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Clinical Characteristics of Necrotizing Soft Tissue Infection and Early Toxic Shock-Like Syndrome Caused by Group G *Streptococcus*: Case Report and Review of Literature

Khalil Choucair, M.D., M.Sc.[1], Katia El Jurdi, M.D., M.Sc.[1], K. James Kallail, Ph.D.[1], Thomas A. Moore, M.D.[1,2]
[1]University of Kansas School of Medicine-Wichita, Wichita, KS Department of Internal Medicine
[2]Infectious Disease Consultants, Wichita, KS

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INTRODUCTION

Necrotizing soft tissue infections (NSTIs) are uncommon, but rapidly spreading infections, that involve the fascia and subcutaneous tissue.[1] NSTIs can be complicated by toxic shock syndrome (TSS), which usually are caused by β-hemolytic streptococci, mostly attributed to group A *Streptococcus* (GAS).[2,3] In fact, the original definition of streptococcal TSS in 1993 required the isolation of GAS, along with parameters indicative of multi-organ dysfunction.[4] TSS remains associated with high mortality rates exceeding 40 - 50%, despite adequate antimicrobial treatment.[5-7] However, group G β-hemolytic streptococci (GGS), historically identified as part of the normal flora of the pharynx, gastrointestinal tract and skin, are an uncommon cause of NSTI-TSS.[8] We report the case of a male with NSTI of the penile shaft, and toxic shock-like syndrome (TSLS) attributable to GGS. Only 16 similar cases have been reported.

CASE REPORT

A 32-year-old previously healthy male presented with penile pain following a 36-hour entrapment of the penile shaft by a plastic ring. He received amoxicillin-clavulanate with urgent surgical ring removal and exploratory flexible cystoscopy. On postoperative day one, he developed fever, chills, and excruciating pain with guarding across the pelvic area. The penile shaft was disproportionately swollen distally, cold to touch, necrotic, and devoid of sensation, with formation of new tense blisters. A new, erythematous skin rash overlying the pubic symphysis and both inguinal canals was observed, with well-demarcated, flat borders (Figure 1). Bilateral inguinal lymphadenopathy was present; identification of crepitus was limited by tenderness.

Labs were remarkable for mild lactic acidosis (2.1 mmol/L), hyperazotemia (25 mmol/L), hyponatremia (126 mEq/L), and thrombocytopenia (107 x 10^3/uL). Interval examination revealed worsening symptoms and rash progression, raising suspicion for NSTI superimposed by early stage streptococcal-induced TSLS. Peripheral blood, fluid from bullae, and penile skin swabs were cultured. IV immunoglobulin (IVIG) was administered and antibiotic therapy was modified to IV piperacillin-tazobactam and clindamycin.

On postoperative day two, he became afebrile and rash progression halted. He underwent penile/scrotum fasciotomy and debridement. Blood cultures remained negative, but fluid from the bullae, the penile skin, and surgical tissue specimen grew GGS. On postoperative day three, the rash receded. Antibiotic therapy was discontinued on day six, and he received a skin graft on day seven.

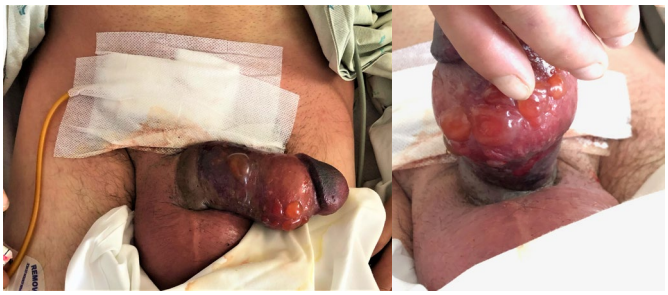

Figure 1. View of the G β-hemolytic *Streptococci* necrotizing soft tissue infection involving the penile area with necrosis of distant shaft, prior to therapy and surgical debridement. (Left) A new, erythematous skin rash overlying the pubic symphysis and both inguinal canals was observed, with well-demarcated, flat borders. (Right) Figure illustrates disproportionate swelling and necrosis distally, with formation of new tense blisters.

DISCUSSION

A review of the English literature revealed 16 additional cases of NSTI caused by GGS.[9-17] Clinical characteristics and outcomes are summarized in Table 1. The mean age of the total of 16 cases was 62.9 years (range: 46 - 80 yrs.). The majority were males (n = 9; 56.2%) and had other co-morbidities (n = 10; 62.5%), including liver cirrhosis (n = 1), malignancy (n = 1), multiple sclerosis (n = 1), syringomyelia (n = 1),[18] arthritis (n = 1), and diabetes mellitus which was the most common co-morbidity (n = 5; 50%).

The mean duration of symptoms prior to presentation was 3.2 days (± 2.2 days) and ranged from one to seven days. Common presenting manifestations were swelling with redness (n = 16; 100%), severe acute pain (n = 8; 50%), and blister formation (n = 7; 43.75%). The lower extremities (leg, ankle, and foot) were the most commonly involved sites (n = 12; 75%), with one case involving the arm,[12] two cases involving the knees,[10] and one case involving multiple sites simultaneously.[13] Progression to TSS or TSLS occurred in nine cases (56.3%). The diagnosis was established by isolating GGS from the site of involvement in all cases (n = 16; 100%): tissue (n = 12), bullae/blisters (n = 2), and joint fluid (n = 2). Bacteremia occurred in 25% of patients (n = 4).[11-13] Treatment included penicillin-based antibiotic regimen in all patients and varying degrees of surgical debridement (n = 15; 93.75%). Four patients received IVIG therapy. The overall mortality rate was 25% (n = 4), with equal rates in those who received IVIG (n = 1/4) and those who did not (n = 3/12); all patients who died developed TSLS.

Our patient presented with less than two days history of penile shaft entrapment with no clear sign of infection. He was treated solely based on clinical presentation which was highly suggestive of streptococcal TSS. Implication of GGS as the organism responsible for this illness and clinical progression was only later established based on an isolated specimen from surgical tissue and blister fluid which showed Gram-positive cocci and GGS growth on culture. The case thus highlighted the importance of early TSLS signs recognition, and the ensuing prompt management based on pure clinical presentation.

Table 1. Characteristics of Group G *Streptococcus* necrotising fasciitis.

Age (years)/sex	Co-morbidities	Site	Source of culture	TSS/TSLS? (Y/N)	Therapy	Outcome	Reference
75/F	Syringomyelia	Left leg	Tissue	N	Antibiotics, debridement	Survived	[36]
80/F	None	Right leg	Tissue	N	Antibiotics, debridement	Survived (skin graft)	[9]
49/F	None	Left ankle	Tissue	N	Antibiotics, debridement	Survived	[9]
75/M	None	Right leg	Tissue	N	Antibiotics, debridement	Survived	[9]
71/M	None	Left foot	Skin/bulla	N	Antibiotics, debridement	Survived (skin graft)	[14]
59/M	Unknown	Right leg	Skin/blister	Y	Antibiotics, debridement	Died	[15]
64/F	DM	Both legs	Tissue	Y	Antibiotics	Died	[17]
65/F	RA	Right arm	Blood/tissue	Y	Antibiotics, amputation	Died	[12]
52/M	DM	Right leg	Tissue	Y	Antibiotics. debridement	Survived	[16]
52/M	DM	Right leg	Tissue	N	Antibiotics, debridement	Survived	[13]
59/M	HCL/FN	Left leg	Blood/tissue	N	Antibiotics, debridement	Survived	[13]
58/M	Liver cirrhosis	Left knee, forearm, wrist, digits	Blood/tissue	Y	Antibiotics, IVIG, debridement	Died	[13]
73/F	Morbid obesity, HTN, DM, PVD	Left leg/ankle	Blood/tissue	Y	Antibiotics, debridement	Survived	[11]
46/F	MS, LLL	Right leg	Tissue	Y	Antibiotics, IVIG, debridement	Survived	[10]
63/M	None	Both knee joints	Joint fluid	Y	Antibiotics, IVIG, arthroscopic washes	Survived	[10]
66/M	DM, TKR	Prosthetic knee	Prosthetic knee/ fluid	Y	Antibiotics, IVIG, debridement	Survived	[10]
32/M	None	Penis	Bulla/tissue	Y	Antibiotics, IVIG, debridement	Survived	Present work

M = Male; F= Female; Y: Yes; N: No; DM: Diabetes Mellitus; RA: Rheumatoid Arthritis; HCL: Hairy Cell Leukemia; FN: Febrile Neutropenia; HTN: Hypertension; PVD: Peripheral Vascular Disease; MS: Multiple Sclerosis; LLL: Lower limb lymphedema; TKR: Total Knee Replacement

While originally identified and described by Lancefield and Hare as part of the normal flora, previous case reports have indicated that GGS also could cause complicated infections, such as cellulitis, osteomyelitis, septic arthritis, meningitis, endocarditis, and bacteremia.[19-22] Invasive disease due to GGS has been reported mostly in patients with underlying debilitating conditions including malignancy, rheumatoid arthritis, diabetes mellitus, injection drug use, and HIV infection, as well as in more elderly patients (Table 1).[10,11,13,16-18]

Our patient was young and healthy with no known history of co-morbid conditions. Whether the penile shaft entrapment and the ensuing low blood flow and necrosis could mimic the low terminal vascular supply and/or local impairment in defense mechanism observed in diabetes mellitus patients remains a plausible hypothesis, particularly in light of the observation that most cases had lower extremity involvement and diabetes mellitus (Table 1). Our review of literature did not always suggest an apparent precipitating cause of GGS-NSTI and TSS.

The presented case was unique in respect to two aspects. The first one pertains to the rarity of the underlying causative organism (only 16 reported cases in the English literature); as mentioned earlier GGS historically has been characterized as part of the normal flora with rare cases describing its involvement in pathologic states. Our case was one of these rare occurrences. Second, within the different reported cases, invasive GGS invariably has been linked to existing underlying co-morbidities. In contrast, our case was unique in that it reflected the occurrence of this potentially lethal infection in an otherwise young and healthy individual, hence highlighting the importance of a low clinical suspicion threshold for GGS-NSTI.

Over the past years, the number of reported GGS-NSTI cases, with or without TSS, has been on the rise. In fact, this observation prompted Wong et al.[18] to conduct a retrospective chart review of patients admitted to Long Island College Hospital in Brooklyn, New York, between January 2003 and December 2007. Only adult patients with microbiologically documented GGS infection were included in the study. A total of 73 patients with GGS infections were admitted to the hospital during the five-year study period, with the number increasing yearly and in an incremental fashion from three cases in 2003 to 28 in 2007. This study, along with the different cases reported (Table 1), reflects a clear increase in trend, and raises the possibility of GGS being an emerging human pathogen. The reasons of this increase remain

unknown and could relate to increase in potential risk factors, such as increased prevalence of diabetes mellitus or cancer, or to improved detection methods. Furthermore, emergence of resistance patterns in response to increased antibiotics use worldwide may explain possible changes/increases in GGS virulence. Hashikawa et al.[23] microbiologically characterized 12 strains of group C and G streptococci that caused TSS. Despite GGS TSS manifesting clinically in a similar fashion to GAS, only the *spegg* gene, which encodes a super-antigen found in GAS stains, was detected in *S. dysgalactiae* (GGS strain), but no other apparent virulence factor responsible for the TSS pathogenesis was identified. Further multi-center studies are warranted to characterize the increasing trend of GGS and define underlying host risk factors, and strain virulence factors.

As mentioned, NSTI and TSS treatment in our patient was initiated solely based on clinical presentation and high index of suspicion with no imaging to characterize the depth of tissue involvement.[24] Prompt initiation of therapy took precedence over establishing a clear diagnosis, based on both high clinical suspicion and the significantly high morbidity/mortality associated with delayed initiation of therapy. The actual diagnosis was validated clinically later when the patient positively responded to therapy and shock progression halted.

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) is a score used in the setting of early infection to define the likelihood of NSTI; it is based on indicators including white blood cell count (WBC), hemoglobin (Hgb), sodium (Na), glucose, creatinine (Cr.), and C-reactive protein (CRP).[25,26] A score greater than six is suggestive of NSTI while less than six is indicative of low risk (but does not exclude risk), suggesting IV antibiotics and serial laboratory monitoring without the need for surgical debridement.

We did not calculate a LRINEC score for our patient. In hindsight, and with the available laboratory values (CRP not obtained), the calculated LRINEC would have been five (WBC = 10.3 x 10^3/ uL; Cr. = 1.8; Na: 126 mEq/L; and Hgb = 12 d/dL), suggestive of low risk. This discrepancy between the low LRINEC score and the actual clinical picture reveals yet again the importance of clinical history and physical exam in clinical decision making. High suspicion for NSTI on clinical ground warrants a straight operative debridement approach, regardless of LRINEC score.

A recent assessment of the LRINEC score has recommended its cautious use given a poor performance in external validation.[27] In this study which involved patients with established diagnoses of cellulitis (n = 948) and necrotizing fasciitis (n = 135), a retrospective computation of the LRINEC score revealed poor predictive value of the score for differentiating between both diseases with a 10.7% false diagnoses of moderate-to-high risk of necrotizing fasciitis in patients with a confirmed diagnosis of cellulitis. Similarly, and within the group of patients with confirmed necrotizing fasciitis, 63.8% were categorized as low risk for necrotizing fasciitis using the LRINC score.

Similar to all NSTI, broad spectrum antibiotics and surgical debridement are necessary for a good outcome. Our patient received piperacillin-tazobactam as a regimen, along with both clindamycin and IVIG. Beyond its antibacterial effects, clindamycin is added for its ability to suppress bacterial toxin production.[28] In fact, use of clindamycin in patients with invasive GAS infection was associated with lower 30-day mortality (15% vs. 39% in those who did not receive clindamycin).[29] Linezolid or tedizolid alternatively can be used in patients with known resistance to clindamycin.[1] The use of IVIG in patients with streptococcal TSS often has been a subject of debate. The proposed rationale for use of IVIG is to boost antibody levels (passive immunity) in the setting of the overwhelming infection seen in TSS. Several mechanisms have been proposed, including bacterial opsonisation, toxin neutralization, inhibition of T cell proliferation, and inhibition of inflammatory cytokines.[30,31] Clinically, IVIG super-antigen neutralizing activity reduced mortality rates in streptococcal TSS.[32-34] A recent meta-analysis including five studies of patients with streptococcal TSS treated with clindamycin revealed an association between IVIG use and 30-day reduction in mortality (33.7 vs. 15.7 %).[35]

In summary, this work illustrated how NSTI due to GGS can progress, similar to GAS-induced fasciitis, to TSS/TSLS and can be life-threatening. Clinicians should keep a high index of suspicion, especially in patients with underlying co-morbid conditions, and understand the crucial role of early IVIG therapy, the choice of antibiotics with anti-toxin properties, and the increasing trend of GGS infections.

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