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Case Report

Drug-Induced Immune Thrombocytopenia or ITP? Dealing with Uncertainty

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Abstract

It may be challenging to distinguish between drug-induced immune thrombocytopenia (D-ITP) and primary immune thrombocytopenia (ITP). Though guidelines provide a useful framework for diagnosis, the particular patient may not fit into the rules. This is illustrated by the case of a 97-year-old man recovering from a coronary event, then aspiration pneumonia, who was started on clopidogrel and amoxicillin treatment, and developed severe thrombocytopenia. In suspecting D-ITP all recently introduced medications were discontinued, but the platelet count remained low. Next prednisolone treatment was started, soon followed by normalisation of the platelet count. The favourable response to prednisolone raised questions concerning the diagnosis, drugs to be avoided in the future, and how to pursue with the management.

Keywords: *Drug-Induced Immune Thrombocytopenia (D-ITP); Primary Immune Thrombocytopenia (ITP); Clopidogrel; Amoxicillin*

Introduction

The differential diagnosis between drug-induced immune thrombocytopenia (D-ITP) and primary immune thrombocytopenia (ITP) may be challenging. Though guidelines provide a useful framework to the diagnosis and treatment, the particular patient may not fit into the rules. This is illustrated in the following.

Case History

A 97-year-old man was admitted for rehabilitation after myocardial infarction. Until recently he was living in the community, receiving assistance in instrumental activities of daily living, and needing little help with the basic activities of living. He was receiving apixaban 2.5 mg b.i.d. for chronic atrial fibrillation, tamsulosin and dutasteride for benign prostatic hypertrophy. When rushed to hospital with chest pain and shortness of breath, he was diagnosed with myocardial infarction and pulmonary oedema. Mechanical ventilation was instituted, followed in emergency by angiography and stenting of the left anterior descendent and circumflex coronary arteries. Treatment with clopidogrel, bisoprolol fumarate and omeprazole was added to the previous regimen. He was extubated in stable condition. A few days later fever emerged. In diagnosing aspiration pneumonia, a course of amoxicillin-clavulanic acid was started. When transferred to our institution he was under the same medications.

On physical examination he was alert, the body temperature, blood pressure, heart rate, and oxygen saturation were within the normal range. There were no bruises, no dependent oedema. The mini-mental test scored 24 out of 30. Remarkable amongst routine laboratory

tests were the platelet count 68.000/mm^3 (versus 199.000 one week before), haemoglobin 11g/dL (essentially unchanged) and normal white blood cell count. Microscopic examination for platelet agglutination was negative and platelet counts were not corrected with citrate sample, excluding pseudothrombocytopenia [1]. On the day of admission to our ward the antibiotic treatment was terminated according to schedule. The main diagnostic considerations at this time were D-ITP to any of the recently introduced medications (clopidogrel, bisoprolol, amoxicillin) or immune thrombocytopenia elicited by recent blood transfusion [2,3] and infection-related thrombocytopenia [4]. Since antiaggregant therapy is strongly indicated after vascular stent implantation and, likewise, anticoagulant treatment for atrial fibrillation, we decided not to withdraw any of the present medications, watchfully following the platelet count and being mindful to bleeding and thrombosis. Two days later the platelet count decreased to 37.000/mm^3. In suspecting D-ITP the patient was referred to a tertiary hospital for diagnostic evaluation and cautious change in the medications. The consultant haematologist suspended clopidogrel and apixaban in agreement with the working diagnosis of D-ITP. However, no improvement of the platelet count occurred over seven days. The diagnosis now moved to ITP. Treatment with prednisolone 60 mg/day was started. Reinstitution of treatment with a different antiaggregant agent was recommended when the platelet count will reach 50.000/mm^3 and of anticoagulant treatment when the count will reach 70.000/mm^3. Within three days the platelet count increased to 145.000/mm^3. Subsequently, under slow tapering of prednisolone the platelet count was in the range 160.000 - 180.000/mm^3. The diagnosis remained ambiguous: D-ITP vs. ITP.

Discussion

Thrombocytopenia is defined as a platelet count below the lower limit of the normal range (150.000/mm^3), but sometimes an expanded definition is appropriate. For example, an abrupt drop in the platelet count can signify the onset of a platelet-destructive process such as heparin-induced thrombocytopenia or bacteraemia even if the platelet count remains above 150.000/mm^3 [5]. Thrombocytopenia can be caused by four mechanisms: platelet underproduction, increased platelet destruction or consumption, platelet sequestration and haemodilution. Platelet underproduction usually occurs in association with underproduction of other blood cell lines, which results in bicytopenia or pancytopenia. Thrombocytopenia from platelet sequestration is caused by redistribution of platelets from the circulation into an enlarged spleen. Haemodilution is characterized by a decrease in the number of platelets, as well as red blood cells and white blood cells because of the administration of crystalloid or platelet-poor blood products. Neither situation was met in the proposito. Thrombocytopenia caused by increased platelet destruction occurs when the rate of platelet loss exceeds the ability of the bone marrow to produce platelets. This latter is relevant in the proposito.

The timing of the onset of thrombocytopenia and the severity of thrombocytopenia are important indicators of possible aetiologies. If the platelet count begins to fall 5 - 10 days after starting a new drug or after a blood transfusion, and reaches a nadir a few days later of less than 20.000/mm^3 the diagnosis of D-ITP or posttransfusion purpura should be considered. The first of the two conditions was met in the proposito, but not the second as the decline of platelet counts was not as fast as usual in D-ITP and did not reach a critical level. Moreover, patients with D-ITP typically have mucocutaneous bleeding and are at risk for intracranial haemorrhage; none occurred in the proposito. In suspecting D-ITP it is recommended to discontinue as many medications as possible, especially those started within the preceding 5 - 14 days; this rule was implemented by us. Spontaneous improvement in the platelet count usually begins within a few days of discontinuing the offending drug, although in some cases, complete recovery may take 2 weeks or longer [5]. Corticosteroids appear to be relatively ineffective for treatment of D-ITP [2,3,5].

Demonstration of drug-dependent binding of IgG to platelets *in vitro* may be important for diagnosis. In other cases, D-ITP tests are negative but the diagnosis still seems likely based on clinical features and supporting literature [5]. Drug-dependent platelet antibodies can persist for many years; thus, patients with a confirmed diagnosis should be counselled to avoid future exposures to the drug. Counselling on drug avoidance is less certain for patients in whom the diagnosis cannot be confirmed. Rechallenge with critically important drugs might be necessary if there are no substitutes [6]. Fortunately, substitutes were readily available in the proposito.

Since no improvement of the platelet count was noticed after withdrawal of the suspicious medications the working diagnosis turned to ITP. ITP is caused by autoantibody-mediated reaction of B cells and T cells to megakaryocytes leading to thrombocytopenia and life-threatening bleeding. The onset of ITP, the adult variant, is insidious and it is manifested as easy bruising and mucosal bleeding. Platelet counts between 30.000/mm^3 and 100.000/mm3 are common. Bleeding complications are of unpredictable frequency and severity; the long-term mortality is approximately 1%. The IgG antiplatelet antibody of ITP is difficult to detect [7,8]. For this reason, antiplatelet antibody testing is usually not recommended for ITP diagnosis [7] and was not pursued in the proposito. Yet, the monoclonal antibody immobilization of platelet antigens assay (MAIPA) or antigen capture enzyme immunoassay are relatively specific for detection of autoimmune thrombocytopenic disorders [5]. These assays can also be adapted for detection of drug-dependent GP-reactive antibodies.

As a general rule, patients with ITP can tolerate long periods of severe thrombocytopenia without major bleeding. Steroids and intravenous immune globulin therapy are reserved for patients with active bleeding [5]. In the proposito, a brittle nonagenarian recovering from critical illness, the dilemma of management was to decide between observation alone vs. corticosteroid treatment with its risks and possible benefit. Steroid treatment was started and the response was favourable. However this is not always so. In a retrospectively review of 400 patients with chronic ITP, prednisolone was the most frequently used drug: in 88% of these patients prednisolone was discontinued because of inefficacy or adverse effects [9].

Conclusion

As illustrated in the present case, the differential diagnosis between primary ITP and D-ITP may be challenging, raising questions concerning drugs to be avoided in the future and how to pursue the management.

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