

A case of recurrent rhabdomyolysis associated with childhood Sjögren's syndrome*

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ABSTRACT

We report a 9-year-old Japanese girl who presented with muscle weakness and elevated serum levels of muscle-derived enzymes following mycoplasma infection. Rhabdomyolysis or myositis was suggested by magnetic resonance imaging and repeated four times within 4 years. Each episode developed following respiratory infection and spontaneously recovered. The diagnosis of Sjögren's syndrome was made by decreased salivary secretion, MR sialography, lip biopsy, and positive anti-SSA/Ro antibody. Given the rarity of rhabdomyolysis/myositis, recurrent episode could be induced by infectious disease on the basis of underlying Sjögren's syndrome. Conclusion: Sjögren's syndrome should be considered as an underlying disease of recurrent infection-induced rhabdomyolysis/myositis.

Keywords: Childhood; Infection; Myositis; Mycoplasma Pneumoniae; Sjögren's Syndrome

1. INTRODUCTION

The diagnosis of rhabdomyolysis or myositis is often challenging in pediatric clinical setting because of various pathogenesis such as drugs, infections, autoimmunity, and metabolic diseases [1]. Sjögren's syndrome (SS), an autoimmune disorder primarily affecting exocrine gland, is often complicated by extra glandular involvement in both adults and children [2,3]. Although complication of rhabdomyolysis/myositis has been reported in adult SS [4-6], to our knowledge, there has been no report of the complication in childhood SS. We, herewith, report a

Japanese girl with primary SS complicated by recurrent rhabdomyolysis/myositis in association with infections.

2. CASE REPORT

A previously healthy 9-year-old Japanese girl was referred to our hospital because of cough, rhinorrhea, and fever up to 39°C, all of which had persisted for nine days. She had been treated with clarithromycin but shown no response. Because muscle weakness of her lower limbs and itchy rash developed a day after changing the antibiotics to azithromycin, she was admitted to our hospital. Physical examination demonstrated erythema on her trunks and conjunctival injection. Chest X-ray showed infiltrative shadow in the S6 segment of her right lung. Laboratory examinations demonstrated; white blood cell (WBC) 4010/mm³, erythrocyte sedimentation rate (ESR) 26 mm/1hr, C-reactive protein (CRP) 12.6 mg/l, and anti-*Mycoplasma pneumoniae* antibody 1:5120 by particle aggregation method suggesting mycoplasma pneumonia. Biochemical examinations demonstrated elevated levels of muscle-derived enzymes and myoglobin (2280 ng/ml) which reached to the peak on the 4th hospital day (Table 1). T2-weighted magnetic resonance imaging (MRI) showed high signal intensity areas in bilateral adductor muscle suggesting rhabdomyolysis or myositis (Figure 1). Both her muscle power and muscle-derived enzyme levels recovered to a normal level by the 12th hospital day without any anti-inflammatory treatment such as corticosteroid. Additional studies revealed positive antinuclear antibody (ANA) at 1:1280 and anti-SSA/Ro antibody at 32 index but negative anti-SS-B/La antibody.

Three years after the first episode, she presented with fever (38°C - 39°C) followed by swelling of cervical lymphnodes and weakness of her lower limbs associated

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Table 1. Clinical and laboratory features of the patient at the time of each episode of muscle weakness.

Episodes of myositis	1	2	3	4
Age	10 y 0 m	13 y 0 m	13 y 9 m	13 y 11 m
Symptoms	Fever, cough, erythema, muscle weakness	Fever, cough, erythema, muscle weakness	Fever, sore throat	General malaise
Medication before onset	CAM, SBT/ABPC	none	Tipepidine hibenzate L-Carbocisteine	none
Intensity of the adductor muscle on T2-MRI	High signal	Slightly high signal	-	-
White blood cells (/mm ³) [*]	9080	6000	6100	4600
ESR (mm/1hr) [*]	26	38	-	-
CRP (mg/L) [*]	12.6	11.2	1.5	1.7
AST (IU/L) [*]	495	187	29	22
ALT (IU/L) [*]	550	165	24	19
LDH (IU/L) [*]	1478	568	211	201
CPK (IU/L) [*]	23,390	7356	482	354
Aldolase (IU/L) [*]	224	28	-	-

^{*}Laboratory data represent the highest values in each episode. Abbreviations: CPK, creatine phosphokinase; CAM, clarithromycin; SBT/ABPC, sulbactam/ampicillin; MRI, magnetic resonance imaging.



Figure 1. Coronal T2-weighted MRI of her lower extremities shows the high signal intensity areas of bilateral adductor muscle (arrowheads).

with elevated level of serum muscle-derived enzymes (**Table 1**). She also had xerostomia, and pink-colored disseminated small erythema on her chest and thigh. Immunological examinations demonstrated; IgG 14.5 g/l, C3 1.27 g/l, C4 0.165 g/l, CH50 57 IU/l, antinuclear antibody 1:1280, positive anti-SS-A/Ro antibody (index 146), negative anti-SS-B/La antibody, soluble interleukin-2 receptor (sIL-2R) 1533 U/ml (normal range; <520 U/ml), and neopterin 19 pmol/ml (normal range; 0-

6 pmol/ml). Similar to the first episode T2-weighted MRI of her lower extremities showed the slightly high signal intensity areas of bilateral adductor muscle. Defervescence was achieved by the 5th hospital day without any specific treatment followed by the disappearance of skin eruption and recovery of the muscle power.

Clinical sicca symptoms associated with positive anti-SS-A/Ro antibody prompted us to perform further investigation for Sjögren's syndrome (SS). ^{99m}Tc₄ salivary gland scintigraphy showed decreased uptake of her left parotid gland and bilateral submaxillary gland. Dilatation of parotid gland peripheral duct was noted on MR sialography. Lip biopsy shows focal lymphoid cell infiltration (Greenspan's grade 4). As a result, she fulfilled both Japanese Criteria for Sjögren's syndrome and American-European Consensus Group Sjögren's syndrome Classification Criteria [7]. Thereafter, she had two additional episodes of transient CPK elevation following common cold (**Table 1**). Serum levels of CPK and aldolase returned to normal ranges after each episode.

3. DISCUSSION

We reported a case of recurrent episodes of muscle weakness associated with elevation of serum muscle-derived enzyme levels. Rhabdomyolysis and inflammatory myopathy/myositis are indistinguishable from each other even by biochemical or MRI findings [1,8]. However, elevated levels of serum sIL-2R and neopterin associated with elevation of serum CPK levels suggest inflammatory mechanisms rather than drug-induced rhabdomyolysis, although muscle biopsy was not carried out [9]. Indeed, there was no history of medication in the

second and fourth episodes. Consistent with this, drug lymphocyte stimulation test was negative for clarithromycin, a possible causative drug of the first episode. Infections of mycoplasma and viruses are major causes of rhabdomyolysis/myositis particularly in a pediatric age group, which is attributed to tissue hypoxia, direct invasion of the agents to the muscle, low oxidative and glycolytic enzyme activity, activation of lysosomal enzymes and mechanisms implicating endotoxins [6,10]. Mycoplasma infection could be associated with the first episode in our case because of elevated titer of the antibody. In the other episodes, self-limiting respiratory symptoms preceding elevation of serum CPK levels without elevation of antibodies to *mycoplasma pneumonia* suggest involvement of some viral infection.

Despite the apparent infections preceding the muscle weakness, recurrence of the rare disease, rhabdomyolysis/myositis, suggests the presence of underlying diseases. She had no history of exercise-induced myalgia, encephalopathy, hypoglycemia, or retinopathy, all of which are commonly observed in metabolic myopathies [1,8]. In addition, analysis of amino acids and acylcarnitine by tandem mass spectrometry showed no abnormalities. On the other hand, elevated ESR and serum IgG levels suggest chronic inflammatory diseases. She was finally diagnosed as having SS by decreased salivation, defective uptake of $^{99m}\text{Tc}_4$ to the salivary glands, positive anti-SS-A/Ro antibody, focal infiltration of the salivary glands on lip biopsy, and apple-tree signs on MR-sialography [7]. Complication of juvenile dermatomyositis/polymyositis is unlikely because of the transient course and lack of typical rashes.

Symptomatic myositis is associated with 3% - 5.6% of adult SS [4,5]. Aoki *et al.* reported that, in adults myositis complicated by SS, histological examination of muscle biopsy shows the variation in muscle fiber diameter and regeneration [4]. Furthermore, Lindval *et al.* have reported that histological myositis is detected in 72% of adult SS regardless of muscle pain, suggesting frequent subclinical myositis in adult SS [6]. Because the complications of adult SS is also observed in childhood SS [3], it is possible that childhood SS is predisposed to myositis as in adult cases. On the other hand, serum CPK levels in our case were much higher than those reported in adult cases [4]. Thus, severe but transient rhabdomyolysis/myositis in our case was likely attributed to both infections and underlying SS. Although our case showed recovery from rhabdomyolysis/myositis without any specific treatment, anti-inflammatory medication such as corticosteroid may be necessary for cases with persistent myositis.

In conclusion, recurrence of infection-induced rhabdomyolysis/myositis is quite rare and suggests underlying chronic disorder. Diagnostic evaluation for collagen vascular diseases including SS is recommended in such cases.

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