Clinical Case Report

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Bullous pemphigoid associated with chronic hepatitis C virus infection in a hepatitis B virus endemic area

A case report

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Abstract

Introduction: Bullous pemphigoid is a type of acute or chronic autoimmune disease that involves subepidermal skin lesions with bulla formation. Although viral infections, such as, human herpes virus (HHV), human immunodeficiency virus, cytomegalovirus, Epstein–Barr virus, HHV-6, hepatitis B virus (HBV), and hepatitis C virus (HCV), are known factors of bullous pemphigoid, HCV infection has only been rarely associated factor, especially in HBV endemic area. A 78-year-old man was admitted to our hospital due to erythematous bulla of onset 3 months before presentation affecting his entire body. Pathologic findings, that is, subepidermal bullae containing eosinophils and neutrophils with superficial perivascular lymphocytic and eosinophilic infiltration, were consistent with bullous pemphigoid. Anti-HCV was positive and HCV quantitative real-time polymerase chain reaction (PCR) was 1.25×10^5 IU/mL. HCV genotype was 2a. After a diagnosis of bullous pemphigoid associated with chronic HCV infection was reached, he was treated with oral methylprednisolone for bullous pemphigoid, and his skin lesions improved. Oral direct-acting antiviral agents (sofosbuvir plus ribavirin) were prescribed for chronic hepatitis C, and sustained viral response was achieved.

Conclusion: The authors report a rare case of bullous pemphigoid associated with chronic HCV infection in a HBV endemic area and advise that HCV should be considered in the differential diagnosis of factors precipitating bullous pemphigoid, even in HBV endemic areas.

Abbreviations: BPAG1 = bullous pemphigoid 230, BPAG2 = bullous pemphigoid 180, HBV = hepatitis B virus, HCV = hepatitis C virus, HHV = human herpes virus, HIV = human immunodeficiency virus, HIV = human immunodeficiency virus.

Keywords: bullous pemphigoid, hepatitis C virus

1. Introduction

Bullous pemphigoid is considered an autoimmune disease type, which manifests subepidermal skin lesions with bulla formation.[1] If untreated, the disease can persist for months or years, during which its symptoms wax and wane. Especially, in older patients with a poor general condition, bullous pemphigoid can be fatal.[2] Therefore, accurate diagnosis and effective treatment are required, and precipitating factors need to be identified and treated. Although such factors may not be confirmed in the majority of cases, genetic predisposition and environmental factors, such as, ultraviolet light, radiation therapy, and nonsteroidal anti-inflammatory drugs, play pivotal roles in the pathogenesis of bullous pemphigoid.[3] Although viral hepatitis infections such as hepatitis B virus (HBV) and hepatitis C virus (HCV) are also known to predispose the disease,[4] HCV infection is only very rarely associated, especially in HBV endemic areas. Here, we present a case of bullous pemphigoid associated with chronic HCV infection in South Korea, a HBV-endemic area. Informed consent was obtained from the patient for publication of this case report, and this case report was approved by the Institutional Review Board of Inha University Hospital, Incheon, South Korea (INHAUH 2018–01–003).

2. Case report

A 78-year-old male was admitted to our hospital due to erythematous bulla that affected his entire body of onset 3 months before presentation. The patient had a history of chronic hepatitis C infection, which had been diagnosed 4 years previously, but he had not received any treatment. In addition, he had a history of dementia, which was diagnosed 4 years before presentation, and had been taking dementia medication. He had no history of alcohol consumption.

Upon presentation at our hospital, large bullas were observed in both soles, and erythematous bullas particularly affected his

Editor: N/A.

Funding/support: This work was supported by an Inha University Research Grant.

All the authors have no conflicts of interest to declare in connection with this study.

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Medicine (2018) 97:15(e0377)

Received: 8 January 2018 / Received in final form: 15 March 2018 / Accepted: 16 March 2018

http://dx.doi.org/10.1097/MD.0000000000010377

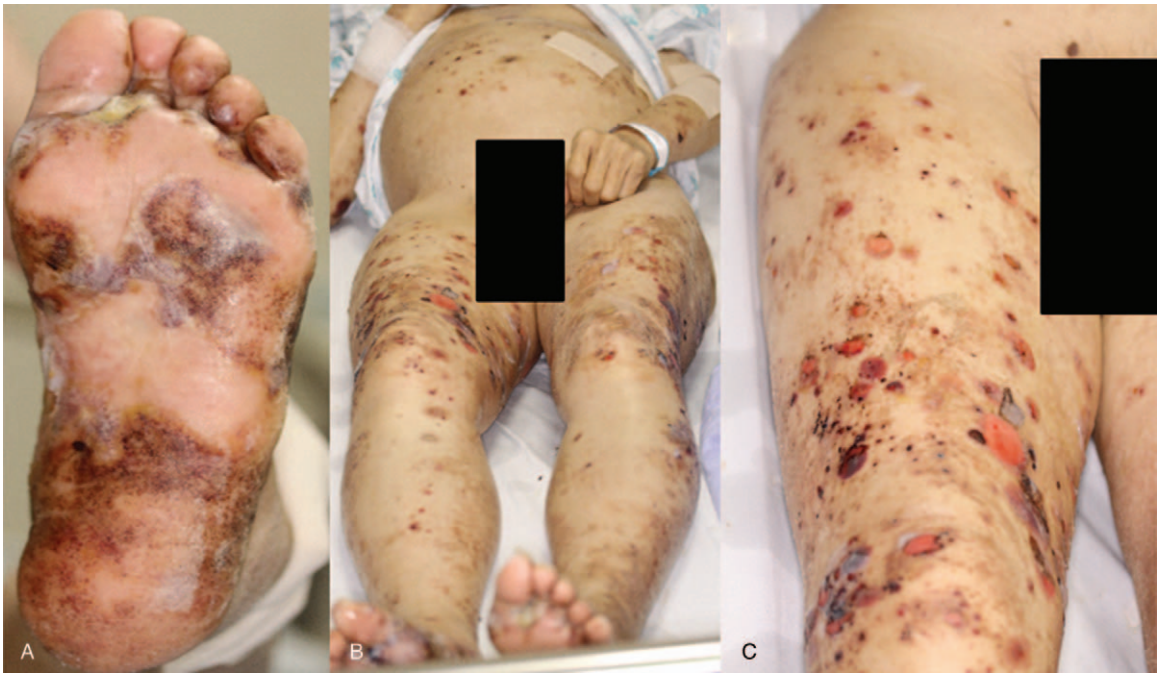

Figure 1. Bullous pemphigoid skin lesions. (A) Sole skin lesions. (B) Skin lesions covered the entire body. (C) Close-up photograph of the patient's right thigh.

legs (Fig. 1). His initial subjective symptoms were an itching sensation and edema of both legs. Physical examination revealed a temperature of 39°C, a pulse rate of 62 beats/min, and a blood pressure of 108/64 mm Hg. The initial laboratory tests showed a white cell count of $3.87 \times 10^3/mm^3$ (neutrophils 38%, lymphocytes 14%, monocytes 2%, and eosinophils 46%), a hemoglobin of 11.0 g/dL, and a platelet count of $58 \times 10^3/mm^3$. The erythrocyte sedimentation rate and C-reactive protein concentration were 23 mm/h and 0.11 mg/dL, respectively. Biochemical tests revealed aspartate aminotransferase 47 U/L, alanine aminotransferase 37 U/L, gamma glutamyl transferase 12 U/L, alkaline phosphatase 60 U/L, total bilirubin 0.7 mg/dL, albumin 3.3 g/dL, and international normalized ratio (INR) 1.25. Anti-HCV was positive, HCV quantitative real-time PCR was 1.25×10^5 IU/mL, and the HCV genotype was 2a. Alpha-fetoprotein was 9.8 ng/mL. Antibody testing was negative for HBV, human immunodeficiency virus (HIV), and human herpes virus (HHV). Anti-nuclear antibody and anti-neutrophil cytoplasmic antibodies (p- and c-) were also negative. IgG and IgG subclass IV were elevated at 2268 mg/dL (reference, 870–1700 mg/dL) and 162.9 mg/dL (reference, 3.9–86.4 mg/dL), respectively, and total IgE was elevated as 5000 (reference, 0–100). Antibodies (IgG) to toxocariasis and clonorchis sinensis were positive, and *Helicobacter pylori* was also identified in biopsied gastric mucosa.

Punch biopsy of a chest area skin lesion was performed on the third day of admission. Pathologic findings consistent with bullous pemphigoid were subepidermal bullae containing eosinophils and neutrophils with superficial perivascular lymphocytic and eosinophilic infiltration (Fig. 2A and B). The result of immunofluorescence stain was all negative for IgG, IgA, IgM, and C4, but positive for C3 along the dermoepidermal junction (Fig. 3).

Due to the low platelet count, abdominal computed tomography and upper endoscopy were performed on the eighth day of admission to determine the presence of liver cirrhosis, and these examinations showed cirrhotic liver, a large amount of ascites,

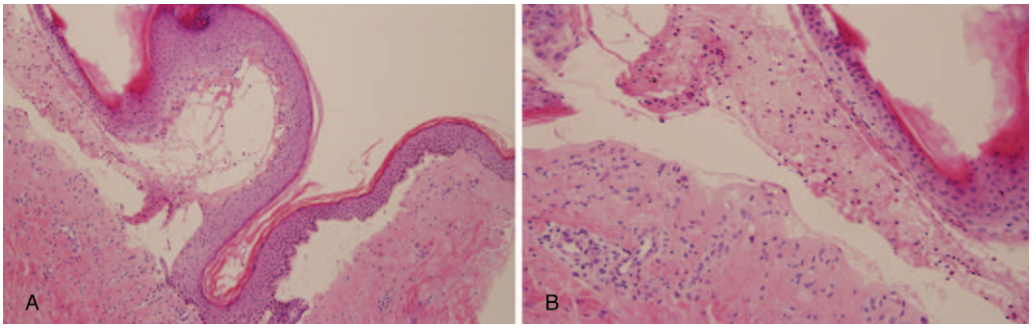

Figure 2. Pathologic findings (hematoxylin and eosin, HE, stain); Subepidermal bullae containing eosinophils and neutrophils with superficial perivascular lymphocytic and eosinophilic infiltration (A, HE stain ×100 and B, HE stain ×200).

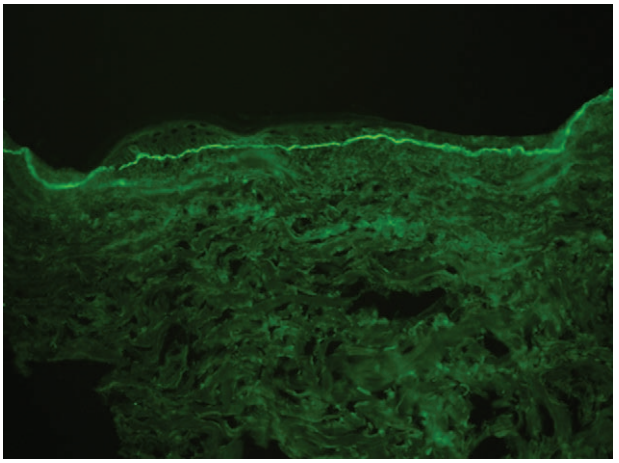

Figure 3. Pathologic findings (Immunofluorescence stain); The result was positive for C3 along the dermoepidermal junction.

and esophageal varix. As a result of these examinations, he was diagnosed as having HCV-related liver cirrhosis. Bone marrow biopsy was also performed to rule out hematologic disease, but showed no specific hematologic disease.

After reaching a diagnosis of bullous pemphigoid associated with chronic hepatitis C infection, he was treated with oral methylprednisolone (24 mg/day) for bullous pemphigoid, which markedly reduced the bullous skin lesions and itching sensation, and thus, he was discharged on oral methylprednisolone and antihistamine on the 14th day of admission. Subsequently, he was followed at an outpatient clinic and oral methylprednisolone was tapered. At his 6-month follow-up, the bullous skin lesions and itching sensation had completely resolved, but IgG and IgG subclass IV were still slightly elevated at 2075 and 113.5 mg/dL, respectively, and total IgE was unchanged at 5000. Accordingly, he was maintained on low-dose methylprednisolone (2 mg/day), which has been maintained despite the skin lesion improvement, and monitored for these antibodies for 3 months. For the chronic hepatitis C, oral direct-acting antiviral drugs (sofosbuvir and ribavirin) were prescribed at the outpatient clinic, and sustained viral response was achieved.

3. Discussion

Bullous pemphigoid is an autoimmune blistering disease characterized by subepidermal bullae formation on normal or erythematous skin.[1] The known common potential causes of bullous pemphigoid are ultraviolet light, radiation therapy, and nonsteroidal anti-inflammatory drugs,[3] and although uncommon, viral infections, such as, HHV, HIV, cytomegalovirus, Epstein–Barr virus, HHV-6, HBV, and HCV have also been associated with the disease.[4] However, relations between these viral infections and bullous pemphigoid remain the topic of debate,[4] and to our knowledge, no known report has yet linked bullous pemphigoid and chronic HCV infection in a HBV endemic area.

Although bullous pemphigoid may be self-limited in some cases, it can be potentially fatal with an estimated 1-year mortality of 6% to 12% in the United States and 19% to 40% in Europe.[2] Moreover, the majority that succumb are elderly, and usually have accompanying diseases.[3] Accordingly, rapid diagnosis and adequate therapy are required and efforts should be made to identify precipitating factors.

The diagnosis of bullous pemphigoid is usually made on the basis of clinical symptoms, histologic findings, and direct or indirect immunofluorescence findings.[3,5,6] As occurred in our patient, most complain of bullous skin lesions with itching. Typically, histologic findings show infiltrations of lymphocytes, histiocytes, and eosinophils in subepidermal blisters,[3] as were observed in our patient. In particular, immunofluorescence staining reveals IgG and/or C3 depositions in a linear manner along the dermoepidermal junction,[5] which have been suggested to be due to autoantibodies against 2 components of hemidesmosomes, that is, bullous pemphigoid 230 (BPAG1) and bullous pemphigoid 180 (BPAG2), respectively.[5,6] Binding of autoantibodies at the basement membrane activates the classical complement pathway and amplifies C3 activation.[5,6] In this case, immunofluorescence staining showed C3 deposition along the dermoepidermal junction (Fig. 3).

The clinical course of bullous pemphigoid depends on diverse interactions between genetic predisposition and precipitating factors.[7] The overexpressions of human leukocyte antigen (HLA) class II alleles, such as HLA-DQβ1*0301l, -DRB1*04, -DRB1*1101, and -DQB1*0302, are commonly observed in bullous pemphigoid,[7] although we did not investigate these associations in this report. Furthermore, it is not easy to investigate genetic susceptibility in the clinical settings, and thus, concerted effort should be made to identify and address potential triggering factors.

Although several factors are known to predispose bullous pemphigoid,[3] the role of viral hepatitis C in its pathogenesis remains to be determined. In a previous study, the prevalence of HCV antibody was found to be higher in patients with bullous pemphigoid than in healthy control.[4] In addition, it has been reported that HCV is associated with various skin diseases, such as, pemphigus vulgaris, cutaneous vasculitis, porphyria cutanea tarda, and lichen planus.[4,8,9] Given that the presence of HCV antibody need not be linked to current or past infection, efforts to diagnose the current HCV infection are required. In this case, HCV RNA and HCV genotype were all detected, which suggests current chronic HCV infection may be directly associated with bullous pemphigoid beyond the simple presence of antibody. However, this suggestion can only be confirmed by a large-scale study.

In addition to HCV infection in this case, we also detected antibodies to toxocariasis and clonorchis sinensis. However, we cannot distinguish current infection from past infection, as no symptoms of these infections were observed and the patient has a previous history of treatment. In addition, despite the identification of *H. pylori* in gastric mucosa, the definite pathophysiological link between *H. pylori* and the development of bullous pemphigoid remains to be unclear.

In conclusion, we report a rare case of bullous pemphigoid associated with chronic HCV infection in a HBV endemic area. HCV should be considered in the differential diagnosis of factors that precipitate bullous pemphigoid even in HBV endemic areas.

Author contributions

Conceptualization: Young-Joo Jin, Hyunil Jang, Cheol-Woo Kim.
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Investigation: Young-Joo Jin.

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Writing – original draft: Young-Joo Jin, Hyunil Jang.
Writing – review and editing: Young-Joo Jin, Hyunil Jang.

Conception and design, collection, assembly, and interpretation of data, drafting of the article, provision of study materials or patients, administrative and technical or logistic support: Hyunil Jang, Young-Joo Jin.

Collection, assembly, and interpretation of the data, and drafting of the article: Chang hwi Yoon, Cheol-Woo Kim, Lucia Kim.

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