AN ELDERLY GENTLEMAN WITH SUSPECTED RECURRENT STROKE AND TICLOPIDINE INDUCED THROMBOTIC THROMBOCYTOPENIC PURPURA

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Summary:
We report a patient with ticlopidine induced thrombotic thrombocytopenic purpura (TTP). He received ticlopidine for four weeks for stroke prophylaxis since he had history of bleeding gastric ulcer. Subsequently he developed typical features of TTP. After ticlopidine was stopped, he recovered gradually without plasmapheresis. Association of ticlopidine and TTP has been increasingly reported in recent years. The mechanism is through an autoimmune dysregulation resulting in IgG inhibitors to a metalloprotease enzyme. This enzyme, normally present in plasma, is responsible for breaking down giant multimers of von Willebrand factors. Without this metalloprotease activity, giant multimers of von Willebrand factors clog up small vessels leading to microangiopathic haemolytic anaemia, renal failure and neurological changes. Increasing use of ticlopidine in stroke prophylaxis in high risk patients and post coronary stenting led to more and more reports of ticlopidine induced TTP. Incidence of natural TTP is 1 in 250,000, while that of ticlopidine induced TTP is 1 in 1600 to 1 in 4000 treated patients. Mortality exceeds 20%, and occurs mostly in patients not treated with plasmapheresis. Regular monitoring of blood counts, renal function tests and neurological status is required for 3 months is necessary to diagnose ticlopidine induced TTP.

Case Presentation
An elderly Chinese gentleman, aged 82, presented to us with acute increased left-sided weakness. He suffered an ischaemic stroke resulting in left hemiplegia one month ago. Recovery was good after the last stroke. He was able to walk unaided and perform ADL independently. He also had history of partial gastrectomy for peptic ulcer 10 years ago. In view of ulcer history and ischaemic stroke, he was put on ticlopidine for stroke prophylaxis.

For the current episode, he developed sudden onset of worsening of his left-sided weakness and slurring of speech. He also complained of a mild headache. Patient’s family members also noted he had gross haematuria. On examination, he was afebrile, conscious and alert. His blood pressure measured at 138/73 mm Hg. There was weakness of left face, upper and lower limbs. Power was grade 3 on his left side. There was no meningism. Cardiovascular, chest and abdomen examinations were unremarkable. ECG showed normal sinus rhythm. CT brain on day one of admission revealed 2 small infarcts over right internal capsule. There was another hyperdense area on right occipital region. Subarachnoid blood collection was suspected. Urinalysis by multistix on admission showed nitrite +, protein +++, bilirubin +++, RBC +++, WBC and urobilinogen both negative. Blood tests revealed a drop of both haemoglobin and platelet counts compared to one month ago. Blood smear examination showed fragmented RBCs and marked thrombocytopenia. Serum creatinine level was elevated at 224 µmol/L. Liver function test showed raised bilirubin with normal ALP and ALT. There was also grossly raised LDH. Urine and blood cultures were both negative. The initial haematological and biochemical results were tabulated in table 1.

Table 1: Haematological and biochemical results

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<thead>
<tr>
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<tbody>
<tr>
<td>WBC (10^9/L)</td>
<td>10.4</td>
<td>8.1</td>
<td>5.3</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>14.1</td>
<td>11.8</td>
<td>7.3</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>91.8</td>
<td>92.8</td>
<td></td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>31.9</td>
<td>32.4</td>
<td></td>
</tr>
<tr>
<td>retic %</td>
<td>1.3</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Platelet (10^9/L)</td>
<td>190</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>urea (mmol/L)</td>
<td>8.9</td>
<td>18.6</td>
<td>15.7</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>123</td>
<td>224</td>
<td>187</td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>3</td>
<td>37</td>
<td>28</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>72</td>
<td>116</td>
<td>107</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>13</td>
<td>39</td>
<td>25</td>
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He was given the usual stroke care. In view of suspected subarachnoid haemorrhage on the hyperdense area on CT, ticlopidine was stopped. Neurosurgical opinion was sought. As there were neither meningism nor severe headache, and that the CT appearance is not typical of subarachnoid haemorrhage, they suggested to trace old CT films for comparison. He was only prescribed with dextropropoxyphene with paracetamol for headache.

Repeated complete blood count on day two revealed a further drop of platelet count to $8 \times 10^9/L$, Hb dropped to 10.6 g/dl. In view of the extreme low platelet count and possible SAH, platelet transfusion was given.

Blood counts repeated after platelet transfusion reviewed the platelet count had risen to $23 \times 10^9/L$, but the haemoglobin has dropped further to 8.4 g/dl. Further investigation for anaemia was done. Iron studies showed adequate iron. Haptoglobin was markedly decreased (<0.06 g/L). Direct and indirect Coombs’ tests were negative. LDH was raised at 1513. CK was normal. INR was normal at 1.1. D-dimer was not increased.

Patient’s condition remained well and alert, although he felt lethargic and anorexic. On day four, he started to run a low grade swinging fever. Amoxicillin/claevulanic acid was started empirically, although there had been no positive culture results. The patient’s haemoglobin dropped further to 6.2g/dl. 2 units of packed cells were transfused. Bone marrow examination revealed a normocellular marrow, megakaryocytes are adequate. This suggested that cytopenia probably caused by a peripheral process. Peripheral blood smear showed mild to moderate schistocytosis and marked thrombocytopenia. The picture is suggestive of microangiopathic haemolytic anaemia.

The clinical picture of microangiopathic haemolytic anaemia, thrombocytopenia, impaired renal function and CNS involvement raised the suspicion of thrombotic thrombocytopenic purpura. The patient has not received any metallic stents, mechanical heart valves nor implants. There was no evidence of sepsisemia nor disseminated intravascular coagulation. Possibility of drug induced TTP was considered.

Ticlopidine was suspected, as it was the only medication that the patient had been taking prior to admission.

The patient improved neurologically. Muscle power on his left side improved from 3/5 to 4/5 from day 5. He could walk with a quadripod, transfer independently. Elderly Mobility Score improved from 4/20 to 15/20. Timed up and go test improved from failure to 53 seconds.

His general well-being also improved. His fever subsided. Renal function tests were normalized on day 13 (urea 7.2, creatinine 89). Haemoglobin level was 9.0 g/dl, platelet count climbed back to $132 \times 10^9/L$. A repeat CT brain on day five showed similar findings. Radiologist’s opinion was sought for the suspected subarachnoid haemorrhage. On review, the hyperdense area about the occipital lobe was due to tentorial shadow rather than SAH.

He was discharged on day 16 and was given a course of rehabilitation in Geriatric Day Hospital. He was put on aspirin 80 mg daily and misoprostol 200µg tds.

Diagnoses
1. Thrombotic thrombocytopenic purpura, likely to be ticlopidine related
2. Recurrent stroke, differential diagnosis was TTP induced neurological deficits
3. History of peptic ulcer and partial gastrectomy

The cause of the neurological deficits in this gentleman could not be ascertained. It might be the results of a genuine recurrent stroke, or might be part of the clinical picture of thrombotic thrombocytopenic purpura. The fact that the patient’s neurological deficits improved rapidly in 4 days supported the latter.

Discussion
TTP can be associated with penicillin, antineoplastic chemotherapy agents like mitomycin, oral contraceptives, penicillamine and more recently, ticlopidine. It is intriguing how an antiplatelet could lead to widespread thrombosis in TTP. With increasing use of ticlopidine in stroke prevention and post coronary stenting, more and more patients are expected to be put on ticlopidine. The following discussion will touch on the mechanism and treatment of TTP and the association of TTP to ticlopidine.

TTP is first described by Dr. Eli Moschowitz in 1924. A 16-year old girl had abrupt onset of petechiae and pallor, followed rapidly by paralysis, coma and death. Terminal arterioles and capillaries were occluded by hyaline thrombi containing mainly of platelets without perivascular inflammation or endothelial desquamation. Dr. Moschcowitz suspected a “powerful poison having both hemolytic and agglutinative properties” causing this disorder later known as TTP. Estimated incidence in the United States is 3.7 cases per million people (1 in 250,000 or 0.0004%)².
Mechanism of TTP

Thrombotic thrombocytopenic purpura (TTP) is classified as a bleeding disorder due to disorders of vessel walls. It is a fulminating, life-threatening disorder characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurological changes, renal failure and sometimes fever. There is microvascular deposition of hyaline thrombi which stain for fibrin. These thrombi may be found in arterioles, venules and capillaries without any inflammatory changes in the vessel wall. The presence of a severe Coombs-negative hemolytic anemia with schistocytes or fragmented RBCs in the peripheral blood smear, coupled with thrombocytopenia, and minimal activation of the coagulation system raise suspicion of TTP. Uveal von Willebrand factor (VWF) multimers are thought to be responsible for the platelet aggregation leading to microthrombi in TTP. The cause of acute TTP appears to be related to transient immune dysregulation and selective antigenic targeting of an enzyme that degrades large multimers of VWF. This metalloprotease enzyme, which is present in the cryosupernatant fraction of the plasma, requires a calcium or zinc cation for its activity. An IgG autoantibody against components of the enzyme may account for a lack of metalloprotease activity in TTP patients. The typical time course of 2 to 4 weeks following a certain drug exposure is consistent with an autoimmune mechanism for TTP. Events like pregnancy, bone marrow transplantation, tumour or chemotherapy and infection were identified as other triggering factors.

In the series by Furlan et al., plasma samples from 30 TTP patients (24 nonfamilial, 6 familial) were analysed for VWF-cleaving protease activity using normal VWF as substrate. Also to determine whether an inhibitor of VWF was present, they measured the protease activity in normal plasma after incubation with plasma from the patients. They found that out of 24 nonfamilial TTP patients, 20 had severe and 4 had moderate protease deficiency during an acute event. An inhibitor was found in 20 of these patients. The inhibitor was found to be IgG in 5 out of 5 tested samples. In the series by Tsai and Lian, plasma samples from 37 patients with acute TTP had severe deficiency of VWF-cleaving protease. No such deficiency was detected in TTP patients in remission and other randomly selected in- and outpatients and patients with haemolysis, thrombocytopenia and thrombosis from other causes. Inhibitory activity against the protease was detected in 67% of plasma samples during the acute phase of the disease. The inhibitors were again identified to be IgG antibodies.

Ticlopidine induced TTP

In the clinical trials stage, the most common serious adverse effect of ticlopidine in the stroke prevention setting was neutropenia, with incidence of 1.0 to 2.4%. The package insert was modified stating the danger of neutropenia and encouraging physicians to check complete blood counts every 2 weeks for 3 months. After initial marketing, ticlopidine induced TTP cases have been increasingly reported in the literature. By 1994, 25 cases of TTP were reported in MedWatch database of FDA, USA. The package insert was amended to include a boldfaced typed statement that ticlopidine can cause TTP rarely. After a publication of 60 cases and 20 deaths from ticlopidine induced TTP, further concern about its safety was heightened. This had led to a change of package insert of ticlopidine for the third time in 1998 to include a black box warning section. It states the estimated incidence of ticlopidine induced TTP of 1 in 2000-4000 individuals, the need for extreme vigilance of TTP, the signs and symptoms of TTP, and the importance of early diagnosis and treatment.

An article from the EPISTENT (Evaluation of Platelet IIb/ IIIa Inhibitor for Stenting) investigators in 1999 gave more information on the incidence of ticlopidine induced TTP. Ticlopidine is given routinely to some 500,000 USA patients receiving a coronary stent each year. From 43322 patients in 63 centres followed in a 1 year period from 1996 to 1997, 9 cases were identified. The incidence calculated was 1 case per 4814 treated or 0.02%. 10 additional cases were collected from other centres for analysis. All received ticlopidine for 2-8 weeks. Mortality rate was 21% (4/19), all 4 deaths occurring in patients not treated with plasmapheresis, whereas no deaths occurred among the 13 patients treated with plasmapheresis.

More detailed information concerning ticlopidine induced TTP and other adverse reactions are collected by Bennett et al. in 1999. From postmarketing surveillance data, including the FDA MedWatch program, the most common ticlopidine-associated toxic effects were haematological, reported in 1756 cases, consisted of leucopenia, thrombocytopenia, TTP, agranulocytosis, pancytopenia and aplastic anaemia. This is the most comprehensive collection to date. The cases collected here probably overlap with previous reports. Among 259 deaths associated with the drug, 85.6% were associated with haematological toxic effects. Detailed information of 98 cases of ticlopidine induced TTP were collected from published case reports, personal contact with haematologists and plasmapheresis centres.
LEARNING POINTS

1. Incidence of ticlopidine related TTP is 1 in 1600 to 5000 patients. Whereas incidence of TTP in general population is estimated to be 1 in 250,000.

2. Pathogenesis of TTP is due to immune dysregulation leading to IgG autoantibody against a metalloprotease which is responsible for degrading giant VWF in blood. Consequently giant VWF aggregate platelets in small vessel walls, giving rise to features of TTP.

3. Mortality of TTP is high, but much improved if plasmapheresis is given. Early diagnosis is of utmost importance.

4. Monitoring of blood count ± clotting profile every 2 weeks within the first 3 months of starting ticlopidine is recommended.

5. Clopidogrel can also be associated with TTP. True incidence cannot be determined at present. Hematological monitoring is also necessary.