

Infectious Causes of Chronic Immune Thrombocytopenia

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KEYWORDS

- Immune thrombocytopenia • Infections • *H. pylori* • HCV
- HIV • Thrombopoietin

Primary immune thrombocytopenia (ITP), the most common cause of severe thrombocytopenia in otherwise healthy young adults, is a diagnosis of exclusion.^{1–3} Thrombocytopenia may accompany or follow a variety of conditions from which ITP must be differentiated. Acute infections such as infectious mononucleosis, cytomegalovirus, rubella, mumps, and varicella may be associated with thrombocytopenia of varying severity that may be, at least in part, immune-mediated.³ In children, symptoms of the primary viral disease are usually well established (1–4 weeks) before the onset of the thrombocytopenia, which is often abrupt and severe. The thrombocytopenia generally resolves spontaneously within 2 to 8 weeks, but in occasional individuals it may persist for months before remitting.⁴ In adults, the most prevalent infections associated with thrombocytopenia are those from hepatitis C virus (HCV), human immunodeficiency virus (HIV), and *Helicobacter pylori*.⁵ In typical cases the thrombocytopenia presents with an insidious onset, has no tendency to remit spontaneously (although its severity may parallel the stage of the infectious disease), and may closely mimic chronic ITP.⁵

The aim of this article is to provide an updated review of thrombocytopenia associated with chronic infections, focusing on the current understanding of the mechanisms leading to the thrombocytopenia and on the evolving therapeutic strategies.

HEPATITIS C VIRUS–ASSOCIATED THROMBOCYTOPENIA

HCV infection evolves toward a chronic state in approximately 85% of patients, as demonstrated by the persistence of HCV-RNA in serum.⁶ However, severe and long-term complications of chronic HCV infection such as liver cirrhosis, end-stage liver disease, and hepatocellular carcinoma develop only in a proportion of infected

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patients, after a period that can exceed 10 to 20 years.⁷ Chronic HCV infection has also been reported to be associated with the development of several extrahepatic alterations, including thrombocytopenia.⁸ Thrombocytopenia may be present even in the absence of clinically evident liver disease or splenomegaly, and may be diagnosed as chronic idiopathic thrombocytopenic purpura.⁹

Epidemiology

HCV is now recognized as the most common viral infection causing chronic liver disease in humans worldwide.¹⁰ Of these individuals, approximately 55% to 85% have chronic infection that might need curative treatment.¹⁰ Thrombocytopenia either preexists and prevents the initiation of treatment with pegylated interferon (PEG-IFN) or develops as a consequence of PEG-IFN treatment, leading to dose modification in 19% of cases and discontinuation in 2% of cases.¹¹ In patients with cirrhosis, thrombocytopenia complicates antiviral treatment much more frequently than in patients with HCV infection without cirrhosis.¹²

Table 1 summarizes the results on the prevalence of HCV infection from several cross-sectional studies in adult ITP patients. The major series published to date evaluated 250 patients fulfilling the diagnostic criteria for ITP of the American Society of Hematology (ASH).¹⁸ A positive serology was found in 76 (30%) of these patients. There were significant differences in demographic characteristics of HCV-positive patients when compared with HCV-negative ITP. HCV-positive patients were older (54.9 ± 8 years vs 40.3 ± 8 years, $P < .001$) and equally distributed between sexes in comparison with the female predominance in HCV-negative ITP. ITP was more frequent in Asian patients compared with the HCV-positive patients.

Whereas retrospective studies^{19,20} suggest that the prevalence of ITP among HCV patients is greater than would be expected by chance, the prevalence of HCV-positive ITP patients in some cohorts may be indirectly related to the background prevalence of HCV infection reported in the general populations.^{14,15,17,18} Chiao and colleagues²¹ calculated the incidence rate of ITP among 120,691 HCV-infected and 454,905 matched HCV-uninfected United States veterans who received diagnoses during the period 1997 to 2004. Their results indicate that HCV infection is actually associated with an elevated risk of developing ITP (hazard ratio, 1.8; 95% confidence interval, 1.4–2.3) among both untreated and treated patients.

Study	Total Number	Number Infected (%)
Pawlotsly et al (1995) ¹³	139 ^a	14 (10)
Pivetti et al (1996) ¹⁴	33	12 (36)
Garcia-Suarez et al (2000) ¹⁵	51	13 (22)
Sakuraya et al (2002) ¹⁶	79	11 (14)
Zhang et al (2003) ¹⁷	247	33 (13)
Rajan et al (2005) ¹⁸	250	76 (30)
Total	799	159 (20)

^a Seven patients of this series had an associated autoimmune disorder. Study only included patients with platelet counts of less than $25 \times 10^9/L$.

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