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【 CASE REPORT 】

Hemodialysis Patient with Streptococcal Toxic Shock Syndrome and Penile Necrosis

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Abstract:
A 72-year-old man on hemodialysis due to diabetic nephropathy presented with a fever and penile pain. Although his physical examination was unremarkable, his general condition deteriorated. Penile necrosis was observed by evening on the same day of presentation, and the patient died the next morning. Blood cultures revealed the presence of Group G *Streptococcus*, leading to a diagnosis of streptococcal toxic shock syndrome (STSS). Autopsy suggested penile necrosis due to septic shock. STSS in hemodialysis patients with vascular calcification, even in the absence of calciphylaxis, can lead to severe organ damage due to ischemia.

Key words: penile necrosis, streptococcal toxic shock syndrome, *Streptococcus dysgalactiae* subsp. *equisimilis*, hemodialysis, elderly patient, diabetes mellitus

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Introduction

Streptococcal toxic shock syndrome (STSS) is a serious condition caused by β-hemolytic streptococci that rapidly leads to septic shock and multiple organ failure, with a mortality rate of over 30%. The most common initial symptom is sudden pain often accompanied by flu-like symptoms, such as a fever, chills, shivering, myalgia, vomiting, and diarrhea (1). The diagnosis is often difficult due to nonspecific initial symptoms.

The penis receives abundant blood flow from the dorsal penile artery and the deep urethral artery, and the penile tissue itself is considered to be resistant to ischemia, making necrosis unlikely. However, there are numerous reports of penile necrosis developing in patients on hemodialysis for diabetic nephropathy, and such cases are considered to have a poor prognosis (2).

We herein report a patient with STSS with initial symptoms of penile pain followed by penile necrosis.

Case report

A 72-year-old-man with a 17-year history of hemodialysis due to diabetic nephropathy was admitted to the emergency room with complaints of a fever, penile pain, vomiting, and diarrhea. He had a history of percutaneous transluminal angioplasty of the lower extremities. His medications included lanthanum carbonate hydrate 500 mg, calcium carbonate 3,000 mg, cilostazol 200 mg, lansoprazole 30 mg, cinacalcet 25 mg, amlodipine 10 mg, enalapril maleate 5 mg, and carvedilol 2.5 mg. The patient was a non-smoker and did not consume alcohol regularly. He had a good general condition, and a physical examination, which included the penis, revealed no significant changes. The penile pain worsened 9 h after the initial examination. He revisited the emergency room and lost consciousness while waiting.

On admission, he had a Glasgow Coma Scale (GCS) score of 3 (E1V1M1). A physical examination demonstrated a blood pressure of 84/58 mmHg, respiratory rate of 28 breaths per minute, heart rate of 102 beats per minute, temperature of 37.6°C, and oxygen saturation of 100% on a facemask with an oxygen flow rate of 15 L/min. He was in a cold sweat, and no physical abnormalities were observed except for swelling and dark brownish changes at the glans. Blood laboratory data showed the following: white blood cell count, 5,600/μL; hemoglobin, 10.2 g/dL; platelets, 81,000/μL; sodium, 141 mmol/L; potassium, 5.3 mmol/L;

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chloride, 103 mmol/L; creatinine, 9.71 mg/dL; blood urea nitrogen, 47.7 mg/dL; albumin, 3.3 g/dL; calcium, 9.4 mg/dL; phosphorus, 5.8 mg/dL; parathyroid hormone, 280 pg/mL; C-reactive protein, 129.8 mg/L; total bilirubin, 1.5 mg/dL; aspartate aminotransferase, 34 IU/L; and alanine aminotransferase, 10 IU/L. Atrial blood gas with oxygen flow rate of 15 L/min revealed the following: pH, 7.031; $PaCO_2$, 62.4 Torr; PaO_2, 80.6 Torr; HCO_3, 15.7 mEq/L; and anion gap (AG), 25.0 mmol/L.

After admission, the patient's respiratory condition deteriorated rapidly, and arterial blood gas indicated worsening metabolic and respiratory acidosis and hyperkalemia. He was intubated and admitted to the intensive care unit. Three hours after admission, blackish changes were observed on the entire penis and scrotum (Fig. 1). A test incision in the perineum, penis, and scrotum was performed; however, no evidence of effusion was detected. Contrast-enhanced computed tomography of the pelvic region showed no intestinal necrosis but did reveal poor contrast enhancement of the penis. There was no evidence of abscess or gas in the penis. The patient was treated with antibiotics (vancomycin and meropenem), vasoactive agents (noradrenaline and vasopressin), hydrocortisone, and continuous hemodiafiltration dialysis (CHDF). However, metabolic acidosis and hyperkalemia progressed, and the patient died 12 h after admission (Fig. 2).

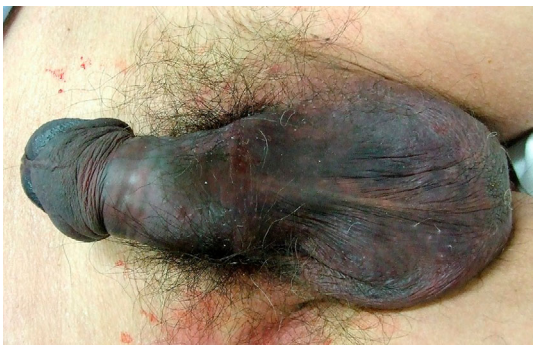

Figure 1. Gross appearance of the penis.

A postmortem blood culture showed *Streptococcus dysgalactiae* subsp. *equisimilis* (SDSE) with intense β-hemolysis, and a diagnosis of STSS was made. The antimicrobial susceptibility results of SDSE were later revealed to be sensitive to β-lactam antibiotics, including meropenem. Pathological autopsy was performed to investigate the etiology of the disease. Calcification of the aorta and ischemic necrosis of the stomach and of the lower gastrointestinal tract were detected. Calcified lesions and numerous infected thrombi were found in the subcutaneous tissue of the penis, scrotum, and arterioles in the muscular layer of the bladder wall

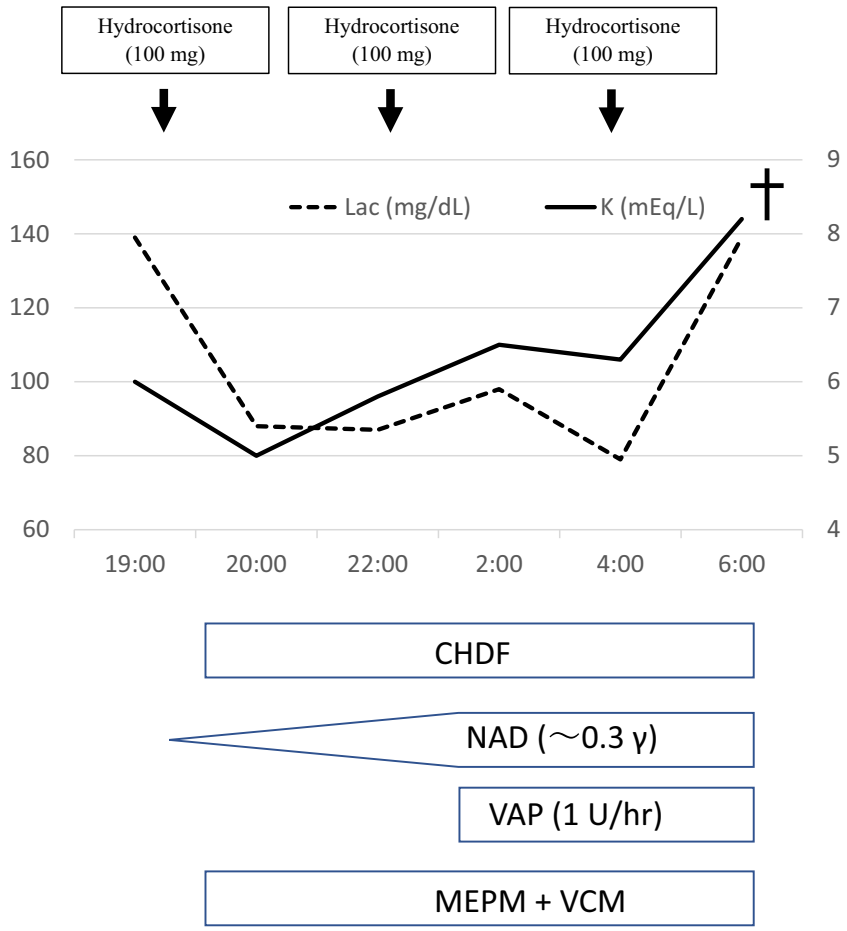

Figure 2. Clinical course after admission. CHDF: continuous hemodiafiltration, MEPM: meropenem, NAD: noradrenaline, VAP: vasopressin, VCM: vancomycin

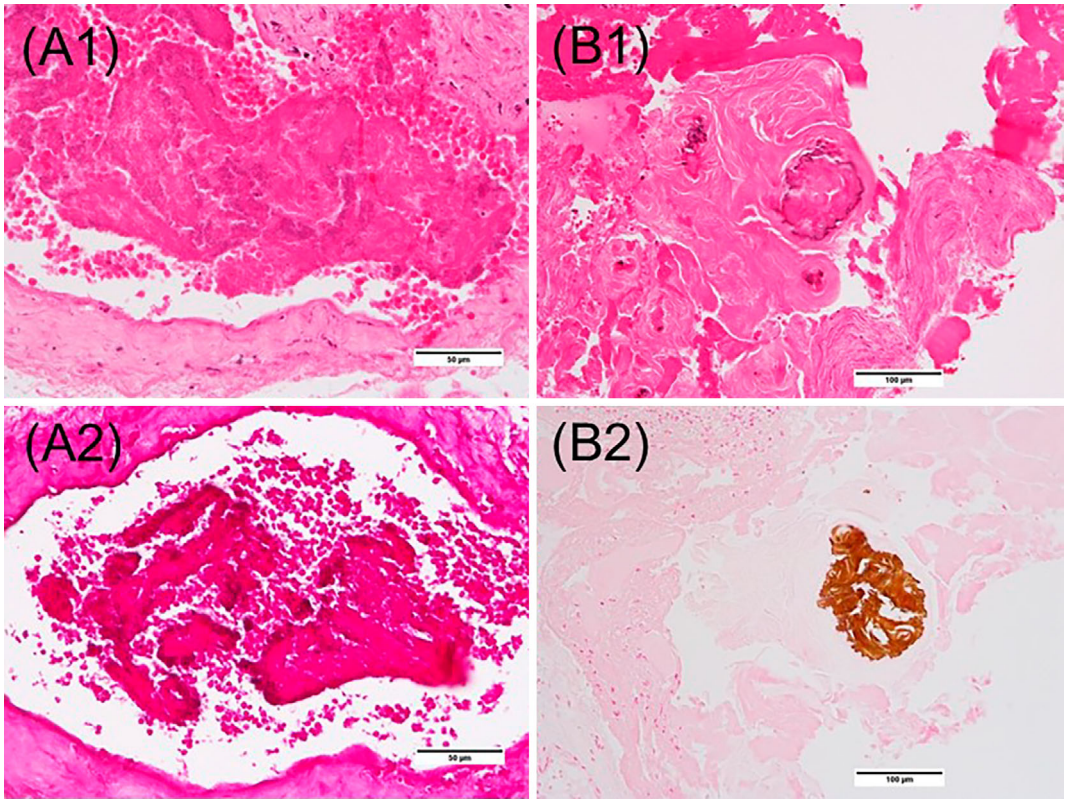

Figure 3. **Pathological findings of the penis. (A1), (A2) Septic emboli associated with Gram-positive *Streptococcus*. Both Gram stain (original magnification ×200). (B1), (B2) Calcium deposition in small arteries (original magnification ×100). (B1) Hematoxylin and Eosin staining. (B2) Von Kossa stain.**

(Fig. 3).

Discussion

We herein report a patient with STSS complicated by rapidly progressive penile necrosis. The differential diagnosis of penile pain in hemodialysis patients includes penile necrosis, infections (e.g. Fournier's gangrene), vascular embolism, foreign body reaction (e.g. to injected silicone), and malignancy. Among these, penile necrosis is a rare complication, typically occurring in hemodialysis patients with calciphylaxis (3). This is because blood is supplied to the penis by multiple vessels, including the dorsal penile artery, deep penile artery, and urethral artery, all of which originate from the internal genital artery. Calciphylaxis is a rare disease caused by the calcification and occlusion of arterioles, and it mainly affects patients with end-stage renal failure (4). In Japan, diagnostic criteria have been proposed for calciphylaxis (5). Although calciphylaxis was suspected in the present patient, no skin lesions with purpura were observed. Therefore, we hypothesized that hypotension due to septic shock and septic embolization, combined with severe systemic vascular calcification, may have led to penile necrosis. Patients with end-stage renal failure due to diabetic nephropathy often develop advanced systemic vascular calcification, which may be complicated by peripheral artery disease, especially in the lower extremities. Therefore, penile necrosis is considered to occur as a result of extremely advanced systemic vascular calcification and is considered to be a poor prognostic factor (2). Autopsy in our patient revealed that various organs other than the penis had circulatory disorders.

STSS, which led to the patient's death in this case, is caused by β-hemolytic streptococci. It develops suddenly and progresses rapidly. It is a serious complication that occurs in about one-third of patients with invasive streptococcal infections, and 30-70% of patients die despite intensive treatment (6). In addition to high-dose penicillin antibiotics, concomitant use of clindamycin is recommended for the treatment of STSS (7, 8). The Eagle effect is known to occur when the density of bacteria in the tissue increases, inhibiting the growth of bacteria and decreasing the efficacy of β-lactams, and treatment with penicillin alone often fails in severe cases (8). Clindamycin shows good intracellular penetration properties and has an anti-toxin effect that inhibits the production of bacterial exotoxins and M proteins (7, 8). Intravenous immunoglobulin therapy (IVIG) is administered to neutralize bacterial enterotoxin, and although its efficacy has been reported in Western countries (7), its efficacy at approved doses in Japan remains uncertain. In this case, multidisciplinary treatment including meropenem, glucocorticoid administration, and CHDF was performed. Surgical debridement was contraindicated due to the patient's poor condition and thus was not performed. However, this multidisciplinary treatment was ineffective. In terms of the choice of antibiotics, the outcome may have

been different if STSS had been suspected from the beginning and if penicillin, clindamycin, and IVIG in combination with meropenem had been administered.

In the present case, SDSE was identified as the causative organism. SDSE belongs to group C and G streptococci of the Lancefield group and is a constituent of the normal flora of the skin, mesopharynx, gastrointestinal tract, and urogenital organs (9). Most STSS cases are caused by group A streptococci, but recently, the incidence of SDSE has been increasing. In a report from Japan, serious streptococcal infections included younger patients affected by group B streptococcus, whereas the median age for SDSE was 75 years old. Seventy-nine percent of patients with severe SDSE had an underlying disease, including 5.8% with kidney disease and 15.9% with diabetes mellitus (10). In a report from the United States, among β-hemolytic streptococci of groups other than A and B, SDSE accounted for 43% of cases, of which 96% were associated with underlying diseases, such as peripheral arterial disease, diabetes mellitus, or end-stage renal failure; in that report, STSS occurred in 9% of patients, which is not uncommon (11). The first-line treatment for SDSE, like other streptococcal infections, is penicillin antibiotics, and resistance to macrolides, minomycins, fluoroquinolones, and clindamycin has been observed (12-16). Although SDSE infection by itself is less severe than group A streptococcus bacteremia, the severity may increase due to the associated conditions, such as the patient's age and underlying diseases. In the present case, the patient was an older adult and had end-stage renal failure due to diabetic nephropathy, which may have contributed to the severity of the infection (17).

Conclusion

Although penile necrosis in hemodialysis patients is typically caused by calciphylaxis, it may develop rapidly due to progressive circulatory disorders in patients at high risk for vascular calcification. In recent years, streptococcal infections caused by SDSE have been increasing in frequency and can be severe in hemodialysis patients with multiple underlying diseases. In particular, it is essential to initiate early multidisciplinary treatment for patients with clinical signs suggestive of STSS.

Informed consent was obtained from the patient's family.

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

References

1. Stevens DL. Invasive group A streptococcus infections. Clin Infect Dis **14**: 2-11, 1992.
2. Karpman E, Das S, Kurzrock EA. Penile calciphylaxis: analysis of risk factors and mortality. J Urol **169**: 2206-2209, 2003.
3. Coates T, Kirkland GS, Dymock RB, et al. Cutaneous necrosis from calcific uremic arteriolopathy. Am J Kidney Dis **32**: 384-391, 1998.
4. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. N Engl J Med **378**: 1704-1714, 2018.
5. Hayashi M. Calciphylaxis: diagnosis and clinical features. Clin Exp Nephrol **17**: 498-503, 2013.
6. Stevens DL, Tanner MH, Winship J, et al. Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. N Engl J Med **321**: 1-7, 1989.
7. Linnér A, Darenberg J, Sjölin J, Henriques-Normark B, Norrby-Teglund A. Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. Clin Infect Dis **59**: 851-857, 2014.
8. Stevens DL. The flesh-eating bacterium: what's next? J Infect Dis **179** (Suppl 2): S366-S374, 1999.
9. Vartian C, Lerner PI, Shlaes DM, Gopalakrishna KV. Infections due to Lancefield group G streptococci. Medicine (Baltimore) **64**: 75-88, 1985.
10. Takahashi T, Sunaoshi K, Sunakawa K, Fujishima S, Watanabe H, Ubukata K. Clinical aspects of invasive infections with *Streptococcus dysgalactiae* ssp. *equisimilis* in Japan: differences with respect to *Streptococcus pyogenes* and *Streptococcus agalactiae* infections. Clin Microbiol Infect **16**: 1097-1103, 2010.
11. Broyles LN, Van Beneden C, Beall B, et al. Population-based study of invasive disease due to β-hemolytic streptococci of groups other than A and B. Clin Infect Dis **48**: 706-712, 2009.
12. Ergin A, Ercis S, Hasçelik G. In vitro susceptibility, tolerance and MLS resistance phenotypes of Group C and Group G streptococci isolated in Turkey between 1995 and 2002. Int J Antimicrob Agents **22**: 160-163, 2003.
13. Ip M, Lyon DJ, Leung T, Cheng AF. Macrolide resistance and distribution of *erm* and *mef* genes among beta-haemolytic streptococci in Hong Kong. Eur J Clin Microbiol Infect Dis **21**: 238-240, 2002.
14. Brown DF, Hope R, Livermore DM, et al. Non-susceptibility trends among enterococci and non-pneumococcal streptococci from bacteraemias in the UK and Ireland, 2001-06. J Antimicrob Chemother **62** (Suppl 2): ii75-ii85, 2008.
15. Sunaoshi K, Murayama SY, Adachi K, et al. Molecular *emm* genotyping and antibiotic susceptibility of *Streptococcus dysgalactiae* subsp. *equisimilis* isolated from invasive and non-invasive infections. J Med Microbiol **59**: 82-88, 2010.
16. Biedenbach DJ, Toleman MA, Walsh TR, Jones RN. Characterization of fluoroquinolone-resistant β-hemolytic *Streptococcus* spp. isolated in North America and Europe including the first report of fluoroquinolone-resistant *Streptococcus dysgalactiae* subspecies *equisimilis*: report from the SENTRY Antimicrobial Surveillance Program (1997-2004). Diagn Microbiol Infect Dis **55**: 119-127, 2006.
17. Rantala S. *Streptococcus dysgalactiae* subsp. *equisimilis* bacteremia: an emerging infection. Eur J Clin Microbiol Infect Dis **33**: 1303-1310, 2014.