Clopidogrel-Associated Thrombotic Thrombocytopenic Purpura: A Case Report and Brief Review

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Introduction

In 1991, Page and colleagues published a report of four cases of thrombotic thrombocytopenic purpura (TTP) attributed to treatment with the platelet ADP receptor antagonist, ticlodipine.[1] Since then, ticlodipine has been established as an immune-mediated cause of TTP with an incidence of approximately 0.02-0.06%.[2, 3] Due to its unfavorable side-effect profile, the use of ticlodipine has been mostly discontinued in the United States and replaced by clopidogrel. Both agents are thienopyridine-derivatives which differ only by a carboxymethyl moiety. In spite of their structural resemblance, no case of TTP was reported in phase III trials of clopidogrel with 19,185 patients.[4] However, reports of clopidogrel-associated TTP have emerged since the FDA approved the drug in 1998, including a seminal publication of eleven cases.[5] Five of these cases passed an independently conducted causality assessment.[6] Despite the identification of additional clopidogrel-associated cases by pharmacologic surveillance,[7] skepticism remains regarding whether clopidogrel actually causes TTP.[8] Here we report a case of clopidogrel-associated TTP and briefly review proposed mechanisms of drug-induced TTP.

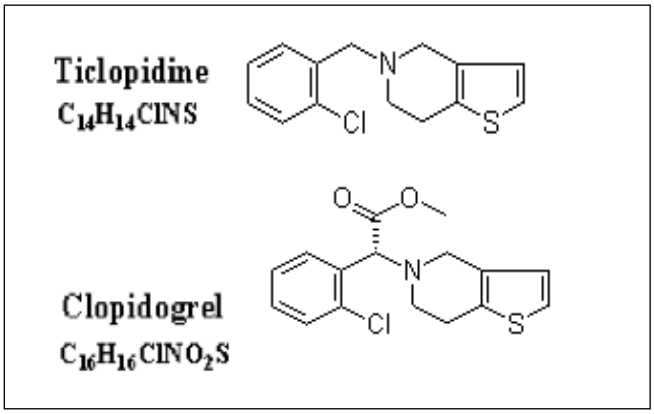

Figure 1. *Chemical structure of ticlopidine (Ticlid®) compared to clopidogrel (Plavix®)* [17]

Case Report

A 55-year-old Caucasian female presented with fever, jaundice, hematuria and painful neuropathy. Three years earlier, the patient was diagnosed with colorectal cancer which was successfully treated with resection. The patient also suffered from severe peripheral vascular disease secondary to diabetes mellitus, for which she had received an axillofemoral and aortafemoral bypass grafts several years prior. Ten years earlier, she also received a total abdominal hysterectomy with bilateral salpingo-oopherectomy for an ovarian cyst. Her medications at admission included coumadin 3 mg qday, premarin 0.3 mg qday, hydroxychloroquine 200 mg qday, glucosamine, lisinopril 20 mg qday, hydrochlorothiazide 12.5 mg qday, cilostazol 100 mg bid, and clopidogrel 75 mg qday. Clopidogrel had been added to her regimen within the past three months, ostensibly as adjunctive therapy for lower extremity claudication. She was an ex-smoker. She had no history of human immunodeficiency virus (HIV) or quinine exposure.

Physical exam was significant for fever (38.0°C), mild jaundice and petechiae of hands and abdomen. Laboratory testing revealed abnormal hemoglobin (5.6 g/dL), platelets (8.0 x 10^9/l), lactate dehydrogenase (2847 IU/L), indirect bilirubin (3.0 mg/dL), serum creatinine (1.6 mg/dL), and haptoglobin (< 0.6 μmol/L). Urinalysis revealed 66 red cells per high power field. Severe schistocytosis was noted on peripheral smear (Figure 1). Direct antiglobulin testing was negative and fibrinogen levels were normal (483 mg/dL). Serum carcinoembryonic antigen to detect recurrence of colorectal cancer was negative, and computed tomography (CT) scan of the abdomen did not show local recurrence or metastases. Blood cultures did not grow organisms. Transthoracic echocardiography showed normal cardiac function.

Although TTP was considered in her differential diagnosis, her clinicans first attributed her microangiopathic hemolytic anemia to suspected urinary tract infection. However, her status did not improve after several days with antibiotics and with consultation from hematology, the diagnosis of TTP was made at hospital day six. Serum von-willebrand factor (vWF) protease (ADAM-TS13) samples drawn during her hospital stay returned with an activity of < 5% (normal > 67%) by fluorescence resonance energy transfer (FRET) assay, and > 8.0 inhibitory units by mixing (normal < 0.4), consistent with immune-mediated TTP. The patient received a total of 8 units of packed red blood cells during her stay, and therapeutic plasma exchange was performed at hospital day #7 with 12 units of fresh frozen plasma (FFP). Twelve hours later, the

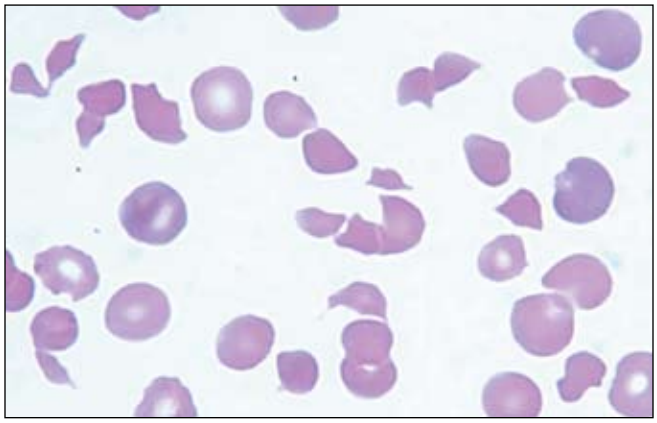

Figure 2. *Peripheral blood smear at admission, 500x. Note schistocytosis, severe thrombocytopenia, and polychromasia*

patient decompensated with acute shortness of breath and hypotension, and was subsequently intubated and admitted to the intensive care unit. Shortly after transfer, she entered into pulseless electrical activity (PEA) and cardiac life support failed to resuscitate her. Her family declined autopsy. No evidence of fluid overload was seen. Based upon review of the events, it is plausible that the patient died from a massive pulmonary embolism likely secondary to her hypercoagulable state.

Discussion

With the addition of this case, there are now 38 identified instances of clopidogrel-associated thrombic microangiopathy in the literature. The time course of drug initiation is consistent with prior case series[5] in which patients presented with TTP within two to three weeks after beginning a thienopyridine-derivative.

Although our patient was also receiving a synthetic derivative of quinine, no association has been made between hydroxychloroquine and TTP. In fact, thrombocytopenia alone is not reported as an adverse effect of hydroxychloroquine therapy. It is conceivable that the added hydroxychloryl group may alter the epitope of quinine[8] that induces drug-dependent antibodies. Indeed, exquisite specificity has been demonstrated in other causes of antibody-mediated drug-induced thrombocytopenia, such as sulfamethoxazole[9] and abciximab[10]. Drug-induced auto-antibodies to ADAMTS13 may exhibit similar specificity, likely accounting for the remarkably fewer cases of TTP documented with clopidogrel compared to ticlopidine.

Plasma exchange treats TTP via two plausible mechanisms: infusion and removal. Infusion of fresh donor plasma supplies the patient's circulation with the missing ADAMTS13 protease, thereby breaking down dangerous excesses of von-Willebrand factor multimers. Exchange of recipient plasma removes platelet aggregates, vWF multimers, and inhibitory autoantibodies to ADAMTS13. Plasma exchange may also filter culprit drug metabolites which may have induced TTP, such as thienopyridine derivatives. Not surprisingly, it has been observed that receipt of plasma exchange within three days of onset of clopidogrel-associated TTP results in 100% survival, vs. 27% if therapy is initiated afterwards.[7] In our case, the fatality of our patient may be attributable to delayed diagnosis and consequent initiation of plasma exchange at hospital day seven.

The finding of a vWF multimer protease inhibitor in this case is consistent with prior reports of ticlopidine and clopidogrel-associated TTP. Immunoglobulins to ADAMTS13 have been found in other etiologies of TTP in which immune dysregulation is suspected, such as human immunodeficiency virus (HIV)[10] and solid organ transplantation.[11] Inhibitory auto-antibodies to vWF protease are almost always an IgG class, although IgA class are occasionally identified in the same sera. The presence of an ADAMTS13-activity inhibitor by mixing does not necessarily mean that an associated immunoglobulin will even be detected; nor does the presence of ADAMTS13 antibodies guarantee that a mixing test result will be positive. The latter situation is rather easily explained by observing that protease-associated antibodies need not necessarily inhibit the activity of the protease. The former situation is more problematic, but fortunately appears to be rare. In a rigorous cohort study of 35 TTP patients, Ferrari *et al.*[14] found that an immunoglobulin was present in 91% of patients. Two of these patients had no detectable IgG/IgM/IgA

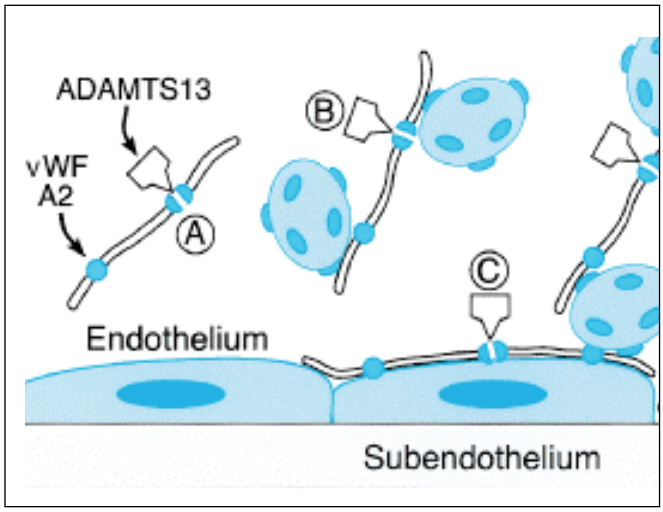

Figure 3. *Endothelial cells secrete vWF multimers into the circulation. The protease ADAMTS13 cleaves these multimers at the A2 domain (**A**). Platelets adhere to these multimers in the bloodstream (**B**) via the platelet glycoprotein Ib (GpIb). These multimers can also bind platelets to the endothelial surface (**C**). Deficiency or inhibition of ADAMTS13 causes vWF multimers to accumulate. Multimer accumulation results in increased platelet adherence and clot activation. This is the hypothesized mechanism of TTP. (diagram from Sadler[15])*

but did have an ADAMTS13 inhibitor. Specialized clinical laboratories have also reported occasional difficulty detecting IgG with samples positive by mixing[16]. The inability to detect immunoglobulin in these cases may simply represent a functional limitation of the assay. Unfortunately in our case, patient blood samples were disposed of before ELISA could be performed to identify ADAMTS13 antigen and immunoglobulins. Nevertheless, the strong inhibition of ADAMTS13 in our sample (>8.0 Bethesda units) makes it likely that an immune-mediated TTP was present, mostly likely secondary to clopidogrel. We also propose that specialized hematologic laboratories implement protocols to label and retain frozen blood samples of TTP for longer periods than the conventional sixty days. This practice may aid future investigators in the development of newer and more effective tests for this rare disease.

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