephritis, may occur. Motile proximal tubular cell cilia have even been reported in a patient with renal sarcoidosis and hypercalcaemia [14]. The idea that sarcoidosis is an inappropriate reaction to an ubiquitous microorganism, *P. acnes*, has interesting therapeutic considerations. Sarcoidosis continues to be a disease that confuses, confounds and surprises the non-aware clinicians.

Conflict of interest statement. None declared.

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Contrast-enhanced sonography as early diagnostic tool of chronic allograft nephropathy

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Keywords: chronic allograft nephropathy; colour Doppler ultrasonography; contrast-enhanced sonography; kidney transplantation; renal allograft

A resistance index (RI) obtained by colour Doppler ultrasonography is a standard procedure in the routine diagnosis of renal allografts, and has recently been shown to be associated not only with allograft, but also with patient survival [1]. Although the value of colour Doppler ultrasonography of the renal allograft—especially in the early post-operative period—is undisputed, uncertainties persist as to its diagnostic and prognostic value and its clinical application. It is worth noting that RI not only reflects renovascular resistance, but also indirectly reflects haemodynamic parameters such as elasticity of the large upstream capacity vessels [2,3]. In the interpretation of RI values, surrogate markers for reduced vascular compliance such as intima media thickness, pulse pressure

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