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A Splenic Infarction Related to Parainfluenza Infection in a Patient with AML: Lessons for COVID-19

Bennett E. Vogt[1], *Kamal Kant Sahu*[2], *Lindsey Shanahan*[3], *Jan Cerny*[3]

[1]University of Massachusetts Medical School, Worcester, MA, United States; [2]Division of Hematology and Medical Oncology, Department of Internal Medicine, Huntsman Cancer Institute, University of Utah Salt Lake City, Utah, United States; [3]Division of Hematology and Oncology, Department of Medicine, UMass Memorial Health Care, University of Massachusetts Medical School, Worcester, Massachusetts, United States

To the Editor,

Infection related thrombosis is a well-known entity. Antigen burden, immune response, complement activation, pro-coagulant condition, and smoking are only a few amongst the multiple risk factors which interplay in the development of thrombosis in any given case. Viral infections are amongst the many inciting factors known to predispose a prothrombotic state. We hereby report a known case of acute myelogenous leukemia, status post allogeneic stem cell transplantation who presented with two discrete episodes of sore throat and left upper quadrant pain. Infectious workup confirmed parainfluenza virus 3 on the first occasion, and rhinovirus infection on the second occasion. Computed tomography of the abdomen during both times suggested a splenic infarction. A comprehensive thrombotic workup was negative which suggested the diagnosis of viral infection-related splenic infarction. This case highlights the importance of caring for the potential eventualities of coagulopathy in cancer and other immunocompromised patients infected during the COVID-19 pandemic.

A 57-year-old female with a past medical history of acute myelogenous leukemia (AML), allogeneic hematopoietic stem cell transplantation (HSCT), mild liver chronic graft versus host disease (cGVHD), and ocular cGVHD presented for her regularly scheduled azacitidine maintenance. During the initial infusion, she developed elevated temperature and rhinorrhea. A respiratory viral panel (RVP) was sent and a few days later resulted positive for parainfluenza virus 3, an RNA virus. Two weeks later, she presented with severe left-upper-quadrant abdominal pain. An abdominal and pelvic computed tomography (CT) scan was done which showed a splenic infarction of up to 50% of the spleen (Figure 1A). Her complete blood count with differentials were normal except for mild thrombocytopenia (105 x 109/L). Her liver, kidney functions, and coagulogram were also unremarkable. A repeated RVP was negative at that time. Laboratory tests for thrombophilia mechanisms including cardiolipin, lupus anticoagulant, and JAK2 V617F mutation were all negative. No previous personal or family history of a thromboembolic phenomenon or unexplained abortion was noted. These results suggested that the parainfluenza infection potentially contributed to splenic infarction. She was started on inj. LMWH which was later transitioned to oral rivaroxaban 15 mg once daily. At follow up, the patient remained asymptomatic and oral anticoagulation was stopped after three months.

11 months later she developed another respiratory infection and tested positive for rhinovirus (once again an RNA virus). One month after that, the patient had completed her azacytidine maintenance, her AML was in remission. Three months later she received her final boosters of posttransplant immunizations. Three weeks after these immunizations she experienced again left upper quadrant pain and CT scan showing a new splenic infarction (Figure 1B). Blood work was

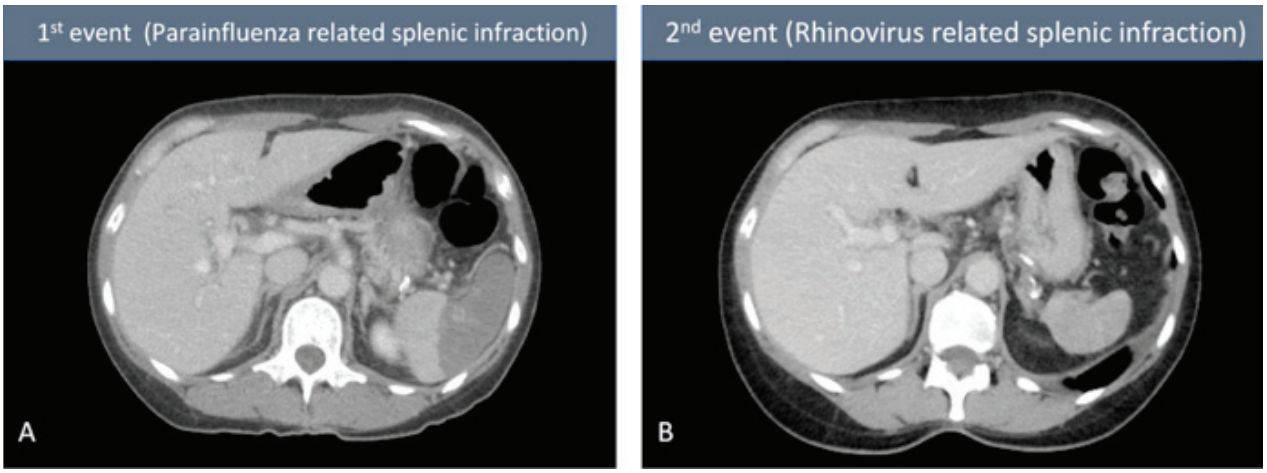

Figure 1. A) CT scan of abdomen and pelvis with contrast showing a wedge-shaped hypoattenuation of approximately 50% of the anterior aspect of the spleen suggesting splenic infarction; B) CT scan of abdomen and pelvis with contrast suggesting shrinkage of the spleen with small residual hypodensities peripherally. There is evidence of a new thrombosis of the splenic artery suggesting an evolution of new infarction.

significant for mild D-dimer elevation (1.04 mg/L FEU: normal <0.05 mg/L FEU) and fibrinogen within normal range at 348 mg/dL (150 – 400 mg/dL). However, repeat thrombotic workup was once again negative. She was treated with enoxaparin sodium at 1.5 mg/kg subcutaneously daily for three months. Due to the two incidents of splenic infarction, and given patient's history of HSCT, she was considered functionally hypo- or asplenic and thus was vaccinated for encapsulated organisms (i.e., N. meningitidis, S. pneumoniae, and H. influenzae). At follow up patient is doing well 3 years after the second event (Figure 2).

The index case is important in the context of the ongoing COVID-19 pandemic. The clinical features of the most severely affected patients by COVID-19 often display endothelial system injury, complement, and coagulation cascade, activation (1,2). Severe infections including respiratory viruses have been associated with coagulopathy (3,4). Mechanisms include direct infection of endothelial cells, effects of virus-specific antibodies, or inflammatory mediators. SARS-CoV-2 has demonstrated an ability to affect coagulation beyond its characteristic respiratory symptoms. Surveillance for thromboembolic symptoms and especially splenic infarction necessitating vaccination for encapsulated organisms might be required in cases with suspected functional hyposplenism.

Respiratory viruses are associated with increased risks of deep vein thrombosis and pulmonary embolism, with greater risk for coagulopathy in the winter months due to seasonal trends in coagulative factors (3). Most recently, SARS-CoV-2, an RNA virus like parainfluenza and rhinovirus seen in this case, has been shown to produce coagulative effects, increasing the risk of stroke beyond those observed with influenza (5,6). These effects are most likely associated with endothelial cell damage, and COVID-19 severity is associated with elevated levels of von Willebrand factor (7,8). Overactivation of the NLRP3 inflammasome has been identified as a mediator of cytokine storm during the SARS-CoV-2 infection and may further

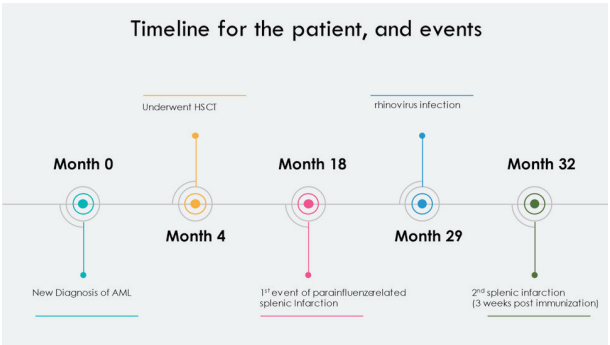

Figure 2. Timeline of the events as they progressed from the AML diagnosis till the date of last follow-up.

perpetrate endothelial cell injury (9). In addition, in our case, the thrombosis may have been exacerbated by (undocumented) count recovery from a course of azacytidine and associated changes in cytokine expression (10).

As cancer patients are at increased risk for suffering complications from SARS-CoV-2, the long-term consequences for recovery and hemostasis must be considered (11,12). Here, we have presented a case report that occurred prior to the current pandemic but indicates the importance of managing coagulative complications in cancer patients. While not all cancer patients warrant anticoagulant management for RNA viruses, in those with elevated risk factors for thromboinflammation, such as cytokine and chemokine expression changes after chemotherapy or cGVHD, preventative therapy might be considered (13,14). Immune dysregulation and impaired hemostasis can contribute to a vicious cycle of infection and coagulopathy. Patients with a history of both COVID-19 and cancer may need to be managed differently long term after we emerge from the acute phase of the pandemic.

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Correspondence:

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Dr. Jan Cerny
Deparment of Medicine,
Division of Hematology/Oncology,
UMass Memorial Medical Center, University of Massachusetts Medical School, Worcester,
MA, USA.
Electronic address: jan.cerny@umassmemorial.org.