CASE REPORT

Thrombotic microangiopathy associated with intravenous injection of extended-release oxycodone

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SUMMARY

We describe the case of a 35-year-old man presenting with thrombotic microangiopathy (TMA) and renal impairment following, as he later disclosed, intravenous injection of oral formulation tamper-resistant extended-release oxycodone hydrochloride (Oxycontin). Recurrent misuse of this agent was associated with relapsing TMA despite treatment with terminal complement inhibitor eculizumab. Cases of TMA have been reported in the USA in association with intravenous misuse of extended-release oxymorphone (Opana ER) after the introduction of a new non-crushable formulation in 2012. There are two reported accounts of TMA associated with tamper-resistant Oxycontin, which became available in Australia in 2014. This is the first documented case in which eculizumab was used. This case illustrates the practical diagnostic challenges in identifying TMA disorders, and the importance of a detailed drug history. It also highlights the need to clarify what role, if any, eculizumab therapy has in cases of drug-associated TMA.

BACKGROUND

Thrombotic microangiopathy (TMA) is a pathological process common to several different rare and potentially fatal conditions, including thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome associated with Shiga-toxin-producing bacterial infection (STEC-HUS), and atypical haemolytic uraemic syndrome (aHUS). TMA is also associated with pregnancy, malignancy, accelerated phase hypertension, and exposure to certain drugs. Cases of TMA have been reported in USA in association with intravenous misuse of extended-release oxymorphone (Opana ER) after the introduction of a new non-crushable formulation in 2012.[1] There are two documented accounts of TMA associated with a similar agent, tamper-resistant extended-release oxycodone (Oxycontin), which became available in Australia in 2014.[2 3] Here we report a case of TMA wherein intravenous misuse of Oxycontin later became apparent. It is the first published case to record the use of terminal complement inhibitor eculizumab in this condition.

CASE PRESENTATION

We describe the case of a 35-year-old man with a history of schizoaffective disorder (treated with intramuscular risperidone) and chronic pain with regular use of paracetamol, but no non-steroidal anti-inflammatory agents. He is a smoker with a 10 pack-year history, and reported intermittent intravenous drug use. He had normal baseline renal function, with serum creatinine 86 umol/L recorded 2 years prior to presentation.

He initially presented to a regional hospital describing 48 hours of fatigue, sweats and epigastric discomfort. He reported intravenous injection 4 days prior with heroin obtained from an unfamiliar provider. On presentation, he was hypertensive (160/90 mm Hg) with a temperature of 37.8°C. He was noted to have palpable lymphadenopathy in the right axilla. Full blood count revealed haemoglobin 59 g/L and platelets 61×10^9/L. The patient received a transfusion of 4 units of red cells, and underwent lymph node biopsy, which showed reactive changes only. He was transferred to a tertiary metropolitan hospital 48 hours after presentation.

On arrival to our institution, the patient was afebrile, and blood pressure was 170/100 mm Hg. He was alert, with no neurological deficits. There were areas of superficial thrombophlebitis in his forearms. There were no peripheral stigmata of infective endocarditis, and no rash. He had no cardiac murmur. The jugular venous pressure was not elevated and there was no peripheral oedema.

Blood tests revealed thrombocytopenia (platelets 69×10^9/L) and anaemia (85 g/L). There was evidence of haemolysis, with elevated lactate dehydrogenase (LDH) at 772 U/L (reference interval (RI) <250) and reticulocytes 239×10^9/L (RI 20–100), and undetectable haptoglobin (<0.1 g/L, RI 0.3–2.0). Blood film analysis confirmed a microangiopathic haemolytic anaemia, demonstrating red cell fragmentation. The coagulation profile was normal, with fibrinogen 2.6 g/L (RI 1.9–4.3). Deteriorating renal function was noted, with creatinine 191 umol/L, and urine dipstick analysis was positive for blood and protein.

TREATMENT

Plasma exchange (PEx) was commenced on the day of admission, using a combination of fresh frozen plasma and albumin, and repeated the following day. The patient also commenced prednisolone 75 mg daily (subsequently weaned off completely over a 3-week period). On the fourth day of admission, the patient underwent percutaneous renal biopsy. This was complicated by retroperitoneal haemorrhage requiring arterial embolisation via angiography. The biopsy demonstrated evidence of TMA: arterioles contained fibrin thrombi and fragmented red cells, glomeruli showed ischaemic change, and mild patchy chronic tubulointerstitial damage was noted.

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The results of further investigations became available at this time. Of note, ADAMTS13 activity (measured prior to PEx) was 80% (RI >70). Antinuclear antibody, rheumatoid factor and antineutrophil cytoplasmic antibody were negative, and there was no evidence of infection with hepatitis B or hepatitis C, cytomegalovirus virus or Epstein Barr virus. C3 and C4 were within the normal range (1.33 g/L (RI 0.90–1.80) and 0.25 g/L (RI 0.16–0.47), respectively). Three sets of blood cultures yielded no growth. The patient had a transthoracic echocardiogram showing normal valves and normal left ventricle. Stool culture excluded Shiga toxigenic *Escherichia Coli* infection. Complement gene analysis was not performed.

PEx was continued over a total of 12 days, with improving haemoglobin and platelets, but persistently abnormal renal function and ongoing elevation of LDH and reticulocytes.

Eculizumab was commenced at a dose of 900 mg weekly for 4 weeks, followed by 1200 mg fortnightly. Meningococcal vaccine and prophylactic amoxicillin (250 mg twice daily) were administered prior to starting. No adverse effects of therapy were noted. PEx was ceased on commencement of eculizumab. The patient was discharged home 4 weeks after presentation, with haemoglobin 129 g/L, platelets 337×10^9/L, reticulocytes 83×10^9/L, haptoglobin 0.3 g/L, LDH 253 U/L and creatinine 170 umol/L.

OUTCOME AND FOLLOW-UP

The patient continued eculizumab as an outpatient, but was readmitted 6 weeks later to investigate recurrent anaemia and deteriorating renal function (creatinine 242 umol/L). At this time, the patient disclosed that he had been regularly injecting oral formulation tamper-resistant Oxycontin, informally obtained from another person to whom it was prescribed. Further discussion revealed that he had been injecting this formulation prior to the initial presentation also. LDH, bilirubin and haptoglobin were within normal limits and blood film did not show red cell fragmentation. His haemoglobin and creatinine improved during admission without intervention other than abstinence from intravenous drug use. Substance abuse counselling services were engaged. Eculizumab was ceased after 6 months of treatment. The patient is now under ongoing monitoring, with no evidence of recurrent TMA to date.

DISCUSSION

TMA is common to several conditions, including TTP, STEC-HUS and aHUS, each with a different underlying pathophysiology. TTP results from the deficiency or inhibition of ADAMTS13, a protease that cleaves large multimers of von Willebrand factor.[4] Clinical manifestations, especially neurological disturbance, can progress rapidly. Prompt treatment with PEx is vital to remove antibodies and replace deficient ADAMTS13, preventing permanent disability and death. In STEC-HUS, a diarrhoeal illness results in a toxin-mediated TMA, whereas aHUS is due primarily to dysregulation of the alternative pathway of complement. Mutations in the genes encoding complement components can lead to unchecked elaboration of complement and endothelial inflammation, usually after a trigger event, such as infection, trauma or pregnancy.[5] Endothelial dysfunction can result in acute kidney injury, as well as neurological, gastrointestinal and cardiac dysfunction. Eculizumab, a monoclonal antibody against terminal complement component C5, can halt the progression to end-organ failure, and has transformed the treatment and prognosis of aHUS.[6]

Drug-associated TMA is a well recognised phenomenon, with many agents implicated, including calcineurin inhibitors, gemcitabine and quinine. Different pathophysiological mechanisms have been proposed, including immune-mediated cell injury by drug-dependent antibodies, and dose-dependent toxicity (eg, by inhibition of prostacyclin or vascular endothelial growth factor).[7] Clinical presentation can vary, from insidious chronic renal impairment to severe acute multiorgan dysfunction. A recent review publication found a definitive causal relationship with TMA for 22 different drugs.[8] Tamper-resistant Oxycontin is a new addition to this list, with the recent publication of two case reports describing TMA associated with intravenous misuse of this oral formulation agent.[2 3] Cases of TMA have been reported in the USA in association with intravenous misuse of Opana ER, after the introduction of a new non-crushable formulation in 2012.[1] Tamper-resistant Oxycontin, released in Australia in 2014, becomes viscous when added to water in order to deter injection, and contains inactive ingredients not found in the previous formulation. While it is not certain which specific components may provoke TMA, the polyethylene oxide coating common to both agents has been postulated to cause direct toxicity to endothelial cells.[9]

This case highlights the practical challenges in diagnosing TMA, identifying the underlying condition, and promptly instituting appropriate treatment. PEx was commenced after interhospital transfer, more than 48 hours afterthe initial presentation with anaemia and thrombocytopenia. Differential diagnosis on arrival was broad: sepsis, endocarditis, disseminated intravascular coagulation and TTP were considered and investigated as above. Diagnostic uncertainty underpinned the decision to perform a renal biopsy. As illustrated in this case, renal biopsy carries a small but significant risk of harm, and a histological specimen is not essential to confirm TMA, which can be identified on blood tests and blood film analysis. Although endothelial injury related to intravenous drug use was the suspected trigger of TMA, a clear association with a specific agent was not initially established. This uncertainty, together with normal ADAMTS13 activity and persistent evidence of haemolysis despite PEx, led to the consideration of a diagnosis of aHUS, and initiation of eculizumab. As there is no single real-time confirmatory diagnostic test for aHUS, diagnosis depends on exclusion of other conditions. The patient's later disclosure of his injecting habits prompted further diagnostic reflection.

Learning points

- Thrombotic microangiopathy (TMA) is a pathological process comprising microangiopathic haemolytic anaemia and thrombocytopenia.
- TMA can be associated with thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome with Shiga-toxin-producing bacterial infection, atypical haemolytic uraemic syndrome, accelerated phase hypertension, pregnancy, malignancy and the use of certain drugs, including intravenous misuse of oral formulation oxycodone.
- A detailed drug history is essential in assessing a patient with TMA.
- Cessation of the drug suspected to have triggered TMA is the mainstay of treatment.

An American case series of 15 patients with TMA related to Opana ER reported clinical improvement in all cases with supportive management only, without PEx or eculizumab.[10] While our patient received eculizumab therapy, the key to recovery was abstinence from injecting, thereby removing the trigger for endothelial injury. Eculizumab may be indicated only in individuals where removal of the trigger for TMA is not sufficient to halt the process and prevent irreversible end-organ damage, such as those with underlying genetic abnormalities of complement regulation. Recognition of novel and rare triggers, such as intravenous injection of oral formulation oxycodone, together with elucidation of predisposing genetic risk factors, could further develop the diagnostic classification of TMA disorders and guide the judicious use of complement inhibitor therapy.

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