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# Review Comorbidities of hidradenitis suppurativa: A review of the literature

# Alexander Cartron, BS\*, Marcia S. Driscoll, MD, PharmD

Department of Dermatology, University of Maryland School of Medicine, Baltimore, Maryland

# ARTICLE INFO

# ABSTRACT

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*Keywords:* Hidradenitis suppurativa comorbidities *Background:* Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition that affects the follicular portion of folliculopilosebaceous units. It causes painful nodules, abscesses, and draining sinus tracts throughout multiple regions of the body. HS primarily affects women; the overall HS prevalence in women is three times that in men. Although cutaneous disease itself causes substantial morbidity, recent evidence has shown that HS is a systemic inflammatory disease with multiple associated comorbidities.

*Objective:* A review of the literature was conducted to elucidate existing information on this topic to assist in clinical decision-making for dermatologists.

*Methods:* A review of the literature using the PubMed database was conducted with the search term "hidradenitis suppurativa comorbidities". The search was conducted from March 3, 2019 to March 20, 2019, and yielded 55 articles, case reports, and reviews.

*Results:* Metabolic and cardiovascular comorbidities were the most commonly associated with HS. HS has a significant comorbidity burden beyond the skin, including metabolic, cardiovascular, endocrine, gastrointestinal, rheumatologic, and psychiatric disorders, which collectively decrease the quality of life of patients.

*Conclusions*: Dermatologists should be aware of these associations to encourage appropriate screening and referral for management of these disorders.

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\* Corresponding Author.

E-mail address: alexander.cartron@som.umaryland.edu (A. Cartron).

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#### Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition that involves hair follicles in intertriginous regions, such as inguinal, axillary, genital, perineal, and perianal areas (Jemec and Kimball, 2015; Vinkel and Thomsen, 2018). Estimates of its prevalence vary from <1% to 4% (Alikhan et al., 2009; Cosmatos et al., 2013; Garg et al., 2017a; Ingram et al., 2018; McMillan, 2014), but its incidence has increased to as high as 11.4 per 100,000 patients in the population (Garg et al., 2017b). HS causes severe morbidity, including painful abscesses and draining sinus tracts throughout multiple regions of the body. Specifically, HS places a significant disease burden on women; the condition affects at least three times as many women as men in the general population (Miller et al., 2016).

HS was previously hypothesized to be an inflammatory disease of the apocrine sweat glands, but it has more recently been understood as a follicular occlusion disorder, leading to the release of proinflammatory cytokines, such as interleukin (IL)-1 beta, IL-12, IL-23, and tumor necrosis factor-alpha (Kurzen et al., 2008; Lim and Oon, 2016). The development of HS is thought to be influenced by genetics; one third of patients with HS report a family history of the condition (Ingram, 2016), but risk factors such as smoking, obesity, and hormonal factors have also been implicated in its pathogenesis (Revuz et al., 2008; Vazquez et al., 2013).

Given this paradigm shift, comorbidities across multiple organ systems have become increasingly recognized in patients with HS and interestingly may be more prevalent than those associated with psoriasis. In 2017, a working group (Aguilar et al., 2017) of various specialties, including dermatology, cardiology, gastroenterology, rheumatology, and psychiatry, was assembled to provide a tool to investigate the diagnosis of HS comorbidities and facilitate decision-making regarding referral and treatment. However, the comorbidities experienced by patients with HS require an ongoing review to reflect new associations emerging in the literature.

# Objective

The primary objective of this narrative review is to provide a summary of the current body of evidence with regard to systemic comorbidities in patients with HS. This area of research has received increased attention in the past 10 years, and consolidating findings in a single, updated review will allow clinicians to better understand the various comorbidities they may anticipate for their patients. In addition, a synthesis of the literature will assist in identifying knowledge gaps that require future study.

# Methods

A review of the literature using the PubMed database was conducted with the search term "hidradenitis suppurativa comorbidities". The search was conducted from March 3, 2019 to March 20, 2019, and yielded 55 articles, case reports, and reviews, which were further refined for inclusion during the development of this manuscript. Additional articles were then identified from cited references. Only English-language articles were included in this study.

This review revealed publications between 2014 and 2019. Inclusion was based on the quality of the research available with a preference for recent meta-analyses and studies using large population databases. However, in areas where sparse literature was available, case reports and brief reports were also included.

#### Results

#### Metabolic and cardiac comorbidities

Patients with HS are thought to carry a greater systemic inflammatory load, which may be associated with increased metabolic and cardiovascular risk factors and poorer clinical outcomes. Specifically, an association between HS and obesity has been posited because adipose tissue is known to release proinflammatory cytokines, such as tumor necrosis factor-alpha and IL-6 (Lim and Oon, 2016; Sabat et al., 2012). The prevalence of metabolic syndrome in patients with HS has been estimated to be as high as 50.6%, which is significantly greater than the prevalence of metabolic syndrome in the general population (Gold et al., 2014) and potentially greater than the prevalence in patients with psoriasis (Gisondi et al., 2015).

A 2015 systematic review and meta-analysis of nine studies (Tzellos et al., 2015) determined that HS is significantly associated with hypertriglyceridemia, elevated low high-density lipoprotein, and even metabolic syndrome. These associations were significant in both hospitalized patients with HS and those in the general population. Similarly, a 2019 systematic review and meta-analysis of five studies (Rodríguez-Zuñiga et al., 2019) determined that patients with HS have an increased risk for metabolic syndrome, and clinicians should consider screening patients with HS for metabolic risk factors.

However, a 2019 systematic review and adjusted meta-analysis of 12 studies (Phan et al., 2019) found a significantly higher proportion of diabetes mellitus in patients with HS versus healthy controls, but the effect size was decreased when the adjusted effect sizes were pooled. Ultimately, the study concluded that HS was associated with a 1.69-fold increased odds of diabetes, but the absolute risk difference was sufficiently small to the extent that clinical relevance was unlikely. Thus, while clinicians should be cognizant of the association between HS and diabetes mellitus, the literature does not indicate a need to perform screening in all patients with HS. Additionally, because obesity is highly correlated with diabetes mellitus, clinicians may focus on lifestyle optimization, such as weight loss, dietary modification, and exercise.

Given these identified metabolic risk factors, a 2016 population-based cohort study (Egeberg et al., 2016) examined the relationship between HS and risk of cardiovascularassociated adverse events and mortality. The study found that HS was associated with a significantly increased risk of adverse cardiovascular outcomes, such as ischemic stroke and myocardial infarction, as well as all-cause mortality independent of measured confounders. Interestingly, the risk of cardiovascular-associated death was higher in patients with HS when compared with patients with severe psoriasis.

The physiologic parameters underlying these risk factors and outcomes were recently explored in a Danish cross-sectional population study (Juhl et al., 2018) Notably, the authors found that the mean resting heart rate in patients with severe HS was significantly higher compared with that of controls, even after adjusting for age and sex. However, for all patients with HS, when adjusting for multivariates, there was no significant difference in heart rate between patients with HS and the general population.

In addition, the mean QRS duration was significantly shorter in the group with mild HS, but not in the groups with moderate and severe HS. Similarly, a Danish cross-sectional study (Miller et al., 2018) compared 32 patients with HS with 430 controls from the general population. An age- and sex-adjusted analysis revealed a significantly higher heart rate in the HS group versus the controls but found no association between HS and atrial fibrillation. In terms of stratifying risk for patients with HS, a Spanish crosssectional study (Lacalle et al., 2018) used a well-established coronary risk assessment tool, the Framingham risk score, to predict the risk of developing coronary heart disease in 10 years in 60 patients with HS. The study found that cardiovascular risk in patients with HS may be underestimated by using the Framingham risk score; rather, carotid ultrasound may be useful to improve the accuracy of cardiovascular risk stratification for patients with HS. The researchers observed carotid plaques in 36.6% of patients with HS; those with plaques were older, had moderate-to-severe HS and a longer duration of HS, and were more frequently current smokers than patients with HS without plaques.

Ultimately, these studies reveal that patients with HS are more likely to have risk factors, such as metabolic syndrome, as well as adverse outcomes, such as ischemic stroke, myocardial infarction, and cardiovascular-associated mortality. Although patients with HS may be more likely to have an increased resting heart rate, they are unlikely to be at increased risk for atrial fibrillation. With regard to screening, coronary risk assessment tools may not be sufficient, and a carotid ultrasound may be considered as an additional modality.

#### Endocrine comorbidities

Various endocrine comorbidities have been identified in patients with HS. Hormone dysfunction is thought to be involved in the HS pathogenesis. Polycystic ovarian syndrome (PCOS) shares many features with HS, such as a predominant disease burden on young women as well as an association with obesity and metabolic syndrome. Given these similarities, a cross-sectional analysis (Garg et al., 2018a) examined the relationship between PCOS and HS. Using a multi-health system analytics platform of >55 million patients across the United States, the study found that the prevalence of PCOS among patients with HS was 9.0%, compared with 2.9% in patients without HS, which was statistically significant. The likelihood of patients with HS having PCOS was 2.14 times greater than that of patients without HS with a 95% confidence interval, and PCOS was associated with HS across all subgroups. Notably, the strength of the HS association with PCOS was similar to that of diabetes mellitus and obesity with PCOS. The directionality of this relationship could not be established, but the authors concluded that patients with HS who have symptoms or signs of androgen excess should be screened for PCOS.

A potential association between HS and thyroid dysfunction has also recently been posited given that the thyroid gland plays an important role in metabolism. A Danish retrospective comparative cross-sectional study (Mogensen et al., 2018) of 430 patients with HS and 20,780 healthy controls found a significantly lower level of thyroid-stimulating hormone and a significantly higher total triiodothyronine level in patients with HS compared with healthy controls after adjustment for age and sex.

Importantly, these findings remained significant even after potential confounders, such as smoking status, oral contraception, and body mass index, were adjusted for in the analysis. The correlation between HS and hyperthyroidism rather than hypothyroidism suggests that HS may be associated with a hypermetabolic state; however, the pathogenesis requires elucidation. Collectively, these studies reveal that patients with HS may be at increased risk of endocrine comorbidities such as PCOS and hyperthyroidism, and patients should be screened if they present with positive symptoms or signs of disease.

# Gastrointestinal Comorbidities

An association between HS and Crohn's disease has been proposed given that smoking and genetics are considered risk factors and fistula formation is a common disease feature. A 2017 Danish study (Thyssen et al., 2017) found that the prevalence of Crohn's disease was 0.8% for HS patients versus 0.3% for the general population. Additionally, the prevalence of ulcerative colitis was 1.3% for HS patients but only 0.3% for the general population. Both of these differences were statistically significant. Interestingly, for both Crohn's disease and ulcerative colitis the risk of new-onset disease was significantly increased among patients with HS. Most recently, a 2018 retrospective cohort study (Bonomo et al., 2018) investigated the in-hospital burden of HS patients with inflammatory bowel disease (IBD) and found that HS patients with IBD were significantly younger and predominantly African American females. These individuals were significantly more likely to be smokers, to be obese, and to have diabetes mellitus, depression, and anemia. However, there was no reported mortality difference between IBD patients with and without HS. The authors found HS patients with IBD had significantly increased hospital length of stay and higher hospitalization costs. The specific role of immune system dysregulation in HS is unclear; however, cytokines such as IL-1 beta and IL-17 appear to play a role in both IBD and HS. Importantly, both diseases respond to TNF alpha inhibitors (Thyssen et al., 2017; Lee et al., 2018; Vossen et al., 2018). Collectively, these studies demonstrate that patients with HS are at increased risk for IBD, and therefore gastrointestinal signs and symptoms should warrant referral to an appropriate specialist.

#### Rheumatologic comorbidities

An association between HS and spondyloarthritis has been widely considered (Richette et al., 2014; Rosner et al., 1993; Shlyankevich et al., 2014). In 2017, a French single-center cross-sectional study (Rondags et al., 2018) found that 28.2% of patients in a cohort had spondyloarthritis, whereas 2.6% of patients in the control group had spondyloarthritis (p = .02). Axial spondyloarthritis was the most common form documented in the HS group.

More recently, a 2018 cross-sectional study from the Netherlands (Rondags et al., 2018) found that in a cohort of patients with axial spondyloarthritis, the prevalence of HS was 9.1%. In comparison with patients with axial spondyloarthritis but without HS, patients with HS were more likely to be female, report a decreased quality of life, and have higher axial spondyloarthritis disease activity.

Interestingly, other rheumatologic conditions have been reported in patients with HS, such as systemic lupus erythematous. In a 2018 case report (Ben David et al., 2018), a 40-year-old female patient with SLE presented with recurrent abscesses and nodules on the extremities and was ultimately diagnosed with HS. Thus, HS may coexist with other autoimmune conditions, suggesting a common disease etiology. However, conclusions from such limited data require substantiation with further research. Ultimately, these studies suggest that patients with HS who present with low back pain, dactylitis, or other osteoarticular signs or symptoms should be referred to a rheumatologist for appropriate work-up.

# Hidradenitis and malignancy

The relationship between HS and malignancy is a newer area of research. Specifically, increased immune activation in HS may be associated with lymphoma. A 2014 retrospective case-control study (Shlyankevich et al., 2014) determined that approximately 2% of the HS population studied carried a diagnosis of lymphoma versus 0.5% in the control population. The authors noted 3.6 greater odds of lymphoma in patients with HS versus control subjects but found that this association was no longer significant with multivariate analysis.

More recently, a 2019 cross-sectional cohort analysis (Tannenbaum et al., 2019) found that the prevalence rates of non-Hodgkin lymphoma, Hodgkin lymphoma, and cutaneous T-cell lymphoma in the general population are low, but patients with HS may have 2 to 4 times the overall risk of developing lymphoma. The chronic inflammatory state caused by HS is thought to generate cell populations that give rise to malignant lymphomas. However, the association between HS and lymphoma is not well understood and requires further investigation.

#### Psychiatric comorbidities

Patients with HS experience chronic pain and face significant physical, emotional, and psychological challenges. A 2018 review (Matusiak, 2018) noted a significant decreased quality of life in patients with HS due to factors such as pronounced impairment of sex life, absenteeism from work, increasing unemployment, and increased feelings of stigmatization and loneliness. A 2018 Canadian observational cross-sectional study (Alavi et al., 2018) found that male patients with HS experienced greater sexual dysfunction and reduced quality of sexual life whereas female patients with HS reported greater levels of sexual distress versus those in the control groups. Thus, patients with HS may be at an increased risk for psychiatric comorbidities in addition to comorbidities that affect the physical organ systems.

A recent 2018 Danish cross-sectional analysis and cohort study (Thorlacius et al., 2018) compared 7732 patients with HS to a general population of 4,354,137 subjects and determined that patients with HS had a significant increased risk for completing suicide even after adjusting for confounding variables. Interestingly, patients had a significant increased likelihood of antidepressant drug use, but HS was not significantly associated with depression or hospitalization due to depression. However, a Finnish study (Huilaja et al., 2018) using data from the Finnish Care Register for Health Care found that mental health disorders were significantly more common in patients with HS than in patients with psoriasis. Specifically, at least one psychiatric diagnosis was noted in 24.1% of patients with HS versus 19.1% of patients with psoriasis. HS was associated with both schizophrenia and bipolar disorder, which has not been described previously in the literature.

Perhaps as a means of coping with these physical and psychiatric disease burdens, patients with HS may also be at an increased risk for substance use disorder. A 2018 cross-sectional analysis (Garg et al., 2018b) determined that the prevalence of substance use disorder among patients with HS was 4.0% versus 2.0% for patients without HS, and this relationship was statistically significant. Notably, patients with HS were at greatest risk for alcohol misuse, followed by opioid drugs and cannabis.

Collectively, these studies demonstrate that patients with HS are at an increased for psychiatric comorbidities, substance use disorders, and suicide completion; therefore, careful attention should be paid to the mental health of patients with HS.

#### Conclusions

HS is a relatively uncommon disease, but it has profound consequences for those affected. HS alters the innate immune system (Vossen et al., 2018), and complications are far-reaching across multiple organ systems. Evidence in the literature for cardiovascular, endocrine, gastrointestinal, rheumatologic, and psychiatric comorbidities as well as malignancy is increasing. Dermatologists should be aware of associated HS comorbidities to refer patients to the appropriate specialists when signs and symptoms present. Ultimately, a greater understanding of the challenges patients with HS face across specialties has the potential to improve the quality of life of patients immensely.

# **Conflict of Interest**

None.

#### Funding

None.

#### **Study Approval**

The authors confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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