Understanding the Systemic Manifestations of Hidradenitis Suppurativa

***Authors**

[1]Sally Engelhart, BA.
Harvard Medical School, Boston, MA.

Email: sally_engelhart@hms.harvard.edu

[2]Mital Patel, MD.
Department of Dermatology, Brigham and Women's Hospital, Boston MA.

Email: mpatel21@partners.org

Abstract:

Hidradenitis suppurativa (HS) is a chronic inflammatory disease of the skin. It is characterized by painful draining nodules, abscesses and sinus tracts. It most commonly affects skin with a high density of apocrine glands including the axilla, inframammary region, inguinal folds, perineum, and buttocks. There is a growing body of evidence that HS is associated with an increased incidence of many systemic comorbidities compared to the general population. HS has been linked to obesity, metabolic syndrome, cardiovascular disease, endocrine disorders, autoimmune disorders, malignancy and psychiatric disorders. In this paper, we reviewed the literature on systemic comorbidities. The strongest evidence exists supporting an association between HS and metabolic syndrome, smoking and cardiovascular disease and moderately strong evidence of an association between HS and inflammatory bowel disease and inflammatory arthropathies. The literature on the skin cancer and endocrine disorders in HS is mixed, and highlights topics that merit further research. Lastly, the literature indicates that HS patients suffer from decreased quality of life, and increased rates of depression and anxiety. While the understanding of HS and its systemic co-morbidities is still in its early stages, we feel that sufficient evidence exists to support a multidisciplinary approach in the treatment of HS patients.

Section 1: "Introduction"

Hidradenitis suppurativa (HS) is a chronic relapsing inflammatory disease of the skin. It is characterized by painful draining nodules, abscesses and sinus tracts, which most commonly occur in the apocrine gland bearing areas of skin (axilla, inframammary region, inguinal folds, perineum, and buttocks) which heal with prominent scarring. The disease typically initially presents in adolescence and has an insidious onset, often making the initial diagnosis difficult to establish. There is a significantly greater female preponderance, which is important to consider in understanding disease pathogenesis.

The pathogenesis of hidradenitis suppurativa has not been established, but it is postulated to begin with follicular occlusion, which leads to chronic inflammation. Pro-inflammatory cytokines such as interleukin (IL)-1 beta, IL-10, IL-12, IL-23, and tumor necrosis factor (TNF)-alpha and over-activation of the mammalian target of rapamycin complex-1 (mTORC1) signalling have all been implicated in HS [1-3].

Although HS has long been considered a localized skin disorder, there is growing evidence to support that HS, like other chronic inflammatory diseases, has a higher incidence of systemic co-morbidities compared to the general population [4-6] . Systemic manifestations that have been associated with HS in the literature include obesity, metabolic syndrome, cardiovascular disease, endocrine disorders, autoimmune disorders, malignancy and psychiatric disorders. The quantity and quality of evidence of these postulated co-morbidities is variable. In this paper, we will review the evidence behind these postulated associations.

Section 2: "Metabolic Syndrome"

There is strong evidence of an association between HS and metabolic syndrome. Metabolic syndrome is defined by having three out of five of the following physiologic alterations: obesity, diabetes mellitus (DM), hypertriglyceridemia, low high-density lipoprotein (HDL) and hypertension. Regarding the components of metabolic syndrome, there is the strongest evidence of an association between HS and obesity, and mixed evidence regarding the association between HS and the other components of metabolic syndrome.

A large retrospective study including 1730 HS patients and 1730 age, gender and race-matched controls found that HS patients were over 17-fold more likely to be obese than patients without HS (95% CI 9.88-30.6) [4]. Controlling for other co-morbidities in a multivariate analysis, HS patients were also more likely to suffer from hypertension (OR 1.84, 95% CI 1.22-2.79), and dyslipidemia (OR 4.06, 95% CI 2.54-6.48). In this study, while HS patients were more likely than controls to have DM in the univariate

analysis (OR 16.8, 95% CI 11.2-25.3), after adjusting for other co-morbidities in the multivariate analysis the significance of this association was lost (OR 1.72, 95% CI 1.00-2.96).

Many smaller studies also support the association between HS and metabolic syndrome. A retrospective study by Gold and colleagues of 243 HS outpatients and 222 age, sex and race-matched controls found a 50.6% prevalence of metabolic syndrome in HS, significantly higher than then 30.2% prevalence in the control group ($p<0.001$) [7]. This study also found a significantly higher prevalence of obesity, DM and hypertriglyceridemia in HS patients as compared to controls, but no significantly higher rates of hypertension or low HDL. In a hospital-based case-control study of 80 HS patients and 100 age and sex-matched controls, there was a 40% prevalence of metabolic syndrome in the HS group, significantly higher than the 13% prevalence among controls (OR 4.46, 95% CI 2.02-9.96, $p<0.001$) [8]. This study also found that HS patients were significantly more likely to have central obesity, DM, hypertriglyceridemia and low-HDL than control patients.

In 2015, a systematic review of the literature was published that included nine studies with 6174 HS patients and 24, 993 controls. It found a significant association between HS and metabolic syndrome (OR 2.22, 95% CI 1.62-3.06, $p < 0.001$), as well as most of the individual component diagnoses including obesity (OR 3.45, 95% CI 2.20-5.38, $p < 0.001$), hypertriglyceridemia (OR 1.67, 95% CI 1.14-2.47, $p = 0.009$), low HDL (OR 2.48, 95% CI 1.49-4.16, $p < 0.001$), and DM (2.85, 95% CI 1.34-6.08, $p = 0.007$).

Of the individual components of metabolic syndrome, the association of HS and obesity is the best supported, with many studies finding a significant association between the two [4, 7-11]. Rates of obesity among HS patients vary depending on the study population but have been estimated as high as 88% [5]. Compared to healthy controls, hospitalized HS patients and HS outpatients have a 6.4-fold, and 3.6-fold increased likelihood of obesity, respectively [7, 10].

One large retrospective cross-sectional study of 3207 dermatologist-diagnosed HS patients and 6421 age and sex-matched controls found that the association between HS and the components of metabolic syndrome was most significant among the HS patients at younger ages [9]. Sabat and colleagues also found that metabolic syndrome disproportionately affects a high percentage of young HS patients [8]. This differs from other chronic inflammatory disorders associated with metabolic syndrome, like psoriasis where the likelihood of having metabolic syndrome is associated with disease duration, and is predominately seen in older patients [12-14]. It has been found

that psoriasis patients have increased mortality from cardiovascular disease [15], and these findings suggest that this may be even worse for HS patients, who develop metabolic disturbances at younger ages.

There is mixed evidence regarding an association between HS disease severity and metabolic syndrome. This large systematic review found stronger associations with the components of metabolic syndrome among hospitalized HS patients as compared to HS outpatients, which could suggest that patients with more severe HS are more likely to suffer from metabolic syndrome and its components, but it could also be due to increased detection and diagnosis of metabolic disturbances in hospitalized patients [6]. A cross-sectional study of 32 hospitalized HS patients, 326 HS outpatients and 14,851 controls found that metabolic syndrome was most common among hospitalized HS patients (53.1%), followed by HS outpatients (32.2%) and was lowest among controls (21.5%). However, it did not find that more severe HS was associated with metabolic syndrome [10], suggesting that ascertainment bias may have been a factor. Further supporting the lack of association, both a retrospective study of 243 HS outpatients, as well as a hospital-based case-control study of 80 HS patients, found no significant association between the HS disease severity and metabolic syndrome [7, 8].

Some, but not all, studies have found obesity to be linked to more severe HS disease and less frequent remission [16-22]. One study compared obese HS patients, to non-obese HS patients and concluded that the latter had 3.9-fold greater chance of disease remission (95% CI 1.4-11.0) [22]. In keeping with these findings, weight loss has been linked to improvement and/or resolution of HS in patients undergoing bariatric surgery [21].

Importantly, obesity has not been linked to HS disease duration [23]. This is important to highlight, since obesity is thought to precede HS in many cases, and likely plays a role in the pathogenesis of HS. The role of obesity in HS has traditionally been thought to arise from increased skin folds and skin-on-skin friction in obese individuals (HS tends to involve intertriginous skin). However another intriguing theory of this association is that the altered hormonal milieu and/or pro-inflammatory state associated with obesity may play a role.

Although HS patients are predominately female and relatively young, they have increased rates of metabolic syndrome and its individual components (especially obesity), and develop metabolic disturbances younger ages than those with other chronic inflammatory disorders. It is important to screen HS patients for the components of metabolic syndrome, which put these

patients at increased risk of cardiovascular morbidity and mortality.

Section 3: "Smoking"

There are significantly higher rates of smoking among patients with HS compared to the general population. Many studies have found that a considerable majority of HS patients have a smoking history (current or past), as high as 70 to almost 90% in some studies [11, 24-26]. One study from Poland found that over 70% of HS patients were smokers at onset of their disease, far higher than the 23% prevalence of smokers in the general Polish population [27]. A large retrospective study with 1730 HS patients and 1730 controls found a 45-fold increased likelihood of smoking in HS patients compared to controls in a univariate analysis, and a 5.3-fold increase after adjusting for potential confounders in a multivariate analysis [4]. Another multivariate analysis estimate a 12.5-fold increased likelihood of smoking in HS patients compared to controls after adjusting for potential confounders [11].

In a systematic review of the literature, HS was significantly associated with both active smoking and a history of smoking [6]. 3997 HS patients and 22,432 controls were included in the analysis of active smoking found an OR 4.34 (95% CI 2.48-7.60, $p<0.001$). 2472 HS patients and 17,732 controls were included in the analysis looking at the association of HS with any smoking history (current or past) and found an OR of 6.34 (95% CI 2.41-16.68, $p<0.001$). This association has been found in hospitalized HS patients, community HS patients, HS patients by self-report and medically assessed HS patients [6, 11].

There is conflicting data regarding an association between smoking and HS disease severity. Most studies, including the large systematic review previously discussed, have found an association between smoking status and disease severity [6, 16, 17, 22, 25]. Of note, while the systematic review previously mentioned did find an association between smoking and disease severity, it found that it was less pronounced than the association between obesity and disease severity. One study that controlled for disease duration when analyzing the association between smoking pack years and disease severity did not find a clinically significant result (OR 1.02, $p=0.001$) [19]. Some studies have found that non-smoking (in addition to non-obesity) is associated with a better chance of HS remission [22].

Several mechanisms have been proposed to explain how smoking may contribute to the pathogenesis of HS, but this is an area that is still poorly understood. Proposed mechanisms include altering chemotaxis of neutrophils, altering of the skin microbiota, induction of inflammatory cytokines leading to

occlusion of hair follicles, occurring through alterations of nicotinic acetylcholine receptors in the skin or even down-regulation of intracellular signalling molecules [25, 27-31].

These findings highlight the importance of screening HS patients for smoking, which may play a pathogenic role in HS, but is also a significant modifiable cardiovascular risk factor that may lead to the development of serious co-morbid conditions and increased overall burden of HS.

Section 4: "Cardiovascular disease"

HS is associated with an increased risk of cardiovascular disease, independent of its associations with the cardiovascular risk factors previously outlined (e.g. obesity, smoking etc.) [26]. Furthermore, HS patients are at an increased risk of adverse outcomes of cardiovascular disease, including MI, stroke and death [32].

A 2016 study from Spain determined that HS patients had an increased prevalence of subclinical atherosclerosis over age, sex and race-matched controls [26]. Participants were 68 HS patients and 136 matched controls, and those with a history of cardiovascular events, DM, chronic kidney disease, and other inflammatory conditions were excluded from the study. Researchers used non-invasive imaging techniques to measure the carotid intima-media thickness (cIMT, an indicator of generalized atherosclerotic arterial disease) and to assess for the presence of carotid plaques (which is associated with coronary atherosclerosis). The study found that HS patients had a significantly greater cIMT compared to controls (r=0.615 +/- 0.097 versus r=0.578 +/- 0.098, p=0.012). It also found a higher rate of carotid plaques among the HS patients compared to controls (30.9% versus 22.1%), which was found to be significant after controlling for age, sex, and traditional cardiovascular risk factors (OR 2.99, 95% CI 1.26-7.15, p=0.013).

One of the largest epidemiological studies of HS (5964 HS patients and 29,404 controls) demonstrated that HS patients are at increased risk of adverse cardiovascular disease outcomes [32]. After adjusting for age, sex, socioeconomic status, medications, smoking and co-morbid conditions (arrhythmias, heart failure, peripheral artery disease, alcohol abuse, depression, DM, HTN, renal disease, IBD, venous thromboembolism), HS patients had a significantly increased risk of major cardiovascular events including myocardial infarction and stroke, and had higher mortality, especially from cardiovascular events, compared to controls. Of note, the authors did not have access to body weight data and were therefore unable to control for body weight, a potentially significant confounder. They attempted to address this by comparing the outcomes of the HS group to a group of patients with

severe psoriasis, which has previously been linked to adverse cardiovascular disease outcomes independent of body weight [33]. Through this comparison it found a similarly increased risk of adverse cardiovascular events between the HS and severe psoriasis groups, and a higher rate of death from cardiovascular events in the HS group than the group with severe psoriasis.

These findings are consistent with the existing literature linking atherosclerosis to several chronic inflammatory diseases including psoriasis, rheumatoid arthritis and inflammatory bowel disease, independent of other cardiovascular risk factors [32]. One possible explanation for this is that both HS and atherosclerosis are chronic inflammatory diseases. HS patients have been found to have elevated markers of systemic inflammation including tumor necrosis factor (TNF) [34], C-reactive protein (CRP) and leukocytosis [35]. Increased expression of the inflammatory cytokines IL-B, IL-10, IL-17 and TNF have also been found in HS lesions [36].

Section 5: "Inflammatory Bowel Disease"

There is growing evidence of an association between HS and inflammatory bowel disease (IBD). This was first highlighted by case series showing clustering of HS in patients with IBD [37]. In 2014, a cross-sectional study of 1093 patients with IBD found a 23% prevalence of HS (26% in Crohn's disease [CD] and 18% in ulcerative colitis [UC]) [38]. In 2016, a population-based epidemiologic study showed that patients with IBD had 9-times the prevalence of HS compared to the general population [39]. Another paper from 2016 (a retrospective study of patients with both HS and IBD) found that HS was more commonly associated with CD than UC, and was also more common among African American women [24]. Interestingly, patients with co-morbid HS and IBD have been found to have both more severe HS disease, and more severe IBD [24, 39].

Patients with CD have been found to have a distinct clinical manifestation of HS that predominantly involves the perineal and perianal regions. Given the predilection of HS for this region in CD patients, it can be difficult to differentiate HS from cutaneous CD. There are key clinical differences that can help make the diagnosis. For example, CD lesions tend to be more ulcerative and have more retractile scars than HS lesions. CD lesions tend to involve the anorectal skin and initial rectal mucosa more than HS. Additionally, CD lesions commonly create fistulas and strictures whereas in HS, comedones, nodules, skin bridging and sinuses are often present. In difficult cases, some authors have suggested that MRI can be useful to distinguish between the two [24, 25].

Section 6: "inflammatory Arthropathies"

Rates of inflammatory arthropathies are significantly higher among HS patients compared to controls. The first prospective study on the topic included 640 HS patients from France in which, 6.9% showed evidence of arthritis, enthesitis, or inflammatory back pain, and 3.7% were diagnosed with spondyloarthropathy by a rheumatologist using stringent diagnostic criteria, a rate that is significantly higher than the 0.3% prevalence of spondyloarthropathy in the general French population [40]. In line with these findings, a large study conducted of 1730 HS patients and 1730 controls found a 52.5% prevalence of arthropathy among HS patients, compared to only 3.0% in controls ($p<0.0001$). In this study, arthropathy was associated with 9.41-fold greater odds of having HS, after controlling for co-morbidities (95% CI 6.81-12.9) [4]. Further supporting a pathogenic link between HS and inflammatory arthritis, there have been reports of patients with HS and inflammatory arthritis who experience arthritis flares in conjunction with HS flares and improvement of arthritis after surgical treatment of HS [41, 42].

It has been postulated that chronic exposure to cutaneous antigens not usually encountered systemically triggers immune activation leading to an inflammatory arthropathy [25]. An alternate hypothesis is that arthropathy develops as a reaction to chronic skin infection in HS patients [43].

Section 7: "Rare inflammatory syndromes"

The co-existence of HS with several other inflammatory conditions has been highlighted in case series and reports. These reports are only anecdotal and these associations have not been formally studied. Because of the lack of quality evidence, we will only briefly mention some of these conditions here.

Case reports and series have linked pyoderma gangrenosum to HS both independently, and in reports describing pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH), pyogenic arthritis, pyoderma gangrenosum, acne and suppurative hidradenitis (PAPASH), psoriatic arthritis, pyoderma gangrenosum, acne and suppurative hidradenitis (PsAPASH) syndrome [5]. It has been hypothesized that pyoderma gangrenosum and HS are both auto-inflammatory diseases, caused by cytokine dysregulation by the innate immune system [44]. There have also been reports of the coexistence of HS with another auto-inflammatory diseases called Adamantiades-Behcet disease [45].

HS can be a manifestation of SAPHO syndrome (an acronym for synovitis, acne, pustulosis, hyperostosis, and osteitis) [46]. SAPHO syndrome can be diagnosed by meeting one of three criteria. The first is chronic recurrent multifocal non-infectious osteomyelitis with or without skin manifestations. The

second is acute or chronic sterile arthritis associated with pustular psoriasis, palmoplantar pustulosis, acne or HS. The third is sterile osteitis associated with pustular psoriasis, palmoplantar pustulosis, acne or HS [43].

Other conditions that have co-existed with HS in the literature include pachyonychia congenital, Dowling-Degos disease and the keratitis-ichthyosis-deafness (KID) syndrome [47-49] .

Section 8: "Skin Cancer"

There is contradictory literature regarding an association between HS and skin cancer, specifically squamous cell carcinoma (SCC). Dozens of case reports have documented the development of SCC in HS patients. Some articles suggest an increased rate of SCC in patients as a result of malignant transformation of their HS lesions. In the largest case series (13 cases) published on the topic, authors found 13 out of 13 of their cases were in men, and that in 12 out of 13 cases, SCC occurred in the perineal, perianal and gluteal regions (areas of high disease activity). They also found that despite the fact that these patients had well-differentiated SCC on histology, a disproportionate number of patients suffered from aggressive disease with poor outcomes. 11 out of 13 of the patients in this case series had recurrence of SCC, 2 patients had lymph node metastases at the time of diagnosis, 3 patients developed visceral metastases, and over half of the patients died within a few months of their diagnosis of SCC. These authors hypothesized that the association of SCC and HS was at least partially due to chronic inflammation of the skin seen in HS [50]. Other articles have found increased rates of SCC in HS, but with no male predominance and no predilection for sites of HS activity [4, 51]. This raises the question of whether the increased prevalence of SCC in HS patients seen in these studies is the result of ascertainment bias, since HS patients see dermatologists more frequently than the general population. That said, even though this was a small, 13 case series, and even though the findings have not been reported again in the literature, the findings that HS patients may be at risk for more aggressive, fatal SCC merits some attention.

Section 9: "Endocrine disorders"

The epidemiology of HS seems to point towards the role of sex hormones in the pathogenesis of HS. HS is over three times more common in females than males. It emerges after puberty, most often in the third to fourth decades of life, and rarely develops after menopause [52]. It associated with premenstrual flare ups and often improves during pregnancy [11]. Additionally, there are reports of the efficacy of anti-androgen therapy in the treatment of HS, bolstering the theory that sex hormones are involved in the pathophysiology of HS [52]. Interestingly, however, there is

little evidence supporting a link between HS and sex hormone disorders.

Some studies have found an association between polycystic ovarian syndrome (PCOS) and HS, even after adjusting for the co-morbidities, including obesity [4]. Other studies, however, have failed to demonstrate a difference in levels of major sex hormones (estrogen, progesterone, testosterone, dehydroepiandrosterone sulfate) in the serum of HS patients compared to controls [53]. Furthermore, HS patients tend to have normal androgen levels and rarely exhibit signs of virilization [23]. It has been postulated that HS may be a disorder of in-situ hormonal dysregulation in the skin. However, studies have found no difference in the peripheral apocrine gland androgen converging enzymes, androgen or estrogen receptor expression in HS patients compared to controls [54, 55].

Section 10: "Psychiatric disorders and quality of life"

Multiple studies have found that patients with HS suffer from a lower quality of life than the general population [56, 57]. Compared to other dermatologic conditions (e.g. neurofibromatosis-1, chronic urticaria, psoriasis, atopic dermatitis), HS has a greater impact on quality of life [56, 58, 59].

HS patients have a higher incidence of depression compared to the general population. Estimates of the rates of depression among HS patients have been as high as 48%, over twice as high as the estimated rate in the general population [16, 18, 60]. In a large study of 3207 dermatologist-diagnosed HS patients and 6412 age and sex-matched controls, there was a significantly higher prevalence of depression and anxiety in the HS group, with odds ratios and 95% confidence intervals of 1.7 (1.4-2.0) and 1.6 (1.3-2.1), respectively ($p<0.001$). No significant difference was found between the HS group and controls for schizophrenia and bipolar disorder [61].

In a randomized controlled trial, researchers have found that depression and quality of life significantly improve after treatment of HS with adalimumab [62]. It is unclear if this effect is related to adalimumab specifically, or if improvement in disease by any means leads to improvement in mental health and quality of life, but it is an intriguing finding and highlights the importance of measuring effects of the psychosocial impact of disease when studying treatments.

Section 11: "Conclusion"

Hidradenitis suppurativa is a chronic inflammatory disease, which is much more than just than just a skin condition. This condition can be debilitating for patients leading to a impaired quality of life. As described above, the understanding of HS and its co-morbid conditions is still in its early stages, but it is evident that these patients are at

higher risk for many other medical conditions. Although guidelines for the management of HS have not yet been established, we feel a multidisciplinary approach should be utilized to improve the overall health of patients.

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