

Acquired factor VIII inhibitors: case reports of paclitaxel and penicillin – induced entities

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Acquired hemophilia A is an uncommon but potentially life-threatening clinical entity mediated by specific autoantibodies direct against coagulation factor VIII.

It may be associated with a number of conditions such as solid malignancies, autoimmune diseases, lymphoproliferative disorders, and drugs.

Early recognition of this entity is necessary to avoid a delay in treatment, which might lead to serious complications including severe bleeding and death.

Hereby, we report a case of acquired hemophilia A caused by a commonly used drug, penicillin, as well as the first reported case, to our knowledge, of acquired Factor VIII inhibitor secondary to paclitaxel. *Blood Coagul Fibrinolysis*

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Introduction

Acquired hemophilia A caused by factor VIII inhibitors is a rare yet a very significant autoimmune disorder. Herein, we present a review of a known complication of a commonly used drug, penicillin, as well as the first reported case of acquired Factor VIII inhibitor secondary to paclitaxel.

Method

The presence of acquired factor VIII inhibitor is demonstrated by the mixing study. It consists of incubating the patient's plasma with equal volume of normal plasma (1:1 PTT mixing study). In congenital hemophilia A, PTT will be corrected because the underlying pathophysiology is the lack of factor VIII, which can be replaced. In acquired hemophilia A, the autoantibodies can inactivate the factor VIII present in the normal plasma, which prevents the correction of the aPTT.

Of note, the mixture should be incubated at 37°C for 2 h since the inhibition is dependent on time and temperature. The aPTT typically correct or partly correct at time 0 but then are prolonged at 2 h in case of acquired hemophilia A. Once the presence of a coagulation factor inhibitor can be demonstrated, further tests should be done to rule out other causes that can inhibit the factor VIII, such as the lupus anticoagulant. In the acquired hemophilia A, lupus anticoagulant is undetected, the factor VIII activity is low, and the measurement of the other coagulation factors is normal. On the contrary, lupus anticoagulants are nonspecific inhibitors, and other coagulation factors beside the factor VIII could be low [1,2].

After a mixing study has confirmed the presence of an inhibitor and other nonspecific inhibitors have been ruled

out, the titer of factor VIII antibodies should be measured. The strength of the Factor VIII inhibitor can be quantified using the Bethesda assay. It measures the residual factor VIII activity after 2 h incubation of normal plasma with serial dilutions of the patient plasma. The dilution that inhibits 50% of factor VIII in the assay defines the titer of the inhibitor [1–3]. For example, if the 1:20 dilution inhibits 50% of the factor VIII in the assay, the patient is reported to have a titer of 20 Bethesda Units (BU) of factor VIII inhibitor.

Clinical case 1

A 76-year-old woman was admitted to our facility for gross isolated hematuria of 5 days duration.

Her past medical history was significant for multifocal ductal carcinoma of the right breast, diagnosed 6 months prior to her presentation, treated with right mastectomy and followed by 8 weeks of trastuzumab and paclitaxel. Her medications included atorvastatin, which she had been taking for 2 years and some multivitamins.

Her physical examination on admission was normal. Vital signs were stable and there was no evidence of purpura or bruising.

The initial laboratory testing revealed the following values: activated partial thromboplastin time (aPTT) 81 s (normal reference, 23–36 s), prothrombin time (PT) INR 1.01, D-dimer 1.1 mg/l (0–2.4 mg/l), fibrin split products absent, bleeding time 6.5 min, fibrinogen 487 mg/dl (160–400 mg/dl), hemoglobin 9.9 g/dl (13–16 g/dl), platelet count 253,000 (150–450,000/μ) and white blood count 17,000/μ (4,000–10,500/μ).

aPTT was not corrected with the coagulation mixing study. aPTT was 33.7s at time 0 and 54.2s at 2 h. Measurement of the coagulation factors showed the following: factor VIII activity was less than 3% (50–150%), factor II activity was 146% (50–150%), factor V activity was 151% (60–140%), factor VII activity was above 1000% (50–150%), Von Willebrand antigen level was 202% (50–150%), Von Willebrand activity was 118% (50–170%), factor IX activity was 28% (50–150%) and factor XII activity was 127% (60–135%). Lupus anti-coagulant was negative. The factor VIII inhibitor titer was 6.1 BU (Bethesda Unit). A diagnosis of acquired hemophilia A was made.

The second day, she was started on recombinant factor VIIa (Novoseven) at a dose of 50 µg/kg every 2 h time 4 then every 4 h intravenous along with prednisone 60 mg per day oral without much improvement in terms of bleeding, although the aPTT decreased from 81s at presentation to about 50s. The Novoseven was titrated up to 120 µg/kg every 3 h. Subsequently, she underwent a cystoscopy, which showed no mass within the bladder or ureter. She had brushings of the right ureter and showed no evidence for malignancy. During her first 9 days in the hospital, she received a total of four units of packed red blood cell. Given the persistence of the gross hematuria, factor VIII inhibitor bypassing agent (FEIBA) at a dose of 50 units/kg intravenous every 8 h was substituted for the recombinant factor VIIa. Also, she was started on rituximab and received two doses. As a result, she experienced steady improvement with complete resolution of the hematuria 6 days after the start of FEIBA and 2 days after her second dose of Rituxan. FEIBA and prednisone were subsequently tapered.

On the day of discharge, the patient was completely stable. Her coagulation profile revealed the following: PTT of 40s, disseminated intravascular coagulation studies negative, factor VIII activity of 19%, and factor VIII inhibitor activity of 1.7 Bethesda Unit.

One month after her discharge, she received two courses of trastuzumab-based chemotherapy without paclitaxel. Coagulation studies done 3, 6 and 9 weeks after her second dose of trastuzumab were all normal.

Clinical case 2

An 86-year-old Caucasian male was seen in consultation for significant gingival bleeding with hemorrhage after a dental cleaning. His pertinent clinical history included routine dental cleaning 8 months prior to consultation that did not have any associated bleeding or any complications. The patient, of note, did not have any clinical or family history of bleeding diatheses. One month prior to consultation, the patient underwent a root canal procedure and received a single dose of penicillin V-K postprocedure for prophylaxis. On a routine dental

follow-up 1 month later, the patient developed significant bleeding with a gingival hemorrhage that required the use of topical thrombin to slow the bleeding. Two days later, the patient presented to the emergency room with right-sided facial swelling with bruising over the right neck, face, and chest. An underlying facial hematoma was present.

Past medical history was significant for Alzheimer's disease, hypertension, hyperlipidemia, osteopenia, and diabetes mellitus. Medications included hydrochlorothiazide, rivastigmine, memantine, metformin, metoprolol, and divalproex sodium. As noted earlier, the patient did not have any personal or family history of bleeding dyscrasias.

Initial laboratories revealed the following values: aPTT 57.1s (23–36s), INR 1.0, factor VIII activity undetectable (50–150%), hemoglobin 10.1 g/dl (13–16 g/dl), and platelet count of 200 000 (150–450 000/µl). The aPTT did not correct on 1:1 mixing study, and the patient had a Bethesda titer of 157.2 units. The balance of factor activities, including Factors II, V, IX, X, XIII, and vWF were all within normal limits.

The patient was started on prednisone at a dose of 1 mg/kg daily for a total of 3 weeks, with consideration of adding additional agents if he did not respond to the initial regimen with close follow-up. In 3 weeks, the aPTT rebounded to 37.7s with hemoglobin of 11.8 g/dl, Factor VIII activity of 12%, and a Bethesda titer of 8.7. Two months after initiation of therapy, the factor VIII activity was 111% and the aPTT was 37.6s. Clinically, the patient did very well, with resolution of the bruising and bleeding within 3 weeks of prednisone initiation.

Discussion

Acquired hemophilia A occurs as a result of the spontaneous development of specific autoantibodies directed against the coagulation factor VIII.

Although more than 50% of the cases are idiopathic with no obvious underlying disease, it may be associated with a number of conditions such as solid malignancies, autoimmune diseases, and lymphoproliferative disorders. Also, it can be drug induced in certain cases [1,2,4,5].

The clinical presentation ranges from asymptomatic to catastrophic bleeding episodes. The bleeding pattern is quite different from the congenital hemophilia. Hemarthroses are the hallmark of the congenital hemophilia; however, purpura, soft tissue and mucosal bleeding are characteristics of the acquired form [1,2].

The most common abnormalities seen on laboratories are an isolated prolonged PTT not corrected by the mixing

study, along with normal INR, platelet count and bleeding time.

The management of this entity is aimed to the control of the hemorrhage and the suppression of inhibitor.

Bleeding can be reversed by the administration of factor VIII concentrates in a patient with low-titer inhibitors (<5 BU) [6]. In case of severe bleeding with an inhibitor titer above 5 BU, it is preferred to give an agent that bypasses the factor VIII such as recombinant factor VIIa or activated prothrombin complex concentrate. The efficacy of the treatment is determined on clinical progression and not on laboratory monitoring [1,2].

Immunosuppressive agents used for the removal of the inhibitors are corticosteroids, as well as cytotoxic agents such as cyclophosphamide, azathioprine and vincristine. Other agents are cyclosporine, intravenous immunoglobulin, and mycophenolate mofetil [1,2]. Recently, the use of the anti-CD20 monoclonal antibody rituximab (Rituxan) proved efficient [6,7].

The two clinical cases demonstrated acquired hemophilia secondary to iatrogenically induced Factor VIII inhibitors. A number of drugs have been implicated in the literature as causes of this clinical entity. The second clinical case, due to penicillin administration, represents a complication of a commonly prescribed drug. It is illustrative of the use of immunosuppressive therapy for patients who develop isolated, prolonged aPTT with suppressed factor VIII activity. Its presentation is a reminder of this particular complication of penicillin use with hope that acquired hemophilia will be considered in the differential of patients presenting with acquired bleeding diathesis.

The clinical case relating to paclitaxel represents a newly recognized clinical entity, in contrast with the penicillin-induced case. Whereas the penicillin-induced case is a reminder of complications in commonly used medications, the paclitaxel-induced case is thought to be the first reported case of this entity in the literature.

In our cases, autoimmune tests including lupus anticoagulant were negative. In the first clinical case, the development of the factor VIII inhibitor followed the treatment with paclitaxel. Although solid tumors are associated with acquired hemophilia A, the patient's breast cancer was in remission at the time she developed the factor VIII inhibitor. Interestingly, coagulation studies done routinely before the beginning of her chemotherapy were normal. In addition, the patient did not develop any coagulation abnormalities after she received trastuzumab without paclitaxel 1 month after her recovery. All these arguments point toward the paclitaxel as a potential cause of the acquired hemophilia A.

Of note, the factor VII was measured while the patient was receiving NovoSeven. This could explain the extremely elevated factor VII level in the first case. Additionally, the moderately low level factor XI might stem from the nonspecific nature of the factor VIII inhibitor.

Multiple other drugs have been described in anecdotal reports. The most frequent are fludarabine, interferon, and penicillin, as noted earlier [3].

Finally, this case underscores the importance of rituximab in the elimination of the inhibitor. Recent studies have shown promising results of durable remission for this drug [6,7]. Further prospective, randomized studies are needed to prove its efficiency.

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