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Letter to the Editor

Immunotherapy-induced acute pulmonary thromboembolism: A case report

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Dear Editor,

Exact pathogenesis involved in immunotherapy-induced thrombosis is not known. A reinvigorated programmed death-1 (PD-1)-positive T-cell response occurs to anti-PD-1 therapy in the peripheral blood which peaks at 3rd week from initiation of treatment. The surge of reinvigorated T-cells soon after pembrolizumab administration can be associated with thrombosis as an immune-related adverse event (irAE).[1]

Immune checkpoint inhibitors have improved the clinical outcomes associated with numerous cancers, but high-grade, irAEs can occur, particularly with combination immunotherapy.[2]

Tsukamoto *et al*. reported a case of two patients who presented rare and severe thromboembolic events after using checkpoint inhibitors. The first case describes multiple organ embolisms at the same time, associated with other autoimmune symptoms. In the second case, distal digital necrosis occurred after initiation of immunotherapy.[3] Boutros *et al*. also reported a few cases of arterial thrombosis but no pulmonary embolism (PE).[4]

Ibrahimi *et al*. in their retrospective analysis of 152 patients who received immunotherapy had similar incidences as previously reported with other systemic therapies.[5] It is difficult to conclude whether this incidence reporting thrombosis is cancer induced or immunotherapy induced. For definitive conclusions, further studies are needed to address the issue.

Fournel *et al*. performed the blind analysis of computed tomography (CT) scans of 62 patients receiving nivolumab. Analysis was done by two radiologists to measure pulmonary artery and ascending aorta (PA/Ao) diameters at bifurcation level. They found that the pre- and post-treatment PA/Ao diameter ratios were significantly different (HR-0.82). Lung parenchyma was found to be normal. This study proved that nivolumab can induce severe pulmonary artery hypertension.[6]

Kunimasa *et al*. reported a case of adenocarcinoma lung in a 48-year-old never-smoking female with no comorbidities, who developed acute pulmonary thromboembolism 7 days from the initiation of pembrolizumab diagnosed on the basis of venous ultrasonography, D-dimer level, and CT images. The patient improved symptomatically after 7 days of initiating continuous heparin infusion. Pembrolizumab was restarted along with direct oral anticoagulant apixaban and no recurrence of thrombosis was observed.[7]

Case Report

A 64-year-old normotensive diabetic male and active smoker was diagnosed with adenocarcinoma lung T2N3M1 (para-aortic lymph nodes, bones and adrenal metastasis, as well as peritoneal deposits) in February 2016. He received six cycles of chemotherapy with paclitaxel and carboplatin till January 31, 2017. Assessment revealed partial response. He was started on maintenance chemotherapy with pemetrexed from February 24, 2017, to June 9, 2017, and after completion of six cycles, disease started to progress, for which the second-line chemotherapy with gemcitabine and cisplatin was initiated. After six cycles of gemcitabine and cisplatin, the patient had partial response. After 3 months of follow-up, disease started progressing and the patient was given two doses of vinorelbine and cisplatin, along with stereotactic body radiation therapy to lung lesion and bilateral adrenals which was not tolerated by the patient. Subsequently, he was started on maintenance

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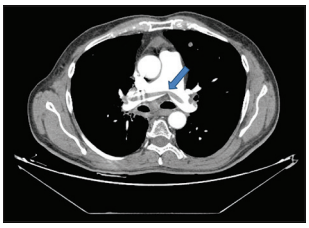

Figure 1: Computed tomography thorax done on the day of admission when patient developed breathlessness after 13 days of starting immunotherapy and scan showing a saddle thrombus in pulmonary artery

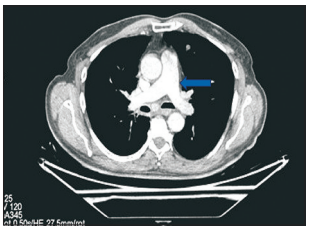

Figure 2: Imaging of thorax done before starting immunotherapy and no thrombus was seen in pulmonary artery

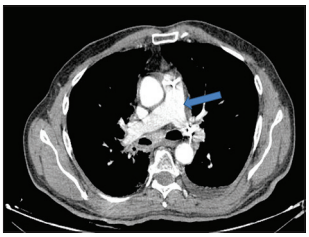

Figure 3: Computed tomography thorax done after 48 h of starting alteplase showing resolution of thrombus

with gefitinib. Positron emission tomography-CT done on November 1, 2018 showed progression in abdominal and mediastinal lymph nodes. The patient was then started on nivolumab and received the first dose on November 14, 2018. On November 26, 2018, the patient presented with grade 4 breathlessness, tachycardia, and hypotension, for which the patient was admitted. On investigations, chest X-ray revealed no abnormality. Electrocardiography showed sinus tachycardia, right ventricular strain pattern with the classic McGinn-White sign S1Q3T3. In addition, biomarkers brain natriuretic peptide and D-dimer were elevated. Furthermore, CT pulmonary angiography revealed an acute massive saddle thrombus in the pulmonary artery [Figure 1], leading to the diagnosis of acute pulmonary thromboembolism. No thrombus in the pulmonary artery was detected in contrast-enhanced CT chest done before immunotherapy [Figure 2]. Time to formation of thrombus was 13 days from start of immunotherapy. Cardiology opinion was sought. The patient was started on alteplase peripheral infusion 100 mg over 2 h as indicated in acute massive PE along with inotrope support. Enoxaparin in dose 1 mg/kg every 12 hourly subcutaneously was given for 5 days sequentially after alteplase infusion was stopped. The patient improved symptomatically with decrease in respiratory distress in addition to stabilization of vitals and no bleeding event. After 48 h, repeat CT pulmonary angiography revealed resolution of thrombus [Figure 3]. The patient was discharged on target-specific oral anticoagulant rivaroxaban 20 mg once daily. Nivolumab was restarted after 15 days and has received six doses till date. The patient is on oral anticoagulation with rivaroxaban without any recurrence of thromboembolic event.

All antineoplastic therapies including chemotherapy, radiotherapy, and immunotherapy can cause tissue damage and release of tissue factor, cancer procoagulant, platelet activation, endothelial activation, etc., leading to hypercoagulability and thrombosis. There are several different risk factors for the development of venous thromboembolism in cancer patients that are well-described in the literature.[8] PE is common whether or not immunotherapy is involved. Further, there are multiple definitions of Trousseau's syndrome because of multiple pathophysiological mechanisms that contribute to hypercoagulability associated with cancer.[9] Can this be malignancy-induced thrombosis is a debate, but to the best of our knowledge, this is the second case of acute pulmonary thromboembolism that has been reported so far. We know that thromboembolic disease is an increasingly recognized feature of several forms of systemic vasculitis. Hypothetically, a vasculitis-like event can cause such an incidence. Vasculitis causing thrombosis in a patient on immunotherapy is a theory that needs to be evaluated. Here, we report a case of a 64-year-old male, who is an active smoker with no history of thrombophilia, diagnosed with adenocarcinoma lung in 2016, postmultiple lines of chemotherapy and palliative radiation presenting with breathlessness after only 13 days of starting immunotherapy and investigations revealing acute pulmonary thromboembolism, and after thrombolysis, embolus dissolved making the patient asymptomatic. Factors to predict immunotherapy-induced pulmonary thromboembolism should be shed light on, for which further detailed studies are needed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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