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CASE REPORT

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Post COVID-19 acquired haemophilia A treated with recombinant porcine factor VIII

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Summary

Acquired haemophilia A (AHA) is a rare bleeding disorder resulting from autoimmune reaction against factor VIII, which may occur in patients with viral infections. Treatment with recombinant porcine factor VIII has been proven to be effective amongst patients with AHA. Its effectiveness is enhanced by the possibility of adjusting the dosage to the peak and trough levels of factor VIII.

We present here a case report of a patient who developed AHA three months after Sars-Cov-2 infection. He was the one of the first persons in Poland to be treated with rpFVIII.

Key words: acquired haemophilia A, post-COVID-19 AHA, recombinant porcine factor VIII

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Introduction

Acquired haemophilia A (AHA) is a rare bleeding disorder caused by autoantibodies (inhibitors) against factor VIII (FVIII). The main groups of patients affected by the disorder are the elderly with comorbidities as well as pregnant women [1].

AHA is a severe bleeding disorder. Its clinical manifestation, in contrast to congenital haemophilia A, includes extensive subcutaneous or mucosal hematomas and prolonged wound bleeding after surgical operations or tooth extractions [1, 2]. No strict relationship between the FVIII activity in plasma and the degree of bleeding disorder has been determined. The treatment of choice are bypassing agents such as recombinant factor VIIa or activated prothrombin complex concentrate (aPCC) along with immunosuppressants such as prednisone, cyclophosphamide or rituximab [3].

A relatively new bypassing agent-option for patients with factor VIII inhibitors is recombinant porcine factor VIII (rpFVIII). It outweighs human FVIII in lower cross-reactivity with inhibitor anti-FVIII antibodies and has the potential to secure hemostasis in patients, who were previously unsuccessfully treated with human FVIII products [3]. Due to high purity it minimizes the risk of infection and toxicity as compared to plasma-derived porcine FVIII [4, 5].

Approximately 50% of AHA patients have concomitant disorders, particularly autoimmune diseases or malignancies [3]. The COVID-19 pandemic has given rise to the question whether the infection may trigger the occurrence of AHA. So far, the knowledge on the subject has been based on

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individual case reports and studies in small groups of patients [6].

We present here a case report of a patient who developed AHA three months after SARSCoV-2 infection. He was one of the first patients in Poland to be treated with rpFVIII.

Case presentation

A 86-year-old caucasian male was admitted through the emergency room to the General Haematology Inpatient Clinic due to spontaneous ecchymoses on the limbs and trunk that had been appearing for about a week. The patient's medical history included coronary artery disease with unstable angina episode and percutaneous coronary intervention with implantation of 2 stents as well as acute ST-elevation myocardial infarction, heart failure (NYHA II class), mitral, tricuspid and pulmonary valve regurgitation, well-controlled hypertension, chronic kidney disease stage II and hearing impairment. Three months prior to admission, he had a COVID-19 infection, which was treated with molnupiravir and required no hospitalization.

On admission, the patient presented extensive subcutaneous ecchymoses on the upper and lower limbs (both left and right), on the thorax and abdomen lateral regions as well as the lumbar region (Fig. 1, 2). Laboratory tests revealed prolonged activated partial thromboplastin time (aPTT) — 79.2 s (normal range 25.4–36.9 s), normocytic anaemia with haemoglobin (Hgb) — 10.4 g/dl and slightly elevated white blood cell count (WBC) — 11.95 × $10^3/\mu$l. No signs of thrombocytopenia were detected; the international normalized ratio (INR) and thrombin time (TT) were within the normal range.

Further tests revealed factor VIII level below 1% and no correction in the mixing study, which was suggestive of the presence of an inhibitor. The results led to the diagnosis of AHA. The treatment consisted in: administration of a bypassing agent (recombinant human coagulation Factor VIIa — eptacog alfa 7 mg intravenously (iv) every 6 hours) and eradication of inhibitor (prednisone 1 mg/kg per day and cyclophosphamide 2 mg/kg per day — factor VIII < 1% and factor VIII inhibitor 21 BU/ml).

After 24 hours, a recombinant porcine factor VIII (susoctocog alfa) was introduced as the bypassing agent at the initial dose of 100 units/kg iv 4 times a day. The dosage control was more effective and the risk of haemorrhagic and thrombotic events was reduced [7] (Fig. 3).

Figure 1. Extensive ecchymosis of the right upper limb

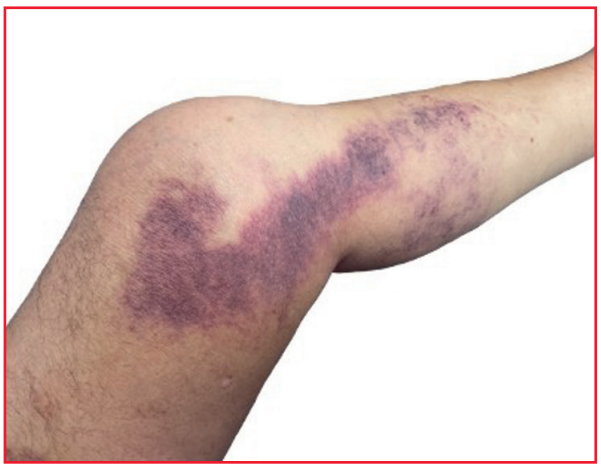

Figure 2. Echymosis of the lower limb

The treatment resulted in the elimination of the inhibitor and improvement of the patient's clinical condition. The daily dose of rpFVIII was gradually reduced until termination of the treatment. At discharge the patient's factor VIII level was 51%, aPTT — 30.7 s, Hgb — 12.5 g/dl, WBC — 9.73 x $10^3/\mu$l and there was no need for haemostatic treatment, only inhibitor eradication drugs.

During hospitalisation the patient was screened for causes of AHA. Whole-body computed tomography (CT) was performed as well as tumour marker tests. The outcome was negative. The results of blood tests for autoimmune diseases and hepatitis panels were negative as well.

Discussion

Although in about 50% of cases, no relationship between AHA and other diseases has been found, the awareness that some disorders may coexist with AHA is crucial for timely diagnosis and more effective treatment [1]. AHA is an autoimmune disorder, which may affect patients with

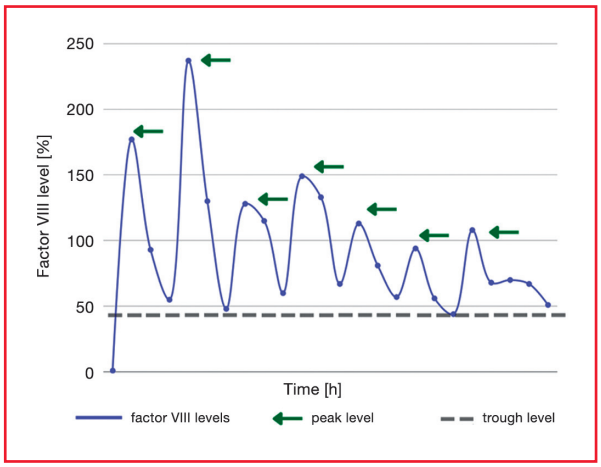

Figure 3. Factor VIII levels according to the dosage of recombinant porcine factor VIII (rpFVIII). The peak levels correspond to the levels achieved 30 minutes after the application of rpFVIII. Green arrow indicates the peak level and grey line the trough level

viral illnesses (eg. human immunodeficiency virus (HIV), Hepatitis B and C viruses or Epstein-Barr virus (EBV) [8]. Thus, the patient's history of Sars-Cov-2 infection three months prior to AHA diagnosis raises the question of a relationship between infection and disease. There are case reports documenting post-COVID-19 AHA [9]. The higher number of T-helper 17 lymphocytes has been found to contribute to the development of AHA. In this context, the dysregulated immune response and interplay between T-helper 17 and suppressor T-cells caused by viral infection (eg. COVID-19) would explain the relationship [10].

Our patient was one of the first in Poland to be treated with rpFVIII which has recently become available as the treatment option for AHA patients. RpFVIII is a highly purified protein with the same biochemical and hemostatic properties as plasma-derived porcine FVIII but much higher safety profile and lower risk of infection and toxicity [11].

The cost of the rpFVIII therapy varies because the dosage of this bypassing agent (as the only one) is adjusted to the peak and trough levels of factor VIII. In terms of cost-effectiveness the economic analysis by Kim et.al., demonstrated that rpFVIII therapy comes second after aPCC [12]. Fortunately, the rpFVIII therapy is refunded in Poland and it is now accessible just as any other bypassing therapy. The monitoring of factor VIII levels serves to optimize the treatment and to minimalize the thromboembolic risk, which is not only beneficial for the patient's clinical condition but also cost-effective [13]. Our patient received a total of 126 000 IU of susoctocog alfaqat at the cost of approximately 800 thousand zloty. The corresponding dosage of eptacog alfa for the same patient would be 315 mg, at a cost of about 900 thousand zlotys [14, 15]. With this in mind, the rpFVIII treatment — though relatively new — should be considered a more affordable therapeutic approach.

The rpFVIII doses are adjusted to FVIII levels which must be closely monitored. The initial recommended dose is 200 IU per kg body weight and should then be adapted to maintain the factor VIII levels above 50% at no clinical signs of bleeding. There are no clear guidelines regarding the length of rpFVIII therapy. The assessment of the therapeutic efficacy is based on the clinical condition of the patient and determined by the physician's experience. For major bleeding (traumatic, intracranial or postoperative bleeds) the ultimate aim is to maintain the FVIII level at above 80% and for all other bleeding episodes at the level of above 50% [3].

Conclusions

There is a possible correlation between COVID-19 and AHA. However, the mechanism underlying this relationship as well as the rationale behind it requires further analysis. Recombinant porcine factor VIII has been proved effective in the treatment of AHA patients. Adjustment of the dose to FVIII levels enables better control of therapy, minimizes the thromboembolic risk and is also more cost-effective.

Authors contributions

MW, and TR suggested the idea of presenting the case report; MW was responsible for patient management; WR, MW contributed to writing the article. All authors (WR, MW, TR) contributed to revising and editing the manuscript.

Conflict of interest: none declared

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