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Purpura Fulminans After Varicella Infection and Pulmonary Embolism After COVID-19 Infection in Familial Mediterranean Fever: Coincidence or Not?

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Familial Mediterranean fever (FMF) is the most common and autosomal recessive inherited autoinflammatory disease, characterized by recurrent fever and serositis attacks resolving within 1-3 days.[1] Systemic inflammation may enhance the procoagulant factors and may reduce the fibrinolytic activity and natural anticoagulants that result in a prothrombotic state.[2] Purpura fulminans (PF) and pulmonary embolism are life-threatening thrombotic complications. Purpura fulminans develops in acquired or hereditary deficiencies of anticoagulant proteins, infections, and/or idiopathically, while pulmonary embolism usually develops after deep-venous thrombosis.[3] The pandemic of the century with coronavirus disease 2019 (COVID-19) started in December 2019 and spread rapidly to the whole world.[4] The increased risk of thrombosis with COVID-19 has been reported in adults but has rarely been reported in children.[5-7] Coronavirus disease infection usually exhibits a milder disease course in autoinflammatory diseases.[8] Herein, we report a pediatric FMF patient who presented with penile necrosis and deep-vein thrombosis, leading to loss of penile tissue due to PF after varicella-zoster virus infection and pulmonary embolism after COVID-19 infection.

An 8-year-old male patient was referred to the hospital with sudden-onset bruising of penis and scrotum. Physical examination revealed a scab lesion due to varicella infection on the trunk and PF on the penis and scrotum (Figure 1). In his medical history, he was diagnosed with FMF at the age of 1 due to recurrent fever attacks with *M694V* homozygous mutation but was non-adherent with daily colchicine treatment. The patient did not have clinical findings of FMF attack. There was parental consanguinity and her sister was diagnosed with FMF, too. He had a history of chickenpox 2 weeks ago. Laboratory workup showed leukocytosis (white blood cell count 13 000/mm^3), anemia (hemoglobin 9.1 g/dL), normal platelet count (213 × 10^3/UL), decreased lymphocyte count (1100/mm^3), elevated neutrophil count (9900/mm^3), and elevated acute-phase reactants (C-reactive protein 308 mg/dL and erythrocyte sedimentation rate 94 mm/h). Urinalysis, renal, and liver function tests were all normal. Penile arterial Doppler ultrasonography revealed a decrease in blood flow in the cavernous bodies. In coagulation parameters, prothrombin time (PT) was prolonged (15.7 seconds) and D-dimer level was elevated (18.8 µg/mL), but activated partial thromboplastin time (25.6 seconds) and fibrinogen (301 mg/dL) levels were normal. Protein C (PC) (64%), protein S (PS) (34%), and anti-thrombin-3 (AT-3) activity (42%) levels were all decreased and then normalized after 6 weeks from PF. Inherited risk factors (factor V Leiden and prothrombin G20210A) for thrombosis were screened and excluded. Neither the patient nor her family had a history of thrombophilia. Anti-nuclear antibody, antiphospholipid antibodies, anti-neutrophilic cytoplasmic antibody, rheumatoid factor, and human leukocyte antigen-B51 (HLA-B51) were negative, while complement levels were normal. Fresh-frozen plasma transfusion with empirical antibiotic therapy was started. During the follow-up, swelling on the legs developed, and deep-vein thrombosis was detected in the bilateral vena saphenous

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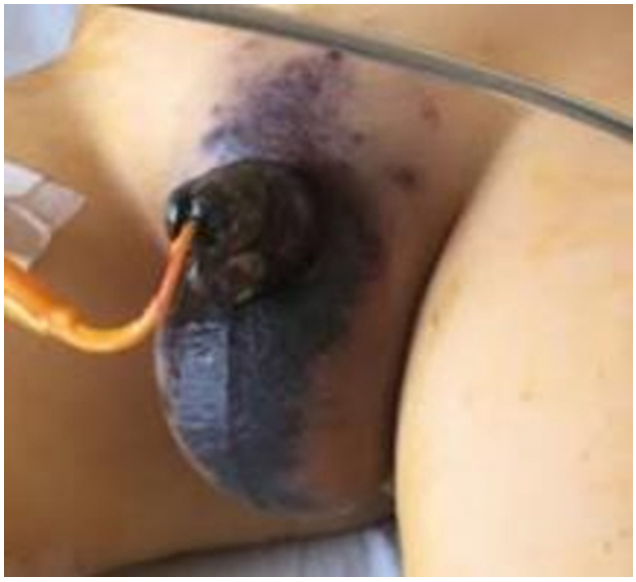

Figure 1. Image of purpura fulminans at the penis and scrotum.

magna and vena saphenous parva. Low-molecular-weight heparin was added and continued for 3 months. Hyperbaric oxygen therapy and surgical debridement were applied due to the development of necrosis in the penile tissue. Penile prosthesis was planned for the patient in the adulthood period. Anakinra, which is a blocker of the interleukin-1 receptor, was started due to persistent elevated acute-phase reactants at the second-year follow-up. At 12 years old, he was admitted to the emergency room for dyspnea and hypoxia. He had a history of COVID-19 1 week ago with a COVID-polymerase chain reaction positivity. Chest-computed tomography revealed partial filling defects consistent with thrombus in the lower lobes of both lungs. Low-molecular-weight heparin was reinitiated and the patient completely resolved after 2 months from pulmonary embolism. Informed consent was obtained from the legal guardian of the patient.

Varicella-zoster virus-related PF is an extremely rare condition with higher mortality and morbidity.[9] Early diagnosis and prompt treatment are important to prevent hemorrhagic necrosis, thrombosis, and irreversible tissue loss.[3] Varicella-zoster virus infection triggers the production of autoantibodies against PS due to molecular mimicry, and deficiency of this molecule develops.[9] Since PC and/or PS are potent anticoagulants, deficiencies result in hypercoagulability and thrombosis, leading to PF as in our patient.[3,9] In contrast to pediatric cases, thromboembolic complications usually occur in adult patients after COVID-19 infection.[7] To our knowledge, this is the first patient with FMF who developed devastating penile PF due to VZV infection and pulmonary embolism after COVID-19 infection.

Mediterranean fever *(MEFV)* gene mutation activates inflammasome and results in the enhancement of proinflammatory cytokines during inflammatory attacks in FMF patients. However, in some patients, subclinical inflammation may continue in the attack-free period. *M694V* homozygous mutation that presents in our patient is responsible for the most severe phenotype.[1,10] Systemic inflammation and cytokines cause endothelial damage that triggers coagulation. In patients with FMF, a predisposition to hypercoagulability has been reported in both attack and attack-free periods.[11] Aksu et al[12] evaluated coagulation parameters in patients with FMF under colchicine therapy on attack-free days and determined decreased PT, thrombin time, and PC activity and increased factor 1 and factor 2 levels, which indicate hypercoagulability in FMF. Demirel et al[13] reported a prolonged PT and increased tissue plasminogen activator levels in patients with FMF, especially in the attack period. However, interestingly, the coexistence of vascular thrombosis with FMF is extremely rare and is limited to anecdotal case reports related to amyloidosis and/or thrombophilia.[11,14] This can be explained by subsided inflammation during attack-free periods and regular use of colchicine therapy which decreases inflammation and prevents subsequent amyloidosis. Additionally, colchicine has a preventive effect on atherosclerosis that results in the reduction of vascular events.[15] Our patient's compliance with colchicine therapy was poor, and PC, PS, and AT-3 levels were low when PF and thrombosis developed after VZV infection.

In conclusion, FMF is an autoinflammatory disease with systemic inflammation that may lead to hypercoagulability. The possible complications of viral infections should be followed carefully in these patients. In our patient, we could not explain whether thrombotic complications during viral infections were coincidental or not. Further studies are needed to elucidate the relationship between FMF and hypercoagulability.

Informed Consent: A written informed consent obtained from the patient's parents.

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