

## Case Report

# Infective Endocarditis Associated with Streptococcal Toxic Shock Syndrome due to *Streptococcus dysgalactiae* subsp. *equisimilis* Infection in a Hemodialysis Patient

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## Keywords

Group G streptococci · Infective endocarditis · End-stage renal disease

## Abstract

The risk of infective endocarditis in chronic hemodialysis patients is markedly higher than that in the general population. We report the first case of a hemodialysis patient with infective endocarditis caused by *Streptococcus dysgalactiae* subsp. *equisimilis* (SDSE) who presented with streptococcal toxic shock syndrome. In the last decade, there has been an increase in the incidence of SDSE infections. Therefore, it is important to recognize SDSE as a possible causative agent of infective endocarditis in an immunocompromised population, such as hemodialysis patients.

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Published by S. Karger AG, Basel

## Introduction

*Streptococcus dysgalactiae* subsp. *equisimilis* (SDSE) belongs to the pyogenic group of streptococci designated as a new subspecies within *S. dysgalactiae* [1] in 1996. SDSE, which

is part of the commensal flora in humans, belongs to  $\beta$ -hemolytic groups C (GCS) and G (GGS) due to its agglutination when exposed to Lancefield group C and G antigens [2]. SDSE has long been considered much less virulent than group A streptococci (GAS), such as *S. pyogenes*. However, recent evidence suggests that SDSE causes various severe invasive infections [3, 4], including cellulitis and deep abscesses, as well as streptococcal toxic shock syndrome (STSS) [5], necrotizing fasciitis, and meningitis [3, 4]. Hemodialysis (HD) patients are prone to infections. Infective endocarditis (IE) is more common and causes greater morbidity and mortality in HD patients than in the general population [14]. We report a unique case of an HD patient presenting with STSS followed by IE development due to an infection with SDSE.

### Case Report

The patient was a 51-year-old man with end-stage renal failure. He received HD for 12 years after replacement surgery for acute thoracic abdominal dissection. His chronic medication included irbesartan for hypertension, calcium carbonate, lanthanum carbonate hydrate, falcacitoriol, and cinacalcet for mineral-bone disease. The patient presented to a scheduled HD session with general fatigue and pain in both legs. During dialysis, his blood pressure fell, accompanied by disorientation, which resulted in immediate admission to the hospital. His vital signs were as follows: blood pressure: 91/56 mm Hg; heart rate: 115 beats/min; body temperature: 39.7°C; respiration rate: 30 breaths/min; and oxygen saturation: 99% while breathing room air. A physical examination revealed a systolic murmur (grade 4/6) above the left upper sternal border. Despite leg pain, the patient did not have signs of inflammation, such as swelling and redness. Furthermore, skin lesions, including the puncture site of his arteriovenous fistula for vascular access, were unremarkable. His blood analysis indicated a white cell count of  $4.9 \times 10^3/\mu\text{L}$  (reference range:  $3.9 \times 10^3$ – $9.8 \times 10^3/\mu\text{L}$ ), anemia (hemoglobin: 10.9 g/dL; reference range: 13.5–17.6 g/dL), thrombocytopenia (platelet count:  $5.3 \times 10^4/\mu\text{L}$ ; reference range:  $13 \times 10^4$ – $36.9 \times 10^4/\mu\text{L}$ ), elevated C-reactive protein (1.42 mg/dL; reference range: 0–0.3 mg/dL), hypoglycemia (56 mg/dL; reference range: 80–110 mg/dL), prolonged prothrombin time and international normalized ratio (1.42; reference value: 1.0), and elevated fibrin/fibrinogen degradation products (56 mg/dL; reference range:  $<5 \mu\text{g}/\text{mL}$ ). Chest radiography revealed no opacities in lung fields. Electrocardiogram findings showed sinus tachycardia only, and transthoracic echocardiography (TTE) demonstrated no vegetation on the aortic, mitral, or tricuspid valves at that time.

The patient's condition and consciousness rapidly deteriorated immediately after admission. He was intubated and put under mechanical ventilation. He was immediately started on broad-spectrum antibiotic therapy of intravenous meropenem (MEPM; 0.5 g every 12 h) and vancomycin (VCM; 500 mg twice per week) due to suspicions of severe septic shock with disseminated intravascular coagulation. Inotropic agents (dopamine and norepinephrine), immunoglobulin, corticosteroids, and recombinant thrombomodulin were intravenously administered, and continuous hemodiafiltration was performed for 2 days. On the third day, GGS, but no other pathogen, was identified in 4 bottles of blood culture and in a nasopharyngeal culture obtained at admission. The patient's symptoms and laboratory results were consistent with the diagnosis of an invasive GGS infection and fulfilled the criteria for STSS defined for GAS [5]. His general status improved. The intubation was removed, and he regained consciousness; inotropic agent administration was decreased by 50%. Intravenous MEPM was continued, and VCM was replaced with clindamycin. Intermittent HD was

continued 3 times per week to remove excess fluid. On day 8 after admission, he complained of left leg paresis. Brain magnetic resonance imaging showed evidence of multiple acute cerebral embolisms (Fig. 1). Although embolic complications of IE were suspected, repeated TTE detected only mitral annular calcification. Transesophageal echocardiogram (TEE) could not be performed immediately due to the frailty of the patient.

On day 21, TEE was performed and floppy vegetation (1.2 cm in size) on the mitral valve was detected (Fig. 2). A diagnosis of IE was consistent with the modified Duke criteria based on the presence of 1 major criterion (vegetation) and 3 minor criteria (fever, cerebral embolism, and GGS bacteremia). Although the patient's status did not deteriorate further, we determined that mitral valve replacement was the preferred therapy to prevent further embolic events. He was transferred to an affiliate hospital, which had a cardiovascular surgery unit. The cardio-surgery team observed the patient and reevaluated his preoperative condition carefully. From the patient's nutritional state and history of previous thoracic aorta replacement, the team made the final decision to not perform surgery for vegetation because of the very high mortality risk present in the perioperative period. The surgeons returned the patient to our hospital. The repetitive blood cultures were performed without administration of any antibiotics again; they revealed no growth of pathogen, indicating that SDSE infection from the blood stream was resolved. However, on hospital day 243 after readmission to our hospital, he died due to the sudden onset of ventricular fibrillation, which was nonrespondent to any emergency procedures.

The patient's GGS had good sensitivity to all antibiotics tested with the minimum inhibitory concentration, including MEPM and penicillin G doses of  $\leq 0.008$  and  $0.008 \mu\text{g/mL}$ , respectively. The isolated GGS was later identified as SDSE by gene sequencing analysis at the National Institute of Infectious Diseases (Tokyo, Japan). The isolated SDSE was defined as stG4974 by M-protein gene (emm) typing.

## Discussion

To the best of our knowledge, this is the first reported case of invasive SDSE infection with STSS followed by IE in a chronic HD patient in the English literature. In the 21st century, invasive SDSE infections leading to a diagnosis of various disseminated diseases have increased in Europe, America, China, and Japan [3, 4]. Recent surveillance studies implicated SDSE as a major causative pathogen of invasive GGS infections, primarily affecting the elderly and those with underlying medical conditions, such as cardiovascular disease, diabetes, malignancies, chronic skin disease, alcoholism, or immunosuppression [3, 4]. However, the epidemiology of invasive SDSE in end-stage renal disease patients remains unknown. The clinical manifestation of invasive SDSE as IE (0–3%) and STSS (1–9%) is not infrequent [6, 7]. Based on emm genes that show polymorphisms similar to *S. pyogenes*, gene sequence analysis has been applied to emm typing for SDSE. The predominance of emm types has been found to vary by geographic region [4]. In Japan, the most prevalent emm type of invasive SDSE infection was stG6792, which is not prevalent in other countries [3]. The stG4974 strain isolated from the present case is very rare in Japan (1.4%) [3]. Further reports are necessary to determine the causal relationship between emm type and IE with STSS.

There have been 6 case reports of septic complications of IE caused by SDSE [8–12]. These cases were not in HD patients, but in patients with other major underlying diseases (aortic valve or aortic arch replacement: 3; pacemaker implantation: 2; type 1 diabetes: 1) [8–12]. Successful treatment with penicillin G and ampicillin, with or without gentamycin,

followed by surgery has been described [8–12]. Our patient was treated with MEPM because of its immediate effectiveness against STSS.

Of note, 3 of 6 cases, as well as the present case, had metastatic complications, such as endophthalmitis and embolisms, suggesting the rapid progression of an invasive SDSE infection. In the present case, TEE was necessary to confirm vegetation on the mitral valve. Owing to the increased sensitivity of TEE over TTE in detecting vegetation (sensitivity for the native valve: TTE 60–65%, TEE 85–95%) [13], TEE should be performed in any HD patient with a high risk of IE. Well-designed studies to address IE management in HD patients are urgently needed.

Using the United States Renal Data System database, Abbott and Agonda [14] found that the HD population has an age-adjusted incidence ratio for IE of 17.9 compared with the general population, suggesting that the risk of IE in end-stage renal disease patients is significantly higher than that in the general population [14]. Potential explanations for the increased incidence of IE in chronic HD patients are as follows: (1) degenerative heart valves, i.e., calcific aortic stenosis or mitral annular calcification due to calcium–phosphorus abnormalities, and the chronic micro-inflammatory milieu of uremia; (2) vascular access-related bacteremia; and (3) immune system impairment, such as polymorphonuclear cell dysfunction and granulocyte mobility [15]. However, there have been no reported cases of IE with STSS caused by SDSE in HD patients. The results from the bacterial culture in the present case showed that SDSE mainly originated from the patient's own flora in the upper respiratory tract. In addition, he had 2 considerable risk factors for IE development: the existence of mitral annular calcification and thoracic aorta graft, which may have led to IE caused by SDSE.

In conclusion, we described a unique case of IE in a patient initially presenting with STSS, both of which were due to SDSE. Based on the emerging evidence of invasive SDSE in the elderly population and in individuals with underlying diseases, clinicians should be on alert for the possibility of SDSE being a pathogen that can cause critical bacteremia in chronic HD patients.

### Acknowledgements

The authors would like to thank Enago (www.enago.jp) for the English language review.

### Statement of Ethics

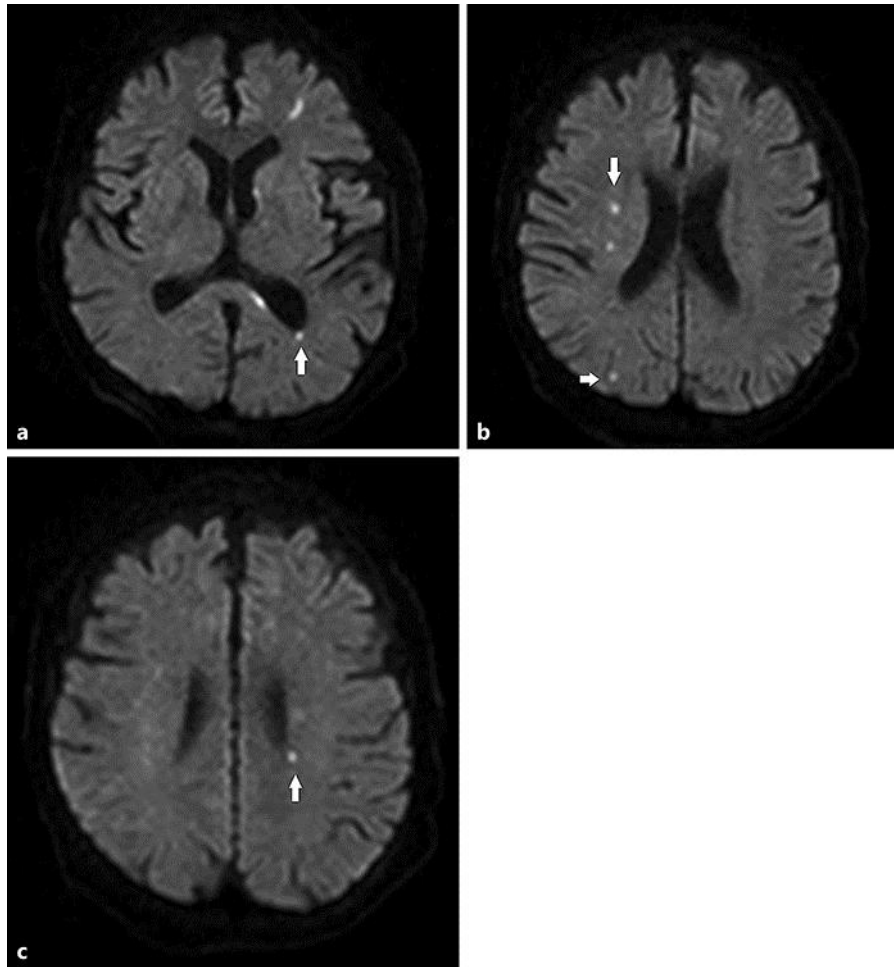
The study of the patient was approved by the Institutional Ethics Committee of Osaka Saiseikai Izuo Hospital, and written informed consent was obtained from the patient for publication of this case report.

### Disclosure Statement

The authors have no conflicts of interest to declare.

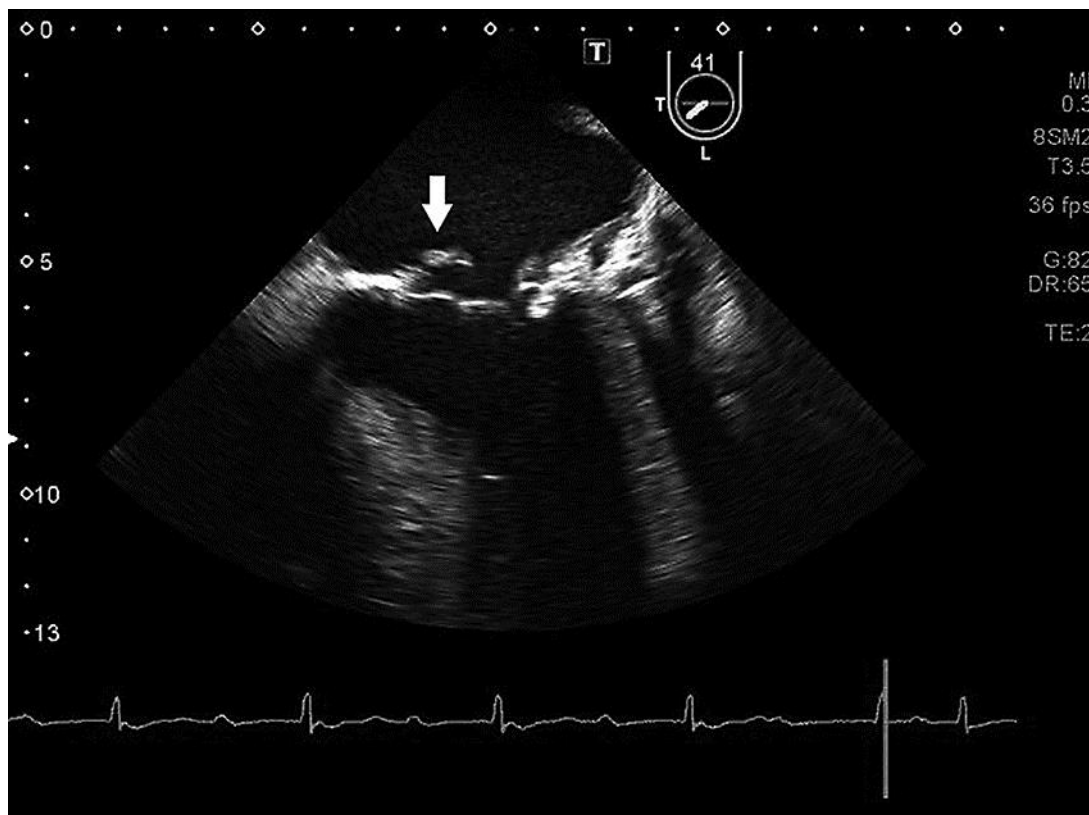
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**Fig. 1.** Diffusion-weighted image from brain magnetic resonance imaging showing multiple acute embolisms (arrows) in the cerebrum: left occipital lobe (a), right corona radiata (b), periventricular zone (c).

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**Fig. 2.** Transesophageal echocardiography showing vegetation (arrow) on the mitral valve.