Immune-mediated pathology following hepatitis B vaccination. Two cases of polyarteritis nodosa and one case of pityriasis rosea-like drug eruption

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ABSTRACT
The association of hepatitis B virus infection and vasculitis or other immune-mediated manifestations is well documented. Reports on such manifestations in relation to hepatitis B vaccination are scarce, however. We report 2 patients who developed polyarteritis nodosa following vaccination against hepatitis B. In one patient this resulted in an ischemic and necrotic digital ulcer, necessitating surgical amputation. The other patient presented with typical cutaneous polyarteritis nodosa which responded well to corticosteroid treatment. A third patient developed a severe pityriasis rosea-like eruption. He was treated with topical steroids with healing of the lesions, leaving only post-inflammatory hyperpigmentation. The literature on these associations is reviewed.

Introduction
The association of hepatitis B virus infection with a broad spectrum of immune mediated clinical manifestations, is well documented (1-3). The occurrence of vasculitis of the small or medium sized vessels (leucocytoclastic vasculitis and polyarteritis nodosa, respectively) illustrates this. Hepatitis B vaccination itself is considered relatively safe on this issue. We report, however, on 2 patients who developed arteritis of medium-sized vessels and 1 patient with major skin eruption of the pityriasis rosea type, following administration of a synthetic hepatitis B vaccine. These complications have rarely or never been reported.

Case reports
RDR is a policeman. He suffered from ventricular fibrillation, probably related to a limited cardiac infarction, at age 41 and was treated with an anti-arrhythmicum for 5 months. At age 45, he received 2 doses of a synthetic hepatitis B vaccin (Engerix-B, Smith Kline-RIT, Genval, Belgium). He was taking no regular medication at that time. Two weeks after the first dose, the patient experienced myalgia, joint pain and morning stiffness. The second dose was administered one month after the first. Following this injection, the patient’s arthralgia and myalgia increased, and he developed an ulcer over the left lower limb. In addition, ischemic lesions appeared over the fingertips: sharply delineated periangual necrosis of the distal phalanx with ulcer formation on the second digit of the right hand, and ischemic discoloration distal to the second and third digits of the left hand.

Blood examination revealed: elevated sedimentation rate (ESR: 31 mm/hr) and C-reactive protein (CRP: 2.3 mg%); normal peripheral blood count; normal renal parameters, liver tests and muscle enzymes; normal complement dosage; normal urinalysis (except for limited proteinuria); absence of cryoglobulins; positive direct Coombs test; positive ANCA fluorescence (confirmed by positive anti-proteinase-3 ELISA); serohesitent rheumatoid factors (Waaaler-Rose test negative, latex-fixation test weakly positive); antinuclear factor weakly positive (anti-DNA and anti-ENA antibodies absent); and slightly raised concentrations of immune complexes. Hepatitis B serology was negative for HBsAg and remained negative for anti-HBs and anti-HBc antibodies.

Arteriographic catheterisation of the left and right artery humeralis revealed a filiform aspect of the second and third arteria digitales palmaris of the left hand. The arteria digitales palmaris proprii of the right hand were absent over the ulnar site of the fifth digit, the radialis site of the second digit, and the ulnar site of the second digit (left hand) (Fig. 1). Some other arterial branches showed an irregular aspect with absent distal filling. The overall arteriographic appearance was compatible with vasculitis. Skin biopsy in the immediate vicinity of the left lower limb ulcer revealed granulation tissue composed of proliferating vessels and fibroblasts together with inflammatory cells. Underneath the granulation tissue a medium-sized vessel presented a concentric fibrosis of the muscle wall accompanied by infiltrating inflammatory cells. The diagnosis of PAN was put forward and the patient was treated with high dose corticosteroids. This resulted in the healing of the lesions on the left hand.
and the lower limb ulcer. However, the distal phalangeal lesion of the right hand did not improve, requiring surgical amputation 7 months after its initial presentation. Corticotherapy was tapered over one year.

IVB is a 35-year-old nurse, without a significant medical history. In view of her professional risk for hepatitis B, she received a successful primo-vaccination with a synthetic hepatitis B vaccine (Engerix-B) at age 30. A booster dose was administered 5 years later. Two weeks after she received the booster dose, she experienced a febrile period (maximum documented temperature 38°C) with myalgia and coughing without expectorations. These symptoms disappeared spontaneously, but then recurred 2 weeks later. The patient presented with a third relapse of symptoms, again after a 2-week interval. This time there was a concomitant skin rash over the lower limbs together with nodular infiltrates. She also complained of mild dyspnoea. Her body temperature was elevated (38°C). A further general physical and specialised lung and renal examinations revealed no abnormalities. Routine blood examination revealed: ESR 21 mm/hr; CRP 0.14 mg%; normal peripheral blood count; normal renal and liver parameters; normal urinalysis; and negative autoantibody tests for rheumatoid factors, antinuclear factor, anticardiolipin antibodies, and ANCA. Her hepatitis serology was as follows: HBs Ag and HBe Ag negative; anti-HBs antibodies strongly positive; anti-HBc and anti-HBe negative. A lesional skin biopsy (Fig. 2) revealed no abnormalities in the epidermis and upper and mid-dermis. At the interface between the dermis and subcutis a medium-sized blood vessel showed extensive changes: complete destruction of the vessel wall by fibrinoid necrosis, heavy infiltration by neutrophils, extensive karyorrhexis, and some extravasation of the red blood cells. In the vicinity of the altered blood vessel, an interstitial infiltrate of lymphocytes, histiocytes, neutrophils and eosinophils was present. There were no signs of leucocytoclastic vasculitis.

A diagnosis of polyarteritis nodosa (cutaneous presentation) was made. Corticosteroid therapy was begun (methylprednisolone 48 mg per day) and tapered slowly, with gradual relief of the symptoms.

CP is a 38-years old paramedic, without a significant medical history. In view of his professional risk he received 5 doses of synthetic hepatitis B vaccine (Engerix B) (9/2/1995, 16/3/1995, 27/4/1995, 28/2/1996 and 18/4/1996). The patient remembered a slight rash after the fifth dose. The rash disappeared spontaneously after several days. Because of his non-responder status, the patient received a booster injection one year after the 5th vaccination (19/3/1997). Two days later he once again developed an itchy rash, starting on the trunk and extending to the extremities. Concomitantly there was fatigue, sensation of burning eyes, and rhinorrhea. Inspection

**Figure 1.** Patient RDR. The arteriographic appearance is compatible with vasculitis.

**Figure 2.** Patient IVB. Lesional skin biopsy of a nodular lesion over the lower limbs. The vessel wall of a medium-sized artery shows typical vasculitic changes with fibrinoid necrosis, infiltration by neutrophils and karyorrhexis.
of the skin 7 days after the 6th injection showed symmetrical erythematous and papulovesicular eruptions on the trunk, arms and thighs with accentuation in the inguinal region and centrifugal extension. There was no fever, adenopathy or organomegaly. Blood and urine analyses revealed no abnormalities. A skin biopsy of a papulovesicular lesion was taken; on histology (Fig. 3) the epidermis was found to be covered with a parakeratotic corneal layer with aggregations of pycnotic nuclei of neutrophils, eosinophils and lymphocytes. The granular layer was absent. The malpighian layer showed spongiosis with exocytosis of lymphocytes. Perivascular lymphocytic and eosinophilic infiltrates were present in the papillary dermis. The middle and deep dermis showed no abnormalities. A diagnosis of papulovesicular dermatitis was made. Direct immunofluorescence was negative.

Symptomatic treatment (tumenol lotion and oral antihistamines) was started. On a follow-up visit 7 days later, the eruption had intensified and expanded to the face and scalp. Multiple erythematousquamous patches with a peripheral collarette of scale were present (“medallions”). The diagnosis of a pityriasis rosea-like drug eruption was made (Fig. 4). Treatment with topical steroids was started and the lesions disappeared within a few days, leaving only post-inflammatory hyperpigmentation. Patch tests were performed and were positive for phenylmercuric borate (48 hr and 96 hr) and mercurochrome (96 hr). Thiomersal remained negative.

Discussion

Hepatitis B vaccination and PAN

The diagnosis of PAN in patients RDR and IVB was well established, and both patients fulfilled the 1990 ACR classification criteria for PAN (4). In patient RDR there were ischemic skin lesions (leg ulcer, periungual infarctions) with ultimately severe digital necrosis, reflecting a vasculopathy of the medium-sized arteries. Hepatitis antibodies remained negative in this patient. One may question whether these antibodies were hidden amid the immune complexes, which were present in elevated concentrations. The myalgia, arthralgia and periodic attacks of synovitis fit best in the general context of PAN. The occurrence of anti-proteinase 3 after vaccination is highly unusual; anti-proteinase 3 antibodies or c-ANCA can, however, be found in 10% of patients diagnosed with PAN (5). Patient IVB presented with constitutional symptoms and specific skin lesions over the lower limbs. Lesional histopathology showed necrotic inflammatory changes of the medium-sized skin vessels, pathognomonic for PAN. Interestingly, the small vessels were spared and there were no signs of associated leucocytoclastic vasculitis. This type of pathology is more suggestive of the isolated cutaneous type of PAN (6). Hepatitis B serology was clearly positive in this patient.

The relationship between hepatitis B virus infection and PAN is well established (1-3). The clinical expression of hepatitis B viral infections is heterogeneous. The basis for this heterogeneity and in particular the factors that determine the occurrence of arteritis remain unknown. In view of the fact that the complete hepatitis B virus may induce an immune pathology, including vasculitis, induction of such complications by immunization with specific hepatitis B-related antigens should not be totally unexpected. However, case reports on such
CASE REPORT

associations are rare. Le Goff et al. (7) reported a 34-year-old female patient who received 3 hepatitis B vaccin doses. Six months after the first administration, she developed a rheumatoid factor seronegative polyarthritis, which was treated with low dose prednisone and gold salts. Eighteen months after the first dose, a mononeuritis appeared. On histopathological grounds (muscle and nerve), PAN was diagnosed. Allen et al. (8) described the history of a 45-year-old patient who developed a rash over the limbs, the face and the chest 2 weeks after a first hepatitis B vaccin dose. Concomitantly, she developed polyarthralgia over the hands, wrists, elbows and feet and breathlessness on minimal exertion. Periungual infiltrations were present. Chest X-ray revealed bilateral basal infiltrates. Skin biopsy showed perivascular lymphocytic infiltrations. Prednisolone therapy was begun and then tapered over a 2-month period, with a good clinical outcome. Occlusion of the vena centralis retinæ following hepatitis B vaccination has also been reported (9, 10). More recently, Vanoli et al. (11) described a case of Churg-Strauss vasculitis. However, the time elapsed between the vaccination and the development of vasculitis made it difficult to identify the vaccination as the causative agent. In a recent report, Le Hello describes the phenomenon of CNS vasculitis in a 19-year-old, previously healthy woman one week after her 3rd vaccination. She experienced arthralgias, left side hemihypesthesia, and unstable gait. Magnetic resonance imaging of the brain revealed many right occipital, lenticular, and thalamic signals. Cerebral angiographic studies showed narrowing of several cerebral arteries. She reported no reaction to the first inoculation, but had transient weakness of the left leg 3 months after the second immunization (12).

The first 2 patient histories reported in the present manuscript add to the current literature on hepatitis B vaccine-related vasculitis. The immune mechanisms underlying this association are not well established. One may postulate that the HBs antigen behaves like a classical heterologous protein and induces the formation of immune complexes. As in acute serum sickness, these immune complexes may then mediate the pathology. 

Hepatitis B vaccination and pityriasis rosea-like drug eruption
Cutaneous side effects of a vaccination for hepatitis B are not rare. Reports have been published on erythema exsudativum multiforme (EEM) (13-16), lichen planus (17-22), pityriasis lichenoides et varioliformis acuta (23), lupus erythematosus (24), nodular reactions (25) and anotaderma (26) after vaccination for hepatitis B. The literature does not include any mention of a pityriasis rosea-like drug reaction as a side effect of vaccination for hepatitis B. However, the association of pityriasis rosea with systemic drug intake has been reported before. More particularly, gold compounds cannot be excluded. The responsible mechanism is not known. Because the pityriasis rosea appears shortly after drug intake (2-3 days), it is unlikely that immune complex formation is involved. The Engerix vaccine contains thiomersal, aluminiumhydroxychloride and the hepatitis B antigen (S protein). We tested whether our patient CP was allergic to any of these components. Patch tests (standard and pharmaceutical Belgian Contact and Environmental Dermatitis series) revealed a contact allergy for pheynmercuric borate and mercurochrome, but not for thiomersal. The former two molecules are of an organic mercurial nature and a type IV exzematous reaction due to a cross-reaction with the tested compounds cannot be excluded. The appearance of the rash 48 to 72 hours after injection of the vaccine is also consistent with the hypothesis of a contact allergic phenomenon. In a second hypothesis, the viral antigen itself would be responsible for the pityriasis rosea-like drug eruption. In this respect it is interesting that recent data incriminate Herpes virus type VII in the etiology of pityriasis rosea (38).

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