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Herpes Zoster in Patients With Bullous Pemphigoid: A Population-based Case-Control and Cohort Study

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Dear Editor

Patients with bullous pemphigoid (BP) are known to have increased risk for infection (1). Prior studies have investigated infections as an aggregate whole but have not examined occurrence of herpes zoster (HZ) specifically. We hypothesize that patients with BP may have an increased risk for HZ because they are most often elderly, receiving immunosuppressive medications, and may have functional impairment (1). Furthermore, a recent case report has suggested HZ as a triggering event for BP development (2). Therefore, the present study was designed to determine if patients with HZ had increased risk of BP development and to determine the risk and complications associated with the development of HZ among patients previously diagnosed with BP.

The Rochester Epidemiology Project (REP), a population-based records linkage system, was used to identify all patients (“cases”) who were residents of Olmsted County, at their first lifetime diagnosis of BP between January 1, 1960, and December 31, 2012 (3). The resources of the REP were also used to randomly match 3 controls based on diagnosis index date, age, and sex.

Confirmation of a BP diagnosis was based on our review of the clinical presentation of patients (symptoms of pruritus, urticaria, erosions, and/or bullae) and the laboratory evidence, including at least 2 of the following: 1) histopathologic findings of BP (eosinophilic subepidermal blister, urticarial tissue reaction, and/or eosinophilic spongiosis); 2) direct immunofluorescence with linear deposition of immunoglobulin G, complement C3, or both; 3) indirect immunofluorescence of circulating immunoglobulin G antibodies against basement membrane proteins; or 4) enzyme-linked immunosorbent assay positive for BP180 or BP230 immunoglobulin G antibody (4,5). Diagnosis of HZ was confirmed on the basis of our review of the physician-documented clinical presentation, evaluation, and available

supporting laboratory evidence (ie, Tzanck test, human herpesvirus 3 [varicella-zoster virus] polymerase chain reaction, viral culture). Medical records of all patients were reviewed longitudinally through the REP. Information was abstracted about demographics, BP disease characteristics, and HZ characteristics.

This study incorporated a case-control design and a cohort design, both of which were aligned around the diagnosis of BP. The association of a history of HZ with the development of BP was evaluated using a conditional logistic regression model and summarized with an odds ratio and 95% CI. The risk for HZ during follow-up was compared for patients with and without BP using a Cox proportional hazards regression model and summarized with a hazard ratio and 95% CI, and a sensitivity analysis was subsequently performed to account for HZ vaccination. For these analyses, we excluded patients with a history of HZ (ie, prevalent HZ). If a patient with BP had prevalent HZ, this patient and the 3 matched patients without BP in the referent cohort were excluded. Characteristics such as method of HZ diagnosis and immunosuppressive treatment were compared using the Fisher exact test. Statistical analyses were performed using the SAS software package (SAS Institute Inc, Cary, North Carolina). All tests were 2-sided and *P* values <.05 were considered statistically significant.

Case-control data and cohort study data are summarized in Tables 1 and 2, respectively. These data revealed an increased risk for HZ in patients with prevalent BP compared with a referent cohort of patients without BP. Patients with BP were more than 2.5 times more likely to develop HZ than were the age- and sex-matched patients without BP, even when controlling for prior vaccination to the varicella-zoster virus. In our cohort of patients with HZ, more patients with BP were receiving immunosuppressive medications compared with patients without BP. However, doses were typically low (Table 2). This same cohort was evaluated by Brick et al (4) and found to have increased prevalence of neurodegenerative disease compared with controls; this finding has been reported as a risk factor for infection in patients with BP (1).

HZ involves the peripheral nervous system, since infection occurs from reactivation of latent varicella-zoster virus in cranial nerve or dorsal root ganglia. A recent case report described the generation of anti-BP180 antibodies in a patient with HZ, raising the question of whether HZ was a risk factor for BP (2). However, in the case-control portion of our study, history of HZ was not significantly associated with subsequent development of BP.

In the cohort study, rates of complications between groups were not significantly different, possibly because of limitations in sample size. However, 1 patient receiving 40 mg of prednisone daily for BP had zoster ophthalmicus develop. Since its approval by the US Food and Drug Administration in 2006, HZ vaccination is an important consideration in the medical care of elderly persons. The Infectious Disease Society of America recommends that persons older than 60 years receive the live attenuated zoster vaccine (6). Zoster vaccination should ideally be administered more than 4 weeks before initiating immunosuppressive treatment, but it can be administered to patients taking azathioprine (3.0 mg/kg per day), methotrexate (0.4 mg/kg per day), or systemic corticosteroids (fewer than 2 weeks or <20 mg/day) (level 2B evidence) (6).

This study had several limitations, which include the relatively low number of patients, prolonged length of recruitment for patients with BP, and retrospective nature of the study design. Our study population is from a single county with a predominantly white population, and our results may therefore not be generalizable to other populations. Treatment of BP has changed with time, although systemic corticosteroids still are consistently used. However, the availability of newer immunosuppressive agents and awareness of the value of potent topical corticosteroids have created additional options in the treatment of pemphigoid (7).

Our study suggests that patients with BP may have increased risk for HZ infection relative to the general population. This relationship may be due to the use of immune-modulating medications, presence of neurodegenerative diseases, and advanced age of this patient population. Dermatologists should carefully consider administering the HZ vaccination to eligible patients with BP before administering high-dose immunosuppressive therapy.

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Table 1

Characteristics of Controls and Cases

Characteristic	Controls	Cases
All Patients^a		
Age, y		
Mean	77.2	77.3
Median (range)	79 (40–99)	79.5 (41–98)
Female sex, No. (%)	162 (59)	54 (59)
Method of BP diagnosis, No. (%)	...	
Clinical		92 (100)
Routine histology		86 (93)
Direct immunofluorescence		82 (89)
Indirect immunofluorescence		55 (60)
Enzyme-linked immunosorbent assay (BP180 or BP230 IgG antibody)		11 (12)
Diagnosis of HZ before index date	23 (8)	9 (10) ^b
Patients With a History of HZ in the Case-Control Study^c		
Method of HZ diagnosis, No. (%)		
Clinical nondermatology	22 (96)	8 (89)
Biopsy	1 (4)	0
PCR	0	1 (11)
Immunosuppressants, No. (%) ^{d,e}		
Oral corticosteroids	2 (9)	1 of 7 (14) ^f
Tacrolimus	0	1 (14)
Complications, No. (%) ^{e,g}		
PHN	4 (17)	0
Cranial nerve involvement	4 (17)	0
Ocular	1 (4)	1 (11)
Hospitalized	0	1 (11)
Meningoencephalitis	0	1 (11)
Multidermatomal	0	1 (11)
Prior or concurrent malignancy, No. (%)	5 (22)	1 (11)
Transplant patient, No. (%)	0	1 (11)
Ever diagnosed with HSV, No. (%)	4 (17)	1 (11)

Abbreviations: HSV, herpes simplex virus [human herpesvirus 1, human herpesvirus 2]; HZ, herpes zoster; IgG, immunoglobulin G; PCR, polymerase chain reaction; PHN, postherpetic neuralgia.

^aControls, n=276; cases, n=92.

^bOdds ratio, 1.18 (95% CI, 0.54–2.60); *P*=.68.

^cControls, n=23; cases, n=9.

^dIndividual patients may have received more than 1 immunosuppressant.

^e*P*=1.00.

^fImmunosuppressant therapy data were missing for 2 patients with a history of BP and prevalent HZ.

^gIndividual patients may have had more than 1 complication.

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Table 2

Characteristics of Patient Cohorts

Characteristic ^d	Without BP	With BP	Hazard Ratio (95% CI)	P Value
All Patients^a				
Diagnosis of HZ after index date, No. (%)	12 (5)	7 (8)	2.59 (1.01–6.61)	.048
Follow-up, y			...	...
Mean	3.9	8.1		
Median (range)	3.1 (0.2–10.6)	8.9 (0.2–10.6)		
Sensitivity analysis	12 (5)	7 (8)	2.63 (1.03–6.72)	.04
Patients With HZ Development After the Diagnosis Index Date^b				
Method of HZ diagnosis, No. (%)			...	...
Clinical nondermatology	8 (67)	5 (71)		
Clinical dermatology	4 (33)	1 (14)		
Tzanck test	0	1 (14)		
Immunosuppressants, No. (%) ^d			...	.01
Oral corticosteroids	1 (8)	3 (43)		
Topical corticosteroids	0	2 (29)		
Methotrexate	0	1 (14)		
Complications, No. (%) ^e			...	1.0
Postherpetic neuropathy	2 (17)	0		
Cranial nerve involvement	1 (8)	0		
Ocular	0	1 (14)		
Secondary infection	1 (8)	0		
Prior or concurrent malignancy	5 (42)	3 (43)		
Ever diagnosed with HSV, No. (%)	0	1 (14)	...	...

Abbreviations: BP, bullous pemphigoid; HSV, herpes simplex virus [human herpesvirus 1, human herpesvirus 2]; HZ, herpes zoster.

^aNone were transplant patients.

^bWithout BP, n=226; with BP, n=83.

^cWithout BP, n=12; with BP, n=7.

^dIndividual patients may have received more than 1 immunosuppressant: triamcinolone 0.1% cream (n=2), prednisone (5 mg daily) and methotrexate (15 mg weekly) (n=1), prednisone (20 mg daily) (n=1), prednisone (40 mg daily) (n=1).

^eIndividual patients may have had more than 1 complication.