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Rhabdomyolysis associated with acute renal failure in patients with severe acute respiratory syndrome

L-L. CHEN, C-W. HSU, Y-C. TIAN, J-T. FANG*
Division of Nephrology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan, ROC

SUMMARY

An outbreak of severe acute respiratory syndrome (SARS) occurred in Taiwan in 2003. SARS complicated with rhabdomyolysis has rarely been reported. This study reported three cases of rhabdomyolysis developing during the clinical course of SARS. Thirty probable SARS patients were admitted to the isolation wards at Linkou Chang Gung Memorial Hospital between 4 April and 4 June 2003. Thirty patients, including four men and 26 women aged from 12 to 87 years (mean age 40). Eleven (36.7%) patients had respiratory failure and required mechanical ventilation with paralytic therapy; three (10%) patients had rhabdomyolysis complicated with acute renal failure and one received haemodialysis; four (13.3%) patients died. Three cases with rhabdomyolysis all received sedative and paralytic therapy for mechanical ventilation. Haemodialysis was performed on one patient. Two patients died from multiple organ failure, and one patient fully recovered from rhabdomyolysis with acute renal failure. SARS is a serious respiratory illness, and its aetiology is a novel coronavirus. Rhabdomyolysis resulting from SARS virus infection was strongly suspected. Immobilisation under paralytic therapy and steroids may also be important in developing rhabdomyolysis.

Keywords: Acute renal failure; rhabdomyolysis; severe acute respiratory syndrome (SARS)

INTRODUCTION

Severe acute respiratory syndrome (SARS) is an emerging disease that has affected the world since February 2003. SARS, a highly contagious respiratory infection, frequently causes rapidly progressive respiratory failure (1). A novel virus the SARS-associated coronavirus has been identified as the causal agent (2–5). From March to July 2003, an outbreak of SARS occurred in Taiwan. The clinical, radiologic, haematological manifestations and elevation of lactate dehydrogenase and creatine kinase (CK) have been described in previous studies (6). Regarding musculoskeletal complications, myalgia is common, but SARS complicated with rhabdomyolysis has only rarely been reported (7–9). This study describes three cases that developed rhabdomyolysis with acute renal failure during the clinical course of SARS.

Correspondence to:
*Dr Ji-Tseng Fang, The Division of Nephrology, Chang Gung Memorial Hospital, 5 Fushing Street, Gueishan 333, Taoyuan, Taiwan, ROC
Tel.: + 886 3 3281200x8181
Fax: + 886 3 3282173
Email: fangjits@adm.cgmh.org.tw

MATERIALS AND METHODS

This study recruited patients with SARS who were admitted to Linkou Chang Gung Memorial hospital between 4 April and 4 June 2003. Thirty patients were enrolled who met the Centers for Disease Control and Prevention (CDC) and World Health Organisation (WHO) criteria for probable SARS (10). These patients were admitted to the isolation wards and received antibiotics, ribavirin, IVIG and steroid therapy. This study used pulsed of methylprednisolone 500 mg intravenously every 12 h for 3 days in cases involving worsening patients, with increasing shortness of breath, oxygen desaturation and respiratory failure (11). Hematological and biochemistry data, including kidney function, liver function and electrolyte, were inspected regularly. Rhabdomyolysis was based on clinical presentations and a fivefold or more elevation in CK levels with myoglobinuria (12).

RESULTS

The mean age of the 30 patients (four men and 26 women) was 40 years (range, 12–87). Eleven (36.7%) patients had respiratory failure and required mechanical ventilation with paralytic therapy; three (10%) patients had rhabdomyolysis complicated with acute renal failure and one of them received haemodialysis; and four (13.3%) patients died (Figure 1). Three cases with rhabdomyolysis all received sedative and paralytic therapy for mechanical ventilation (Table 1).

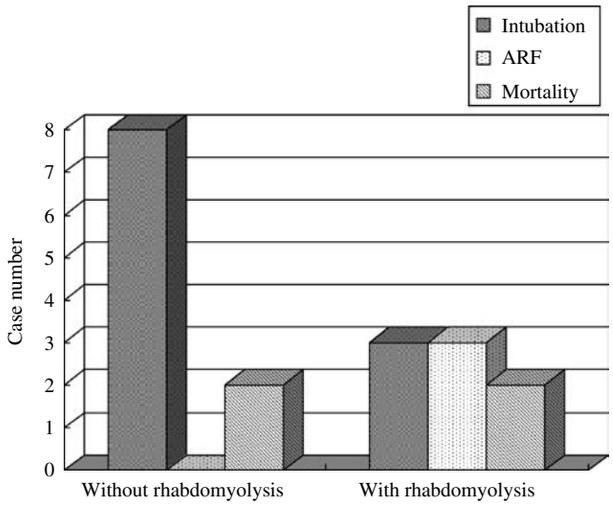

Figure 1 Comparison of severe acute respiratory syndrome (SARS) patients with or without rhabdomyolysis in respiratory failure, acute renal failure and mortality

Midazolam and atracurium were used for sedative and paralytic therapy. Intravenous methylprednisolone pulse therapy (500 mg) was administered every 12 h for 3 days. Among them, two patients developed rhabdomyolysis 10 days following intubation with ventilator support. Moreover, one patient with hypoxic encephalopathy in prolonged bed-ridden status suffered respiratory failure and was diagnosed with rhabdomyolysis on the same day following transferal from a local clinic. During admission, one patient received right quadriceps muscle biopsy, which demonstrated active muscle cell necrosis with atrophy and fatty infiltration (Figure 2).

The three patients who developed rhabdomyolysis all had acute renal failure (Table 2). These patients received intravenous hydration, urine alkalisation and mannitol infusion. One patient (case 1) who developed oligouric renal failure required haemodialysis therapy. Notably, the clinical condition of the patient with hypoxic encephalopathy (case 3) deteriorated too rapidly for haemodialysis to be administered. These two patients (case 1 and case 3) died from multiple organ failure; the other one (case 2) fully recovered from rhabdomyolysis with acute renal failure (Figures 3,4 and 5).

DISCUSSION

Rhabdomyolysis, a potentially lethal syndrome, characterised by raised concentrations of serum CK and myoglobinuria, frequently produces acute renal failure. The aetiologies of rhabdomyolysis include crush injury, skeletal muscle overuse, heat, alcoholism, myopathies, drugs, toxins and metabolic abnormalities (e.g. hypokalemia, hypo- or hyper-natremia, hypocalcemia and hypophosphatemia), as well as various viral and bacterial infections (12–14). Generally, the cause of rhabdomyolysis is clear from the history or from the circumstances immediately preceding the disorder, for example post-operative surgical trauma, a comatose or postictal state, or extraordinary physical exertion. Occasionally, the precipitant is not obvious. Some of these cases result from muscle enzyme or electrolyte abnormalities, infections, drugs, toxins or endocrinopathies. Various viruses have been reported to cause rhabdomyolysis, including influenza virus, Coxsackievirus, parainfluenza, adenovirus, echovirus, Epstein–Barr virus, varicella-zoster virus, cytomegalovirus, herpes simplex and human immunodeficiency virus (15). Bacterial and viral infections represent 5% of rhabdomyolysis cases in adults, and influenza virus accounts for 42% of cases of viral-mediated rhabdomyolysis (16,17).

Patients generally present with typical viral symptoms 1–14 days before the onset of severe myalgias and pigmenturia.

Table 1 Cases of rhabdomyolysis associated with acute renal failure

Case	*Age*	*Sex*	*Intubation with paralytic tx*	*Steroid use*	*Haemodialysis*	*Outcome*
1	41	Female	Y	Y	Y	Expire
2	48	Female	Y	Y	N	Completely recovered from rhabdomyolysis with acute renal failure
3*	26	Female	Y	Y	N	Expire

*This patient is a case of hypoxic encephalopathy with prolonged bed-ridden status. Y = yes; N = no; tx = therapy.

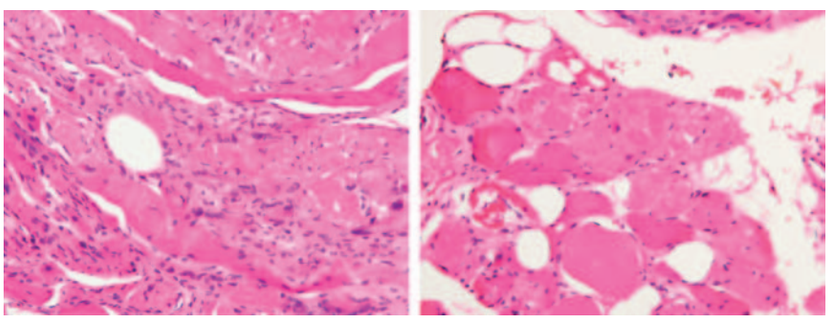

Figure 2 Right quadriceps muscle biopsy in case 1 demonstrated active muscle cell necrosis with atrophy and fatty infiltration. (H & E stain)

Table 2 Peak level of creatine kinase (CK) and creatinine (Cr) in the three cases of rhabdomyolysis associated with acute renal failure

Case	*Peak level of CK (U/l)*	*Peak level of Cr (mg/dl)*
1	93112	4.1
2	23511	3.0
3	9916	6.2

Mild-to-moderate diffuse myalgias occur frequently during the prodrome or early phase of any acute viral infection. These self-limited myalgias probably result from the effect of viral-induced cytokines on muscle tissue rather than direct viral invasion of the muscle. The diagnosis of viral myositis is suspected on clinical grounds. Serologic evidence of a recent viral infection provides additional support for the diagnosis. The mechanism of muscle damage from viral infections remains uncertain. Some possible pathogenesis have been proposed. First, direct invasion of muscle tissue by a viral agent; however, the presence of virus in affected muscle has been difficult to demonstrate consistently. Second, myotoxic cytokines were released in response to viral infection. For example, a case of rhabdomyolysis secondary to Coxsackievirus myositis has been reported in which patient serum contained raised tumour necrosis factor capable of inducing skeletal muscle breakdown in an animal model (18), and immunological processes induced by the viral infection could lead to muscle damage. CK levels range from below 10,000 IU/l to over 100,000 IU/l. Transaminase elevations may also occur along with various degrees of renal dysfunction. The classic findings on urinalysis include dark coloured urine which tests positive for blood by dipstick, without red cells being visible on microscopic examination. Muscle biopsy can be normal, or may display various degrees of necrosis ranging from scattered necrotic muscle fibers to widespread diffuse necrosis. Even with extensive necrosis, inflammatory cell infiltration is usually minimal or non-existent. In the absence of specific diagnostic findings, muscle biopsy is rarely performed in cases of suspected viral myositis, except to exclude other causes of rhabdomyolysis such as inherited metabolic myopathy or polymyositis. Viral and viral-like particles have been described on electron micorscopy, but it is uncertain whether these findings truly demonstrate the presence of viral pathogens in affected muscle or are merely artifacts (19). Most of the reports of acute viral myositis have found no viral particles on biopsy.

SARS is a serious respiratory illness, the aetiology of which is a novel coronavirus (8). Two of the three patients with probable SARS developed rhabdomyolysis 10 days following paralytic therapy with atracurium. Sedation and paralytic therapy with midazolam and atracurium were used for mechanical ventilator support. Atracurium is a non-depolarising neuromuscular blocking agent. The other patient developed rhabdomyolysis on the same day as receiving ventilator support and was a case of hypoxic encephalopathy that had been bed-ridden for over 1 year. Furthermore, all patients received corticosteroid therapy during the course of their disease. Myopathy has been recognised as a side effect of corticosteroid administration since shortly after the introduction of corticosteroids as therapeutic agents in the 1950s. Steroid myopathy can occur with any corticosteroid preparation. Elderly patients and those with cancer or negative nitrogen balance before the administration of corticosteroids may have an increased risk. Meanwhile, patients requiring large doses of intravenous corticosteroids and a neuromuscular blocking agent (frequently owing to mechanical ventilation) may develop acute necrotising myopathy characterised by severe diffuse proximal and distal weakness (20). The

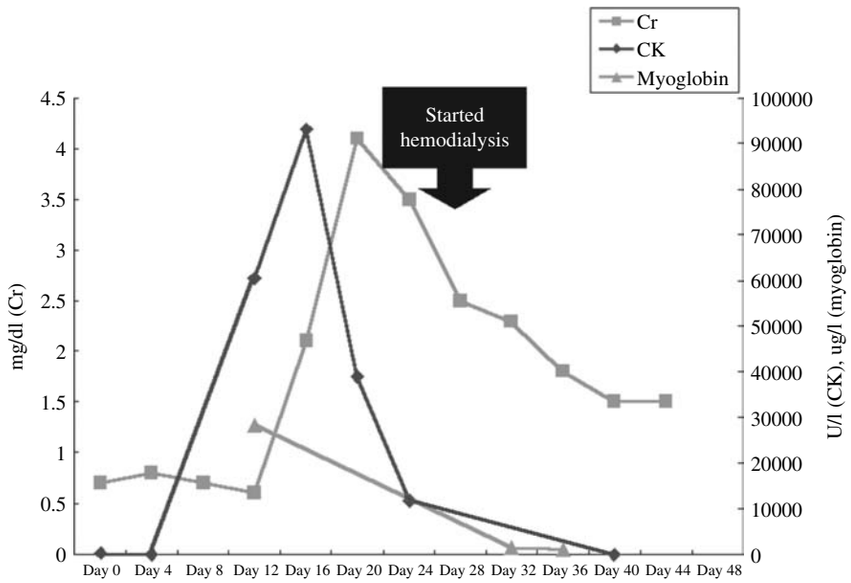

Figure 3 Case 1, a 41-year-old female, creatinine (Cr), creatine kinase (CK) and serum myoglobin level during admission course

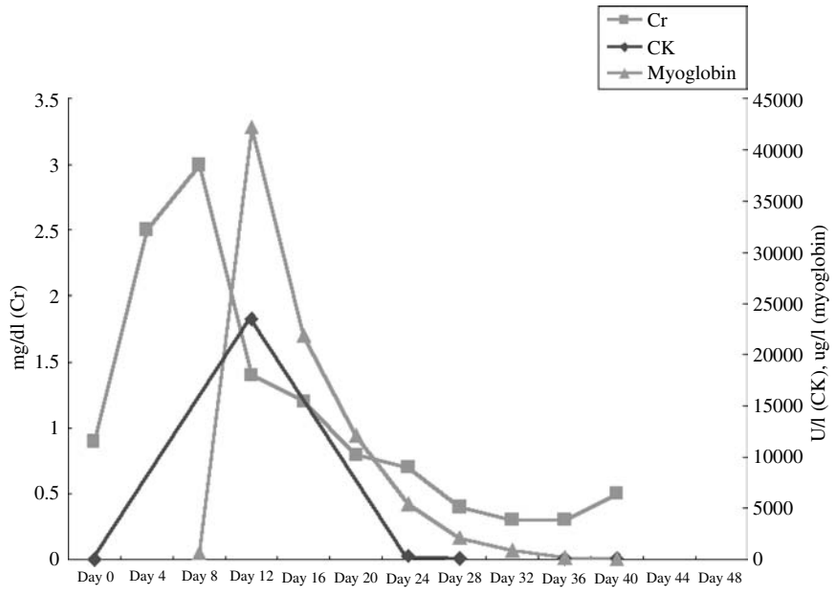

Figure 4 Case 2, a 48-year-old female, creatinine (Cr), creatine kinase (CK) and serum myoglobin level during admission course

mechanism of muscle injury following combined use of neuromuscular blocking drugs and corticosteroids is uncertain. Previous studies have hypothesised that pharmacologic denervation increases corticosteroid receptors in muscle and enhances steroid-induced myosin degradation. Muscle strength recovers completely within several weeks to several months of discontinuing the neuromuscular blocking agent and reducing the corticosteroid dose. Corticosteroid, which has myotoxicity, especially when used with neuromuscular blocking agents, can contribute to rhabdomyolysis. Moreover, paralytic therapy and underlying encephalopathy can result in immobilisation, which may also have played a role in the development of rhabdomyolysis in the three patients.

In conclusion, raised serum creatine kinase level was reported in SARS patients. However, rhabdomyolysis represented by a high-creatine kinase level with myoglobinuria, which causes acute renal failure, was rarely reported. Other predisposing factors of rhabdomyolysis such as toxin and electrolytes problems were excluded in this study. Rhabdomyolysis associated with SARS virus infection was strongly suspected. Corticosteroid and immobilisation under paralytic therapy may also be important in the development of rhabdomyolysis.

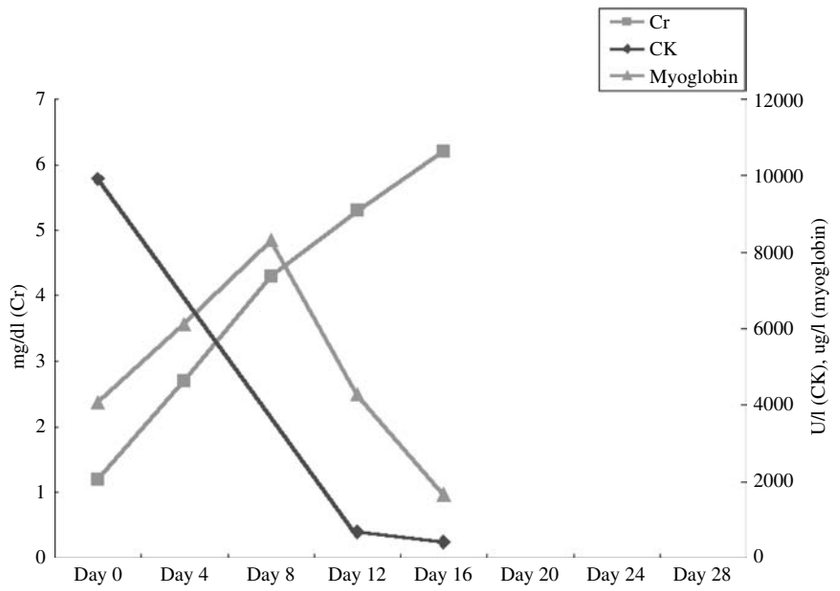

Figure 5 Case 3, a 26-year-old female, creatinine (Cr), creatine kinase (CK) and serum myoglobin level during admission course

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