STEČENA HEMOFILIJA KOD BOLESNIKA NA ORALNOJ ANTIKOAGULANTNOJ TERAPIJI - PRIKAZ SLUČAJA

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CASE REPORT

ACQUIRED HEMOPHILIA IN PATIENTS ON ORAL ANTICOAGULANT THERAPY – CASE REPORT

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SAŽETAK

Uvod: Stečena hemofilija je teško, nekada i fatalno stanje poremećene koagulacije. Najčešće dovodi do teških mukokutanih, gastrointestinalnih, urinarnih, retko i intrakranijalnih krvarenja. Razlog ovakvog poremećaja je stvaranje antitela na faktor VIII koagulacije (F VIII), što ometa njegovu normalnu funkciju. U laboratorijskim analizama se uočava produženo aktivirano parcijalno tromboplastinsko vreme (engl. *activated partial thromboplastin time – aPTT*), koje se ne može normalizovati ni posle mešanja sa plazmom zdrave osobe.

Prikaz bolesnika: U ovom radu prikazan je klinički tok kod bolesnika sa stečenom hemofilijom, koji je bio na oralnoj antikoagulantnoj terapiji, a inicijalno je imao i produženo protrombinsko vreme, izraženo jedinicama međunarodnog normalizovanog odnosa (engl. *International normalized ratio - INR*), koji se proračunava na osnovu vremena potrebnog da se formira ugrušak u uzorku krvi. Hemoragijski sindrom je tumačen jatrogenim efektom, a kako se krvarenje nastavilo i nakon normalizacije *INR*-a, posumnjano je na drugi uzrok hemoragijskog sindroma. Urađen je test mešanja plazme bolesnika i plazme zdrave osobe (mešanje jednake zapremine pacijentove plazme i plazme zdrave osobe, te ponavljanje *aPTT* testa odmah, i jedan sat nakon inkubacije), posle čega je *aPTT* ostalo produženo. Ovo je bio dokaz postojanja inhibitora koagulacije, koji je pobudio sumnju na stečenu hemofiliju. Bolesnik je upućen u tercijarnu ustanovu gde je dalje sprovedena dijagnostika i lečenje.

Zaključak: Cilj ovog prikaza slučaja je da se pokaže da bolesnici sa hemoragijskim sindromom koji sa na terapiji antikoagulansima mogu da razviju hemoragijski sindrom i iz drugog, nejatrogenog razloga. Svrha rada je da se skrene pažnja lekara na različite uzroke hemoragijskog sindroma kod bolesnika na antikoagulantnoj terapiji.

Ključne reči: stečena hemofilija, oralna antikoagulantna terapija, produženo aktivirano parcijalno protrombinsko vreme, hemoragijski sindrom

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

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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, takozvani faktor koagulacije VIII (F VIII), poznat kao antihemofilni faktor. Stvaranje antitela na F VIII dovodi do poremećaja u zgrušavanju [1-7]. Javlja se kod osoba koje prethodno nisu imale poremećaj koagulacije. Incidencija je slična kod oba pola, sa bifazičnom krivom distribucije 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 najčešeći uzročnici pojave antitela na faktor VIII, u okviru stečene hemofilije, navode se autoimune bolesti (reumatoidni artritis, sistemski eritemski lupus, Sjogrenov sindrom, miastenija gravis, multipla skleroza, autoimuni hipotireoidizam, Grejvsova bolest), zapaljenske bolesti creva, astma, bolest kalema protiv domaćina (engl. *graft versus host disease – GVHD*) posle alogene transplantacije koštane srži, trudnoća, kao i period od 4 meseca do godinu dana posle porođaja. Sekundarni uzroci su maligniteti – hematološki maligniteti (limfoproliferativne bolesti, osteomijelofibroza, eritroleukemija) i solidni tumori (tumori prostate, dojke, bubrega, gastrointestinalnog trakta, pankreasa, melanom). Nekada se antitela zadržavaju i nakon što je tumor uklonjen. Neki lekovi utiču na protrombinsko vreme, na primer penicilin, sulfonamidi, hinoloni, hloramfenikol, fludarabin, fenitoin, klopidogrel, levodopa, kao i BCG vakcina. U vodičima za dobru kliničku praksu postoje opisane mogućnosti udruženosti sa direktnim oralnim antikoagulansima kao i sa hirurškim intervencijama [1-5,8,9].

Klinička slika se obično manifestuje teškim mukokutanim krvarenjem, krvarenjem u mekim tkivima (uz pojavu kompartment sindroma), gastrointestinalnim i urogenitalnim krvarenjem, a ponekad i intrakranijalnim krvaranjem. Za razliku od nasledne hemofilije, ovde su krvarenja u zglobovima jako retka [2,3,5]. U laboratorijskim nalazima, hemoglobin može biti snižen, dok su broj trombocita, protrombinsko vreme (*INR*) i fibrinogen uredni, ali je aktivirano parcijalno tromboplastinsko vreme (*aPTT*) produženo. Prisustvo antitela se dokazuje testom mešanja sa normalnom plazmom. Lako izvodljiv test mešanja plazme bolesnika i plazme zdrave osobe na temperaturi 37 °C u trajanju od 2 sata, pri čemu se *aPTT* bolesnika ne normalizuje, ukazuje na prisustvo inhibitora faktora koagulacije i na stečenu hemofiliju [6,10-11]. Nakon pozitivnog testa radi se određivanje nivoa F VIII i nivoa inhibitora na F VIII,

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 antihemophilic 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 (lymphproliferative 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]. After

izraženog u *Bethesda* jedinicama. Lečenje podrazumeva kontrolu krvarenja i terapiju koja će smanjiti nivo inhibitora. U cilju zaustavljanja krvarenja, 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 (dezmopresin) [1,6,8].

Istovremeno se uvodi i terapija kortikosteroidima ili čak ciklofosfamidom, čiji je cilj smanjenje sinteze inhibitora koagulacije, a u rezistentnim oblicima može se ordinirati i rituksimab, takrolimus, ciklosporin i mikofenolat mofetil, kao i primeniti procedura 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 antikoagulansima 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 (ejekciona frakcija = 30%, mitralna regurgitacija = 3+, end-dijastolni dijametar leve komore = 71 mm), a kome je zbog postojanja perzistentne atrijalne fibrilacije uvedena oralna antikoagulantna terapija kumarinskim derivatom. Tokom dve godine, pacijent je redovno praćen ambulantno, bez hemoragijskog sindroma i bez značajnog povećanja protrombinskog vremena (engl. *prothrombin time – PT*). Oko 4 nedelje pre prezentacije opisane u ovom radu, bolesnik je primetio pojavu sveže krvi u stolici, uz bolove u donjem delu trbuha.

Pacijent je hospitalizovan na odeljenju hirurgije, sa sledećim vrednostima: *INR* = 4,84 (0,70 - 1,20), *aPTT* = 83,9 s (26.00 s – 36.00 s). Primio je tri jedinice sveže smrznute plazme, *INR* je nakon toga bio 2,8, *aPTT* nije ponavljano, krvarenje se zaustavilo, nije bilo pada vrednosti hemoglobina. Zakazana je kolonoskopija i pacijent je pušten na kućno lečenje.

U daljem toku, pacijent se javio u tercijarnu ustanovu na zakazanu koronarografiju ali je ista odložena zbog povišenog C reaktivnog proteina, koji je iznosio 30 mg/L. Pacijent je ponovo hospitalizovan, sada na

a positive test is established, the Bethesda method is used to determine the level of clotting factor VIII and the level of F VIII inhibitors. Treatment involves bleeding control and therapy aimed at reducing the level of inhibitors. In order to stop the bleeding, treatment with bypassing agents, such as recombinant factor VII (rVII NovoSeven) or the activated prothrombin complex FEIBA (factor eight inhibitor bypassing activity) is necessary – if the level of inhibitors is higher than 5 Bethesda units. If the level of inhibitors is lower than 5 Bethesda units, clotting factor VIII concentrate or DDAVP (desmopressin) is prescribed [1,6,8].

At the same time, treatment with corticosteroids or even cyclophosphamide, aimed at reducing the synthesis of coagulation inhibitors, is introduced. In resistant forms, rituximab, tacrolimus, cyclosporine, and mycophenolat mofetil may be administered, and extracorporeal plasmapheresis and immunoadsorption may be applied. Usually, the level of inhibitors gradually decreases over the following months [6,8,10-11]. In patients on oral anticoagulant therapy who have hemorrhagic syndrome, this condition can be overlooked, since, usually, only the prothrombin time is monitored [12–15].

The aim of this case report is to show that patients with hemorrhagic syndrome who are on oral anticoagulant therapy can develop hemorrhagic syndrome for a different, non-iatrogenic, reason. Such a possibility should be especially considered when, despite the correction of INR, hemorrhagic syndrome still persists, clinically [15].

CASE PRESENTATION

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.

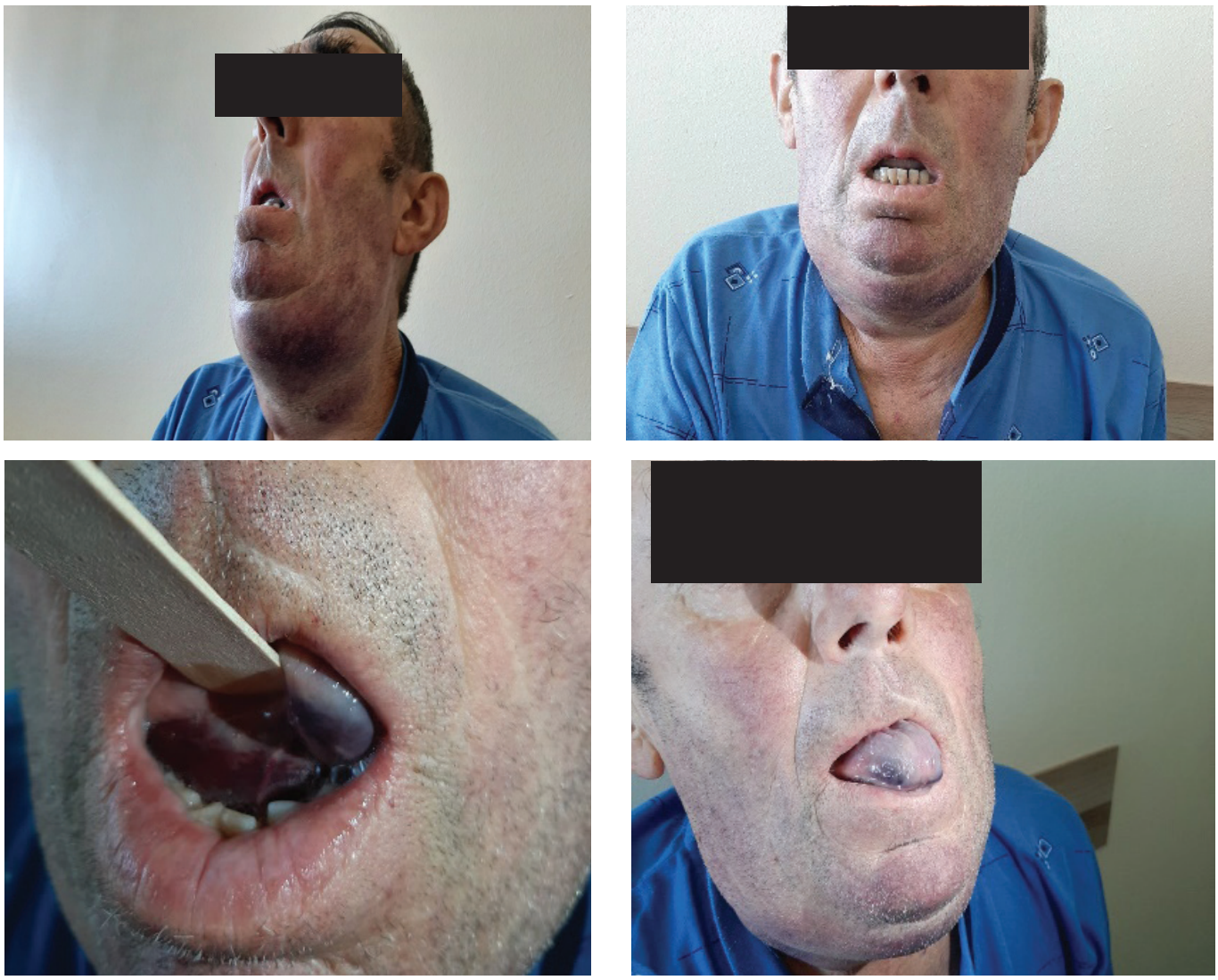
When the patient came in for coronary angiography, scheduled at a tertiary healthcare facility, he

internom odeljenju, radi daljeg ispitivanja. Zbog loše saniranih zuba pregledan je od strane maksilofacijalnog 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, uočena je pojava hematoma na levoj natkolenici; 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 heparin – LMWH*). U laboratorijskom nalazu, *INR* je bio u fiziološkim okvirima, a *aPTT* vrednost nije određivana. Četvrtog dana hospitalizacije, na levoj podlaktici, na mestu gde je bila plasirana braunila, dolazi do pojave intenzivnog krvarenja koje se moralo hirurški zaustaviti. Bolesnik se 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. Kompjuterizovana tomografija vrata opisala je supraglotično, na zadnjem zidu vrata, sa propagacijom desno, nepravilnu formaciju (hematom) dijametra 25 x 20 mm, koja je gotovo u potpunosti sužavala vazdušni stub opisane regije. Obe submandibularne žlezde su bile otečene, uvećane, heterodenzne, komprimujući okolne mekotkivne strukture i mišićne strukture od kojih su se teško diferencirale, sužavajući lumen vazdušnog stuba na tom nivou. Tada je u laboratoriji zabeležen pad vrednosti hemoglobina za 30 g, *INR* je bio normalan, a po prvi put je urađeno i *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 dalje bilo produženo, što je bio razlog da se posumnja na postojanje inhibitora koagulacije u plazmi bolesnika.

S obzirom na preporučeno lečenje, kao i nemogućnost dalje dijagnostike (određivanje nivoa F VIII i nivoa inhibitora *Bethesda* metodom), bolesnik je upućen u tercijarnu 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 ustanovljeno sekundarno stanje koje bi moglo biti uzrok stečene hemofilije. S obzirom na perzistentnu atrijalnu fibrilaciju, bolesniku je, po normalizaciji nivoa F VIII nakon primenjene navedene terapije, nastavljena oralna antikoagulantna terapija, oko 6 nedelja od početka lečenja.

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 edematous 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 submandibular glands were swollen, enlarged, heterodense, compressing the surrounding soft tissue structures and muscular structures. It was difficult to differentiate 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 present 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



Slika 1. Hemoragijski sindrom kod bolesnika sa stečenom hemofilijom
a) Hematom podvilične regije
b) Hemoragijska bula desne strane jezika

Figure 1. Hemorrhagic syndrome in a patient with acquired hemophilia
a) Hematoma of the submandibular region
b) Hemorrhagic bulla of the right side of the tongue

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 krvarenje 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 krvarenja, 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 gastroskopijom. I u literaturnim podacima se navodi kašnjenje u dijagnozi stečene hemofilijie 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 pripisati 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, rivaroksaban, apiksaban, 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 izmenjeni [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 spontanih, 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, apixaban), 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]. Ovakvo stanje zahteva neodložnu terapiju specifičnim agensima i zato je važno blagovremeno postaviti dijagnozu.

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CONCLUSION

In conclusion, although acquired hemophilia is a rare condition, caution should be exercised in clinical practice in severe spontaneous, usually mucocutaneous bleeding, in patients (especially elderly patients) on oral anticoagulant therapy who have excessively prolonged aPTT [11,13,15,18]. It should always be remembered that a readily available plasma mixing test can be performed in any medical biochemical laboratory which can prove the presence of coagulation inhibitors leading to the suspicion of acquired hemophilia [6-7,10-11,15]. This condition requires immediate treatment with specific drugs which is why it is important to establish a timely diagnosis.

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