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RESEARCH ARTICLE

TREATMENT OF IMMUNE THROMBOCYTOPENIA AS AN EXTRA HEPATIC MANIFESTATION IN AN HCV-CARRIER MAN WITH NORMAL LIVER FUNCTION TEST- A CASE REPORT

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ABSTRACT

Rationale: The authors report a case of immune thrombocytopenia (ITP) as an extra hepatic manifestation in a hepatitis C virus (HCV)-carrier man with normal liver function tests.
Presenting concern: A 42 year old male visited Dr. Prabhakar Kore Hospital on 21/6/15 in the medicine OPD. He had complaints of Fever for two days and rashes on both the forearms and also complaints of passing black colored stools.
Diagnosis: The physical and laboratory examinations showed results within normal range except for very Low platelet counts and positive for HCV antibody (third generation).These findings suggested chronic infection with HCV, but there seemed to be no involvement of liver disease.
Intervention: Patient was admitted and treatment was primarily aimed at improving platelet counts. Anti-viral therapy was prescribed. Interferon (IFN) and ribavirin to render HCV-PCR copies negative.
Outcome: After 9 days of inpatient treatment the platelet counts were normalized and the patient discharged.
Lesson learnt from this case: There are numerous papers reporting that HCV causes ITP as an extrahepatic manifestation, but a case report of ITP caused by chronic HCV infection without liver disease has not been found. The present case report discusses the specificity of HCV infection on extrahepatic manifestation, and the treatment of ITP caused by chronic HCV infection.

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INTRODUCTION

The authors examined a middle-aged HCV-carrier man with no abnormal liver function test results who showed a decreased platelet count. Anti-viral therapy was prescribed, Interferon (IFN) and ribavirin to render HCV-PCR copies negative and subsequently to recover the platelet count. This case was assumed to be secondary immune thrombocytopenia (ITP) as an extra hepatic manifestation of chronic HCV infection because the platelet-associated immunoglobulin G (PAIgG) being positive.

Worldwide, 145 million individuals have been estimated to be infected with HCV, equivalent to 2.2% of the world's population (Global surveillance and control of hepatitis C. 1999). The prevalence of ITP among patients infected with HCV has been reported to be 10% to 36 % (total of 159 ITP/799 HCV patients; 20%) (Liebman, 2008).

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Moreover, the review noted as follows: thrombocytopenia may be present even in the absence of clinically evident liver disease orsplenomegaly and may be mistakenly diagnosed as primary ITP (Liebman, 2008; Garcia-Suarez *et al*., 2000; Rajan *et al*., 2005; Pivetti *et al*., 1996). Although the latter part of this statement is correct and important for hematologists, the former part requires clarification. Although one literature was found (not available and not yet examined in detail) (Beyan *et al*., 2002), any case without clinically evident liver disease was described in the cited papers (Garcia-Suarez *et al*., 2000; Rajan *et al*., 2005). The detailed information in these papers showed the presence of chronic hepatitis C or HCV-related cirrhosis with or without splenomegaly Garcia-Suarez *et al*., 2000; Rajan *et al*., 2005). Another paper reported immunological alterations in HCV-positive patients with lymph proliferative and connective tissue disorders[5]. Therefore, the present authors decided to report this case to contribute to the body of information for hepatologists and hematologists as well as to assist in the treatment of ITP as an extra hepatic manifestation in chronic HCV infection.

ITP is usually a complication in chronic hepatitis C to HCV-infected cirrhosis patients (Beyan *et al*., 2002) 20% as noted above. The present case showed no clinically evident liver disease, the size of the spleen was normal, and abdominal ultrasonography showed no abnormal findings in the liver. The precise clinical course of this case is presented here and the possible pathogenesis of ITP in this case is discussed. Moreover, the extra hepatic manifestations of hepatitis Avirus (HAV), hepatitis B virus (HBV) and HCV are compared with those in the literature, and the treatment of ITP caused by chronic HCV infection is discussed.

Case Presentation

A 42-year-old man visited Dr. Prabhakar Kore hospital and MRC, Belgaum. He had complaints of Fever for two days and rashes on both the forearms and also complaints of passing of black colored stools. Fever was intermittent type with no diurnal variation. He had purpuric rashes on both forearms as well as on abdomen. Patient also complained about passing black colored stools. Laboratory findings showed positive for HCV antibody (third generation) beside a very low platelet count of 4000 Other physical and clinical data (BMI 20.3, blood pressure 106/60, urinalysis, stool blood, blood chemical examination including liver function tests and abdominal ultrasonography) were normal. There was nothing out of the ordinary in his own or his family history. He did not smoke or consume alcohol. Peripheral blood examination showed decreasing platelet counts. He had not taken any drugs or supplements. His physical and laboratory data were almost normal except for thrombocytopenia. His abdominal ultrasonography showed normal size of spleen and no abnormal findings in the liver. Patient had history of multiple blood donations. suggested normal liver. Helicobacter pylori antibody was negative. Anti-viral treatment for HCV was started because the platelet count was continuously low. Subdermal injection of interferon α2a (IFNα2a) (180 or 90 μg/week) and per oral ribavirin (600 mg/day) was administered. The treatment with IFNα2a and ribavirin was effective for thrombocytopenia consistent with negative HCV-PCR. Antibodies against platelet surface antigen could not be examined before and during treatment. Very recently, platelet-associated immunoglobulin G (PAIgG) was found to be slightly high. As a result, the authors diagnosed ITP to be an extra hepatic manifestation of chronic HCV infection with normal liver function test results. After 9 day splatelet count improved and patient discharged with continuation of antiviral treatment.

DISCUSSION

This case was diagnosed to be ITP as an extrahepatic manifestation by chronic HCV infection. ITP is defined as an acquired disorder in which there is immune-mediated destruction of platelets and possible inhibition of platelet release from megakaryocytes (Beyan *et al*., 2002). Serological evidence of platelet autoantibodies is not found easily (Konke *et al*., 2012; Stasi *et al*., 2009) In general ITP is a complication in chronic hepatitis C, found in 20% of patients with chronic HCV hepatitis, as noted above (Liebman, 2008; Stasi *et al*., 2009). If patients with chronic hepatitis C or HCV-related cirrhosis show extensive fibrosis and thrombocytopenia, the pathophysiology of thrombocytopeniamay be hypersplenism due to portal hypertension, bone marrow suppression resulting from either HCV itself or IFN treatment, immune dysfunction or anti-viral therapy (Liebman, 2008; Konke *et al*., 2012; Stasi *et al*., 2009; Weksler, 2007).

Table 1. Laboratory data of a 42-year-old HCV-carrier man

Before treatment **(13/8/13),** During treatment **(21/6/15 TO 29/6/15)**

Date	13/8/13	21/6/15	22/6/15	23/6/15	24/6/15	25/6/15	26/6/15	27/6/15	28/6/15	29/6/15
Hb(g/dl) (13-16)	17.4									
Haematocrit/ PCV (40-50)	51.6									
Platelets (150,000-450,000)	309,000	5000	4000	4000	14000-M 21000-E	22000-M 28000-E	35000	54000	57000	105000
M.P.V	10.8	7.8	5.9	5.5	9.0- M 10.0- E	10.9- M 11.1-E	10.9	10.6	10.8	10.8
Red cell count (4.6-6)	5.71									
T.L.C. (4000-10000)	17400									
E.S.R (0- 10mm/1sthr)	2									
HCV-										
Tot.prot.(g/dl) (6.4-8.2)	6.6									
Alb.(g/dl) (3.4-5.0)	3.6									
A:G ratio	1.2									
Tot.bil.(mg/dl) (0.20-1.00)	0.47									
Dir. Bil (md/dl) (0.00-0.20)	0.09									
AST(IU/L) (15-37)	27									
ALT(IU/L) (30-60)	60									
ALP (IU/L) (50-136)	104									

Abbreviations- M.P.V- mean platelet count; HCV- Hepatitis C virus; A:G- Albumin Globulin ratio; AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; ALP- Alkaline Phophatase; M- Morning sample; E- Evening Sample

The authors discussed the pathogenesis of thrombocytopenia and concluded that chronic HCV infection may cause ITP as an extrahepatic manifestation although liver function tests Thrombocytopenia is caused by bacterial and viral infection as well as by drugs (Konke *et al*., 2012; Giannini, 2006; Stasi, 2009). The following viral infections have been reported:

varicella, Epstein- Barr virus, human immunodeficiency virus, parvovirus and HCV[7]. In the present case, no history of infectious disease or drugs was found, and conventional liver function tests showed normal values over a 7-year clinical course, as shown in Table 1. If this case had any liver disease, the ALT levels would have shown some change after IFNα2a and ribavirin treatment because the biological stress of these treatments affect liver function tests. The reason why this case had not manifested chronic hepatitis C must be considered. As for the cause of ITP in this case, chronic HCV infection is strongly suggested because IFN and ribavirin therapy led to negative HCV-RNA, followed by recovery of the platelet count to normal range. In addition to successful treatment PAIgG was detected and measured quantitatively with a result of 66 ng/107 cells (normal range: less than 46)Therefore, the authors at present believe that ITP in this case may be due to some kind of immunological alteration (Nakajima *et al*., 2005; Aref *et al*., 2009).

Pascal *et al*. first described an association between HCV and extrahepatic manifestation in 1990, reporting two patients with mixed cryoglobulinemia (Pascual *et al*., 1990). It has been reported that 40% to 74% of patients with HCV infection developed at least one extrahepatic manifestation during the clinical course (Cacoub *et al*., 1999; Cacoub *et al*., 2000; Ali and Zein, 2005; Galossi *et al*., 2007; Jacobson *et al*., 2010). HCV infection causes extrahepatic manifestations. One case with rheumatoid arthritis was caused by chronic HCV infection without any liver disease confirmed by liver biopsy (Akhtar and Funnyé, 2005). Sometimes, extrahepatic syndrome represents the first sign of an HCV infection (Liebman, 2008; Garcia-Suarez *et al*., 2000; Rajan *et al*., 2005; Pivetti *et al*., 1996). As noted above, however, no report on ITP as extrahepatic manifestation in chronic HCV infection without chronic hepatitis could be found in a search of Pub Med using the keywords HCV infection and ITP, and HCV infection and extrahepatic manifestation. There are numerous papers on extrahepatic manifestations in HCV infection while very few papers exist regarding extrahepatic manifestations in hepatitis A virus (HAV) infection and hepatitis B virus (HBV) infection. Concerning HAV infection, 4 papers reporting a total of 4 cases were found (Scott *et al*., 2003; Tanir *et al*., 2005; Yoon *et al*., 2012; Zis *et al*., 2012). Two cases were autoimmune thrombocytopenia (Scott *et al*., 2003; Tanir *et al*., 2005). As for HBV infection, 7 papers reported membranoproliferative glomerulonephritis, nodular polyarteritis, myositis, otological sensory disease, and Sjogrene syndrome as extrahepatic manifestations of chronic hepatitis B (Trepo and Guillevin, 2001; Elefsiniotis *et al*., 2003; Cacoub *et al*., 2005; Gan *et al*., 2005; Baig and Alamgir, 2008; Chan, 2010; Kong *et al*., 2013). Four papers were clinical research originals (Elefsiniotis *et al*., 2003; Cacoub *et al*., 2005; Gan *et al*., 2005; Kong *et al*., 2013) and three were reviews (Tanir *et al*., 2005; Baig and Alamgir, 2008; Kong *et al*., 2013). The authors did not find any case reports because patients with chronic hepatitis B and extrahepatic manifestations are more numerous than patients with acute hepatitis A infection and extrahepatic manifestations, but absolutely less than the number of patients with chronic hepatitis C and extrahepatic manifestations. From the viewpoint of virus tropism to organ, HCV is different from HAV and HBV. Most extrahepatic manifestations seen in patients with chronic HCV infection has revealed autoimmune diseases. Even if the extrahepatic manifestations in HAV and HBV infections are also autoimmune diseases, the number of patients with HCV infection showing extrahepatic manifestations is much greater. Pivetti *et al*. (1996) reported that autoimmune abnormalities were significantly more frequent in anti-HCV-positive than in anti-HCV-negative patients, and in anti-HCV-positive as compared to anti-HBc-positive subjects among patients with lymph proliferative disorders. Forty-five to 65% of HCV-infected patients have various autoantibodies (Bockle *et al*., 2011). Galossi *et al*. wrote that an important feature of HCV is to avoid immune elimination (Galossi *et al*., 2007). The present authors propose that the name HCV be changed to "immune modulating virus."

The present case showed successful treatment of IFNα2a and ribavirin on ITP in chronic HCV infection without any liver disease. Corticosteroids or intravenous immunoglobulin was not used as the first line therapy in this case, because this case was secondary ITP followed by chronic HCV infection and no complication of chronic hepatitis may progress to severe state. As HCV-related ITP had a higher prevalence of cirrhosis and demonstrated more immunological markers than controls, Dufour *et al*. proposed from the results of their patients' treatment that severe ITP patients with chronic HCV infection require a different strategy as follows: first line therapy of corticosteroids or intravenous immunoglobulin injection, and the second line therapy of splenectomy and antiviral therapy (Dufour *et al*., 2009). If the second line therapy fails, rituximab or thrombopoietic growth factor is recommended (Dufour *et al*., 2009). Other authors also reported very similar strategies (Garcia-Suarez *et al*., 2000; Stasi *et al*., 2009; Giannini, 2006; Stasi, 2009). In general, at the present time, if the symptom of purpura is seen (the platelet count may be under 20x109/l), new thrombopoietic agents such as eltrombopag and romiplostim have been reported to be effective for ITP as extrahepatic manifestation in chronic hepatitis C (Panzer, 2009; Buccoliero *et al*., 2014).

Informed Consent

A written informed consent was obtained by the patient regarding use of the demographic profile, diagnostics reports and treatment history in publishing and further research.

Conclusion

The authors report here a case of ITP as extrahepatic manifestation in chronic HCV infection without hepatitis. HCV is very different from HAV and HBV in the organ tropism, and we suggest changing the name from HCV to "immunomodulating virus". Patient management in the follow-up of HCV carriers should be undertaken from the viewpoint of extrahepatic manifestation.

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