

Urticaria and Hepatitis

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Abstract

Acute urticaria is commonly observed in the prodromic stage of hepatitis A and B infection as well as in hepatitis C infection, although only rare cases have been published regarding the latter. Urticaria is considered one of the pre-icteric symptoms of viral hepatitis and is related to immune-complex deposits; subsequently, it may be associated with arthritis and headache (Caroli's triad). The absence of specific presentation of acute urticaria in patients with viral hepatitis is not surprising because many other viral infections can induce similar cutaneous symptoms.

On the other hand, no convincing evidence exists in which hepatitis virus infection caused chronic urticaria. Data are lacking for hepatitis B, but several series and one controlled study showed the absence of a link between hepatitis C and chronic urticaria. Systematic hepatitis virus investigations in patients with chronic urticaria probably are not cost-effective.

Hepatitis B or C can occasionally induce urticarial vasculitis, but this is probably related more to vasculitis than to true urticaria.

Index Entries

Urticaria; chronic urticaria; hepatitis; immune complex vasculitis.

Introduction

There has been a growing interest in the field of cutaneous diseases related to hepatitis virus infections since the 1970s, after the hepatitis B antigen was found in the skin of patients with polyarteritis nodosa. Many associations

were further described in the 1990s as a result of the discovery of hepatitis C virus (HCV). HCV infection has been demonstrated as the major cause of mixed cryoglobulinemia and is strongly associated with porphyria cutanea tarda. Links were also established with lichen planus, but only a minority of patients with the

disease is infected with HCV. Finally, there are numerous anecdotal reports of single patients or small series of cases suggesting associations with hepatitis viral infection, but there is no clear-cut demonstration of a possible link.

Regarding urticaria, the association with viral hepatitis was suspected early in the history of virology because urticarial eruptions classically had been described in patients with jaundice. The analysis of the current knowledge accounts for the clinical forms of urticaria—that is, acute urticaria, chronic urticaria, and urticarial vasculitis.

Acute Urticaria and Hepatitis Viruses

Mention of urticaria and fever plus arthritis preceding jaundice was made by Graves as early as 1843 (1). Before the hepatitis viruses were identified, many cases of urticaria preceding the icteric stage of hepatitis were described in the early 1970s. At that time, it was generally agreed that urticaria might occur as a rare event in the pre-icteric phase of hepatitis resulting from viral infection. A link was made between patients who had infectious mononucleosis and then developed urticaria and elevated liver enzymes (2). Such cases were attributed to “viral hepatitis” in general (3) or “serum hepatitis” (4) because the viral cause was suspected but could not be demonstrated. Some of these patients were intravenous drug users (3). A free interval of 4 to 17 d between rash and icterus is generally observed (4). Based on the available descriptions, most of these cases probably resulted from hepatitis B virus (HBV) infection.

In the classic “Caroli’s triad,” urticaria is associated with arthritis and excruciating headache and precedes icteric hepatitis. The description of this triad was made in the early 1930s in the French literature, and these symptoms were rediscovered in the English literature in the 1970s and were attributed to serum-sickness manifestations (5).

Hepatitis A Virus

At the acute phase of hepatitis A virus (HAV) infection, several skin signs were described (6)—mainly in small series of cases or exceptionally after outbreaks of HAV. Urticaria was only rarely noticed, whereas poorly specific maculopapular exanthemas appeared to be more common (7). Although up to 14% of patients with acute hepatitis A can present with skin lesions, less than 2% develop urticaria. In rare single case reports, patients with acute urticaria were shown to have authentic HAV infection (8).

Hepatitis B Virus

After the virus was isolated, cases of patients with urticaria in the prodromic phase of HBV infection were described (9), suggesting that the majority, if not all, of previously published cases probably resulted from the same virus.

Prodromic symptoms are observed in 14 to 42% of patients in the pre-icteric phase of HBV infection, and urticaria is the most common skin sign at this stage (10,11). Urticaria and angioedema could occur in up to 4% of patients (12). In general, acute urticaria associated with HBV infection does not differ from urticaria. Therefore, there is no specific sign to suggest the viral cause, with the exception of one extraordinary case in which icter was preferentially located in the urticarial lesions (13).

A prospective study followed 38 patients and showed that prodromic extrahepatic signs, including urticaria, were not related to the biochemical severity of liver disease (14). Moreover, the description of a small series of 14 patients with arthritis or rash and documented HBV infection confirmed that urticaria also occurs in patients who have no icteric phase of the disease (15). Such symptoms related to serum-sickness-like illness were also described in children with documented HBV infection (16).

Activation of both classic and alternative complement pathways occurs in patients with urticaria and HBV. Hepatitis B surface anti-

gen-antibody complexes were identified in the cryoprecipitate during urticaria, and cutaneous biopsy revealed necrotizing vasculitis (17). Therefore, it is likely that some cases of apparently classic acute urticaria may represent transient urticarial vasculitis. Nevertheless, hepatitis B antigen can also be demonstrated in patients with acute urticaria and no histopathological sign of vasculitis (18).

Another possible cause of acute urticaria related to HBV is vaccination. Urticaria is considered as a possible complication of HBV immunization. Urticaria lasting for 1 d to 3 wk was described in 5 patients 1 to 10 d after immunization for hepatitis B (19). Patch- and prick tests were realized, showing sensitization to the hepatitis B antigen itself, hyperimmunization, or nonallergic reactions.

Hepatitis C Virus

Acute urticaria preceding icteric phase of HCV infection can occur but has only been mentioned infrequently in the literature (20). We observed a case of severe acute urticaria with fever and headache in a patient who had elevated liver enzymes. Seroconversion for HCV antibodies was noted a few weeks after all symptoms spontaneously resolved.

Finally, acute urticaria in the course of hepatitis virus infection does not differ from urticaria occurring in many infections resulting from viruses, such as enterovirus, parvovirus, or Epstein-Barr virus. Therefore, acute urticaria is considered as a classical manifestation of viral infection in general, especially in children (21) but also in adults.

Chronic Urticaria

Hepatitis A

To our knowledge, no systematic study has ever investigated the prevalence of HAV antibodies in chronic urticaria (CU)—that is, urticaria lasting longer than 6 wk. This is not surprising because HAV is responsible for

acute and subacute infection but not for chronic/persistent infection. Moreover, the finding of HAV antibodies associated with CU cannot be considered as a good argument to support a causal role of HAV (22).

Hepatitis B

Regarding HBV, it is logical to believe that a chronic viral infection might be responsible for CU, because HBV was clearly documented as a possible cause of acute urticaria. Nevertheless, evidence is lacking to support this hypothesis. In one study conducted in Boston, 85 patients with CU were investigated (23). In this open, uncontrolled series, markers of HBV infection were found in 17.6% of patients, but only two had positive HBV antigen. Although the prevalence of HBV markers appeared to be higher than in the general population (5%), the absence of age- and sex-matched controls makes this result difficult to interpret. In another open study of 100 patients conducted in France, HBV markers were found in 9% of patients, which was not significantly different from the prevalence in blood donors in the same geographical area (24). Since then, no controlled study has been published and no clear-cut link between CU and chronic HBV infection has been established.

Hepatitis C

More documented data can be found for HCV and CU. In a large prospective study of 321 patients with chronic HCV infection, various cutaneous signs were observed, but no case of urticaria was noticed (25). A single case report showed active HCV infection in a patient with a 5-yr history of urticaria (26). Urticaria persisted even after improvement of viral hepatitis using interferon- α .

HCV markers were also systematically investigated in series of patients with chronic urticaria. In an uncontrolled Japanese study, 15 of 58 patients with urticaria were found to be HCV-positive (27), but the same authors also

published high prevalence of HCV in many other unrelated dermatological diseases. Therefore, these results must be interpreted cautiously, because no other study has shown similar results. In all other series of patients, the prevalence of HCV-positive subjects with chronic urticaria was similar to that observed in the general population: 0 of 50 cases in the United Kingdom (28), 0 of 124 cases in Italy (29), 2 of 173 cases in the southeast of France (30), and 1 of 50 cases in southwest France (31). Moreover, a large, case-control study including 110 patients and 110 age- and sex-matched controls showed a similar prevalence of HCV (0.9%) and hepatitis G infection (1.8%) in both groups, using both enzyme-linked immunosorbent assay and reverse transcriptase-polymerase chain reaction tests (32).

Finally, no convincing argument exists to suggest a causal role of hepatitis viruses in chronic urticaria. In any case, positive enzyme-linked immunosorbent assay, or even positive reverse transcriptase-polymerase chain reaction, is not indicative of a link between the virus and skin signs, although single case reports affirming a causal link without any documented argument are still published (33).

Urticarial Vasculitis

As previously mentioned, both HAV and HBV can be responsible for infraclinical urticarial vasculitis, which occurs in the prodromic phase of both infections. Cutaneous vasculitis can be significantly associated with HAV, HBV, or HCV. Therefore, it is not surprising to find urticarial vasculitis in association with all hepatitis viruses. In HAV infection, rare cases of small vessel vasculitis, including urticarial vasculitis (34), were described, but they usually were short in duration.

Vasculitis is not uncommon in patients chronically infected by HBV, and cases of urticarial vasculitis have occasionally been described, and still others have been associated with cryoglobulinemia.

Rare cases were also mentioned in HCV infection, often in association with cryoglobulinemia (35,36). In certain cases, urticarial vasculitis might be induced by interferon- α therapy for HCV infection (37).

Therefore, because it is a rule for small vessel vasculitis, investigation of HBV and HCV might be recommended in urticarial vasculitis.

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