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 $1.25 \times 10^5$ 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, HLV = 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.\cite{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.\cite{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.\cite{3} Although viral hepatitis infections such as hepatitis B virus (HBV) and hepatitis C virus (HCV) are also known to predispose the disease,\cite{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 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
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 $1.25 \times 10^5$ 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.

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,
Bullous pemphigoid is an autoimmune blistering disease characterized by subepidermal bullae formation on normal or erythematous skin. The known common potential causes of bullous pemphigoid are ultraviolet light, radiation therapy, and nonsteroidal anti-inflammatory drugs and uncommon viral infections such as HHV, HIV, cytomegalovirus, Epstein–Barr virus, HHV-6, HBV, and HCV have also been associated with the disease. However, relations between these viral infections and bullous pemphigoid remain the topic of debate, 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. Moreover, the majority that succumb are elderly, and usually have accompanying diseases. 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. 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 as were observed in our patient. In particular, immunofluorescence staining reveals IgG and/or C3 deposits in a linear manner along the dermoepidermal junction, 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. Binding of autoantibodies at the basement membrane activates the classical complement pathway and amplifies C3 activation. 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. The overexpression of human leukocyte antigen (HLA) class II alleles, such as HLA-DQβ1*0301, -DRB1*04, -DRB1*1101, and -DQB1*0302, are commonly observed in bullous pemphigoid, 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, 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. 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. 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

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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.
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References

[1] Rapini RP, Jorizzo JL, Bologna JL. Dermatology. 2nd edn. Mosby; 2008.
[2] Joly P, Benichou J, Lok C, et al. Prediction of survival for patients with bullous pemphigoid: a prospective study. Arch Dermatol 2005;141:691-8.
[3] Lo Schiavo A, Ruocco F, Brancaccio G, et al. Bullous pemphigoid: etiology, pathogenesis, and inducing factors: facts and controversies. Clin Dermatol 2013;31:391-9.
[4] Sagri L, Baum S, Agnon-Levin N, et al. Autoimmune bullous diseases: the spectrum of infectious agent antibodies and review of the literature. Autoimmun Rev 2011;10:527-35.
[5] Beutner EH, Jordon RE, Chorzelski TP. The immunopathology of pemphigus and bullous pemphigoid. J Invest Dermatol 1968;51:63-80.
[6] Thoma-Uzynski S, Uter W, Schwietzke S, et al. Autoreactive T and B cells from bullous pemphigoid (BP) patients recognize epitopes clustered in distinct regions of BP180 and BP230. J Immunol 2006;176:2015-23.
[7] Delgado JCTD, Yunis EJ, Yunis JJ, et al. A common major histocompatibility complex class II allele HLA-DQB1*0301 is present in clinical variants of pemphigoid. Proc Natl Acad Sci U S A 1996;93:8569-71.
[8] Daoud MS, Gibson LE, Daoud S, et al. Chronic hepatitis C and skin diseases: a review. Mayo Clin Proc 1995;70:559-64.
[9] Pakula AS, Garden JM, Roth SL. Cryoglobulinemia and cutaneous leukocytoclastic vasculitis associated with hepatitis C virus infection. J Am Acad Dermatol 1998;38:850-3.