bjh research paper

Hepatitis C virus-related thrombocytopenia: clinical and laboratory characteristics compared with chronic immune thrombocytopenic purpura

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Received 9 March 2005; accepted for publication 19 April 2005

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Summary

Thrombocytopenia can be a complication of hepatitis C viral (HCV) infection. However, there is little published data regarding the clinical and laboratory manifestations of HCV-related thrombocytopenia (HCV-TP) compared with adult chronic immune thrombocytopenic purpura (CITP). We reviewed the medical records for all patients evaluated for chronic thrombocytopenia by the Haematology Service between January 1996 and June 2000. All patients were screened for HCV infection at the time of initial diagnosis. Of 250 patients who fulfilled American Society of Hematology criteria for CITP, 76 (30%) were HCV seropositive. HCV-TP patients were older [mean age (±SD) 54·9 ± 8 years vs. 40·3 ± 8 years, $P \leq 0{\cdot}001$] and equally distributed between both sexes. HCV-TP patients had less severe thrombocytopenia, defined as platelet count $\leq 10 \times 10^9$/l (4% vs. 46% for CITP, $P \leq 0{\cdot}001$). However, 56 (74%) had a platelet count $\leq 50 \times 10^9$/l. Symptoms and signs of thrombocytopenia were less frequent in HCV-TP, but major bleeding was more frequent (25% vs. 10%, $P = 0{\cdot}0059$). Serum cryoglobulins and anticardiolipin antibodies were more frequent in HCV-TP (90% and 62% respectively), but rare in CITP (7% and 15%, $P \leq 0{\cdot}001$ compared with HCV-TP). HCV infection can be associated with significant thrombocytopenia and appears to be a distinct clinical entity.

Keywords: cryobulinaemia, hepatitis, thrombocytopenia.

The American Society of Hematology (ASH) expert panel has defined chronic immune thrombocytopenic purpura (CITP) as isolated thrombocytopenia in patients with no clinical conditions that can cause thrombocytopenia (George *et al*, 1996). Infection with human immunodeficiency virus (HIV), systemic lupus erythematosis, antiphospholipid antibody syndrome, lymphoproliferative disorders, myelodysplasia, liver disease with portal hypertension, drug therapy and hereditary thrombocytopenia are well recognized causes which need to be excluded prior to diagnosis of CITP (George *et al*, 1996). Thrombocytopenia has also been described in association with hepatitis C virus (HCV) infection (Pawlotsky *et al*, 1995; Linares *et al*, 1996; Nagamine *et al*, 1996; Pivetti *et al*, 1996; Kosugi *et al*, 1997; Hernandez *et al*, 1998; Garcia-Suarez *et al*, 2000; Sakuraya *et al*, 2002) and may be present even in the absence of clinically evident liver disease or splenomegaly (Linares *et al*, 1996; Nagamine *et al*, 1996; Pivetti *et al*, 1996; Hernandez *et al*, 1998; Garcia-Suarez *et al*, 2000).

All patients attended by the Haematology Service at Los Angeles County, University of Southern California with clinical and laboratory findings consistent with CITP are routinely screened for the presence of HCV antibodies. In this report, we present the results of this retrospective analysis on the presence of HCV antibodies in patients with chronic thrombocytopenia. A significant proportion of the patients were infected with HCV and HCV-related thrombocytopenia (HCV-TP) appeared to be a distinct clinical entity with similarities and differences from CITP.

Patients and methods

Patients

Medical records for patients that were evaluated for chronic thrombocytopenia between 1 January, 1996 and 30 June, 2000 were reviewed. This study was approved by the Institutional

Review Board (IRB) of the University of Southern California, Keck School of Medicine (IRB no. 008023). The haematology consultation service utilizes a clinical and laboratory algorithm for the evaluation of all patients with suspected CITP. Patients diagnosed as having chronic immune thrombocytopenia, defined by a platelet count $<100 \times 10^9$/l of at least 3-months duration were included in this analysis. All patients had a minimum of 1-year follow-up at the time their medical records were reviewed. Medical records were evaluated for causes of thrombocytopenia by history, physical examination and review of peripheral blood smears. Palpable splenomegaly was considered present when the splenic border was felt below the left costal margin by an experienced haematologist. Fifty-three patients (23 HCV-TP and 30 CITP) had bone marrow biopsies. All were normocellular without dysplasia and had normal or increased megakaryocytes.

Patients were tested for antibodies to HIV, hepatitis B and C at the time of diagnosis. Patients also had serologic studies for presence of antinuclear antibodies (ANA), anticardiolipin antibodies (ACA), lupus anticoagulant and cryoglobulins. Patients with HIV infection or a diagnosis of a haematological or non-haematologic malignancy were excluded. Patients were excluded who had clinical and/or laboratory evidence of acute or chronic liver disease, defined as elevations of hepatic transaminases (aspartate transaminase and alanine transaminase) greater than three times the upper limits of normal, albumin <33 g/l, a prothrombin time international normalized ratio >1·3, or physical findings consistent with chronic liver disease. All HCV seropositive patients had ultrasound examinations to exclude occult portal hypertension and splenomegaly using established ultrasound criteria (Tchelepi *et al*, 2002). Splenomegaly was considered present when the splenic length was >120 mm. Patients with a history of blood transfusion for bleeding secondary to thrombocytopenia prior to documentation of HCV infection were also excluded, because of the possibility of HCV infection from transfused blood products.

Major bleeding was defined as a decrease in haemoglobin of at least 2 g/dl, transfusion of two or more units of red blood cells or intracranial bleeding. All patients with significant abnormalities in coagulation screening assays, including prothrombin time, activated partial thromboplastin time and fibrinogen levels were excluded. However, patients with documented lupus anticoagulants were included in the analysis. In patients receiving therapy, response was defined as an increase in platelet count to $>50 \times 10^9$/l or at least greater than twice baseline level.

Laboratory methods

Hepatitis C viral antibodies were detected using the Anti HCV EIA-2 (Ortho Diagnostics Systems, Raritans, NJ, USA). Serum immunoglobulin-G (IgG), IgA and IgM ACA were measured by a standard enzyme-linked immunosorbent assay (Inova Diagnostics, San Diego, CA, USA) as per manufacturer's instructions and validated using reference samples. Values above 15 IgG phospholipid units for IgG, 10 IgA phospholipid units for IgA and 20 IgM phospholipid units for IgM were considered positive. ANA were determined by standard methods. For the determination of serum cryoglobulins, blood was drawn, maintained and centrifuged at 37°C. Three millilitre of serum were incubated at 4°C for 72 h, centrifuged at 2000 ***g*** at 2–8°C and the supernatant discarded. The cryoprecipitate was washed twice in cold phosphate buffer and then resuspended in 3 ml of 1 mol/l NaOH. The protein concentration of the precipitate was determined spectrographically against a protein standard curve. Values >2·5 mg were reported as positive. HCV quantitative viral load, when measured, was performed by a reverse transcription polymerase chain reaction (Amplicor HCV test; Roche Molecular Systems, Somerville, NJ, USA).

Statistical analysis

Differences in demographic, platelet counts and clinical symptoms between the two patient groups were examined using Fisher's exact test (Mehta & Patel, 1983). Differences in continuous data were compared between HCV-TP and CITP patients using Student's *t*-test (SAS Institute, 1999).

Results

Between January 1996 and June 2000, 592 patients with chronic thrombocytopenia were evaluated. The diagnoses and reasons for exclusion of patients not included in the final analysis are given in Table I. A total of 250 patients fulfilled ASH guideline criteria for CITP. All had medical records sufficient for evaluation of clinical characteristics and therapeutic outcome. Of the 250 patients, 76 (30%) were HCV seropositive (HCV-TP), whereas 174 patients were negative for any viral serology.

There were significant differences in demographic characteristics of HCV-TP patients when compared with HCV seronegative CITP. HCV-TP patients were older (mean age ± SD; 54·9 ± 8 years vs. 40·3 ± 8 years, $P < 0{\cdot}001$) and equally distributed between both sexes in comparison with the female predominance in CITP (Table II). There was a significant difference in the ethnic background of CITP patients when compared with the HCV-TP patients (Table II). CITP was more frequent in Asian patients. Patients diagnosed with HCV-TP closely reflected the patient population with HCV clinical liver disease reported from our institution (Bonacini *et al*, 2001). There was a significant difference in platelet count distribution when patients were compared according to their HCV status. HCV-TP patients were less likely to have severe thrombocytopenia as defined by a platelet count $<10 \times 10^9$/l (4% vs. 46% for patients with CITP, $P < 0{\cdot}001$). However, 56 (74%) HCV-TP patients had platelet counts $<50 \times 10^9$/l.

Clinical signs and symptoms associated with thrombocytopenia were less frequently reported in HCV-TP (Table II).

Table I. Diagnoses in 592 chronic thrombocytopenic patients.

All patients evaluated (January 1996 to June 2000)	592
Diagnosis of systemic lupus erythematosis	26
Diagnosis of malignancy (seven follicular non-Hodgkin lymphoma, eight diffuse large B-cell lymphoma, five natural killer T-cell lymphoma, 12 solid tumours)	32
Decreased or ineffective production (confirmed by bone marrow biopsy) (pernicious anaemia: 29, myelodysplastic syndrome 27, paroxysmal nocturnal haemoglobinuria/aplastic anaemia 26)	82
Drug related	34
Palpable splenomegaly	70
HCV-related cirrhosis (26 had abnormal liver test)	28
Hepatitis B-related cirrhosis (all had abnormal liver tests)	10
Alcoholic cirrhosis (all had abnormal liver tests)	22
Cryptogenic cirrhosis (all had abnormal liver tests)	8
Amyloidosis	2
Others (pseudothrombocytopenia, 12; familial macrothrombocytopenia, nine; type IIB von Willebrand's disease, five; Gaucher's disease, three)	29
Excluded because of HIV seropositivity	6
Excluded because of transfusion before HCV analysis	9
Excluded because of pre-existing malignancy	4
Excluded because of inadequate follow-up	21
Excluded because of incomplete records	29
Chronic idiopathic thrombocytopenic purpura	250
CITP (HCV serology negative)	174
HCV-TP	76

Table II. Characteristics of HCV-TP and CTP patients.

	HCV^+ (%)	HCV^- (%)	*P*-value
n	76	174	
Sex			<0·001
Male	36 (47)	44 (25)	
Female	40 (53)	130 (75)	
Ethnicity [*n* (%)]			
C	17 (22)	39 (22)	
L	43 (57)	83 (48)	
AS	5 (7)	35 (20)	0·02
AA	11 (14)	17 (10)	
Mean age (±SD) at presentation	54·9 (±8)	40·3 (±8)	<0·001
Range	32–79	18–69	
Platelet count at diagnosis ($\times 10^9$/l) [*n* (%)]			<0·001
<10	3 (4)	80 (46)	<0·001*
10–25	16 (21)	33 (19)	
25–50	37 (49)	40 (23)	
50–100	20 (26)	21 (12)	
Clinical symptoms [*n* (%)]			
Asymptomatic	29 (38)	18 (10)	<0·001
Bruising and petechiae	10 (13)	154 (89)	<0·001
Mucosal (ENT) bleeding	14 (19)	56 (32)	0·03
Major bleeding	19 (25)	18 (10)	0·006

C, Caucasian; L, Latino-white; AS, Asian; AA, African American; ENT, ear, nose and throat.

*Comparing platelet count $<10 \times 10^9$/l vs. $>10 \times 10^9$/l.

Fatigue, lethargy and a perception of poor health were more common in HCV-seronegative patients (10% asymptomatic CITP vs. 38% asymptomatic HCV-TP, $P < 0{\cdot}001$). Minor bleeding complications, such as ecchymosis and petechiae (89% vs. 13%, $P < 0{\cdot}001$) and mucosal bleeding (32% vs. 19%, $P = 0{\cdot}03$), were more frequently observed in HCV-seronegative CITP, most likely reflecting their lower platelet counts.

Despite higher platelet counts, major bleeding episodes were more frequent in HCV-TP (Tables II and III). Epistaxis and gastrointestinal blood loss were common sites of major bleeding in both HCV-TP and CITP patients (Table III). Other sites of bleeding included the urinary tract, lung and central nervous system. The increased frequency of major bleeding in the HCV-TP patients cannot be explained by any associated coagulopathy as all patients had normal haemostatic screening tests.

The HCV-TP patients were more likely to have mild elevations (less than three times upper limits of normal) of hepatic transaminases when compared with the HCV seronegative patients [26/76 (34%) vs. 22/138 (16%); $P = 0{\cdot}034$]. It should be noted that these liver enzyme abnormalities were determined at the time of diagnosis and that some patients with documented HCV infection later demonstrated normal levels on repeat study. Ultrasound examinations of liver and spleen performed on the 76 HCV-TP patients showed mild splenomegaly without evidence of hepatic cirrhosis or portal hypertension in 20 (26%) patients (Table IV). Additional radio-isotopic liver scans in all 20 patients failed to show increased bone marrow activity, which would be consistent with portal shunting. No evidence of oesophageal varices was found in 14 of the 20 patients who underwent endoscopy. In addition, there was no difference in the degree of thrombocytopenia between the HCV-TP patients with and without ultrasound documented splenomegaly [Table IV; mean platelet count ($\times 10^9$/l) ±SD $37{\cdot}5 \pm 17{\cdot}2 \times 10^9$/l vs. $38{\cdot}9 \pm 19{\cdot}8 \times 10^9$/l; $P = 0{\cdot}79$]. This contrasted with the HCV positive patients with palpable splenomegaly who were twice as likely to have platelet counts $<25 \times 10^9$/l (Table IV). These patients had ultrasound evidence of hepatic cirrhosis and portal hypertension with hepatic dysfunction, as shown by their lower serum albumins (Table IV).

Serologic studies evaluating the frequency of acquired autoantibodies in HCV-TP and CITP are presented in Table V. ANA were detected in a third of both HCV-TP and CITP patients. However, the ANA results in HCV-TP were predominantly of low titre with a speckled pattern. Cryoglobins were detected in nearly all HCV-TP patients, but rarely in CITP (90% vs. 7%, $P = <0{\cdot}001$). There was no correlation between the concentration of cryoglobulins detected and the degree of thrombocytopenia. ACA were more frequently detected in

Table III. Major bleeding episodes in chronic thrombocytopenic patients.

	HCV seropositive	Mean platelet count [$\times 10^9$/l (range)]	HCV seronegative	Mean platelet count [$\times 10^9$/l (range)]
Total	19		18	
GI bleeding	8	36 (6–78)	5	5 (<5–8)
CNS bleeding	3	20 (8–34)	2	7 (5, 10)
Epistaxis requiring transfusion	7	19 (11–30)	9	9 (<5–24)
Haematuria	1	12	1	10
Haemoptysis	0	–	1	8

HCV, hepatitis C virus; GI, gastrointestinal; CNS, central nervous system.

Table IV. Characteristics of HCV-positive and -negative patients with and without splenomegaly.

			HCV-TP with no palpable splenomegaly‡	
	Non-HCV palpable splenomegaly*	HCV palpable splenomegaly†	Splenomegaly by ultrasound§	No splenomegaly
n	42	28	20	56
Splenomegaly by palpation	Yes	Yes	No	No
Splenomegaly by ultrasound, mean (range)¶	Yes, 180 (130–220)	Yes, 140 (131–170)	Yes, 123 (122–125)	No (<120)
Evidence of cirrhosis or portal hypertension	Yes	Yes	No	No
Overt liver disease†	Yes	Yes	No	No
Male:female	29:13	16:12	9:11	27:29
Albumin, mean (range)	3·0 (2·4–3·4)	2·9 (2·5–3·3)	3·5 (3·3–3·9)	3·6 (3·3–4·1)
Median age in years (range)	51·9 (35–61)	56·4 (39–79)	54·9 (36–79)	54·9 (32–78)
Platelet count at diagnosis ($\times 10^9$/l) [*n* (%)]				
<10	0	2 (7·15)	1 (5)	2 (3·6)
10–25	0	13 (46·4)	4 (20%)	12 (21·4)
25–50	6 (14·3)	11 (39·3)	10 (50%)	27 (48·2)
50–75	14 (33·3)	2 (7·15)	4 (20)	10 (17·9)
75–100	22 (52·4)	0	1 (5)	5 (8·9)
Major bleeding [*n* (%)]	7 (16·7)	8 (28·6)	5 (25)	14 (25)

*Includes patients with hepatitis B and alcoholic cirrhosis with palpable splenomegaly. Only 13 patients had additional splenic measurements by ultrasound.

†Includes patients with overt HCV liver disease and palpable splenomegaly including elevations of hepatic transaminases (AST and ALT) greater than three times upper limit of normal, albumin <3·3 g/dl or a prothrombin time international normalized ratio >1·3, or physical findings of ascites, icterus or spider angioma.

‡Patients included in this study.

§Patients with splenic size >120 mm without cirrhosis or portal hypertension by ultrasound. Also no evidence of overt liver disease by the criteria are listed in Patients and methods section and above.

¶Values of mean and range are expressed as mm.

Table V. Serological studies.

Test	HCV-TP *n* (%)*	CITP *n* (%)*	*P*-value
Antinuclear antibody	31/73 (42)	55/167 (33)	0·19
Cryoglobulins	66/73 (90)	10/140 (7)	<0·001
Anticardiolipin antibodies	45/73 (62)	22/150 (15)	<0·001
IgG ACA	23	17	
IgM ACA	28	4	
IgA ACA	5	5	

HCV, hepatitis C virus; CITP, chronic immune thrombocytopenic purpura; ACA, anticardiolipin antibodies.

*Number of patients positive over the number of patients tested.

HCV-TP (62% vs. 15%, $P < 0{\cdot}001$), with IgM ACA most often reported. In CITP patients, IgG ACA predominated and nine patients had additional clinical and laboratory findings, including thrombosis, fetal loss and/or a positive assay for the lupus anticoagulant, to classify them as having the antiphospholipid antibody syndrome.

The results of therapeutic interventions in these patients are summarized in Table VI. A minority of HCV-TP patients received some form of treatment [29 (38%) vs. 158 (91%) for CITP], most likely resulting from their higher platelet counts, less frequent clinical symptoms and clinician reluctance regarding the use of corticosteroids in HCV infected patients. In seven patients treated with prednisone (Table VI), six

Table VI. Response to treatment.

Treatment modality	HCV-TP (*n*)	HCV-TP, responders (%)	CITP (*n*)	CITP, responders (%)
Prednisone	7	4 (57)	116†	81 (70)
IVIg/anti-RhD	20	18 (90)	98	90 (92)
Interferon	5*	4 (80)	None treated	–

Intravenous immunoglobulin, IVIg; HCV-TP, hepatitis C virus-related thrombocytopenia; CITP, chronic immune thrombocytopenic purpura.

*Two patients were treated with prednisone and IVIg prior to interferon.

†Some patients also received IVIg or anti-RhD.

patients developed elevations of hepatic transaminases of greater than twice pretreatment levels while receiving prednisone. Two patients developed elevated serum bilirubin levels, with one patient developing overt jaundice. Serial serum HCV viral load measurements were performed in six patients treated with prednisone, including the one patient with normal hepatic transaminases. All six patients had a documented increase in HCV viral load.

Treatment with either intravenous Ig or anti-RhD Ig proved effective in increasing platelet counts in both the HCV-seropositive and -seronegative patients (Table VI). Of five HCV-TP patients treated with interferon-alpha (INF) in a pilot study, four patients responded with increased platelet counts (Rajan & Liebman, 2001). Responders to INF could be distinguished from the non-responder by a decrease in HCV quantitative RNA, hepatic transaminases and cryoglobulins. These patients have previously been reported (Rajan & Liebman, 2001).

Discussion

Beginning in January 1996, all patients at Los Angeles County, University of Southern California Medical Centre, who fulfilled ASH guideline criteria for CITP (George *et al*, 1996), were routinely screened for HCV infection at the time of diagnosis and before the initiation of therapy. We found serologic evidence of HCV infection in 76 of 250 (30%) CITP patients. While other investigators (Pivetti *et al*, 1996; Garcia-Suarez *et al*, 2000) have reported an equally high incidence of HCV infection in patients with CITP, some investigators have not documented this degree of HCV infection in their patients with CITP (Pawlotsky *et al*, 1995; Sakuraya *et al*, 2002). This may be explained in part by the criteria chosen to define CITP and/or the background incidence of HCV infection in the study population. As the incidence of HCV infection in the patient population at our institution ranged from 3·4% to 5% (Saxema *et al*, 1995; Zuckerman *et al*, 1997), nearly twice the estimated incidence of HCV infection in the USA (Alter *et al*, 1999), we would predict that the overall incidence of HCV infection in American patients with CITP would be lower than observed in our patient population. However, in view of the estimated 2·7 million persons in the USA infected with HCV (Alter *et al*, 1999), it is highly probable that HCV infection may still account for a significant proportion of the patients diagnosed with CITP.

A number of mechanisms have been proposed to explain the development of thrombocytopenia in HCV infection. HCV infection is associated with the development of various autoantibodies including ANA, rheumatoid factor, anti-phospholipid antibodies and cryoglobulins (Gumber & Chopra, 1995; Pivetti *et al*, 1996; Prieto *et al*, 1996; Kosugi *et al*, 1997; Leroy *et al*, 1998; Cacoub *et al*, 2000; Garcia-Suarez *et al*, 2000). Therefore, thrombocytopenia could represent another extrahepatic immunologic manifestation of HCV infection with the development of anti-platelet glycoprotein antibodies. We and others have failed to detect specific anti-platelet glycoprotein antibodies in patients with HCV-TP (Kosugi *et al*, 1997; Rajan & Liebman, 2001). However, no study has evaluated a large population of HCV-TP patients for anti-platelet glycoprotein antibodies to definitely exclude their presence. ACA and cryoglobulins were detected in our HCV-TP patients with a much greater frequency than in CITP patients. In fact, the frequency of ACA and cryoglobulins detected in the HCV-TP patients was significantly greater than reported in the majority of studies of the autoimmune manifestations of HCV infection (Gumber & Chopra, 1995; Pivetti *et al*, 1996; Prieto *et al*, 1996; Kosugi *et al*, 1997; Leroy *et al*, 1998; Cacoub *et al*, 2000). Therefore, thrombocytopenia in HCV infection may result from an 'innocent bystander' effect, with anti-phospholipid antibodies and/or cryoglobulins binding to the platelet membranes resulting in accelerated platelet clearance. HCV has also been reported to bind to platelet membranes by multiple cell surface receptors (Hamaia *et al*, 2001). In patients with high HCV viral loads, platelet membranes may be heavily coated with HCV. Anti-HCV antibodies may bind to the platelet surface-associated HCV, leading to phagocytosis of the antibody-coated platelets. A relationship between the HCV plasma viral load and thrombocytopenia is supported by the observation that reduction of HCV viral load with INF therapy can result in increased platelet counts (Garcia-Suarez *et al*, 2000; Rajan & Liebman, 2001).

In our series, 74% of HCV-TP patients had platelets counts below 50×10^9/l. Many of these patients would have received treatment with corticosteroids. However, 38% of the HCV-TP patients were asymptomatic and only a minority of patients had clinical findings of ecchymosis, petechiae or mucosal bleeding. Patients with HCV-TP respond to treatment with corticosteroids, intravenous Ig and anti-RhD, supporting an immune clearance mechanism for their thrombocytopenia (Hernandez *et al*, 1998; Garcia-Suarez *et al*, 2000; Rajan & Liebman, 2001). Although treatment with corticosteroids can result in increased platelet counts, responses are usually short lived and can be associated with an increase in hepatic inflammation and HCV viral replication, as observed in our

patients (Muratori *et al*, 1994; Calleja *et al*, 1996; Blanche & Bouscary, 1997; Hernandez *et al*, 1998; Garcia-Suarez *et al*, 2000; Rajan & Liebman, 2001).

Even though significantly fewer patients with HCV-TP had severe thrombocytopenia (platelet count $<10 \times 10^9$/l), major bleeding episodes were more frequent in the HCV-seropositive patients. As none of the patients had underlying cirrhotic liver disease or apparent abnormalities in haemostatic function, no explanation for the increased frequency of major bleeding is readily apparent. However, an acquired defect in platelet function cannot be excluded as platelet function studies were not obtained in these patients. It is also possible that bleeding could be the result of a cryoglobulin-associated vasculitis (Gorevic *et al*, 1980; Willems *et al*, 1994; Gumber & Chopra, 1995; Cacoub *et al*, 2000; Vassilopoulus & Calabrese, 2002). Fatal hemorrhagic complications have been reported in patients with HCV-related cryoglobulinaemia (Gomez-Tello *et al*, 1999). Some of our patients eventually developed other manifestations of mixed cryoglobulinemia, including neuropathy and purpuric skin lesions. A monoclonal cryoglobulin has been reported to inhibit fibrin polymerization, but similar coagulation abnormalities have not been reported with mixed cryoglobulins (Panzer & Thaler, 1993).

There is a close relationship between HCV viral replication, as characterized by HCV viral load, and thrombocytopenia, with evidence that thrombocytopenia can improve with INF therapy (Garcia-Suarez *et al*, 2000; Rajan & Liebman, 2001). A decrease in HCV viral replication resulting from INF therapy may result in less HCV association with platelet membranes, a decrease in serum cryoglobulins and anti-phospholipid antibodies. However, a major side effect of INF treatment is mild to moderate thrombocytopenia because of suppression of megakaryopoiesis (Ganser *et al*, 1987; Hoofnagle, 1991). In patients with HCV infection without cirrhotic liver disease, suppression of megakaryopoiesis with INF therapy results in an appropriate compensatory endogenous thrombopoietin response and, therefore, these patients should manifest less suppression of megakaryopoiesis with treatment (Shiota *et al*, 1997; Peck-Radosavljevic *et al*, 1998; Adinolfi *et al*, 2001).

Infection with HCV appears to be a frequent cause of thrombocytopenia. Therefore, we would recommend screening all patients presenting with chronic thrombocytopenia for the presence of HCV, as a different treatment strategy should be employed in these patients. In patients diagnosed with HCV-TP without clinically evident liver disease, treatment with INF combination therapy should be considered. Improvements in platelet count should parallel a reciprocal suppression of viral load and eradication of HCV infection should result in complete remission of the thrombocytopenia.

Acknowledgement

This study was supported by a grant from the Vanoff Family Foundation.

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