



Urticaria and Periorbital Edema as Prodromal Presenting Signs of Acute Hepatitis B Infection

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A 34-year-old patient presented with giant, transient urticarial skin lesions and periorbital edema after a 3-month stay in DR Congo. Retrospective analysis of stored samples revealed that these signs were prodromal manifestations of acute hepatitis B infection. The hepatitis B infection was spontaneously cleared; the skin lesion did not recur.

Skin diseases are a common reason for returning travelers to seek medical care.^{1–4} Skin diseases develop as a result of a variety of factors, which include infectious skin diseases of exotic or cosmopolitan origin as well as environmental skin diseases. Urticaria is the cause of consultation in about 5% of the returning travelers with skin problems.^{1–3} Common causes of urticarial skin manifestations in travelers are noninfectious causes such as adverse drug reactions and dermatoses related to viral infections such as hepatitis A, as well as parasitic infections.⁴ In this case report, we describe a returning traveler with giant urticaria and periorbital edema as prodromal signs of acute hepatitis B infection.

Case Report

A 34-year-old wildlife photographer was admitted to our Institute for Tropical Diseases with recurrent skin lesions. Before presentation at our clinic, he had lived for 3 months in the rural areas of Kinshasa (DR Congo) under primitive conditions. He did not use any medication, except mefloquine (Lariam[™]) for malaria prophylaxis and did not mention significant mosquito

bites during his stay. In addition, he denied unprotected sex with local inhabitants.

Two weeks after his return to the Netherlands, he suffered from extreme exhaustion and transient itching skin lesions on his trunk. Physical examination revealed periorbital edema (Figure 1) and giant urticarial-like skin lesion (Figure 2). Laboratory tests, in particular no abnormal liver function tests, showed no abnormalities nor eosinophilia ($0.09 \times 10^9 \text{ L}^{-1}$; normal limits $0.05\text{--}0.5 \times 10^9 \text{ L}^{-1}$). During the next months, the giant urticaria relapsed several times on his trunk, back, and extremities, lasting for 1 or 2 days. Schistosomiasis, filariasis, strongyloidiasis, ascariasis, fascioliasis, toxocariasis, trichinellosis, and gnathostomiasis were ruled out on several occasions. Stool examinations showed a clinically not relevant *Entamoeba dispar* infestation [confirmed by polymerase chain reaction (PCR)].

Four months after his return to the Netherlands, the liver function tests deteriorated with alanine transaminase levels exceeding 1,000 IU/L. A liver biopsy showed portal and lobular hepatitis, compatible with a toxic drug reaction or an acute viral infection. An abdominal computed tomography scan showed no abnormalities. An acute hepatitis B infection was diagnosed [HBsAg positive, HBeAg positive, and presence of HBc immunoglobulin (Ig) M, and IgG antibodies]. Cytomegalovirus, Epstein Barr virus, hepatitis A, hepatitis C, hepatitis E, and human immunodeficiency virus infections were excluded. A toxic drug reaction was considered unlikely, because mefloquine was already stopped for several months.

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Figure 1 Periorbital edema of the right eye of the patient (reprinted with explicit written permission of the patient).

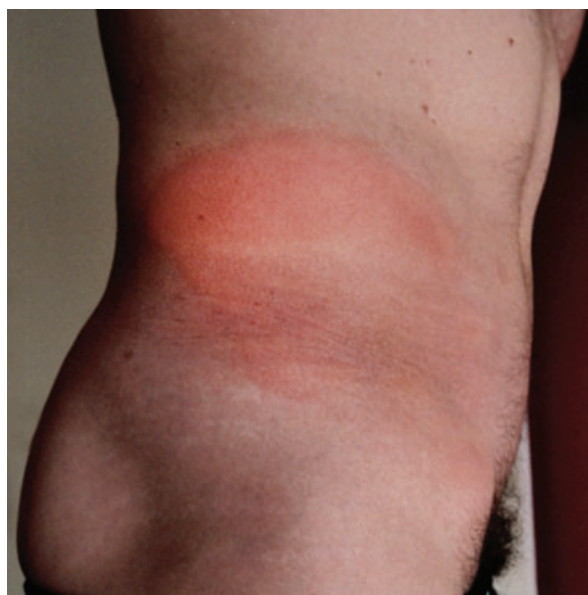


Figure 2 Giant urticarial skin lesion on the trunk of the patient.

In retrospect, all stored blood samples, taken at presentation and at several times of follow-up, were tested by quantitative real-time PCR for hepatitis B DNA and found positive, including the samples taken at the time of first presentation [hepatitis B virus (HBV) DNA viral load at presentation 4,450 copies/mL; the maximal

viral load of 1.35×10^9 copies/mL was documented almost 4 months after presentation]. Additional analysis showed the genotype A of HBV. Reevaluation of his vaccination status revealed that he had never received hepatitis B vaccination, in contrast to our national guidelines for long-term travelers. Two months later, his liver function tests normalized and after 4 months the patient became HBsAg negative. The skin lesions did not recur.

Discussion

An infection with HBV may lead to several hepatic complications including an acute hepatitis, which may be associated with a number of extrahepatic manifestations such as urticarial skin lesions and periorbital edema.⁵ The association is supposed to be commonly observed during the prodromal phase of the hepatitis B infection, but is only anecdotically reported in the ancient literature.⁵ The occurrence of these prodromal cutaneous manifestations of acute hepatitis B infection is ascribed to immune-mediated mechanisms⁶ and can be easily misinterpreted as a feature of allergic disease. Our case highlights the importance of considering an acute HBV infection in the differential diagnosis of recurrent urticaria, even when liver function tests are normal.

Declaration of Interests

P. J. v G. has received speaker's fee from GlaxoSmith-Kline (GSK) and reimbursements from GSK and Sanofi Pasteur MSD for attending symposia.

The other authors state that they have no conflicts of interest to declare.

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