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Clinical Observation

Rivaroxaban-induced hemorrhage – Acquired hemophilia as a rare cause

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Hemorrhage is a common problem associated with anticoagulation. After introduction of new oral anticoagulants (NOAC) a drug monitoring is no longer necessary. At advanced age, hemorrhage may become a serious side effect of NOAC, especially when other age-associated alterations such as impaired renal function occur. It has been reported that the frequency of fatal or major bleeding is less common under treatment with NOAC compared to Vitamin K antagonists [1]. Here, we report a 88 years old woman with an abdominal hematoma without any accident. The cause of hemorrhage in this case is not due to a new started treatment under NOAC but newly diagnosed acquired hemophilia. Acquired hemophilia A is a rare autoimmune disorder caused by an autoantibody (inhibitor) to factor VIII (FVIII) that interferes with its coagulation function and predisposes to severe, potentially life-threatening hemorrhage [2]. If acquired hemophilia is not detected, the combination with NOAC increases the risk for major potentially life-threatening bleeding.

Key words: Rivaroxaban, Acquired hemophilia, Hemorrhage, Bleeding

INTRODUCTION

NOACs are getting more and more popular in indications where long-term anticoagulation is necessary. The reasons are their relatively easy use and less common bleeding complications under NOACs in comparison to phenprocoumon/warfarin [1 2]. Therefore, after diagnosis of e.g. atrial fibrillation a new therapy under NOACs will be started and regularly check ups of coagulation are not necessary. Minor bleedings under therapy with NOACs are common and underdiagnosed. Therefore, other diseases causing an increased risk of bleeding [3 4] are not well diagnosed, because treatment under NOACs is expected to be the cause. If other coagulopathies are not being detected treatment with NOACs may cause life-threatening major bleed [5]. In this case report, hemophilia A could be identified for a major risk of bleeding. In most cases the reason for hemophilia is idiopathic [6]. Under treatment along the guidelines [7 8] the hematoma declined.

CASE PRESENTATION

A 88 years old woman was admitted to our surgery ward with new onset of pain in the lower abdomen. Due to previously diagnosed atrial fibrillation, the cardiologist had put her on NOAC therapy with Rivaroxaban. A recent fall was denied. On admission, she suffered from an upper respiratory tract infection with a slight cough for three days (Geriatric Assessment see table I) Palpation of the abdomen revealed a painful mass in the right abdominal wall. The laboratory tests showed a hemoglobin of 6.4 mg/dl, altered coagulation parameters (INR 1.2, PTT 173 seconds), the signs of impaired renal function (creatinine 1.5 mg/dl, GFR 34.6 ml/min), and slightly elevated infection parameters (CRP 1.43 mg/dl). The remaining laboratory tests were normal. On CT-scan a 12 x 8.5 x 5 cm hematoma was detected in the abdominal wall (Fig. 1).

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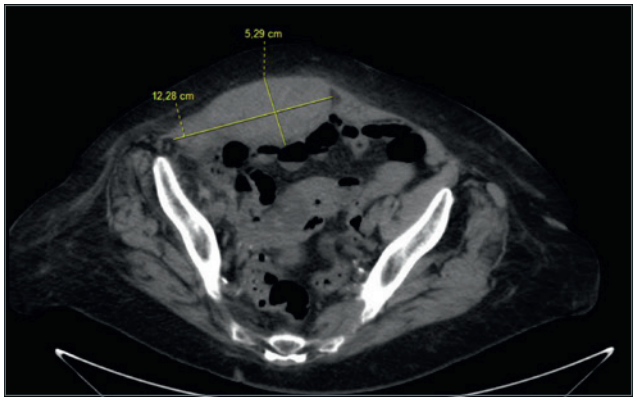

Figure 1. Hematoma in the right abdominal wall due to acquired hemophilia A and NOAC therapy.

The surgeons recommended a conservative management. The bleeding was interpreted as the result of the newly started NOAC therapy in combination with frequent coughing due to the respiratory tract infection. Therapy with Rivaroxaban was discontinued, and the patient was transferred to our geriatric ward to adjust pain management and to start mobilisation.

During therapy in the geriatric department laboratory findings revealed a persistently increased PTT (> 100 sec.), although the therapy with anticoagulants had been discontinued. The INR has been normalized in the meantime. Extended blood coagulation analysis revealed antibodies against FVIII with significantly decreased FVIII blood levels (< 1%, range of normal values 60-130%) as indication for the diagnosis of an acquired hemophilia A.

We further investigated the patient's history which revealed several minor skin hematomas in the past. The patient's opinion was that treatment with acetyl-salicylic acid (ASA) has been the reason for the previous hematomas.

To eliminate the antibodies against FVIII immunosuppressive treatment with prednisolone in combination with cyclophosphamide was initiated according to the current recommendations for the treatment of acquired hemophilia [8]. As the patient's renal function was impaired cyclophosphamide treatment required close monitoring of renal function tests. After two weeks, renal function decreased further. Therefore, cyclophosphamide treatment was discontinued and steroid monotherapy was continued. Within 6 weeks of therapy, FVIII blood levels returned to normal levels. A new bleeding did not occur and the patient could be discharged home free of symptoms. A further anticoagulation has been started by her general practitioner.

DISCUSSION

To our knowledge this is the first case report in the literature with hemorrhaged caused by acquired hemophilia in combination with NOAC therapy. Acquired hemophilia A is often diagnosed rather late. Although acquired hemophilia rarely occurs in the older age population, the incidence is 1:100.000. In our case the diagnosis was masked by therapies with ASA and NOAC. Persistent prolongation of the PTT despite discontinuation of NOAC therapy led to the diagnosis of FVIII antibodies. Isolated prolongation of the PTT with normal INR values can also be seen in patients with antiphospholipid antibody syndrome, medications such as heparin, or antibodies against factor IX and XII, and deficiency of factor VIII [3 4].

Acquired hemophilia A is most frequently associated with autoimmune diseases, solid tumors, lymphoproliferative diseases, pregnancy, and drug reactions. However, about 50% are idiopathic [6]. In emergency cases also treatment with recombinant activated FVIII is possible [7]. In our case FVIII substitution was not necessary because of a non life-threatening situation. It should be pointed out that even major bleedings, e.g. with cerebral hemorrhage, may occur spontaneously or due to trauma as cause of acquired hemophilia [5]. The overall mortality of acquired hemophilia-induced hemorrhage has been reported to be 31-33% [9 10].

CONCLUSIONS

Analyzing coagulation blood parameters before starting therapy with NOAC is necessary to exclude hemophilia or other coagulation pathologies.

Table I. Geriatric Assessment (on admission).

Time up and go	Not possible due to pain
Geriatric depression scale	1 (normal)
Clock test	2 (light restrictions)
Mini mental state status	30 (normal)
Time up and go (14th day)	20 seconds
Social assessment	Lives alone, until admission independent, use of walking frame

Conflicts of Interest Statement

Authors disclose that they have no potential conflicts of interest. Authors also ensure that they have no potential financial and nonfinancial conflicts of interest.

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