Rapidly progressing dyspnea and retiform purpura

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HISTORY
A 71-year-old female was admitted with respiratory failure and rapidly progressive lower extremity retiform purpura (Fig 1). She was on warfarin for a mechanical aortic valve and left saphenous vein superficial thrombus and had stage 3A lung adenocarcinoma, for which she started durvalumab 3 months earlier. The patient presented with international normalized ratio >8 secondary to interaction from antibiotics taken several weeks earlier for
suspected community acquired pneumonia. Partial thromboplastin time (75 seconds), prothrombin time (33 seconds), and D-Dimer (>20 μg/mL) were elevated. Peripheral blood smear showed no hemolysis and fibrinogen was normal. COVID-19 polymerase chain reaction, blood, tissue, and bronchial cultures (bacterial, fungal, and acid-fast bacillus) were negative. Lupus anticoagulant was positive. Antinuclear antibody, antineutrophil cytoplasmic antibodies, cryoglobulins, anti-β-2 glycoprotein I, antiphospholipid, and antiphosphatidylserine antibodies were negative. Skin punch biopsy demonstrated diffuse dermal microthrombi, endothelial cell damage, and red blood cell extravasation, without perivascular inflammation (Figs 2 and 3). Echocardiogram showed no vegetation. Chest computed tomography demonstrated diffuse pneumonitis with negative workup for infection and metastases, and the patient was diagnosed with checkpoint-inhibitor pneumonitis.

**Question 1: What is the most likely diagnosis?**

A. Warfarin-induced skin necrosis  
B. Antiphospholipid syndrome (APLS)  
C. Immune checkpoint inhibitor (ICI)-induced vasculitis  
D. ICI-induced thrombotic vasculopathy  
E. Cryoglobulinemic vasculopathy  

**Answer:**  
D. Correct — With recent ICI initiation, concomitant pneumonitis, diffuse vasculopathy, and negative infectious workup, the most likely diagnosis is ICI-induced thrombotic occlusive vasculopathy. Although the mechanisms for thrombotic vasculopathy associated with ICI are not fully elucidated, a pro-inflammatory state and elevated inflammatory cytokines likely play a role. To our knowledge, this is a novel case of durvalumab-induced retiform purpura. Other causes of thrombotic occlusive vasculopathy, including disseminated intravascular coagulation, are unlikely with normal fibrinogen and no hemolysis. ICI toxicities, or immune-related adverse events (irAEs), usually affect the integumentary, gastrointestinal, endocrine, and pulmonary systems. Cardiovascular toxicities, including acute vascular events (AVEs) such as vasculopathy, are rare, but may occur months after ICI initiation. In a retrospective review of 1215 patients on ICIs, the overall AVE event rate was 2.6%. Among lung adenocarcinoma patients, this rate doubled. History of prior AVE, hypertension, and dyslipidemia were also risk factors. Median survival was worse in those who developed an AVE versus those who did not (3 months vs 14 months; P < .0001).

**Question 2: Which of the following is true regarding AVEs and other cardiovascular irAEs associated with immune checkpoint inhibitors?**

A. Venous thromboembolic events represent approximately 10% of AVEs in the setting of ICI therapy.  
B. In lung adenocarcinoma, the risk of AVE is higher in patients treated with chemotherapy compared to those treated with ICIs.  
C. Prior to initiation of ICI therapy, routine baseline electrocardiogram should be obtained.  
D. AVEs typically occur after 6 months of ICI therapy.  
E. Combination immunotherapy with 2 ICIs of different mechanisms (ie, anti-CTLA-4 plus anti-PD-1 inhibitors) reduces the risk of cardiovascular irAEs as versus treatment with a single immunotherapy agent.

**Answer:**  
A. Correct — Venous thromboembolism represents about 10% of AVEs associated with ICI therapy and may lead to pulmonary embolism, cardiac mural thrombus, arterial insufficiency, or cerebrovascular events. Vasculitis and vasculopathy are far less common AVEs in the setting of ICI treatment. Durvalumab-associated acral vasculitis has previously been reported. Cardiovascular irAEs other
than AVEs include those that primarily affect the heart, such as myocarditis, cardiomyopathy, heart failure, and heart block. Though cardiovascular irAEs are overall rare, they can quickly cause severe morbidity and mortality, often due to arrhythmia or shock. Cardiovascular irAEs have been reported with all currently approved ICIs.3

B. Incorrect – In a single-center retrospective study, the rate of AVEs was similar in lung adenocarcinoma patients treated with either chemotherapy or an ICI.4 Chemotherapy is a known risk factor for AVE in patients with lung adenocarcinoma, and ICIs appear to carry a similar risk.

C. Incorrect – There is no evidence to support that baseline or serial electrocardiograms should be obtained in asymptomatic patients undergoing ICI therapy.5

D. Incorrect – Time of onset is not a useful predictor for cardiovascular irAEs, including AVEs. AVEs may occur later than other irAEs, but often present within the first 6 months of treatment.4

E. Incorrect – Combination immunotherapy may be used to improve anti-tumor activity and survival in the treatment of certain cancers (eg, melanoma). However, patients on combination therapy also appear to be at increased risk of irAEs, including cardiovascular complications.3 Many patients are unable to tolerate combination immunotherapy.

Question 3: Which of the following is indicated in this patient?

A. Continue durvalumab and closely monitor.

B. Continue durvalumab and administer prednisone at 1 to 2 mg/kg/d.

C. Hold durvalumab and administer prednisone at 0.5 to 1 mg/kg/d. Consider resuming durvalumab when laboratory values return to the normal range.

D. Hold durvalumab and administer prednisone at 1 to 2 mg/kg/d, with a taper for at least 4 to 6 weeks. Consider infliximab if no improvement within 48 to 72 hours.

E. Permanently discontinue durvalumab and administer high-dose steroids and low-molecular-weight heparin.

Answer:

A. Incorrect – This is the management for non-cardiovascular grade 1 irAEs, which are often mild and do not require medical intervention. ICI therapy is typically held indefinitely for all grades of cardiovascular irAEs.3

B. Incorrect – Durvalumab should be discontinued in this patient.

C. Incorrect – Grade 2 irAEs may be treated with corticosteroids. In non-cardiovascular grade 2 irAEs, ICIs may be resumed if symptoms and/or laboratory values improve to grade 1.3

D. Incorrect – Grade 3 irAEs may be treated with corticosteroids and, in refractory cases, infliximab.3

E. Correct – Grade 4 irAEs are life-threatening. In nearly all grade 4 irAEs, ICIs should be permanently discontinued, except for endocrinopathies controllable with hormone replacement. American Society of Clinical Oncology clinical practice guidelines for the management of irAEs in ICI-treated patients provide specific recommendations for cardiac disease (eg, myocarditis, pericarditis, arrhythmias, and impaired ventricular function) and for venous thromboembolism, though no recommendations specifically pertain to diffuse vasculopathy. In general, cardiovascular irAEs warrant permanent ICI discontinuation due to high risk of morbidity and mortality. Due to disease severity, high-dose steroids should be given. Our patient received pulse-dose steroids and tocilizumab, which may also be considered for ICI-induced pneumonitis. Low-molecular-weight heparin is the preferred immediate and long-term anticoagulant for ICI-related AVEs due to lower bleeding risk. Warfarin is not preferred in a patient who already failed this agent. Anticoagulation should be continued for at least 9 to 12 months but may be continued indefinitely, given the hypercoagulable state caused by cancer.3

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Abbreviations used:

ANA: antinuclear antibody ANCA: antineutrophil cytoplasmic antibodies AFB: acid-fast bacillus AVE: acute vascular event CT: computed tomography EKG: electrocardiogram ICI: immune checkpoint inhibitor INR: international normalized ratio irAE: immune-related adverse event PCR: polymerase chain reaction PD-L1: programmed death-ligand 1 PTT: partial thromboplastin time VTE: venous thromboembolism
Conflicts of interest
None disclosed.

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