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Case Report

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Asymptomatic COVID-19-Associated Acquired Hemophilia A and Disseminated Intravascular Coagulation From a Bypassing Agent

Abraham Attah[a], Deanna Huffman[b], Palash Asawa[a], Vinay Edlukudige Keshava[c], Deep Shah[c, d]

Abstract

Acquired hemophilia A (AHA) is a clotting disorder characterized by the presence of neutralizing antibodies that inhibit factor VIII, resulting in increased bleeding risk. Known etiologies include malignancy, autoimmune conditions, graft-vs-host disease, and more recently coronavirus disease 2019 (COVID-19) infection. In this case report, we describe an 86-year-old female who was found to have AHA incidentally during preoperative workup for meningioma resection. She was subsequently found to have COVID-19 infection which was the likely cause of her development of AHA. She was treated with factor eight inhibitor bypassing agent (FEIBA) and recombinant factor VII (rVII) for a small hematoma on her right arm along with prednisone and cyclophosphamide. She then developed disseminated intravascular coagulation (DIC) initially secondary to FEIBA and subsequently rFVII. DIC resolved after these factor concentrates were withheld. The aim of this case report was to emphasize the importance of monitoring partial thromboplastin time (PTT) in patients with COVID-19 and proceeding with AHA workup if indicated. It is also imperative to know and understand the potentially life-threatening, albeit rare, adverse effects of DIC associated with the administration of factor concentrates, especially in the elderly population and withholding these factor concentrates once DIC is suspected.

Keywords: Hemophilia; COVID-19; Factor VIII inhibitor; Bypassing agent; Disseminated intravascular coagulation

Introduction

Acquired hemophilia A (AHA) is a clotting disorder characterized by the presence of neutralizing antibodies that inhibit factor VIII (FVIII), resulting in alteration in the coagulation cascade and ultimately increased risk for bleeding [1]. This is an extremely rare bleeding disorder with a yearly incidence of approximately 1 per million population [2, 3]. Roughly 50% of cases are sporadic and the other 50% are associated with autoimmune conditions, malignancy, viral infection, pregnancy and puerperium, and graft-vs-host disease (GVHD) following hematopoietic stem cell transplantation [3]. Most recently, cases of coronavirus disease 2019 (COVID-19) associated AHA have been reported [4-6]. The clinical presentation is vastly varied ranging from asymptomatic or mild mucocutaneous bleed to moderate to severe bleeding involving deeper tissues [3].

In this case report, we present AHA as an immune-hematologic complication of COVID-19 infection. We also highlight the rare complication of disseminated intravascular coagulation (DIC) from administration of coagulation factor concentrates.

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[a]Allegheny Health Network, Internal Medicine Department, Pittsburgh, PA 15212, USA
[b]Louisiana State University Health Sciences Center New Orleans, New Orleans, LA 70112, USA
[c]Division of Hematology/Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA 15212, USA
[d]Corresponding Author: Deep Shah, Division of Hematology and Cellular Therapy, Allegheny Health Network Cancer Institute, Pittsburgh, PA 15224, USA. Email: deep.shah@ahn.org

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Case Report

Investigations

An 86-year-old female presented to an outside hospital after sustaining a mechanical fall. Her past medical history was significant for a "triple negative" (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER-2)/neu receptor negative) invasive ductal carcinoma of the right breast status post lumpectomy and chemoradiation, with oligo-metastasis to the right lung status post lobectomy, which was completed in 2014, currently in remission and on active surveillance; hypertension, hypothyroidism, and chronic obstructive pulmonary disease.

Diagnosis

Upon arrival, the patient underwent a trauma workup which included a computed tomography (CT) scan of the head revealing a right middle cranial fossa mass measuring 42 × 50 × 44 mm. This was better characterized as a meningioma on a subsequent magnetic resonance imaging (MRI) of the brain. Given the size of mass and her recent history of a mechanical

fall, a surgical resection of the meningioma was planned. Preoperative workup revealed an elevated partial thromboplastin time (PTT) at 44.4 s (normal: 22 - 33.8 s). A prothrombin time (PT) was normal at 13.1 s (normal: 11 - 13.5 s), with an international normalized ratio (INR) of 1 (normal < 1.2). The complete blood count and a comprehensive metabolic panel were unremarkable. PTT mixing study was done and an incomplete correction was noted immediately after mixing. A FVIII activity was obtained which was low at 9% (normal: 50-150%). A FVIII inhibitor level was obtained and came back elevated at 3.5 Bethesda unit (BU) (normal: < 0.5 BU). Factors II, V, VII, IX, and XI were within normal limits. The patient was subsequently transferred to our facility for further neurosurgery and hematology evaluation. At the time of presentation, she denied any personal history of mucocutaneous bleeding. She denied any known family history of bleeding disorder as well. She reported a personal history of abnormal vaginal bleeding from a known leiomyoma that was re-demonstrated on a CT of the chest, abdomen, and pelvis. The scan was otherwise negative for lymphadenopathy or findings suggestive of malignancy. Further workup done at our facility included a dilute Russel viper venom time (DRVVT) which was negative for the presence of a lupus anticoagulant. Repeat FVIII activity was 7% with FVIII inhibitor level at 0.8 BU. Serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP) and serum immunofixation (sIFE) did not reveal any evidence of monoclonal gammopathy.

Treatment

Subsequently, the patient had a deep tissue hematoma in the right upper extremity, about 5 cm in its largest diameter, without any clinical evidence of compartment syndrome. She was started on 1 mg/kg of prednisone and 50 mg cyclophosphamide daily for immunosuppression. Her height and weight were 165.1 cm and 74 kg, respectively. We chose the relatively lower, 50-mg dose of cyclophosphamide, for anticipated tolerance and due to her underlying diagnosis of COVID-19, to balance the immunosuppression risks versus the benefits. She was also started on FVIII inhibitor bypassing agent (FEIBA), 50 IU/kg every 6 h to facilitate hemostasis in the setting of hematoma. Within 48 h of receiving FEIBA, the patient was diagnosed with DIC with a peak INR at > 16.8, peak PTT > 223 s, a platelet count range of 143 to 278 cells/µL (normal: 150 - 450 cells/µL), a fibrinogen < 60 mg/dL (normal: 200 - 400 mg/dL) and an elevated fibrinogen degradation product (FDP) concentration > 160 µg/mL (normal < 10 µg/mL). DIC was thought to be secondary to FEIBA, and hence was promptly discontinued. She then received cryoprecipitate and fresh frozen plasma (FFP) with improvements in coagulation parameters within 24 h. Given that the hematoma was still present with the same size and consistency on examination, she was started on recombinant factor VII (rFVII) 90 µg/kg every 4 h. She was again diagnosed with DIC within 24 h of starting rFVII evidenced by elevated PT/INR, PTT, FDP and decreased fibrinogen levels. DIC parameters improved within 24 h of discontinuing rFVII. Other potential causes of DIC such as infection and malignancy were ruled out. Given her coagulopathy, surgical resection of the meningioma was deferred pending negative inhibitor levels and improvement in FVIII activity.

Follow-up and outcomes

Roughly 2 weeks into hospitalization, an asymptomatic COVID-19 swab was obtained in anticipation of patients transfer to a skilled nursing facility. This was resulted as positive. For this reason, cyclophosphamide was discontinued after 3 weeks of therapy while she was maintained on prednisone. She was isolated for 20 days and remained completely asymptomatic throughout this time. She had not been vaccinated against COVID-19 previously and had not been tested initially upon presentation. Within 1 week from the presentation, her hematoma resolved. Prior to discharge, which was roughly 4 weeks after initial hospitalization, FVIII activity was rechecked and found to be improved at 27%. FVIII inhibitor levels were undetectable. PTT subsequently improved to 35 s while on steroids. She was discharged to a skilled nursing facility on prednisone taper. Unfortunately, 1 month after discharge from hospital, the patient passed away from an unknown cause. Based on discussion with skilled nursing facility, cause of death was unlikely related to bleeding.

Discussion

AHA is a potentially life-threatening bleeding disorder that requires prompt diagnosis and management to prevent complications. Etiologies vary and are mostly related to autoimmune conditions like systemic lupus erythematous, rheumatoid arthritis, etc. It also has a close association with malignancy. This however represents only 50% of cases of AHA, and the other 50% of cases are thought to be sporadic [1]. AHA has been previously described in other viral illnesses including influenza virus, human immunodeficiency virus, hepatitis C virus and parvovirus B19 [2]. Most recently, there have been cases of COVID-19-related AHA. The first case described a 66-year-old male who initially presented with his first episode of AHA in 2011. He was treated with bypassing agents, prednisone, and cyclophosphamide, after which he achieved complete remission. He then presented in 2020 with COVID-19 pneumonia and was found to have recurrence of AHA at that time. He was treated with the same anti- hemorrhagic and immunosuppressive regimen in addition to lopinavir/ritonavir. He achieved complete remission in 20 days [3]. The second case describes an 83-year- old female who presented with worsening spontaneous bruising. She was diagnosed with AHA. At the time of presentation, COVID-19 polymerase chain reaction (PCR) was negative. A serologic test was subsequently done which showed a negative COVID-19 immunoglobulin M and a positive immunoglobulin G indicating prior infection. This was thought to be a case of post-COVID AHA. She was treated with a course of prednisone and rituximab with resolution of symptoms noted in weeks [4]. The third case described a 73-year-old male who presented 4 months after admission

for COVID-19 pneumonia with generalized bruising. Workup at that time was consistent with AHA. He was started on immunosuppressive with remission noted within weeks [5].

Our patient presented with AHA in the setting of subcutaneous bleeding. Although she had no symptoms of COVID-19, she was found to be positive by PCR 2 weeks from presentation. It is highly likely that the patient had asymptomatic COVID-19 at the time of presentation and following the administration of immunosuppressive with cyclophosphamide, which led to persistent infection. This would explain her positive test 2 weeks from the initial presentation. Although our patient was asymptomatic, this does not preclude the possibility of COVID-19-related AHA. Other causes of AHA including malignancy, plasma dyscrasia, autoimmune processes were ruled out.

Like AHA, other immune-hematologic disorders have been described in patients with COVID-19 infection. Lazarian et al reported seven cases of Coombs positive autoimmune hematologic anemia in COVID-19 patient [7]. Immune thrombocytopenic purpura (ITP) has also been extensively described in COVID-19 patients [2, 7, 8]. The mechanisms of these immuno-hematologic disorders are currently unclear, but it is thought that COVID-19 induces immune dysregulation, leading to the activation of autoreactive B and T lymphocytes, which ultimately results in the development of autoantibodies against platelets, red blood cells and coagulation factors [8-10]. Lastly, there has been a few case reports on development of AHA following administration of COVID-19 vaccine [11]. Perhaps this has a similar pathophysiologic process as COVID-19-associated AHA.

Regardless of etiology, the mainstay treatment remains the same. As seen in our patient, if there is any evidence of bleeding, the patient should receive hemostatic treatments with bypassing agents in addition to immunosuppressive therapy with the main aim of inhibitor eradication. In those without any evidence of bleeding, the mainstay of treatment is solely immunosuppressive therapy [1]. Another unique aspect of this case report is the development of DIC with FEIBA and rFVII. The very first case of FEIBA-induced DIC was described in 1981 in a 17-year-old patient with AHA, who presented with intracranial hemorrhage. He was started on FEIBA but developed DIC after 8 days of treatment. FEIBA was stopped and DIC subsequently resolved [12]. Following this, complications of thrombosis were described and is known to be an adverse effect of FEIBA and rFVII with a temporal association with age [13]. A retrospective study by Aledort was done in 2004 to compare thrombotic events with FEIBA and rFVII. They reported rFVII to have a slightly higher risk for thrombosis compared to FEIBA although overall risk for thrombosis with both factor concentrates were low [14]. This might explain an earlier onset of DIC in our patient following administration of rFVII in comparison with FEIBA. A possible explanation would be the temporal association of tissue factor (TF) expression with age. For this reason, older patients tend to have more TF expression on the endothelial surface of blood vessels as well as white blood cells [15]. Given that TF acts as a cofactor for FVIIa, this could potentially trigger the coagulation cascade and result in DIC [16, 17]. Our patient received FEIBA and rFVII, both of which contain FVIIa. Perhaps given her age, more interactions between TF and FVIIa led to DIC.

Learning points

AHA remains a potentially fatal bleeding disorder requiring prompt diagnosis and management. Our case report joins other emerging case reports on COVID-19-associated AHA. For this reason, we would recommend monitoring PTT in patients with COVID-19, who present with bleeding rather than thrombosis as its complication and proceeding with AHA workup if indicated. Once diagnosis is confirmed, treatment should not be delayed. In patients who develop DIC on FEIBA/rFVII, use of alternative factor concentrates such as porcine FVIII may decrease risk of DIC.

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Conflict of Interest

All authors have no conflict of interest to disclose.

Informed Consent

The consent was deemed inappropriate for this research as it was a case report without any disclosure of protected health information.

Author Contributions

Dr. Attah, Dr. Huffman and Dr. Asawa contributed to writing the manuscript. Dr. Edlukudige Keshava and Dr. Shah helped with reviewing manuscripts and making necessary edits. All authors contributed to the necessary literature search used to write this manuscript. All authors certify that they have participated sufficiently in the intellectual content, and the analysis of data. Each author has reviewed the final version of the manuscript and approves it for publication.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

1. Tiede A, Collins P, Knoebl P, Teitel J, Kessler C, Shima

M, Di Minno G, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020;105(7):1791-1801. doi pubmed pmc
2. Yousphi AS, Bakhtiar A, Cheema MA, Nasim S, Ullah W. Acquired hemophilia a: a rare but potentially fatal bleeding disorder. Cureus. 2019;11(8):e5442. doi pubmed pmc
3. Huth-Kuhne A, Baudo F, Collins P, Ingerslev J, Kessler CM, Levesque H, Castellano ME, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica. 2009;94(4):566-575. doi pubmed pmc
4. Molinaro E, Novara E, Bonometti R, Sacchi MC, Stobbione P, Lauritano EC, Boverio R. Isolated immune thrombocytopenic purpura in a young adult Covid-19 patient. Eur Rev Med Pharmacol Sci. 2020;24(20):10850-10852. doi pubmed
5. Olsen GM, Rinder HM, Tormey CA. De novo acquired hemophilia as an immune dysregulation phenomenon following SARS-CoV-2 infection. Transfusion. 2021;61(3):989-991. doi pubmed
6. Hafzah H, McGuire C, Hamad A. A case of acquired hemophilia a following SARS-CoV-2 infection. Cureus. 2021;13(7):e16579. doi pubmed pmc
7. Lazarian G, Quinquenel A, Bellal M, Siavellis J, Jacquy C, Re D, Merabet F, et al. Autoimmune haemolytic anaemia associated with COVID-19 infection. Br J Haematol. 2020;190(1):29-31. doi pubmed pmc
8. Pena-Munoz F, Parras E, Compan O, Gutierrez N, Martin C, Gonzalez-Porras JR, Bastida JM. Acquired haemophilia A in association with influenza A and urinary tract infection. Eur J Case Rep Intern Med. 2020;7(9):001678. doi pubmed pmc
9. Zulfiqar AA, Lorenzo-Villalba N, Hassler P, Andres E. Immune thrombocytopenic purpura in a patient with COVID-19. N Engl J Med. 2020;382(18):e43. doi pubmed pmc
10. Kewan T, Almhana F, Schwartzman L, Daw H, Haddad A. COVID-19 patient with immune thrombocytopenic purpura. Int J Lab Hematol. 2020;42(6):e260-e262. doi pubmed pmc
11. Radwi M, Farsi S. A case report of acquired hemophilia following COVID-19 vaccine. J Thromb Haemost. 2021;19(6):1515-1518. doi pubmed pmc
12. Fukui H, Fujimura Y, Takahashi Y, Mikami S, Yoshioka A. Laboratory evidence of DIC under FEIBA treatment of a hemophilic patient with intracranial bleeding and high titre factor VIII inhibitor. Thromb Res. 1981;22(1-2):177-184. doi pubmed
13. Mahendra A, Padiolleau-Lefevre S, Kaveri SV, Lacroix-Desmazes S. Do proteolytic antibodies complete the panoply of the autoimmune response in acquired haemophilia A? British Journal of Haematology. 2012;156(1):3-12.
14. Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity. J Thromb Haemost. 2004;2(10):1700-1708. doi pubmed
15. Rajpurkar M, Croteau SE, Boggio L, Cooper DL. Thrombotic events with recombinant activated factor VII (rFVIIa) in approved indications are rare and associated with older age, cardiovascular disease, and concomitant use of activated prothrombin complex concentrates (aPCC). J Blood Med. 2019;10:335-340. doi pubmed pmc
16. Abshire T. Safety update on recombinant factor VIIa in the treatment of congenital and acquired hemophilia. Semin Hematol. 2008;45(2 Suppl 1):S3-6. doi pubmed
17. Grover SP, Mackman N. Tissue factor: an essential mediator of hemostasis and trigger of thrombosis. Arterioscler Thromb Vasc Biol. 2018;38(4):709-725. doi pubmed