

FULMINANT THROMBOTIC THROMBOCYTOPENIC PURPURA IN CHRONIC HEPATITIS B VIRUS INFECTION WITH SEVERE FIBROSIS

Chee-Kin Hui^{1,2}

¹Centre For Alimentary Studies, Hong Kong SAR, CHINA

²Quality Healthcare Medical Services, Hong Kong SAR, CHINA

ABSTRACT

A 57-year old man with chronic hepatitis B virus (HBV) infection, mild thrombocytopenia and mild hemolytic anaemia was started on Entecavir for treatment of chronic HBV. He was readmitted for fever, confusion, severe hemolytic anaemia, and, severe thrombocytopenia eight weeks later. A disintegrin and metalloproteinase with a thrombospondin type-1 motifs 13 (ADAMTS13) activity and antigen were severely low with a positive ADAMTS13 autoantibody. His serum HBV DNA at this stage was less than 20 IU/ml. He was diagnosed with fulminant TTP. In conclusion, fulminant TTP can occur in those with chronic HBV upon immune recovery induced by potent anti-HBV therapy.

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KEY WORDS

Thrombotic thrombocytopenic purpura; hepatitis B virus; ADAMTS13; human immunodeficiency virus; von Willebrand factor; Computerized tomography

*Corresponding author: Email: bckhui@gmail.com; Tel.: +852 2723 1183; Fax: +852 2723 6620

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is an uncommon disease. It is characterized by microangiopathic hemolytic anaemia, thrombocytopenia, neurologic symptoms, renal involvement and fever. TTP has been reported to be associated with viral infections such as the human immunodeficiency virus (HIV) [1], influenza A [2], and, also in chronic hepatitis C virus infected patients on interferon treatment [3]. Here, is a case of chronic hepatitis B virus (HBV) infection who developed fulminant TTP after viral suppression was achieved with Entecavir.

CASE REOPORT

A 57 year old Chinese gentleman presented with a 3-month history of progressive malaise. He was found to have deranged liver function with albumin 42 g/dl (normal range 35-50), alanine aminotransaminase 284 IU/L (normal range 6-53), aspartate aminotransaminase 189 IU/L (normal range 13-33), total serum bilirubin 30 µmol/L (normal range 3-22), and, direct bilirubin 3 µmol/L (normal range <3) with indirect bilirubin 27 µmol/L (normal range <14).

Complete blood count and coagulation profile were as follows: haemoglobin 11.1 gm/dl (normal range 13.0-17.0), platelets 104 K/uL (normal range 140-400), prothrombin time (PT) 13.70 seconds (normal range 10.10-12.60), International Normalized Ratio 1.18 (normal range 0.90-1.10), activated partial thromboplastin time 33.4 seconds (normal range 24.4-32.0).

He was found to be hepatitis B surface antigen positive, hepatitis B e antigen negative with a positive hepatitis B e antibody. The serum HBV DNA was 8.75×10^5 IU/ml (COBAS TaqMan HBV assay, Roche Diagnostics, Branchburg, New Jersey, USA). Computerized tomography (CT) of the whole abdomen showed a normal sized liver but with lobulated contour and heterogenous attenuation suggestive of liver cirrhosis. The size of the spleen was normal on CT scan. Fibroscan of the liver was 11.4 kPa.

A disintegrin and metalloproteinase with a thrombospondin type-1 motifs 13 (ADAMTS13) activity, performed with a commercially available assay based on the fluorescence resonance energy transfer (FRET) method using an artificial von Willebrand factor (vWF) fragment, was 35% (normal range 70-160). ADAMTS13 (vWF cleaving protease) antigen level, performed by a commercial ELISA assay in accordance with the manufacturer instructions, was 130.5 ng/ml (normal range 253-2238). However, ADAMTS13 autoantibody, performed by a commercial ELISA assay, was negative. His blood film was not reviewed at this stage.

He was started on Entecavir 0.5 mg daily. His serum alanine aminotransaminase and HBV DNA after commencement of Entecavir are shown in **Table-1**.

Table: 1. Table showing serial blood results.

Week on Entecavir	0	1	4	8	16
Serum HBV DNA (Log10 IU/ml)	5.94	4.23	1.30	1.30	1.30
Serum Alanine aminotransaminase (IU/L)	286	55	43	22	20
Haemoglobin (g/dl)	11.1	11.6	12	8.6	10
Platelet (K/ul)	104	100	101	21	147
Total Bilirubin (umol/l)	30			53.6	22.6
Direct Bilirubin (umol/l)	3			9	7.6
Indirect Bilirubin (umol/l)	27			42	15
Lactate Dehydrogenase (U/L)	514			966	383
Prothrombin Time (seconds)	13.7			19.7	11.2
ADAMTS13 Activity (%)	35			3	62
ADAMTS13 Antigen (ng/ml)	130.5			48	234
ADAMTS13 Autoantibody	Negative			Positive	Positive
Fibroscan (kPa)	11.4			11.0	11.6

Eight weeks after commencement of Entecavir, he was readmitted for fever and confusion. Physical examination was unremarkable with no flapping tremor or focal neurological sign.

His blood investigation on readmission showed haemoglobin 8.6 gm/dl, platelets 21 K/ul, serum alanine aminotransaminase was normal, serum total bilirubin 53.6 umol/L, direct bilirubin 9 umol/L with indirect bilirubin 42 umol/L, serum HBV DNA < 20 IU/ml, serum lactate dehydrogenase 966 IU/L (normal range 197-401), prothrombin time 19.70 seconds, activated partial thromboplastin time 35.0 seconds, and, a low plasma haptoglobin level 4 mg/dl (normal range 20-190).

Blood film review showed considerable variation in red cell size and shape. Elliptocytes and a few target cells were found in association with fragments **[Figure-1]**. Platelets were reduced and large forms were frequent.

His ADAMTS13 activity had decreased to 3% with ADAMTS13 antigen reduced to 48 ng/ml. He had developed a positive ADAMTS13 autoantibody as well. Bone marrow aspirate showed megakaryocytic hyperplasia with left shifted granulocytic series and reactive changes.

Autoimmune antibodies, Coombs test, cytomegalovirus pp65, cytomegalovirus immunoglobulin (Ig) M and, HIV I and II antibody were all negative. Arterial ammonia, urine for routine microscopy and serum creatinine were all normal.

He was diagnosed with fulminant TTP and remission was achieved with fresh frozen plasma infusion, Rituximab and corticosteroid. His platelet count, bilirubin, haemoglobin, reticulocyte count, ADAMTS13 activity, ADAMTS13 antigen and ADAMTS13 autoantibody 8 weeks after treatment for fulminant TTP was started (16 weeks after commencement of Entecavir) are shown in **Table-1**.

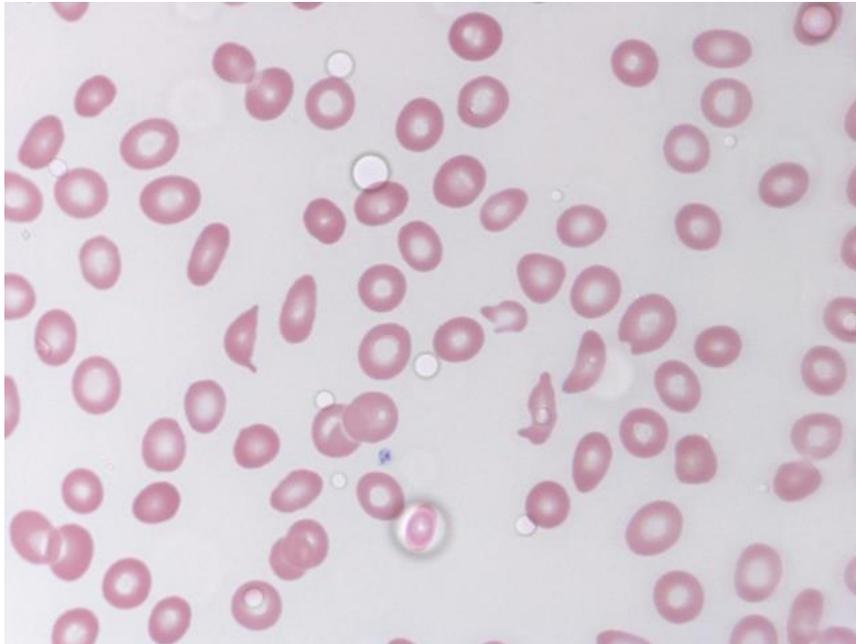


Fig: 1. Slide showing fragmented red blood cells

DISCUSSION

Most of the reported cases of HIV infection associated TTP were characterized by fulminant syndrome [1]. Veenstra et. al. were the first to report low-grade TTP associated with HIV-infection [4]. These low-grade TTP would usually occur late in the natural history of HIV-related disorders [4].

Here, is the first reported case of TTP associated with chronic HBV infection. Retrospectively, he may have been suffering from low-grade TTP at the time of presentation. This is because he already had thrombocytopenia, and, anaemia with raised indirect serum bilirubin and PT [Table-1] suggestive hemolysis.

However, as the ADAMTS13 activity was only mildly to moderately reduced along with a negative ADAMTS13 autoantibody, it was presumed to be a secondary reduction due to his acute reactivation of chronic HBV infection and severe liver fibrosis, based on his liver stiffness score on Fibroscan [5,6]. Whether this low-grade TTP would occur late in the natural history of chronic HBV infection, when the chronic HBV has been complicated by severe liver fibrosis or liver cirrhosis similar to that observed in HIV-related disorders, is uncertain [1].

He developed fulminant TTP after complete viral suppression was achieved. This is probably because rapid viral suppression by potent anti-HBV therapy has been shown to be associated with immune recovery or immune reconstitution [7].

This immune recovery can result in an immune reconstitution inflammatory syndrome similar to that most commonly observed in HIV infection [8]. The pathogenesis of immune reconstitution inflammatory syndrome has been postulated to be due to a combination of thymic-independent homeostatic peripheral expansion, immune dysregulation between effector and regulatory T-cells, increased inflammatory cytokines and dysregulated dendritic cells [8].

The immune recovery achieved with potent anti-HBV therapy may have resulted in neutralizing IgG-autoantibodies being produced [7]. This autoantibody would inhibit vWF-cleaving protease activity, thus impairing the ability of ADAMTS13 to cleave ultra-large vWF in the plasma and on the surface of endothelial cells. This is similar to the clinical picture of acute TTP observed in acquired idiopathic TTP.

These IgG antibodies that inhibit ADAMTS13 activity have been reported in 48% to 80% of those with recurrent or acute TTP [9]. This suggests that their presence have a role in recurrent or acute TTP.

This case report suggests that fulminant TTP may occur in chronic HBV infection with severe fibrosis. When immune recovery was achieved with potent anti-HBV therapy, it may have triggered the production of anti-ADAMTS13 antibodies. The anti-ADAMTS13 antibodies subsequently resulted in an episode of fulminant TTP.

CONCLUSION

In conclusion, chronic HBV infection with severe fibrosis may be associated with fulminant TTP. This calls for a high index of suspicion and vigilance on the possibility of this association. Therefore, TTP should be considered as a differential in a chronic HBV infected patient with thrombocytopenia and anaemia. This fulminant TTP is associated with severe ADAMTS13 deficiency and antibody formation.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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