

## Spontaneous and antiviral-induced cutaneous lesions in chronic hepatitis B virus infection

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### Abstract

**AIM:** To describe spontaneous, or interferon (IFN)- or immunization-induced skin lesions in hepatitis B virus (HBV) infection.

**METHODS:** A comprehensive literature search of all the papers presenting case reports of dermatological lesions in patients with chronic HBV infection was carried out. We included only patients with histologically proven skin lesions that appeared in the normal course of hepatitis B infection, or after immunization for hepatitis B or antiviral treatment.

**RESULTS:** We found 44 papers on this topic, reporting 151 cases. About 2% of patients with hepatitis B infection, mainly men, presented with skin lesions. Among patients with chronic hepatitis B, vasculitis and essential mixed cryoglobulinemia seemed to be the most frequent skin lesion (53.3%), followed by papular changes, rashes and Gianotti-Crosti syndrome, skin carcinoma and Henoch-Schönlein purpura were rare. IFN treatment seemed to be effective against HBV-associated and immunoglobulin-complex-mediated disease (vasculitis). Two cutaneous lesions (lichen planus and

granuloma annulare) were described after hepatitis B vaccination. Systemic lupus and lupus-like lesions were the most frequently encountered lesions after antiviral treatment. Immunosuppressive and steroid therapy ameliorates lichen planus lesions in 50% of cases.

**CONCLUSION:** Vasculitis was the most frequent spontaneous skin lesion found in chronic hepatitis B. Lichen planus was most frequent after immunization and lupus/lupus-like lesions after IFN.

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**Key words:** Hepatitis B; Skin diseases; Adverse effects; Immunization

**Core tip:** Chronic hepatitis B is a common infection with various etiologies, including the involvement of several systems. We investigated the skin lesions of patients with chronic or acute hepatitis B. We also looked for skin lesions related to vaccination and antiviral therapy. Most common lesions in chronic hepatitis B virus infection encountered in a comprehensive literature search are: 41% essential mixed cryoglobulinemia and 15.3% vasculitis; 10.5% (lichen planus-like lesions) respectively 7.2% of all lesions included in the review were associated with immunization (lichen planus) and antiviral therapy (lupus-like lesions).

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### INTRODUCTION

Skin lesions represent one of the extrahepatic manifesta-

tions in hepatitis B virus (HBV) infection. The aim of the present review was to describe the cutaneous manifestations in HBV infection that can appear either spontaneously or after antiviral therapy or even after hepatitis B vaccination and to review their pathogenesis.

## MATERIALS AND METHODS

A systematic literature search of electronic databases, including PubMed, EBSCO, ISI Thomson, was performed (1976 to February 2014) for all studies assessing skin lesions in HBV infection or after hepatitis B vaccination/antiviral therapy. The search strategy included text terms and MeSH headings for skin lesions and HBV infection: “Skin lesions induced by HBV”, “Skin lesions in viral hepatitis B”, “Cutaneous lesions in viral hepatitis B”, “Cutaneous lesions after interferon (IFN)”. The “related articles” function in PubMed was also used to identify articles not found in the original search.

### Inclusion criteria

The inclusion criteria used were: full journal publication, abstracts of articles, including patients with skin lesions after hepatitis B vaccination, antiviral therapy or during the normal course of the disease. Papers in English, German and French were included in the study, or in any language but with an English abstract.

### Exclusion criteria

Studies were excluded if they did not meet the inclusion criteria; these were abstracts/articles containing general literature data about extrahepatic manifestations in hepatitis B without any case report or abstracts without mentioning the exact type of skin lesion.

### Types of participants

We included only patients with histologically proven skin lesions that appeared in the normal course of hepatitis B infection, after immunization for hepatitis B, or after antiviral treatment. The titles and abstracts of all identified studies were reviewed by two independent authors (DDL, GI) according to the MOOSE criteria.

## RESULTS

The first search resulted in a total of 44 articles. After reviewing the abstracts, 35 studies addressed the description of skin lesions in hepatitis B and 31 met our inclusion criteria. Included articles were published between 1976 and February 2014 and reported a total of 151 patients. The four excluded articles did not mention the exact name of each type of skin lesion.

Regarding the incidence of the lesions in patients with acute or chronic HBV infection, 94.3% (117/124) of the patients had chronic infection, without exact data about genotype or gender predominance, only 5.6% (7/124) had acute infection; 10.5% (16/151) from all persons included in the review were related to vaccination and 7.2%

(11/151) to antiviral treatment.

### Skin involvement in chronic HBV

Among the 17 articles including 117 cases (Table 1) found with skin lesions that appeared in patients with chronic hepatitis B infection, essential mixed cryoglobulinemia (EMC;  $n = 48$ ) and vasculitis were the most frequent ones ( $n = 18$ ), followed by papular changes ( $n = 13$ ) and purpuric and maculopapular rash ( $n = 11$ ). Skin carcinoma and Henoch-Schönlein purpura were reported as singular cases and Gianotti-Crosti syndrome was described in a single article.

Vasculitis was reported by three authors in 18 cases, all who were already known to have chronic HBV infection<sup>[1-3]</sup>. Significant skin changes after histamine intradermal injection were detected only in hypersensitivity vasculitis, even in the absence of cutaneous vasculitis, and other forms were of nonpalpable purpura with acute-onset distal symmetric sensorimotor polyneuropathy, and painful petechia rash on both lower legs and the inner surface of the thighs. Administration of intravenous immunoglobulin with entecavir, prednisolone in addition to the entecavir,  $\alpha$ -IFN improved these types of lesions. An intradermal histamine provocation test proved to be a simple, noninvasive method for diagnosing hypersensitivity vasculitis<sup>[3]</sup>.

There were also 48 patients described with HBV-related EMC syndrome among the category of systemic vasculitis of the small/medium size vessels by 11 authors; 10/48 (20.8%) of them appeared in a group of North African Jewish women with Raynaud syndrome<sup>[4]</sup>; one in a patient with recurrent purpura<sup>[5]</sup>; one in a quiescent HBV carrier<sup>[6]</sup>; one in a woman with precore/core HBV mutant unable to synthesize hepatitis B e antigen (HbeAg)<sup>[7]</sup>; and one case referred to a 12-year-old boy presenting with pseudoleukocytosis<sup>[8]</sup>. Galli *et al*<sup>[9]</sup> reported a large number of EMC patients, but no data regarding the exact number of the HBV-associated EMC patients was given by the Italian Study Group on Cryoglobulinemia.

Van Voorst Vader *et al*<sup>[10]</sup> cited a case of epidermodysplasia verruciformis and multiple skin cancers in a patient with viral B cirrhosis.

Henoch-Schönlein purpura was observed only in one patient: a 32-year-old man with recurrent purpura in association with chronic hepatitis B infection of 10 years duration. The skin lesions disappeared after antiviral treatment (lamivudine and IFN- $\alpha$ ) and reappeared after the end of treatment<sup>[11]</sup>.

Infantile papular acrodermatitis (Gianotti-Crosti syndrome) was described by Ishimaru *et al*<sup>[12]</sup> in the context of the epidemic in 1974-1975 in 48 patients from Southeast Japan; 42 of them having the genotype *ayw* (genotype D), and three the *adr* type, with the impossibility of determination in the rest of the patients.

### Skin involvement in acute HBV

In three articles, skin lesions related to acute hepatitis B infection (Table 2) were single cases of urticaria, perior-

**Table 1 Articles including skin lesions in chronic hepatitis B**

Ref.	Year	No. of patients	Skin lesion
Ergin <i>et al</i> <sup>[11]</sup>	2005	1	Henoch-Schönlein purpura
Glück <i>et al</i> <sup>[2]</sup>	1994	1	Vasculitis
van Voorst Vader <i>et al</i> <sup>[10]</sup>	1986	1	Epidermodysplasia Verruciformis, skin carcinoma
Weiss <i>et al</i> <sup>[45]</sup>	1978	1	Erythematous maculopapular and purpuric rashes
Chossegros <i>et al</i> <sup>[3]</sup>	1987	16	Hypersensitivity vasculitis
Popp <i>et al</i> <sup>[26]</sup>	1981	1	10 rashes, 1 lichenoid lesion
Levo <i>et al</i> <sup>[30]</sup>	1977	25	EMC
Horowitz <i>et al</i> <sup>[4]</sup>	1986	10	EMC
Löhr <i>et al</i> <sup>[7]</sup>	1994	1	EMC
La Civita <i>et al</i> <sup>[5]</sup>	1996	1	EMC
Yamazaki <i>et al</i> <sup>[6]</sup>	2014	1	EMC
Yadav <i>et al</i> <sup>[8]</sup>	2011	1	EMC
Garcia-Bragado <i>et al</i> <sup>[46]</sup>	1981	6	EMC
Cupella <i>et al</i> <sup>[47]</sup>	1985	1	EMC
Pasquet <i>et al</i> <sup>[31]</sup>	2012	1	EMC
Bouhsain <i>et al</i> <sup>[48]</sup>	2007	1	EMC
Ishimaru <i>et al</i> <sup>[12]</sup>	1976	48	Gianotti-Crosti syndrome

EMC: Essential mixed cryoglobulinemia.

bital edema, vascular polyneuropathy, lichenoid reaction and four cases of rashes.

**Skin involvement after hepatitis B immunization**

We found 16 patients in the eight articles (Table 3) related to hepatitis B vaccination. Cutaneous changes associated with hepatitis B immunization were predominantly represented by lichen planus and lichen-planus-like lesions (*n* = 14), and only rare cases of granuloma annulare and polyarteritis nodosa (PAN) were described.

Lichen planus and lichenoid lesions (*n* = 14) were found predominantly in male patients, with ages between 11 and 19 years, and four of them were described in black people. They were located over the upper and lower extremities, upper trunk, neck, thighs, and abdomen, and followed Blaschko’s lines in two cases<sup>[13]</sup>. They appeared as itchy violaceous papules and plaques, widespread pruritic erythematous eruption, and in one case evolved to produce strikingly blue macules before spontaneously disappearing. The immunization-associated lichenoid lesions appeared 8-10 d after the first injection, and also after the booster doses. Half of the cases were treated successfully with oral retinoids or corticosteroids<sup>[14,15]</sup>.

Granuloma annulare was described as papular and patch lesions in a 51-year-old white woman 2 mo after the second dose of hepatitis B vaccine<sup>[16]</sup>. In another report it appeared in a 40-year-old woman as disseminated, non-pruriginous eruption with small, orange/flesh colored, non-annular papules on the upper extremities, then on the trunk and the lower extremities, 1 mo after the last

**Table 2 Articles including skin lesions in acute hepatitis B**

Ref.	Year	No. of patients	Skin lesion
Mehndiratta <i>et al</i> <sup>[1]</sup>	2013	1	Vasculitic polyneuropathy
van Aalsburg <i>et al</i> <sup>[35]</sup>	2011	1	Urticaria and periorbital edema
Popp <i>et al</i> <sup>[26]</sup>	1981	5	10 rashes, 1 lichenoid lesion

**Table 3 Articles including skin lesions after hepatitis B immunization**

Ref.	Year	No. of patients	Skin lesion
Mérigou <i>et al</i> <sup>[13]</sup>	1998	8	Lichen planus
Saywell <i>et al</i> <sup>[14]</sup>	1997	1	Lichenoid reaction
Criado <i>et al</i> <sup>[15]</sup>	2004	2	Lichen planus, granuloma annulare
Wolf <i>et al</i> <sup>[16]</sup>	1998	1	Generalized granuloma annulare
Agrawal <i>et al</i> <sup>[49]</sup>	2004	1	Lichen planus
Ventura <i>et al</i> <sup>[17]</sup>	2009	1	Polyarteritis nodosa
Al-Khenaizan <i>et al</i> <sup>[50]</sup>	2001	1	Lichen planus
Usman <i>et al</i> <sup>[51]</sup>	2001	1	lichen planus

booster, and 3 wk after the 5-year booster of GenHevac B Pasteur<sup>[15]</sup>. Treatment with dapsone 50-100 mg/d led to complete regression of the lesions within 4 mo.

Cutaneous PAN (CPAN) and microscopic polyangiitis were described 1 wk after injection of the third dose of hepatitis B vaccine in an 11-year-old boy with a 3-mo history of extensive livedo reticularis mainly affecting the lower extremities, abdomen and upper extremities; prednisolone (1 mg/kg per day) and azathioprine reduced the skin lesions after 6 wk of treatment.

Livedo reticularis of the extremities and abdomen, and absence of any cutaneous nodule, was the only skin manifestation in an 11-year-old boy in the PAN type of skin changes<sup>[17]</sup>.

**Skin involvement in HBV after IFN therapy**

Since 1998 only three authors have described cutaneous changes related to IFN administration for HBV infection in 11 patients (Table 4). Lupus and lupus-like lesions together with alopecia were the most frequent skin lesions described after IFN treatment in hepatitis B. Bullous pemphigoid was described in only one article.

Lupus and lupus-like lesions were the skin lesions detected after 8 mo administration of pegylated (Peg)-IFN- $\alpha$ 2b (160  $\mu$ g/wk)<sup>[18]</sup> and in another study we could not establish the exact time and type of antiviral medication<sup>[19]</sup>. In both cases, lupus-like reactions occurring during IFN therapy were reversible after treatment withdrawal.

Bullous pemphigoid was described in a 12-year-old Turkish Caucasian girl 1 wk after HBV immunization (Gen-Hevac) as a generalized itchy blistering skin lesion (vesicles and tense hemorrhagic/purulent bullae and urticarial/annular plaques) starting at the vulval and perianal region, and then with widespread changes on almost

**Table 4** Articles including skin lesions due to antiviral treatment

Ref.	Year	No. of patients	Skin lesion	Type of IFN
Yilmaz <i>et al</i> <sup>[18]</sup>	2009	1	Lupus	Peg-IFN- $\alpha$ -2b
Kartal <i>et al</i> <sup>[44]</sup>	2007	9	Skin lesions (4), alopecia (9)	IFN- $\alpha$ -2a
García-Porrúa <i>et al</i> <sup>[19]</sup>	1998	1	Lupus-like	IFN- $\alpha$

Peg IFN: Pegylated interferon.

the whole body (except palms, soles and mucous membranes), associated with important weight loss<sup>[20]</sup>. She had a good response to 2 mo combination therapy with systemic prednisone and azathioprine, and the lesions gradually decreased within 6 mo; no scars or side effects were noticed.

## DISCUSSION

The present review identified articles, most of them being case reports, on skin lesions in HBV during natural evolution of after preventing or therapeutic interventions. The strength of all the articles included in this review was the histological proof of every specific lesion. Study limitations comprised the low number of patients involved in each study, and the language of some articles, which prevented access. Only 9% of the retrieved papers were not included in this review, thus the missing information should not have caused any distortion of our results. The main reason for excluding articles was the absence of the exact name of each type of skin lesion. Another limitation was the impossibility of establishing an incidence rate of skin lesions in hepatitis B, or after antiviral therapy or hepatitis B vaccination, due to the low number of patients in all the included articles.

The percentage of patients who developed skin lesions, from all patients with hepatitis B infection, was approximately 2%, with a predominance of men (72.3%), as reported by the FDA<sup>[21]</sup>. The exact prevalence of skin lesions among all the patients with HBV infection or those receiving HBV vaccination could not be established. We did not find any comparative study with hepatitis C patients regarding the cutaneous changes, as in autoimmune thyroid disease, where hepatitis C patients are more susceptible than those with hepatitis B<sup>[22]</sup>. Although some authors noticed a correlation between HBe antibody positivity, or an elevated platelet count and the incidence of extrahepatic clinical and biological manifestations in chronic hepatitis B patients<sup>[23]</sup>, we could not find any significant association with such parameters.

The exact mechanisms responsible for the development of different skin lesions is not known. There was no association between HBV conditions (HBeAg/Ab, serum levels of HBV DNA), HLA haplotype, or race, that would explain predisposition to development of specific skin changes. Nor was any correlation found between chronic infection and HBV genotype, similar

to other data from the literature<sup>[23]</sup>, except the association of the Gianotti-Crosti syndrome and the D genotype<sup>[12,24]</sup>. From the pathogenetic point of view, it is believed that disorders of primarily immunocomplex genesis generate skin vasculitis, Raynaud's syndrome, nodular periarteritis, and mixed cryoglobulinemia<sup>[25]</sup>. Cutaneous lesions associated with liver disease may result from immune-complex-mediated vascular injury, proven histologically by vascular deposits of immunoglobulins, complement, and fibrin in the skin, as well as hypocomplementemia, circulating immune complexes, and mixed cryoglobulinemia<sup>[26]</sup>. Vaccination against hepatitis B has been associated with various complications including the occurrence or worsening of immunologically mediated diseases such as vasculitis, myasthenia gravis, multiple sclerosis and systemic lupus. Several lesions in chronic HBV infection are related to immune complex deposition, rashes with neutrophil infiltration that leads to small vessel necrosis. Regarding bullous pemphigoid, hepatitis B surface antigen (HBsAg) seems to have a trigger function for inducing nonspecific immune reactivation or by stimulating specific antibody production that may crossreact with BP antigens<sup>[27]</sup>. Type II (monoclonal IgM and polyclonal IgG) and type III (polyclonal IgM and monoclonal IgG) cryoglobulins are found in patients with chronic HBV infection.

The case described by Chossegros *et al*<sup>[3]</sup> and the published reports about hypersensitivity vasculitis indicate that IFN treatment is effective against HBV-associated and immunoglobulin-complex-mediated disease. Blood vessels of the superficial dermis with HBsAg, complement components C1q and C3, transient urticarial skin lesions, and periorbital edema were demonstrated in three patients with the pre-icteric phase of acute hepatitis B<sup>[28,29]</sup>. The case of epidermodysplasia verruciformis and multiple skin cancers in a patient with hepatitis B cirrhosis emphasizes the importance of immune surveillance in the protection against virus-associated tumors, because human papillomavirus type 5 was detected by skin histology<sup>[10]</sup>. Henoch-Schölein purpura may be considered a rare cutaneous complication in hepatitis B, but this infection should always be suspected when diagnosing purpura. HBV infection seems to be involved in the appearance of EMC, therefore, Levo *et al*<sup>[30]</sup> suggest that the term essential mixed cryoglobulinemia should be replaced by "mixed cryoglobulinemia secondary to HBV". On the contrary, the greater prevalence of HBsAg found in cryoglobulinemia secondary to chronic liver disease compared with that found in EMC led to the conclusion that there was no association between HBV and EMC<sup>[9]</sup>. Antiviral treatment (with IFN- $\alpha$  2b3 MIU three times weekly) led to negative serum cryoglobulins, even in the presence of HBe-negative HBV mutants<sup>[7]</sup>, even if sometimes this led to concomitant worsening of neuropathy, which might be an indication of treatment discontinuity<sup>[5]</sup>. Entecavir and plasmapheresis<sup>[6]</sup>, and even rituximab along with entecavir<sup>[31]</sup>, may have a beneficial effect in treating EMC, although systemic corticoid therapy might be added. Suspicion of cryoglobulinemia should be raised any time

patients have leukocytosis and thrombocytosis unsubstantiated by examination of a peripheral blood film and manual count<sup>[8]</sup>. Although the pathogenesis of EMC in patients with HBV remains unclear, similar processes to those proposed in cases of hepatitis C, such as positive selection of B cells releasing monoclonal cryoglobulins and B-cell populations producing polyclonal cryoglobulins, may be involved<sup>[32]</sup>.

HBsAg can function as the triggering factor for bullous pemphigoid by inducing a nonspecific immune reactivation or by stimulating a specific antibody production that may crossreact with bullous pemphigoid antigens<sup>[20]</sup>. Baykal *et al*<sup>[27]</sup> explains vaccination as a triggering factor of bullous pemphigoid of any age by stimulating the immune system with an unexplained mechanism.

The first case of lichen planus occurring after hepatitis B vaccine was reported in 1990<sup>[33]</sup>. Chronic graft *vs* host-like autoimmune reaction has been suggested as possible pathogenetic mechanism. It occurs irrespective of the type of vaccine used and might appear a few days to 3 mo after any of the three doses<sup>[34]</sup>. Predominance of lichen planus in children with pigmented skin suggested a genetic predisposition. The eruption following Blaschko's lines suggests that a clonal keratinocytic population is the target of lichenoid inflammation. HBV immunization could be a stimulus triggering a cytotoxic lymphocyte-mediated reaction. In Nepal, HBV and hepatitis C virus do not seem to be important in the pathogenesis of lichen planus<sup>[35]</sup>. Generalized granuloma annulare affects older patients with a more chronic course, which is resistant to treatment, and an association with diabetes mellitus in 21% of cases<sup>[16]</sup>. Its pathogenesis and etiology are still not well understood: autoimmune response originating from a delayed hypersensitivity reaction against the similarity to an antigen of the skin, mediated by T lymphocytes<sup>[36]</sup>; an immune-mediated type III reaction<sup>[37]</sup>. The literature describes observations of generalized granuloma annulare in predisposed subjects after BCG vaccination<sup>[38]</sup>. Relapse after the 5-year booster injection makes hepatitis B vaccination involvement credible. CPAN and microscopic polyangiitis are two distinct additional categories of PAN<sup>[24]</sup>, which are characterized by necrotizing inflammatory changes in small and medium-sized arteries<sup>[39,40]</sup>, and were first reported in a child by Ventura *et al*<sup>[17]</sup>. The absence of systemic involvement and the benign, but chronic and relapsing course characterize classical PAN<sup>[41]</sup>. Bourgeais *et al*<sup>[42]</sup> explains its pathophysiological mechanism as being related to vascular deposits of excess circulating immune complexes of antigens. High HBV replication and HBe antigenemia were seen in almost all cases of PAN associated with wild-type HBV infection, suggesting that lesions could result from the deposit of viral Ag/Ab complexes soluble in Ag excess, possibly involving HBeAg. Traditional immunosuppressive and steroid therapy should no longer be used for HBV PAN cases, as the efficacy of antiviral agents and plasma exchanges was proven in HBV-associated PAN<sup>[43]</sup>.

Regarding the skin lesions connected to IFN treat-

ment, Kartal *et al*<sup>[44]</sup> found that 8% of patients who were treated with  $\alpha$ -2a IFN treatment had this type of complication. Among the treated patients, lupus and lupus-like lesions seemed to be the most frequent skin lesions encountered in  $\alpha$ -2b Peg-IFN administration<sup>[18]</sup>.

Vasculitis was the most frequent skin lesion found in chronic hepatitis B infection, due to immunological reactions. The most common dermatological adverse reactions caused by IFN administration were lupus/lupus-like lesions. The most frequent skin disease caused by hepatitis B immunization was lichen planus.

## COMMENTS

### Background

Chronic hepatitis B is a common infection with various etiologies, including the involvement of several systems. Skin lesions represent one of the extrahepatic manifestations in hepatitis B virus (HBV) infection. The authors aimed to describe systematically these cutaneous manifestations in HBV infection, but also those that can appear after antiviral therapy or even after hepatitis B vaccination, and to review their pathogenesis.

### Research frontiers

Around 2% of patients with hepatitis B developed skin lesions, with a predominance of men (72.3%). The exact prevalence of skin lesions among patients with HBV infection or people receiving HBV vaccination could not be established. There was no comparative study of hepatitis C patients regarding cutaneous changes, as in autoimmune thyroid disease, where hepatitis C patients are more susceptible than those with HBV.

### Innovations and breakthroughs

Vasculitis was the most frequent skin lesion in chronic hepatitis B infection, due to immunological reactions. The most common dermatological adverse reactions after interferon (IFN) administration were lupus/lupus-like lesions. The most frequent skin disease caused by hepatitis B immunization was lichen planus.

### Applications

Patients with vasculitis should always undergo screening for chronic hepatitis infection. Further data, implying genetic analysis, are needed to detect special susceptibility of patients for developing skin reactions after immunization or antiviral treatment. New correlations between different parameters (hepatitis B e antigen/antibody, serum levels of HBV DNA) could establish the patient's risk of developing skin reactions due to antiviral treatment or HBV immunization.

### Terminology

Vasculitis is a group of disorders that involve inflammation of arteries and veins, leading to their destruction. Lupus-like reactions are drug-induced lupus erythematosus and include an autoimmune response caused by chronic medication (IFN in their case) producing symptoms similar to those of systemic lupus. Lichen planus is a disease of the skin and/or mucous membranes that resembles lichen, with a possible autoimmune cause, but unknown initial trigger. Purpura is the appearance of red/purple discolorations measuring 0.3-1 cm on the skin that do not blanch on applying pressure and are caused by bleeding underneath the skin usually secondary to vasculitis or dietary deficiency of vitamin C. Cryoglobulinemia is a medical condition that is caused by proteins called cryoglobulins, which are present in the blood. When the cryoglobulin proteins are a mixture of various antibody types, and forming for unknown reasons (essential), the condition is referred to as essential mixed cryoglobulinemia. It is characterized by joint pains and swelling (arthritis), enlargement of the spleen, skin vasculitis with purplish patches, and nerve and kidney disease.

### Peer review

The manuscript is an interesting review of literature regarding skin lesions related to HBV infection. It represents the first review addressing this aspect, thus it could be useful from a clinical perspective. The review is well structured. The search strategy and the selection criteria of papers included in the analysis are right. They also discuss the mechanism of the described skin lesions. The data are interesting and important in the management of patients with HBV infection and subjects who received HBV vaccination.

## REFERENCES

- 1 **Mehendiratta M**, Pandey S, Nayak R, Saran RK. Acute onset distal symmetrical vasculitic polyneuropathy associated with acute hepatitis B. *J Clin Neurosci* 2013; **20**: 331-332 [PMID: 23164826 DOI: 10.1016/j.jocn.2012.03.029]
- 2 **Glück T**, Weber P, Wiedmann KH. [Hepatitis-B-associated vasculitis. Clinical course with glucocorticoid and alpha-interferon therapy]. *Dtsch Med Wochenschr* 1994; **119**: 1388-1392 [PMID: 7924948 DOI: 10.1055/s-2008-1058850]
- 3 **Chossegros P**, Wu R, Hermier C, Doutre MS, Brette R, Treppe C. [Satellite vasculitis of B or non-A non-B hepatitis. Diagnostic value of a provocation test by intradermal injection of histamine]. *Ann Med Interne (Paris)* 1987; **138**: 193-198 [PMID: 3619249]
- 4 **Horowitz J**, Klein M, Sukenik S. Cryoglobulinemia and hepatitis B markers in North African Jews with Raynaud's disease. *Arthritis Rheum* 1986; **29**: 1026-1028 [PMID: 3741513 DOI: 10.1002/art.1780290813]
- 5 **La Civita L**, Zignego AL, Lombardini F, Monti M, Longombardo G, Paseri G, Ferri C. Exacerbation of peripheral neuropathy during alpha-interferon therapy in a patient with mixed cryoglobulinemia and hepatitis B virus infection. *J Rheumatol* 1996; **23**: 1641-1643 [PMID: 8877939]
- 6 **Yamazaki T**, Akimoto T, Okuda K, Sugase T, Takeshima E, Numata A, Morishita Y, Iwazu Y, Yoshizawa H, Komada T, Iwazu K, Saito O, Takemoto F, Muto S, Kusano E. Purpura with ulcerative skin lesions and mixed cryoglobulinemia in a quiescent hepatitis B virus carrier. *Intern Med* 2014; **53**: 115-119 [PMID: 24429450 DOI: 10.2169/INTERNALMEDICINE.53.1203]
- 7 **Löhr H**, Goergen B, Weber W, Gödderz W, Meyer zum Büschenfelde KH, Gerken G. Mixed cryoglobulinemia type II in chronic hepatitis B associated with HBe-minus HBV mutant: cellular immune reactions and response to interferon treatment. *J Med Virol* 1994; **44**: 330-335 [PMID: 7897364 DOI: 10.1002/jmv.1890440404]
- 8 **Yadav YK**, Aggarwal R, Gupta O, Ranga S. Hepatitis-B associated cryoglobulinemia presenting as pseudoleucocytosis. *J Lab Physicians* 2011; **3**: 133-135 [PMID: 22219576 DOI: 10.4103/0974-2727.86854]
- 9 **Galli M**, Monti G, Invernizzi F, Monteverde A, Bombardieri S, Gabrielli A, Migliaresi S, Mussini C, Ossi E, Pietrogrande M. Hepatitis B virus-related markers in secondary and in essential mixed cryoglobulinemias: a multicentric study of 596 cases. The Italian Group for the Study of Cryoglobulinemias (GISC). *Ann Ital Med Int* 1992; **7**: 209-214 [PMID: 1298331]
- 10 **van Voorst Vader PC**, Orth G, Dutronquay V, Driessen LH, Eggink HF, Kallenberg CG, The TH. Epidermodyplasia verruciformis. Skin carcinoma containing human papillomavirus type 5 DNA sequences and primary hepatocellular carcinoma associated with chronic hepatitis B virus infection in a patient. *Acta Derm Venereol* 1986; **66**: 231-236 [PMID: 2426900]
- 11 **Ergin S**, Sanli Erdoğan B, Turgut H, Evliyaoğlu D, Yalçın AN. Relapsing Henoch-Schönlein purpura in an adult patient associated with hepatitis B virus infection. *J Dermatol* 2005; **32**: 839-842 [PMID: 16361739]
- 12 **Ishimaru Y**, Ishimaru H, Toda G, Baba K, Mayumi M. An epidemic of infantile papular acrodermatitis (Gianotti's disease) in Japan associated with hepatitis-B surface antigen subtype ayw. *Lancet* 1976; **1**: 707-709 [PMID: 56530]
- 13 **Mérigou D**, Léauté-Labrèze C, Louvet S, Bioulac-Sage P, Taïeb A. [Lichen planus in children: role of the campaign for hepatitis B vaccination]. *Ann Dermatol Venereol* 1998; **125**: 399-403 [PMID: 9747294]
- 14 **Saywell CA**, Wittal RA, Kossard S. Lichenoid reaction to hepatitis B vaccination. *Australas J Dermatol* 1997; **38**: 152-154 [PMID: 9293664 DOI: 10.1111/j.1440-0960.1997.tb01134.x]
- 15 **Criado PR**, de Oliveira Ramos R, Vasconcellos C, Jardim Criado RF, Valente NY. Two case reports of cutaneous adverse reactions following hepatitis B vaccine: lichen planus and granuloma annulare. *J Eur Acad Dermatol Venereol* 2004; **18**: 603-606 [PMID: 15324406 DOI: 10.1111/j.1468-3083.2004.00989.x]
- 16 **Wolf F**, Grezard P, Berard F, Clavel G, Perrot H. Generalized granuloma annulare and hepatitis B vaccination. *Eur J Dermatol* 1998; **8**: 435-436 [PMID: 9729059]
- 17 **Ventura F**, Antunes H, Brito C, Pardal F, Pereira T, Vieira AP. Cutaneous polyarteritis nodosa in a child following hepatitis B vaccination. *Eur J Dermatol* 2009; **19**: 400-401 [PMID: 19467971]
- 18 **Yılmaz S**, Cimen KA. Pegylated interferon alpha-2B induced lupus in a patient with chronic hepatitis B virus infection: case report. *Clin Rheumatol* 2009; **28**: 1241-1243 [PMID: 19653058]
- 19 **García-Porrúa C**, González-Gay MA, Fernández-Lamelo F, Paz-Carreira JM, Lavilla E, González-López MA. Simultaneous development of SLE-like syndrome and autoimmune thyroiditis following alpha-interferon treatment. *Clin Exp Rheumatol* 1998; **16**: 107-108 [PMID: 9543579]
- 20 **Erbagci Z**. Childhood bullous pemphigoid following hepatitis B immunization. *J Dermatol* 2002; **29**: 781-785 [PMID: 12532044]
- 21 Review: could Hepatitis b cause Skin lesion? Accessed date Feb. 23, 2014. Available from: URL: <http://www.ehealthme.com>
- 22 **Fernandez-Soto L**, Gonzalez A, Escobar-Jimenez F, Vazquez R, Ocete E, Olea N, Salmeron J. Increased risk of autoimmune thyroid disease in hepatitis C vs hepatitis B before, during, and after discontinuing interferon therapy. *Arch Intern Med* 1998; **158**: 1445-1448 [PMID: 9665354 DOI: 10.1001/archinte.158.13.1445]
- 23 **Cacoub P**, Saadoun D, Bourlière M, Khiri H, Martineau A, Benhamou Y, Varastet M, Pol S, Thibault V, Rotily M, Halfon P. Hepatitis B virus genotypes and extrahepatic manifestations. *J Hepatol* 2005; **43**: 764-770 [PMID: 16087273 DOI: 10.1016/j.jhep.2005.05.029]
- 24 **Baig S**, Alamgir M. The extrahepatic manifestations of hepatitis B virus. *J Coll Physicians Surg Pak* 2008; **18**: 451-457 [PMID: 18760074]
- 25 **Aprosina ZG**, Serov VV, Krel' PE, Ignatova TM. [Extrahepatic manifestations of chronic viral liver diseases]. *Arkh Patol* 1999; **61**: 51-55 [PMID: 10598263]
- 26 **Popp JW**, Harnist TJ, Dienstag JL, Bhan AK, Wands JR, LaMont JT, Mihm MC. Cutaneous vasculitis associated with acute and chronic hepatitis. *Arch Intern Med* 1981; **141**: 623-629 [PMID: 7224743 DOI: 10.1001/archinte.1981.00340050075018]
- 27 **Baykal C**, Okan G, Sarica R. Childhood bullous pemphigoid developed after the first vaccination. *J Am Acad Dermatol* 2001; **44**: 348-350 [PMID: 11174412 DOI: 10.1067/mjd.2001.103034]
- 28 **Ciaccio M**, Reborra A. Lichen planus following HBV vaccination: a coincidence? *Br J Dermatol* 1990; **122**: 424 [PMID: 2138913 DOI: 10.1111/j.1365-2133.1990.tb08294.x]
- 29 **Ferrando MF**, Doutre MS, Beylot-Barry M, Durand I, Beylot C. Lichen planus following hepatitis B vaccination. *Br J Dermatol* 1998; **139**: 350 [PMID: 9767265 DOI: 10.1046/j.1365-2133.1998.02386.x]
- 30 **Levo Y**, Gorevic PD, Kassab HJ, Zucker-Franklin D, Franklin EC. Association between hepatitis B virus and essential mixed cryoglobulinemia. *N Engl J Med* 1977; **296**: 1501-1504 [PMID: 865530 DOI: 10.1056/NEJM197706302962605]
- 31 **Pasquet F**, Combarnous F, Macgregor B, Coppere B, Mautservey C, Ninet J, Hot A. Safety and efficacy of rituximab treatment for vasculitis in hepatitis B virus-associated type II cryoglobulinemia: a case report. *J Med Case Rep* 2012; **6**: 39 [PMID: 22284897 DOI: 10.1186/1752-1947-6-39]
- 32 **Lamprecht P**, Gause A, Gross WL. Cryoglobulinemic vasculitis. *Arthritis Rheum* 1999; **42**: 2507-2516 [PMID: 10615995 DOI: 10.1002/1529-0131(199912)42:12<2507::AID-ANR2>3.0.CO;2-#]
- 33 **Garg VK**, Karki BM, Agrawal S, Agarwalla A, Gupta R. A

- study from Nepal showing no correlation between lichen planus and hepatitis B and C viruses. *J Dermatol* 2002; **29**: 411-413 [PMID: 12184637]
- 34 **Neumann HA**, Berretty PJ, Folmer SC, Cormane RH. Hepatitis B surface antigen deposition in the blood vessel walls of urticarial lesions in acute hepatitis B. *Br J Dermatol* 1981; **104**: 383-388 [PMID: 7236503 DOI: 10.1111/j.1365-2133.1981.tb15307.x]
- 35 **van Aalsburg R**, de Pagter AP, van Genderen PJ. Urticaria and periorbital edema as prodromal presenting signs of acute hepatitis B infection. *J Travel Med* 2011; **18**: 224-225 [PMID: 21539670 DOI: 10.1111/j.1708-8305.2011.00507.x]
- 36 **Morhenn VB**. Cell-mediated autoimmune diseases of the skin: some hypotheses. *Med Hypotheses* 1997; **49**: 241-245 [PMID: 9293469 DOI: 10.1016/S0306-9877(97)90209-7]
- 37 **Dahl MV**, Ullman S, Goltz RW. Vasculitis in granuloma annulare: histopathology and direct immunofluorescence. *Arch Dermatol* 1977; **113**: 463-467 [PMID: 322621 DOI: 10.1001/archderm.1977.01640040071010]
- 38 **Catteau B**, Delaporte E, Piette F, Bergoend H. Granulome annulaire généralisé après vaccination par le BCG. *Ann Dermatol Venereol* 1996; **17**
- 39 **Dillon MJ**, Ozen S. A new international classification of childhood vasculitis. *Pediatr Nephrol* 2006; **21**: 1219-1222 [PMID: 16821024 DOI: 10.1007/s00467-006-0181-8]
- 40 **Ozen S**, Anton J, Arisoy N, Bakkaloglu A, Besbas N, Brogan P, García-Consuegra J, Dolezalova P, Dressler F, Duzova A, Ferriani VP, Hilário MO, Ibáñez-Rubio M, Kasapcopur O, Kuis W, Lehman TJ, Nemcova D, Nielsen S, Oliveira SK, Schikler K, Sztajnbock F, Terreri MT, Zulian F, Woo P. Juvenile polyarteritis: results of a multicenter survey of 110 children. *J Pediatr* 2004; **145**: 517-522 [PMID: 15480378 DOI: 10.1016/j.jpeds.2004.06.046]
- 41 **Fathalla BM**, Miller L, Brady S, Schaller JG. Cutaneous polyarteritis nodosa in children. *J Am Acad Dermatol* 2005; **53**: 724-728 [PMID: 16198807 DOI: 10.1016/j.jaad.2005.03.065]
- 42 **Bourgeois AM**, Dore MX, Croue A, Leclech C, Verret JL. [Cutaneous polyarteritis nodosa following hepatitis B vaccination]. *Ann Dermatol Venereol* 2003; **130**: 205-207 [PMID: 12671586]
- 43 **Trepo C**, Guillevin L. Polyarteritis nodosa and extrahepatic manifestations of HBV infection: the case against autoimmune intervention in pathogenesis. *J Autoimmun* 2001; **16**: 269-274 [PMID: 11334492 DOI: 10.1006/jaut.2000.0502]
- 44 **Kartal ED**, Alpat SN, Ozgunes I, Usluer G. Adverse effects of high-dose interferon-alpha-2a treatment for chronic hepatitis B. *Adv Ther* 2007; **24**: 963-971 [PMID: 18029321 DOI: 10.1007/BF02877700]
- 45 **Weiss TD**, Tsai CC, Baldassare AR, Zuckner J. Skin lesions in viral hepatitis: histologic and immunofluorescent findings. *Am J Med* 1978; **64**: 269-273 [PMID: 147025]
- 46 **García-Bragado F**, Vilardell M, Fonollosa V, Ruibal A, Gallart T, Cuxart A. [Essential mixed cryoglobulinaemia and hepatitis B virus (author's transl)]. *Nouv Presse Med* 1981; **10**: 2955-2957 [PMID: 7290950]
- 47 **Cupella F**, Fasani F. [Mixed cryoglobulinemia with peripheral neuropathy in a case of HBsAg-positive chronic active hepatitis]. *Boll Ist Sieroter Milan* 1985; **64**: 332-334 [PMID: 3000405]
- 48 **Bouhsain S**, Ouzzedoun N, Tellal S, Dami A, Biaz A, Elmechtani S, Kazmouhi L, Derouiche M, Mikdame M. [Kidney vasculitis connected to cryoglobulinemia IIA and hepatitis B]. *Ann Biol Clin (Paris)* 2007; **65**: 643-646 [PMID: 18039609 DOI: 10.1684/abc.2007.0172]
- 49 **Agrawal A**, Shenoj SD. Lichen planus secondary to hepatitis B vaccination. *Indian J Dermatol Venereol Leprol* 2004; **70**: 234-235 [PMID: 17642622]
- 50 **Al-Khenaizan S**. Lichen planus occurring after hepatitis B vaccination: a new case. *J Am Acad Dermatol* 2001; **45**: 614-615 [PMID: 11568757]
- 51 **Usman A**, Kimyai-Asadi A, Stiller MJ, Alam M. Lichenoid eruption following hepatitis B vaccination: first North American case report. *Pediatr Dermatol* 2001; **18**: 123-126 [PMID: 11358552]

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