

Acquired Hemophilia A Secondary to an Immune Checkpoint Inhibitor: A Case Report



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ABSTRACT

We report a case of a patient with extensive-stage SCLC who developed acquired hemophilia A during maintenance atezolizumab therapy. The patient initially presented with asymptomatic anemia, a prolonged acquired prothrombin time, and factor VIII (FVIII) deficiency. Acquired FVIII autoantibodies were detected, confirming the diagnosis of acquired hemophilia. Atezolizumab was ceased and high-dose prednisolone was initiated. He subsequently developed an extensive spontaneous upper limb subcutaneous hematoma and shoulder hemarthrosis despite improving FVIII inhibitor titers on prednisolone. His acute bleeding was successfully treated with recombinant factor VII, and rituximab was added to prednisolone. Given the quiescent malignancy, 16 months of preceding treatment with atezolizumab, and improvement with immunosuppression, a diagnosis of immune checkpoint inhibitor-induced hemophilia A was made. Severe hematologic immune-related adverse events such as this case of acquired hemophilia have rarely been reported in the literature.

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Introduction

Atezolizumab, an anti-programmed death-ligand 1 antibody, is an immune checkpoint inhibitor (ICI) approved for use in extensive-stage SCLC (ES-SCLC) in conjunction with platinum and etoposide chemotherapy. Whereas ICIs are generally well tolerated, patients may

experience a range of immune-related adverse events (irAEs). Severe hematologic irAE are rare and remain poorly described.¹

Acquired hemophilia A (AHA) develops as the result of acquired factor VIII (FVIII) autoantibodies.² It generally presents with spontaneous and potentially life-threatening bleeding in adults with no history of bleeding disorders, and the cause may be cryptogenic in up to half of cases. In the remainder, it has been associated with concomitant autoimmune or inflammatory diseases, underlying malignancies, hepatitis, diabetes, and other causes. There have been four previous reports in the context of ICI (see [Table 1](#)).³⁻⁵

Case Presentation

A 56-year-old man was diagnosed with ES-SCLC with a 40 mm by 63 mm primary tumor in the left upper lobe and extensive-stage disease involving mediastinal lymph nodes, sternum, and the left pectoral muscle (stage T3N1M1b). His medical history included hypertension, obesity, peripheral vascular disease, and cirrhosis with portal hypertension secondary to a history of eradicated hepatitis C, alcohol, and nonalcoholic fatty liver disease.

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Table 1. Summary of Reports of ICI Induced Hemophilia A and Their Management

Author, Year	Characteristics	ICI and Time Since Initiation	Presentation	Coagulation Studies	Disease Status and Follow-Up	Treatment	Response
Delyon 2011 ³	44M Metastatic melanoma	Ipilimumab 2 mo	Macroscopic hematuria Hemorrhagic bladder metastases	APTT 102 s FVIII < 1% FVIIIi 26 BU/mL	NR Died 2 mo later	Acute bleeding: rFVIIa 7 mg QID, activated prothrombin complex Inhibitor suppression: prednisone	Treatment response. Bleeding controlled, but recurrent.
Kato 2018 ⁵	68M Metastatic lung squamous cell carcinoma	Nivolumab 17 mo	Melena Gastric ulcer secondary to NSAID Hemorrhagic shock	APTT 71s FVIII 3% FVIIIi 15 BU/mL	Continued disease response	Acute bleeding: rFVIIa Inhibitor suppression: prednisone 1 mg/kg, cyclophosphamide 15 mg/kg	Hemorrhage despite initial FVIII response to prednisone. Controlled with rFVIIa and immunosuppression.
Gozokan 2019 ⁴	76M Metastatic lung squamous cell carcinoma	Nivolumab 6 wk	Extensive bruising and hematuria	APTT 93s FVIII <1% FVIIIi 31 BU/mL	Disease response maintained further 10 mo until censor	Acute bleeding: rpFVIII 100 U/kg, then activated prothrombin concentrate (1000 U/kg daily) until FVIIIi resolved Inhibitor suppression: steroids, four doses of weekly rituximab 375 mg/m ²	Clinical response, however persistent FVIIIi and prolonged APTT persisted for two weeks after discharge. Resolution of bruising, undetectable FVIIIi, and normal FVIII after 4 mo.
Kramer 2021 ⁵	71M NR	Pembrolizumab 128 wk	NR	NR	NR	Acute bleeding: rFVIIa, FEIBA Inhibitor suppression: corticosteroids, rituximab	Resolved after 29 d. Pembrolizumab was continued. Further details not reported.
Present case	57M Metastatic lung squamous cell carcinoma	Atezolizumab 16 mo	Asymptomatic anemia Extensive bruising and hemarthrosis	APTT 78 s FVIII 4% FVIIIi 14.6 BU/mL	Continued disease response for further 3 mo until censor	Acute bleeding: rFVIIa 42 mg Inhibitor suppression: prednisolone 100 mg, four doses of weekly rituximab 100 mg	Progressive haematoma and haemarthrosis despite initial factor response. Clinical improvement after rFVIIa. Weaned to prednisone 10 mg. No further bleeding events. Not rechallenged.

APTT, activated prothrombin time; BU, Bethesda Units; FEIBA, factor eight bypassing agent; FVIII, factor VIII; FVIIIi, factor VIII inhibitor; ICI, immune checkpoint inhibitor; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; QID, four times daily; rpFVIII, recombinant porcine factor VIII; rVIIa, recombinant activated factor VII.

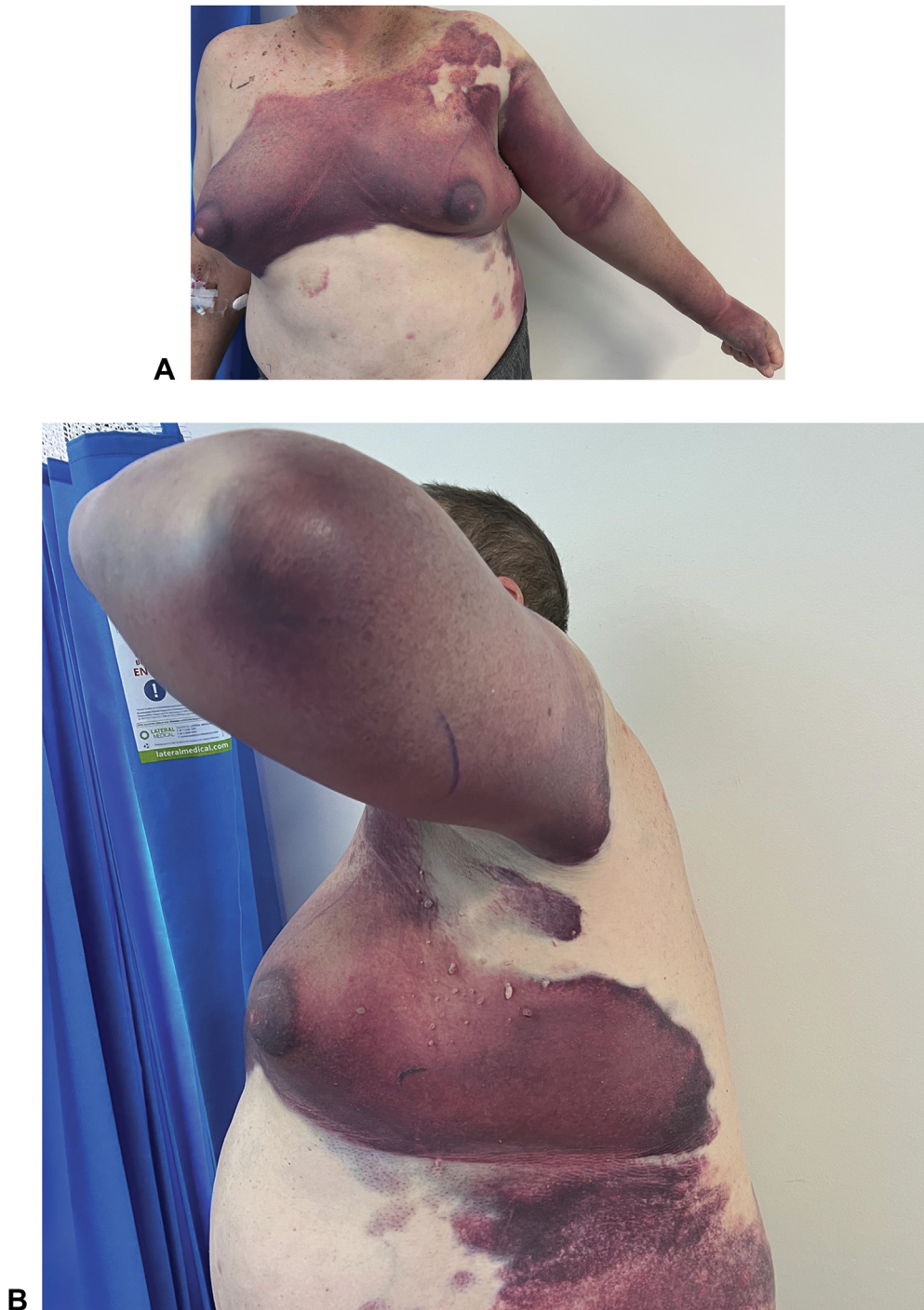


Figure 1. Clinical photographs taken on day five of admission from (A) anterior, and (B) lateral aspects. The patient had been treated with prednisolone 100 mg and was clinically responding to therapy. Incidental note is made of gynecomastia as a stigmata of chronic liver disease.

He was an active smoker with a 40-pack-year history. There was no personal or family history of hematologic disorders.

The patient completed four cycles of palliative systemic therapy with carboplatin, etoposide, and atezolizumab, and achieved a substantial partial

response on follow-up computed tomography (CT) scan.

After 16 months of therapy with atezolizumab and continued disease control, the patient presented with asymptomatic normocytic anemia (hemoglobin [Hb] = 67 g/liter, reference range: 135–180 g/liter). He was

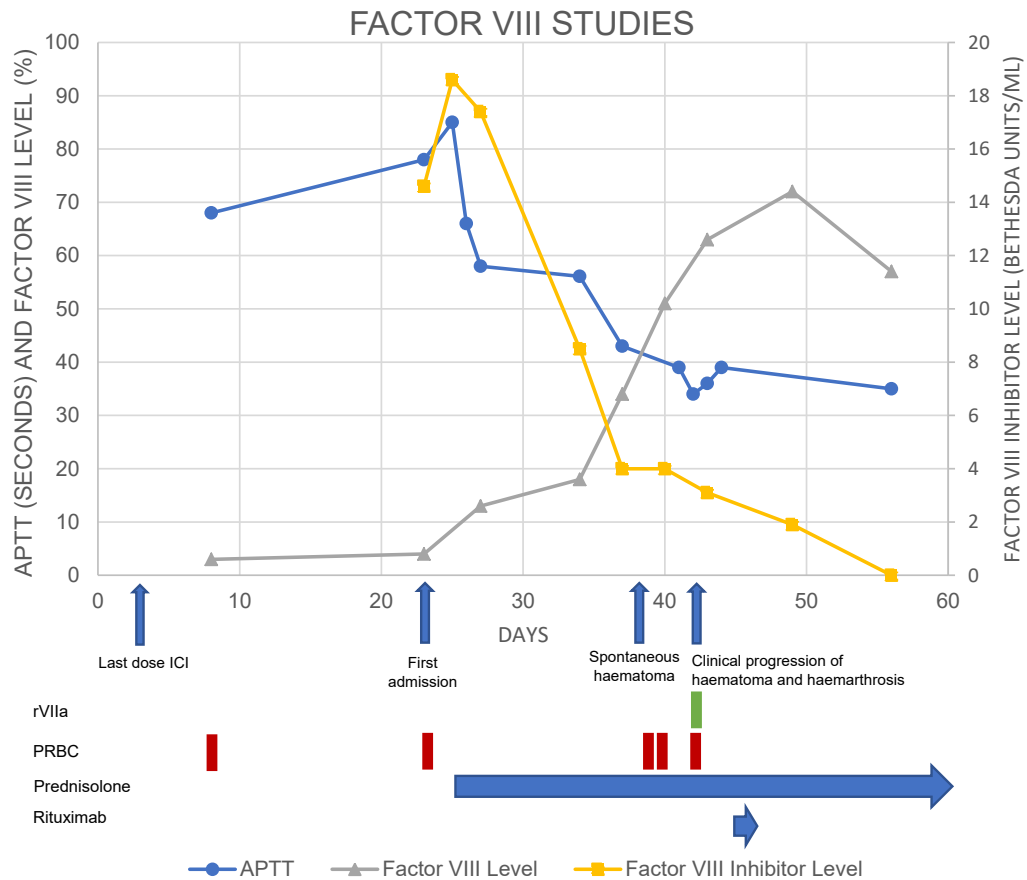


Figure 2. A timeline of key clinical developments, laboratory findings, and interventions. Presented as days after initial presentation with asymptomatic anemia. APTT, activated partial thromboplastin time; ICI, immune checkpoint inhibitor; rVIIa, activated recombinant factor VII; PRBC, packed red blood cell.

referred for outpatient hematologic investigation and a blood transfusion.

After 1 week, investigations revealed recurrent anemia (Hb = 67 g/liter) and evidence of an acquired FVIII inhibitor (FVIIIi). Clinical examination revealed no evidence of bleeding, bruising, decompensated liver disease, or cancer progression. The platelet count, thrombin time, and fibrinogen studies were normal. There was no evidence of decompensated liver function, hemolysis, or rise in urea levels. Activated partial thromboplastin time (APTT) was elevated (68 s, reference range: 25–38 s), which was only partially corrected with mixing studies (40 s, reference range: 25–38 s). FVIII activity was reduced (3%, reference range: 50%–150%), and acquired FVIIIi activity was detected (14.6 Bethesda units per milliliter [BU/mL]), establishing a diagnosis of AHA. CT revealed stable disease and no hemorrhage.

The differential diagnosis of the cause of acquired hemophilia was: (1) irAE, (2) paraneoplastic phenomenon, (3) cirrhosis, or (4) cryptogenic. There were no clinical or laboratory findings to suggest concurrent hematologic, immunologic, or infectious diagnoses, nor

contributing medications that have previously been associated with AHA. Paraneoplastic acquired hemophilia, although possible, was considered less likely in view of greater than 12 months of disease control and continued disease response on restaging imaging. An irAE was considered most likely because of ongoing ICI before presentation.

The initial management was blood transfusion, followed by correction of factor deficiency and suppression of factor inhibition. Atezolizumab was discontinued. The patient represented to the hospital after 1 week with a spontaneous and progressive left upper limb and chest wall hematoma (Fig. 1), despite initially responding to prednisolone 100 mg (FVIII 13%, APTT 58) (Fig. 2). He was managed with transfusion support and continued prednisolone with ongoing factor response and falling inhibitor titers (FVIII = 51%, FVIIIi = 4 BU/mL, APTT = 36). However, the hematoma clinically progressed, and imaging revealed a new left shoulder hemarthrosis. Impaired factor function was addressed with three doses (42 mg total) of activated recombinant factor VII (rFVIIa) over 6 hours, and rituximab 100 mg weekly was

commenced. There were no further bleeding sequelae and the patient was discharged home.

Over the next 4 weeks, prednisolone was weaned to 15 mg and four total doses of rituximab were administered. Factor levels recovered to the reference range (57%) and the inhibitor was suppressed (1.4 BU/mL). After 3 months of the initial presentation, there had been no further bleeding sequelae, and positron emission tomography with CT confirmed a complete metabolic response.

Discussion

Here, we present an interesting case of AHA manifesting with spontaneous subcutaneous hemorrhage and hemarthrosis in the context of ICI for SCLC. Acute bleeding complications were managed with rFVIIa, and inhibitor suppression with prednisolone and rituximab was successful.

There have been four previous reports of ICI-induced AHA (Table 1).^{1,3-5} The onset ranged from 6 to 128 weeks after initiating ICI, in keeping with delayed-onset severe irAE.¹ In each case, acute bleeding complications were addressed with hemostatic factor support, and immunosuppression was initiated. Similar to our case, escalation of immunosuppression to include cyclophosphamide,⁴ or more recently rituximab,⁵ was clinically effective and in keeping with published guidelines.² Despite clinical improvements, prolonged APTT, and elevated FVIIIi persisted for some months in our case, and in two previous cases.^{4,5} A case of pembrolizumab-associated AHA was successfully managed with corticosteroids, rituximab, rFVIIa, and FVIII bypassing agent.¹ Pembrolizumab was continued in this case; however, further clinical and laboratory details were not available. There are no other further reports of outcomes regarding rechallenging ICI in the context of ICI-induced AHA.

A strength of this report was the consideration of a paraneoplastic cause, as AHA has been reported in association with ES-SCLC.^{6,7} One recent case documented successful eradication of FVIIIi with corticosteroids before initiation of chemotherapy and atezolizumab, which resulted in more than 12 months of disease control without recurrence of the FVIIIi.⁷ Two of the previous case reports have addressed this differential diagnosis and, similar to our present case, thought this was unlikely owing to disease response on imaging.^{4,5} The duration of continued ICI also lends weight to this conclusion.⁴ However, differentiating the cause can be fraught with uncertainty. In a separate case of AHA presenting as melena in the context of ES-SCLC with stable disease on atezolizumab, authors considered the diagnosis of paraneoplastic AHA to be

more likely as the prolonged APTT was refractory to corticosteroids and cessation of ICI.⁸ In contrast with the present case, the patient did not receive additional immunosuppressive therapy, and they were subsequently rechallenged with ICI.⁸ It is difficult to draw further comparisons as data regarding their bleeding history, APTT, FVIII activity, and FVIIIi activity over time were not reported, nor whether reintroduction of ICI at a later date affected these. Nevertheless, the increased incidence of AHA with SCLC as compared with other malignancies, and the shorter period of follow-up remains a limitation in our case. Paraneoplastic processes may predate cancer diagnoses and herald further disease progression, though this has not been reported with AHA.

Though rare, physicians using ICI should be aware of this diagnostic possibility in clinical scenarios of unexplained considerable bleeding. This case also highlights that we cannot be complacent with ICI use, as severe late irAEs (>12 mo) do occur.

Conclusions

Clinicians should be alert to the possibility of severe immune-related hematologic toxicity secondary to ICIs. The management of immune-mediated AHA was in keeping with published guidelines, and to date, all reported cases have revealed improvement with factor support and immunosuppression. Further data are required to determine longer-term outcomes of this rare complication.

CRedit Authorship Contribution Statement

James Fletcher: Conceptualization, Investigation, Data curation, Writing – original draft, Visualization, Project administration.

Robert Bird: Conceptualization, Writing – review and editing, Supervision.

Andrew JW McLean: Investigation, Data curation, Writing – review and editing.

Kenneth O'Byrne: Writing – review and editing, Supervision, Funding acquisition.

Wen Xu: Conceptualization, Writing – review and editing, Supervision.

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