LETTER TO THE EDITOR

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Cutaneous vasculitis and renal involvement in *Mycoplasma pneumoniae* infection

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To the Editor,

Mycoplasma pneumoniae is one of the smallest bacteria capable of independent replication, and its infection in humans produces various clinical manifestations. Indeed, *M. pneumoniae* infection can present with many extrapulmonary and pulmonary symptoms. Moreover, the severity of infection varies greatly, from a simple upper respiratory tract infection to multiorgan failure. This variability is attributable to differences in the immunological responses after local mucosal destruction induced by *M. pneumoniae*. This paper describes an adult case of *M. pneumoniae* infection, presenting with systemic vasculitis in the absence of pulmonary involvement. In this patient, *M. pneumoniae* infection resulted in cutaneous vasculitis, oligoarthritis, and renal involvement with massive proteinuria. To our knowledge, it is very rare for patients, especially adults, with mycoplasma infection to present with only extrapulmonary manifestations, such as those related to skin, joint, and kidney involvement.

A 52-year-old male with high fever presented with multiple subcutaneous indurations. About 3 weeks earlier, he had developed mild throat pain and a sudden fever, with temperatures up to 38.5°C to 39.5°C and chills. Two days after the onset of fever, the generalized subcutaneous indurations began to enlarge. The indurations varied in size, from 1 to 10 cm, and they appeared over the entire body almost simultaneously. The overlying skin was intact with no discoloration.

He underwent a skin biopsy, which showed features of panniculitis and necrotic vasculitis. Culture studies from blood and urine were negative. Antibodies to *Leptospira, Rickettsia tsutsugamushi*, and Hantaan virus were not detected. The subcutaneous indurations eventually decreased in size, and pustules developed in the center of the indurations. The pustules underwent ulceration and formed crusts. Thereafter, generalized edema, proteinuria, hematuria, and azotemia developed. The patient was treated empirically with doxycycline for 8 days, but the fever and knee pain only partially improved.

Because the etiology of the fever, skin lesions, and acute renal dysfunction remained unknown, he was referred to our hospital for further evaluation. His initial body temperature was 36.7°C, and his blood pressure was 155/95 mmHg. His body weight was 83 kg, which was 6 to 7 kg greater than his usual weight. He had multiple crusted skin lesions on his face, trunk, and extremities (Fig. 1), and pitting edema on both lower extremities.

The initial laboratory findings were as follows: white blood cell count 13.1

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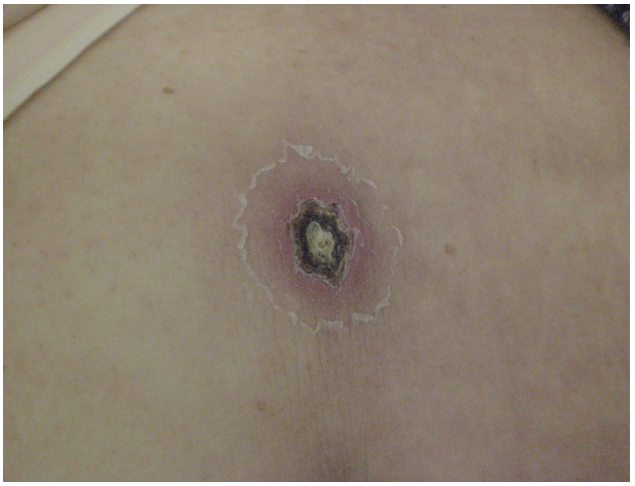

Figure 1. Cutaneous vasculitis. One of multiple skin indurations is seen in the mid-abdomen area. The about 2-cm-sized induration included central ulceration and crusting with time.

× 10^3/μL (4.0 to 10.0 × 10^3/μL) and hemoglobin 8.8 g/dL (range, 12 to 16). The blood urea nitrogen level was 69 mg/dL (range, 10 to 26), creatinine 4.3 mg/dL (range, 0.6 to 1.4), total protein 6.6 g/dL (range, 6.0 to 8.0), albumin 2.0 g/dL (range, 3.3 to 5.2), and C-reactive protein 19.68 mg/dL (range, 0 to 0.5).

On urinalysis, 10 to 19 red blood cells (RBCs) were observed per high-power field, and 70% of them were dysmorphic; 20 to 49 white blood cells were observed per high-power field. The total protein concentration in a 24-hour urine sample was 3,346 mg.

Serological tests for antinuclear antibodies, anti-streptolysin O, rheumatoid factor, anti-double strand DNA antibodies, anti-neutrophil cytoplasmic autoantibodies, and cryoglobulins were all negative. Serum complement 3 and 4 levels were in normal ranges. An indirect particle-agglutination assay of blood samples

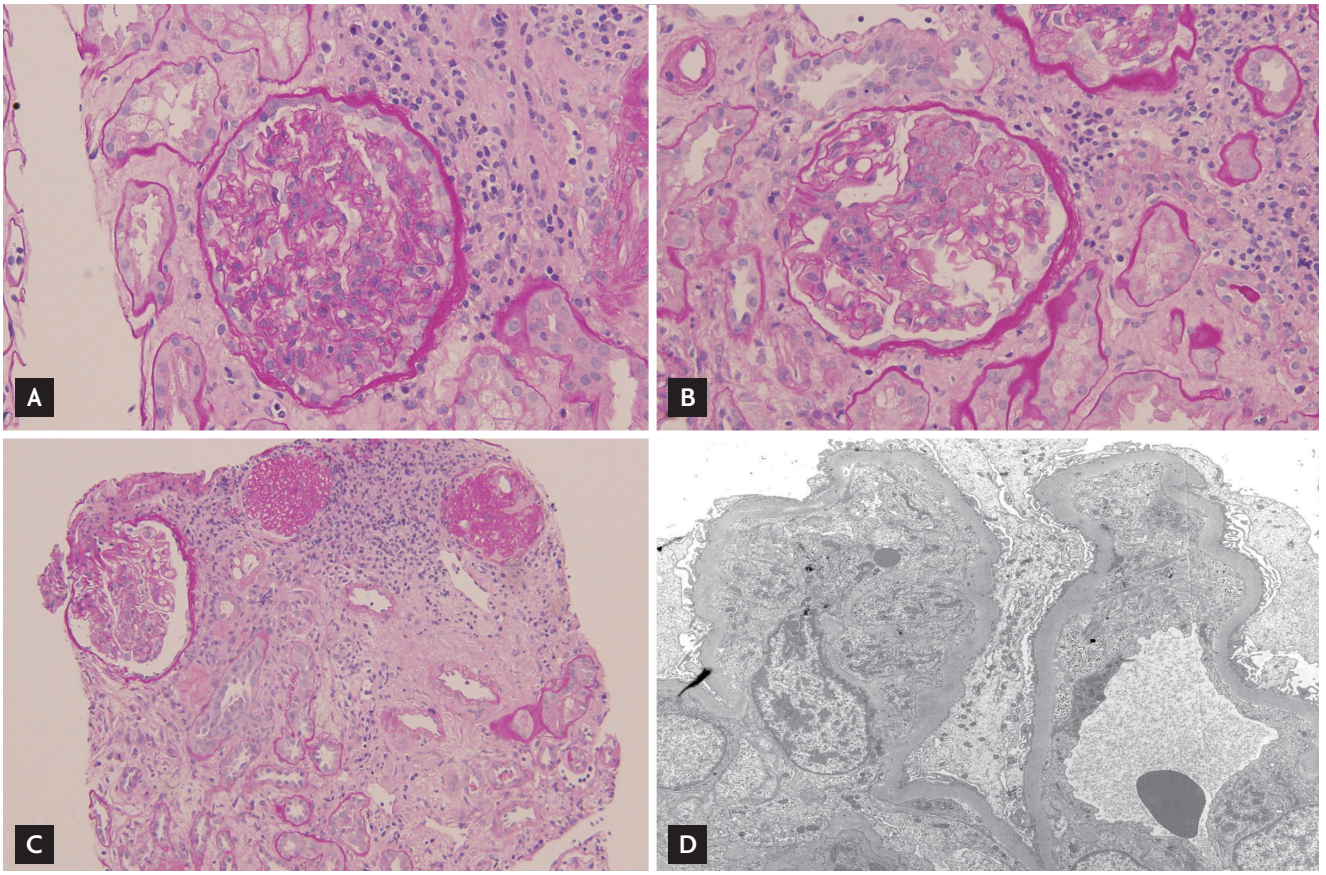

Figure 2. Renal pathology. In H&E staining, the remaining glomeruli were mildly increased in size and mildly hypercellular, involving mesangial cells. Some glomeruli showed endothelial cell proliferation (A, B, ×200), interstitial edema and focal moderate infiltration of inflammatory cells including some lymphocytes, plasma cells, and a few eosinophils were also noted (C, ×100). (D) In electron microscopic examinations, there were focal mild thickening of glomerular basement membrane, focal endothelial activation, and hyperplasia and moderate effacement of epithelial foot processes. Such findings are compatible with focal proliferative glomerulonephritis and acute tubulointerstitial nephritis.

showed that the *M. pneumoniae* antibody titer had increased to 1:1,280. After 5 days, the *M. pneumoniae* antibody titer doubled (1:2,560). Circulating cold agglutinins were not detected. The serum immunoglobulin G (IgG) level was elevated markedly, to 3,008 mg/dL (range, 700 to 1,700). Monoclonal antibodies were not detected on electrophoresis of serum and urine proteins, and immunofixation tests. On bone marrow examination, only reactive plasmacytosis was detected. Parenchymal infiltration of the lung was not observed on a chest roentgenogram.

To determine the cause of the acute renal failure, a kidney biopsy was performed, which revealed focal proliferative glomerulonephritis and acute tubulointerstitial nephritis (Fig. 2). Portions of 30 glomeruli were included in this biopsy; 6 (20%) show global sclerosis. An immunofluorescence study did not show any evidence of immune complex or complement deposition in the glomeruli. Polymerase chain reaction (PCR) for *M. pneumoniae* was performed on renal tissue; the results were negative. The PCR assay targeted the 144-bp adenosine triphosphatase operon gene of *M. pneumoniae*.

The patient was diagnosed with extrapulmonary *M. pneumoniae* infection and was prescribed oral azithromycin. On day 5 of azithromycin treatment, a low-grade fever was observed, and the C-reactive protein level had not returned to baseline. Thus, steroid treatment (prednisolone, 30 mg one a day) was started for treating vasculitis-related fever. Thereafter, his skin lesions resolved, and the fever subsided completely. After 10 days of azithromycin treatment and 5 days of prednisolone treatment, the serum creatinine decreased to 1.2 mg/dL. The urine RBC level decreased to 5 to 9 cells per high-power field, and the C-reactive protein level returned to normal levels. Blood tests and urinalysis were performed 3 months after the onset of renal manifestations, and the results indicated that the renal function had recovered completely (serum creatinine 0.9 mg/dL, random urine protein/creatinine ratio 0.32 mg/g).

Although *M. pneumoniae* is an important microorganism that causes community acquired pneumonia, it has rarely been documented as the causative organism of pneumonia because of the typically mild clinical course of mycoplasma infection. Apart from respiratory tract infections, *M. pneumoniae* causes various extrapulmonary manifestations in as many as 25% of patients with mycoplasma infection [1]. Central nervous system involvement is known to be a severe manifestation of *M. pneumoniae* infection. Dermatological symptoms, such as erythematous maculopapular rashes, vesicles, and urticaria, are also common presentations and account for up to 25% of cases with extrapulmonary manifestations. Other extrapulmonary manifestations include hematological, renal, gastrointestinal, osteoarticular, and ocular manifestations. Extrapulmonary manifestations appear at varying intervals after the onset of pulmonary infection and occasionally occur even in the absence of respiratory tract symptoms. Because of the variable clinical presentations, *M. pneumoniae* infection is difficult to diagnose.

Cutaneous vasculitis, as observed in our patient, is a very rare cutaneous manifestation of *M. pneumoniae* infection. In the literature, cutaneous vasculitis caused by *M. pneumoniae* infection has been reported in only six patients [2,3]. In three of them, cutaneous vasculitis was associated with pneumonia [2], and it was not accompanied by any lung parenchymal infection in the other three. Ages of the patients ranged from 7 to 75 years. Two patients were prescribed prednisolone for the treatment of vasculitis [3], while the others were treated only with antibiotics, including macrolides. All patients showed good clinical outcomes. In our patient, the correlation of cutaneous vasculitis with *M. pneumoniae* infection was well documented, both clinically and histologically. However, antibiotic treatment did not completely reverse the generalized cutaneous vasculitis or fever; thus, prednisolone was also administered.

M. pneumoniae-associated nephritis in adults has rarely been reported. The renal pathological findings in adults are variable and include membranous proliferative glomerulonephritis, endocapillary glomerulonephritis, IgA nephropathy, and tubulointerstitial nephritis. One case of transient massive proteinuria accompanied by *M. pneumoniae* infection was reported in a 23-year-old woman [4]. However, because no renal biopsy was performed, the renal pathology findings in that case are unknown. In a similar case of a 5-year-old child, the pathological findings on electron microscopy included minimal fusion of the foot processes and regular non-thickened glomerular basement membrane, but no electron-dense deposits. Further, immunofluorescence staining of the glomeruli for Igs and com-

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plement was negative. From these previously reported cases, it can be concluded that the pathological and laboratory findings in nephritis vary greatly, depending on factors such as the timing of the tissue biopsy, age and immune status of host, the causative organism, and timing of therapeutic intervention.

The pathogenesis of *M. pneumoniae* has been suggested to involve transient massive cytokine production and macrophage activation, which are triggered by opsonized *M. pneumoniae*. This initial immunological effect is then amplified by lymphocyte proliferation, mainly $CD4^+$ T cell proliferation, and by various inflammatory modulators, such as tumor necrosis factor-α, interferon-γ, and interleukins [5]. Our patient was previously healthy, with no evidence of immunological dysfunction. The renal biopsy was performed after doxycycline treatment for 8 days. Thus, the bacterial load should have already been decreased at the time of the biopsy. This is thought to be the reason for the absence of any evidence of immune complex deposition on electron microscopy and of IgG or C3 staining in immunofluorescence studies. This may also explain why the results of PCR of renal tissue for *M. pneumoniae* were negative. There was no definite evidence regarding the duration of the disappearance of immune deposits in the histopathological findings. Additionally, treatment with a macrolide antibiotic alone did not elicit a complete cure, and systemic steroid therapy was required to completely suppress the immunological response in our patient.

In conclusion, the occurrence and aggravation of systemic involvement in *M. pneumoniae* infection may occur via multiple immunological pathways. The exclusive occurrence of extrapulmonary manifestations of *M. pneumoniae* infection is very rare, especially in adults with normal immunological function. Moreover, the pathological and laboratory data in cases of mycoplasma infection can vary widely. It is possible that many of these cases go through a benign subclinical course and remain undetected. In some cases though, the prognosis can be grave. Thus, there is a need for a high index of suspicion for mycoplasma infections and to manage them appropriately in the early stages.

Keywords: Skin; Glomerulonephritis; Mycoplasma infections

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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