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Abstract: Acquired haemophilia A is a severe bleeding disorder caused by formation of autoantibodies against coagulation factor (F) VIII leading to important morbidity and mortality if not diagnosed early in the course of the disease. In a proportion of patients this condition is associated with underlying diseases such as malignancy or autoimmune disorders. Here, we report a 45-year old male patient with non-systemic chronic discoid lupus erythematoses who presented with spontaneous severe soft tissue haemorrhage in his left lower limb (compartment syndrome) due to autoantibody formation against factor VIII. The patient underwent emergency surgery after recombinant FVIIa administration followed by an immunosuppressive regimen consisting of prednisolone, cyclophosphamide and immunoadsorption. By these measures the bleeding was stopped, the FVIII activity gradually increased and the patient could be discharged from the hospital without signs of recurrent haemorrhage and no neurologic sequelae. One year after the diagnosis the patient is still in complete remission.

Response to Reviewers: Dear reviewers,

Thank you very much for your helpful comments.

According to your suggestion the introduction was shortened (1). The case description now contains more detailed information, especially concerning laboratory values and an illustration of aPTT and factor VIII activity is now included (2). Furthermore, the applied therapy is now described in more detail with cumulative dose (5). Immunoadsorption is more thoroughly described as well as the local outcome and the possible side effects of immunosuppressive therapy (6,7,8). Page numbers have been included (3). The importance of immediate hemostatic therapy rather than surgery is delineated as well as the association of lupus and acquired haemophilia (9, 10).

Acquired Haemophilia in a patient with discoid lupus

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Acquired Haemophilia in a patient with discoid lupus

Summary

Acquired haemophilia A is a severe bleeding disorder caused by formation of autoantibodies against coagulation factor (F) VIII leading to important morbidity and mortality if not diagnosed early in the course of the disease. In a proportion of patients this condition is associated with underlying diseases such as malignancy or autoimmune disorders. Here, we report a 45-year old male patient with non-systemic chronic discoid lupus erythematoses who presented with spontaneous severe soft tissue haemorrhage in his left lower limb (compartment syndrome) due to autoantibody formation against factor VIII. The patient underwent emergency surgery after recombinant FVIIa administration followed by an immunosuppressive regimen consisting of prednisolone, cyclophosphamide and immunoadsorption. By these measures the bleeding was stopped, the FVIII activity gradually increased and the patient could be discharged from the hospital without signs of recurrent haemorrhage and no neurologic sequelae. Two years after the diagnosis the patient is still in complete remission.

Introduction

Acquired haemophilia A is a rare but potentially life-threatening bleeding disorder caused by autoantibodies against the coagulation factor (F) VIII (FVIII inhibitor) which is in some cases associated with autoimmune diseases, solid tumors, haematologic malignancies or can occur in the post-partum period. For further information concerning the pathophysiology of acquired haemophilia please refer to [1].

Mortality is rather high in newly diagnosed acquired haemophilia ranging from 8 to 22 % in different studies [2-5]. A major cause of significant mortality and morbidity is the frequent confusion with other life-threatening conditions such as disseminated intravascular coagulation (DIC), thus often leading to uncontrolled bleeding prior to correct diagnosis of the disease.

Effective treatment involves not only the initial treatment of acute haemorrhage with factor VIII concentrates, a factor-VIII-bypassing-agent such as recombinant FVIIa or activated prothrombin complex concentrate but also the eradication of the inhibitor by

1 immunosuppression, plasmapheresis or immunoabsorption or a combination of these
2 modalities [1, 5, 6].
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5

6 **Case Report**

7 A 45-year old man with known and untreated chronic discoid lupus erythematoses presented
8 to a district hospital with rapidly worsening pain in his left lower limb without any traumatic
9 event. A soft tissue haemorrhage (compartment syndrome) was diagnosed by clinical
10 examination and ultrasound. Neither the patient's history nor his family history gave evidence
11 for bleeding disorders. Laboratory findings revealed an isolated prolonged activated partial
12 thromboplastin time (aPTT) with a normal prothrombin time (PT), a normal platelet count and
13 a reduced haemoglobin level. After repeated, unsuccessful surgical treatment and recurrence
14 of the severe tissue haematoma the patient was referred to the University Hospital of
15 Muenster. The coagulation work-up revealed a tremendously reduced level of FVIII activity
16 (<1%), which did not normalize in mixing assay. The FVIII inhibitor titer was 6 Bethesda
17 Units per mL (BU/mL) initially. All other levels of coagulation factors were within the
18 normal range. Computed tomography of thorax and abdomen did not give any evidence for an
19 underlying malignancy. Furthermore, a systemic autoimmune disease could be excluded by
20 further laboratory tests such as anti-ds-DNA, ANA and ANCA.
21
22

23 Immediate administration of high-dose rFVIIa (Novoseven®, 130 µg per kilogram
24 bodyweight, 960 kIE abs.) was followed by emergency surgery and subsequent
25 immunoabsorption with a protein A column in order to rapidly reduce the inhibitor level.
26 Besides immunoabsorption the immunosuppressive regimen consisted of prednisolone (100
27 mg daily) and cyclophosphamide (100 mg daily). The anticoagulant regime during
28 immunoabsorption consisted of heparin (2000 I.E. per hour) and ACDA. The repeated
29 infusion of rFVIIa (Novoseven®, 50 µg per kilogram bodyweight, [360 kIE]) initially six
30 times per day for three days, then three times per day for four days) controlled bleeding. The
31 cumulative dose of rFVIIa given was 16600 kIE or 2,3 mg per kg bodyweight.
32 Immunoabsorption was performed daily for a total of five days and rVIIa was given for seven
33 days with gradually prolonging the time interval. Under this regimen the FVIII inhibitor titer
34 declined to 1,5 BU so that haemostatic treatment was switched from rFVIIa to rFVIII
35 (Advate®, 1000 IE three times daily) thus achieving sufficient factor VIII plasma levels
36 (FVIII activity 1 hour after administration). The course of aPTT and FVIII are shown in
37 Figure 1.
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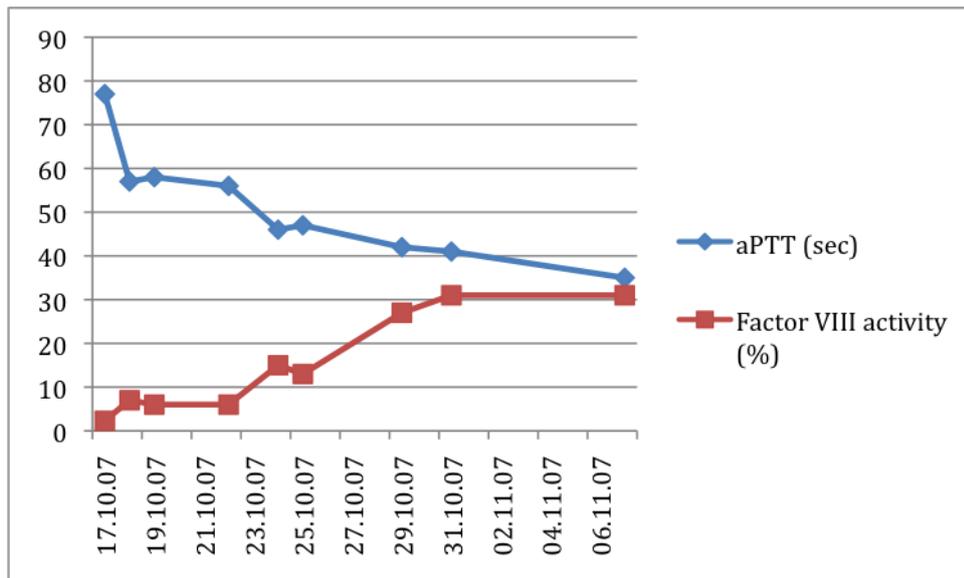


Figure 1: FVIII activity and aPTT after referral to the University Hospital of Muenster

After three weeks the patient was discharged from the University Hospital without signs of recurrent haemorrhage or neurologic sequelae and with a stable haemoglobin value and was followed up in our outpatient facility. The immunosuppression was continuously tapered within a period of three months and the spontaneous FVIII residual activity rose to 57 % three weeks after initiation of treatment. Two years after this episode the patient is still in complete remission (FVIII residual activity 119 %).

Discussion:

Early diagnosis and treatment of acquired haemophilia is essential for the reduction of morbidity and mortality. Although acquired haemophilia is a very rare condition, it should be suspected if an adult patient presents with severe spontaneous haemorrhage combined with an isolated prolonged aPTT that does not normalize in mixing studies. Subsequently, acquired haemophilia is confirmed by severely reduced or even undetectable levels of FVIII clotting activity with normal activity of the other coagulation factors of the intrinsic pathway (FIX, XI and XII). Mixing studies and measurements of the inhibitor titer are required for appropriate therapeutic management. Therefore it is mandatory to refer such patients to specialized centres with the laboratory and clinical expertise in haemostasis. In the case described above, however, referral to a specialized centre took place as late as thirteen days after admission without adequate diagnosis and treatment. This fact demonstrates the importance of continuous medical education on the cardinal symptoms of this serious disease in order to increase the level of suspicion.

1
2 Since various studies have described solid or haematologic malignancy or autoimmune
3 disease as underlying condition in up to 60% of the cases, these concomitant diseases should
4 be looked for [7-10]. In our case, malignancy was excluded with sufficient probability. It is
5 unclear whether the known and untreated chronic discoid lupus erythematoses is a
6 predisposing factor for the development of acquired haemophilia A. Since rare cases of
7 underlying non-systemic cutaneous diseases have been described in the literature [1, 2], we
8 assume that the discoid lupus in our patient might well be a predisposing disease.
9

10
11 By administration of high doses of rFVIIa rapid haemostasis was achieved. Because of the
12 severe bleeding complications threatening his limb function we decided on a multimodal
13 immunosuppression regimen consisting of steroids, cyclophosphamide and
14 immunoabsorption in order to decrease the inhibitor titer rapidly. This combined aggressive
15 strategy turned out to be successful in terms of reducing the inhibitor titer. This even allowed
16 us very early in the post-surgical period to switch from a FVIII bypassing agent such as
17 rFVIIa to FVIII replacement therapy. After tapering the dose of steroids and continuing
18 cyclophosphamide the patient's FVIII levels finally rose to 57 % three weeks after initiating
19 treatment. Thus, this combined treatment approach is suggested when rapid decrease in
20 inhibitor titers is desired.
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