CASE REPORT

Opana ER abuse and thrombotic thrombocytopenic purpura (TTP)-like illness: a rising risk factor in illicit drug users

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SUMMARY

We report the case of a 22 year-old-woman who presented with upper extremity cellulitis secondary to an infiltration of illicit intravenous drug use. She confessed to the intravenous use of Opana ER (an extended release oral formulation of oxymorphone) which is an opioid drug approved only for oral use. She was found to have clinical evidence of profound thrombotic microangiopathy which resulted due to the intravenous use of Opana ER. She showed full clinical improvement after withholding drug and supportive clinical care. Recent report of Opana ER intravenous abuse was published from Tennessee county and has now been increasingly recognised as one of the causes of thrombocytopenia which mimicks clinically as thrombotic thrombocytopenic purpura. Physicians should be aware of this association as the lack of familiarity to this can pose serious management dilemmas for our patients (especially the polysubstance abusers).

BACKGROUND

Drug related thrombotic thrombocytopenic purpura (TTP) is rare but a well-described phenomenon in the literature. Various drugs (eg, ticlopidine, mitomycin, cyclosporine, etc) have been reported to cause TTP or TTP-like illness. We herewith report an interesting case report of a young woman who presented with TTP-like illness after illicit intravenous use of Opana ER, which is approved and recommended only for oral use. This is a novel rising risk factor among intravenous drug misusers which has been only recently recognised. We hope to highlight this intriguing association with our case.

CASE PRESENTATION

A 22-year-old woman presented with a 3-day history of acute onset left upper extremity redness and pain. Three days ago, she attempted intravenous self-injection of Opana ER (extended release oral formulation of oxymorphone) which inadvertently infiltrated into the subcutaneous space. She also reported subjective fever and chills. She denied any other significant medical or surgical history except occasional illicit intravenous Opana ER and marijuana abuse. She denied use of routine prescription or over-the-counter medications.

On presentation, she was afebrile and haemodynamically stable. She was alert and oriented. Systemic examination was remarkable for mild pallor, left upper extremity erythema, swelling and tenderness extending from mid upper arm to mid forearm. Intravenous track marks were noted in the antecubital fossae of both the arms. There was also associated left axillary lymphadenopathy.

INVESTIGATIONS

Laboratory examination was remarkable for anaemia (haematocrit=29%), normal white cell count, and thrombocytopenia (platelet count 29 000/UL). Further workup revealed presence of intravascular haemolysis (elevated lactate dehydrogenase (LDH 670 IU/L), undetectable haptoglobin levels and increased reticulocytes (4%)). The patient had normal fibrinogen level (310 mg/dL), normal fibrinogen degradation product (FDP <10 μg/mL), normal prothrombin time (13.3 s, international normalized ratio=0.9) and normal activated plasma thrombin time (28 s). Direct Coombs test was negative. Peripheral blood smear showed schistocytes and decreased platelets confirming ongoing microangiopathic haemolytic anaemia (MAHA). Renal and hepatic function tests were within reference range.

Blood, urine and wound cultures were sent. Serological tests including HIV and viral hepatitis panel were ordered. Acquired deficiency of metalloproteinase (ADAMTS13) activity level was also sent out.

DIFFERENTIAL DIAGNOSIS

- Disseminated intravascular coagulation (DIC)
- Immune thrombocytopenic purpura
- Haemolytic uremic syndrome (HUS)
- TTP
- TTP–HUS illness spectrum
- Sepsis
- Scleroderma renal crisis
- Evans syndrome

TREATMENT

The patient was given empiric antibiotic therapy (vancomycin and piperacillin–tazobactam), while awaiting culture results and was managed with supportive care therapy with preliminary diagnosis of TTP-like illness.

OUTCOME AND FOLLOW-UP

Subsequently, blood and urine culture results returned negative. Wound cultures showed presence of methicillin-sensitive *Staphylococcus aureus*. Workup for HIV and hepatitis panel returned negative. Decision was made for supportive care and watchful waiting given the patient's clinical stability

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and thus aggressive management measures including plasmapheresis were not employed promptly. Serial monitoring revealed complete normalisation of haematocrit and platelet counts over a course of 4 days. ADAMTS13 activity level was in the normal range (94%). The patient was discharged on oral cephalexin with appropriate outpatient follow-up and was extensively educated against the illicit use of Opana ER.

DISCUSSION

TTP is characterised by widespread platelet-rich thrombi leading to organ hypoperfusion and associated microangiopathic haemolysis. The classic clinical presentation of TTP is a pentad of MAHA, thrombocytopenia, fever, neurological symptoms and renal insufficiency. However, mere presence of MAHA and thrombocytopenia are sufficient for the diagnosis of TTP-like illness. The annual incidence rate of TTP could be as high as 3% in adults.[1] For the majority of cases, TTP is idiopathic. However, there is definite association of TTP with infection, medication and autoimmune disorders.[2 3] The congenital or ADAMTS13, have known to manifest as TTP.[4] ADAMTS13 is a metalloproteinase which breaks down ultra-large endothelial-derived von Willebrand factor and thus prevents platelet aggregation.[5] The prognosis of patients with TTP is quite poor without treatment with estimated mortality as high as 90%.[6]

Drug-induced TTP is a well-established entity for several years. Various drugs such as mitomycin, cyclosporine, ticlopidine, etc have been implicated in causing TTP or TTP-like illness.[7] However, the mechanism of drug-induced TTP is not clearly known. The proposed mechanisms include direct injury to the endothelium or by autoimmune pathway. For instance, antibodies against ADAMTS13 are implicated in ticlopidine-induced TTP.[8]

There has been a recent report by the Centres for Disease Control and Prevention (CDC) that intravenous injection of Opana ER can lead to clinical manifestation of TTP (OR=35.0; CI 3.9 to 312.1).[9] Opana ER is the extended release formulation of oxymorphone which is intended and approved for oral use.[10] This novel formulation of oxymorphone in combination with polyethylene glycol and oxide was made with the intention to prevent its use by any other route except oral. The exact culpability or mechanism leading to TTP-like illness from Opana ER is still to be elucidated. The TTP-like illness could either be due to oxymorphone itself or polyethylene component or the combination of both.

In the presence of schistocytes, elevated LDH and low platelet counts, the diagnosis of TTP-like illness is evident. Evans syndrome, an autoimmune cause of haemolytic anaemia and thrombocytopenia could be considered a close masquerader.[9] However, the patient had normal direct Coombs test which argues against Evans syndrome. Furthermore, DIC is unlikely in the setting of normal FDP, fibrinogen levels and coagulogram.

In our case, the only possible cause of TTP-like illness was Opana ER especially in light of other reported cases in the neighbouring county of Tennessee and the recent CDC alert. The first report of likely association between the illicit use of Opana ER and TTP was reported from the Department of Nephrology of one of our sister institutions to the Tennessee Department of Health (TDH) which resulted in a state wide investigation and led to the confirmation of this association.[10] In addition, the US Food and Drug Administration (US FDA) has issued a warning against misuse of Opana ER in any other form other than the advised oral route.[11] With concurrent improvement in platelet count over the course of 4 days with discontinuation of Opana ER abuse, we can make an assumption that the inciting pathogenic process is possibly reversible. The plasma exchange therapy was deferred in our patient because of the absence of neurological features and kidney insufficiency.

Learning points

- Opana ER intravenous abuse can cause thrombotic thrombocytopenic purpura (TTP)-like illness and is associated with normal levels of acquired deficiency of metalloproteinase.
- Exact mechanism of Opana ER-related TTP-like illness is not known, however it may be related to direct endothelial injury or an autoimmune phenomenon.
- Treatment involves serial blood count monitoring and platelet transfusions in actively bleeding individuals.
- Exchange therapy is rarely needed in the presence of neurological derangements or renal failure.

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