Severe Thrombocytopenia and Response to Corticosteroids in a Case of Nephropathia Epidemica

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● **Nine days after working in the woods, a previously healthy 32-year-old man fell seriously ill. His symptoms included high fever, chills, diffuse myalgia, severe headache, and back pain. On the fifth day of onset of symptoms, blood tests showed creatinine levels of 5.4 mg/dL accompanied by marked proteinuria. After admission to the hospital, a diagnosis of nephropathia epidemica (NE) caused by Puumala virus was made using solid-phase enzyme-linked immunosorbent assay (ELISA). The patient gradually recovered renal function without requiring dialysis. However, he surprisingly experienced a sharp decline in platelet count to a minimum of 2,000/μL with concomitant occurrence of petechiae and conjunctival hemorrhage. Prednisolone was intitiated, resulting in a swift rise in platelets. Six days later, when the medication was withdrawn, a sharp decrease in platelets recurred. The steroids were then readministered for the next 3 months, thus reestablishing a stable platelet count. The immediate rise of platelets after administration of prednisolone supports the pathophysiological view of hantavirus infection as an immunologically mediated disease. Corticosteroids in the treatment of hantavirus-associated thrombocytopenia might need further systematic evaluation.**

INDEX WORDS: Hantavirus; nephropathia epidemica; Puumala virus; thrombocytopenia; treatment; prednisolone.

UNTIL THE KOREAN War, the clinical manifestation of hantavirus infection, hemorrhagic fever with renal syndrome (HFRS), did not attract much attention. In the following years, similarities between the so-called Korean hemorrhagic fever[1] and other illnesses outside southeast Asia, particularly nephropathia epidemica (NE) first encountered in Scandinavia,[2] were noted. Today, hantavirus infection has emerged as a worldwide zoonosis.[3] Only recently another clinical manifestation of hantavirus infection, the hantavirus pulmonary syndrome (HPS), has been described in the United States.[4]

NE is prevalent in northern and central Europe and is caused by a specific hantavirus serotype, the so-called Puumala virus. Usually, NE is a benign disease with virtually no mortality and mild hemorrhage at worst.[5,6] Mild to moderate thrombocytopenia and acute renal failure are common, generally reversible complications not requiring treatment or dialysis. However, cases published in recent years have shown that Puumala virus infection can proceed with a highly variable course, and sporadic fatal cases have been described.[7-11] What follows is the report of a case of a young man suffering from NE with associated uncomplicated renal failure but life-threatening thrombocytopenia.

CASE REPORT

History

In October 1995, a 32-year-old white man suffering from proteinuria and rapidly deteriorating renal function was referred to our department. His medical history was unremarkable except for the passage of a kidney stone in 1993.

Five days before admission, the patient reported the sudden onset of a high fever (40.5°C), chills, and devastating muscle pain, particularly in the lower limbs. Two days later, after being put on clarithromycin, a severe left-sided retrobulbar headache, nausea, and loin pain developed. For pain relief, the patient was prescribed a medication containing caffeine, acetaminophen, and acetylsalicylic acid; however, no nonsteroidal anti-inflammatory drugs had been administered. He had not been swimming in ponds or rivers but had been woodcutting in the forest around Schorndorf, Baden-Württemberg, on two separate occasions, one 14 days and the other 6 days before admission. On admission, the patient still felt weak but reported that his initial complaints had disappeared. No reduction in urine volume had been observed.

Diagnostic Tests

Electrocardiogram was normal. Ultrasound examination showed splenomegaly (15.2 × 5.5 cm); kidneys were normal in size but showed increased echogenicity and a gentle subcapsular fluid rim. A chest radiograph was unremarkable.

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Received November 5, 1996; accepted in revised form July 11, 1997.

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0272-6386/98/3101-0018$3.00/0

Laboratory Results

White blood cell count was 10,900/μL (2% bands, 59% polymorphonuclear leukocytes, 27% lymphocytes, 1% eosinophils, 9% monocytes, 2% plasma cells); hemoglobin, 149 g/L; platelet count, 62,000/μL; no fragmented red blood cells were noted; blood urea nitrogen, 50.9 mg/dL; creatinine, 4.9 mg/dL; uric acid, 9.7 mg/dL; sodium, 132 mmol/L; potassium, 3.8 mmol/L; total protein, 6.3 g/dL; γ-GT, 111 U/L; lactate dehydrogenase, 372 U/L; haptoglobin, 418 mg/dL; C-reactive protein, 7.9 mg/dL. Antibodies against hepatitis A, B, C, and E virus and the hepatitis B surface antigen were negative. Within normal limits were calcium, phosphate, transaminases, prothrombin time (PT), and activated partial thromboplastin time (aPTT). Antistreptokinase, antinuclear, and antineutrophil cytoplasmic antibody titers were negative. On urine analysis, protein was 500 mg/dL; leukocytes, 26,000/mL; erythrocytes, 24,000/mL; and phase contrast microscopic examination showed 14% dysmorphic erythrocytes and 2% acanthocytes. No casts were detected.

Solid-phase enzyme immunoassay using recombinant nucleocapsid antigen of a Puumala serotype and a Hantaan serotype strain (Progen Biotechnik GmbH, Heidelberg, Germany) enabled the diagnosis of nephropathia epidemica caused by a Puumala serotype (Table 1). The results were expressed as the ratio of the photometric extinction of patient serum and a reference control.

Clinical Course

The patient never did show any uremic symptoms and did not require dialysis. Creatinine had risen to its maximum (5.8 mg/dL) on day 7 (days were counted beginning with the onset of symptoms) but had returned to normal (1.4 mg/dL) on day 14. However, the thrombocyte count showed a dramatic decline from 62,000/μL on day 6 to 2,000/μL on day 12 (Fig 1). Ethylenediaminetetraacetic acid–induced thrombocytopenia was ruled out by evaluating thrombocytes in citrated blood. PT and aPTT were normal, as was the fibrinogen level (344 mg/dL), but fibrin D-dimers were found to be increased to 8.0 mg/L (normal, <0.5 mg/L). A bone marrow sample disclosed that thrombopoiesis was slightly increased, and megakaryocytes of all stages could be observed. Granulopoiesis and erythropoiesis were normal. Studies done by Mueller-Eckhardt of Gießen did not detect any free antithrombocyte antibodies and showed normal immunoglobulin (Ig) G covering of glycoprotein complexes Ib/IX and IIb/IIIa.

On day 10 (thrombocytes, 3,000/μL), the patient developed petechiae to his soft palate. On day 12 (thrombocytes, 2,000/μL), petechiae on the fore edge of the shin were noted. Concomitantly the patient showed conjunctival hemorrhage of his right eye, which resolved within 3 days.

Table 1. Serological Data

Recombinant Nucleocapsid Antigen	Serum OD/Cutoff OD-Ratio*	
	IgM	IgG
Puumala serotype	19.2	13.9
Hantaan serotype	3.6	0.6

Abbreviation: OD, optical density.
*Values >1.5 are considered positive.

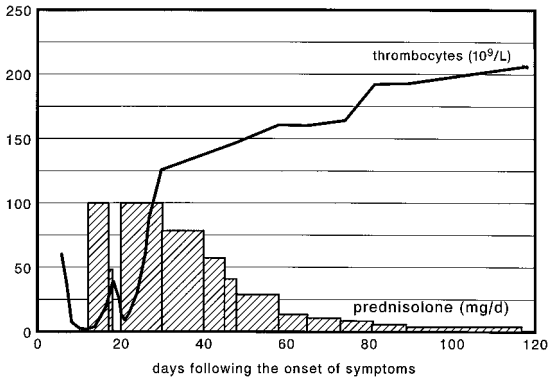

Fig 1. Thrombocytopenia and steroids.

At this point, on day 12, the patient received one unit of packed thrombocytes, resulting in no increase in thrombocyte count (2,000/μL) after 6 hours. The same day, intravenous administration of prednisolone (100 mg daily) was begun.

The following day, the thrombocyte count rose to 4,000/μL, and 6 days later (by day 18) had risen to 40,000/μL. By way of trial, medication was then stopped, only to have the thrombocyte count drop to 9,000/μL by day 21. Prednisolone was then reinitiated at a continuous dose of 100 mg per day, and by day 27, the day of discharge, thrombocytes had recovered to 88,000/μL. Renal studies were within normal limits, although slight proteinuria persisted.

In an outpatient setting, the patient was doing reasonably well except for the occurrence of prednisolone-induced Cushing's disease and a slightly elevated blood pressure, which was treated with hydrochlorothiazide. When platelets reached a high of 126,000/μL on day 30, prednisolone was slowly tapered off over a period of 11 weeks. After discontinuation of steroids on day 105, the patient's platelet counts remained normal (day 117; 206,000/μL; see Fig 1). Twenty months after the initial episode, proteinuria had completely resolved. Platelets and renal function were normal. However, labile hypertension with blood pressure values up to 160/90 mm Hg required close follow-up. At this point HLA typing showed the patient being negative for HLA B8 DRB1*0301.

DISCUSSION

NE is the European type of HFRS. However, hemorrhagic manifestations in NE are rare and mild if present. In general, they consist of petechiae (present in 2% to 12% of patients at risk),[5,12] conjunctival bleeding (6% to 12%),[5,13] and epistaxis (1% to 28%).[13,14] Moderate to severe gastrointestinal bleeding (melena, hematemesis) was seen in 2% to 3% of infected patients.[5,13] Macroscopic hematuria, hemoptysis,

Table 2. Association of Severe Complications in NE With Thrombocytopenia

Country	Year	Complications	Thrombocytes
Germany[7]	1992	1 Case with severe cerebral bleeding	20,000/μL
Germany[8]	1994	1 Case with bleeding, pulmonary edema	4,000/μL
Sweden[9]	1991	1 Fatality after DIC, anuria, shock	37,000/μL
Finland[10]	1992	1 Fatality after severe bleeding and uremia	12,000/μL
Finland[11]	1995	4 Fatalities after possible DIC	9,000-20,000/μL

and ecchymoses occasionally occur. In the Asian type of HFRS, hemorrhagic complications contribute in a significant proportion of cases to the overall mortality of 2% to 10%.[15]

NE has long been considered a benign disease normally associated with no mortality.[5,13] However, severe complications and sporadic fatal cases have been reported in recent years (Table 2). All of them were associated with severe thrombocytopenia (9,000 to 37,000/μL). Five of these six fatalities showed laboratory data suggesting disseminated intravascular coagulation (DIC). In Belgium, a growing number of NE cases were complicated by pulmonary edema resembling HPS.[16]

Thrombocytopenia (<100,000/μL) as one cause of bleeding has been noted in 20% to 70% of European patients.[2,5] Platelet counts below 30,000/μL were very rare, with lowest values ranging between 6,000 and 26,000/μL in some of the larger study populations (Table 3). In Asian studies, thrombocytopenia occurred in 69% to 90% of patients with HFRS.[1,15]

At its outset, the case reported here reflects the typical clinical manifestation of Puumala virus infection as meticulously delineated by Lähdevirta.[2] After the acute onset with fever, chills, myalgia, headache, back pain, and nausea, finally renal failure developed. Remarkable, and very unusual, was the profound decrease of platelets (down to 2,000/μL) on the 12th day of the disease without clear-cut clinical evidence of DIC.

Table 3. Thrombocytopenia in HFRS

Study population		Thrombocyte Count		
Country	n	Lowest	Mean	<100,000/μL (%)
Finland[2]	35	26,000/μL	—	20
Finland[5]	126	10,000/μL	117,000/μL	75*
Sweden[14]	74	22,000/μL	96,000/μL	52
Germany[17]	42	6,000/μL†	—	50*†
Korea (HTN)[18]	11	15,000/μL	54,000/μL	91

*<150,000/μL.
†Personal communication.

Differential Diagnosis

Anticipating other disorders predisposing thrombocytopenia, a bone marrow sample of our patient ruled out diminished platelet production. In light of possible interstitial nephritis, drug-induced thrombocytopenia then had to be the primary suspect explaining increased platelet consumption. Directly before admission, the patient was taking clarithromycin and a combination of acetylsalicylic acid, acetaminophen, and caffeine. The administration of all of these drugs could be associated with thrombocytopenia; nevertheless, in absolute terms, the probability would be extremely low. Some minor evidence against drug-induced thrombocytopenia was the absence of the rise of platelets after discontinuation of the drugs. Other conditions were ruled out by laboratory results or on clinical grounds.

Virus-Induced Thrombocytopenia

General causes of thrombocytopenia in a viral infection may include impaired platelet production, vasculopathy, DIC, and a variety of immune mechanisms.

Vascular dysfunction most likely attributed to virus replication in the endothelium is the hallmark of the pathophysiological derangements in HFRS.[19] It not only accounts for hemorrhagic complications and renal failure; it can also initiate DIC.

The diagnosis of DIC can usually be made by careful consideration of both the clinical situation and laboratory data. The best screening tests for DIC are measurements of the fibrin degradation products (FDP), PT, fibrinogen level, and platelet count.[20] The situation in our thrombopenic patient first disclosed some contradictory aspects. As an indicator of reactive hyperfibrinolysis in late-stage DIC, FDP (d-dimeric form) were elevated. The normal fibrinogen could not rule out DIC because fibrinogen is also an

acute-phase protein with the possibility of pseudonormal levels. However, the absence of major bleeding, shock, and early-stage laboratory markers such as prolonged PT or aPTT militated against high-grade DIC. Moreover, FDP (d-dimeric form) have been described as being falsely positive in about 20% of patients.[21] In renal failure, elevated levels of FDP are often primarily related to delayed clearance rather than to increased production.[22]

A growing body of data support the view of HFRS as an immunologically mediated disease.[3,19] Specific immune mechanisms such as early IgE production, T cell activation, and activation of both the classical and alternative complement pathways have been identified. Immune complexes were shown especially in serum,[15] and on renal tubules and glomeruli[23] of affected patients. Of particular interest in our setting was the demonstration of immune complexes on platelets.[24,25] By activating complement, triggering mediator release, and inducing platelet aggregation, they could result in further thrombocytopenia and vascular injury. However, some immunologic findings such as missing perivascular infiltrates of mononuclear cells and others differ from those seen in classic immune-complex disease.[3]

Only recently an association of certain major histocombatibility complex markers (HLA B8 DRB1*0301) with a more severe course of NE was found. Interestingly, the HLA B8 DRB1*0301 haplotype is very strongly associated with various autoimmune diseases.[26] These results probably imply that the immune system of the host contributes to the damage seen in Puumala virus infection. A vigorous immune response can be considered a predisposing factor of more severe disease. However, our patient was negative for HLA B8 DRB1*0301.

Considering platelet-associated immune complexes as a possible cause of thrombocytopenia, the patient was started on 100 mg prednisolone intravenously. After 6 days, an increase in platelets from 2,000/μL to 40,000/μL was noted. The close relationship between corticosteroid therapy and thrombocyte count was shown when, 3 days after discontinuation of the drug, the platelet count fell sharply from 40,000/μL to 9,000/μL. Under subsequent prolonged prednisolone therapy at 100 mg each day orally, the patient developed normal platelet counts, which persisted after discontinuation of the drug 3 months later. Circulating immune complexes were indeed observed in some patients up to 8 months after onset of NE. Almost 2 years after the acute phase of the disease, the patient was asymptomatic except for labile arterial hypertension. Indeed, hantavirus infections might account for a certain percentage of chronic renal disease or hypertension now considered idiopathic.[3]

The response to treatment with steroids is further evidence of the immunologically mediated pathogenesis of the disease. Immune complexes activate the classical complement pathway. The action of corticosteroids does not significantly decrease the concentration of circulating antibodies; it rather interrupts cytokine-mediated cellular communication among leukocytes.[27] As one consequence, complement-triggered phagocytosis of immune complex–loaded thrombocytes might be decreased.

More systematic investigations on the action of corticosteroids in HFRS seem to be warranted.

ACKNOWLEDGMENT

The authors thank Maurice Mareschal for reviewing the manuscript.

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