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CHAPTER 9

Clinical case: use of thienopyridines in a patient with acquired idiopathic thrombotic thrombocytopenic purpura

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Abstract

Thienopyridines are commonly used anti-platelet drugs that may be associated with the development of secondary, drug-induced thrombotic thrombocytopenic purpura (TTP), a rare but potentially life-threatening condition. We report the case of a 70 year-old man with a history of recurrent idiopathic TTP episodes who was treated with clopidogrel and then ticlopidine for thromboprophylaxis after percutaneous coronary intervention. Treatment was successful with no signs of TTP recurrence. Platelet counts and ADAMTS13 activity levels remained normal for months after the initiation of anti-platelet therapy, with no reappearance of anti-ADAMTS13 autoantibodies. This report suggests that thienopyridines can be used in patients with a history of TTP who are in disease remission.
Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening disease characterized by single or multiple episodes of disseminated microvascular thrombosis, with thrombocytopenia, microangiopathic hemolytic anemia and damage of multiple organs. TTP can be idiopathic or secondary. Secondary TTP is defined when the disease develops in association with medical conditions (i.e. HIV infection, bone-marrow transplantation and disseminated malignancy) or with the use of certain drugs. Drug-induced TTP is very rare, accounting for a tiny proportion of all TTP cases. Drugs that have been reported in association with TTP include quinine and thienopyridines (ticlopidine and clopidogrel), a class of inhibitors of platelet ADP-receptor commonly used for anti-platelet therapy in patients with cardiovascular disease. Idiopathic TTP is associated with severe deficiency of the von Willebrand factor cleaving protease, ADAMTS13, due to the presence of circulating anti-ADAMTS13 autoantibodies. By contrast, secondary TTP is rarely associated with the presence of anti-ADAMTS13 autoantibodies. However, case-series and reviews of reported cases of thienopyridine-induced TTP showed a high prevalence of anti-ADAMTS13 autoantibodies, suggesting that the use of these drugs in genetically susceptible patients may elicit an anti-ADAMTS13 autoimmune response similar to that of idiopathic TTP patients. There are no data on the use of thienopyridines in patients with a history of idiopathic TTP.
Case description

A 70 year-old Italian man was admitted to the Cardiology unit for elective coronary angiography, after a recent stress-test had shown evidence of stress-induced angina with reversible ischemia of the inferior surface. The patient had a history of idiopathic thrombotic thrombocytopenic purpura with severe deficiency of ADAMTS13 due to anti-ADAMTS13 autoantibodies. At the age of 69 he was admitted to another hospital for the sudden appearance of fatigue, diarrhea and focal neurological signs (aphasia and right upper limb weakness and paresthesia). Laboratory tests showed severe thrombocytopenia (platelet counts: 20 \(10^9\)/L), and Coombs-negative mechanical hemolytic anemia (hemoglobin: 7.6 g/dL), increased lactate dehydrogenase (LDH: 1968 IU/L) and hemoglobinuria. A diagnosis of TTP was made and the patient was treated with corticosteroids (prednisone, 75 mg daily) and plasma exchange (PEX), achieving remission with normalization of the laboratory parameters after 4 PEX procedures. Two months later, a new TTP episode developed. Measurement of ADAMTS13 activity by collagen binding assay\(^8,9\) on plasma sampled before the initiation of PEX revealed severe deficiency of ADAMTS13 (ADAMTS13 activity: <6%; normal values, n.v.: 46-160%) with presence of anti-ADAMTS13 IgG auto-antibodies at western blotting analysis and ELISA measurement (antibody titre: 18%; n.v.: <1%).\(^8,9\) The second episode resolved after 12 plasma exchanges. Measurement of ADAMTS13 at 6 months after remission, when corticosteroid maintenance treatment was discontinued, showed normal ADAMTS13 activity (ADAMTS13 activity: 85%; n.v.:46-160%) with absence of anti-ADAMTS13 autoantibodies. Table 1 summarizes ADAMTS13-related laboratory measurements at acute
disease and remission. After remission, the patient started regular follow-up at the out-patient clinic for thrombotic microangiopathies of the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center (Milan, Italy), with regular measurement of ADAMTS13 activity and follow-up clinical visits every 3-4 months. At coronary angiography, the patient showed coronary artery bivascular disease with 80% stenosis of the anterior descending and circumflex arteries. Bare metal stents were successfully placed after pre-dilatation. During the procedure, the patient was treated with clopidogrel (75 mg daily) and ASA (100 mg daily). After the procedure, a cutaneous rash developed, which was treated with corticosteroids. Clopidogrel was precautionarily suspended. Dual anti-platelet therapy with ticlopidine (250 mg twice a day) and ASA (100 mg daily) was prescribed for the duration of one year. Complete blood counts before, during and after the intervention consistently showed normal platelet counts. ADAMTS13 activity was normal in 4 measurements 2-weeks after the procedure, at 3, 6 and 12 months, with no appearance of anti-ADAMTS13 autoantibodies (Figure).

Discussion
We reported the case of a 70 year-old patient with a history of autoimmune idiopathic TTP treated with thienopyridines after percutaneous coronary intervention. The development of drug-induced TTP is a rare side effect of treatment with thienopyridines with an incidence rate of 1/5000 treated patients for ticlopidine and 1/1 million treated patients for clopidogrel.\textsuperscript{6} Thienopyridine-induced TTP has been reported to be associated with the presence of anti-
ADAMTS13 autoantibodies in a large proportion of cases, suggesting the assumption of these drugs can elicit anti-ADAMTS13 autoimmune responses. The still unexplained mechanisms leading to anti-ADAMTS13 autoimmune response in patients with thienopyridine-induced TTP could share pathophysiological pathways with autoimmune idiopathic TTP. There are no data on the use of thienopyridines in patients with a history of autoimmune TTP. In this case, thienopyridines were administered in a patient with a history of recurrent autoimmune TTP with severe ADAMTS13 deficiency and anti-ADAMTS13 IgG autoantibodies. At the time of treatment the patient was in remission and had no evidence of anti-ADAMTS13 autoantibodies. Autoantibodies did not reappear and TTP did not develop after treatment with thienopyridine. This indicates that thienopyridines do not necessarily induce TTP when used in patients with a history of TTP who are in clinical remission and suggests that the mechanisms that lead to anti-ADAMTS13 autoimmunity in patients with idiopathic and those with drug-induced TTP are likely distinct.
Figure

Figure 1. Platelet count and ADAMTS13 activity and antibody levels after the initiation of anti-platelet therapy. PCI indicates percutaneous coronary intervention.
Table 1. ADAMTS13-related laboratory profile of the patient.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal values</th>
<th>Acute disease - second episode</th>
<th>Remission - 6 months after the second episode</th>
</tr>
</thead>
</table>
| A13:Activity, %
| 46-160%  
<6  
90 | | |
| A13:Antigen, %
| 40-155%  
40  
85 | | |
| WB
| Absent  
Present  
Absent | | |
| ADAMTS13 inhibitor, bethesda units
| Absent  
2  
Absent | | |
| IgG, %
| <1.18%  
18  
0 | | |
| IgG1, %
| <0.006%  
0.012  
0 | | |
| IgG2, %
| <0.019%  
0.109  
0 | | |
| IgG3, %
| <0.019%  
0  
0 | | |
| IgG4, %
| <0.003%  
1.161  
0 | | |
| IgM, %
| <0.034%  
0  
0 | | |
| IgA, %
| <0.014  
0  
0 | | |
References


