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Case Report

Newly acquired factor VIII deficiency in a male Ex-smoker – A case report

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ABSTRACT

Introduction: Acquired hemophilia A (AHA) also known as acquired factor VIII (FVIII) deficiency is an acquired inhibition of coagulation by antibodies that either inhibit the activity or increase the clearance of a clotting factor (FVIII). Mortality in patients presenting with AHA is related to bleeding and hemorrhage, therefore rapid diagnosis and effective treatment are needed.

Case presentation: We present a case of a 59-year-old male with acquired VIII deficiency presenting with diffuse ecchymosis and bleeding diathesis. The patient was treated successfully with steroids and rituximab.

Clinical discussion: It is a rare autoimmune disorder caused by neutralization of Factor VIII by IgG antibodies. This can lead to severe, life threatening bleeding. Treatment involves replacement of FVIII and immunosuppression.

Conclusion: A key point to successfully treating AHA is to remove inhibitors and stop bleeding. Mortality in patients presenting with AHA is related to the bleeding and hemorrhage, therefore rapid diagnosis and effective treatment are needed.

1. Case report

A 59-year-old male with a medical history of chronic obstructive pulmonary disease and tobacco use presented with symptoms of weakness, left hip pain and diffuse ecchymosis. Two weeks prior to admission, the patient reported a skin tear which had been bleeding persistently that was evaluated in the emergency department (ED) and he was advised to stop his home aspirin and discharged home. However, his symptoms never resolved and no etiology was identified. Records from that visit showed labs remarkable for an isolated elevated partial prothrombin time without any other abnormalities and a mild normocytic anemia of unknown chronicity. On the patient's second visit, he reported lightheadedness with palpitations and shortness of breath. He denied any melena, hematochezia, or mucosal bleeding.

Upon review, his family history was positive for prostate cancer however no bleeding disorders were identified. He reported a personal history of negative colonoscopies, no alcohol use, no illicit substance abuse, and no recent medication changes. He had a long-standing history of smoking and had quit 2 years prior to presentation. He denied any history of autoimmune disorders. Of note, he had a recent follow up with his primary care physician and a lung cancer screening computed tomography (CT) was performed that noted a new multiloculated right upper lobe 2.9 cm nodule. A follow up positron emission tomography scan performed two days prior to admission showed a standardized uptake value of 2.1 which was nonspecific in etiology. He was admitted for hematologic workup for symptomatic anemia in the presence of persistent bleeding and diffuse ecchymosis.

On admission, his vital signs were remarkable for a blood pressure of 88/50 mmHg, tachycardia with 120 beats per minute. Physical exam findings were consistent with diffuse ecchymosis and petechiae throughout his extremities as can be noted in Figs. 1–3. His labs were notable for a white count of 15,300/mm3, hemoglobin 11.4 gm/dL, MCV 91.4fL and platelet count 478,000/mm3. Reticulocyte count of 4.7%, ferritin 123 ng/mL, iron saturation 14% and TIBC 261 mcg/dL. Coagulation studies revealed a fibrinogen of 301 mg/dL, PT of 9.7 seconds, APTT of 55 seconds and repeat of 61 seconds.

Hematology was consulted and further imaging of CT abdomen and pelvis revealed enlargement of the left iliacus muscle with what appeared to be intramuscular hemorrhage, findings that were consistent with a spontaneous hematoma with some extension into the peritoneum (Fig. 4). Further workup revealed a PTT mix 1:1 41.6 (upper limit 36.5), Factor VIII antigen 38 (lower limit 64), Factor VIII activity 1%, and Factor IX activity 146% (65–150). The patient was given prothrombin complex concentrate and high dose prednisone and transferred to a university hospital for further management. There he was treated with steroids and rituximab and achieved complete remission. The patient's lung nodule was followed up and noted to be a confluence of tissue from emphysema.

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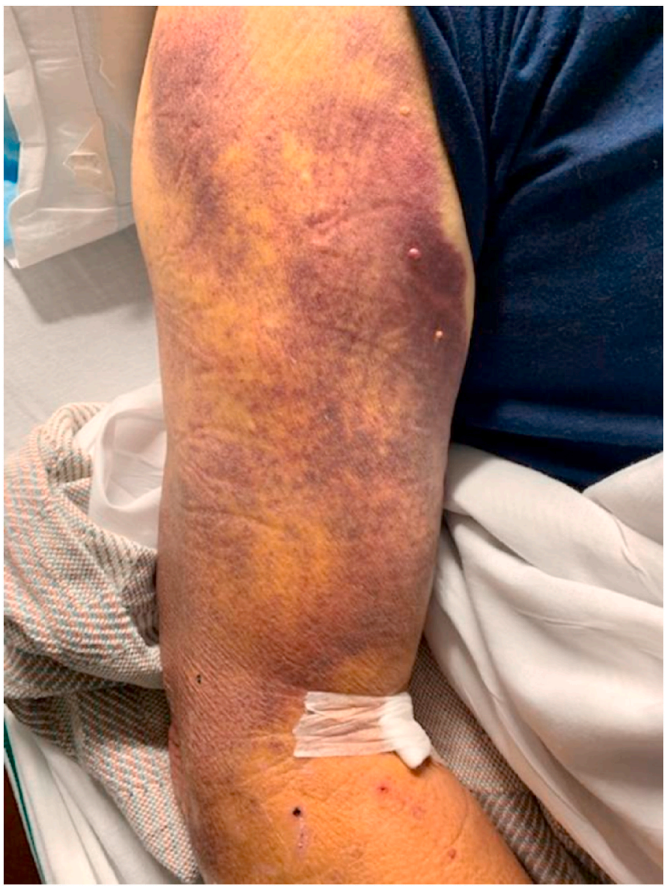

Fig. 1. Picture of patients arm after blood pressure measurement.

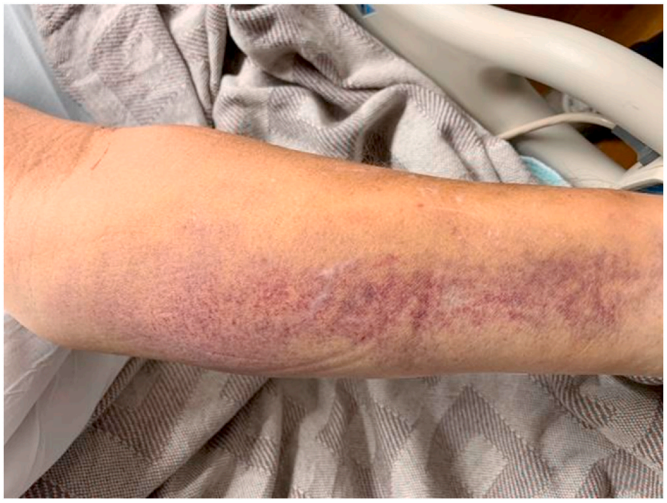

Fig. 2. Left arm with diffuse ecchymosis.

2. Discussion

Factor VIII (FVIII) is produced in the liver and is an important protein in the coagulation cascade. It is normally bound to and stabilized by von Willebrand factor in the circulation. Acquired Hemophilia A is caused by neutralization of Factor VIII by IgG antibodies (an acquired 'inhibitor'). This is a rare immune process that is most commonly idiopathic but has been associated with cases of malignancy, pregnancy, postpartum period, and rheumatologic disease. Incidence is 1.3–1.5 cases per million population per year and individuals with predisposing factors such as HLA phenotype are at higher risk. Age of presentation is bimodal and more incidence of disease arises in patients over the age of 50. Hematologic cancer and solid tumors have both been cited as the most common causal malignancies [1,2]. However, it has also been noted in gastric cancer, hepatocellular carcinoma, lung cancer, colon cancer, and prostate cancer [3–6]. Factor VIII deficiency is most commonly diagnosed concurrently with the underlying cancer although in rare cases it

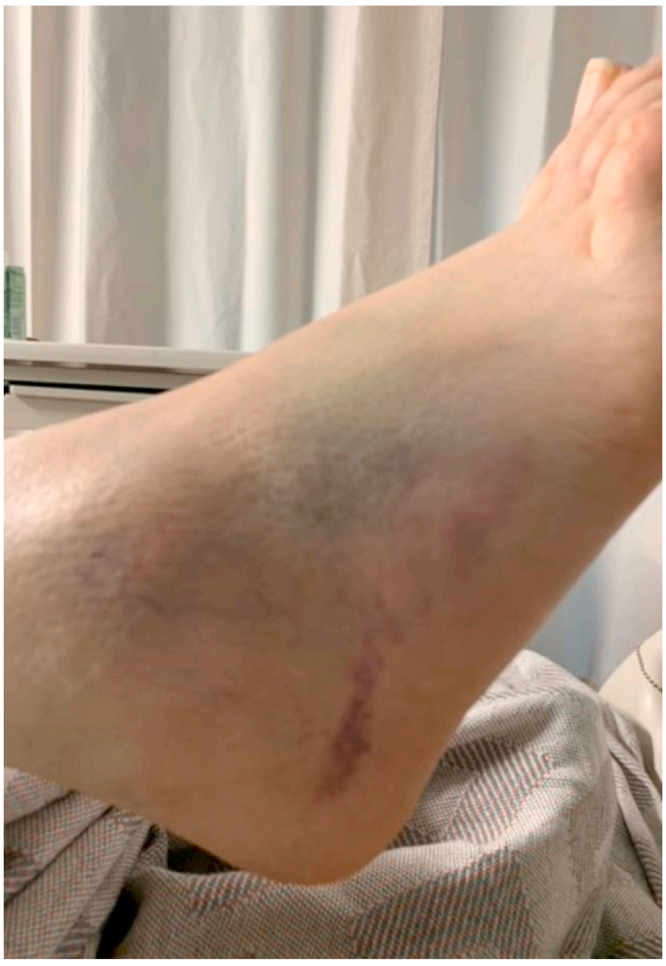

Fig. 3. Right foot with dorsal surface petechial lesions and ecchymosis.

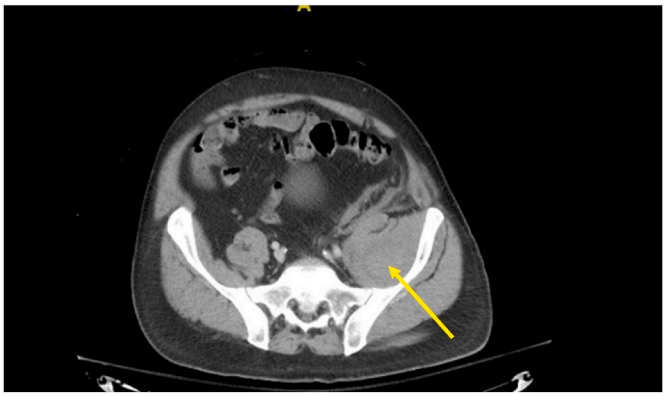

Fig. 4. Computed tomography of abdomen and pelvis revealing enlargement of the left iliacus muscle representing an intramuscular hemorrhage. Findings were noted to be consistent with a spontaneous hematoma with some extension into the peritoneum.

has been diagnosed two to seven months before or one to six months after surgical resection [1].

Hereditary hemophilia A mainly present with spontaneous hemarthrosis. In contrast, patients with acquired hemophilia A will present with bleeding diathesis and ecchymosis. The bleeding is commonly severe and could include intramuscular hemorrhage, hematuria, epistaxis, GI bleeding, and intracranial hemorrhage. Workup shows isolated elevated partial thromboplastin time (PTT) with normal prothrombin time (PT). Since heparin causes an elevated activated PTT, the first step is to rule out the recent use of heparin products. A detailed history may suffice, but retesting a second sample at a later time is also an option. A blood test that may be utilized is 'reptilase time' and 'thrombin time' since heparin prolongs thrombin time but does not affect reptilase time. Next a 'mixing' study can be utilized to differentiate factor deficiency from factor inhibitors. Addition of normal plasma to the patient's plasma in a 1:1 ratio would result in an initial shortening or PTT, and subsequent prolongation in the presence of an inhibitor. Had the PTT improved on mixing study, the likely diagnosis would be factor deficiency which can be seen in acquired von Willebrand factor deficiency. Bethesda Assay can then be used to quantify the concentration of Factor VIII inhibitors. Factors VIII activity and factor inhibitor antibodies may also be measured directly. Bleeding is a cause of mortality along with sepsis which can arise when a patient is undergoing treatment with immunosuppressive therapies.

Treatment is targeted at controlling the bleeding and eliminating the inhibitor. Controlling the bleeding depends on the severity of the bleed and utilizes a variety of regimens. Some commonly used are desmopressin (DDAVP), factor VIII concentrates, activated prothrombin complex concentrate (bypass factor VIII activity), recombinant human factor VIIa, and recombinant porcine sequence factor VIII concentrates. Eliminating the inhibitors involves the use of steroids in combination with rituximab or cyclophosphamide. In cases of severe bleeding extracorporeal removal of antibody may be indicated such as plasmapheresis and immunoadsorption to staphylococcal protein A [8]. Disease course can then be monitored by PTT in two to four weeks and a repeat of Factor VIII activity level in about four weeks. Complete remission has varying definitions however it can be defined as an undetectable inhibitor and FVIII more than 70 IU/dL when immunosuppression is stopped [7].

Of note, although rare, bleeding diathesis may be a presenting symptom in a cancer patient. In a review of 27 analyzable cases, there was a close temporal relationship between detection of the inhibitors and diagnosis of the tumor [8]. This warrants a thorough workup for a possible underlying malignancy in these patients. Our patient had a lung nodule noted on a recent CT chest and although it was found to be negative for malignancy, a workup was warranted given his presenting signs and symptoms.

3. Conclusion

A key point to successfully treating AHA is to remove inhibitors and stop bleeding. Agents chosen for therapy depend on severity of bleeding and inhibitor titre. Most effect treatment involves increasing plasma FVIII levels to sufficiency control bleeding and immuno-modulators to eradicate the inhibitors at play. The patient mentioned above was able to achieve complete remission with use of steroids and rituximab. Mortality in patients presenting with AHA is related to bleeding and hemorrhage, therefore rapid diagnosis and effective treatment are needed. Prognosis remains variable and a meta-analysis reveals independent factors that are associated with variable clinical outcome. Future studies and analysis can focus on other prognostic factors which can further help understand the biology of disease and tailor treatment accordingly.

Ethical approval

This study was approved by Ethics Committee.

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Author contribution

Study concept or design – PS, MF. Data collection – PS. Data interpretation – PS. Literature review – PS, NA. Drafting of the paper – PS, NA, BG. Editing of the paper – PS, BG, NA, MF.

Registration of research studies

Name of the registry: Not Applicable.
Unique Identifying number or registration ID: N/A.
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Guarantor

Pratishtha Singh, M.D.

Financial disclosure

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Declaration of competing interest

The authors declare no conflict of interest.

References

[1] B.N. Reeves, N.S. Key, Acquired hemophilia in malignancy, Apr, Thromb. Res. 129 (Suppl 1) (2012) S66–S68, https://doi.org/10.1016/S0049-3848(12)70019-1. PMID: 22682137.
[2] M. Napolitano, S. Siragusa, S. Mancuso, C.M. Kessler, Acquired haemophilia in cancer: a systematic and critical literature review, Jan, Haemophilia 24 (1) (2018) 43–56, https://doi.org/10.1111/hae.13355. Epub 2017 Sep 27. PMID: 28960809.
[3] M. Saito, R. Ogasawara, K. Izumiyama, A. Mori, T. Kondo, M. Tanaka, M. Morioka, M. Ieko, Acquired hemophilia A in solid cancer: two case reports and review of the literature, Nov 26, World J. Clin. Cases 6 (14) (2018) 781–785, https://doi.org/10.12998/wjcc.v6.i14.781. PMID: 30510943; PMCID: PMC6264993.
[4] Sep J. Cuilleron, P. Mas, L. Kiakouama, L. Gaillot-Durand, P. Seve, G. Devouassoux, Une hémophilie A acquise ayant révélé un cancer du poumon [Acquired hemophilia A revealing lung cancer], French, Rev. Mal. Respir. 35 (7) (2018) 727–730, https://doi.org/10.1016/j.rmr.2017.08.005. Epub 2018 Aug 8. PMID: 30098880.
[5] S. Ichikawa, K. Kohata, Y. Okitsu, M. Suzuki, S. Nakajima, M.F. Yamada, Y. Onishi, J. Yamamoto, S. Suzuki, K. Ishizawa, J. Kameoka, H. Harigae, Acquired hemophilia A with sigmoid colon cancer: successful treatment with rituximab followed by sigmoidectomy, Jul, Int. J. Hematol. 90 (1) (2009) 33–36, https://doi.org/10.1007/s12185-009-0347-9. Epub 2009 May 30. PMID: 19484333.
[6] M. Girardi Dda, D.R. Silva, P.R. Villaça, C.E. Souza, L.G. da Fonseca, D.A. Bastos, P. M. Hoff, Acquired hemophilia A in a patient with advanced prostate cancer, Jun 30, Autops Case Rep. 5 (2) (2015) 55–59, https://doi.org/10.4322/acr.2015.008. PMID: 26484336; PMCID: PMC4584669.
[7] J. Delgado, V. Jimenez-Yuste, F. Hernandez-Navarro, A. Villar, Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors, Br. J. Haematol. 121 (1) (2003) 21–35, https://doi.org/10.1046/j.1365-2141.2003.04162.x.
[8] I. Hauser, K. Lechner, Solid tumors and factor VIII antibodies, Sep, Thromb. Haemostasis 82 (3) (1999) 1005–1007. PMID: 10494753.