Overall and subgroup prevalence of pyoderma gangrenosum among patients with hidradenitis suppurativa: A population-based analysis in the United States

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Background: Hidradenitis suppurativa (HS) and pyoderma gangrenosum (PG) are reported to coexist, although the prevalence of PG among patients with HS has not been systematically evaluated.

Objective: To evaluate PG prevalence among patients with HS.

Methods: Cross-sectional analysis of adults with PG among patients with HS and patients without HS through use of electronic health records data from a population-based sample of 55 million patients.

Results: The prevalence of PG among 68,232 patients with HS was 0.18% (125 of 68,232), compared with 0.01% (1835 of 31,435,166) among those without HS ($P < .0001$). Prevalence was markedly higher among patients with HS and Crohn's disease (CD) (3.68%) than among patients with HS but without CD (0.12%). The odds of having PG were 21.14 (95% confidence interval [CI], 17.51-25.51) times greater among patients with HS than among those without HS. Patients with HS with CD had 12.38 (95% CI, 9.15-16.74) times the odds of having PG than did patients without HS but with CD. Among patients without CD, compared with patients without HS, those with HS had 26.51 (95% CI, 21.07-33.36) times the odds of having PG.

Limitations: We could not establish HS phenotype among those having coexistent PG, nor could we distinguish syndromic from nonsyndromic cases.

Conclusion: Patients with HS have an increased prevalence of PG, regardless of CD status. Painful ulcerations among patients with HS warrant additional evaluation for PG. (J Am Acad Dermatol 2019;80:1533-7.)

Key words: acne; ankylosing spondylitis; conglobata; Crohn's disease; Explorys; hidradenitis suppurativa; PADH; PAPASH; PASS; pyoderma gangrenosum; pyogenic arthritis.

Hidradenitis suppurativa (HS) and pyoderma gangrenosum (PG) appear to share several clinical features. HS and PG are both characterized by an intense inflammatory response that results in suppurating painful lesions. Both conditions occur more commonly among women,[1,2] and both have disease onset among young and middle aged adults.[2-6] Both conditions have also been linked to Crohn's disease (CD)[2,5-8] and ulcerative colitis.[2,8,9] Tumor necrosis factor-α inhibitors

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are effective in treating both HS[10,11] and PG.[12-14] Finally, HS and PG comprise components of the autoinflammatory syndromes PASH (PG, acne conglobata, and suppurative hidradenitis), PAPASH (pyogenic arthritis, acne, PG and suppurative hidradenitis), and PASS (pyoderma gangrenosum, acne vulgaris, hidradenitis suppurativa, and ankylosing spondylitis).

Coexistence of HS and PG has been described in both syndromic and nonsyndromic forms in cases and case series.[4,15-23] However, the burden of PG among patients with HS is largely unknown. The objective of this study was to investigate overall and subgroup prevalences of PG among patients with HS in the United States.

CAPSULE SUMMARY

- The link between hidradenitis suppurativa and pyoderma gangrenosum is anecdotal.
- Given our observations, painful ulcerations in patients with hidradenitis suppurativa that do not appear typical for the disease may warrant further evaluation for pyoderma gangrenosum.

METHODS

Patient population

This was a cross-sectional analysis using a multiple health system data analytics and a research platform (Explorys) developed by IBM Watson Health (IBM, Armonk, NY).[24] Clinical information from electronic medical records, laboratories, practice management systems, and claims systems is matched by using the single set of Unified Medical Language System ontologies to create longitudinal records for unique patients. The data are standardized and curated according to common controlled vocabularies and classification systems, including the *International Classification of Disease* (ICD), Systemized Nomenclature of Medicine—Clinical Terms (SNOMED-CT), Logical Observation Identifiers Names and Codes, and RxNorm.[25-29] At present, the Explorys database encompasses 27 participating integrated health care organizations. Data from more than 55 million unique patients, representing approximately 17% of the population across the 4 US census regions, are captured. Patients with all types of insurance, as well as those who are self-pay, are represented.

The SNOMED-CT term *hidradenitis* has 1-to-1 mapping to code 705.83 of the ninth revision of the ICD [ICD-9] and was used to identify patients with HS. In a previous and independent validation study, we observed a positive predictive value of 79.3% and an accuracy of 90% for diagnosis of HS with use of a single ICD-9 code for HS.[30] To identify patients with PG, we used 3 counts of the ICD-9 code 686.01, which maps to the SNOMED-CT term *pyoderma gangrenosum*. This method has a positive predictive value of 76.1% for the diagnosis of PG.[31]

Statistical analysis

The analysis was limited to patients aged 18 years or older with an active status in the database within the past 5 years who were not missing demographic data on age and sex. Age in years was recorded as a categoric variable within 1 of 3 groups: 18 to 44, 45 to 64, and 65 years and older. The SNOMED CT term *Crohn's disease* (ICD-9 code 555.x) was used to identify the cohort of patients with CD.

We obtained population-level counts of the number of patients with and without a diagnosis of PG for each combination of categoric explanatory variables (HS, sex, age, and CD). Frequencies and percentages were produced to describe the characteristics of patients with and without HS. We calculated the overall prevalence of PG in patients with and without HS, as well as the prevalence within subgroups of these cohorts. Multivariable logistic regression was performed to evaluate the relationship between HS and PG while controlling for sex, age, and CD status. We assessed potential subgroup differences in the relationship between HS and PG by testing the significance of the interaction between HS and the explanatory variable of interest individually. All analyses were performed by using SAS software (version 9.4, SAS Institute, Cary, NC). This study was approved by the human subjects committee at the Feinstein Institute for Medical Research at Northwell Health. This investigation was also approved by the IRB of the Feinstein Institute for Medical Research at the Northwell Health.

RESULTS

We identified 68,232 patients with HS and 31,435,166 control patients, whose demographic characteristics are described in Table I. The patients with HS were predominantly female (74.7%), were aged 18 to 44 years (58.1%) and had CD in 1.9% of cases.

The overall and subgroup prevalences of PG are described in Table II. The overall prevalence of PG among patients with HS was 0.18% (125 of 68,232), compared with 0.01% (1835 of 31,435,166) among those without HS. Prevalence of PG was similar between male and female patients with HS, and it

Abbreviations used:

CI:	confidence interval
HS:	hidradenitis suppurativa
ICD:	International Classification of Diseases
ICD-9:	International Classification of Diseases, Ninth Revision
PAPASH:	pyogenic arthritis, acne, PG and suppurative hidradenitis
PASH:	pyoderma gangrenosum, acne conglobata, suppurative hidradenitis
PASS:	pyoderma gangrenosum, acne vulgaris, hidradenitis suppurativa and ankylosing spondylitis
PG:	pyoderma gangrenosum
SNOMED-CT:	Systemized Nomenclature of Medicine—Clinical Terms

was higher among those patients with HS who were at least 45 years old (0.23%) than among those who were 18 to 44 years old (0.15%). Prevalence was markedly higher among patients with HS who had CD (3.68%) than among patients with HS who did not have CD (0.12%).

In multivariable analyses, patients with HS had 21.14 (95% confidence interval [CI], 17.51-25.51) times the overall odds of having PG than did patients without HS. In subgroup analyses, patients with HS had significantly higher odds of having PG than did those without HS across all of the demographic subgroups (Table II). Among those with CD, patients with HS had 12.38 (95% CI, 9.15-16.74) times the odds of having PG than did patients without HS. Among patients without CD, those with HS had 26.51 (95% CI, 21.07-33.36) times the odds of having PG than did those without HS. This suggests that the association between HS and PG is independent of CD status.

DISCUSSION

In this study, we observed the prevalence of PG among patients with HS to be 0.18%. In other words, approximately 1 in 546 patients with HS may have coexisting PG. The overall odds of PG among patients with HS were more than 20 times higher than those among patients without HS. The association between HS and PG is independent of CD status.

Case report and small series comprise most of the literature describing coexistent HS and PG.[4,15-23] These cases describe the occurrence of PG months to decades after onset of HS. PG has been reported to occur both at sites of HS lesions and at distant sites. Overall, even with detailed reports of cases, the phenotype of patients with HS with PG is poorly characterized.

Table I. Demographic characteristics

Characteristic	Patients with HS, n (%) (n = 68,232)	Patients without HS, n (%) (n = 31,435,166)
Sex		
Female	50,963 (74.7%)	17,817,604 (56.7%)
Male	17,269 (25.3%)	13,617,562 (43.3%)
Age, y		
18-44	39,671 (58.1%)	12,950,474 (41.2%)
45-64	22,640 (33.2%)	10,303,758 (32.8%)
≥65	5921 (8.7%)	8,180,934 (26.0%)
Crohn's disease	1305 (1.9%)	154,731 (0.5%)

HS, Hidradenitis suppurativa.

One prior study has described the burden of PG in a population of patients with HS. In a Korean analysis for which the objective was to evaluate a broad range of comorbidities among patients with HS, the prevalence of PG among 28,516 patients with HS was observed to be 0.04%. In the adjusted model, patients with HS were 3 times more likely to have PG than matched controls were.[32] Both the prevalence and the adjusted odds of having PG in the Korean analysis were significantly lower than the observations reported herein. Interestingly, there was a predominance of male patients with HS in the Korean cohort, and so the results from this cohort may not be generalized to cohorts of those with HS in the United States or in other parts of the world where females represent the predominant sex.[1] Moreover, as the Korean analysis included a broad survey of comorbidities among patients with HS, the covariates used in the adjusted model (age, sex, socioeconomic status, diabetes, hypertension, and hyperlipidemia) were not all related to the outcome of PG, and CD status was not included in the model. As such, the results related to PG were difficult to interpret in this analysis.

Although the potential pathophysiologic links between HS and PG are speculative, additional insight may come from the autoinflammatory syndromes that include both conditions. PASH and PAPASH both appear to involve the proline-serine-threonine phosphate interacting protein 1 gene (*PSTPIP1*).[33] *PSTPIP1* regulates immune activation through its interaction with pyrin. Pyrin downregulates interleukin 1b (IL-1B) production, which results in diminished production and release of a number of inflammatory cytokines. Mutation in *PSTPIP1* may exert a dominant-negative effect on pyrin, resulting in increased IL-1B levels and subsequent recruitment and activation of neutrophils.[33,34]

There are limitations that warrant consideration when interpreting the results of the present study.

Table II. Overall and subgroup prevalence of pyoderma gangrenosum among patients with HS and controls

Group	Prevalence of pyoderma gangrenosum, n (%)		Odds ratio* (95% CI)	Interaction *P* value
	Patients with HS (n = 68,232)	Patients without HS (n = 31,435,166)		
Overall	125/68,232 (0.18%)	1835/31,435,166 (0.01%)	21.14 (17.51-25.51)	
Sex				.89
Female	98/50,963 (0.19%)	1245/17,817,604 (.007%)	21.67 (14.63-32.10)	
Male	27/17,269 (0.16%)	590/13,617,562 (.004%)	20.99 (16.97-25.96)	
Age, y				.03
18-44	59/39,671 (0.15%)	393/12,950,474 (0.003%)	28.78 (21.79-38.01)	
45-64	51/22,640 (0.23%)	738/10,303,758 (0.007%)	17.07 (12.76-22.82)	
≥65	15/5921 (0.25%)	704/8,180,934 (0.009%)	17.25 (10.23-29.09)	
Crohn's disease				<.0001
Yes	48/1305 (3.68%)	476/154,731 (0.31%)	12.38 (9.15-16.74)	
No	77/66,927 (0.12%)	1359/31,280,435 (0.004%)	26.51 (21.07-33.36)	

CI, Confidence interval; *HS*, hidradenitis suppurativa.
*Odds ratios comparing patients with HS and patients without HS were derived from separate logistic regression models, including models containing terms for sex, age, Crohn's disease, and the interaction between HS and the explanatory variable of interest in the subgroup analyses.

Directionality or causality could not be established in this cross-sectional analysis. Although the algorithms used to identify the cohort of patients with HS and the cohort of patients with PG have been independently validated in previous studies,[30,31] use of coded data has the potential to result in misclassification bias. However, this method of cohort identification has also allowed for the systematic collection and analysis of clinical data from large sample sizes, which is difficult to achieve through manual record review. There may be additional confounders that influence the relationship between HS and PG. We could not assess the influence of disease severity in HS on the strength of the association in this claims-based analysis, nor could we establish an HS phenotype for those having coexistent PG. Finally, we were unable to distinguish syndromic from nonsyndromic cases in the cohort with coexistent disease. Despite these limitations, the present study reports important data describing the association between HS and PG. To our knowledge, this is the first population analysis having the primary objective to evaluate the burden of PG among patients with HS. The quantity of lives included in the analysis permitted evaluation of an uncommon occurrence, as well as subgroup analyses that allowed identification of groups at highest risk. Because the population sample is drawn from various health care settings across US census regions, this study overcomes selection biases associated with tertiary single-center or multicenter investigations. We believe that these results may be generalized to the US population.

In conclusion, patients with HS are at risk of PG. Painful ulcerations among patients with HS warrant additional evaluation for consideration of PG. Early recognition of this important association may minimize disease complications and affect management strategies. The results reported herein may support future areas of study, including phenotypic characterization of patients with coexisting disease and identification of treatment strategies that effectively address both conditions.

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