

## CAS CLINIQUE / CASE REPORT

# THROMBOTIC MICROANGIOPATHY ASSOCIATED WITH OPANA ER INTRAVENOUS ABUSE A Case Report

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**ABSTRACT** • Thrombotic microangiopathy is characterized by endothelial changes and microvascular stenosis. Several entities such as pregnancy, infection, connective tissue diseases, and drugs are associated with secondary thrombotic microangiopathy. Recently, new reformulation of Opana ER had been associated with thrombotic microangiopathy when injected intravenously. Here, we report the case of a 37-year-old man who developed renal failure and hemolytic anemia secondary to Opana ER intravenous abuse. Renal biopsy pathology was consistent with thrombotic microangiopathy likely caused by Opana ER intravenous abuse.

Keywords: thrombotic microangiopathy, renal failure, hemolysis, Opana

## INTRODUCTION

Opana or oxycodone (14-hydroxydihydromorphinone) is a potent opioid that carries an abuse liability. If overdosed, it can cause severe respiratory depression, coma, cardiac arrest and death. In this report, we describe renal failure secondary to thrombotic microangiopathy as another potential complication of Opana ER intravenous abuse.

## CASE REPORT

A 37-year-old man presented with cough and pleuritic pain for several days. He smokes one pack of cigarettes per day and misuses Opana ER by crushing, dissolving (by mixing with water and heating) and then injecting it intravenously, about 90 grams daily for three months. He denied using any other drugs.

Chest X rays showed bilateral basilar lung infiltrates. Blood workup revealed positive serum Mycoplasma IgM antibodies, Mycoplasma pneumonia antibodies 1144 u/ml (0-99 u/ml), white blood cells count 10900/mm<sup>3</sup>, hemoglobin 6.6 g/dl, hematocrit 19%, platelets 142,000/mm<sup>3</sup>, creatinine 4.3 mg/dl, INR 1.3, and C reactive protein of 25. Anemia blood workup revealed iron 16, ferritin 414 (18-350), reticulocytes count 6.40% (0.5-1.5%), haptoglobin 9 mg/dl (30-200 mg/dl), LDH 623 units/L (100-190).

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**RÉSUMÉ** • La microangiopathie thrombotique est caractérisée par des modifications endothéliales et une sténose microvasculaire. Plusieurs entités telles que grossesse, infections, maladies du tissu conjonctif et médicaments sont associées à la microangiopathie thrombotique secondaire. Récemment, une nouvelle reformulation d'Opana ER a été associée à la microangiopathie thrombotique lorsqu'elle était injectée par voie intraveineuse. Nous rapportons ici le cas d'un homme de 37 ans qui a développé une insuffisance rénale et une anémie hémolytique secondaires à l'abus d'Opana ER par voie intraveineuse. La pathologie de la biopsie rénale était compatible avec une microangiopathie thrombotique probablement causée par l'abus d'injections intraveineuses d'Opana ER.

Complements levels were C3 118 mg/dl (90-180 mg/dl), C4 of 34 mg/dl (10-40 mg/dl). ANA and RF were negative. Cryoglobulins were negative. HIV test was negative and hepatitis C antibody testing was positive and hepatitis C viral RNA was elevated. Peripheral blood smears showed rare red blood cells fragments.

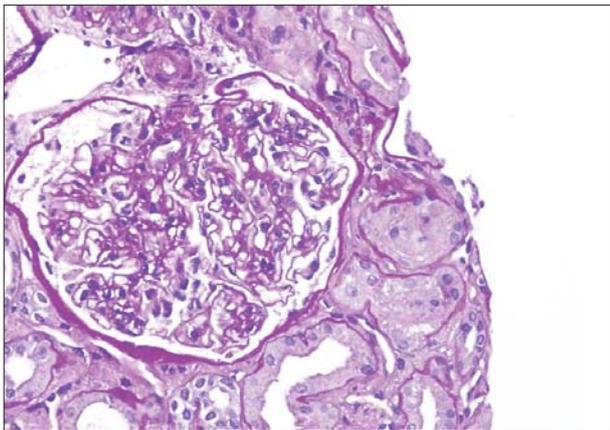
He was started on azithromycin for the Mycoplasma pneumonia. A 2D echocardiogram revealed tricuspid regurgitation but transesophageal echocardiogram was normal and showed no vegetations. His serum creatinine was 5.5 mg/dl after 7 days of current treatment, so a percutaneous renal biopsy was done.

The biopsy revealed thrombotic microangiopathy with marked arterial intimal thickening associated with extensive glomerular ischemic changes and acute tubular injury. Under light microscopy, the glomeruli showed diffuse global marked glomerular basement membrane (GBM) corrugation, patchy mild endothelial swelling, and mild mesangiolysis. Few glomeruli showed segmental sclerosis with adhesions to Bowman's capsule. There were no fibrin thrombi and no crescents or fibrinoid necrosis (Figure 1). Arterioles showed concentric intimal fibrosis and intimal proliferation with mucoid change. Interlobular arteries showed marked occlusive intimal thickening with fibrosis and marked mucoid change with focal fibrin strands in the lumen (Figure 2). There was no vasculitis and the Congo red stain was negative for amyloid. The immunofluorescence stain was essentially negative. Electron microscopy showed significant GBM corrugation in glomeruli. There was moderate to marked expansion of lamina rara interna involving most loops. The foot processes were extensively effaced.

Thrombotic thrombocytopenic purpura (TTP)-like syndrome or thrombotic microangiopathy (TMA) secondary to Opana intravenous use was suspected and the patient had five sessions of plasmapheresis. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was more than 100%. The LDH improved to 177 u/L, and haptoglobin improved to 200 mg/dl. Creatinine stabilized at 4.5 without further improvement. The patient, however, did not require hemodialysis. He received two units of packed red blood cells and was discharged home and advised to stay away of Opana misuse.

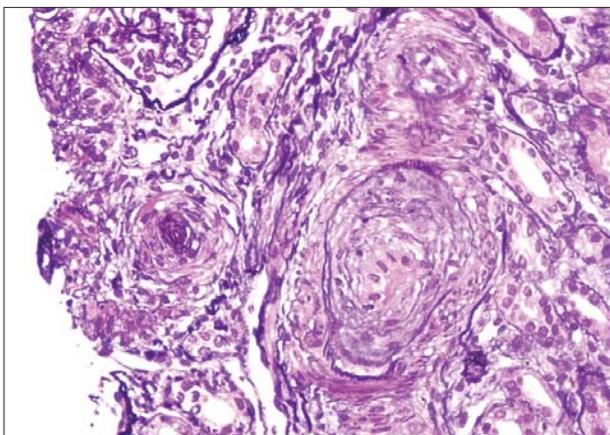
#### DISCUSSION

Opana or oxycodone (14-hydroxydihydromorphinone), a potent schedule II opioid analgesic drug was first marketed in the USA for medical use in 1959 as injectable and rectal suppository forms. The oral tablets of Opana and Opana ER (extended release) were approved by FDA in June 2006 [1]. In addition to its analgesic effects,



**FIGURE 1**

Under light microscopy, a glomerulus is showing diffuse global marked glomerular basement membrane (GBM) corrugation. There were no fibrin thrombi.



**FIGURE 2**

Interlobular artery showing marked occlusive intimal thickening with fibrosis.

Opana causes euphoria, feelings of relaxation, and anxiety. It also carries an abuse and addiction liability [1]. If overdosed, it can cause severe respiratory depression, coma, cardiac arrest and death. In Florida alone, oxycodone related death increased by more than 242% from 69 in 2008 to 236 in 2009 surpassing other opioids such as fentanyl, hydromorphone and heroin. In the first six months of 2010, 223 deaths were related to oxycodone [1]. Snorting crushed tablets, or dissolving them for injection are some routes of administration [1]. In an effort to inhibit crushing and dissolving tablets, a new formulation of Opana ER was released into the market in February 2012. The new formulation contains inactive ingredients not found in the original formulation, including polyethylene oxide (PEO) and polyethylene glycol.

Recently, three cases of TTP-like illness associated with dissolving and injecting tablets of Opana ER were reported to the Tennessee department of health (TDH). Further statewide investigation, a case-control study, conducted by the TDH identified a total of 15 such cases of TTP-like illness associated with injection of reformulated Opana ER [2]. The earliest diagnosis of TTP-like illness was in April 16, 2012, several weeks after the release of the new formulation of Opana ER in February 2012.

In this study, the clinical presentations included nausea, abdominal pain, fatigue and fever. The platelets counts of these patients ranged from 9,000 to 49,000 per mm<sup>3</sup>, creatinine level ranged from 0.5 to 11.4 mg/dl, LDH 131 to 3,007 U/L, hemoglobin ranged from 5.2 to 7.3 g/dl, ADAMTS13 activity level ranged 42 to 131%, and schistocytes were detected in all of them [2]. Of these patients, 12 had plasmapheresis, 11 had renal failure, 2 had dialysis, 12 had hepatitis C, 7 had infection or sepsis on admission, 13 were women, and all were white and none were pregnant. The age ranged 22 to 49 years (median 34). The patients reported a first injection of reformulated Opana ER, 21 to 120 days prior to hospital admission (median 60 days) and the last reported injection occurred 0-2 days before admission [2]. Based on this investigation, the Food and Drug Administration released a statement regarding the association of intravenous abuse of reformulated Opana ER and TTP-like illness on October 2012.

In our case, there is evidence of thrombotic microangiopathy on renal biopsy and we think it is secondary to the use of intravenous Opana ER injections. TTP was unlikely as the activity level of ADAMTS13 is normal (more than 100%). ADAMTS13 cleaves von Willebrand factor into smaller inactive multimers whenever it is undergoing shear-induced conformational change, thus intravascular von Willebrand factor-platelet aggregation is prevented [3]. In the absence of adequate ADAMTS13, von Willebrand factor will be gradually activated by shear stress leading to intravascular von Willebrand factor-platelet aggregation and microvascular thrombosis of TTP [3]. In TTP, a severe ADAMTS13 deficiency (5 to 10% of normal) is needed as platelets consumption does not occur

if the level is greater than 10% [3]. This is mostly due to autoantibodies against ADAMTS13 (such as associated with ticlopidine and clopidogrel) or genetic (mutations in the ADAMTS13 gene and extremely rare autosomal recessive disease of incidence 1:1,000,000) [3]. The overall incidence of TTP is estimated to be 2-15 cases/106 patient-years. Other etiologies of thrombotic microangiopathy are hemolytic uremic syndrome (HUS) triggered by infection with Shiga-like toxin producing *Escherichia coli* (STEC) mostly seen in children or streptococcus pneumonia infection (neuraminidase) [3]. Our patient did not recall symptoms of diarrhea and his pneumonia was secondary to Mycoplasma infection. Also, HUS occurs mostly in children. Therefore, it was unlikely that he had HUS. In atypical HUS (aHUS), there are genetic abnormalities or immune system alterations of the complement system, and patients have a poorer prognosis with a high mortality and progression to end-stage renal disease in 50% of the cases [4]. However, this may change with the use of a new drug, eculizumab, a recombinant monoclonal anti-C5 antibody which binds to C5 and blocks its cleavage into C5b thus preventing the formation of the anaphylatoxin C5a and membrane attack complex C5b-9 [4-5].

Secondary causes of TMA are numerous and they include pregnancy (postpartum, and HELLP [hemolysis, elevated liver enzymes and low platelets]), systemic lupus erythematosus, anti-phospholipid syndrome, HIV and H1N1, malignancy, and drugs such as gemcitabine, cisplatin, calcineurin inhibitors (e.g. tacrolimus and cyclosporine), and bone marrow transplants [3].

The renal findings may differ between TTP and the other thrombotic microangiopathies. In TTP, there are mostly von Willebrand factor-rich thrombi in the kidney arterioles with intact endothelial cells and vessel walls [3]. On the other hand, in TMA associated with HUS, aHUS, and drugs, etc. (i.e. TMAs with normal ADAMTS13 activity) there is swelling of the endothelial cells, arteriolar fibrosis and stenosis with or without thrombosis, intima thickening, and interstitial edema [3]. The findings of marked arterial intimal thickening and extensive glomerular ischemic changes in the renal biopsy of our patient are in favor of the second category. Our hypothesis is that the intravenous reformulated Opana ER had caused TMA through endothelial damage. Interestingly, almost all of the cases, including our case, of microangiopathy induced by Opana ER were reported after the release of the new formula of Opana ER which contains the inactive ingredient polyethylene oxide (PEO) [2]. It

is possible that this ingredient is responsible for TMA. In one study on rats, PEO caused thrombocytopenia when injected intravenously [6]. Also, it is possible that the drug might have been adulterated by drug dealers though in the literature, at least two patients obtained the drugs directly from a licensed pharmacy with prescriptions [2].

Treatment of TMA secondary to drug or toxin is mostly preventative and supportive. Although plasma exchange therapy and plasmapheresis may be of value, the effectiveness of this approach has yet to be proved in randomized clinical studies [7]. Furthermore, plasma exchange and plasmapheresis may not be necessary if ADAMTS13 activity is unaltered [8]. Monitoring of kidney function is very important.

In summary, Opana ER is meant to be taken orally and as directed through a prescription. Physicians should consider microangiopathy in the differential diagnosis of patients presenting with renal failure and anemia. Asking these patients about possible oxymorphone intravenous abuse and performing urine drug tests is important.

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