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【 CASE REPORT 】

# Biopsy-proven *Streptococcus suis*-associated Infectious Glomerulonephritis

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**Abstract:**

A 64-year-old Japanese man who worked at a butcher shop was hospitalized for a fever, headache, and deafness. We diagnosed him with sepsis and meningitis caused by *Streptococcus suis* infection. The patient's renal function declined rapidly, and hemodialysis was performed temporarily. A renal biopsy was performed, and the renal function tended to improve with antimicrobial therapy. This case seemed rather similar to one of staphylococcal-associated nephritis in that it showed mesangial proliferative nephritis with immunoglobulin A deposition, even though the nephritis was caused by streptococci. Similarly, intramembranous electron-dense deposits were characteristic findings. We present new findings of an *in vivo* renal biopsy in a case of *S. suis*-associated glomerulonephritis.

**Key words:** acute kidney injury, infectious glomerulonephritis, *Streptococcus suis*, renal biopsy, case report

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## Introduction

*Streptococcus suis* is a facultative anaerobic Gram-positive bacterium that forms colonies in the mucous membranes of the upper respiratory tract and reproductive organs of pigs. It is a zoonotic agent that often causes meningitis and septicemia in infected pigs and humans who come in contact with them (1). *S. suis* infections have been reported in many countries since the first human cases were reported by Perch et al. (2). Although 35 serotypes of *S. suis* have been identified, most of the patient-derived strains are of serotype 2. The pathogenicity of *S. suis* is characterized by its ability to diffuse into the blood and invade the cerebrospinal fluid and systemic tissues, such as the kidneys, lungs, and spleen. In addition, it has mechanisms to evade the complement system and phagocytosis (3). *S. suis* infection commonly causes meningitis, pneumonia, infective endocarditis, and deafness. In addition, it also causes acute kidney injury (AKI) (1).

*S. suis* infection is often associated with AKI and may require renal replacement therapy (4). Approximately 80% of patients with septic shock develop AKI (1). However, few reports have examined whether AKI is merely secondary to sepsis or is complicated by renal lesions characteristic of *S. suis* infection. Although there have been reports of renal pathology in *S. suis* infections in autopsy cases, there have been few renal biopsy studies.

We herein report a case of meningitis due to *S. suis* infection with AKI for which we performed a renal biopsy.

## Case Report

A 64-year-old Japanese man with no significant medical history who worked as a butcher and handled pork daily presented with headache, deafness, nausea, and malaise starting 2 days before admission. He was admitted to the hospital with fatigue, a low-grade fever, vomiting, anorexia, watery diarrhea, tinnitus, deafness, and multi-joint pain.

His vital signs were blood pressure of 128/74 mmHg, pulse rate of 84 beats/min, temperature of 38.5℃, respira-

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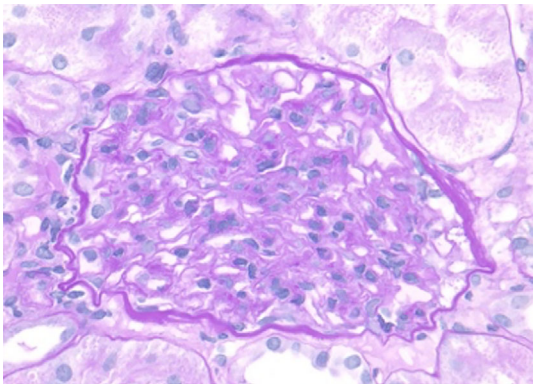

**Figure 1.** **Results of a light microscopic analysis. Prominent mesangial proliferation and deposition are observed in the mesangial regions (Periodic acid-Schiff stain, ×400).**

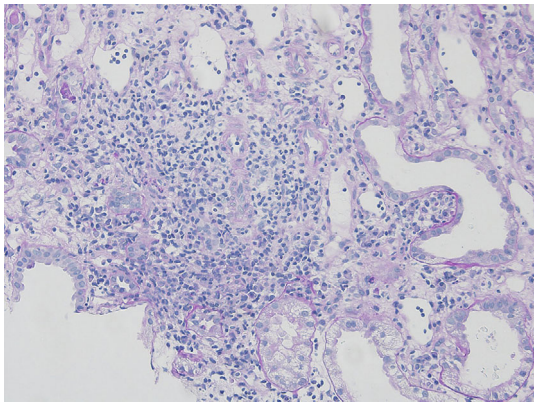

**Figure 2.** **Results of a light microscopic analysis. Hydropic degeneration of tubular epithelial cells and inflammatory cell infiltration into the interstitium are observed.**

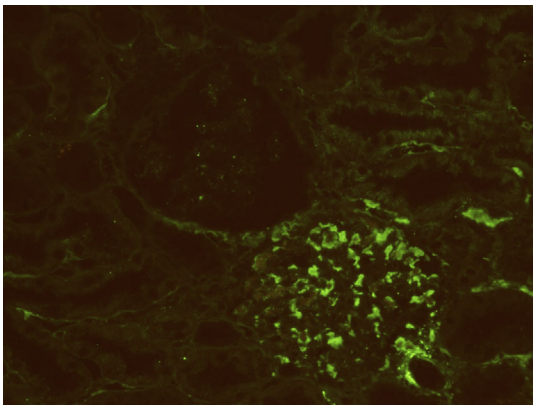

**Figure 3.** **Immunofluorescence staining. Immunofluorescence staining showing immunoglobulin A deposition in the mesangial region.**

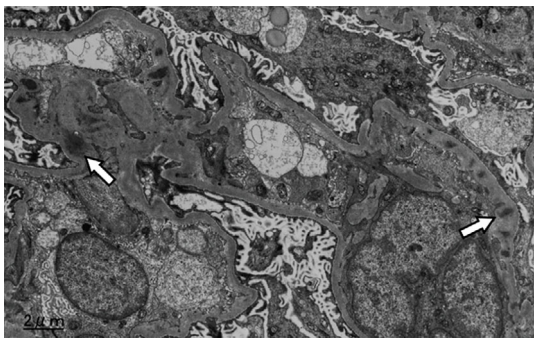

**Figure 4.** **Results of an electron microscopy analysis. Electron microscopy showing mesangial (left arrow) and intramembranous (right arrow) electron-dense deposits.**

tory rate of 20 breaths/min, and Glasgow Coma Scale E4V4 M6. Neck stiffness and bilateral perceptive deafness were revealed on a physical examination. A laboratory examination performed at the time of admission revealed a white blood cell count of 11,200/μL, blood urea nitrogen level of 49.9 mg/dL, serum creatinine level of 2.15 mg/dL, and no hypocomplementemia or hypergammaglobulinemia. In addition, liver dysfunction, coagulopathy, and decreased platelet count were observed: aspartate aminotransferase, 67 IU/L; alanine aminotransferase, 36 IU/L; activated partial thromboplastin time, 32.9 s; prothrombin time, 107.1%; fibrin degradation product, 14.1 μg/mL; and platelet count, 6.3× $10^3$/μL. His urinalysis showed urine protein 2+ (0.43 g/day) and urine occult blood 3+ (100/high-power field). A cerebrospinal fluid (CSF) analysis revealed neutrophil-predominant pleocytosis with elevated CSF protein levels. Blood and CSF cultures on admission indicated the presence of *S. suis*. Therefore, meningitis and sepsis due to *S. suis* infection was diagnosed.

Ceftriaxone and vancomycin were administered. His vancomycin blood level trough values were within the normal range during treatment. After blood culture and drug-sensitivity results were obtained, ampicillin monotherapy was initiated. Although his vital signs were stable, the urine output gradually decreased. Oliguria, dyspnea, and an elevated serum creatinine level (6.2 mg/dL) were observed on day 6 of hospitalization. Thus, hemodialysis was performed for three days.

The renal function gradually improved, and a renal biopsy was performed on day 17 after hospitalization (serum creatinine level of approximately 3.0 mg/dL). A light microscopic analysis revealed mesangial proliferation and diffuse and segmental proliferative endocapillary glomerulonephritis (Fig. 1). No evidence of glomerulosclerosis or crescent formation was observed. The renal tubules showed hydropic degeneration of the epithelium. Abundant mononuclear cells and neutrophils were observed in the interstitium (Fig. 2). Although a small degree of interstitial fibrosis was evident, diffuse tubular necrosis was not observed. Immunofluorescence studies showed positive results for mesangial immunoglobulin A (IgA) and C3 deposits (Fig. 3). Furthermore, IgA-positive plasma cells and neutrophils were present in the renal tubular basement membrane. Immunoglobulin G (IgG) was only slightly deposited on the glomerular capillary wall. Electron microscopy showed mesangial interposition and mesangial and segmental intramembranous electron-dense deposits (EDDs) (Fig. 4).

On day 34, the patient was discharged with mild deafness, balance disorder, and mild renal dysfunction (serum creatinine 1.1 mg/dL).

## Discussion

In the present case, a man working as a butcher was infected with *S. suis* and developed meningitis, deafness, and AKI. Although septic shock was not observed, the patient's renal function declined rapidly, and hemodialysis was required temporarily. A renal biopsy showed diffuse mesangial and endocapillary proliferative glomerulonephritis with IgA-dominant deposition and moderate tubulointerstitial nephritis. Electron microscopy revealed EDD in the mesangial area and intramembranous segment. The renal function tended to improve with antimicrobial therapy.

Exposure to pigs and pork, consumption of raw pork, and pig-related occupations are considered risk factors for *S. suis* infection (5). Since the patient worked as a butcher, pork was suspected as a potential source of his infection. Sepsis or septic shock occurs in 24.2% of patients infected with *S. suis*, and 82% of patients with septic shock develop AKI (1). Huong et al. evaluated the clinical features of *S. suis* infection in a systematic review and meta-analysis and reported that 7.1% of patients developed acute renal injury (6). However, the mechanism underlying AKI caused by *S. suis* infection is not well understood.

Renal lesions associated with *S. suis* infection have been reported in autopsy cases. Yang et al. reported autopsy cases of four patients who died of *S. suis* infection with the following findings: increased renal volume, microthrombi in the glomerulus, hyaline cast in the renal tubules, hydropic changes in tubular epithelial cells, and tubular necrosis with neutrophilic infiltration (7). Hanterdsith et al. performed autopsies of cases of sudden death due to *S. suis* infection and reported that fibrin thrombi were found in approximately 80% of the glomeruli (8). In the present case, a renal biopsy showed findings of glomerulonephritis with mesangial and endocapillary proliferation but not fibrin thrombi. Immunofluorescence staining showed IgA and C3 depositions in the mesangial region. Electron microscopy showed mesangial interposition and EDD in the mesangial and intramembranous regions.

In general, streptococcal-associated glomerulonephritis is characterized by diffuse endocapillary proliferative nephritis. In electron microscopy, it may show subepithelial deposits, such as humps, which is typical of post-streptococcal acute glomerulonephritis (9). However, despite the fact that the present patient had nephritis related to streptococcal infection, the pathological image resembled that of mesangial proliferative glomerulonephritis with IgA deposits. Infection-related mesangial proliferative glomerulonephritis with IgA deposit is often observed in staphylococcal-associated glomerulonephritis cases and similarly in superantigen-related glomerulonephritis cases after methicillin-resistant *Staphylococcus aureus* (MRSA) infection (9, 10). Western blotting against *Staphylococcus aureus* cell membrane fractions using sera from patients with MRSA-associated glomerulonephritis as primary antibodies revealed the presence of IgG and IgA recognizing a common antigen of approximately 35 kDa in several patient sera, suggesting the presence of a specific antigen involved in the pathogenesis of MRSA-associated glomerulonephritis (11). The virulence of *S. suis* has not yet been determined. The finding of IgA deposition in the renal pathology of this case may provide a clue to help identify the virulence of *S. suis*, but further studies are needed for confirmation. In addition to the findings of mesangial proliferative glomerulonephritis with IgA deposition, this case showed characteristic intramembranous EDDs, which are not observed in varicose glomerulonephritis. The aforementioned pathological features of *S. suis* infection that were observed in the *in vivo* renal biopsy are notable findings in this case.

This case has an aspect of infection-related glomerulonephritis (IRGN). The etiology of bacterial IRGN has been proposed to include the deposition of circulating immune complexes in the subendothelium and mesangium to activate the complement pathway (12). This phenomenon involves superantigen, an antigen derived from staphylococcus, and streptococcal pyrogenic exotoxin B, a streptococcal exotoxin. In contrast, locally activated plasmin degrades the glomerular basement membrane and promotes inflammation. Staphylokinase from staphylococcus and nephritis-associated plasmin receptor from streptococcus are involved in this process. Thus, both staphylococcal and streptococcal infections can cause nephritis by similar mechanisms; however, the antigens are different. IgA-dominant infection-associated glomerulonephritis (IgA-IRGN) is typically observed in older patients with diabetes mellitus and chronic infections, such as skin and soft tissue infections, and is often caused by staphylococcus (13). However, the clinical background of this case is different from that of common IgA-IRGN, and the causative organism was streptococcus rather than staphylococcus. Furthermore, the prognosis of IgA-IRGN is poor, with 41% of patients progressing to end-stage renal disease; however, the renal function improved significantly in this case.

It is unlikely that this case resulted from the exacerbation of preexisting IgA nephropathy due to infection. The pathological findings, such as endocapillary proliferation and intramembranous deposits, cannot be explained by IgA nephropathy. Furthermore, the fact that the patient had never been diagnosed with proteinuria or hematuria would similarly exclude the possibility of preexisting IgA nephropathy.

Although autopsy cases with interstitial damage have been reported (7), this case showed only mild inflammatory cell infiltration. The autopsy case had a poor outcome, and we speculate that it involved a high degree of interstitial damage. In contrast, the changes in the present case were relatively mild and might have been pre-renal ischemic changes due to sepsis.

The renal lesions associated with *S. suis* infection have

not been well defined. Therefore, additional reports similar to this case are needed to understand the pathological mechanisms underlying this disease.

**The authors state that they have no Conflict of Interest (COI).**

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Hideto Kajitani and Hiroki Nishiwaki contributed equally to this work.

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