Non-granulomatous Interstitial Nephritis in a Chinese Man with Sarcoidosis

Sze-Kit Yuen, Chee-Wung Chow, Yat-Wing Lee, Sai-Ping Yong, Mo-Lin Wong, Lin-Kiu Lau, Fung-Yee Siu, King-On Cheung

Clinical renal involvement in sarcoidosis is rare and has not been previously reported in Chinese patients. We report a case of non-granulomatous interstitial nephritis that presented with acute renal failure in a Chinese man with underlying sarcoidosis. Use of prednisolone led to dramatic renal improvement and partial resolution of his asymptomatic lung parenchymal lesions. Unfortunately, the patient subsequently died of cryptococcal meningitis and episodes of nosocomial pneumonia. One should closely monitor a patient with a presumptive diagnosis of sarcoidosis after embarking on treatment since infections like tuberculosis may mimic or coexist with the disease. This is particularly important in areas where sarcoidosis is exceedingly rare. [Hong Kong J Nephrol 2008;10(1):42–5]

Key words: acute renal failure, interstitial nephritis, non-granulomatous, sarcoidosis, steroid, tuberculosis

INTRODUCTION

Sarcoidosis is a common disease in the West, but is rare in Chinese [1,2]. On the other hand, tuberculosis is so prevalent in Hong Kong that it should always be borne in mind if granuloma is found in any tissue. Reasonable efforts should be made to rule out infections like tuberculosis before making a diagnosis of sarcoidosis in Southern Chinese. On the other hand, clinical renal involvement is rare even in active sarcoidosis. Here, we report a local case of non-granulomatous interstitial nephritis due to sarcoidosis.

CASE REPORT

The patient was a 69-year-old Chinese man with a history of hypertension being controlled with slow-release nifedipine for many years. He had bilateral submandibular swelling for 10 years without seeking any medical advice. He had no history of chemical exposure including beryllium.

In February 2005, he was hospitalized for fever and deranged liver function. Physical examination revealed a perfectly-well man with firm bilateral submandibular swelling. Needle aspiration of the masses yielded normal salivary cells. Given their presence for more than 10 years, surgeons suggested monitoring rather than excisional biopsy. Chest X-ray only showed left middle zone fibrotic streak. Alkaline phosphatase was elevated but computed tomography (CT) of the abdomen failed to reveal any abnormality. After a course of antibiotics, his fever subsided and liver function normalized. He defaulted follow-up and went to Guangzhou, China.

In June 2005, he was incidentally found to have hilar
lymphadenopathy on chest X-ray and came back for work-up. Bronchoscopy showed no endobronchial lesion. Sputum and bronchial aspirate did not yield any acid fast bacilli or malignant cells. Transbronchial biopsy showed non-caseating granulomas and fibrosis. Polymerase chain reaction for mycobacterium tuberculosis DNA was negative. CT showed bilateral hilar and mediastinal lymphadenopathy and striated enhancement of the kidneys, compatible with infiltrative kidney disease. Serum creatinine was 126 µmol/L. Sarcoidosis was suspected but he defaulted follow-up again.

In September 2005, he noticed fatigue, malaise and nausea. There was no urinary or chest symptoms. He had taken lingzhi (Ganoderma lucidum) capsules from April to June, but he had never taken any analgesic, diuretic or antibiotic. Physical examination was unremarkable except for his similarly enlarged bilateral submandibular swelling and his recently developed left eye scleritis.

His serum creatinine and 24-hour creatinine clearance were 652 µmol/L and 6.15 mL/min/1.73 m², respectively. Serum albumin was 31 g/L whilst proteinuria was 0.78 g/day. Serum calcium and 24-hour urine calcium excretion were within normal ranges. Urine sediment was bland. Chest X-ray showed progression of bilateral hilar lymphadenopathy but lung fields remained clear. Work up for his renal failure included negative HBsAg, HCV and HIV antibodies, VDRL, cryoglobulin, ASOT, ANCA, anti-GBM, serum and urine protein electrophoreses. Antinuclear factor titer was elevated to 1/160 but anti-dsDNA and ENA antibody screen were negative. C3 was 54 mg/dL (normal, 76–150 mg/dL) while C4 was normal. Serum IgG was elevated at 2,300 mg/dL (normal, 819–1,725 mg/dL) and IgM was slightly depressed at 48 mg/dL (normal, 55–307 mg/dL); IgA was normal. Renal biopsy showed quite normal glomeruli but diffuse interstitial infiltration of plasma cells and activated lymphoid cells. There was also focal tubular damage and atrophy. Vessels demonstrated some arteriolar hyalinosis. No granuloma was found. Eosinophils were inconspicuous. Immunofluorescence showed focal granular stains of IgG, C3 and Clq basement membrane of a few tubules only. A diagnosis of sarcoidosis with non-granulomatous interstitial nephritis was made (Figures 1 and 2).

Various investigations were performed to support this hypothesis but more importantly, to rule out infections (particularly tuberculosis). Mantoux test was nonreactive over the forearm twice. Sputum and urine culture yielded no bacteria, fungus or mycobacterium. Serum cryptococcal antigen, galactomannon test, Brucella antibody (abortus and melitensis) and toxoplasma antibody were all negative. A repeat bronchoscopy showed no endobronchial lesion. Bronchial aspirates were again negative for bacteria, virus, acid fast bacilli and malignant cells.

Serum lysozyme was elevated to 1,771 U/mL (reference range, 150–500 U/mL), and serum angiotensin-converting enzyme (ACE) was 42 µ/L (reference range, 0–52 µ/L). Lung function test confirmed restrictive lung disease, while whole-body gallium scan and thoracic SPECT scan showed hot spots in the kidneys and faintly over both hilar regions. High-resolution CT showed multiple tiny nodules with upper zone predominance, located subpleurally or along fissures, suggestive of sarcoidosis (Figure 3).

His serum creatinine crept up to approximately 800 µmol/L. We started him on prednisolone 1 mg/kg/day. Renal function markedly improved. Serum creatinine stabilized at about 350 µmol/L 3 weeks later. Moreover, his bilateral submandibular swelling disappeared completely. CT of the thorax 1 month later showed near-complete resolution of pulmonary parenchymal changes.

Figure 1. Periodic acid-Schiff stain, high power: glomeruli are unremarkable.

Figure 2. Periodic acid-Schiff stain, high power: tubulitis, invasion of tubules by activated lymphocytes and plasma cells.
He remained very well until 2 months later, when he was hospitalized for right lower lobe pneumonia. Sputum culture confirmed the presence of *Mycobacterium tuberculosis*. Treatment of pulmonary tuberculosis was complicated by immune reconstitution syndrome, which was successfully managed with prednisolone. However, 3 months later, he presented with generalized tonic-clonic convulsion due to meningitis and obstructive hydrocephalus. Cerebrospinal fluid was sterile but positive for cryptococcal antigen. He was managed with extraventricular drainage, antibiotics and fluconazole. Initial treatment was successful but he died after episodes of nosocomial bacterial pneumonia.

In summary, this elderly man had bilateral mediastinal and hilar lymphadenopathy with non-caseating granulomas in transbronchial biopsy. He also had scleritis, submandibular gland enlargement and non-granulomatous interstitial nephritis compatible with a diagnosis of sarcoidosis. His submandibular swelling, lung parenchymal lesions and renal failure responded to oral steroid therapy, but he subsequently died of pulmonary tuberculosis, cryptococcal meningitis and nosocomial bacterial pneumonia.

**DISCUSSION**

Sarcoidosis is a multisystem granulomatous disease of unknown etiology [1]. It is a relatively common disease in the West but rarely reported in Hong Kong. It usually presents in adults younger than 40 years old, although it can affect any age group [3]. Incidence is 6.3 and 5.9 cases per 100,000 person-years in women and men, respectively [1]. The disease occurs more commonly among nonsmokers and during winter. Geographic, occupational and family clustering, as well as positive and negative associations with some HLA alleles, have been reported [4,5]. Various immunologic abnormalities and exposure to infectious agents, organic or inorganic substances have also been implicated in the pathogenesis [6].

Sarcoidosis most often presents with bilateral hilar lymphadenopathy, pulmonary infiltrates, ocular or skin lesions [3,7]. It is a clinical diagnosis supported by histologic demonstration of non-caseating epithelioid-cell granulomas in affected tissues or organs [1,6]. Typical CT findings give further support [8]. A staging system based on chest X-ray findings is in use (Table). Recommended evaluation includes comprehensive history taking and physical examination, chest radiography, lung function test, blood counts, serum chemistries, liver enzymes and urinalysis. Electrocardiography must be performed since cardiac involvement is an important cause of mortality. Routine ophthalmologic examination and tuberculin skin testing should also be done. Efforts should be made to exclude infections like tuberculosis, fungal infections (such as cryptococcosis, aspergillosis), hypersensitivity pneumonitis and Wegener’s granulomatosis [6]. Serum ACE levels of healthy individuals overlap considerably with levels in patients suffering from active sarcoidosis [9], rendering it useless in diagnosis.

Tuberculosis is so prevalent in Hong Kong that it must be excluded before a diagnosis of sarcoidosis is made. Moreover, concurrent occurrence of tuberculosis and sarcoidosis has also been reported [10]. Unpleasant side effects, particularly among the elderly and patients with renal failure, mean that a trial of antituberculous therapy may not always be appropriate in patients with working diagnoses of sarcoidosis. Our patient first presented with asymptomatic bilateral hilar lymphadenopathy and non-caseating granulomas in transbronchial biopsies. Bronchoscopic aspirates were negative for acid fast bacilli on two occasions. Extensive investigations also reasonably excluded other granulomatous diseases. His radiologic and clinical response to steroid also spoke against an initial diagnosis of tuberculosis. Empirical antituberculous therapy was therefore not considered. Nonetheless, it

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<th>Stage</th>
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<td>0</td>
<td>Normal chest radiograph</td>
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<tr>
<td>I</td>
<td>Bilateral hilar lymphadenopathy</td>
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<td>II</td>
<td>Bilateral hilar lymphadenopathy and pulmonary infiltrations</td>
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was unfortunate that he developed tuberculosis and cryptococcal meningitis a few months later. His immune incompetence was likely to be due to prolonged use of steroid but might also be due to sarcoidosis itself [11].

Any organ may be involved in sarcoidosis, but clinical renal disease is rare [3]. Renal involvement may manifest as hypercalcemia, hypercalciuria, nephrocalcinosis or nephrolithiasis [12–15]. However, renal biopsy is more likely to be performed for renal failure rather than these indications alone [16]. Interstitial nephritis is typically found if renal biopsy is done [17], although various glomerulopathies have also been reported in sarcoidosis [16,18].

There is no sex predilection in patients affected by sarcoidosis-associated interstitial nephritis. Extrarenal manifestations are common but serum ACE levels are usually normal, even in active renal disease [16,19]. Also, 24–41% of sarcoidosis-related interstitial nephritis cases are devoid of granulomas [13,16,17], as in our patient. This might be due to sampling error.

Immunosuppression is only indicated if sarcoidosis is symptomatic, as in patients with impaired lung function, significant cardiac or neurologic disease, severe hypercalcemia, hypercalciuria or interstitial nephritis [6]. Despite lack of evidence from randomized controlled trials [1,7], steroid is most commonly used. Its dosage is unknown but prednisolone initiated at a dose of 0.5–1.0 mg/kg/day and then tapered off is probably appropriate [16,19]. Mycophenolate mofetil [20] and infliximab [21] may be used in refractory cases. Renal impairment typically improved dramatically after initiation of steroid [13,16], but recovery may be incomplete, presumably due to irreversible kidney damage [19].

This is the first local reported case of non-granulomatous interstitial nephritis in a patient with sarcoidosis. Sarcoidosis is an extremely rare clinical diagnosis in Chinese and requires careful exclusion of other granulomatous diseases, particularly tuberculosis. Interstitial nephritis is one of the manifestations of the disease and may be responsive to steroid therapy.

REFERENCES