CLINICAL VIGNETTE

Blues Toes: An Unusual Presentation After COVID-19 Vaccination

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Introduction

Antiphospholipid antibodies (APLs) are associated with the risk of antiphospholipid syndrome (APS) but they may also appear following infections or vaccinations and have been reported in patients with COVID-19. However, their association with COVID-19 vaccination is unclear. We describe a case of chilblains that developed after mRNA COVID-19 vaccine with associated triple positive APLs and discuss the potential role of APLs as a pathogenic contributor to the thrombotic events following COVID-19 vaccination.

Case Presentation

A 72-year-old male presented to rheumatology with blues toes. He had received his first Pfizer COVID vaccine 2 months prior to this visit. He initially felt well after the vaccination but several days later noticed blue toes. He was evaluated for obstructive and vascular disease and started on nitroglycerin ointment and apixaban with minimal improvement in his symptoms. His review of systems was otherwise negative. Past medical history was significant for GERD and hypertension, as well as tremor which was previously treated with beta-blocker, but not in the past few months. His family history was significant for a son with ITP.

On examination he was afebrile, normotensive with a pulse of 67, and a BMI of 28.5 kg/m2. His examination was essentially normal, except for bluish hue in the fingers and bilateral blue toes with intact peripheral pulses. The most significant finding was well-demarcated findings of gangrene at the tip of the left 5th digit without any discharge (Figure 1).

His labs included normal CBC, creatinine, Hb A1c, and chemistries. ESR and CRP were also normal. ANA was positive at 1:80 in a homogenous pattern but all sub-serologies including ds- DNA, smith, RNP, centromere and scleroderma antibodies were negative. Viral hepatitis panel, ANCA antibodies, serum protein electrophoresis and cryocrit were negative.

Additional labs included cardiolipin IGM of 21.6 CU (20 normal), beta2 glycoprotein IGM 40 SMU (20 normal) and a positive lupus anticoagulant. Complements were normal and COVID nasopharyngeal PCR was negative. He was started on oral sildenafil 50 mg three times a day for 10 days with dramatic improvement in symptoms. Apixaban was discontinued, with continued aspirin and calcium channel blocker (CCB). He subsequently received the 2nd dose of the Pfizer vaccine with recurrence of the initial symptoms but with better control with the combination of aspirin, sildenafil and CCB. His APL antibodies continued to be positive with higher titers of the anticardiolipin IGM at 80, Beta2 Glycoprotein at 144 and a positive lupus anticoagulant. He was maintained on aspirin.

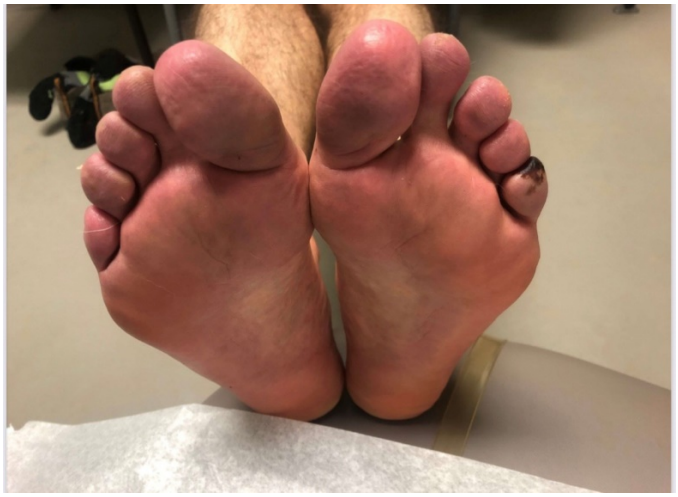

Figure 1. Bluish discoloration of all toes with gangrene of left 5th toe-picture taken at initial presentation.

Discussion

APLs and APS

APS is characterized by venous or arterial thrombosis and/or adverse pregnancy outcome in the presence of persistent laboratory evidence of APL.

APLs can be detected in 1–5 % of young healthy individuals with increasing prevalence in the elderly and those with chronic diseases.[1] A"two hit theory" has been proposed. In addition to circulating APLs, a second trigger would be necessary for the development of a full-blown APS.[2] Infections or chronic diseases, like systemic lupus erythematous or malignancies create a pro-inflammatory background, and together in the presence of the APL antibodies contribute to the activation of the coagulation cascade. The endothelium appears central player in this scenario. After an injury it becomes pro-coagulant and pro-inflammatory unmasking the coagulation cascade and activating neutrophils leading to further inflammation and

thrombus development. The variations noted in the clinical presentation of APLs positivity have been attributed to the heterogeneity of these antibodies.[3] The APLs induce thrombophilia based on this complicated pathway, which merges coagulation with immune response and is referred to as immunothrombosis.[4]

APLs and COVID-19

COVID-19 is associated with increased risk of thrombosis. APLs have been detected in the serum of COVID-19 patients but their role in causing thrombosis is unclear.[5,6]

Elevated serum levels of D-dimer, fibrinogen and prolonged prothrombin time and aPTT are common findings in COVID-19 patients with more aggressive disease.[7] COVID-19 activates many signaling pathways within immune cells resulting in cytokine release, complement and coagulation cascade activation, platelet recruitment and fibrinolysis inhibition leading to a cytokine storm that can increase risk of DIC (disseminated intravascular coagulation). NETosis is an especially important pathogenic step that contributes to COVID-19 hypercoagulability. The viral infection or even the antiviral immune response can cause endothelial cells to become more pro-thrombotic. In this scenario, APLs may play a role in the interaction between inflammation and coagulation. A few studies have reported presence of APLs in the serum of COVID-19 patients, though the association with thrombotic events remains controversial. A systematic review on occurrence of acute ischemic stroke found a high prevalence of APLs in COVID-19 patients, with lupus anticoagulant antibody being positive in 41.7 % of cases.[8]

COVID-19 Vaccines and APLs

A few studies have shown that APLs, with or without APS manifestations, may appear in the serum of vaccinated patients who received tetanus toxoid, seasonal influenza and HPV vaccines.[9,10] The main underlying mechanism is cross-reactivity between antigenic epitopes present in the vaccine formulations and self-epitopes.[11] Similar antibodies may contribute to thrombotic events following COVID-19 vaccination. Due to their nucleic acid structure, mRNA-based vaccines are highly immunogenic and might precipitate the development of APS in asymptomatic APL-positive individuals following the introduction of a markedly pro-inflammatory entity.

The immunothrombotic pathway triggered by mRNA vaccine has been hypothesized. Minimal amounts of mRNA are unwantedly released from liposomal capsules activating Toll-like receptors (TLR) in plasmacytoid dendritic cells contributing to the synthesis of type I IFN-related cytokines. These may trigger the production of APLs and exacerbate NETosis. mRNA may also promote the initiation of the coagulation cascade. Finally, liposomal formulations may interfere with the physiological interaction occurring between platelets and endothelial cells and favor the activation of the endothelial cells.[12,13]

Late coagulation disorders occurring in recipients of COVID-19 vaccines may be secondary to anti-idiotype antibodies, which usually develop 1–3 months after immunization. Anti-idiotype antibodies reacting against anti-spike antibodies might recognize epitopes within the angiotensin-converting enzyme (ACE)2 expressed on platelets. The binding of anti-idiotype antibodies to platelet ACE2 could favor platelet aggregation and activation in a comparable way to SARS-CoV-2 infection subsequently triggering the coagulation cascade.[14]

Conclusion

Thrombophilia represents an important clinical aspect of COVID-19 infection. The abnormal activation of the coagulation cascade is a serious adverse event that rarely follows COVID-19 vaccinations. Circulating APLs may be the link that connects the coagulation system and the immune response increasing the risk of thrombosis.

Further research may help identify predisposed recipients at higher risk of these rare but serious adverse events.

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