Severe Thrombocytopenia Associated with Acute Hepatitis E Virus Infection

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Received 29 November 2007/Returned for modification 9 January 2008/Accepted 1 May 2008

We describe here what is, to the best of our knowledge, the third reported case of severe thrombocytopenia associated with acute hepatitis E virus infection. The patient was a 72-year-old French woman. It seems likely that the cause of the thrombocytopenia was acute hepatitis E virus infection, possibly occurring via an immune mechanism. No complications were noted, in contrast to the two previous reports.

CASE REPORT

A 72-year-old woman was admitted in December 2006 with a 4-day history of fever (39°C), jaundice, abdominal pain, and nausea. Past medical history included hypertension, arthrosis, and obesity (110 kg for 160 cm). On admission, her alanine amino transferase level was strongly elevated (197 IU/liter), total bilirubinemia (39 µmol/liter), and serum creatinemia (168 µmol/liter) were concomitantly high. Hemoglobin and white blood cell and neutrophil counts were within usual ranges (12.9 g/dl, 5.4 G/liter, and 1.5 G/liter, respectively). In contrast, a severe thrombocytopenia was observed (platelet count, 16 G/liter) (Fig. 1).

At 2 days after admission, the platelet count fell to 9 g/liter, and the neutrophil count fell to 0.4 g/liter. All pharmacological treatments were stopped at admission. The patient had previously received nimesulide, the dose of which has been increased 1 week before admission, as well as diosmine, allopurinol, and levocetirizine. Liver echography showed a normal spleen and liver. A centimetric adenopathy was present at the liver hilum. Importantly, no previous history of hematological trouble, including thrombocytopenia, was noted. Thus, platelet count was 254 g/liter in February 2006. Splenomegaly was absent.

Hepatitis E virus (HEV) diagnosis was first suggested by detection of anti-HEV antibodies in the serum (Adaltis EIAGen kits; Adaltis Italia, S.p.A., Casalecchio di Reno, Italy) according to the manufacturer’s instructions. Optical density ratios for immunoglobulins G (IgG) and IgM anti-HEV antibodies were 2.6 and 2.5, respectively (positive threshold, 1.0).

HEV RNA was thereafter detected from serum using an in-house real time PCR assay targeting the open reading frame 2 (ORF2) region of the HEV genome, as previously published (3). Furthermore, an ORF2 region of HEV genome was directly sequenced with in-house protocols using the BigDye terminator cycle sequencing kit (version 1.1) on the ABI Prism 3130 genetic analyzer (Applied Biosystems, Branchburg, NJ), as previously described (3). The HEV genotype was 3f (GenBank accession no. EU116333), according to phylogenetic analysis with Mega v.3.1 software (http://www.megasoftware.net/), using the neighbor-joining method with a set of published HEV sequences (7). HEV RNA was also detected from a stool sample. Serological testing for hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, human immunodeficiency virus, parvovirus B19, Borrelia spp., Coxiella burnetii, and Leptospira spp. were negative or showed past immunization. No anti-smooth muscle, anti-liver kidney microsome, or anti-mitochondrial antibodies or rheumatoid factor were found. Anti-nuclear antibodies were detected at low titers (1/160), whereas anti-native DNA antibodies and soluble nuclear anti-antigen antibodies were absent. Monoclonal IgG with kappa light chain were transiently detected. Circulating immune complexes were detected at a significant level (14.1 µg eq/ml, usual values of <4), whereas total and fractionated complement were normal.

A bone marrow aspirate showed a rich medullar tissue, a normal number of megakaryocytes, and a blockage of maturation of the myeloid elements, together with signs of dyserythropoiesis. These data might argue for a recent and peripheral origin for thrombocytopenia, although they might also traduce a central origin due to an immuno-allergic mechanism or to toxic medications. Pharmacological analysis concluded that the bicytopenia was not linked to drugs.

The platelet count rapidly increased beginning 2 days post-admission, reaching 51 G/liter after 3 days and then a normal value (>150 G/liter) 12 days later (Fig. 1). Thereafter, it briefly...
decreased again to ca. 100 G/liter 1 month postadmission, prior to renormalization. Similarly, the neutrophil count promptly improved from 0.4 G/liter at 2 days postadmission to 2.8 G/liter 5 days later. Creatininemia normalized after rehydration and the suspension of all potentially nephrotoxic medications but subsequently increased (267 μmol/liter) at day 20 and then slowly normalized. Bilirubinemia peaked at 450 μmol/liter at day 27 postadmission.

The clinical outcome was slowly but spontaneously favorable, without any episode of cutaneo-mucous bleeding at the time of severe thrombocytopenia. Platelet count, serum creatininemia, and transaminase levels were fully normalized at week 7. HEV RNA was no more detected in serum at week 4.

The patient did not report any recent travel abroad or contacts with travelers; she did not eat wild boar meat, shellfish, and she did not ingest presumed unsafe water. Nevertheless, an occasional consumption of medium-cooked pig meat was noted, including within a period compatible with the hepatitis E virus incubation period. The patient’s husband tested negative for HEV RNA and anti-HEV antibodies during the month after her acute hepatitis.

An increasing number of sporadic HEV infections have been recently reported in industrialized countries (10). Moreover, there is increasing evidence that autochthonous transmission might account for a substantial proportion of these cases, and that hepatitis E is a zoonosis in swine, which might be a source of contamination to humans (10). Although hepatitis E is typically self-limiting, fulminant hepatitis E and associated deaths have been reported from various places, including Europe (5, 8). Mortality rates of 0.1 to 2% have been reported, being ca. 20% in pregnant women in countries where hepatitis E is hyperendemic (5, 8, 10).

No severe hematological disorder has been classically observed during HEV infection, except coagulation disorders in the setting of fulminant hepatitis (8). We describe here what is, to our knowledge, the third reported case of severe thrombocytopenia associated with acute hepatitis E (1, 13). A temporary but moderated thrombocytopenia was reported in another case for which no platelet count was available (2). Thrombocytopenia has been previously reported in children and adults in primary infections with various other viruses, including severe forms that involved, for instance, hepatitis A virus (12), Epstein-Barr virus (9), or parvovirus B19 (6). The mechanisms of severe thrombocytopenia in the setting of acute viral infection is believed to be immune mediated, and platelet-associated antibodies have been frequently reported (9, 11). In the two previous reports of severe thrombocytopenia along with acute hepatitis E, the mechanism was also thought to be immune mediated (1, 13). Anti-platelet antibodies were detected in the case reported by Singh and Gangappa (13), whereas they were absent in the patient described by Ali et al. (1) and were not tested for in our patient. In our case, it seems likely that the causal effect of thrombocytopenia was acute hepatitis E, possibly through an immune mechanism leading to peripheral destruction of thrombocytes. Indeed, the bone marrow aspirate argues for a recent peripheral mechanism, although an immuno-allergic or toxic central origin could not be excluded. In addition, transient and moderate neutropenia, alteration of renal function, and circulating immune complexes were concomitantly observed. Another argument for an immune-mediated mechanism was regression of thrombocytopenia concomitantly with the disappearance of serum HEV RNA. In the case described by Singh and Gangappa, bone marrow aspirate showed a normocellular marrow, as in our patient, whereas no result is available from the case report by Ali et al. (1, 13). In the latter case, immune complexes deposited in the kidney.
were observed (1). Importantly, neither the two patients whose cases had been reported previously nor our patient had splenomegaly, which might have traduced the splenic sequestration of platelets.

In the present case, pharmacological analysis did not find a link between drugs and thrombocytopenia. Although the involvement of allopurinol, nimesulide, and possible cumulative effect due to the whole therapy cannot be ruled out, this is unlikely. Indeed, even if an increase of nimesulide dose occurred 1 week prior to admission, all drugs had been taken since several weeks before the onset of thrombocytopenia. In contrast to its very rare involvement in cases of thrombocytopenia, nimesulide has been frequently associated with acute hepatitis (14). This must be underscored since it questions whether the association of HEV infection and treatment with nimesulide may have concurrently led to hepatitis.

The two previously reported cases of severe thrombocytopenia associated with acute hepatitis E occurred in India and involved young male adults (34 and 38 years old), whereas our patient was a 72-year-old woman originating from and living in France. The HEV sequence detected in our patient was classified genotype 3f, which is the most widely described genotype in Europe in cases of autochthonous hepatitis E infection of humans or swine (7). No information about HEV sequence was available for the cases described by Ali et al. or Singh and Gangappa (1, 13). However, human HEV strains from India have been described to belong to genotype 1, which suggests that severe thrombocytopenia might involve acute infection with various HEV genotypes (7).

Importantly, both patients whose cases have been previously reported presented with hematuria and purpura concurrently with acute hepatitis E in an adult. Am. J. Hematol. 82:942–943.

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4. Reference deleted.