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Fatal thrombotic microangiopathy with rhabdomyolysis as an initial symptom after the first dose of mRNA–1273 vaccine: A case report

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ABSTRACT

We report a case of a Japanese man with severe rhabdomyolysis and multiple thrombosis of arterioles after the first dose of mRNA-1273 vaccine. He developed rapidly progressive rhabdomyolysis and infarctions of multiple organs. Antiplatelet factor 4 antibody test was negative. Despite the intensive supportive care, including aggressive fluid administration, hemodialysis, administration of anticoagulants, high-dose steroid, and eculizumab, the patient ultimately died of multiple organ failure. Autopsy revealed multiple thrombosis in the arterioles and organ necrosis. Low serum complements and C3 deposition in the renal glomeruli detected by immunofluorescence suggested a possible immune-mediated mechanism. To our knowledge, this is the first case report of rhabdomyolysis and multiple thrombosis of the arterioles as an adverse event following COVID-19 vaccination.

Introduction

Although the messenger RNA (mRNA)-based mRNA-1273 vaccine is highly efficacious against COVID-19 (Baden et al., 2021), it has been reported to cause rare but serious thrombotic adverse events such as vaccine-induced immune thrombocytopenia and thrombosis (VITT) (Greinacher et al., 2021). In addition to VITT, cases of rhabdomyolysis after COVID-19 vaccination have recently been reported (Ajmera, 2021; Faissner et al., 2021).

Herein, we report a rare case of rhabdomyolysis with fatal systemic thrombosis after the first dose of mRNA-1273 vaccine.

Case presentation

A 57-year-old Japanese man, without a significant medical history or comorbidities, developed subacute leg pain 2 weeks after receiving his first dose of mRNA-1273 vaccine. Four weeks after vaccination, he was diagnosed with rhabdomyolysis at the previous hospital, and referred to our hospital on day 35. He was not taking any medications and had no history of heparin use. Physical examination revealed livedo reticularis on the skin of the extremities (Figure 1A). His body mass index was 21.5 kg/m^2. Peripheral blood smear was normal. Laboratory tests showed a hemoglobin level of 13.3 g/dL, low platelet count (4.5 $\times$ 10^9/L), a normal haptoglobin level (111 mg/dL; normal range: 25–176 mg/dL), a prolonged activated partial thromboplastin time (APTT) (42.0 seconds; normal range: 20–38 seconds), a normal prothrombin time (11.6 seconds; normal range: 10–13 seconds), and an elevated levels of D-dimer (7.2 μg/mL; normal range: 0.1–0.5 μg/mL), and creatine kinase (CK) (12,096 U/L; normal range: 60–287 U/L). The ADAMTS-13 activity measured by enzyme-linked immunosorbent assay (ELISA) was 67%. Paroxysmal nocturnal hemoglobinuria (PNH) clones were not detected by flow cytometry analysis. The anti– SARS-CoV-2 spike and nucleocapsid antibodies were 169 U/mL and negative, respectively, consistent with SARS-CoV-2 vaccination. The diluted Russell viper venom time (dRVVT) was 1.5 (normal: $\leq$1.2) and the lupus APTT was 72.5 seconds (normal: $\leq$46.5 seconds). T2-weighted magnetic resonance imaging (MRI) of the legs showed increased signal intensity in the thigh muscles, consistent with

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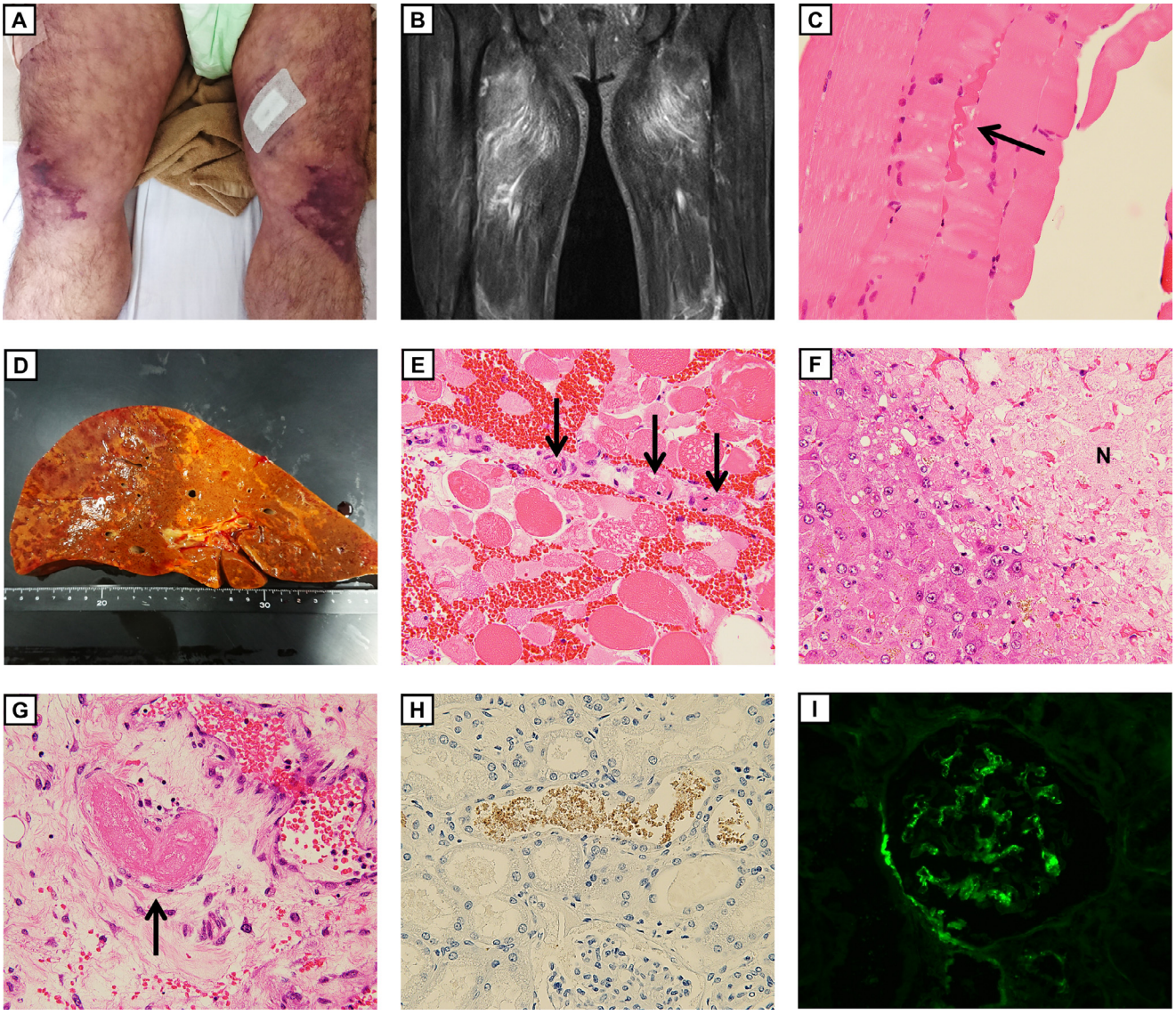

Figure 1. Skin changes and histopathologic findings
(A) Livedo reticularis on admission. (B) Magnetic resonance imaging findings of the extremities on T2 weighted-imaging demonstrates increased signal intensity in the thigh muscles, consistent with myositis. (C) Quadriceps femoris biopsy showed slight rhabdomyolysis without inflammatory cell infiltration (magnification: × 400). (D) Autopsy reveals acute to subacute infarction with scattered white changes surrounded by hemorrhagic areas. The pathological findings demonstrate degeneration and necrosis of the myocytes (E; magnification: × 200) and hepatocytes (F; magnification: × 100). Extensive hemorrhagic necrosis of the mucosa involves the entire intestinal tract, and there is microvascular thrombosis (G; magnification: × 100. The arrow points to the thrombosis in the duodenum). Myoglobin deposition is observed in renal tubules (H; magnification: × 400). Immunofluorescence reveals C3 deposits in renal glomeruli (I; magnification: × 400).

acute myositis (Figure 1B). However, despite the apparent signal change on MRI, quadriceps femoris biopsy showed neither rhabdomyolysis or inflammatory cell infiltration (Figure 1C). Antibodies related to immune myositis and antiphospholipid syndrome (APS) were negative. Bone marrow biopsy revealed normal marrow cellularity. Computed tomography (CT) of the abdomen revealed massive ascites that was negative for malignant cell invasion.

The patient's clinical course was complicated by severe rhabdomyolysis, severe kidney failure, and massive bleeding in the gastrointestinal tract and iliopsoas due to multiple thrombosis of the small arteries. We initially treated the rhabdomyolysis with intravenous fluid administration but his serum CK level continued to rise with a peak level of 74,804 U/L 4 days after admission and his renal function deteriorated rapidly, requiring hemodialysis. Follow-up CT revealed the multiple contrast defects in the liver and kidneys, suggesting hepatic and renal infarctions; however, thrombosis of the large vessels was not identified. We started the patient on argatroban therapy, followed by anticoagulation with heparin, high-dose methylprednisolone, and intravenous immunoglobulin. However, massive bleedings in the gastrointestinal tract and right iliopsoas muscle developed, which prevented further use of anticoagulants. Because serum complement levels of C3c, C4, and CH50 were decreased to 29, 19 mg/dL, and 14.3 U/mL, respectively, we started the patient on eculizumab for the potential complement activation but no beneficial effect was obtained. The patient ultimately died 18 days after admission to our hospital.

Autopsy revealed acute to subacute liver infarction with scattered white changes surrounded by hemorrhagic areas (Figure 1D). Both iliopsoas muscles and the right quadriceps femoris were extensively necrotic with massive hemorrhage. Histological examination revealed multiple small arterial thrombosis, degeneration, and necrosis of the myocytes and hepatocytes (Figure 1E, 1F).

The extensive hemorrhagic necrosis of the mucosa that involved the whole intestinal tract was thought to be the consequence of thrombosis of involved arterioles (Figure 1G, arrow head). Microscopic findings were consistent with the features of a thrombotic microangiopathy (TMA). Myoglobin deposition was observed in the renal tubules (Figure 1H). Immunofluorescence revealed the deposition of C3 in the glomeruli (Figure 1I). The anti-PF4 antibody measured by ELISA was negative. Finally, we diagnosed the patient with vaccine-induced TMA with rhabdomyolysis as an initial symptom.

Discussion

We described a patient with extensive rhabdomyolysis associated with TMA after mRNA-1273 vaccination. Multiple microvascular arterial thrombosis, muscle necrosis, and C3 deposition in the renal glomeruli were confirmed on autopsy, suggesting immune-mediated complement activation following COVID-19 vaccination.

To date, we were unable to find any previous similar case reports of rhabdomyolysis, systemic arteriole thrombosis, and complement activation after mRNA-1273 vaccination. Abnormal complement activation can occur after COVID-19 (Yu et al., 2021). This is not only due to the potential complement regulation disorders but also direct activation of the alternative pathway of complement exposed to the SARS-CoV-2 spike proteins (Yu et al., 2020; Yu et al., 2021). Microvascular injuries associated with complement activation have been reported in patients with severe COVID-19 (Magro et al., 2020). However, there have been no reports of complement activation after the COVID-19 vaccinations. The histological findings in our case suggest the presence of vascular endothelial damage and platelet thrombosis, which was similar to microvascular injuries that can occur after COVID-19 (Magro et al., 2020). Eculizumab, a C5 inhibitor, has been shown to be effective in patients with severe COVID-19 and complement activation (Peffault de Latour et al., 2020) but was not effective in our patient.

Our case is unique in that rhabdomyolysis was present at the initial diagnosis. There have been 2 previous case reports describing rhabdomyolysis after COVID-19 vaccination (Ajmera, 2021; Faissner et al., 2021). Both patients received mRNA-1273, similar to our patient. However, they did not experience thrombotic events or thrombocytopenia. We hypothesize that the rhabdomyolysis was induced by the mRNA-1273 vaccination because our patient did not have any other trigger for rhabdomyolysis such as viral infection, medications, trauma, alcohol abuse, malignancies, or specific autoantibodies.

The lupus anticoagulant (LA) was positive at diagnosis. Catastrophic APS (CAPS), an aggressive type of APS, is diagnosed when the antiphospholipid antibody is positive and multiple thrombosis develop rapidly (Erkan et al., 2010). Our case had some of the clinical features found in CAPS but also had several different features, such as the presence of rhabdomyolysis as an initial symptom and low dRVTT titers that became negative despite the prolonged APTT. It is possible that the spike antigen of SARS-CoV-2 binds to platelets and cooperates with aPL to activate inflammatory cytokines, coagulation factors, and complement cascades (Talotta and Robertson, 2021). In our case, exposure to the SARS-CoV-2 spike antigen (mRNA-1273 vaccination) is likely to have promoted LA production.

VITT should be considered in thrombocytopenia with thrombosis after COVID-19 vaccination (Greinacher et al., 2021). Unlike VITT, the thrombosis in our case was mainly in the small arteries of the organs and not in the veins. Furthermore, we could not make a diagnosis of VITT because anti-PF4 antibodies by ELISA was negative. Because it was difficult to make a definitive diagnosis immediately, VITT also needed to be targeted for treatment until negative anti-PF4 antibody result was confirmed. As for the differential diagnoses for TMA, thrombotic thrombocytopenic purpura was ruled out because of normal red cell morphology in peripheral blood smear and normal range of ADAMTS-13 activity (67%). Because complement genetic testing was not performed in this case, we could not completely rule out the complement-mediated hemolytic uremic syndrome. However, eculizumab, a monoclonal antibody to C5, was ineffective in this patient.

In conclusion, this is a unique case of rhabdomyolysis and TMA following mRNA-1273 vaccination. It is conceivable that an immunological mechanism such as vaccine-induced complement activation syndrome may have caused the lesions.

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Disclosure of Conflicts of interest

The authors declare no conflicts of interest associated with this manuscript.

Author contribution

Y.Kamura. T.T., and K.M. wrote and edited the manuscript and performed patient care and literature review. S.A. and Y.Kouno. provided patient care. K.H. performed the pathological review. K.M. also supervised the study. All authors read and approved the final manuscript.

Informed consent

The patient's family provided consent for the publication of this case with the removal of all identifying information to remain anonymous and retain his privacy.

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