

## Case Report

# A rare case of acquired hemophilia A associated with myelodysplastic syndrome

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Received December 11, 2011; accepted April 23, 2012; Epub June 15, 2012; Published June 30, 2012

**Abstract:** 84 year old male with past medical history of myelodysplastic syndrome (MDS) presented with progressive subcutaneous and muscle bleed in the right forearm and arm. Workup revealed elevated activated partial thromboplastin time (aPTT) - 71.8 seconds (normal 23 - 32 seconds) which was persistently elevated after mixing study (37.1 seconds immediately and 51.1 seconds after 1 hour). Further laboratory work up revealed low factor VIII level (3%) and elevated factor VIII inhibitor by Bethesda assay (3 units/ml of blood). Acquired hemophilia A (AHA) diagnosis was established and patient was treated with recombinant factor VIIa (rFVIIa) to control the bleeding and also prednisone for immunosuppression. Subsequent monitoring suggested reduction of factor VIII inhibitor - antibody levels to undetectable level in 3 days and increase of factor VIII level from 3% to 50% in 5 days. Despite of improvement in the laboratory values he continued to have progression of his bleeding which involved posterior chest wall and also left arm. Due to the progression of the condition and prior expressed wish family decided to stop the aggressive treatment and patient died nine days after the diagnosis. The case report describes a rare presentation of AHA in MDS (With bone marrow cytogenetics abnormality) patient with fatal outcome.

**Keywords:** Factor VIII, acquired hemophilia A, rFVIIa, bethesda assay, myelodysplastic syndrome, aPTT, factor VIII inhibitor

## Introduction

Acquired hemophilia A (AHA) is a rare but fatal hematological condition. The condition is caused by autoantibodies directed against coagulation factor VIII. The incidence of AHA is 1.48 cases/million/year reported in a study conducted in United Kingdom [1]. The mortality rates are reported to be 7.9% to 22% [2].

The fatality is usually associated with unusual presentation coupled with delayed diagnosis of the case secondary to lack of family/past history of bleeding and also due to unusual site of bleeding. More than 80% patients with acquired hemophilia usually bleeds in skin, muscles, soft tissues and mucous membrane rather than joint which is the most commonly affected site in congenital hemophilia [3]. The bleeding can be life threatening and serious like retroperitoneal hematoma or muscle bleed leading to compartment syndrome [4].

The most common etiology thought to be responsible for the AHA are Idiopathic, other autoimmune diseases (sjogren's disease, systemic lupus erythromatosus, rheumatoid arthritis, multiple sclerosis etc.), post partum, diabetes, solid and hematological malignancies (prostate, lung, pancreas, colon, breast, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, myelodysplastic syndrome, etc.), medications (penicillin, sulfamides, phenytoin etc.), asthma, chronic obstructive lung disease etc. [3].

International recommendations on the diagnosis and treatment of patients with acquired hemophilia A have been published [5]. The diagnosis should be suspected in elderly presenting with sudden onset of large hematoma/ ecchymoses and no bleeding disease history. The laboratory work up suggests elevated activated partial thromboplastin time (aPTT) and normal prothrombin time (PT); and the aPTT test is per-

sistently abnormal after mixing study that suggests presence of inhibitors to coagulation factor. Next step is to perform a specialized test called Bethesda test that establishes the diagnosis of factor VIII inhibitor and also quantifies the antibody titer [5, 6].

The treatment is focused at controlling the bleeding and then inhibiting the antibody. The bleeding control is via use of similar treatment as congenital hemophilia using, desmopressin acetate (DDAVP), factor VIII concentrate, activated prothrombin complex and recombinant human factor VIIa (rFVIIa; NovoSeven, Novo Nordisk A/S, Bagsvaerd, Denmark). Immunosuppression is achieved via administration of prednisone, and cyclophosphamide either alone or in combination as a first line of treatment. Also rituximab, azathioprine, mercaptopurine is sometimes used as a treatment but not as a primary line of treatment. Serial measurement of Bethesda assay is sometimes warranted to check the effectiveness of the treatment. Intravenous immunoglobulin is no longer recommended for treatment of AHA [5].

The incidence of AHA is rare and its association with myelodysplastic syndrome (MDS) though mentioned in past was only reported in two case reports so far [7, 8]. The first one suggested AHA in setting of refractory anemia due to MDS and other one in setting of chronic myelomonocytic leukemia and MDS [7, 8]. One other case report presented suggested AHA in myeloproliferative disorder [9]. We are reporting a case of MDS presenting with AHA in elderly gentleman with details of bone marrow cytogenetics.

### Case report

84 year old male with past medical history of Myelodysplastic syndrome on bone marrow biopsy that showed refractory anemia with excess blasts-1 (RAEB-1) pattern that was diagnosed for evaluation of refractory anemia. The patient was followed by hematology oncology for frequent blood count checks and transfusions as needed for anemia. Other significant medical history included chronic obstructive pulmonary disease, essential hypertension, hypercholesterolemia, vitamin B 12 deficiency, and Alzheimer's dementia.

He presented to the hospital with complaints of right arm pain and swelling that started sud-

denly and gradually got worse over one week. He had tachycardia at the rate of 120 beats/minute and the blood pressure was stable. Also the patient had good peripheral pulses but the right upper extremity was having swelling and erythema of the forearm area that extended to the cubital fossa anteriorly and posteriorly and also to the mid arm level. He was having swelling, tenderness of the area on palpation and bruising of the overlying skin on the cubital fossa. Laboratory work up showed white blood cell count of 3600/microliter with 1% blasts and 8% bands, hemoglobin 8.3gm/dL, hematocrit 25.7 percentage, platelets 2,31,000/microliter and CK was 34 unit/liter. The baseline hemoglobin was around 10gm/dL. Initial admission impression was established as questionable cellulitis and he was started on piperacillin + tazobactam and vancomycin. Symptomatic treatment including transfusion was given for low hemoglobin. Patient was evaluated with MRI of the extremity that suggested that there were extensive abnormal hyperintense T2 signal alterations involving the subcutaneous tissues circumferentially in the upper forearm and upper arm. There was associated increased signal on T2 weighted images within the musculature of the upper arm to include the deltoid, biceps, brachioradialis and incomplete involvement of the triceps muscle. Triceps involvement was primarily in the superior aspect of the muscle. While these changes were consistent with diffuse myositis/ myofascitis/ cellulitis based on presentation, there was no evidence of associated myofascial abscesses.

However as there was no objective clinical evidence of infection such as elevation of white cells, or fever other etiologies were sought. One of the differentials was subcutaneous tissue and muscle bleeding or disseminated intravascular coagulation (DIC) and to evaluate that further coagulation work up was ordered. On day 1 of admission - INR was 1.1, PT 11.0 seconds and aPTT was 71.8 seconds (normal range-23 - 32 seconds). D- Dimer was 1.17 mg/L (Normal-0.00-0.49mg/L) and fibrinogen was 557mg/dL (Normal 200-400mg/dL). Mixing study suggested aPTT of 37.1 seconds which was still high after mixing with normal blood and around 51.1 seconds after 1 hour of mixing. Factor VIII level was ordered that was low- 3% (Normal range 77-158). Ristocetin cofactor was 330%. Factor VIII inhibitor level was checked via Bethesda assay and it was 3 units/ml of blood

(Normal range is no inhibitors). So it was suggested based on findings that the swelling in the arm and forearm was actually intramuscular and subcutaneous bleeding.

On day two he was treated with rFVIIa at 90mcg/kg (patient's weight 80kg) dose, total of 7000 mcg x 2 times over two days for anti hemorrhagic treatment. Immunosuppression was provided with prednisone 100 mgs daily. Over next few days his coagulopathy improved. On day two the aPTT was 62.7 seconds, and hemoglobin dropped to 6.3gms/dl that was treated with transfusion. Haptoglobin was normal but lactate dehydrogenase (LDH) was elevated to 227u/ml (normal range 100-200). On day three aPTT improved to 56.1 seconds. On day four factor VIII levels increased to 50% and the inhibitor level went down to undetectable Bethesda unit. The aPTT improved to 44.4 seconds and, 36.4 seconds on day four and day five subsequently. Despite of improvement in the counts he continued to have increase in the swelling and erythema that started from right fingers, fore arm, arm, and shoulder and also now reached the trapezius muscles on the back and crossed the chest to involve the left arm up to elbow. CT abdomen was done to evaluate for the retroperitoneal bleed that was negative but he had bleeding in the anterior abdominal wall. Due to declining clinical status and comorbid conditions and prior expressed wishes non aggressive options were adopted and all the laboratory tests were discontinued. Patient's condition declined over next five days and he passed away after total nine days of presentation.

### Discussion

We presented a case of 84 year old male who was admitted with severe subcutaneous and muscle bleed progressively getting worse and extending from the right arm to the left arm and also on back. He was found to have factor VIII deficiency and also high level of inhibitor. He was treated with factor VIIa concentrate to stop the bleed and also with prednisone for immunosuppression. He was monitored with frequent laboratory check for inhibitor level with Bethesda assay and factor VIII level. Patient's laboratory workup was improving and the factor VIII inhibitor level was undetectable after four days of treatment and factor VIII level was 50%. Despite of improvement in the inhibitor titer he had progressive bleed also involving the poste-

rior chest wall. Due to progression of the bleeding aggressive treatment was stopped as per his prior expressed wish and due to poor prognosis in light of presence of multiple co-morbid conditions.

Patient was diagnosed with myelodysplastic syndrome two years before this presentation by bone marrow biopsy that suggested RAEB-1 in a hypercellular (40%) bone marrow with decreased numbers of megakaryocytes, mild-moderate reticulin fibrosis, increased iron stores, and 5% blasts.

The cytogenetics showed abnormal results with 44-45 XY, add (1) (p13), del (2) (q23q33), add (3) (p13), add (4) (q12), add (5) (q31), -7, -10, del (11) (q21q23), -20, -21, add (21) (q21), der (22) t (21;22) (q11.2;p12), +2-3mar [cp20]. Each metaphase was hypodiploid and had structural and numeric abnormalities including monosomy 7, an abnormal 5 resulting in a 5q deletion and an 11q deletion. Hypodiploidy and abnormalities of chromosomes 5 and 7 have been associated with de novo and therapy-related MDS and AML. There is no study describing bone marrow picture in patients of MDS presenting with AHA.

It has been suggested in research that the level of factor VIII and inhibitor assay level does not correlate with the severity of bleeding [10, 11]. For the same reason the international recommendations on diagnosis and treatment for acquired hemophilia suggested anti-hemorrhagic treatment in bleeding patients irrespective of the inhibitor titer and residual factor VIII level [5]. This was taken into consideration before starting the patient on rFVIIa treatment though the use of rFVIIa is not well documented in patients with AHA [5]. It was suggested in an editor letter using a case as an example that sometimes rFVIIa may fail to control the bleeding in AHA patients [12]. In that case the titer of factor VIII inhibitor was 532 units/ml as compared to our patient's 3 units/ml. So it is hard to compare the results to suggest failure of rFVIIa. Our patient was having extension of his intramuscular bleeding despite being on the rFVIIa treatment. Evidence suggests that rFVIIa concentrate is most effective in hemostasis and has been considered a first line treatment but there is no literature on treatment failure in AHA due to rarity of occurrence [5]. Again there are no guidelines on the duration of the rFVIIa treat-

ment before considering a treatment failure. Usually the treatment is provided till the bleeding stops which is via clinical assessment and usually the treatment duration needed is for total of 24-72 hours [5]. There are no monitoring guidelines to suggest therapeutic dosing of rFVIIa [13, 14].

There are only two case reports so far suggesting association of MDS with AHA in which one had refractory anemia with ringed sideroblast and the patient recovered from the AHA with treatment but with persistence of ringed sideroblast in follow up bone marrow biopsy [7]. The other case report was about AHA in MDS patient in setting of chronic myelomonocytic leukemia [8]. The advanced age, presence of underlying condition other than post partum and also the lack of complete remission were three prognostic factors identified by Delgado and colleagues [11]. Our patient was older than 65 and also had underlying MDS giving poor prognostic values from his AHA. The prognosis was also poor in people having low factor VIII level, high antibody titer and transfusion requirements [15].

We do not know the exact molecular mechanism of AHA in MDS patients. The incidence of AHA is very low and we do not have detailed information from literature about the cytogenetics abnormality of the bone marrow in MDS patients who develop AHA. The case report is a third case report so far suggesting the occurrence of such an entity along with first ever reported associated bone marrow cytogenetics abnormality to our knowledge.

## Conclusion

AHA is a rare but fatal heterogeneous presentation that may be diagnosed late due to extremely low incidence. This case report adds to the literature about the rare presentation of the AHA in MDS patient with details of the bone marrow cytogenetics. Also the research brings up an interesting topic of progression of bleeding despite being on rFVIIa treatment. Further research/review is needed to compare the bone marrow cytogenetics in order to derive at a useful associated genetic abnormality leading to AHA in MDS patients. Also clinicians should be reporting diagnosed cases to add to the literature to help understand the disease better.

## Consent

Written informed consent was obtained from the patient's keen for the publication of this case report. A copy of written consent will be available for review by editor in chief of this journal upon request.

## Acknowledgements

There is no funding source for this case report.

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