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OLGU YAZISI / CASE REPORT

POSTPARTUM EDİNSEL HEMOFİLİ A OLAN BİR HASTADA İMMÜNSUPRESSİF TEDAVİ: OLGU SUNUMU

IMMUNOSUPRESSIVE THERAPY IN A PATIENT WITH POSTPARTUM ACQUIRED HEMOPHILIA A: CASE PRESENTATION

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ÖZ

Edinsel faktör inhibitörleri çoğunlukla kan pıhtılaşma proteinlerini direk olarak engelleyen antikorlardır. Bu antikorlar; hemofili A'daki antikor gelişimi, post partum dönem, çeşitli immünolojik hastalıklarla ilişkili olan durumlar, çeşitli kanserlerle ilişkili olan durumlar ve yaşlı hastalar gibi birçok klinik durumda görülür. Önemli oranda mortalite ve morbiditeye neden olan edinsel hemofili A (AHA); öz geçmiş ve soy geçmişinde kanama hastalığı olmayan, kanama ve uzamış aPTT'si olan hastalarda ayırıcı tanıda düşünülmelidir. Edinsel hemofilinin tedavi stratejisi hakkında henüz bir görüş birliği yoktur. Biz burada; immünsupressif tedavi ile başarılı bir şekilde tedavi edilen post partum edinsel (AHA)'lı bir vaka bildirdik.

ANAHTAR KELİMELER: Edinsel, hemofili A, inhibitör.

ABSTRACT

Acquired factor inhibitors are antibodies that inhibit directly blood clotting proteins. These are seen in many clinical situations such as inhibitors in hemophilia A, postpartum, in older patients, in association with various immunologic disorders and various malignancies. Acquired hemophilia A which can cause a considerable proportion of mortality and morbidity, should be taken in consideration as a differentional diagnosis in patients who have prolonged aPTT and bleeding without a personal or family history of bleeding disorder. There is no consensus about the treatment strategy of acquired hemophilia A yet. We reported a case of postpartum acquired hemophilia A who was treated with immunosupressive therapy.

KEYWORDS: Acquired, hemophilia A, inhibitor.

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INTRODUCTION

Acquired inhibitors of blood coagulation, also known as circulating anticoagulants, are antibodies in blood that directly inhibit blood clotting proteins. These inhibitors arise secondary to transfusion of plasma proteins in patients with hereditary bleeding disorders or de novo in patients with previously normal hemostatic mechanism such as various immunologic disorders, various malignancies, in older patients without any associated disorders and in the postpartum period. The gender incidence is approximately equal, and almost 60% of the patients are older than 60 years of age. In approximately 13,5% of cases, the disorder has occured during the postpartum period. Overall mortality is 22%. Factor VIII inhibitors can usually occur during the postpartum period and rarely during pregnancy. Most often, the inhibitor occurs after the birth of the first or second child. The course in these patients is variable, but the inhibitor disappears spontaneously in many patients after 12–18 months. In a review of 51 patients with postpartum inhibitors, the survival rate was 97% at 2 years, and Kaplan-Meier analysis revealed a probability of complete remission of almost 100%. The median time to complete remission was 11 months, an interval shortened with immunosuppressive drugs (1). Acquired Factor VIII inhibitor can cause significant morbidity and mortalitiy. Therefore treatment should be started whenever the patient is diagnosed with acquired Hemophilia A. The aim of the management is to control the bleeding and suppression of inhibitor. Control of the acute bleeding is the priority because of the high early mortality rates (2).

Here we report a case of acquired hemophilia A (AHA) developed at third months after delivery and successfully treated with immunosuppressive therapy.

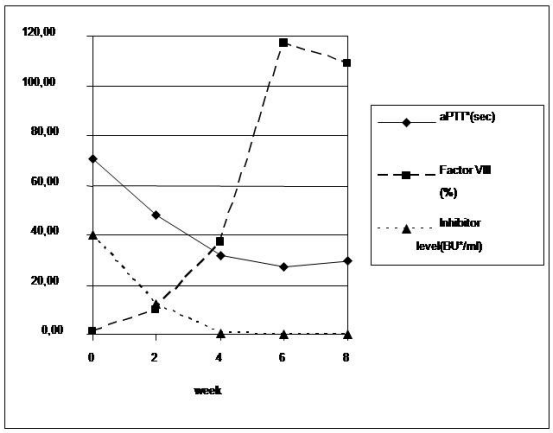
CASE REPORT

A 23 years old female patient admitted to our clinic with complaints of ecchymosis in hands and legs, bilateral swelling in elbows and right ankle. In her physical examination, everything was normal except ecchymosis and edema in right arm and forearm, edema and ecchymosis in bilateral ankles and inability to move in right elbow and bilateral ankles. In her personal history, we learned that three months after she had given birth to her first child with vaginal delivery, swelling, pain and erythema occured in both legs and she was admitted to cardiovascular surgery clinics. Venous doppler ultrasonographic imaging of legs revealed thrombophlebitis in the right popliteal vein. Oral antibiotics, acetylsalicylic acid and enoxoparin 6000 IU/L two times a day were prescribed. However, with treatment no regression in her complaints occurred, besides painful swelling in her right elbow and both ankles and ecchymosis in both legs and arms took place. She was admitted to an emergency service in a hospital with these complaints where she was given a non-steroidal antiinflammatory drug intramuscularly. She developed an erythematous swelling in her hip just after intramuscular injection of the drug. Doppler ultrasonographic imaging of right arm and right hip and MR imaging of joints revealed hematoma in muscles and intraarticular bleeding in corresponding joints, respectively. So the patient was hospitalized to explore the underlying bleeding pathology as she did not have a relative having bleeding diathesis. Complete blood count results revealed Hgb:8,25g/dl, HCT: 25,5%, MCV:81,7fL, Plt:342000/mm3, WBC:7210/mm3, Neu:4810/mm3. Her renal function tests and transaminase levels were within normal limits. Prothrombin time (PT) was 12 seconds INR:0.93, activated partial thromboplastin time (aPTT) was prolonged (70.6 sec). So factor VIII and factor IX levels and tests for detection of inhibitors if any were ordered. Factor VIII level was 1%, factor IX level was 69% . Mixing test detected inhibitor with a level of 16 Bethesta Units (BU). According to these results she was diagnosed as acquired hemophilia A. In order to investigate the probable autoimmune diseases which can give rise to inhibitor formation, a series of tests were ordered (ANA, dsDNA, anticardiolipin antibodies, etc.) revealing no underlying autoimmune disease. All these results suggested postpartum acquired hemophilia A. Meanwhile, we gave her recombinant factor VIIa 90 microgram/kg every 2 hour until stabilization of hemoglobin levels. In accordance with literature, we deci-

ded to give her immunosuppressive therapy. At that time we measured the level of inhibitor as a control before the start of immunosuppressive therapy revealing inhibitor with a level of 40 BU. We started methylprednisolone at a dosage of 1mg/kg/day and cyclophosphamide 150mg/day per orally. 2 weeks after the start of therapy aPTT and inhibitor level decreased to 48.1 seconds and 12 BU/ml, respectively and factor VIII level increased to 10%. So, we continued immunosupressive therapy at the same dose. At the first month of therapy, aPTT and inhibitor levels decreased to 31.6 sec and 0.36 BU/ml, respectively. Factor VIII level increased to 37%. Hence, the dosage of methylprednisolone was decreased gradually while keeping the cyclophosphamide dosage at the same level. Six weeks after the start of the therapy, aPTT (27.1 sec) and factor VIII level (117%) were within normal limits and inhibitor level decreased to 0.05 BU/ml. We decreased the dosage of methylprednisolone to 8mg/day. At the 2nd month visit, aPTT was 29.6 sec, factor VIII level was 109% and inhibitor level was still 0.05 BU/ml. We stopped methylprednisolone therapy. We decided to continue cyclophosphamide at a dose of 100 mg/day until disappearance of inhibitor. Changes in aPTT, factor VIII and inhibitor levels during immunosupressive therapy are shown in **Figure 1**.

Figure 1: Changes in aPTT, factor VIII and inhibitor levels during immunosupressive therapy.

*: aPTT: activated partial thromboplastin time, BU: Bethesta Units.



DISCUSSION

Acquired hemophilia A is a rare disease, characterized by autoantibodies against circulating coagulation factor VIII. Therefore, the factor VIII activity is decreased. These antibodies may induce spontaneous bleeding in a patient without an existing history of a bleeding disorder. In up to 50% of patients with acquired hemophilia A, an underlying medical disease can be identified. These underlying diseases include autoimmune diseases, solid tumors, lymphoproliferative malignancies and pregnancy (3). Patients with acquired hemophilia A mostly have soft tissue and systemic bleeding attacks. However, intraarticular bleedings are rare, unlike in congenital hemophilia. Major bleeding occurs in a majority of patients and is either spontaneous or secondary to trauma or surgery. Acquired hemophilia A associated with pregnancy or postpartum period counts up to 13,5 % of total reported cases (2, 4). Mortality rate with AHA patients has been reported 9,7–33% in different series (5).

In our patient, we observed soft tissue and intraarticular bleeding instead of a life-threatening bleeding mimicking congenital hemophilia. In patients, like our patient who don't have a pre-existing bleeding disorder and have aPTT elongation, acquired hemophilia A should be considered. Mixing test which is performed by mixing the patients' and a healthy controls' serum in order to search for inhibitor existence should be ordered. If the mixing test results are positive designating the existence of an inhibitor, factor VIII and factor IX levels should be measured to diagnose either acquired hemophilia A or B (2, 3, 6). In our patient we determined an inhibitor neutralizing the effects of factor VIII. As the patient had grade 2 anemia due to soft tissue bleeding, we transfused fresh frozen plasma and recombinant factor VIIa in accordance with literature to maintain hemostasis. The inhibitor level was > 5 BU, therefore we chose recombinant factor VIIa as the hemostatic agent (1, 7). Our patient was ordered an analgesic via an intramuscular route in a local medical centre and this is the reason why she had gluteal hematoma leading to grade 2 anemia. Abstaining from intramuscular injections in patients with coagulation disorders like our patient should be emphasized. We started immunosupressive therapy in order to eradicate inhibitors of factor VIII in addition to hemostatic therapy in our patient. We gave methylprednisolone and cyclophosphamide together. In literature, it's emphasized that though corticosteroid can be

given solely as immunosuppressive therapy, remission rates are higher when corticosteroid and cytotoxic therapy are used together. In a study conducted by Spero et al, it is found that prednisolone at 1mg/kg/day results in inhibitor abolition in approximately 30% of acquired hemophilia patients (8). Meanwhile, the results of a study conducted by Green et al suggests the addition of cyclophosphamide at 50-100 mg/day can increase the response rate as the remission rates in patients taking both prednisolone and cyclophosphamide came out to be 60-70% (9). Along with cyclophosphamide; other agents that have been used are azathioprine, vincristine, mycophenolate mofetil and 2-chlorodeoxyadenosine. There are some case reports in literature pointing out successful treatment strategies with plasmapheresis, immunoadsorption with staphylococcal protein A, intravenous immunoglobulin, cyclosporin and anti-CD20 monoclonal antibody (10).

Our patient's coagulation tests became normal after 4 weeks of therapy and in the meantime factor VIII level increased to 37% and inhibitor level decreased to 0.36 BU/ML. After 4 weeks of therapy to abstain from the side effects of corticosteroid therapy we gradually decreased the dosage of methylprednisolone and stopped after 2 months of therapy. Meantime, we continued cyclophosphamide treatment. At the 2nd month visit, inhibitor level was still 0.05 BU/ml. and we decided to continue cyclophosphamide at a dose of 100 mg/day until disappearance of inhibitor. In literature, median time to response is reported to be 3-6 weeks, but it's cited that some patients may have a prolonged response time of months (10, 11). The time to response in our patient is in accordance with literature.

In conclusion, acquired hemophilia A which can cause a considerable proportion of mortality and morbidity, should be taken in consideration as a differential diagnosis in patients who have prolonged aPTT and bleeding without a personal or family history of bleeding diathesis. In such a patient the treatment plan should be to maintain hemostasis while eradicating the inhibitor. We hereby reported a case of postpartum acquired hemophilia A who was successfully treated with immunosupressive therapy.

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