Case report
Prikaz bolesnice

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Drug – induced immune thrombocytopenia – a case report

Lijekovima uzrokovana imuna trombocitopenija – prikaz bolesnice

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Summary

Thrombocytopenia is defined as a reduced platelet count. Drug-induced immune thrombocytopenia (DITP) is a condition mediated by antibodies developed following the ingestion of a certain medication. A sudden drop in platelet count accompanied by ecchymosis, petechiae, and mucosal bleeding following the introduction of a new medication should raise suspicion for DITP.

This case report describes the case of a 76-year-old female patient who first appeared at the Emergency Department (ED) with symptoms related to heart failure and atrial fibrillation. The patient was taking warfarin as an anticoagulant therapy when she presented herself to the ED. Following a short hospitalization at the Cardiology Department, the patient was discharged home with dabigatran instead of warfarin as the anticoagulant therapy. After several days of taking dabigatran, the patient came to the ED with a chief complaint of dark-colored urine. Her platelet count (measured using a machine and manually counted) was 13×10^9/L, and the urinalysis was positive for microhematuria. Dabigatran was excluded from the patient's medication list. At a later date, following the patient's request, she started with rivaroxaban prescribed by her general practitioner. The test for anti-platelet IgG antibodies (performed while the patient was taking dabigatran and later rivaroxaban) was positive. Therefore, rivaroxaban was also excluded from the patient's medication list. After the platelet count normalized, warfarin was reinstituted into the patient's therapy.

Due to the diagnosis of DITP being most often empirical, clinicians should suspect DITP if there is a sudden drop in the platelet count accompanied by signs of bleeding following the introduction of a new medication in the patient's therapy. Additional laboratory workup for transfusion reactions should be conducted, while the culprit medication should be excluded from the patient's medication list without delay.

Keywords: Direct Oral Anticoagulants; Emergency Medicine; Side Effects; Thrombocytopenia.

Sažetak

Pojam trombocitopenije podrazumijeva snižen broj trombocita u krvi. Lijekom uzrokovana imuna trombocitopenija (eng. drug-induced immune thrombocytopenia - DITP) posljedica je djelovanja antitijela razvijenih posljedično unosu određenog lijeka, koja dovode do uništenja trombocita. Naglo nastao pad trombocita, uz ekhimoze, petehije, te krvarenje sluznica, nakon uvođenja novog lijeka treba pobuditi sumnju da se radi o DITP-u.

Ovaj prikaz bolesnice opisuje 76 godina staru bolesnicu koja se javila prvi puta u hitnu službu radi tegoba vezanih uz srčano popuštanje i fibrilaciju atrija, te je uzimala varfarin. Nakon hospitalizacije na Zavodu za kardiologiju, varfarin je zamijenjen dabigatranom. Nakon nekoliko dana uzimanja dabigatrana bolesnica se ponovno javila u hitnu službu jer je uočila mutniju boju urina, misleći da se radi o urinarnoj infekciji. Broj trombocita mjeren strojno, te ručnim brojanjem bio je 13×10^9/L, a u urinu je bila prisutna mikrohematurija. Iz terapije je izostavljen dabigatran. Na inzistiranje bolesnice, od strane nadležnog LOM-a ponovno je uveden DOAK - rivaroksaban. Test na antitrombocitna protutijela klase IgG (uzet pri drugom

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dolasku u Hitnu službu, te ponovljen uz rivaroksaban) bio je pozitivan. Rivaroksaban je također izostavljen iz terapije. Varfarin je ponovno uveden po normalizaciji broja trombocita.

Obzirom na to da je dijagnoza DITP-a najčešće empirijska, treba posumnjati na istu ukoliko neposredno nakon uvođenja novog lijeka dođe do naglog pada broja trombocita uz znakove krvarenja, te učiniti dodatnu transfuziološku obradu. Iznimno je važno bez odgode isključiti lijek za koji se sumnja da je potencijalni uzrok neželjenog štetnog događaja.

Ključne riječi: izravni oralni antikoagulansi; hitna medicina; nuspojave; trombocitopenija

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Introduction

Thrombocytopenia is defined as a reduced platelet count. There are numerous causes of thrombocytopenia, from infectious diseases such as AIDS to medications. The cause may also be unknown, in which case the condition is referred to as idiopathic thrombocytopenic purpura. This case report will describe drug-induced thrombocytopenia. Drug-induced thrombocytopenia can be a consequence of both immunological and non-immunological events in the body. Drug-induced non-immune thrombocytopenia is thrombocytopenia caused by bone marrow suppression. Cytostatic drugs cause thrombocytopenia by suppressing the bone marrow, usually as part of general myelosuppression. There are reports that thiazide diuretics, ethanol, and tolbutamide can lead to thrombocytopenia by selective suppression of megakaryocytopoiesis.[1,2,3] In addition to causing bone marrow suppression, some cytotoxic drugs can cause antibody-mediated immune thrombocytopenia. Examples of such cytostatics are oxaliplatin and irinotecan.[4,5] On the other hand, drug-induced immune thrombocytopenia (DITP) is thrombocytopenia caused by drug-dependent antibody- mediated destruction of platelets. DITP is a form of secondary immune thrombocytopenia (ITP). A "drug" in this context can be a prescribed drug (or its metabolite), an over-the-counter drug, a herbal supplement, a food, drink, or other substance.

Case description

A 76-year-old female patient presented to the Emergency Department (ED) with dyspnea was initially hospitalized at the Cardiology Department in March 2016 due to heart failure with underlying atrial fibrillation. Until October 20th, 2016, she had been taking warfarin as anticoagulant medication for atrial fibrillation, but it was replaced by dabigatran 110 mg twice daily following discharge from the hospital; the patient came to the ED on February 10th, 2017, due to newly verified isolated thrombocytopenia and microhematuria. On clinical examination, arrhythmic heart action and three small hematomas on the right hand were found. The laboratory workup confirmed thrombocytopenia (platelet count 13×10^9/L; counted both by the machine and manually) and microhematuria (10 erythrocytes per large field of vision on urinalysis). DITP was suspected, following the exclusion of other differential diagnoses: primarily pseudo thrombocytopenia (excluded by repeated blood draw using collection tubes that did not contain EDTA), TTP (excluded by peripheral blood smear analysis and the absence of anemia), and vitamin B12/folate deficiency thrombocytopenia (excluded by normal serum concentrations of vitamin B12 and folate). Dabigatran was excluded from the patient's medication list as the culprit medication. On March 1st, 2017, the laboratory findings demonstrated an increase in platelets to 47×10^9/L, while a peripheral blood smear showed a considerable number of platelets. The following day, the test result for anti-platelet autoantibodies of the IgG class was positive. The antibodies were directed to the platelet membrane's GP complex IIb – IIIa and Ia – IIa, as assessed using the commercially available Monoclonal Antibody-Specific Immobilization of Platelet Antigen (MAIPA) assay kit (MAIPA Assay 480T; manufactured by Advanced Practical Diagnostics BV). The withdrawal of dabigatran was accompanied by an increase in platelets from 13 to 70 ($\times10^9$/L) over five months and a decrease in microhematuria. Following the patient's request, her general practitioner instituted another direct oral anticoagulant (DOAC) in her medication list - rivaroxaban 15 mg once daily. Following the introduction of rivaroxaban (which she used for only ten days), a drop in platelet count from 70×10^9/L to 42×10^9/L was observed, which prompted the exclusion of rivaroxaban from the patient's medication list. Another blood sample was taken for antiplatelet antibody tests, which returned positive. Two days later, a further drop in platelet count to 33×10^9/L was observed, and anticoagulation therapy was halted until the platelet count stabilized at 100×10^9/L, at which point warfarin was reinstituted.

Both instances of (suspected) drug-induced thrombocytopenia described (with dabigatran and rivaroxaban) were reported to the Croatian Agency for Medicinal Products and Medical Devices

(HALMED) using an online form available on the Agency's website.

Discussion

Drug-induced immune thrombocytopenia (DITP) is an uncommon clinical disorder, with epidemiologic studies estimating its incidence to be 10 cases per million patients annually.[6] It is more common in adults than in children.[7] The expected course of the disease is a rapid onset of thrombocytopenia within 2-3 days from the introduction of the drug if it was used earlier or within seven or more days if the drug was not used earlier.[8] Thrombocytopenia caused by GP IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide) can occur within 24 hours of the first exposure to the drug or even after a few minutes.[9] There are reports of thrombocytopenia caused by vancomycin that occurred after one day of exposure to the drug but with earlier use of the drug, i.e., prior sensitization.[10] The patient presented in this case report had an unusually late onset of DITP, with five months elapsing from starting the drug to the appearance of thrombocytopenia. Although such a late onset is unusual, other authors have described it in the literature. Cisarovsky et al. described a case of a female patient with relapsing-remitting multiple sclerosis developing DITP 10 years after starting regular taking of interferon 1-beta.[11] The most common mechanism of DITP is the binding of drug-dependent antibodies to specific epitopes on glycoproteins (GP) of platelet membranes in the presence of a sensitizing drug.[12] Drug-dependent antibodies are very specific to the structure of the drug. These antibodies may be natural, weakly reactive autoantibodies that have a slight affinity for epitopes on GP platelet membranes but cannot bind to them without the presence of the drug. Sensitizing drugs are assumed to contain charged and/or hydrophobic elements that enable them to bind to both platelet GP and antibodies. Quinine and other drugs that cause DITP modify the binding site for the antigen by creating a hybrid paratope that increases the binding affinity of antibodies to platelet glycoproteins. The binding between drug and antibody and drug and platelets is non-covalent and reversible, usually at sites on GP IIb-IIIa and/or GP Ib-V-IX. The resulting "sandwich" facilitates the formation of a tight bond between the antibody and the platelet epitope. With its Fab domain, the antibody recognizes the drug bound to the platelets' epitope.[13] Another potential mechanism is that the binding of the drug to the platelet surface causes a conformational change of the surface protein, which leads to the exposure of the neoepitope, which stimulates the formation of antiplatelet antibodies.[14] Drug-dependent antibodies may have specificity for the main metabolites of the drug and/or the parent drug. Still, they usually do not react with different drugs that have a similar molecular structure (e.g., they react to sulfamethoxazole but not to almost identical sulfisoxazole, or they react to quinine but not to the optical stereoisomeric quinidine).[15] Due to this, patients with DITP can receive another drug from the same group, although even this is not entirely safe due to possible cross-reactivity. In patients with DITP, moderate to severe thrombocytopenia usually occurs suddenly. The platelet count is often less than 20,000/μL.[16] Bleeding can present as ecchymoses and petechiae, mucosal bleeding, or clinically significant and life-threatening intracranial bleeding. Deaths from bleeding have also been described.[17] For unknown reasons, platelets are the target of drug-dependent antibodies much more often than neutrophils or erythrocytes. In recent years, direct oral anticoagulants (DOACs) have established themselves as safe and effective options for anticoagulant therapy. The group of DOACs consists of dabigatran, a reversible thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban, specific inhibitors of activated factor X (FXa). Indications for the use of DOAC are the treatment of venous thromboembolism (VTE), prevention of recurrent VTE, prophylaxis in orthopedic surgeries, and prevention of thromboembolism in non-valvular atrial fibrillation (AF). By searching the available databases and literature, we found only 11 previously described cases of thrombocytopenia due to DOAC therapy worldwide. 9 cases of the 11 occurred following dabigatran therapy, and 2 cases occurred after rivaroxaban therapy.[18-21] None of these case reports provided a possible explanation or pathophysiological mechanism by which DOACs could cause thrombocytopenia.

The diagnosis of DITP is often empirical. Before making a final diagnosis of DITP, it is important to exclude other differential diagnoses, the most common of which shall be succinctly discussed here.

Pseudothrombocytopenia is characterized by in-vitro platelet aggregation due to the interactions with the anticoagulation agent in the blood collection tube. The most common culprit is EDTA, - a routine anticoagulation agent used for hematologic laboratory tests. Pseudothrombocytopenia can be excluded using blood collection tubes containing citrate or heparin instead of EDTA on a repeat blood draw. Primary immune thrombocytopenia (ITP) is an autoimmune disease in which antibodies cause thrombocytopenia. It can be either transient or last for months to years. The main difference between ITP

and DITP is that in ITP, platelet levels do not recover with the cessation of a culprit medication.

Heparin-induced thrombocytopenia is a condition characterized by thrombocytopenia and thromboembolic complications following the application of heparin, irrespective of the route of administration or dose.

Thrombotic thrombocytopenic purpura (TTP) / Hemolytic uremic syndrome (HUS) is a life-threatening disease characterized by thrombocytopenia and microangiopathic hemolytic anemia. TTP can cause damage to any organ due to the microangiopathic changes it involves. However, most clinical manifestations result from the damage sustained by the central nervous system and the kidneys. The diagnosis is made based on severe thrombocytopenia (platelet levels usually 10-30×10^9/L), Coombs-negative hemolytic anemia, and the presence of mechanically fragmented erythrocytes and schistocytes, visible on cytological peripheral blood smear analysis.

The antiphospholipid syndrome (APS) is an acquired systemic autoimmune disorder characterized by the presence of thrombosis and/ or pathology related to pregnancy, with a positive laboratory test for antiphospholipid antibodies. Thrombocytopenia is often seen in APS, with an incidence ranging from 22% to 42%. Post-transfusion purpura is a rare complication of packed red blood cell transfusion. It is a consequence of creating antibodies to platelet antigen 1a (HPA-1a). Thrombocytopenia usually occurs 7-10 days following the transfusion and is generally self-limiting, with intravenous immunoglobulins and plasma exchange available as therapeutic options in case of persistence.

Vitamin B12/folate deficiency may cause isolated thrombocytopenia, although this is usually accompanied by macrocytic anemia.

The recovery of the platelet count in a patient exposed to one drug after discontinuation of the drug is evidence that the thrombocytopenia is drug-induced.[22] In addition to clinical criteria, demonstrating drug-dependent anti-platelet antibodies is important to confirm the DITP diagnosis. Various tests demonstrate the presence of antibodies: thrombocyte immunofluorescence test (PIFT), ELISA, flow cytometry, and many others. Tests confirming the presence of antibodies require some time and can be falsely negative in patients with probable DITP. The decision to stop taking a specific drug must be made before the test results are available. It is prudent to obtain a peripheral blood smear when thrombocytopenia is suspected. Coagulation tests, such as the measurement of prothrombin time (PT) and activated partial thromboplastin time (APTT), serve to measure the extrinsic pathway (PT) and the intrinsic pathway of coagulation (APTT). Decreased results or prolonged time in these tests may be an indication of coagulation factor deficiency or may be an indication of the presence of coagulation inhibitors such as heparin. Coagulation tests such as platelet count (reference interval 150–400×10^9/L) and fibrinogen concentration can give us a better insight into the differential diagnosis of a patient with hematomas and microhematuria, as was the case with our patient. If the above tests show normal results, and the patient's family history and personal medical history indicate that they are prone to bleeding, additional workup and testing such as measurement of the von Willebrand factor or platelet function testing are required.[23] In our case, the patient was carefully monitored first due to a decrease in platelet count to 13×10^9/L. This required special attention because platelet counts below 20×10^9/L can cause spontaneous bleeding and is considered a high-risk condition. There are several treatment options for thrombocytopenia, depending on its cause. It can be treated with corticosteroids or immunoglobulins (ITP), treatment of the underlying disease that causes thrombocytopenia, repeated plasma exchange (thrombotic thrombocytopenic purpura) or immediate discontinuation of the culprit drug in the context of suspected DITP. An increase in platelets is expected after one to two days of stopping the drug, with a return to normal values within a week, unless the metabolism and elimination of the drug from the body are slowed down due to renal or hepatic insufficiency. In certain situations, supportive treatment with intravenous immunoglobulins and plasma exchange is necessary.[23] Platelet transfusions are indicated in severe thrombocytopenia when there is a high risk for spontaneous bleeding or in the case of active bleeding. Corticosteroids are used when the diagnosis of ITP cannot be ruled out. When DITP is confirmed, corticosteroids should be stopped, as they seem ineffective in treating DITP. Drug-dependent antibodies can persist for many years, and patients must be advised not to take the drug that caused the thrombocytopenia.

Drug-induced thrombocytopenia can have a non-immunological or immunological underlying mechanism. Although the diagnosis of DITP is primarily empirical, it is important to carry out coagulation tests and a further transfusion reactions workup to determine the cause of DITP. It is of the utmost importance to discontinue the culprit drug without delay and carefully monitor the patient's clinical condition and laboratory values.

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