

Case Report

Evidence of latent pathogenesis of *Propionibacterium acnes* infection in a patient with renal sarcoidosis

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Abstract

A 49-year-old man with pulmonary sarcoidosis was admitted to our hospital because of nephrotic syndrome. Renal biopsy revealed membranous nephropathy and granulomatous interstitial nephritis. DNA and cell membrane constituents of *Propionibacterium acnes* were detected in the patient's glomeruli and tubular epithelial cells. Treatment with corticosteroids and an antimicrobial agent resulted in remission of the nephrotic syndrome. This is the second case in which components of *P. acnes* were found in renal tissue, suggesting latent pathogenesis of *P. acnes* infection in renal sarcoidosis.

Keywords: granulomatous interstitial nephritis; membranous nephropathy; *Propionibacterium acnes*; sarcoidosis

Case Report

A 49-year-old man visited our hospital in December 2006 with leg oedema and proteinuria. Bilateral hilar lymphadenopathy on a chest X-ray had been pointed out. At the age of 35, he underwent transbronchial lung biopsy, and pulmonary sarcoidosis was diagnosed. No findings that suggested lung tuberculosis were involved in this tissue. Then he was followed up at the outpatient clinic. He developed leg oedema from the summer of 2006. His condition deteriorated, and he was admitted to our hospital because of nephrotic syndrome. He was 163 cm in height and weighed 66 kg, his blood pressure was 128/60 mmHg and pulse rate was 72/min. He presented with pitting oedema in the lower extremities. Laboratory data were as follows: white blood cell count $5.3 \times 10^3/\mu\text{l}$, red blood cell count $5.13 \times 10^6/\mu\text{l}$, haemoglobin 15.4 g/dl, haematocrit 44.3%, platelets $263 \times 10^3/\mu\text{l}$, total protein 5.9 g/dl, albumin 2.7 g/dl, total cholesterol 303 mg/dl, BUN 11 mg/dl (3.9 mmol/l), sCr 0.71 mg/dl (62.8 $\mu\text{mol/l}$), uric acid 6.9 mg/dl, serum sodium 138 mEq/l, potassium 3.7 mEq/l, chloride 102 mEq/l, calcium 8.3 mg/dl, phosphate 3.6 mg/dl, IgG 1148 mg/dl, IgA 335 mg/dl, IgM 74 mg/dl, CH50 49.5 U/ml, C3 137 mg/dl and C4 36 mg/dl. The level of angiotensin-converting enzyme (ACE) was 31.1 U/l (normal range 8.3–21.4 U/l). In urinalysis, pH was 5.0, SG 1.013, protein (2+), glucose (–) and occult blood (–). Urine sediment revealed 6–10 red blood cells/HPF and 1–5 white blood cells/HPF. In a chest X-ray, bilateral swelling of the hilar lymph nodes was observed. His electrocardiogram was normal.

Percutaneous renal biopsy was performed on 8 December 2006. In light microscopy specimens, 29 glomeruli were present, and two glomeruli showed global sclerotic change. Periodic acid silver methenamine (PAM) staining showed thickening of the glomerular capillary walls with subepithelial spike formation (Figure 1A). In the interstitium, epithelioid granulomas, plasma cells and lymphocytes were also observed (Figure 1B). In immunofluorescence staining, IgG and C3 were marked in

Background

Sarcoidosis is recognized as a multiorgan disorder of unknown etiology characterized by the accumulation of T lymphocytes, mononuclear cells and non-caseating granulomas in the involved tissues [1]. *Propionibacterium acnes* and *Mycobacterium tuberculosis* have been studied extensively and are thought to be the causative agents [2–4]. The results of an international study were published in 2002. Eishi *et al.* reported that the lymph nodes derived from sarcoid patients, but not from non-sarcoid patients, contained DNA from *P. acnes* and *Propionibacterium granulosum* [5]. Our previous report indicated the association between *P. acnes* and renal involvement in a sarcoid patient [6]. Thus, *P. acnes* may well play a crucial role in the pathogenesis of sarcoidosis with renal involvement typical of this granulomatosis.

Here, we report the second case of nephrotic syndrome, which occurred in the course of pulmonary sarcoidosis, and DNA and cell membrane antigen of *P. acnes* were detected in renal tissues.

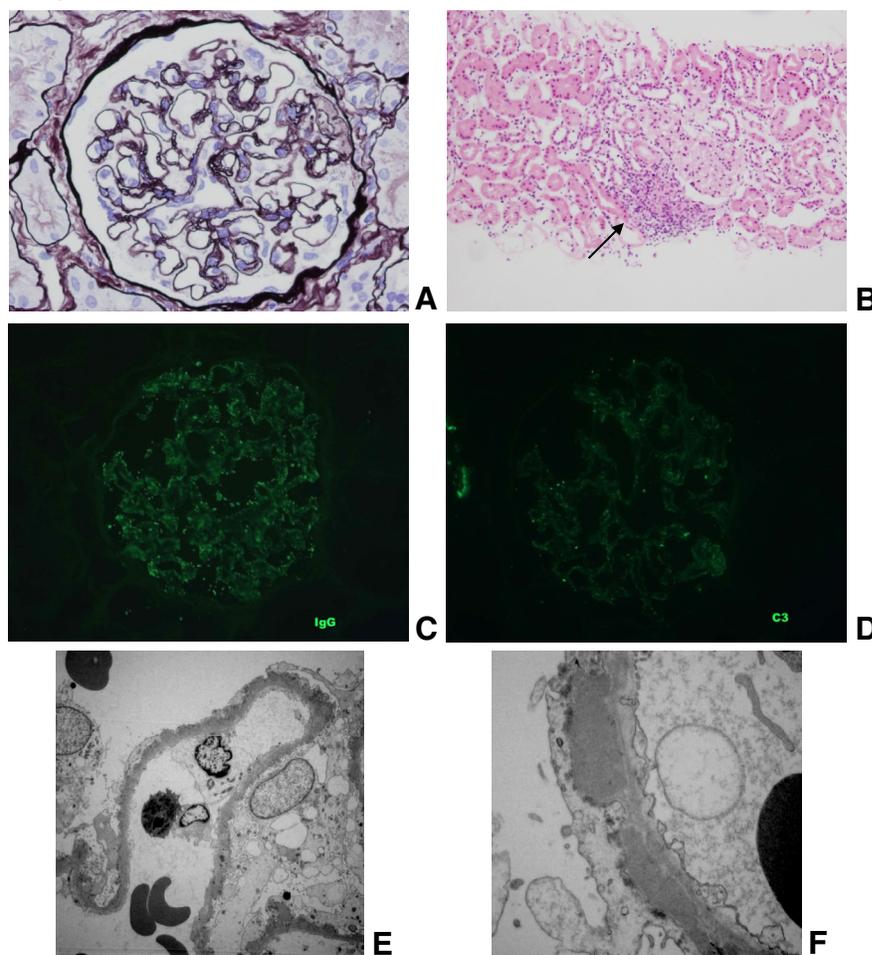


Fig. 1. (A) Light microscopic specimen; spike lesions on the basement membrane were seen (PAM stain, $\times 400$); (B) granulomatous interstitial nephritis was observed and a non-caseating epithelioid granuloma was present (arrow) (HE stain, $\times 100$); (C, D) immunofluorescence stain; granular IgG and C3 deposits were found along capillary walls; (E, F) electron microscopic specimen; subepithelial deposits were visible (E $\times 2500$, F $\times 12\,000$).

the glomerular capillary walls with a coarse granular pattern (Figure 1C and D). IgM and C1q were negative. In electron microscopy, subepithelial deposits were observed in the basement membrane of the glomeruli (Figure 1E and F).

He was then given 30 mg/day (0.5 mg/kg) of oral prednisolone, an angiotensin II receptor blocker (ARB) and dipyridamole for 3 months. For prophylaxis of opportunistic infection, sulfamethoxazole/trimethoprim (TMP/SMX) was added. After treatment, his serum ACE decreased, but proteinuria was maintained in the nephrotic range. In April 2007, he was admitted again and was given 500 mg/day of intravenous methylprednisolone for 3 days followed by 40 mg/day of oral prednisolone. With the tapering of prednisolone, his oedema and proteinuria were ameliorated. In October 2007, he showed complete remission of nephrotic syndrome.

Additional histological studies

We also performed *in situ* hybridization (ISH) with signal amplification by catalyzed reporter deposition

(CARD) of a renal specimen [7]. In the renal tissues, brown dots which represented DNA of *P. acnes* were detected in the cytoplasm of tubular epithelial cells, mononuclear cells in epithelioid granulomas and glomerular endothelial cells (Figure 2A–C). We also performed immunohistochemical staining using a monoclonal antibody that recognized specific lipoteichoic acid on the *P. acnes* surface [8]. In both additional studies, components of *P. acnes* were located in glomerular endothelial cells and tubular epithelial cells (Figure 2D and E). However, we could not detect the structure of *P. acnes* itself in a glomerulus for electron microscopy. We also performed ISH with CARD of another case of idiopathic membranous nephropathy (MN) as the control; components of *P. acnes* were not detected in renal tissue (Figure 2F).

Discussion

In general, lungs and thoracic lymph nodes are the main sites of sarcoidosis, but renal involvement is rare. Renal sarcoidosis can be divided into three groups as follows: ne-

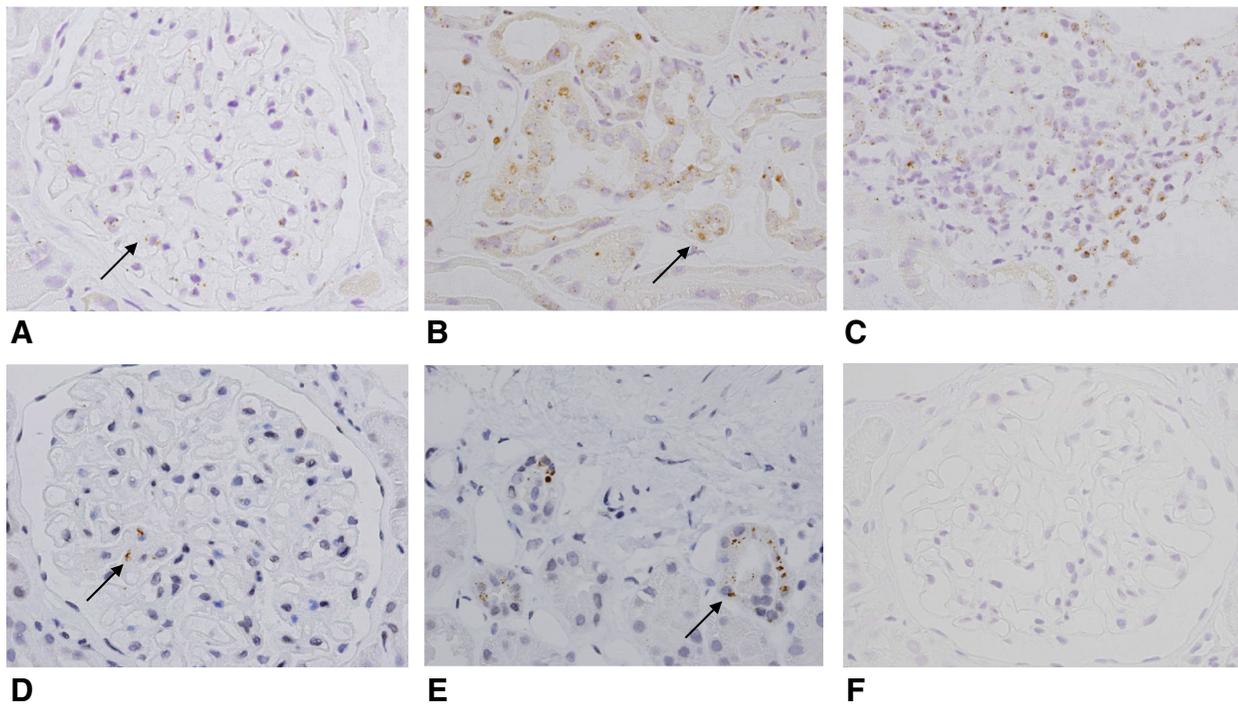


Fig. 2. (A–C) ISH with CARD; *P. acnes* DNA was detected in cytoplasm of glomerular endothelial cells, tubular epithelial cells and a granuloma (arrows); (D, E) immunohistochemical staining by a monoclonal antibody against *P. acnes*; signals of brown dots expressed the localization of components of *P. acnes*; (F) any positive signal of ISH with CARD of idiopathic MN as the control; *P. acnes* DNA were not detected in renal tissues.

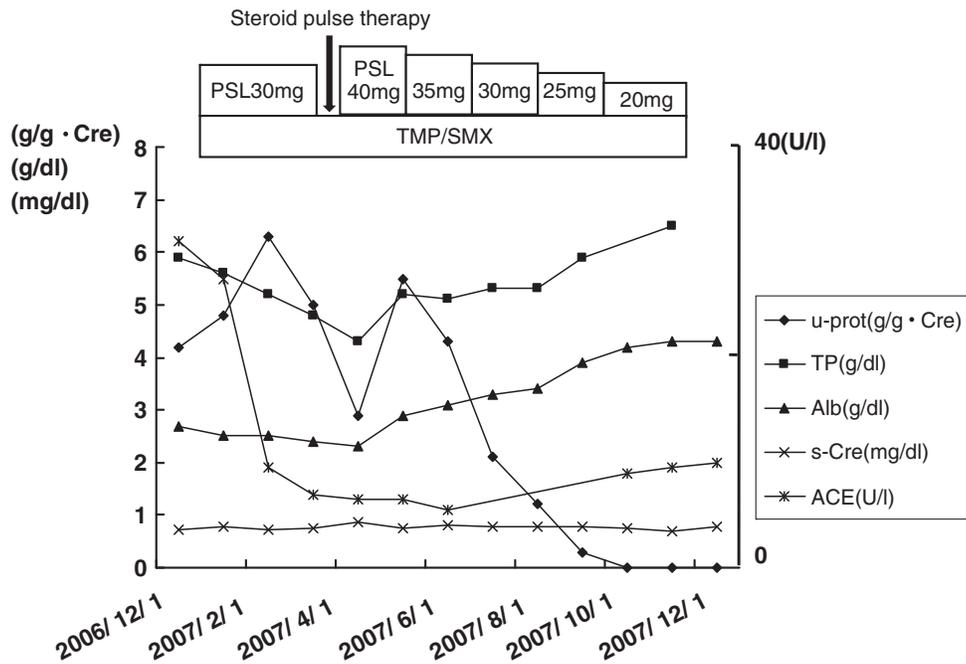


Fig. 3. Clinical course of hospitalization of this patient.

phropathy due to aberrant calcium metabolism, sarcoid interstitial nephritis and sarcoid glomerulopathy [9]. A variety of different glomerular lesions have been described in isolated cases, including membranous nephropathy, IgA nephropathy, renal amyloidosis, crescentic glomerulonephritis, minimal change disease and focal seg-

mental glomerulosclerosis [10]. Glomerular disease in patients with sarcoidosis is rare and may stand alone or coexist with granulomatous interstitial nephritis. Our case developed renal involvement and presented membranous nephropathy with GIN histologically. However, the glomerular findings were not typical of idiopathic

MN because coarse granular deposition of IgG and C3 was detected by IF and a large subepithelial deposit by EM.

We detected components of *P. acnes* in the renal specimens by ISH with CARD and immunohistochemical staining. Mycobacteria are suspected as causative agents of sarcoidosis in European countries. An international study was organized to search for suspected bacterial agents in 2002. *Propionibacteria* was found in almost all sarcoid samples. *M. tuberculosis* was found in 0 to 9% of the sarcoid samples [5]. Previous reports stated that components of *P. acnes* were detected in various organs such as the lungs, lymph nodes, eyes, skin, muscles and kidneys [6,8,11]. Although *P. acnes* is an indigenous bacterium and survives latently as the intracellular 'L form' in lungs or lymph nodes of healthy people, some environmental factors might lead to dissemination to other organs. It has been suggested that sarcoid granulomas are formed as a Th1 immune response to one or more antigens of *P. acnes* indigenous to or proliferating in the affected organ after intracellular proliferation [12]. A recent study indicated that the Toll-like receptor 2 (TLR) polymorphism might explain the variance of cytokine production that was stimulated by *P. acnes* and *M. tuberculosis* [13]. Accordingly, there is a close association between latent organism infection and host innate immunity in the context of sarcoidosis.

Initially, this patient received steroid therapy. ACE, a marker of activity for sarcoidosis, decreased rapidly, but proteinuria was not ameliorated. Since steroid pulse therapy was performed in addition to TMP/SMX, proteinuria disappeared (Figure 3). In the USA, it is reported that antimicrobial therapy is effective in about 60% of sarcoidosis patients. In patients with muscular sarcoidosis, minocycline (MINO) might modulate the immune system in addition to its antibiotic effect [8]. The animal study showed MINO and azithromycin suppressed the granuloma formation [14]. In our case, TMP/SMX might contribute to remission of nephrotic syndrome.

We reported a case of renal sarcoidosis whose renal histology demonstrated DNA and cellular components of *P. acnes*. Together with our previous case, this is the second case in which pathogenesis of renal sarcoidosis was asso-

ciated with latent *P. acnes* infection. Studies on larger numbers of patients are needed to clarify this issue.

Conflict of interest statement. None declared.

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