

CASE REPORT

## The occurrence of thrombotic thrombocytopenic purpura during treatment of HCV with direct-acting antiviral agents

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### Abbreviations:

ACA: Anticardiolipin antibodies.

ADAMTS-13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.

AHA: Autoimmune hemolytic anemia.

CHC: Chronic hepatitis C.

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GCC: Glasgow Coma Scale.

PCR: Polymerase chain reaction.

TMA: Thrombotic Microangiopathy

TTP: Thrombotic thrombocytopenic purpura.

## Abstract

### Background and aim

Experts have reported thrombocytopenia is linked to chronic liver disease in up to 70% of patients with advanced fibrosis and portal hypertension. The occurrence of thrombotic thrombocytopenic purpura (TTP) with HCV infection is a rare and life-threatening event. **We aim** to investigate the causes of disturbed conscious levels, acute hemolytic anemia, and severe thrombocytopenia in a patient with chronic HCV and under treatment with direct-acting antivirals.

**Case report:** Development of severe thrombocytopenia, acute hemolytic anemia, neurological symptoms in the form of fits and coma in a 32- year- older man with chronic HCV infection after one week of treatment with direct-acting antivirals (sofosbuvir 400mg PO daily, and daclatasvir 60 mg daily PO). Brain CT was normal, with a negative Coombs test and the presence of schistocytes in the peripheral blood smear. The patient presentation was suggestive of thrombotic thrombocytopenic purpura (TTP).

**Conclusion:** This is a case of TTP after one week of direct-acting antiviral drugs despite the safety profile of these medications. Studying the pathophysiology of TTP after DAAs needs more clarification.

**Keywords:** HCV; Thrombocytopenic purpura, direct-acting antivirals

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## Introduction

Low platelet count could be the initial manifestation of viral infections as chronic hepatitis C (CHC) or HIV or an underlying life-threatening disorder such as the thrombotic microangiopathies or myelodysplastic syndromes.

Thrombocytopenia is defined as a platelet count below 150,000/UL as the lower limit of normal. However, platelet count between 100 and 150,000/ UL may not show disease if it has been stable for over six months, and a cutoff value of 100,000/ UL may be more appropriate to determine a pathologic condition (1)

Degrees of thrombocytopenia can be further subdivided into mild (platelet count 100,000 to 150,000/ UL), moderate (50,000 to <100,000/ UL), and severe (<50,000/UL) (2).

The risk of bleeding increases in the presence of platelet count less than 10,000/ UL. The etiology of thrombocytopenia is diverse, artifactual due to platelet clumping, or true thrombocytopenia as seen in congenital thrombocytopenia with giant platelets. Also, consumption thrombocytopenia as in disseminated intravascular coagulation, hemolytic syndromes and thrombotic thrombocytopenic purpura (TTP), decreased synthesis due to bone marrow suppression or bone marrow replacement as in leukemia, immune-mediated thrombocytopenia with or without autoimmune hemolytic anemia and other causes (3), (4).

Thrombocytopenia related to chronic liver disease has been reported in up to 70% of patients with advanced fibrosis and portal hypertension, depending on the severity of fibrosis (5)

The pathophysiology of thrombocytopenia in HCV is complicated, and causes are related to the severity of histological staging (6), hypersplenism due to pooling of platelets in the spleen (7), bone marrow suppression. Also, immune dysfunction is caused by autoantibodies directed against platelet surface antigens due to change in conformation of platelet membrane glycoproteins, high level of platelet-associated immunoglobulin G (8), and decreased thrombopoietin levels or activity.

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Treatment-related thrombocytopenia is a well-known adverse effect of peg-interferon, which is known to cause a 50% decrease in the platelet count. It is more severe with pegylated interferon-ribavirin combination therapy induced by bone marrow suppression, inhibition of megakaryocytes, and secretion of thrombopoietin (9)

TTP is a severe disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurological disturbances, and renal impairment. These symptoms are related to the occlusion of arterioles and capillaries with von Willebrand factor-rich platelet thrombi that shear red blood cells and consume platelets (10).

Atypical presentation of TTP may include acute coronary syndrome (11), acute stroke (12), and pancreatitis (13), postoperative due to widespread endothelial cell activation by cytokines or vascular injury (14).

TTP is induced by IgG autoantibodies that inhibit the von Willebrand factor-cleaving protease ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) in plasma, so plasmapheresis with fresh frozen plasma replacement improves survival of these patients (10).

Viral infections that may induce TTP are HIV, CMV, and HCV; only a few cases of TTP had been reported in patients after interferon therapy (15).

## Case report

A 32-year-old Egyptian man with a history of chronic hepatitis C, genotype 4, started treatment with sofosbuvir 400 mg and daclatasvir 60 mg (PO once daily) for one week before admission. His HCV RNA titer by PCR was 206 KIU/ml with average complete blood count; WBC's 4500 cells/UL, hemoglobin 13.4 g/dl, platelet count 167000/ U/L. AST/ALT 55/67 IU/L, serum albumin 4.2 gm/dl, total bilirubin 1.2 mg/dl, prothrombin concentration 80%, abdominal ultrasonography revealed bright liver with splenomegaly (bipolar diameter 15.3cm). One week after initiating medications, he suddenly developed a bilateral massive subconjunctival hemorrhage; his caring physician urgently asked for a complete blood picture that revealed normocytic normochromic anemia (hemoglobin 6.5 gm/dl) and severe thrombocytopenia with a platelet count of 7,000/ U/L. The patient was admitted to the

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hospital for platelet transfusion and followed up in the ICU. Suddenly 4 hours after admission and before platelet transfusion, the patient developed tonic-clonic fits with loss of consciousness with the Glasgow Coma Scale (GCS) 7 and hypoxia which necessitated mechanical ventilation. Laboratory tests revealed low hemoglobin of 6.8 gm/dL (11.7-16.1), severe thrombocytopenia with a platelet count of 7000 (150,000-450,000/mL), hematocrit of 26 (37-51%) with an average white blood cell count. His prothrombin time and partial thromboplastin time were reasonable. His renal functions were average, with a BUN of 25 mg/dl and serum creatinine of 1.1 mg/dl. AST was 100 U/L (14-36 U/L), ALT was 70 U/L (9-52 U/L) with a standard alkaline phosphatase of 95 U/L (38-125U/L) with total bilirubin 6 mg/dl mainly indirect hyperbilirubinemia, albumin 2.7 gm/dl, abdominal ultrasonography revealed mild ascites with the patent portal and hepatic veins.

The patient received two units of fresh blood and six platelets; however, platelet count did not improve significantly and was 11,000/ U/L.

Direct Coomb's test was done and proved to be negative, an elevated reticulocyte count of 5.3% (0.5-2.5%) with a high LDH of 2650 IU/L (313-618 IU/L), high D dimer (1000mg/dl), serum ammonia was done to exclude hepatic cause of confusion and was normal 94 mg/dl, computed tomography of the brain was normal.

A peripheral blood smear showed evidence of microangiopathic hemolysis with plenty of schistocytes, nucleated red blood cells, and severe thrombocytopenia. He was diagnosed with TTP. Plasma exchange with an equal volume of fresh frozen plasma and pulsed therapy of steroids was planned for the patient's treatment. Still, he developed severe respiratory distress, worsening GCS (3), and passed away before initiation of the planned regimen.

## **Discussion**

HCV infection has been associated with various extrahepatic hematological complications as autoimmune hemolytic anemia (AHA), which is frequently observed in HCV patients and recognized as a possible side effect of antiviral treatment. A small number of treatments-naïve HCV patients present as coomb's positive AHA (16), which is responsive to prednisone. Also, several mechanisms explain HCV-related thrombocytopenic purpura as decreased production of thrombopoietin, binding

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to the human CD81 receptor on the platelet membrane, thus causing auto-antibody production against HCV-bound platelets. Also, HCV can infect and replicate in megakaryocytes leading to their depletion (17).

TTP with HCV, even though rare, has been most frequently reported in only (few) cases of TTP in patients after administration of interferon. The first suspected case of interferon-induced TTP occurred after more than 20 weeks of recombinant interferon therapy. The patient died before the initiation of plasmapheresis (18).

Anticardiolipin antibodies (ACA) had been linked with chronic HCV infection. Renal thrombotic microangiopathy (TMA) in HCV positive renal allograft recipients with a positive ACA has been recently documented (19).

ADAMTS13 inhibition was described as a mechanism of HCV-related TMA (20).

It is highly suggested that chronic HCV and its treatment with new agents may, on rare occasions, alter the immune system response and induce anti-ADAMTS13 antibody formation leading to acquired TTP. Initial therapy with plasmapheresis and steroid can be tried. If there is no improvement, then plasmapheresis with Rituximab in a dose of 375 mg/m<sup>2</sup> and steroids 1 mg/kg/day can be used to induce remission with the improvement of ADAM TS 13 level.

Although a rare event, a case report of thrombotic thrombocytopenic purpura directly related to chronic HCV infection rather than to interferon therapy was described by El Garf et al. (21), drug-induced TTP during HCV treatment was documented, and this was induced by pegylated interferon and responded to Rituximab and plasmapheresis (22).

We recommend testing for TTP in patients who show a sudden, unexpected and significant decrease in platelet count during direct-acting antiviral therapy.

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## Footnotes

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