Case Report

Acquired Hemophilia A After Nivolumab Therapy in a Patient With Metastatic Squamous Cell Carcinoma of the Lung Successfully Managed With Rituximab

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Clinical Practice Points

- Immunotherapy on the basis of inhibition of programmed death 1 is increasingly used for cancer treatment.
- Acquired hemophilia A (AHA) is a rare but serious condition.
- Acquired hemophilia A is associated with cancer, old age, pregnancy/postpartum period, autoimmune diseases, and certain medications.
- We report a case of AHA in a lung cancer patient during nivolumab therapy, successfully managed with recombinant porcine factor VIII and rituximab.

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Introduction

Immunotherapy is a recent therapeutic option that targets the patient's self-tolerance against tumor cells. After its successful use in metastatic melanoma, programmed death 1 (PD-1) and PD-1 ligand inhibitors have become a major therapeutic option in many tissue and hematologic malignancies. One such PD-1 inhibitor, nivolumab, is Food and Drug Administration-approved for treatment in malignant melanoma, non−small-cell lung carcinomas, head and neck squamous-cell carcinomas, gastric carcinomas, urothelial carcinomas, and solid tumors with high microsatellite instability or mismatch-repair protein deficiency.[1] Because its therapeutic effects are mediated by altering the immune system, autoimmune-related adverse effects can be seen in up to 80% of patients during treatment and after treatment completion.[2] The toxicity profile is not specific to a particular organ system. Immune-related adverse events associated with PD-1 inhibitors have been described in the skin, gastrointestinal tract, lungs, endocrine glands, liver, joints, nervous system and muscles, and rarely, hematologic.[3,4] Hematological immune-related adverse events associated with PD-1 inhibitors were recently characterized in a French observational study that reported a frequency of 0.5%.[3] Among the types of adverse events reported, neutropenia, autoimmune hemolytic anemia, and immune thrombocytopenia were the most common.[3] We report a case of nivolumab-related acquired hemophilia A (AHA). It represents 1 of 3 known cases of immunotherapy-related severe AHA, and the first reported case treated with recombinant porcine factor VIII (rpFVIII) and rituximab. AHA can be life-threatening, hence, it is important to recognize it clinically, confirm the diagnosis with appropriate laboratory tests, and properly manage this serious disorder.

Case

A 76-year-old male former smoker presented with cough and dyspnea. An initial computed tomography (CT) scan showed a large mass centered within the left hilum with invasion of the left pulmonary vein and left bronchus, complete occlusion of the left lower lobe bronchus, and partial occlusion of the left upper lobe bronchus

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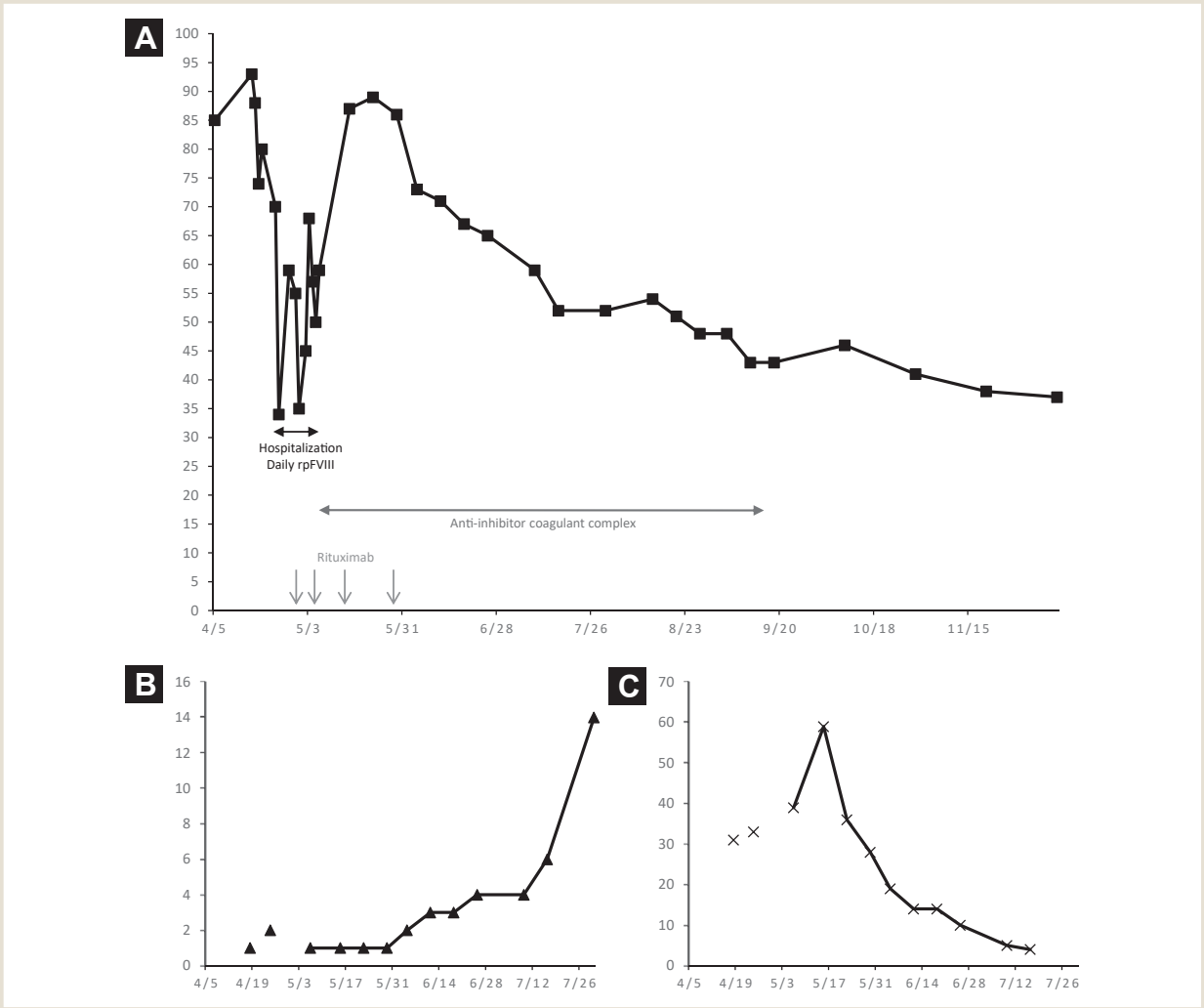
with left hilar lymph node involvement (stage IIIA T3N2bM0, according to the American Joint Committee on Cancer 2017). Biopsy of the left hilar mass revealed squamous-cell carcinoma of the lung. The patient underwent chemoradiation including paclitaxel and carboplatin with significant reduction in the mass shown on CT scans after completion of treatment. At 6-month follow-up, a CT scan showed the development of metastatic lesions in liver and lung. Because the patient had a primary tumor with a tumor proportion score for PD-1 ligand of 95%, therapy with PD-1 inhibitor was initiated. He received three 240-mg fixed doses of nivolumab every 2 weeks. A follow-up CT scan revealed treatment response with a decrease in the size of the hilar mass, and decreased number and size of lesions within the lung and liver. One week after the third dose, he was admitted to the hospital for extensive bruising on the left side of his body and hematuria. Although baseline hemostasis studies were normal at the time of cancer diagnosis, the workup during admission revealed an elevated activated partial thromboplastin time (APTT; 93 seconds [normal reference range, N: 28-38 seconds]; Figure 1A) but normal platelet count, prothrombin time/international normalized ratio, and fibrinogen. Factor VIII (FVIII) activity was <1% (N: 55%-180%; Figure 1B). A Bethesda assay was performed, which revealed the presence of an FVIII inhibitor (31 Bethesda units [BU]/mL; N: <1 BU/mL; Figure 1C). The diagnosis of AHA was made because of the absence of previous personal or familial history of hemophilia A.

The patient's management was twofold: (1) control bleeding; and (2) eliminate the inhibitor. He received rpFVIII at 100 U/kg correcting his APTT to normal and raising his initial post-treatment FVIII level to 115%. At discharge, he was managed with outpatient activated prothrombin concentrate (100 U/kg daily) until the inhibitor resolved. Of note, a prolongation of APTT and increased FVIII inhibitor levels were observed 2 weeks after hospital

Figure 1 **Key Laboratory Findings and Therapeutic Interventions of the Case. (A) Activated Partial Thromboplastin Time (APTT) in Seconds. During Hospitalization, the Patient Was Treated With Daily Recombinant Porcine Factor VIII (rpFVIII). The Patient Was Given Anti-Inhibitor Coagulant Complex in the Outpatient Setting. The Patient Received 4 Doses of Rituximab Indicated by the Arrows on the Timetable. (B) and (C) Indicate the Trend of Factor VIII (FVIII) Activity (%) and FVIII Inhibitor Levels (Bethesda Units), Respectively**



discharge. The inhibitor was eliminated by combined steroid treatment and 4 doses of weekly rituximab 375 mg/m^2.[4] Approximately 4 months after completion of rituximab treatment he had complete resolution of bruising, an undetectable FVIII inhibitor, and normal FVIII levels. The patient's follow-up includes oncology visits every month with coagulation studies and CT imaging of the chest every 3 months. Approximately 10 months after the last rituximab dose, the patient was admitted to the hospital for shortness of breath and found to have a large pleural effusion requiring drainage and lysis of adhesions, and no malignancy was detected. He was discharged after approximately 1 week. To date, there has been no progression of his malignancy.

Discussion

The antitumor properties of PD-1 inhibition are on the basis of its mediator roles between T cells and the malignant cells. When PD-1 is bound to its ligand (PD-L1) on tumor cells, this interaction results in immune resistance. Thus, PD-1 inhibition enhances T-cell responses against the tumor.[5] However, this enhancement might cause widespread T-cell activation resulting in autoimmune disease because of lack of self-tolerance.[6] PD-1 is also expressed in human B cells, and is recruited to the B-cell receptor upon triggering. Furthermore, blockade of PD-1/PD-L1 pathways increase B-cell activation.[7] It has also been shown that patients with antithyroid autoantibodies at baseline have an increase in autoantibodies after immunotherapy that might be due to an enhanced humoral response.[8] A similar mechanism might play a role in production of FVIII inhibitors after immunotherapy in addition to T cell-related mechanisms.

Immune-related adverse events usually develop within the first few weeks to months after treatment initiation. However, immune-related adverse events can present at any time including after cessation of immune checkpoint blockade therapy, and might wax and wane over time.[1] Described hematologic side effects of immunotherapy include autoimmune hemolytic anemia, pure red blood cell aplasia, immune thrombocytopenia, and AHA.[9-13]

Acquired hemophilia A is related to anti-FVIII autoantibodies. Unlike congenital FVIII deficiency, which commonly presents with hemarthroses, AHA presents with skin, mucosal or soft tissue hemorrhages. In nonhemophiliac patients, the disorder mainly affects elderly individuals with a mean age of 68 years. The disorder can be associated with autoimmune disorders (12%), malignancy (12%), pregnancy or postpartum period (8%), infections (4%), medications (3%), and other various conditions including blood component transfusions, although nearly half remain idiopathic (52%).[14] On the basis of a systematic review conducted by Napolitano et al, lung cancer (16%) is the second most common solid tumor after prostate (25%) that has been associated with the development of AHA, and treating the tumor either surgically or with chemoradiation might help with the eradication of the inhibitor. However, the causative relationship between cancer and AHA remains unknown.[15] In this patient, the immunosuppressive therapy suggests it is more immune in etiology than paraneoplastic.

Medications associated with AHA include: penicillin and its derivatives, sulfonamides, phenytoin, chloramphenicol, methyldopa, depot thioxanthene, interferon-alpha, and fludarabine.[16] Immunotherapy-related AHA has been described in 2 previous case reports: a case of melanoma treated with ipilimumab and another report of squamous-cell carcinoma of lung treated with nivolumab, similar to our case.[12,13]

The main goals of AHA management are to manage the coagulopathy and identify and eliminate the underlying etiology. The patient's AHA was severe (Grade 3-4) because of undetectable FVIII activity,[4] so nivolumab was stopped. The next step was to stop bleeding since the patient developed deep intramuscular hemorrhages requiring blood transfusions. rpFVIII was used to stop bleeding during his hospitalization. Two weeks after the hospital discharge, a prolongation of APTT and increased FVIII inhibitor levels were observed, which might be attributed to rpFVIII used during the hospitalization. High-dose steroids are usually insufficient to manage these patients; therefore rituximab was used in addition with successful elimination of the inhibitor. Data from the European Acquired Haemophilia Registry showed an increasing use of rituximab either alone or in combination with other agents as first-line immunosuppression in the setting of AHA, with a stable complete remission rate of 59% in rituximab-based regimens.[17] Because immunosuppression opposes the adverse effects caused by immunotherapy, one wonders if there would be a loss of the therapeutic effect of the immune checkpoint inhibitors. However, no clinical difference has been shown in outcomes from patients who received immunosuppression after immunotherapy than those who had not.[18]

Guidelines on the management of immune toxicities were recently published by the American Society of Clinical Oncology, which recommend permanent discontinuation of the immune checkpoint inhibitor in settings of Grade 3 to 4 AHA.[4] The relapse rate for AHA is approximately 10% to 20%,[19] however, relapse rates specific to AHA in the setting of nivolumab use have not been documented. In a recent study of 35 patients who had hematological toxicities after anti-PD-1 or anti-PD-L1 therapy, 7 were rechallenged with the drug and of those patients 3 (43%) had a recurrence of the hematological immune-related adverse event.[3] Although the cohort was small the results do indicate a risk of recurrence with rechallenge and the authors recommend that a rechallenge should be carefully considered and patients should be closely monitored.[3]

Our patient was diagnosed with AHA associated with immunotherapy, specifically the PD-1 inhibitor, nivolumab. His bleeding was managed with rpFVIII as an inpatient and activated prothrombin concentrate as an outpatient. Of note, unlike 4 other patients at our institution with AHA who received rpFVIII, this patient did not develop an inhibitor to rpFVIII. Elimination of FVIII inhibitor was achieved with the use of a combination of steroids and rituximab. At the time of this report, the patient's cancer has not progressed and he is free of any signs and symptoms of coagulopathy.

Conclusion

Tumor immunotherapy has provided novel treatments for some difficult to manage diseases, but it also opens the door to a wide spectrum of new side effects with uncharted morbidity and mortality. Our case report represents one of the very few cases of AHA associated with immunotherapy, and ours is one with complete clinical and laboratory evaluation, and follow-up. The medical

community must remain vigilant in reporting common adverse effects as well as pursuing the rare but serious side effects, such as AHA.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018; 378:158-68.
2. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer* 2016; 54: 139-48.
3. Delanoy N, Michot JM, Comont T, et al. Haematological immune-related adverse events induced by anti-PD-1 or anti-PD-L1 immunotherapy: a descriptive observational study. *Lancet Haematol* 2019; 6:e48-57.
4. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2018; 36:1714-68.
5. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; 366:2443-54.
6. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. *PLoS One* 2016; 11:e0160221.
7. Thibult ML, Mamessier E, Gertner-Dardenne J, et al. PD-1 is a novel regulator of human B-cell activation. *Int Immunol* 2013; 25:129-37.
8. Osorio JC, Ni A, Chaft JE, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non—small-cell lung cancer. *Ann Oncol* 2017; 28:583-9.
9. Algaze SD, Park W, Harrington TJ, et al. Autoimmune haemolytic anaemia in a patient with advanced lung adenocarcinoma and chronic lymphocytic leukaemia receiving nivolumab and intravenous immunoglobulin. *BMJ Case Rep* 2018; 2018, bcr-2017-221801.
10. Yuki A, Takenouchi T, Takatsuka S, et al. A case of pure red cell aplasia during nivolumab therapy for cardiac metastatic melanoma. *Melanoma Res* 2017; 27:635-7.
11. Shiuan E, Beckermann KE, Ozgun A, et al. Thrombocytopenia in patients with melanoma receiving immune checkpoint inhibitor therapy. *J Immunother Cancer* 2017; 5:8.
12. Delyon J, Mateus C, Lambert T. Hemophilia A induced by ipilimumab. *N Engl J Med* 2011; 365:1747-8.
13. Kato R, Hayashi H, Sano K, et al. Nivolumab-induced hemophilia A presenting as gastric ulcer bleeding in a patient with NSCLC. *J Thorac Oncol* 2018; 13:e239-41.
14. Knoebl P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *J Thromb Haemost* 2012; 10:622-31.
15. Napolitano M, Siragusa S, Mancuso S, et al. Acquired haemophilia in cancer: a systematic and critical literature review. *Haemophilia* 2018; 24:43-56.
16. Franchini M, Gandini G, Di Paolantonio T, et al. Acquired hemophilia A: a concise review. *Am J Hematol* 2005; 80:55-63.
17. Collins P, Baudo F, Knoebl P, et al. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *Blood* 2012; 120:47-55.
18. Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol* 2015; 33:3193-8.
19. Charlebois J, Rivard GE, St-Louis J. Management of acquired hemophilia A: review of current evidence. *Transfus Apher Sci* 2018; 57:717-20.