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Case Report

Systemic capillary leak syndrome induced by influenza type A infection

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A 42-year-old man visited the emergency department complaining of lower extremity swelling and myalgia. His influenza A antigen test was positive, and he was admitted for supportive care of severe myalgia. On the first hospital day, the swelling in his lower legs was aggravated with intolerable pain, and his creatine phosphokinase and hemoglobin levels were elevated. He was treated with massive hydration, albumin replacement, continuous venovenous hemofiltration, phlebotomy, and oseltamivir. The swelling and pain in his extremities were decreased without renal dysfunction, even though peripheral neuropathy and muscular complication persisted. Systemic capillary leak syndrome is a rare but life-threatening condition. The diagnosis is made clinically based on a classic triad of hypotension, hypoalbuminemia, and hemoconcentration. In our case, the influenza A infection was related to the capillary leakage.

Keywords Capillary leak syndrome; Influenza A virus; Edema; Hypoalbuminemia; Rhabdomyolysis

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Capsule Summary

What is already known

Influenza A infection may cause severe myalgia, and can be treated with antiviral medication.

What is new in the current study

In patients with hypoalbuminemia, edema, and rhabdomyolysis, the compartment syndrome from capillary leak syndrome should be considered.

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INTRODUCTION

Rhabdomyolysis after influenza virus infection has been recently reported;[1-3] however, compartment syndrome caused by swelling of a massive muscular compartment is an uncommon complication. In addition, hemoconcentration, hypoalbuminemia, and hypovolemic shock due to a marked shift of plasma are not the features of simple rhabdomyolysis but those of systemic capillary leak syndrome (SCLS).[4] SCLS can be diagnosed in the case of hypotension, hemoconcentration, and hypoalbuminemia without any special cause to induce shock. The cause of capillary leakage has not been elucidated, although monoclonal proteins, menstruation, and viral infection might be related to SCLS.[5,6] Here, we describe the case of an influenza A-infected patient with rhabdomyolysis, polycythemia, and hypoalbuminemia.

CASE REPORT

A previously healthy 42-year-old man visited our emergency department (ED) complaining of calf muscle pain and severe myalgia that had developed 1 day ago. Two days before his ED visit, he had a sore throat, cough, and myalgia and was treated with over-the-counter cold medications (acetaminophen and antihistamine). He had not eaten any raw or undercooked oysters during the past week and denied having any diarrhea or abdominal pain. He did not have any relevant medical or family history and reported no recent travel, trauma, or extraordinary exercise. He was used to having general edema whenever he had a cold. His initial vital signs in the ED were as follows: blood pressure, 110/83 mmHg; pulse rate, 111/min; respiratory rate, 20/min; and body temperature, 36.6°C. He was 168 cm in height with a weight of 80 kg. On examination, pharyngeal injection and muscle tenderness in both lower legs were observed. The dorsalis pedis pulse was weak but palpable on both sides, and distal capillary refilling was intact. Influenza A antigen was positive by immunochromatography (SD Bioline rapid influenza kit; Standard Diagnostics, Yongin, Korea). Initial serum laboratory tests revealed the following: white blood cell count, 9,700/mm^3; hemoglobin (Hb), 21.5 g/dL; hematocrit, 60.2%; creatine phosphokinase (CPK), 656 IU/L; lactic dehydrogenase, 426 IU/L; creatinine (Cr), 1.4 mg/dL; blood urea nitrogen, 23.6 mg/dL; C-reactive protein, 2.41 mg/dL; procalcitonin, 0.232 μg/L; aspartate aminotransferase (AST), 40 IU/L; alanine aminotransferase, 40 IU/L; protein, 6.0 g/dL; albumin, 3.2 g/dL; and lactate, 33.7 mg/dL. Serologic tests for human immunodeficiency virus, hepatitis A virus, leptospira, hantavirus, and *Orientia tsutsugamushi* were negative. The fluorescent antinuclear antibody test was negative. *JAK2* V617F mutation and *BCR/ABL* rearrangement were not detected. A coagulation test, chest radiography, lower extremity computed tomography angiography (Fig. 1), and electrocardiography results were normal. Thus, influenza A with rhabdomyolysis was diagnosed. The patient was given a neuraminidase inhibitor (oseltamivir phosphate, 75 mg). On the first night of admission, he complained of more pain in both lower legs and was thirsty with massive sweating. His posterior calf compartment pressure, measured with a needle-injection technique, was 5 mmHg, and compartment syndrome was ruled out. We infused dextrose fluid mixed with bicarbonate and normal saline fluid through a central venous route (initial central venous pressure [CVP], 9 cmH_2O; blood pressure, 111/82 mmHg; pulse rate, 108/min; respiratory rate, 20/min; body temperature, 36.4°C). Twelve hours after ED presentation, hypoproteinemia (3.4 g/dL), hypoalbuminemia (1.8 g/dL), and elevated CPK (1,502 IU/L) and Hb (23.4 g/dL) were observed in addition to oliguria. Continuous venovenous hemofiltration was started, and albumin was replaced. During the continuous venovenous hemofiltration, the hemofilters were obstructed several times by blood clots, so phlebotomy was performed. With an increase in the albumin level, the swelling of the extremities decreased, although muscle ache (compartment pressure of the posterior calf and volar forearm was 10-15 mmHg) and oliguria were aggravated for the first 2 days. During this period, norepinephrine was started, and volume resuscitation was

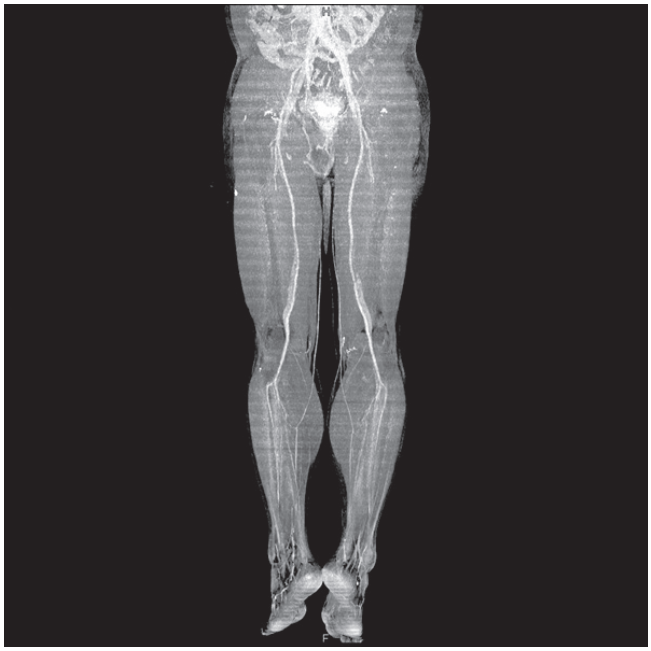

Fig. 1. Computed tomography angiography of the lower extremities before the acute phase. The arterial systems of both lower extremities are grossly normal without remarkable stenosis or obstruction. There is no evidence of deep vein thrombosis in either lower extremity. Mild subcutaneous edema is observed in both lower legs.

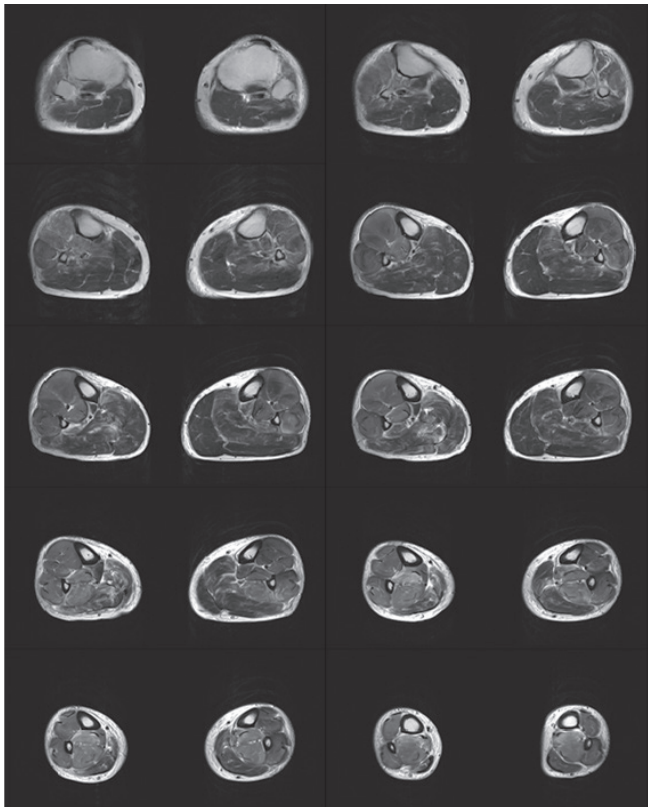

Fig. 2. T2-weighted magnetic resonance imaging of the lower extremities in the late phase. The anterior, lateral, and deep posterior compartments of both calf muscles are swollen, and the signal intensity is increased. Inner compartment enhancement is not observed, but the fascia rim is enhanced. The superficial posterior compartment shows mild swelling, and signal intensity is increased heterogeneously. There is patchy enhancement in the superficial posterior compartment.

continued owing to low arterial blood pressure and CVP (1-2 cm-H_2O) (blood pressure, 86/46 mmHg; pulse rate, 128/min; respiratory rate, 23/min; body temperature, 36.2°C). On hospital day 5, peak CPK, Cr, and AST levels were 65,142 IU/L, 2.6 mg/dL, and 1,846 IU/L, respectively. On hospital day 7, edema, muscle ache, and oliguria were improved without dyspnea; however, pretibial compartment syndrome (Fig. 2) associated with peripheral neuropathy and dorsal flexion limitation were noted. The patient's renal function recovered, but bilateral foot drop persisted.

DISCUSSION

SCLS was first described in 1960 by Clarkson et al.[7] It presents with recurrent episodes of hypovolemic shock, due to plasma leakage to the extravascular compartment reflected by accompanying hemoconcentration, hypoalbuminemia, and anasarca.[5] The disruption of endothelial junctions and cell retraction is suggested as a molecular mechanism, and in a recent study, an elevation of vascular endothelial growth factor and angiopoietin-2 was found in the sera of patients with acute SCLS.[8]

Treatment in the acute leak phase is mainly intravenous fluid therapy including albumin and bicarbonate. If needed, proper supportive care such as inotropic infusion and renal replacement therapy should be performed. The acute phase is managed in an intensive care setting and requires CVP monitoring. Rather than aiming for normotension and normal CVP, the aim is to use vasopressors and fluid boluses (rather than continuous infusions) to prevent shock, and some degree of oliguria is expected.[9] It is important to make a timely switch from the management of severe hypovolemia to that of acute fluid overload when the recruitment phase starts.[10] Very aggressive fluid infusion in the leak phase carries a risk of causing pulmonary edema in the recovery phase.[5]

Intravenous immunoglobulins, corticosteroid, theophylline, and terbutaline were reported to show clinical efficacy in the acute treatment of SCLS.[10-12] Various other agents have been tested, but their efficacy remains controversial. We treated our patient without these agents but administered only oseltamivir for the influenza.

Extremity compartment syndrome and ischemic cerebral stroke are caused by the hyperviscosity state and intravascular volume depletion during the shock and acute leak phase.[12,13] In a recent pediatric SCLS case associated with influenza A, a boy treated medically without decompressive fasciotomy recovered without sequelae, despite the initial painful calves and thighs with elevated CPK.[14] In other cases treated surgically, early treatment played an important role in achieving good outcomes.[4,15] In addition to strict control of fluid volume resuscitation, an evaluation of complications such as compartment syndrome is essential during the leak phase of fluid remobilization.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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