

CASE REPORT

Opana-induced thrombotic microangiopathy masquerading as thrombotic thrombocytopenic purpura

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Abstract

Opana (oxymorphone) is a powerful semi-synthetic opioid agonist used for chronic pain management that is ingested orally. However, improper injection of Opana can lead to a rare and fatal blood disorder known as thrombotic microangiopathy. Opana-induced thrombotic microangiopathy can be easily mistaken for thrombotic thrombocytopenic purpura (TTP), leading to the initiation of therapeutic plasma exchange. Current literature has conflicting views on the necessity of therapeutic plasma exchange for the treatment of Opana-induced thrombotic microangiopathy. In our case report, a 47-year-old Caucasian male was admitted with a presentation suspicious for TTP then underwent therapeutic plasma exchange without clinical improvement. With supportive treatment only, the patient eventually improved and later admitted to intravenously abusing oral Opana 1–2 days prior to becoming ill.

INTRODUCTION

Opana (oxymorphone) is a powerful semi-synthetic opioid agonist ingested orally that is used for management of chronic pain. However, abuse of Opana by improperly injecting it can lead to a rare and fatal blood disorder known as thrombotic microangiopathy. Opana-induced thrombotic microangiopathy can be easily mistaken for thrombotic thrombocytopenic purpura (TTP) due to their similar presentation, leading to the initiation of therapeutic plasma exchange. However, published literature has conflicting views on the necessity of therapeutic plasma exchange for treatment of Opana-induced thrombotic microangiopathy. In our case report, a 47-year-old Caucasian male presented with microangiopathic hemolytic anemia and thrombocytopenia suspicious for TTP. Therefore, he underwent therapeutic plasma exchange

but did not show signs of clinical improvement. After completion of plasma exchange therapy, he was continued on supportive treatment only and clinically improved several days later. Upon further history taking, he admitted to intravenously abusing oral Opana 1–2 days prior to becoming ill.

Opana-induced thrombotic microangiopathy should be considered in the differential diagnoses for patients presenting with clinical features of TTP, especially if there is a history of substance abuse.

CASE REPORT

A 47-year-old Caucasian male with a history of substance abuse presented with nausea, vomiting, watery diarrhea, abdominal

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pain, anuria, fatigue and paresthesia in his extremities for 4 days. His medications included trimethoprim-sulfamethoxazole and clindamycin for rashes on his arms. On examination, he was hypotensive (67/48 mmHg), tachycardic (HR 115) and altered. Petechiae were present on all extremities and abdominal tenderness was elicited on palpation. Initial labs revealed leukocytosis ($WBC\ 35.2 \times 10^3/\mu L$), anemia (Hb 11.5 g/dL), acute kidney injury (BUN 64 mg/dL, Cr 5.3 mg/dL) and thrombocytopenia (platelets $21 \times 10^3/\mu L$). Since the patient was taking clindamycin and experiencing watery diarrhea, we suspected septic shock secondary to *Clostridium difficile*-associated diarrhea. Surprisingly, the stool test for *Clostridium difficile* returned negative along with negative stool (*Escherichia coli* 0157:H7, *Shigella*, *Campylobacter*, etc.), blood and sputum cultures.

On further investigation, he was found to have microangiopathic hemolytic anemia evident by elevated lactate dehydrogenase (4473 U/L), decreased haptoglobin (<10 mg/dL), indirect hyperbilirubinemia (2.2 mg/dL) and schistocytes on peripheral smear (Fig. 1). The patient underwent 5 days of therapeutic plasma exchange for presumed TTP. However, his altered mental

status, leukocytosis and thrombocytopenia were not improving with plasma exchange therapy. Multiple tests and procedures were performed to work up an extensive list of differential diagnoses without success, including infective endocarditis, hemophagocytic lymphohistiocytosis and mixed cryoglobulinemia (Table 1). After completion of plasma exchange therapy, ADAMTS13 levels obtained prior to plasma exchange returned mildly decreased (28%), which did not support the diagnosis of TTP. Since the patient was not improving with therapeutic plasma exchange, we decided to provide supportive care only. After four days, his thrombocytopenia, altered mental status, and leukocytosis began to improve so he was transferred to the floor. Upon further history taking, he admitted to injecting Opana intravenously 1–2 days prior to becoming ill. Renal biopsy revealed acute tubular injury with cortical necrosis and collapsing glomerulopathy. There were no morphologic features to suggest hepatitis C-related glomerular disease or HIV-associated nephropathy. The patient was eventually discharged from the hospital on Day 17 with hemodialysis-dependent end-stage renal disease.

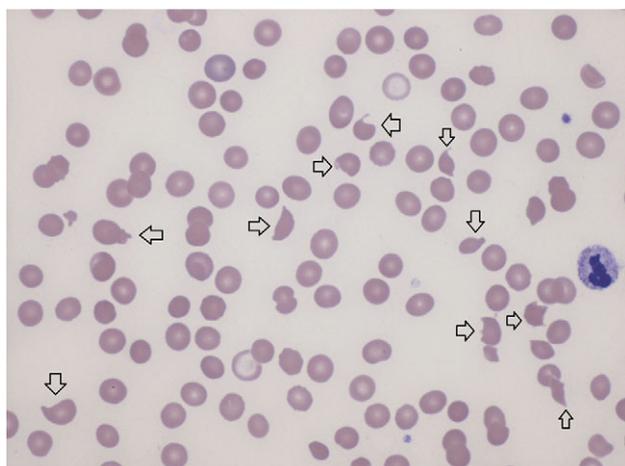


Figure 1: Peripheral smear revealing multiple schistocytes (black arrows), including helmet cells and keratocytes, and thrombocytopenia.

DISCUSSION

In January 2013, the Centers for Disease Control and Prevention reported a TTP-like illness associated with intravenous Opana abuse [1]. Since then, several case reports have been published with conflicting views on the necessity of therapeutic plasma exchange for Opana-induced thrombotic microangiopathy [2, 3]. In TTP, the goals of therapeutic plasma exchange are to remove anti-ADAMTS13 autoantibodies and to replace functional ADAMTS13. However, the pathogenesis of Opana-induced thrombotic microangiopathy is believed to be dose-dependent rather than immune-mediated, which would explain the ineffectiveness of therapeutic plasma exchange as there are no autoantibodies to remove from the plasma. Current guidelines on management of TTP recommend daily therapeutic plasma exchange until 2 days after the platelet count has normalized ($>150 \times 10^3/\mu L$), with a majority of patients (85–90%) responding to a 5–7 days course of plasma exchange [4, 5]. However, our patient received 5 days of therapeutic plasma exchange with minimal improvement in his platelet count and clinical status.

Table 1: Differential diagnoses and test results

Differential diagnosis	Reason(s) for exclusion
Septic shock	Negative pancultures Unremarkable imaging Afebrile
Thrombotic thrombocytopenic purpura (TTP)	No purpura present ADAMTS13 28%—greater than 10% cutoff for TTP No improvement with therapeutic plasma exchange
Disseminated intravascular coagulation (DIC)	ISTH DIC score 4—suggestive for non-overt DIC No underlying cause was identified
Infective endocarditis	Unremarkable transesophageal echocardiogram Negative blood cultures
Hemophagocytic lymphohistiocytosis	Unremarkable bone marrow analysis Normal soluble CD25 level Ferritin 1078 ng/mL (<3000 ng/mL commonly seen in hemophagocytic lymphohistiocytosis)
Mixed cryoglobulinemia	Undetectable serum cryoglobulins HCV viral load 192 000 IU/mL (low)
Rheumatologic diseases	Negative rheumatologic antibody panel (C-ANCA, P-ANCA, anti-Smith antibody, ANA, anti-RNP, SS-A, SS-B, anti-dsDNA)

Renal biopsy played an essential role in determining the etiology of our patient's presentation. When the patient's hepatitis panel returned positive for hepatitis C infection, we were concerned for hepatitis-C related diseases including mixed cryoglobulinemia and membranoproliferative glomerulonephritis Type 1. However, the labs (no serum cryoglobulins, low HCV viral load 192 000 IU/mL) and renal biopsy were not consistent with these diagnoses. Instead, the renal biopsy revealed collapsing glomerulopathy, which is commonly found in the setting of thrombotic microangiopathy and can rapidly progress to end-stage renal disease [6].

When clinicians encounter a patient with suspected TTP and unknown ADAMTS13 levels, they are forced to decide on initiating or withholding therapeutic plasma exchange. Most clinicians proceed with therapeutic plasma exchange because the risks of not treating TTP heavily outweigh the risks associated with therapeutic plasma exchange. Most hospitals, including our hospital, send their ADAMTS13 tests to outside laboratories due to significantly cheaper costs of testing. However, results are delayed by several days, leading to the challenging situation outlined earlier of initiating or withholding therapeutic plasma exchange. If hospitals would implement rapid in-house ADAMTS13 testing (~\$300 per test) rather than sending out the ADAMTS13 tests, physicians can definitively rule out TTP, safely withhold therapeutic plasma exchange, procure financial savings of \$12 000 per patient by withholding prophylactic therapeutic plasma exchange, and spare patients from complications associated with therapeutic plasma exchange (i.e. systemic infection, venous thrombosis, hypotension requiring dopamine) [7, 8].

In summary, Opana-induced thrombotic microangiopathy is diagnostically challenging due to its similar presentation to TTP. Since we were unable to obtain a thorough history from the patient when he initially presented, this case proved to be quite challenging to arrive at a diagnosis, taking into account the patient's untreated Hepatitis C infection, history of intravenous drug abuse, hemodynamic instability and negative pancultures. Case reports to date have conflicting views on the role of therapeutic plasma exchange and whether it offers any benefit to the patient. By proactively treating the patient with plasma exchange therapy for 5 days, our case unintentionally demonstrated the ineffectiveness of plasma exchange in treatment of Opana-induced thrombotic microangiopathy. We can also confirm that clinical resolution can be achieved with supportive care only. Our patient received an adequate course of plasma exchange with negligent improvement in his thrombocytopenia; thus, we can strongly argue that plasma exchange should not play a role in the treatment of Opana-induced thrombotic microangiopathy. With the knowledge gained from our case, we can make two suggestions to the medical community so that they may avoid the costly decisions that we inadvertently made. Firstly, increasing awareness of Opana-induced thrombotic microangiopathy with our case report will allow clinicians to arrive at the diagnosis sooner by conducting a thorough history including focused questions on recent intravenous abuse of Opana. Secondly, implementing in-house ADAMTS13 tests would allow physicians to safely withhold therapeutic plasma exchange after ruling out TTP and produce significant financial savings for the hospital. In conclusion, the underlying principles of

management of Opana-induced thrombotic microangiopathy are further avoidance of Opana use, treatment of any underlying infections and supportive care.

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None.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

FUNDING

No sources of funding.

ETHICAL APPROVAL

Ethical approval is not required for this case report.

CONSENT

Consent was given by the patient.

GUARANTOR

Dr Ashish Verma.

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