

## Rhabdomyolysis after group C streptococcal infection

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### Abstract

We describe a young woman with a group C streptococcal throat infection complicated by rhabdomyolysis. Muscle biopsy from quadriceps was normal, and molecular studies showed no evidence of direct microbial invasion. This is only the second case in which the usually benign group C streptococcus has been linked with muscle destruction.

### Introduction

Acute rhabdomyolysis during bacterial infection is recognised, but rare.<sup>1</sup> Muscle destruction can arise either due to direct invasion or secondary to toxic damage. Group C streptococci (GCS) are usually associated with minor pharyngeal or dermatological infections and only one report has previously documented rhabdomyolysis in a patient with GCS infection.<sup>2</sup>

### Case Report

A previously healthy, 21-year old woman was admitted to our hospital with a three day history of pain in the back and lower extremities. Nine days before admission she had had a sore throat and cough that had disappeared without treatment after approximately four days. Two days later she developed pain in the upper extremities, but not in the muscles of the jaw, eye or throat. On the day of admission she developed swelling of the right leg and was referred to us with a tentative diagnosis of deep vein thrombosis. Apart from small doses of paracetamol and ibuprofen for pain relief, her only regular medication was a low dose combined oral contraceptive (etinylestradiol/levogestrel). She had not taken any herbal medications. There was no history of direct trauma, but she was an active player of floor-

ball. Examination on admission showed a low grade fever of 38.1°C and bilaterally enlarged tonsils. The right calf was approximately 1 cm larger in diameter than the left. She had pain in the muscles of both legs on palpation and Homan's sign was positive. There were no signs of inflammation involving the skin or subcutaneous tissues of the calf and the remainder of the examination was normal. Two days after admission she also developed a general swelling of the left hand.

Initial blood tests (with normal range values in parentheses) were as follows: C-reactive protein 55 mg/L (CRP; <5), d-dimer 7.03 mg/L (0.00-0.50), s-creatinine kinase 35506 U/L (35-210), s-myoglobin 2848 µg/L (<50), erythrocyte sedimentation rate 36 mm, (ESR;<20) leukocyte count 12.9×10<sup>9</sup>/L (3.5-11.0), neutrophil count 8.9×10<sup>9</sup>/L (1.7-8.2), lymphocyte count 2.5×10<sup>9</sup>/L (0.7-5.3), monocyte count 1.02×10<sup>9</sup>/L (0.04-1.3), eosinophil count 0.4×10<sup>9</sup>/L (0.0-0.7), basophil count 0.0×10<sup>9</sup>/L (0.0-0.3), platelet count 445×10<sup>9</sup>/L (165-387), s-creatinine 51 µmol/L (45-90), s-potassium 4.4 mmol/L (3.5-5.0) and s-phosphorus 0.99 mmol/L (0.85-1.50). U-stix was positive for hemoglobin 3+ and protein 1+. Urine-microscopy showed physiological urine. Blood cultures were not performed as she had no signs of bacteremia/sepsis. Ultrasound examination showed no sign of deep vein thrombosis and due to the clear indication of muscular pathology, venography was not performed. No further imaging was performed.

Viral myositis was suspected, but antibodies against enterovirus, parainfluenza virus, adenovirus, influenza virus A and B, herpes simplex virus, varicella zoster virus, measles virus, parvovirus, Epstein Barr virus and cytomegalovirus were negative or only showed evidence of previous infection. Group C streptococci (GCS) were cultured from a tonsillar swab and anti-streptolysin (ASO) and anti DNase B-titers showed a typical rise and fall indicating active infection. ASO titre was initially 573 (normal range <400 IU/mL) rising to 2490 two weeks later and falling to 1720 IU/mL after 6 weeks; anti DNase B titers were 250-393-360 IU/mL (normal range <200 IU/mL) at the same time points.

Her rhabdomyolysis was treated with forced alkaline diuresis, but on the fourth day she developed a skin rash when given sodium hydrogencarbonate and received only fluids and a diuretic thereafter. The CK level fell slowly. On day 3 after admission, when positive serology for streptococci was identified and the tonsillar swab showed growth of group C streptococci, she started a 14 days course of oral penicillin. The pain and stiffness in her muscles gradually resolved as did the swelling of the right leg and left hand.

Muscle biopsy was performed under local anaesthesia on day 5 after admission. Muscle

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Contributions: HHN treated the patient when she was hospitalized, found references, participated in the discussion and wrote the case report; BRK found references, planned the sequencing of the bacterial 16rRNA in the muscle and participated in the discussion from the view of an infectious disease specialist; LAB evaluated the patient neurologically, did the muscle biopsy, saw the patient on follow up, initiated the work with the article and participated in the discussion from the view of a specialist in muscle disease.

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from the right quadriceps was examined by light- and electron microscopy and showed no evidence of necrosis, no inflammatory cell infiltrate, no accumulation of lipid or glycogen and no evidence of MHC1 upregulation. Enzyme histochemical staining showed normal myophosphorylase, myoadenylate deaminase, phosphofructokinase, aldolase, lactate dehydrogenase, cytochrome oxidase and succinate dehydrogenase activities. Electron microscopy showed a normal muscle ultrastructure. Subsequently, we have examined her muscle for the presence of bacteria. We found no evidence of GCS in her muscle on bacterial culture, and bacterial DNA was not amplified from the muscle biopsy using a broad-range PCR targeting the 16S ribosomal RNA gene as described,<sup>3</sup> with the following primers: F: 5'-TTG-GAG-AGT-TTG-ATC-MTG-C-3'<sup>4</sup> and R: 5'-GTA-TTA-CCG-CGG-CTG-CTG-3'.<sup>5,6</sup>

She was discharged after 17 days in hospital, and returned to work after 4 weeks after discharge. One month later, s-CK and s-CRP were normal and s-CK has remained normal (5

months follow up). She has returned to work and playing floorball and has no further muscle related symptoms.

## Discussion

We describe a patient with rhabdomyolysis complicating a streptococcal throat infection. The common causes of rhabdomyolysis, including both metabolic and structural myopathies, were excluded by muscle biopsy. Initially, we suspected a viral aetiology, but serological tests for the common viral causes were negative. The presence of a throat infection with GCS cultured from a throat swab and rising anti-streptolysin and anti-DNAse B titres raised the possibility that this might be the cause of her rhabdomyolysis.

GCS are  $\beta$ -haemolytic streptococci that occasionally cause pharyngitis or mild skin infections and are only rarely associated with severe, invasive infections. There have, however, been reports of GCS associated with disease manifestations including primary bacteremia, arthritis, endocarditis, meningitis, pneumonia, necrotising fasciitis, myositis and even fatal toxic shock-like syndrome has been described.<sup>7,9</sup> Acute rhabdomyolysis during bacterial infection is recognised, but rare. The most commonly implicated bacterial pathogen is *Legionella*, although streptococci, staphylococci and gram-negative bacteria have also been reported in association with muscle destruction.<sup>1</sup> A search of The Cochrane Library, PubMed and Medline with the keywords "group C streptococci" and "rhabdomyolysis" revealed only one case report describing a severe invasive GCS-infection associated with rhabdomyolysis and disseminated intravascular coagulation in a previously healthy adult.<sup>2</sup>

While there appears to be a relationship between a mild GCS throat infection and rhabdomyolysis, the nature of any causal association, particularly the pathophysiological mechanism linking them, remains unclear. Our patient had no history of recent muscle injury, and, while the biopsy was taken 2 days after starting oral penicillin, we could not isolate streptococcal DNA from her muscle. She did not develop symptoms or clinical signs compatible with streptococcal toxic shock syndrome or

necrotising streptococcal myositis. The clinical picture could reflect the first stages of pyomyositis that is characterised by local swelling, relatively mild pain and fever,<sup>10</sup> but pyomyositis is most often associated with recent muscle trauma, bacteremia and normal CK values. Furthermore, the lack of inflammatory cell infiltrate and absence of bacterial DNA in the muscle biopsy indicate that the marked CK elevation cannot be explained by general bacterial muscle invasion. Moreover, the muscle biopsy was taken to rule out underlying metabolic disorders from a muscle without obvious swelling. Endotoxins or exotoxins are believed to play a role in the pathogenesis of *Legionella*-associated rhabdomyolysis,<sup>11,12</sup> and the cysteine protease *speB* was shown to enhance local skin, subcutaneous tissue and muscle damage of strains of *Streptococcus pyogenes* in a mouse model.<sup>13</sup> However, the GCS isolate associated with a previous case of severe systemic infection and rhabdomyolysis did not show sign of exotoxin activity inducing T-cell mitogenicity.<sup>2</sup> Unfortunately, our GCS isolate was not available for further analysis. Hence, we were neither able to check for the presence of bacterial endotoxins nor for a possible mitogenic response.

This is only the second case in which GCS infection has been linked with rhabdomyolysis. In contrast to the previous case, our patient had a relatively mild GCS-infection, and we found no obvious clinical, microbiological, molecular or histological signs of muscle invasion. While the exact mechanism remains unknown, we feel it is important to alert other physicians to the possibility that GCS can be associated with significant muscle destruction.

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