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SHORT COMMUNICATION

Will Emicizumab be the support for surgeons in acquired haemophilia?

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ABSTRACT

Life-threatening bleeding during surgery is always a problem for the surgeon. In this paper, we have highlighted the problem of insufficient diagnosis of acquired haemophilia, as issues omitted by non-haematologists. Based on a clinical case and available literature, we presented the problem of acquired haemophilia and the latest methods for its treatment. Haemophilia is a problem for non-haematologist professionals. It is important to note that prolonged bleeding may be its symptom. There is now a new antibody emicizumab that has the potential to become an important aid in the work of surgeons.

***Keywords*:** emicizumab, bleeding, acquired haemophilia

1. INTRODUCTION

Surgeons have to deal with numerous problems that may appear during perioperative period. One of the most serious, life-threatening issue is unmanageable bleeding. Some of the

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causes of bleeding can be predicted earlier, such as chronic use of anticoagulants, liver failure or genetic coagulation disorders. Unfortunately, we can not predict the acquired coagulation disorders and it is the risk of each surgical procedure, especially in infected patients. When we analysed literature about the acquired coagulation disorders, we focused on acquired haemophilia (AH). This disorder is combined with the appearance of autoantibodies against endogenous FVIII. Clinically, acquired haemophilia is similar to severe hemophilia A. Both men and women can suffer on this disease. It is rare disorder, because the estimated annual incidence oscillates around 1-2 people per million.

The clinical picture is dominated by spontaneous and traumatic extensive extravasation of blood under the skin, less frequent mucous bleeding or massive hemorrhage directly life-threatening. It is assumed that the mortality rate is 9-33%, however, these values may be underestimated due to the low recognition of this disease. It is dictated by a small awareness about it, but also because of its acute course. The scale of the problem can be seen on the basis of EACH2 data, which shows the time needed to make an accurate diagnosis. Data showed that although 37% and 26% of patients were definitely diagnosed with AH within 1 d and 1 wk of initial bleeding, respectively, a considerable diagnostic delay of >1 wk to 1 month, 1–6 months and >6 months occurred in 22%, 10% and 1% of cases, respectively. [1-3]

Partial thromboplastin time after activation (APTT, activated partial thromboplastin time) at correct results of other hemostasis screening tests (platelet counts, prothrombin time, thrombin counts, and fibrinogen content) are characteristical factors of acquired hemofilia. Final recognition of AH is determined by the determination of antibody neutralizing FVIII. In the treatment of bleeding, recombinant activated factor VII (rVIIa) and activated prothrombin complex agents (aPCC, activated prothrombin complex concentrate) are used. Transfusion of freshly frozen plasma and cryoprecipitate are ineffective. The use of immunosuppressive drugs allows the majority of patients with acquired haemophilia to eliminate autoantibodies and restore the proper activity of FVIII in plasma. [4]

2. DISCUSSION & RESULTS

Patient, aged 53 was admitted to Pulmonology Department because of complicated pneumonia. CT scans revealed pyothorax and the patient was transferred to Thoracic Surgery Department where he underwent thoracotomy and decortication. Due to ventilation insufficiency patient was then admitted to ICU. On the first postoperative day the patient's state normalized and he was extubated. On the third day decrease in patient's blood count was notified. CT revealed hematoma in pleural cavity and patient was qualified for rethoracotomy. Blood clots were evacuated, however the source of bleeding couldn't be found.

On the fourth day due to symptoms of massive bleeding an urgent rethoracotomy was performed. Again the source of bleeding wasn't found so pleural tamponade with the use of surgical gauze was performed.

Bleeding to pleural cavity continued, demanding consecutive reoperations and blood transfusions. Laboratory tests showed significant increase of APTT time (143,4s, reference 25,4–36,9), decrease of VIII factor activity (4%) and presence of VIII factor inhibitor (7,5jB), which eventually allowed to diagnose the acquired haemophilia. Patient was administered NovoSeven (Novo Nordisk) 90μm/kg every 3 hours and Solumedrol (Pfizer Europe) 160 mg/day.

On the following days surgical gauzes were being exchanged, administration of blood substitutes and NovoSeven were continued. The activity of VIII factor was systematically increasing, count of antibodies decreasing. On the twentieth day final closer of thoracostomy was possible.

In literature, we can find numerous cases of patients with acquired haemophilia. Sometimes after long-term illness, like the patient treated for 7 years due to rheumatoid arthritis [5]. In others, the sudden appearance of spontaneous spinal epidural haematoma [6]. We also can not disregard minor medical procedures that may also contribute to the apperance of HA as, for example, tooth extraction [7]. The presence of major bleeding in patients with solid tumors, massive inflammation or need for serious surgical procedure should also give us suspicions. [8]

Currently, there are numerous methods used to treat acquired haemophilia. However, the most important thing is the suspicion of the disease itself.

Table 1. Treatment products for patients with Acquired Haemophilia [1, 9, 10].

Category	Product
Hemostatic agents	Activated prothrombin complex concentrates, Recombinant factor VIIa, Factor VIII concentrates
Immunosuppressive agents	Prednisolone, cyclophosphamide, Cyclosporine, intravenous immunoglobulin, vincristine, mycophenolate, azathioprine
Monoclonal antibody	Rituximab
Other inhibitor eradication procedures	Immunoadsorption, immune tolerance induction, Plasmapheresis

Research on new treatments for haemophilia A, B as well as acquired haemophilia is ongoing. Currently works are underway (Phase 3) on the use of Emicizumab (ACE910) which is recombinant, humanized, asymmetric bispecific antibody that functions to bring activated FIX (FIXa) and zymogen FX into an appropriate steric approach to medicate the FX of FXa thus mimicking the cofactor function of FVIIIa.

The studies that have appeared so far show a number of advantages of its use. By some authors, it is described as a breakthrough in the treatment of haemophilia. Due to its effectiveness, as well as a convenient dosage method. Subcutaneous emicizumab-kxwh (Hemlibra®) has been approved in the United States for 12 months of age with a haemophilia A with FVIII inhibitors. Regulatory approval in several countries around the world, including EU and Japan is awaited. [11-14]

It is important to expect more papers on the effects of distant use of Emicizumab, as well as cases of use with acquired haemophilia.

3. CONCLUSIONS

Although AH is rare, but it is treatable coagulation disorder. Development of autoantibody inhibitors against endogenous FVIII can lead to lifethreatening problems. Early diagnosis is essential to provide appropriate treatment and reducing morbidity and mortality associated with this condition. Diagnosis of Acquired Haemophilia is often difficult due to the lack of history of bleeding (both in patient and is family) and the heterogeneous nature of the condition.

The dissemination of knowledge about this entity among all medical specialties is essential, as non-haematologist professionals will often be those who establish the suspected diagnosis. This allows patients to access the specialists in coagulopathy, allowing diagnostic confirmation and the best treatment.

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