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**Case Report**

# Thrombotic Thrombocytopenic Purpura Induced by Acute Pancreatitis

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**Thrombotic thrombocytopenic purpura (TTP) is a rare blood disorder characterized by clotting in small blood vessels of the body (microthrombi), resulting in a low platelet count. The disease consists of the pentad of microangiopathic hemolytic anemia, thrombocytopenic purpura, neurologic abnormalities, fever and renal disease. Many symptoms could develop with acute pancreatitis but being able to differentiate when it is associated with any hematological conditions such as TTP is crucial to initiate a proper medical treatment. We present a rare case of a thirty-eight years old African American female, who presented to the Emergency department with an abdominal pain associated with a pancreatic condition. A vital piece in medical practice is recognizing lifesaving decisions in critical conditions cases. Acute Pancreatitis (AP) is a well-described consequence of TTP but acute pancreatitis triggering TTP is still not as frequent.**

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**Key Words:** acute pancreatitis, TTP, HUS, ADAMTS13, MAHA

## INTRODUCTION

The annual incidence of Thrombotic thrombocytopenic purpura (TTP) is approximately three cases per one million adults per year, which makes the disease not as frequent as other conditions.<sup>1</sup> At least a minimum of two diagnostic criteria are required to make the diagnosis, one of them being microangiopathic hemolytic anemia (MAHA) and thrombocytopenia, which may be accompanied by central nervous system, renal, gastrointestinal and cardiac involvement.<sup>2</sup> The decisive cause of TTP is not well known, but one of the etiologies described by the investigators is the deficiency or dysfunction of A Disintegrin and Metalloproteinase with a Thrombospondin type 1 motif Member 13 (ADAMTS13) leading to accumulation of ultra-large von Willebrand factor molecules; and subsequent von Willebrand factor (vWF)/platelet-rich microvascular thrombosis.<sup>3</sup> Most of the time TTP in adults is idiopathic; however in our case TTP may be secondary.<sup>4</sup>

During acute pancreatitis, pancreatic tissue damage is a result of intracellular activation of enzymes that lead to an inflammatory response and release of cytokines.<sup>5</sup>

TTP as a consequence of acute pancreatitis continues to be rare.

## CASE REPORT

This is a 38 yrs. old African American female who was admitted to the hospital with abdominal pain of 5 days after binge alcohol abuse. Pain was mainly on the epigastrium with severe intensity, radiating to the left flank, left upper back and associated with nausea and vomiting.

Patient's medical history is significant for HIV since 2008 with latest CD4 of 169/13%, alcohol abuse and two episodes of pancreatitis in the past. Laboratory findings during this admission showed an elevated amylase of 2000 U/L (N < 115 U/L), lipase 800 U/L (N < 190 U/L). Her urea 28 mg/dl and creatinine 1.29 mg/dl. Total bilirubin 1.2 mg/dl, direct bilirubin 0.7 mg/dl, aspartate aminotransferase (AST) was 65 IU/L, alanine aminotransferase 27 IU/L, blood glucose of 88 mg/dl, albumin 2.9 g/dl and lactate dehydrogenase (LDH) was 68 IU/L. Her white blood count was elevated to 8000 mL. Hematocrit was 26.8 %, with hemoglobin of 8.6 g/dL and platelets were  $10 \times 10^3/\text{mm}^3$ . Latest platelets count on our medical record system before this admission was of  $292 \times 10^3/\text{mm}^3$  on September 21<sup>st</sup>, 2013 (patient did not have blood work done since then). Ultrasound abdomen showed no gallstones and enlarged pancreas, reflecting underlying pancreatitis. Computed tomography of abdomen also showed mild pancreatic inflammation with no gallbladder stone and small pericardial fluid. Patient was diagnosed as acute pancreatitis secondary to alcohol use.

Patient was immediately evaluated by the medical intensive care unit (MICU) for severe thrombocytopenia in acute pancreatitis and was started on intravenous fluids as part of

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her medical treatment. Patient received a total of 3 liters of normal saline divided in between bolus and continuous infusions with input and output well documented as per MICU protocol.

- Second blood set showed elevated amylase of 579 U/L, lipase of 1362 U/L, platelets  $10,000 \times 10^3/\text{mm}^3$ ; Hct 20.4%, Hgb 6.7 g/dl. Urea and creatinine remained stable but LDH rose up to 319 associated with peripheral smear showing significant schistocytes of 4%. Reticulocytes count 6.9 % with fibrinogen levels and the coagulation profile normal. ADAMTS 13 enzyme assay test was less than 10%. Based on the abnormal labs values, patient was diagnosed with TTP with evident MAHA and elevated creatinine level compared to patient baseline. All signs and symptoms on this patient, plus thrombocytopenia and mild renal impairment favor TTP rather than HUS as our diagnosis. Patient had pan CT scan with negative results performed in order to rule out any possible malignancy as associated triggering factor for TTP in a patient with HIV. She was already on HAART therapy with a CD4 count more than  $150 \text{ cells}/\text{mm}^3$  and without evidence of any opportunistic infections.

Plasmapheresis on this patient was started in addition to Methylprednisolone, which is a well-established TTP treatment.

Patient received three plasmapheresis sessions as an inpatient with an evident improvement of platelet counts, urea and creatinine along with hemoglobin level. Patient's hospital course took an unexpected turn when she on her 11<sup>th</sup> day of admission signed out against medical advice returning within 24 hrs. of leaving. During re-admission blood work remained stable with Hg 10 g/dl, HCT 30.2%, persistent low platelets of  $31,000 \times 10/\text{mm}^3$ , WBC  $15 \text{ cells}/\text{mm}^3$ , AST 45 IU/L, ALT 45 IU/L, Alkaline Phosphatase 68 U/L and bilirubin 1.9 mg/dl. Abdominal CT scan was not repeated this time. As her medical treatment was reinstated, the recovery course was complicated resulting in altered mental status from her second session of plasma exchange post re-admission with normal EEG and CT head as a part of her neurological evaluation. Patient's baseline mental status recovered 3 days post corticosteroids dose adjustment and four more session of plasmapheresis given. Patient was discharged on the 7<sup>th</sup> day of second admission with a follow up appointment scheduled within a month after discharge from hospital. Patient was stable with normal platelet count and anemia resolved.

## DISCUSSION

TTP by itself is a well-known life-threatening condition and could be deadly if it is present during acute pancreatitis. MAHA and thrombocytopenia characterized TTP as a result of microvascular platelet clumping most of the time associated with ischemic organ dysfunction as neurological signs and renal insufficiency.

In all published TTP cases, less than 12% shows a recognized triggering factor for this condition. Well known

causes of secondary TTP are pregnancy, cancer, bone marrow transplantation and certain drugs such as clopidogrel.<sup>6</sup> In this case, TTP association in between HIV and acute pancreatitis could trigger the question: which was the main starting point for TTP to develop?<sup>7</sup> Recently, TTP has also been associated with Human immunodeficiency virus (HIV) infected patients with CD4 count less than 100/microliters. Nevertheless, in the great majority of cases, TTP usually develops even without any triggering condition.

Severe deficiency of ADAMTS13 has been present on most idiopathic cases, which prevent to process unusually large vWF multimers released from endothelial cells. Formations of microvascular thrombus may be part of the consequences. In adults, the main result of severe ADAMTS13 deficiency is often caused by ADAMTS13 auto antibodies. Plasma exchange with replacement of fresh frozen plasma remains as treatment of choice on all patients with acute TTP.

The evidence of immunological component on the course of the disease as auto-antibodies against ADAMTS13 in a relevant number of patients; provides the rationale for the use of corticosteroids along with plasmapheresis as part of the medical management.

Pancreatic manifestation is common in TTP; evidence of this is revealed on post mortem cases by Hosler et al. in their study, where they found pancreatic involvement in 30 out of 51 cases diagnosed with TTP. The mechanism for pancreatic injury during TTP is thought to be due to impairment of pancreatic circulation by thrombus occlusion of small vessels; resulting in ischemia.<sup>8</sup>

On the other hand, as reported by Swisher et al. during the revision of 16 cases in which the acute inflammatory response present during acute pancreatitis triggered the onset of TTP on five of them with a median of three days. It has been demonstrated in in-vitro studies that inflammatory cytokines stimulated endothelial cell release of ultra large vWF multimers and inhibited the cleavage of ultra large vWF ADAMTS13.

Prompt treatment with available effective options is imperative, which makes it vital to recognize this disease early in relation with acute pancreatitis.

Our case is another example of what Swisher et al. reported during the series case evaluation, which revealed the short interval in between the first sign of acute pancreatitis and the subsequent TTP manifestations.

## CONCLUSION

As acute pancreatitis incidence tends to increase, it is important to recognize its association with TTP; despite the presence of any other possible factors. A high clinical suspicion and detailed physical examination is necessary for an early diagnosis an initiation of plasma exchange therapy remains as a lifesaving option.<sup>9,10</sup>

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**CONFLICT OF INTEREST**

The authors have no conflict of interest to disclose.

**ABBREVIATIONS**

TTP, Thrombotic thrombocytopenic purpura; HUS, Hemolytic uremic Syndrome; AP, Acute pancreatitis; MAHA, Microangiopathic hemolytic anemia; vWF, von Willebrand factor.

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