CASE REPORT

OXYMORPHONE INDUCED THROMBOTIC MICROANGIOPATHY MIMICKING ATYPICAL HAEMOLYTIC UREMIC SYNDROME

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Background: Atypical Haemolytic Uremic Syndrome (aHUS) is a rare life threatening entity characterized by thrombocytopenia, haemolytic anaemia and renal dysfunction. It is a thrombotic microangiopathy related to genetic mutations in the alternate complement pathway and has a distinct pathophysiology which makes it harder to distinguish from other microangiopathies. We present a case of a 25-year-old male patient with history of polysubstance abuse who presented with chest pain and dyspnoea. He admitted to using injectable oxymorphone (Opana) two weeks before presentation. Patient’s vital signs were stable except for tachycardia and high blood pressure. On physical examination, epigastric tenderness and mild splenomegaly was appreciated. Urine Drug Screen was positive for oxycodone and opiates. Laboratory work up revealed haemolytic anaemia, thrombocytopenia and acute kidney injury. Extensive evaluation resulted in our impression of the disease being atypical haemolytic-uremic syndrome. He was managed with dialysis, intravenous steroids and plasmapheresis with improvement in his hematologic parameters.

Keywords: Acute renal failure; Atypical Haemolytic uremic syndrome; Opana; oxymorphone use; Endothelial dysfunction; Drug abuse

INTRODUCTION
Thrombotic microangiopathies (TMA) are caused by thrombosis of capillaries walls and arterioles leading to thrombocytopenia, haemolytic anaemia, acute kidney injury and sometimes neurological manifestations.1 TMA can be categorized into Thrombotic thrombocytopenic purpura (TTP) and Haemolytic Uremic Syndrome (HUS); the latter is further divided into typical and atypical HUS (aHUS). Atypical HUS accounts for 5–10% cases of TMA, and compared with typical manifestations, it features poorer prognosis.2,3 Opana ER or Oxymorphone is an extended release form of the potent opioid pain reliever. The Food and Drug Administration (FDA) approved Opana ER in 2006 for oral use. Following the reformulation of Oxycodone and Oxycodin, the misuse of intravenous (IV) Opana ER gained popularity among recreational drug users.4 It is a growing risk factor for TTP - like illness in the past few years.5 Herein, we report the case of young adult male who was diagnosed with TMA after the IV Opana use. Whether his TMA was aHUS or TTP was a diagnostic challenge.

CASE
A 25-year-old male with past medical history of polysubstance abuse presented with chest pain and shortness of breath. He admitted to IV use of Opana ER two weeks prior to admission.

On presentation, the patient was afebrile, had a pulse of 116/ minute, blood pressure of 160/110 mmHg, respiratory rate was 18/minute and O2 saturation, 95% on room air. On abdominal examination, he had voluntary guarding with tenderness in the epigastrium and right upper quadrant. His spleen was mildly palpable 1–2 finger-breadths below the costal margin. Cardiovascular and pulmonary examinations were unremarkable. Laboratory findings were remarkable for anaemia with haemoglobin 12 g/dl (120 g/L). Platelet count, 172000 /µL (172x109/L), and leucocyte counts were normal on admission. On day 2 of presentation patient’s platelet count dropped to 112000/µL (112x109/L). Urine drug screen resulted positive for Oxycodone and opiates. The patient was found to be in acute kidney injury (AKI) with a creatinine of 7.9 mg/dl (698.36 µmol/L). Further workup showed evidence of intravascular haemolysis with elevated LDH level 1477 IU/L, low haptoglobin level <8 mg/dl (0.08 g/L), and high fibrinogen degradation product 4.6 mg/L. Fibrinogen level, activated partial thromboplastin time and prothrombin time were normal. Patient had low C3 complement level 34 mg/dl (0.34 g/L) and C4 complement level <3 mg/dl (0.03 g/L). As low complement levels are more consistent with a diagnosis of mixed cryoglobulinemia, cryoglobulin test was ordered which came back negative. Patient’s ADAMTS-13 activity level was also evaluated which was normal.

The patient was tested for Hepatitis C two months prior to admission and was found to be Hepatitis C negative, however repeat testing on this admission was positive with viral load of 1160000 IU/ml. Serologic tests for hepatitis B surface antigen, http://www.jamc.ayubmed.edu.pk

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hepatitis A IgM, hepatitis B core antibody, HIV, ANA, ANCA and rheumatoid factor were negative. His peripheral smear showed approximately three schistocytes per HPF suggesting microangiopathic haemolytic anaemia (Figure-1). Kidney biopsy revealed the findings of thrombotic microangiopathy (TMA) with a majority of the morphologic findings being focused on the arteries and arterioles and with focal thrombosis.

Based on clinical history and laboratory findings, patient was treated with plasmapheresis every alternate day and IV steroids. Throughout the hospitalization, the patient's platelets stayed stable between 90000–100000/µL (90–100x 109/L). Patient was also started on haemodialysis for acute kidney injury. Eventually, he was discharged home with extensive education against use of Opana ER. At follow-up, his hematologic parameters showed improvement. The patient had gradual but partial recovery of his renal function and was no longer haemodialysis dependent.

**DISCUSSION**

Atypical HUS presents with renal symptoms, neurological dysfunction and high blood pressure due to renal involvement. Improper management of patients can lead to complications such as chronic renal failure whereas half of the patients can end on dialysis for end stage renal disease (ESRD). Hyperactivation of the complement pathway is the common pathogenic mechanism in shiga toxin producing Escherichia coli (STEC)- HUS, TTP, and aHUS. In STEC- HUS Shiga toxins (Stxs) activates the complement pathway via upregulation of P-selectin while in TTP severe deficiency of ADAMTS13 deficiency causes massive platelet thrombi via complement activation. Atypical HUS is a disease of complement regulation affecting the alternative pathway of complement activation. About 50–60% cases of aHUS carry genetic mutation encoding complement proteins. There are more than 120 different mutations and it has a prognostic value as Factor H (CFH) mutations are associated with worst prognosis with 70–80% cases progress to ESRD or death, while Membrane cofactor protein (MCP) mutations are rarely associated with ESRD.

Penetrance rate is around 50% in genetic forms of aHUS. Although aHUS mostly occur in children, around 30% of aHUS cases do not manifest until middle age. Additionally, many patients with underlying complement activation abnormalities experience prolonged symptom-free periods which indicates possible concurrent genetic and environmental factors affecting disease expression. With regards to environmental factors, certain infections including streptococcal pneumonia, varicella, influenza, HIV, pertussis, medications such as quinine, mitomycin, cisplatin, bleomycin, cyclosporine, clopigidogrel, ticlopidine, and pregnancy have been reported to be associated with aHUS. Opana-ER is probably one of the environmental factors for aHUS too.

FDA approved Opana ER for chronic pain in 2006. Since 2010, illicit use of Opana ER has significantly increased following the reformulation of the oxycodone and oxycotin to make them crush resistant. In 2012 to address this increase, Endo Pharmaceutical developed a reformulated tamper-resistant Opana ER to prevent inappropriate use of the drug. However, FDA declared that a new crush-resistant tablet still can be compromised and used via injection.

The first case control study was conducted by the Tennessee Department of Health (TDH) in 2012 after a first case was reported to them by a nephrologist associating IV Opana use and TTP-like illness. Based on the clinical and laboratory findings, TDH identified 15 cases of TTP-like illness associated with misuse of Opana ER. Millet et al published a case series including the clinical diagnoses of 15 patients having had 18 episodes of Opana ER induced TMA. ADAMTS13 activity ranged from 12–119% with mean of 63% in this case series. Diagnosis in our patient was one of exclusion as detailed history did not reveal any other cause of TMA other than significant use of Opana ER; however, the clinical presentation of our patient seems similar to patients with aHUS.

Our patient met criteria for aHUS according to the joint Committee of the Japanese Society of Nephrology and the Japan Paediatric Society (JSN/JPS) including a triad of thrombocytopenia (platelets less than 150000/µL), microangiopathic haemolytic anaemia and acute renal failure with no association with Shiga toxins. As our patient did not have clinical correlation suggesting infection by Shiga toxins producing bacteria, it was not tested. As
ADAMTS13 activity is normal, TTP was excluded.\textsuperscript{12} The exact mechanism of Opana ER induced aHUS is unknown. Possibly, it is one of the contributing factors that triggered our patient’s underlying unknown complement activation abnormality. The process to convert the Opana ER tablets to be used IV may be a contributory factor.\textsuperscript{12} Unfortunately, we do not know which process was used by our patient.

Another unproven aetiology is an inactive polyethylene oxide (PEO) and polyethylene glycol (PEG) components used to make tamper-resistant Opana-ER might be the contributing factors.\textsuperscript{2,3,13} Animal models showed thrombocytopenia after administration of the PEO.\textsuperscript{3,13} Additionally, there is a case of IV reformulated OxyContin induced TMA recently reported in Australia.\textsuperscript{13} It is noted that IV reformulated OxyContin also contains PEO as an inactive ingredient.\textsuperscript{7,13} The mechanism contributing to the aHUS in association with Opana ER and other reformulated opioid might be multifactorial, and further studies are needed to clarify it.

By year 1980 plasma exchange therapy was the most recommended therapy for aHUS, and around 70% of cases received hematologic remission. It should begin within 24 hours after diagnosis and is continued till platelet count, LDH and haemoglobin levels improved, then alternative treatment therapy should be considered such as management with the eculizumab.\textsuperscript{1} In our patient complete haematological remission was obtained with plasmapheresis and steroids.

CONCLUSION

Because of the increasing epidemic of prescription drugs misuse including Opana ER, it is important to teach the patients regarding serious outcomes of misusing it. Moreover, given the evidence to support the link between illicit drug use and TMA, it is important to obtain a detailed patient history in patients presenting with TMA of unknown aetiology.

REFERENCES


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