

Original article

Association of hidradenitis suppurativa with autoimmune disease and autoantibodies

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Abstract

Objective. There is thought to be an association between hidradenitis suppurativa (HS) and autoimmune diseases. This retrospective longitudinal cohort study looked to identify whether certain autoimmune diseases or autoantibody specificities are more closely associated with HS than others and whether such associations are related to the severity of HS.

Methods. Patients were identified using the SlicerDicer search tool in Epic from 1 January 2010 to 15 August 2020. Search criteria included HS diagnosis by ICD-10 code (L73.2) and at least one visit to the dermatology department. Charts were reviewed to determine HS disease severity, treatment modalities, presence of autoimmune disease and autoantibody positivity.

Results. Six hundred and twenty-seven patients were identified. Most patients were female (75.3%) and had obese BMIs (71.1%), but there were no significant demographic differences between HS patients with and without autoimmune diseases. One hundred and one (16.1%) patients in the total cohort had at least one autoimmune disease, most commonly thyroid disease, lupus, psoriasis and IBD. Two hundred and twelve patients were also tested for the presence of autoantibodies. The most common positive autoantibody, found in 54 patients (28.4%), was ANA. Fifty-four patients with more severe HS disease manifestations required biologic medications to treat their HS. Neither HS severity nor biologic treatment was associated with presence of autoimmune disease or positive autoantibodies.

Conclusion. In a large cohort of patients with HS followed longitudinally, autoimmune disorders (especially lupus, psoriasis and IBD) and presence of autoantibodies were more commonly observed than expected in the normal population.

Key words: autoimmune disease, autoinflammatory disease, autoantibodies, hidradenitis suppurativa, biologics, dermatology, rheumatology

Key messages

- There is a higher prevalence of autoimmune diseases and autoantibodies in the hidradenitis suppurativa population.
- No specific correlation between presence of autoimmune disease or autoantibodies and hidradenitis suppurativa severity was identified.

Introduction

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory dermatological condition that usually occurs in intertriginous areas [1–10]. HS is a very painful

disease that causes tender nodules, abscesses, sinus tracts, fibrosis and scarring [1–10]. The severity of HS is assessed via the Hurley staging system [1–6, 9]. Hurley stage I (mild) is recurring nodules and/or abscesses [1–6]. Hurley stage II (moderate) is recurring, separated

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nodules and/or abscesses with sinus tract formation and/or scarring [1–6]. Hurley stage III (severe) is multiple, interconnected sinus tracts and scarring in an anatomical region [1–6]. Commonly affected areas include the neck, axillae, breasts, inframammary areas, abdomen, inguinal areas, groin, perineum, buttocks and perianal areas [1–9, 11].

The prevalence of HS in the USA and Europe ranges from 0.3 to 4% [1–5, 8, 9]. Peak incidence is in the second and third decades of life [1–4, 8]. Females are more commonly affected than males, with a ratio of ~3:1 [1–4, 8].

Although the exact cause of HS is still unknown, evidence from both clinical and pathological studies suggests that it might be related to an inflammatory or autoimmune process [1, 3–8, 10, 12]. The occurrence of HS has a strong correlation with tobacco use, whether current or previous, and obesity [1–5]. In addition to these, other diseases have been associated more recently with HS, including many inflammatory disorders [2–5, 7, 8, 11]. Some of the diseases most frequently associated with HS include metabolic syndrome, polycystic ovarian syndrome (PCOS), pyoderma gangrenosum, IBD and seronegative spondyloarthropathies [2, 4–6, 8, 11]. Other autoimmune diseases that are less commonly cited in connection with HS include SLE, SS, psoriasis, PsA and RA [4–6, 8, 11]. The relationship between HS and autoimmune diseases is especially interesting, considering the relatively recent use of immunosuppressive medications to treat HS [2–8]. It has been observed that HS and rheumatological diseases can overlap in clinical and laboratory findings, diagnoses and treatment [2–8]. This study examines the association between HS and autoimmune diseases further.

Methods

This was a retrospective observational study that was approved by the MetroHealth system institutional review board. Requirement for informed consent was waived. Patients were identified through our electronic medical record (EMR) platform (Epic) using the SlicerDicer search tool. Patients were retrieved from 1 January 2010 to 15 August 2020 by searching for the HS ICD-10 code (L73.2) with at least one dermatology visit. Patient data extracted from chart review included patient age, sex, year of diagnosis, duration of symptom presence, disease severity, medications used to treat HS, co-morbidities, smoking status and BMI. Patient data were collected from two major academic institutions: a large urban public hospital (Case Western Reserve University at MetroHealth Medical Center) and a large international referral center (Cleveland Clinic Foundation).

Statistical analysis was performed on the collected data. The odds ratio (OR) of association between sex and autoimmune disease was calculated at a 95% CI. Relative risk of autoimmune disease among different HS severities was calculated at a 95% CI. Multiple regressions were performed to determine which variables, of those listed in the

analysis, were most closely associated with HS disease severity and autoimmune disease. Variables studied were either previously known to have associations with HS or were of clinical interest for this study.

Results

Six hundred and twenty-seven patients were identified. Demographic information for this cohort is presented in Table 1. As has been found in other studies previously, our HS patients were predominantly female with a ratio of almost exactly 3:1 [1–4, 8]. There were two patients who were transgender (one male to female and the other female to male). Most of our patients had obese BMIs (71.1%) and exposure to tobacco (73.4%), which supports their known associations with HS [1–5]. Most patients were of middle age (26–55 years).

The HS severity/Hurley staging was available for 385 of the 627 patients. Where listed, disease severity was classified as either Hurley stage I (mild), II (moderate) or III (severe). If multiple stages or severities were found in a single patient chart, we used the highest severity grading. One hundred and sixty-one patients were classified as Hurley stage I or mild (41.8%). One hundred and twenty-six patients were classified as Hurley stage II or moderate (32.7%). Ninety-eight patients were classified as Hurley stage III or severe (25.5%). Relative risk of autoimmune disease in mild vs moderate HS was 1.77 (95% CI: 1.01, 3.12, $P=0.04$). Relative risk of autoimmune disease in severe vs moderate HS was 1.63 (95% CI: 0.87, 3.04, $P=0.14$).

There were 101 (16.1%) HS patients with concurrent autoimmune disease. We recorded specific autoimmune diseases and their associations with HS severities (Table 2). The prevalence of autoimmune diseases in HS patients was much higher than the 3–5% prevalence observed in the general population [13]. There were numerically more women than men with autoimmune disease (OR 1.14, 95% CI: 0.69, 1.88, $P=0.71$).

In addition to autoimmune diseases, we also looked for autoimmune serologies in HS patients. Two hundred and twelve patients were tested for the presence of autoantibodies. One hundred and ninety patients were tested for ANAs and ENA antibodies. The prevalence of positive ANAs among the HS patients in our study (54, 28.4%) was higher than in the general population (~3–5%) and in a previous study of HS patients (5.5%) [14]. Twenty-five patients with positive ANA results did not have any autoimmune disease. Five of these 25 patients also had positive ENA antibodies. Not unexpectedly, 10 positive ANA test results were found in patients with non-rheumatological autoimmune diseases, including alopecia areata, pyoderma gangrenosum, multiple sclerosis, Grave's disease, Hashimoto's thyroiditis, scleritis, pernicious anaemia and DM1. One hundred and twenty-two patients were tested for the presence of RF. Six positive RF tests were detected in patients with no history of autoimmune disease, although one of those patients had HCV, which is known to be associated

TABLE 1 Patient demographics

Characteristic	Total (n = 627)	Patients with autoimmune disease (n = 101)	Patients without autoimmune disease (n = 526)
Mean age, years	42.17	45.38	41.57
Age range, n (%)			
<18 years	2 (0.3)	0 (0)	2 (0.38)
18–25 years	50 (7.97)	5 (5)	45 (8.6)
26–40 years	249 (39.7)	32 (31.7)	217 (41.3)
41–55 years	201 (32.1)	42 (41.6)	159 (30.2)
56–65 years	101 (16.1)	17 (16.8)	84 (16.0)
≥66 years	24 (3.83)	5 (5)	19 (3.6)
Sex, n (%)			
Male	155 (24.7)	23 (22.8)	132 (25.1)
Female	472 (75.3)	78 (77.2)	394 (74.9)
BMI, n (%)			
Normal	64 (10.2)	13 (12.9)	51 (9.7)
Overweight	113 (18)	18 (17.8)	95 (18.1)
Obese	446 (71.1)	69 (68.3)	377 (71.7)
No BMI or height available	4 (0.6)	1 (0.99)	3 (0.6)
Mean BMI, kg/m ²	35.93	35.33	36.04
Tobacco use, n (%)			
Never (but with passive exposure)	12 (1.9)	0 (0)	12 (2.3)
Never	154 (24.6)	31 (30.7)	122 (23.2)
Former tobacco use	156 (24.9)	23 (22.8)	133 (25.3)
Current tobacco use	304 (48.5)	46 (45.5)	258 (49.1)
Unknown	1	1 (0.99)	0 (0)

TABLE 2 Hidradenitis suppurativa severity by autoimmune disease (excluding non-rheumatologic and uncommon rheumatologic autoimmune diseases)

Autoimmune disease	Total number of patients	No severity [n (%)]	HS stage I/mild [n (%)]	HS stage II/moderate ^a [n (%)]	HS stage III/severe ^b [n (%)]
SLE	14	6 (42.9)	4 (28.6)	3 (21.4)	1 (7.1)
Psoriasis/PsA	14	3 (21.4)	9 (64.3)	1 (7.1)	1 (7.1)
IBD	13	4 (30.8)	2 (15.4)	3 (23.1)	4 (30.8)
Inflammatory arthritis (including ReA) ^c	9	2 (22.2)	1 (11.1)	1 (11.1)	5 (55.6)
RA	6	1 (16.7)	3 (50)	1 (16.7)	1 (16.7)

^aIncludes HS stage I–II/mild–moderate and stage II/moderate. ^bIncludes HS stage II–III/moderate–severe and HS stage III/severe. ^cBoth patients with ReA had stage III/severe HS. HS: hidradenitis suppurativa.

with positive RFs. One positive RF was associated with Hashimoto's thyroiditis without any rheumatological disease, but this patient also had HCV. Sixty patients were tested for CCP antibodies. Only one patient with positive CCP antibodies had a non-rheumatological autoimmune disease (Grave's disease). Twenty-eight patients were tested for ANCAs. Eighteen patients were tested for HLA-B27. Sixteen patients were tested for aPL.

We also investigated which medications were used to treat HS. Most patients were treated with oral antibiotics, topical antibiotics, antibacterial washes, intralesional CSs, surgical excision, and incision and drainage.

Biologic agents were also used to treat HS in some patients. We queried specifically how many patients received biologic agents for HS treatment. Among 54 patients who required biologic treatment for their HS, 60 courses of TNF inhibitors were used to treat HS (adalimumab: 48; infliximab: 9; etanercept: 2; golimumab: 1). Six patients were treated with ustekinumab, an IL-12 and IL-23 inhibitor. One patient was treated with apremilast, a phosphodiesterase 4 inhibitor. Another 39 patients either discussed starting a biologic or switching biologics with their treating physician. The average number of treatments tried before starting biologics was 7.9.

TABLE 3 Multiple regression for variable association with severity of hidradenitis suppurativa

Parameter	Odds ratio	95% CI	P-value
Age	1.01	0.98, 1.04	0.510
Male sex	14.23	4.83, 41.94	0.000
Autoimmune disease	1.02	0.46, 2.25	0.967
Tobacco status	4.10	0.78, 21.66	0.096
BMI	1.02	0.98, 1.05	0.366
ANA positivity	0.67	0.30, 1.50	0.329

There were 133 observations. Bold indicates significant results.

Of the 54 patients treated with biologic medications for whom disease severity was available, all had at least Hurley stage II or moderate disease, and most (36, 66.7%) were classified as stage III or severe. Thirteen (24%) of the patients who required biologics had concomitant autoimmune disease. Nine (16.7%) of the patients on biologics had positive serologic tests. Five of those with positive serologies did have a diagnosed autoimmune condition.

Eleven patients were on biologics for their autoimmune disease and not for HS. The biologics for these patients included: adalimumab (9), ustekinumab (7), infliximab (3), apremilast (4), etanercept (3) and 1 each on abatacept, ixekizumab and vedolizumab. All the patients on biologics for their autoimmune disease had less severe HS than those on biologics specifically for their HS.

Multiple regression analysis was performed to determine whether age, sex, tobacco use, autoimmune disease, positive ANA or BMI could significantly predict HS disease severity (Table 3). Male sex (OR 14.23, 95% CI: 4.83, 41.92, $P=0.000$) seemed to be the best predictor of HS disease severity. Another multiple regression was performed to determine whether HS disease severity, age, sex, BMI or tobacco use was associated with development of autoimmune disease (Table 4). Age (OR 1.03, 95% CI: 1.01, 1.05, $P=0.011$) seemed to have the closest association with development of autoimmune disease.

Discussion

Hidradenitis suppurativa is a dermatological condition that has long been associated with autoimmune conditions [2–6, 8, 11]. In our cohort of 627 HS patients, autoimmune disease was much more prevalent than in the general population [13]. Autoimmune thyroid disease, the most common autoimmune disease in humans, was also the most prevalent autoimmune disorder in patients with HS. Among rheumatic diseases, lupus and psoriasis/PsA, both of which have prominent dermatological involvement, were the most frequent disorders associated with HS. We also found a higher prevalence of autoimmune serologies, particularly ANA, among HS patients. The higher rates of autoimmune diseases and autoantibodies among HS

TABLE 4 Multiple regression for variable association with autoimmune disease

Predictor	Odds ratio	95% CI	P-value
Male sex	0.84	0.40, 1.68	0.640
Age	1.03	1.01, 1.05	0.011
Moderate HS	0.53	0.26, 1.03	0.065
Severe HS	0.82	0.41, 1.60	0.564
Current smoker	1.28	0.64, 2.66	0.490
Never smoker	1.76	0.82, 3.89	0.150
BMI	1.01	0.98, 1.04	0.581

There were 382 observations. Bold indicates significant results. HS: hidradenitis suppurativa.

patients underscores that HS is itself, possibly, an autoinflammatory or autoimmune condition [1, 3–8, 10, 12]. Future research into the pathogenesis of HS might elucidate its autoimmune or autoinflammatory mechanisms. In the meantime, it is prudent to ensure that patients presenting with HS do not have any signs or symptoms of other autoimmune diseases.

Although there definitely seems to be a strong correlation between HS and autoimmune disease, the mere co-existence of autoimmune disease and/or autoantibodies does not seem to be related to the severity of HS or to whether biologics are used for treatment of HS. The constraints of retrospective chart review and missing information in patient charts limited the value of the multiple regression analysis, because patients with missing data were excluded from the analysis. However, of the patients included in the analysis, male sex seemed to have the highest predictive value for HS severity and age seemed to have the highest predictive value for concurrence of autoimmune disease. Autoantibodies or the presence of autoimmune disease did not appear to influence HS disease severity. Given the rarity of some autoimmune diseases, our sample sizes are too small to generalize about patterns of specific autoimmune diseases and their association with HS disease severity.

Biologics are used to treat both autoimmune disease and HS, which raises the question of whether there is an association between treatment of HS with biologics and presence of autoimmune disease. Given that having an autoimmune disease does not seem to influence HS disease severity, HS severity seems to be the determining factor in whether it is treated with biologics. The most common biologics used were TNF inhibitors, specifically adalimumab. Future prospective studies might be warranted to investigate whether those with autoimmune disease and/or autoimmune serologies respond better to treatment of their HS with biologics.

Given the correlation between HS and autoimmune diseases, patients who present with HS should probably be assessed and followed for occurrence of autoimmune disease. Given that autoantibodies are present in patients both with and without autoimmune disease,

serology laboratory testing should be performed selectively on patients, focused primarily on those with symptoms of autoimmune disease. Moreover, the presence of autoimmune disease and/or autoantibodies might not assist with treatment strategies, according to our review.

Our study provided information and insight from a large number of patients with HS. Given that our study relied on retrospective chart review, not all the relevant information was available for every patient. Owing to this limitation, we did not have information on disease severity for all patients involved. Also, because of the retrospective nature of this study, not all patients had autoimmune status tested, even over the substantial duration of follow-up for many patients. It is unclear whether the number of autoantibodies present might have been higher if they had been tested for in all patients. We only had access to the information within the Case Western Reserve University at MetroHealth Medical Center and Cleveland Clinic hospital systems. Owing to the limited exchange of information between hospital systems, we were unable to confirm whether any patients had been diagnosed with an autoimmune disease elsewhere. Access to many patients from these two large academic institutions was, however, one of the strengths of this study because of the large and diverse patient population we were able to evaluate.

Despite the limitations, this review suggests that patients with HS should be evaluated routinely for concurrent autoimmune diseases and, possibly and selectively, for the presence of autoantibodies. Our longitudinal retrospective review supports that there is a compelling connection between HS and autoimmune disease that requires further exploration.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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