Acquired Hemophilia A After Neoadjuvant Immunotherapy for Renal Cell Carcinoma

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ABSTRACT

While many eligible cancer patients now receive immune checkpoint inhibitor (ICI) therapy, a significant number will develop immune-related adverse events (irAEs). Hematologic irAEs are rarely reported, in part due to their infrequent occurrence, but possibly also due to their under recognition. We report a case of acquired hemophilia A (AHA) associated with the use of combined therapy ipilimumab and nivolumab for a patient with renal cell carcinoma and discuss the clinical course and events leading to the diagnosis. AHA is an exceedingly rare yet potentially fatal hematologic irAE and presents most commonly with subcutaneous and mucosal bleeding. The mainstay of treatment for irAE-related AHA includes the use of immunosuppressive therapy to decrease the inhibitor level and risk of recurrent bleeding. This case highlights the importance of early and thorough diagnostic work-up for bleeding disorders in cancer patients with bleeding symptoms and a history of ICI treatment. IrAEs can be difficult to diagnose, and when they are not considered by the clinician, can result in prolonged work-ups without a diagnosis. Ultimately, our patient had a therapeutic response to emicizumab despite a delayed diagnosis. This case underscores the critical need for early recognition and tailored management of rare irAEs to improve patient outcomes.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have changed the cancer treatment landscape, and function therapeutically by recruiting the body's immune system to increase antitumor activity. Many eligible patients receive ICIs as a part of their cancer therapy; among those who do, a significant number develop a novel class of toxicities called immune-related adverse events (irAEs). IrAEs can occur at any time during treatment, including after discontinuation of therapy, and symptoms may oscillate thereafter.[1] There are currently no screening tests available to help risk stratify or predict severity. Furthermore, it is now understood that irAEs can impact any organ system of the body, most commonly being GI, dermatologic, hepatic, endocrine, and pulmonary toxicities.[2] Hematologic irAEs are rarely reported, in part due to their infrequent occurrence, but possibly also due to their poor recognition.[3] As such, acquired hemophilia A (AHA) resulting from ICI-related toxicity is exceedingly rare and presents differently from inherited hemophilia A. Notably, AHA can arise as a rare complication of malignancies such as lymphoproliferative disorders and gastrointestinal cancer, as well as an iatrogenic side effect of medications such as sulfonamide antibiotics. To date, six cases on AHA irAE have been described, five of which involved either nivolumab or ipilimumab.

CASE DESCRIPTION

A 70-year-old adult patient with multiple medical comorbidities presented with right-sided abdominal pain and macroscopic hematuria and subsequently diagnosed with unresectable stage III renal cell carcinoma (RCC). As first line therapy, the patient pursued palliative vascular embolization of the lower pole of the right kidney followed by neoadjuvant combination immunotherapy consisting of ipilimumab (1mg/kg) and nivolumab (3mg/kg) (ipi/nivo) every three weeks per Checkmate-214 protocol for advanced/unresectable locally-advanced RCC. After two cycles of ipi/nivo, the patient developed grade 3 nephritis, grade 1 pancreatitis, and grade 1 hypothyroidism, which have been previously reported side effects of the combination therapy.[4] This was treated with a prednisone taper over two months, leading to resolution of nephritis. At this time ipi/nivo was discontinued. They also underwent one cycle of cabozantinib but this was discontinued due to hematuria. Ultimately, the patient completed curative radical nephrectomy of the right kidney at roughly nine months after the last dose of ipi/nivo with no additional therapy following surgery.

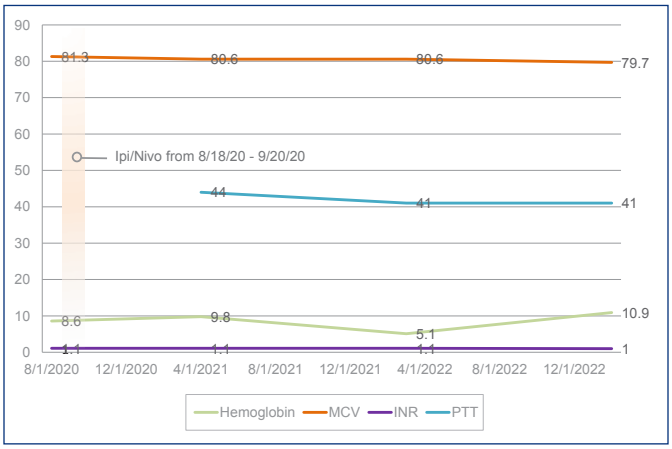
About seven months after cessation of ipi/nivo, the patient's labs were notable for an isolated prolonged activated partial thromboplastin time (aPTT) test at 44 seconds. The prolonged aPTT value was longer than one drawn a month prior to initiation of ipi/nivo (aPTT = 33 seconds). Institutional reference range for normal aPTT is 24.0 to 37.0 seconds. The prolonged aPTT persisted for over two years. As shown in **Table 1** and **Figure 1**, the patient's prior coagulation studies (prothrombin time, PT and aPTT) were both normal. Diagnostic evaluation to determine the etiology of the prolonged aPTT test occurred approximately 10 months

Table 1. Summary of laboratory results for bleeding disorder evaluation

	Reference Range	Day 0*	Day 91	Day 98	Day 111	Day 119†	Day 333
Hgb	13.5–16.0g/dl	10.9	9.1	–	8.9	9.2	7.6
Hct	37.0–47.0%	33.1	27.2	–	27.0	27.9	24.4
MCV	80.0–98.0fL	79.7	81.3	–	83.1	83.2	86.5
PT	10.0–13.0s	11.3	–	11.4	10.9	11.0	–
INR	0.8–1.2s	1.0	–	–	1.0	1.0	–
aPTT	24.0–37.0s	41.0	–	64.0	47.0	45.0	–
Factor VIII Activity	50–150%	–	37	4	–	7	–
Chromogenic Factor VIII	50–135%	–	–	–	–	–	39
Factor VIII inhibitor		–	–	negative	negative	negative	–
Factor IX Activity	60–170%	–	107	–	–	–	–
Factor XI Activity	60–160%	–	100	–	–	–	–
Factor XII Activity	50–150%	–	44	48	49	–	–
von Willebrand Antigen	50–180%	143	–	–	–	–	–
Ristocetin Factor	40–180%	162	–	–	–	–	–

* Initial hematology clinic visit for evaluation of bleeding disorder
† When a diagnosis of acquired hemophilia A was made
Hgb, hemoglobin; Hct, hematocrit; MCV, mean corpuscle volume; PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time

Figure 1. Trend for lab values prior to diagnosis of acquired hemophilia A.



later, after the patient's medical course was complicated by multiple episodes of bleeding from small intestinal arteriovenous malformations (AVMs). The first episode occurred approximately 17 months after the first infusion of ipi/nivo, when the patient was admitted to the hospital for an elective procedure. At the time, the patient's baseline hemoglobin (Hgb) ranged from 7.5–8.5 g/dL. During the hospitalization, the patient reported new melenic stool with an acute drop in Hgb. The patient was not on systemic anticoagulation therapy. The patient promptly underwent an esophagogastroduodenoscopy (EGD) procedure which revealed multiple actively bleeding AVMs in the duodenum that were stabilized with argon plasma coagulation (APC). The patient underwent EGD three more times for the stabilization of bleeding AVMs in the small bowel.

The patient eventually presented to the hematology clinic over a year after the first diagnosis of small bowel AVMs. This was approximately three years after the last dose of ipi/nivo. The patient was initially referred to a hematologist for workup of iron deficiency anemia. At the initial visit, the patient reported easy bruisability. The patient denied no personal or familial bleeding history or excessive bleeding with procedures. Physical examination revealed prominent ecchymosis on the flexor surface of the right forearm.

The patient underwent screening for disorders of the intrinsic pathway of the coagulation cascade. They had decreased factor VIII (FVIII) at 4–37%, that dropped to 4% and 7% within a month [**Table 1**]. Strangely, the inhibitor to FVIII remained negative. Otherwise, they had normal serum protein electrophoresis, negative lupus anticoagulant, and negative studies for von Willebrand's disease. The patient was subsequently diagnosed with mild to moderate AHA, that was determined to be immune mediated from ipi/nivo. Despite the patient being negative for an inhibitor on lab work, there are proposed mechanisms (discussed below) for those who clinically present as having an inhibitor but the titer is negative.

For the patient's newly diagnosed mild-moderate AHA, they were offered treatment options which would include immunosuppressive therapy with glucocorticoids alone or in combination with the agents cyclophosphamide, rituximab, or IVIG in the front-line setting. In this case, the hematologist was in favor of using prednisone 1mg/kg daily (100mg) along with plans for initiating low-dose rituximab (100mg weekly for four weeks) given that previous studies showed this regimen to be efficacious.[5] Ultimately after

shared-decision making, this patient elected to hold on starting prednisone with rituximab given that their FVIII level was greater than 1%. The patient was concerned that the use of immunosuppressive therapy could potentially lead to loss of antitumor response, risking the development of recurrent or metastatic RCC.

Eventually, after review of risks and benefits, the patient elected to start on replacement therapy with emicizumab (Hemlibra) 3mg/kg every two weeks. The patient has since achieved FVIII activity levels of 65% on this medication, indicating response.

DISCUSSION

Here, we present a case of ipi/nivo-associated AHA in a patient with RCC. The formal diagnosis was made approximately two-and-a-half years after the first dose of ICI [**Figure 1**]. The first elevated aPTT was documented about eight months after the last dose of ipi/nivo. Leading up to the diagnosis of AHA, the patient experienced multiple bleeding AVMs in the small bowel requiring hospitalizations. This case urges clinicians to maintain a high suspicion of hematologic irAEs including AHA for a timely diagnosis and subsequent appropriate management.

Ipilimumab is a monoclonal antibody targeting the CTLA-4 pathway and received FDA approval in 2011 for solid tumors. Nivolumab was approved in 2014 and targets the PD-1 pathway in T-lymphocytes. Several mechanisms have been proposed to explain irAEs, including autoreactive T-cells, B-cells/autoantibodie and cytokines/chemokines.[6] Ipilimumab toxicity has been shown to be dose dependent, often arising after the third to fourth dose.[7] When ipilimumab is combined with nivolumab, the incidence of high-grade toxicities is roughly double that observed with single-agent PD-1 pathway therapy.[8] In solid tumor patients, the incidence of any-grade irAEs was found to be 66% with PD-1/PD-L1 inhibitors and 72% with CTLA-4 inhibitor monotherapy.[9] One meta-analysis that included 5923 patients from studies using single-agent ICI therapy found a hematologic irAE rate of 3.6%.[10] Hematologic irAEs also tended to be characterized as serious adverse reactions with a mortality rate of 14%. Most frequently, hematologic toxicities present as hemolytic anemia, thrombocytopenia, neutropenia, bone marrow failure, and hemophagocytic lymphohistiocytosis.[11]

AHA is a bleeding disorder where autoantibodies are formed against FVIII. Extremely rare, with an incidence of one to two cases per million per year,[12] the most common presentation are bleeding in subcutaneous tissue (80%), then muscular (45%), gastrointestinal (21%), genitourinary (9%) and retroperitoneal (9%) spaces.[13] AHA has been associated with pregnancy, autoimmune disorders such as rheumatoid arthritis, malignancy such as lymphoproliferative disorders and gastrointestinal cancer, and certain medications sulfonamide antibiotics.[14]

The first case of irAE AHA was reported in 2011 arising from ipilimumab treatment for metastatic non-small cell lung cancer (NSCLC) [**Table 2**]. Since then, ipilimumab or nivolumab monotherapy linked to AHA has been reported in the treatment of two cases of NSCLC[15,16] and two cases of melanoma[17,18] [**Table 2**]. Macroscopic hematuria and anemia resulted from ipilimumab monotherapy, while bruising, macroscopic hematuria, and anemia resulted from nivolumab monotherapy. One case linked to nivolumab presented with a bleeding gastric ulcer. Additionally, two cases of AHA were reported with pembrolizumab[18] and atezolizumab[19] monotherapy that presented as bruising and hemarthrosis. The timing from initial dose of immunotherapy to onset of bleeding disorder symptoms varied, spanning from two months to more than a year.

There are currently no published diagnostic guidelines highlighting the work-up of AHA irAE. Furthermore, there are currently no screening tests available to help risk stratify or predict severity. Therefore we rely on the diagnostic guidelines for general AHA. AHA should be suspected in patients, especially the elderly, who experience recent onset of abnormal bleeding and on lab work are found to have an isolated prolongation in aPTT with normal PT.[20] Recommended work-up includes obtaining a mixing study, FVIII level, von Willebrand factor-antigen (VWF:Ag), Willebrand factor-Ristocetin co-factor (VWF:RCo), and anti-human factor VIII inhibitor (anti-h-FVIII) level. A FVIII inhibitor is confirmed and quantified by the Bethesda assay (BA) or Nijmegen Bethesda assay (NBA).

The diagnosis of mild to moderate irAE-related AHA in our patient resulted from their history of exposure to ipi/nivo, clinical presentation of bleeding AVMs, easy bruisability, and distinct lab values. Our patient was found to have a low FVIII activity level at 4%. Of note, when the patient was evaluated by hematology, a mixing test was not performed. Kruse-Jarres et al recommend that a mixing test may not be needed if an AHA diagnosis can be confirmed by a low FVIII activity.[20] Interestingly, the anti-h-FVIII level was negative in our patient. While this is uncommon, cases can be negative in the setting of low titer inhibitor, non-specific inhibitors (such as antiphospholipids antibodies) which can interfere with the assay, or improper handling of the specimen. Furthermore, the BA and NBA may underestimate the inhibitor titer through mechanisms of a nonlinear inactivation of FVIII and residual FVIII activity.[21,22] The BA used to measure inhibitor potency assumes a log-linear relationship between inhibitor concentration and effect on residual FVIII activity to allow exact quantification. However, this mechanism is not present for the type 2 inhibitors typically seen in AHA.[22]

For our patient, a test using a different method to assess for FVIII activity level, known as the chromogenic FVIII activity assay, was utilized and returned positive with an abnormal level at 39% (institutional reference range is 50–135%).

Table 2. Summary of preceding case reports of AHA irAE

Authors	Cancer, stage	ICI	Time to irAE (months)	Case Summary
Delyon et al.	Melanoma, metastatic	Ipilimumab	2	Patient had hematuria and anemia. AHA suspected from prolonged aPTT. First treated with prednisolone therapy, then hemostatic agents: rFVIIa, NovoSeven; and tranexamic acid. Bleeding resolved within 2 weeks.
Kato et al.	NSCLC, metastatic	Nivolumab	17	Patient developed melena and anemia. Endoscopy found a bleeding gastric ulcer. A prolonged aPTT led to diagnosis of AHA. They were treated was treated with prednisone, cyclophosphamide, and rFVIIa.
Gokozan et al.	NSCLC, metastatic	Nivolumab	1	Patient hospitalized for bruising and hematuria, labs with prolonged aPTT. First given FVIII, then activated prothrombin concentrate. Lab evidence of AHA resolved after steroids and weekly rituximab.
Gidaro et al.	Melanoma, metastatic	Nivolumab	Not reported	Patient developed hematuria and anemia with a prolonged aPTT and they were diagnosis with AHA. They received multiple doses of prednisone and rFVIIa, but bleeding persisted, leading to the use of rituximab plus prednisone with eventual resolution.
Gidaro et al.	Melanoma, metastatic	Pembro-lizumab	3.5	Patient reported easy bruising and asthenia at which time he was referred to a hemophilia center and AHA was diagnosed. They were successfully treated with rFVIIa, prednisone, and later with rituximab.
Fletcher et al.	Small cell lung cancer, extensive stage	Atezo-lizumab	16	Presented with asymptomatic anemia. First managed with blood transfusion, correction of factor deficiency, and suppression of factor inhibition, but rehospitalized with spontaneous hematomas. Bleeding resolved following the use of rituximab, prednisone, and rFVIIa.

AHA, acquired hemophilia A; irAE, immune related adverse event; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; rFVIIa, recombinant activated Factor VII; aPTT, activated partial thromboplastin time

Chromogenic FVIII differs from the assay for standard FVIII activity in that chromogenic FVIII is less likely to be affected by interference from heparin or direct thrombin inhibitors.[23]

Current guidelines recommend acute bleeding control and immunosuppressive therapy to decrease the inhibitor and reduce the risk of recurrent bleeding. A retrospective study showed that an upfront combination of cyclophosphamide, dexamethasone, and rituximab (CyDRi) for AHA resulted in overall higher rates of complete remission in addition to more tolerable side effects compared to prolonged steroid therapy.

IrAEs can be difficult to diagnose—and when they are not considered by the clinician—can result in prolonged work-ups without a diagnosis. This has the potential for unintended but detrimental consequences for the patient, such as multiple hospitalizations or emotional distress for patients. As demonstrated by our case, the diagnosis of AHA irAE, is possible through multidisciplinary collaboration. In a cancer patient who presents with recurrent bleeding episodes and persistently abnormal APTT who has a history of undergoing ICI treatment, our key takeaway is to maintain a high suspicion of AHA irAE.

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Disclosures

Ethical Approvals: Our institution does not require ethical approval for reporting individual cases.

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