J Microbiol Immunol Infect.
2008;41:437-439

Case Report

Erythema nodosum and hepatitis B: a case report and literature review

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Received: March 16, 2007 Revised: November 2, 2007 Accepted: November 18, 2007

Erythema nodosum (EN) is the most common of the panniculitides, and is associated with many underlying etiological conditions. Herein, we report a case of EN with probable association with hepatitis B virus (HBV) and review previous reports in the English literature. Since hepatitis B is still an endemic infection in Taiwan, EN related to HBV may not be as uncommon as in developed countries. The incidence and pathogenesis of EN associated with HBV demand further investigation.

Key words: Erythema nodosum; Hepatitis B virus; Panniculitis; Review

Introduction

The panniculitides represent a group of heterogeneous inflammatory diseases that involve subcutaneous fat, of which the most common type is erythema nodosum (EN) [1]. The relative frequencies of the causative diseases of EN are variable among different studies [2-5]. Nonetheless, hepatitis B virus (HBV) is not a common causative agent in any cohort. We report a case of EN with probable association with HBV, and review the English literature on EN associated with HBV.

Case Report

A 37-year-old female HBV carrier presented with multiple painful, coin-sized, erythematous nodules over bilateral thighs and shins intermittently for more than 7 years. The eruption would often resolve slowly in weeks with bruise-like color evolution, and there was no concomitant fever, hair loss, or joint pain. Facial erythema, dryness of eyes and mouth, and oral ulcers had occurred occasionally, but photosensitivity, Raynaud's phenomenon, genital ulcers, and serious inflammation of eyes were never noted. Because of frequent recurrence of the skin lesions, she had undergone skin biopsy a couple of years ago, and EN was diagnosed.

The patient denied any major systemic disease in the past, except a history of HBV infection. She was not taking any medication when she presented at the outpatient clinic. Physical examinations were unremarkable, except for a tender erythematous induration, about 1 cm in diameter, over the medial side of left lower leg. Urinalysis and serial blood tests, including complete blood count/differential count, erythrocyte sedimentation rate, C-reactive protein, antistreptolysin-O, rheumatoid factor, antinuclear antibodies, Sjögren's (anti-SSA/SSB) antibodies, anti-Sm (Smith) antibody, anti-ribonucleoprotein antibody, anticardiolipin antibodies (immunoglobulin G and immunoglobulin M [IgM], respectively), lupus anticoagulant, complement C4, and Venereal Disease Research Laboratory (VDRL) were all negative. The patient also reported negative chest radiogram 1 year earlier in a routine examination. When the patient was seen again 1 month later, the skin lesion left a yellowish brown macule without specific treatment.

Discussion

The panniculitides are a group of heterogeneous inflammatory diseases, and a specific diagnosis relies on

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histopathological findings. All panniculitides are somewhat mixed because the inflammatory infiltrate involves both the septa and lobules, among which the most frequently seen is EN, with predominantly septal inflammation and absence of vasculitis. Most cases of EN appear between the second and fourth decades of life, but can occur at any age. Several studies have demonstrated that EN occurs 3 to 6 times more frequently in women than in men. EN usually consists of a sudden onset of symmetric, tender, erythematous, warm nodules and raised plaques on the knees, shins, and ankles. Often the lesions are bilaterally distributed. In rare instances, more extensive lesions may appear, involving the neck, extensor aspects of arms, thighs, and even the face. At first, the nodules are bright red and slightly raised. Within a few days, they become flat, and turn a livid red or purplish hue. Finally, they exhibit a yellow or greenish appearance, often taking on the look of a deep bruise (erythema contusiformis). Ulceration is never seen in EN, and the nodules heal without atrophy or scarring. The eruption generally lasts for 3 to 6 weeks, but persistence beyond this time is not unusual and recurrences are frequent.

EN is considered to be a hypersensitivity response to many variable inciting factors [1]. Although there are considerable geographic variations related to endemic infections, streptococcal infections are the most frequent etiological factor for EN in children, whereas drugs, sarcoidosis, and inflammatory bowel diseases top the list in adults [1,5]. Streptococcal infection was less likely in our patient because of the protracted course and normal level of antistreptolysin-O. The patient manifested no symptoms and signs of sarcoidosis and inflammatory bowel diseases in the past, and denied any drug intake before each recurrence. Intriguingly, our patient has contracted HBV infection for years. A review of the English literature in *MEDLINE* (Medical Literature Analysis and Retrieval System [MEDLARS] online) database, revealed only a few case reports addressing the association of EN with HBV.

Maggiore et al reported the case of a 6-year-old boy admitted to hospital because of EN and hepatomegaly [6]. The boy had been treated bimonthly from 2 to 5 years of age with intramuscular injections of gamma (γ)-globulins for recurrent respiratory infections. EN, hepatomegaly, and elevated aminotransferase levels were found 2 months prior to this hospitalization. Serological evaluation of HBV serum markers during the hospital stay showed evidence of complete viral replication (hepatitis B surface antigen [HBsAg]-positive, hepatitis B e antigen-positive) with positive circulating immune complexes. He was treated with low-dose corticosteroids, and EN disappeared within 2 weeks without recurrence. It was inferred that repeated injections of γ-globulins probably played an important role in the development of the cutaneous lesions through the formation of immune complexes in the skin.

In a further published case, a 24-year-old medical student [7] received her first dose of hepatitis B vaccine in January 1986 with good tolerance and no complications. Fifteen days after the second vaccine dose in late February, she presented with red, tender nodules on the left pretibial area. EN was diagnosed clinically. The lesions subsequently developed a bruise-like appearance, and disappeared in typical fashion over the next 13 weeks, leaving only some macular hyperpigmentation. The third vaccine dose was administered in early July. Three days later, 2 new nodules appeared, again consistent with EN.

Goolsby [8] reported the case of a 43-year-old woman developing several painful nodules on the anterior tibial portion of each leg 4 days after receiving her first dose of Recombivax HB (a hepatitis B vaccine). A punch biopsy of a lesion on the right leg confirmed the diagnosis. The lesions disappeared gradually over several weeks, while prednisolone was given concurrently for pulmonary interstitial fibrosis. Three weeks after beginning a course of steroids, the patient received her second dose of Recombivax HB. Three days later, EN recurred, and gradually resolved without recurrence.

Rogerson and Nye [9] reported a 31-year-old male afflicted with pain in the metacarpophalangeal and proximal interphalangeal joints of both hands, and painful wrists, hips, elbows, knees, ankles, and sacroiliac joints with swelling, most notably of both ankles, the day after a standard 20 μg dose of Engerix B (a hepatitis B vaccine). He also noted tender, raised, purplish skin lesions with a red margin on the left shin, which lasted a few days and were consistent in appearance with EN. The eruption lasted for 1 week, but the arthritis persisted for 6 weeks. The authors thought that these symptoms were immune complex-mediated, since a serum sickness-like illness due to circulating immune complexes occurred in 10% to 20% of patients with acute hepatitis B infection.

Castresana-Isla and colleagues [10] described a patient who developed EN, hepatic granulomas, and

clinical and arteriographic manifestations of Takayasu's arteritis after inoculation with plasma-derived hepatitis B vaccine. Based on the demonstration of HBsAg in the circulating immune complexes, the authors suggested that HBsAg had triggered a vasculitic process in this patient.

In the series of Cribier et al [5], anti-hepatitis B core antigen IgM and HBsAg were found in a human immunodeficiency virus-positive male patient. In addition, a female patient developed EN 1 month after HBV vaccination, but she had developed a high level of *Chlamydia trachomatis* antibodies. It was difficult to establish a definite link between EN and HBV in both patients.

We had not performed detailed screening tests for our patient, and several other diseases, such as chronic infections by Epstein-Barr virus, cytomegalovirus, *Chlamydia* and *Rickettsia* would need to be ruled out to confirm the diagnosis. It is difficult to tell if the occurrence of EN and HBV infection in our patient are coincidental or related clinically. Review of the literature, however, reveals an association between EN and either infections by or vaccination of HBV, probably through formation of circulating immune complexes. The paucity of case reports may be because HBV infection is relatively uncommon in developed countries. Since HBV remains an endemic infection in Taiwan, and large-scale vaccination has been undertaken for years, the real incidence and pathogenesis of EN in relation to HBV demand further investigation.

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