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Acquired hemophilia A with intramuscular hematoma at an unusual age: a case report*

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Background. *Acquired factor VIII (FVIII) deficiency or acquired hemophilia A (AHA) is very uncommon in children. Patients with AHA usually present with abnormal or unexpected bleeding which may be life-threatening. These patients usually have unexplained, prolonged, and isolated activated partial thromboplastin time (aPTT). Consequently, FVIII activity should be immediately evaluated. Bleeding prevention is important in patients with AHA.*

Case report. *We present a case of a previously healthy 13-year-old female who presented with intramuscular hematoma, soft tissue hemorrhage, and epistaxis who was eventually diagnosed with AHA.*

Conclusion. *To our knowledge, the present report is one of the few reported cases of an Asian patient that was diagnosed with acquired hemophilia A at a young age.*

Key words: acquired hemophilia A, acquired FVIII deficiency, factor VIII, bleeding, aPTT prolongation

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Authors' contributions

All authors passed the four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. All authors had equal contribution to this study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Written informed consent was obtained from the patient' parents for publication of this case report and any accompanying images.

Conflicts of interest

The authors declare no competing financial interests.

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Introduction

Acquired factor VIII (FVIII) deficiency, also known as acquired hemophilia A (AHA), is a rare disorder and is very uncommon in children with an incidence rate of 0.045 per 1 million [1, 2]. AHA is an antibody-mediated autoimmune disease in which autoantibodies target FVIII. However, the exact underlying immunopathology of this disorder is still unclear. Studies have suggested that gene polymorphisms and $CD4^+$ T-cell lymphocytes are involved in triggering this disease [2]. The most common risk factor of acquired hemophilia A has been reported to be age over 50 years. Moreover, pregnancy, the postpartum period rheumatoid arthritis (RA), malignancy, systemic lupus erythematosus (SLE), solid tumors and some medical drugs such as penicillin, sulfamides, and phenytoin have been suggested as predisposing factors. On the other hand, there may be no underlying condition in almost half of the subjects (the idiopathic type) [3, 4]. The distribution of acquired FVIII inhibiting factors is similar between the two genders. However, they are more in younger ages of the female population [5]. These patients mostly present with spontaneous and unexpected bleeding that may occur at multiple sites and may even be severe and life-threatening bleeding [2, 6]. In the pediatric population, the symptoms are similar to adult patients [7]. Therefore, despite the lower incidence, early detection and management are necessary.

In this article, we report a case of a previously healthy 13-year-old female who presented with intramuscular hematoma, soft tissue hemorrhage, and epistaxis that was eventually diagnosed with AHA.

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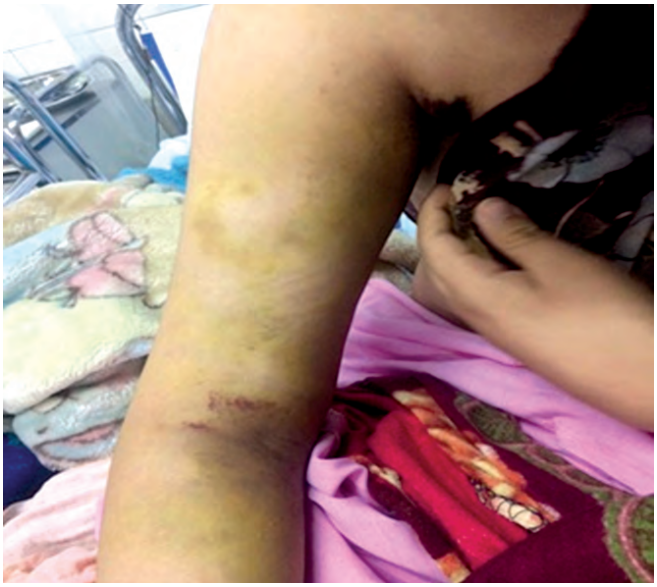
Case report

A 13-year-old girl *presented to the Emergency Department of Imam Khomeini Hospital, Tehran, Iran with painless swelling, ecchymosis, and pain in her right arm (Figure). She had a two-week history of frequent epistaxis that would take a long time to cease. Her medical history was not significant. She had not experienced trauma, fever, or surgery within the month before her admission. She did not have any personal or familial history of bleeding disorders. The patient had been experiencing frequent unusual epistaxis and diffuse ecchymosis in the dorsal side of her left leg associated with swelling and pain since two weeks before her admission. On admission, she had a blood pressure of 110/80 mmHg, a heart rate of 106 beats/minute, and a body temperature of 36.8 ºC. On physical examination, there were antecubital fossa ecchymosis (size: 5 × 4 cm) and right axillary fossa ecchymosis (size: 10 × 6 cm). The non-pitting swelling of her arm had disseminated to the right hemi-thorax without any evidence of swelling in the hand and forearm. The radial and ulnar pulses were normal. There was no pain or abnormal neurologic findings in the distal of upper limbs. Evaluation with ultrasonography reported compressible jugular and proximal subclavian veins with normal flow. Doppler sonography of the veins and arteries of the right upper limb was normal, but there was a hematoma in the soft tissue. Disseminated superficial ecchymosis was determined following the above evaluations. The patient's coagulation test, factor assay, and laboratory test results are shown in Table. These results confirmed the diagnosis of acquired hemophilia A. After the initial evaluations, underlying inhibitory or immunologic etiologies were presumed to be the cause of the disease. In addition, due to the severity of the hematoma, the patient was given one dose (4.8 mg) of factor VII (90 μg/kg) immediately after the initial evaluations as factor VII could alleviate the symptoms. In the first days of admission and after laboratory confirmation of antibody-involved hemophilia, intravenous immunoglobulin (IVIG) (1 g/kg) was prescribed. Symptoms and the color of skin lesions alleviated in response to treatment after a few days. Consequently, the patient was discharged from the hospital after her condition became relatively stable. She was prescribed cortisone acetate (1 g/kg per day) for one month and azathioprine (50 mg per day) for three months. She was regularly followed up with prothrombin time (PT), activated partial prothrombin time (aPTT), international normalized ration (INR), and anti-FVIII antibody tests. After one month of treatment initiation, cortisone acetate was tapered and stopped within two weeks. In about two months, antibody level decreased to the normal upper limit level. After three months, the levels of PT, PTT, INR, and antibody were normal, and the patient was in a good physical condition. Subsequently, azathioprine was tapered (after three months of treatment).*

Discussion

In this study, we reported a novel case of acquired hemophilia in a 13-year-old female. Acquired hemophilia A is very uncommon in children. The incidence of acquired hemophilia has been reported to be 1 in 1.48 million/year the United Kingdom [1]. A study reported six cases of hemophilia A in children in the U.S. and a literature review revealed another eight presumed or definite cases [8]. In addition, a large retrospective study reported another six cases [9].



Massive hematoma and swelling of the patient's arm and forearm after obtaining a blood sample

The results of the patients' coagulation test, factor assay, and laboratory tests

Laboratory test	Laboratory result
Hemoglobin	5.6 g/dL (normal: 12–16 g/dL)
Hematocrit	16.1 % (normal: 36–48 %)
Von Willebrand factor activity	93 % (normal: 50–160 %)
aPTT	104.6 seconds (normal: 32–40 seconds)
Mixed aPTT	52 seconds (high-not corrected)
PT	13.4 seconds (normal: 12.3–14.5 seconds)
Bleeding time	3 minutes (normal: 2–7 minutes)
Factor 8 inhibitor	16.8 Bethesda Units (< 0.4 none)
Platelet count	Normal
Liver function	Normal
Activity of factors 2, 5, 7, 9, 10, 11	Normal
Anti-thyroid peroxidase (anti-TPO)	1.8 (negative)
Antinuclear antibodies (ANA)	2.3 (negative < 10)
Anti-double-stranded DNA (anti-dsDNA)	0.6 (normal < 100)
Anti-phospholipid (IgM)	2.7 (negative < 10)
Anti-phosphplipid (IgG)	2.6 (negative < 10)
Anti-cardiolipin (IgM)	3 (negative < 7)
Anti-cardiolipin (IgG)	2.4 (negative < 10)

However, studies on acquired hemophilia A in Asian countries are rare. To our knowledge, the present report is one of the few reported cases of an Asian patient that was diagnosed with acquired hemophilia A at a young age. A study reported that the weighted mean (SD) age at diagnosis of acquired hemophilia was 58.10 (16.96) years in Asian countries compared to 75.70 (14.47) years in an European series (with an absolute difference of 17.6 years) [10]. There seems to be no significant difference in the occurrence of acquired hemophilia in the two genders. However, younger age (< 50 years) and female gender have been reported to be associated with more risks for AHA [5]. AHA usually occurs in women in the postpartum period, in patients with connective tissue disease, paraneoplastic

syndrome, or following the use of some medical drugs such as penicillin, sulfamides, and phenytoin. In addition, there have been some reports of an association between AHA and trauma or minor surgeries [3]. Among the connective tissue disorders, AHA is mostly associated with RA and SLE. In addition, a few cases have been reported to occur with Sjogren's syndrome [4]. However, no identifiable causes have been reported in about half of the patients. Although some herbal medications have been associated with autoimmunity, no association has been reported between AHA and herbal medications [3]. The presented case is an idiopathic case. She had no medical, drug, or family history.

Patients with hemophilia A usually present with abnormal or unexpected bleeding which may even be life-threatening. In addition, there may be soft tissue or subcutaneous (ecchymosis) bleedings [6]. Our patient also had severe hematomas, mostly on her upper limb. On workup, these patients usually have unexplained, prolonged, and isolated aPTT. Therefore, FVIII activity should be immediately evaluated. The main differential diagnoses of prolonged aPTT are the deficiencies of other coagulation factors (such as factor IX and XI), lupus anticoagulant, and anticoagulation drugs. The differential diagnoses of impaired FVIII activity are von Willebrand disease and congenital hemophilia A. Consequently, evaluation with the Bethesda assay should be performed to detect and quantify the antibodies against FVIII [11]. However, it is important to note that the lupus anticoagulant and pharmacological anticoagulants can have false-positive effects in the Bethesda assay [12]. In the present case, the aPTT level was elevated and anti-FVIII antibody was positive which in addition to the clinical manifestations and positive response to IVIG and factor VII led to the diagnosis of AHA.

Bleeding prevention is important in patients with AHA. Therefore, surgery and invasive procedures should be avoided or postponed until the patient has received adequate treatment. The recommendations for treatment of active bleeding includes desmopressin (dDAVP), factor VIII concentrates, activated prothrombin complex concentrates (aPCCs), recombinant human factor VIIa (rfVIIa), and recombinant porcine factor VIII (rpFVIII). The treatment options in patients with low inhibitor titers include DDAVP (in patients with non-life-threatening bleedings) and initial control of active bleeding using human factor VIII products (in patients with active bleeding and low titer factor VIII inhibitor). In addition, aPCC, rfVIIa, and rpFVIII are the treatment options that are recommended in patients with high titer factor VIII inhibitor and active bleeding [13–15]. In most cases of AHA in pediatric patients, steroids are prescribed. However, the choice of therapy may vary and depends on the availability, previous responses, initial response, and physician preference [16]. The management of our case included treatment with factor VII, IVIG, cortisone acetate, and azathioprine. To our knowledge, the outcome of similar cases has resulted in the resolution of the disease within three months [7] which is similar to the present case.

Conclusion

Acquired FVIII deficiency or AHA is very uncommon in children. Patients with AHA usually present with abnormal or unexpected bleeding which may be life-threatening. These patients usually have unexplained, prolonged, and isolated aPTT. Consequently, FVIII activity should be immediately evaluated. Bleeding prevention is important in patients with AHA.

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