ABSTRACT

Introduction: Acquired hemophilia is a severe, sometimes even fatal condition of impaired coagulation. It most often leads to severe mucocutaneous, gastrointestinal, urinary, and, rarely, intracranial bleeding. This disorder occurs due to the production of antibodies against clotting factor VIII (F VIII), which interfere with its normal function. In laboratory analyses, prolonged activated partial thromboplastin time (aPTT), which cannot be normalized after being mixed with pooled normal plasma, is noticeable.

Case report: In this article, the clinical course of the disease is described in a patient with acquired hemophilia, who was treated with oral anticoagulant therapy, and who initially also had prolonged prothrombin time, measured in international normalized ratio (INR) units, which measure how long it takes for a clot to form in a blood sample. Hemorrhagic syndrome was explained by iatrogenic effect. However, since bleeding continued after INR normalization, it was suspected that there was a different cause of hemorrhagic syndrome. The aPTT mixing test was performed (mixing an equal volume of the patient’s plasma and normal pooled plasma (NPP) and repeating the aPTT test immediately and after one-hour incubation), after which the aPTT remained prolonged. This proved the presence of coagulation inhibitors, which is why acquired hemophilia was suspected. The patient was referred to a tertiary medical institution for further diagnostics and treatment.

Conclusion: The objective of this case report is to show that patients with hemorrhagic syndrome, who are on anticoagulant therapy, may develop hemorrhagic syndrome for a different, non-iatrogenic reason. The purpose of the study is to draw the attention of medical doctors to various causes of hemorrhagic syndrome in patients receiving anticoagulant therapy.

Key words: acquired hemophilia, oral anticoagulant therapy, prolonged activated partial thromboplastin time, hemorrhagic syndrome
INTRODUCTION

Acquired hemophilia is a rare condition of impaired coagulation with a yearly incidence of around 0.2 to 1 case per 1,000,000 population. The cause of the disease is the presence of antibodies to an essential blood-clotting protein, the so-called factor VIII (F VIII), also known as anti-hemophilic factor VIII. The production of antibodies to F VIII leads to clotting inefficiency [1-7]. It occurs in individuals who had previously not had any bleeding disorder. The incidence is similar in both genders, with a biphasic incidence distribution curve, between 20 and 40 years (more common in women) and between 60 and 80 years (more common in men). The most commonly occurring antibodies are polyclonal IgG4. In about 50% of cases, the cause of the disease is idiopathic, and in 50% of cases it is associated with various conditions [1-4].

The conditions that are referred to as the most common causes of the presence of antibodies against factor VIII within acquired hemophilia are the following: autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome, myasthenia gravis, multiple sclerosis, autoimmune hypothyroidism, Graves’ disease), inflammatory bowel diseases, asthma, graft versus host disease (GVHD) after bone marrow transplantation, pregnancy, as well as the period of 4 months to one year after delivery. The secondary cause are malignancies – hematological malignancies (lymphoproliferative diseases, osteomyelofibrosis, erythroleukemia) and solid tumors (prostate, breast, renal, gastrointestinal, pancreatic, melanoma). Sometimes antibodies are retained even after the tumor has been removed. Drugs that affect prothrombin time are the following: penicillin, sulfonamides, quinolones, chloramphenicol, fludarabine, phenytoin, clopidogrel, levodopa, as well as the BCG vaccine. Cases associated with direct oral anticoagulants, as well as surgical procedures, have also been described in good clinical practice guides [1-5,8,9].

The clinical manifestation is usually severe mucocutaneous bleeding, as well as soft tissue bleeding (with the development of the compartment syndrome), gastrointestinal and urogenital bleeding, sometimes even intracranial bleeding. Unlike congenital hemophilia, bleeding in the joints is very rare [2,3,5]. The laboratory results may show reduced levels of hemoglobin, while the platelet count, prothrombin time (INR), and fibrinogen remain within the normal range. However, activated partial thromboplastin time (aPTT) is prolonged. The presence of antibodies is proven by the mixing test. An easily performed mixing test of the patient’s plasma and the plasma of a healthy person at 37 °C for 2 hours, wherein the patient’s aPTT is not normalized, indicates the presence of coagulation factor inhibitors as well as the presence of acquired hemophilia [6,10-11].

UVOD

Stečena hemofilija je retko stanje poremećene koagulacije sa incidencijom od oko 0,2 do 1 slučaja na 1.000.000 stanovnika godišnje. Uzrok bolesti je pojava antitela na esencijalni protein zgrušavanja krvi, tako- zvani faktor koagulacije VIII (F VIII), poznat kao antihe- molifni faktor. Stvaranje antitela na F VIII dovodi do po- remećaja u zgrušavanju [1-7]. Javlja se kod osoba koje prethodno nisu imale poremećaj koagulacije. Inciden- cija je slična kod oba pola, sa bifazičnom krivom dis- tribucijom incidencije između 20 i 40 godina (češće kod žena) i između 60 i 80 godina (češće kod muškaraca). Sama antitela su najčešće poliklonski IgG4. U oko 50% slučajeva uzrok bolesti je idiopatski, a u 50% slučajeva, uzrok je povezan sa različitim stanjima [1-4].

Kao najčešći uzročnici pojave antitela na faktor VIII, u okviru stečene hemofilije, navode se autoimmune bolesti (reumatoidni artritis, sistemski eritemski lupus, Sjogrenov sindrom, miastenija gravis, multipla sklero- za, autoimuni hipotireoidizam, Grejsova bolest), zapaljenske bolesti creva, astma, bolest kajma protiv domaćina (engl. *graft versus host disease* – GVHD) posle allogene transplantation of bone marrow. The aPTT is not normalized, indicates the presence of acquired hemophilia [6,10-11]. After
izraženog u Bethesda jedinicama. Lečenje podrazumeva kontrolu krvačenja i terapiju koja će smanjiti nivo inhibitora. U cilju zaustavljanja krvačenja, neophodna je terapija bypassing sredstvima, kao što su rekombinantni faktor VII (rVII NovoSeven) ili aktivirani protrombinski kompleks FEIBA (Factor Eight Inhibitor Bypassing Activity) — ako je nivo inhibitora veći od 5 Bethesda jedinica. Ako je nivo inhibitora manji od 5 Bethesda jedinica, ordinira se koncentrat faktora VIII ili DDAVP (dez-mopresin) [1,6,8].

Istovremeno se uvodi i terapija kortikosteroidima ili čak ciklofosfamidom, čiji je cilj smanjenje sinteze inhibitora koagulacije, u a rezistentnim oblicima može se ordinirati i rituximab, takrolimus, ciklosporin i mikofenolat mofetil, kao i primeniti proceduru ekstrakorporalne plazmafereze sa imunoadsorpcijom. Obično se nivo inhibitora postepeno smanjuje tokom više narednih meseci [6,8,10-11]. Kod bolesnika koji su na oralnoj antikoagulantnoj terapiji a imaju hemoragijski sindrom ovo stanje se može prevideti, jer se obično kontroliše samo protrombinsko vreme [12-15].

Cilj ovog prikaza slučaja jeste da se pokaže da bolesnici sa hemoragijskim sindromom koji sa na terapiji antikoagulantima mogu da razviju hemoragijski sindrom i iz drugog, nejatrogenog razloga. Na takvu mogućnost posebno treba misliti kada se, i pored korekcije vrednosti INR-a, hemoragijski sindrom klinički i dalje održava [15].

PRIKAZ SLUČAJA

Prikazan je bolesnik starosti 66 godina, koji se dve godine unazad lečio od dilatativne kardiomiopatije (ejeckcija frakcija = 30%, mitralna regurgitacija = 3+, end-dijastolni dijametar leve komore = 71 mm), a kome je zbog postojanja perzistentne atrialne fibrilacije uvedena oralna antikoagulantna terapija kumarinskim derivatom. Tokom dve godine, pacijent je redovno praćen ambulantno, bez hemoragijskog sindroma i bez izraženog u

Rekombinantni faktor VII (rVII NovoSeven) ili aktivirani protrombinski kompleks FEIBA (factor eight inhibitor bypassing activity) je sredstvo koji može da pomogne u zaustavljanju krvarenja kod bolesnika na oralnoj antikoagulantnoj terapiji. Ako nivo inhibitora je veći od 5 Bethesda jedinica, ordinira se koncentrat faktora VIII ili DDAVP (dez-mopresin) [1,6,8].

Ako je nivo inhibitora manji od 5 Bethesda jedinica, se smatra da je 'životna' hemofilija kod bolesnika na oralnoj antikoagulantnoj terapiji – prikaz slučaja

Acquired hemophilia in patients on oral anticoagulant therapy – case report

We present a 66-year-old patient who had previously been treated for dilated cardiomyopathy for two years (ejection fraction = 30%, mitral regurgitation = 3+, left ventricular end-diastolic diameter = 71 mm). Due to the presence of persistent atrial fibrillation, oral anticoagulant therapy with coumarin derivatives was introduced. He was regularly monitored for two years with no sign of hemorrhagic syndrome and without a significant increase in prothrombin time (PT). Four weeks before the presentation described in this paper, the patient noticed fresh blood in his stool with pain in the lower abdomen. He was hospitalized in the surgery department with the following laboratory results: INR = 4.84 (0.70 - 1.2), aPTT = 83.9 s (26.00 s – 36.00 s). The patient received three units of fresh frozen plasma, upon which INR was 2.8, aPTT was not repeated, bleeding was stopped, and there was no decrease in the hemoglobin level. Colonoscopy was scheduled for the patient, and he was released to recover at home.

When the patient came in for coronary angiography, scheduled at a tertiary healthcare facility, he
introduced odeljenju, radi daljeg ispitivanja. Zbog loše saniranih zuba pregledan je od strane maksilofacialnog hirurga, a zbog prethodne pojave krvi u stolici urađena je i gastroskopija. U tom trenutku je laboratorijska analiza pokazivala da je INR bio u terapijskom opsegu, aPTT nije rađeno, dok su svi ostali parametri bili uredni, uključujući i nivo hemoglobina. Trećeg dana hospitalizacije, ovočena je pojava hematoma na levjoj natko- lenici; bolesnik je naveo da je prethodno ambulantno primio intramuskularnu injekciju. Ukinuta je oralna antikoagulantna terapija i pacijent je preveden na nisko molekularni heparin (engl. low molecular weight he- parin – LMWH). U laboratorijskom nalazu, INR je bio u fiziološkim okvirima, a aPTT vrednost nije određivana. Četvrtog dana hospitalizacije, u levjoj podlaktici, na mestu gde je bila plasirana braunila, dolazi do pojave intenzivnog krvasculara koje se moralo hirurški zaustaviti. Bolesnik je naredna dva dana žalio na progresivno otežano gutanje. Pet dana posle gastroskopije, uočava se gotovo nemoguće gutanje, stridorozno disanje, kao i ogroman hematom prednjeg zida vrata, poda usne duplje i jezika (Slike 1a, 1b). Ultrazvuk vrata ukazao je na izrazito edematozno izmenjeno tkivo praktično svih regija vrata. Komputerizovana tomografija vrata opisala je supraglotično, na zadnjem zidu vrata, sa propagacijom desno – an irregular formation (hematoma), 25 x 20 mm, koja je gotovo u potpunosti sužavala vazdušni stub opisane regije. Obe submandibularne žlezde su bile otečene, uvećane, heterodenzne, komprimujući okoline mekotkive strukture i mišićne strukture od kojih su se teško diferencirale, sužavajući lumen vazdušnog stuba na tom nivou. Tada je u laboratorijskoj zabeležen pod vrednosti hemoglobina za 30 g, INR je bio normalan, a aPTT, koje je bilo 58,3 s (26,00 s – 36,00 s). Urađen je test mešanja sa normalnom plazmom, posle čega je aPTT i da- lje bilo produženo, što je bio razlog da se posumnja na postojanje inhibitora koagulacije u plazmi bolesnika.

S obzirom na preporuku lečenje, kao i nemogućnost dalje dijagnostike (određivanje nivoa F VIII i nivoa inhibitora Bethesda metodom), bolesnik je upoćen u terciarnu ustanovu, gde je ustanovljen snižen nivo F VIII, kao i povišen nivo inhibitora F VIII od 9 Bethesda jedinica. Ordinirana je FEIBA terapija uz istovremeno započinjanje terapije pronisonom i ciklofosfamidom. Detaljnim kliničkim i imunološkim analizama nije usta- novljeno sekundarno stanje koje bi moglo biti uzrok stečene hemofilije. S obzirom na persistentnu atrijalnu fibrilaciju, bolesniku je, po normalizaciji nivoa F VIII nakon primenjene navedene terapije, nastavljena oralna antikoagulantna terapija, oko 6 nedelja od početka le- čenja.

had an elevated C reactive protein level of 30 mg/L. Coronary angiography was, therefore, postponed and he was again hospitalized for further examination, this time at the internal medicine department. Due to the poor condition of his teeth, the patient was examined by a maxillofacial surgeon. Due to previously registered blood in his stool, gastroscopy was also performed. At that point, the INR level was within the normal therapeutic range, while aPTT was not tested, and all other parameters were normal, including the hemoglobin level. On the third day of hospitalization, a hematoma was registered on the left thigh, and the patient stated that he had previously received an intramuscular injection. Oral anticoagulant therapy was discontinued and replaced with low molecular weight heparin (LMWH). The INR level was within the normal range, while aPTT was not tested. On the fourth day of the patient’s hospital stay, there was copious bleeding at the site where a cannula had been placed on the patient’s left forearm. The bleeding had to be surgically stopped. Over the next two days, the patient complained of progressively greater and greater difficulty swallowing. Five days after gastroscopy, it was evident that it was almost impossible for the patient to swallow, stridor was present, as well as a massive hematoma of the front wall of the neck, floor of the oral cavity, and tongue (Figures 1a, 1b). Ultrasound of the neck revealed extremely edema- tous tissue of virtually all compartments of the neck. The CT of the neck showed – supraglottically, on the posterior wall of the neck, with propagation to the right – an irregular formation (hematoma), 25 x 20 mm in diameter, which almost completely narrowed the airway in the described region. Both subman- dibular glands were swollen, enlarged, heterodense, compressing the surrounding soft tissue structures and muscular structures. It was difficult to differenti- ate the glands from the surrounding tissue and they were narrowing the lumen of the airway. Laboratory test results showed a drop in the level of hemoglobin by 30 g, the INR value was normal, aPTT was tested for the first time, and was 58.3 s (26.00 s – 36.00 s). The mixing test with normal plasma was then performed showing that aPTT was still prolonged, which led to the suspicion that coagulation inhibitors were pres- ent in the patient’s plasma.

Given the recommended treatment, as well as the fact that it was not possible to perform further diagnostics (determining F VIII levels and inhibitor levels with the Bethesda method) within the facility that the patient was hospitalized in, the patient was referred to a tertiary medical facility, where a decreased level of F VIII was found, as well as an increased level of F
DISKUSIJA

Poznato je da kumarinski derivati produžavaju INR i aPTT zbog zajedničkog efekta na nivo faktora koagulacije IX [6,10-11]. U literaturi se navode slučajevi bolesnika sa hemoragijskim sindromom koji su na oralnoj antikoagulantnoj terapiji kumarinskim derivatima, kod kojih se i INR i aPTT obično kontrolišu samo pri prezentaciji bolesti, dok se nadalje prati samo INR. [15–18]. Ako je krvenje značajnije, ordinira se sveža smrznuta plazma ili vitamin K, obično samo uz kontrolu INR-a u daljem toku bolesti. S obzirom na veliki broj pacijenata na ovoj terapiji i relativno retku pojavu drugih uzroka krvenja, posebno stečene hemofilije, drugi razlozi hemoragijskog sindroma se retko razmatraju.

Međutim, u situacijama kada se hemoragijski sindrom i dalje održava po normalizaciji INR-a, potrebno je posumnjati na neki drugi uzrok ovakvog stanja i VIII inhibitors, measuring 9 Bethesda units. FEIBA was administered and the patient was also started on prednisone and cyclophosphamide at the same time. Detailed clinical and immunological examinations and analyses could not identify a secondary condition that could be the cause of acquired hemophilia. Due to persistent atrial fibrillation, the patient continued with oral anticoagulant therapy after the normalization of F VIII levels, about 6 weeks after the beginning of treatment.

DISCUSSION

Coumarin derivatives are known to prolong INR and aPTT due to their combined effect on coagulation factor IX levels. [6,10-11]. Cases have been reported of hemorrhagic syndrome occurring in patients on oral anticoagulant therapy in the form of coumarin derivatives, in whom both INR and aPTT are usually monitored only on presentation of the disease, while only
naložiti ponovno testiranje celokupnog koagulacionog statusa. Produženo aPTT, uz normalizaciju INR-a, uvek ukazuje na stečeni poremećaj koagulacije, posebno kod starijih bolesnika sa komorbiditetima koji imaju opsežna mukokutana krvarenja i krvarenja u mekim tkivima [5]. Kod bolesnika kojeg smo prikazali, a koji je imao krvarenje iz digestivnog trakta i opsežno mukokutano krvarenje, posebno u predelu orofarinksa, inicijalno značajno produženo aPTT je shvaćeno kao posledica oralne antikoagulantne terapije. Iako je bolesnik gotovo svo vreme bio pod kontrolom lekara, sumnja da se radi o nekom pridruženom poremećaju koagulacije je postavljena tek nakon 5 nedelja od prve manifestacije bolesti. U trenutku kada je postavljena dijagnoza, bolesnik je imao po život opasno krvarenje u orofarinksu, koje je bilo isprovocirano gastroskopiom. I u literaturnim podacima se navodi kašnjenje u dijagnozi stečene hemofilije kod bolesnika na oralnoj antikoagulantnoj terapiji, što dovodi do često fatalnih krvarenja [13–15]. Svaka invazivna dijagnostika ili hirurška intervencija kod bolesnika sa neprepoznatom stečenom hemofilijom može isprovocirati obilna krvarenja, kao što je bio slučaj kod našeg bolesnika [6,8,18].

Važno je istaći da antiagregacioni lek klopidogrel može dovesti do razvoja stečene hemofilije [20–22]. S obzirom da stečena hemofilija uglavnom daje mukokutana krvarenja, ovakvo krvarenje se lako može pripišati jatrogenom efektu klopidogrela, posebno ako je u kombinaciji sa acetilsalicilnom kiselinom. I kod ovih bolesnika se kasno postavlja dijagnoza stečene hemofilije [18].

U današnje vreme, kada je sve veća upotreba novih oralnih antikoagulantnih lekova (engl. *novel oral anticoagulants – NOACs*) – dabigatran, rivaroksabana, apikabana, važno je napomenuti da su i kod upotrebe ovih lekova opisani slučajevi stečene hemofilije [16,17]. Prilikom ordiniranja NOAC-a obično se ne kontroliše koagulacioni status, ali je značajno naglasiti da vrednosti INR-a i aPTT-a, takođe mogu biti u manjoj meri izmene [5–17,23]. Stoga, svaku pojavu krvarenja, posebno mukokutanog, kod bolesnika na terapiji NOAC-ima treba propratiti novim analizama INR-a i aPTT-a.

**ZAKLJUČAK**

U zaključku, iako je stečena hemofilija retko stanje, treba biti oprezan u kliničkoj praksi kod teških spon-tanih, obično mukokutanih krvarenja, kod bolesnika (posebno starijih) na oralnoj antikoagulantnoj terapiji koji imaju neadekvatno produženo aPTT [11,13,15,18]. Uvek treba imati na umu da se u svakoj medicinskoj biohemijskoj laboratoriji može izvesti lako dostupan test mešanja plazme i tako dokazati prisustvo inhibitora koagulacije i posumnjati na stečenu hemofiliju INR is further monitored on follow-up [15–18]. If the bleeding is significant, fresh frozen plasma or vitamin K is prescribed, with usually only INR being controlled in the further course of the disease. Given the large number of patients on this therapy and the relatively rare occurrence of other causes of bleeding, especially acquired hemophilia, other causes of hemorrhagic syndrome are rarely considered.

However, in situations where hemorrhagic syndrome continues to persist after the normalization of INR, it is necessary to suspect a different cause of this condition and order re-testing of the overall coagulation status. Prolonged aPTT, with normalized INR, always indicates an acquired coagulation disorder, especially in elderly patients with comorbidities who have extensive mucocutaneous bleeding and soft tissue bleeding [5]. In the patient we have presented, who had digestive tract bleeding and extensive mucocutaneous bleeding, particularly in the oropharynx, the initial significantly prolonged aPTT was understood as an effect of oral anticoagulant therapy. Although the patient was under medical supervision almost all the time, the suspicion that it was an associated coagulation disorder was established only 5 weeks after the first manifestation of the disease. At the time of diagnosis, the patient had life-threatening bleeding in the oropharynx, which was provoked by gastroscopy. Delays in the diagnosis of acquired hemophilia leading to frequently fatal bleeding, in patients on oral anticoagulant therapy, have also been reported in literature [13–15]. Any invasive diagnostics or surgical procedure in patients with unrecognized acquired hemophilia can provoke heavy bleeding, as was the case with our patient [6,8,18].

It is important to point out that the antiplatelet drug clopidogrel can lead to the development of acquired hemophilia [20–22]. Since acquired hemophilia mainly causes mucocutaneous bleeding, such bleeding can easily be attributed to the iatrogenic effect of clopidogrel, especially if it is combined with acetylsalicylic acid. Diagnosis of acquired hemophilia in these patients is also delayed. [18].

Nowadays, when the use of new oral anticoagulant drugs (NOAC) is increasing (dabigatran, rivaroxaban, apikaban), it is important to note that cases of acquired hemophilia have also been described with the use of these drugs [16,17]. Coagulation status is not usually monitored with the administration of NOAC, but it is important to note that INR and aPTT values may also be altered to a lesser degree [5–17,23]. Therefore, any occurrence of hemorrhagic, especially mucocutaneous bleeding, in patients on NOAC therapy should be accompanied by new INR and aPTT analyses.
[6-7,10-11,15]. Okavko stanje zahteva neodložnu terapiju specifičnim agensima i zato je važno blagovremeno postaviti dijagnozu.

Sukob interesa: Nije prijavljen.

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