Hidradenitis suppurativa

Epidemiology, clinical presentation, and pathogenesis

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Learning objectives
After completing this learning activity, participants should be able to recognize the clinical features of hidradenitis suppurativa and describe the mechanism of hidradenitis suppurativa progression based on recent literature.

Disclosures
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Hidradenitis suppurativa (HS) is an inflammatory disorder that is characterized by chronic deep-seated nodules, abscesses, fistulae, sinus tracts, and scars in the axilla, inguinal area, submammary folds, and perianal area. This disfiguring condition is accompanied by pain, embarrassment, and a significantly decreased quality of life. Although the mechanism of HS has not been entirely elucidated, lesion formation is believed to center around follicular hyperkeratosis within the pilosebaceous—apocrine unit. Recent research has provided new insight into the role of cytokines in the pathogenesis of HS, helping close some existing knowledge gaps in the development of this condition. The first article in this continuing medical education series reviews HS epidemiology, clinical presentation, and classification. We also provide an update on the most recent understanding of HS pathogenesis, including the central role of inflammatory cytokines and other contributing factors, such as genetics, hormones, and pathogenic microorganisms. (J Am Acad Dermatol 2020;82:1045-58.)

Key words: hidradenitis; hidradenitis suppurativa; IL-17; pathogenesis; TNF-α.

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Hidradenitis suppurativa (HS) was first described by a French surgeon in 1839.[1] In 2009, the HS Foundation adopted a consensus definition: "HS is a chronic, inflammatory, recurrent, debilitating, skin follicular disease that usually presents after puberty with painful deep-seated, inflamed lesions in the apocrine gland–bearing areas of the body, most commonly, the axillary, inguinal, and anogenital regions."[2] There is agreement that the diagnosis requires a history of ≥5 typical lesions (erythematous papules, nodules, or abscesses) in flexural sites,[3] with a recurring nature over time.[4]

EPIDEMIOLOGY

Key points

- **The prevalence of HS is unknown, but estimates range from 0.00033% to 4.10%**
- **HS most frequently occurs in young adults**
- **HS is more than twice as common in women compared with men, and is more common in African Americans and biracial individuals than whites**

HS prevalence is unclear. Estimates range from 0.00033% to 4.10%.[5] Higher estimates are derived from prospective[6] and self-reported studies[7,8]; lower estimates derive from registries.[9-12] A retrospective analysis of >48 million patients in the United States found an HS prevalence of 0.1%. The adjusted prevalence for women was more than twice that for men, and there was a 3-fold and 2-fold higher prevalence in African Americans and biracial individuals, respectively, compared with whites.[13]

HS incidence is also uncertain. The same retrospective study found an annual incidence of 11.4 cases per 100,000, with twice the incidence in women compared with men; in African Americans, it was 2.5 times that of whites.[14] Data from 1968 to 2008 revealed an annual age- and sex-adjusted incidence of 6 cases per 100,000; women 20 to 29 years of age had the highest incidence.[15] A 5-year retrospective cohort study from across the United States validated these findings: among 40,585 patients with HS, the majority (63.3%) were 18 to 44 years of age and were women (75.6%).[16]

QUALITY OF LIFE

Key points

- **HS significantly decreases patients' quality of life**
- **Depression and pain are associated with HS**
- **HS leads to social and work impairment**

HS dramatically decreases quality of life (QoL). Patients report embarrassment, self-consciousness, and an inability to participate in social and athletic activities.[17] Depression, anxiety, pain, high body mass index (BMI), and work impairment are the main factors affecting QoL.[18,19] Depression occurs in 5.9% to 42.9% of patients with HS[15,19-22] in both pediatric[18] and adult populations.[15,17,21] Pain affects ≤97% of patients[23-25] and is significantly worse compared with psoriasis and other diseases.[26] Higher BMI (>25 kg/m^2) also impacts self-evaluated health, QoL, and work impairment.[27] Two studies found that 21.3% to 25.2% of patients with HS patients are unemployed[17,28] and that 9.4% are out of work because of disability.[17] Substance use is also common, occurring in 4% of patients with HS (n = 32,625) compared with 2% of patients without HS (n = 9,581,640; $P < .001$).[22] The most common substances used were alcohol followed by opioids and cannabis.[22] Of greatest concern, there is an increased risk of completed suicides in patients with HS,[29] which is greater than 2-fold the risk of suicide in patients with psoriasis.[30]

PRESENTATION AND CLINICAL CLASSIFICATION

Key points

- **HS is diagnosed by clinical features and history, and there are multiple scoring systems used for the classification of disease severity**
- **Lesions include deep-seated nodules, abscesses, and sinus tracts that rupture and form scars**
- **The Hurley staging system is the most widely used HS classification system**
- **There are several clinically distinct HS phenotypes**

HS is diagnosed clinically; pathologic confirmation is unnecessary.[31-33] There are 3 criteria for diagnosis: characteristic lesions, predilection for flexural sites, and lesion recurrence.[34]

While disease presentation varies,[35] characteristic lesions are deep-seated nodules that expand to form abscesses[36] that subsequently rupture and drain.[33] The initial lesions are "blind boils," which can progress to draining sinuses, bridged scars, and open "tombstone" comedones.[33] Fibrosis results in scarring.[33] Lesions favor the axillae and the inguinal area, but also occur in the submammary folds, perineal area, buttocks, mons pubis, scalp, the postauricular area, and the back.[37,38] There is often

a significant delay between symptom onset and the establishment of diagnosis (average 7.2 years), which underscores the need for familiarity with the above diagnostic criteria.[39]

Most patients have >1 lesion at the time of diagnosis.[37] Lesions are usually accompanied by discomfort, pruritus, and pain[23,36]; many patients experience prodromal pain symptoms.[33] Factors including heat, sweating, physical activity, shaving, and friction exacerbate symptoms.[21,40] Acute exacerbations alternating with periods of quiescence is typical.[33]

The most common HS classification system is the Hurley staging system,[41] which is a 3-stage classification of disease severity designed to help select treatment[42]; unfortunately, it fails to assess disease activity or treatment response. However, other classification and scoring methods exist. The modified Sartorius score quantifies disease intensity in a more clinically meaningful way on an open-ended scale.[43,44] The Hidradenitis Suppurativa Severity Score Index also assesses disease activity and severity.[45,46] The Hidradenitis Suppurativa Clinical Response is a dichotomized clinical tool that measures treatment response.[47-49] The Physician's Global Assessment, commonly used for diseases like psoriasis and acne,[50,51] has also been adapted into an HS-specific version.[52] Table I summarizes these systems.

The Hurley staging system has been shown to have good interrater reliability and is considered an acceptable instrument for the classification of HS.[42] The modified Sartorius score, Hidradenitis Suppurativa Severity Score Index, Hidradenitis Suppurativa Clinical Response, and HS Physician's Global Assessment have been found to have lower agreement between assessors.[42] More recently, a refined Hurley staging system that subdivides stages I and II into mild (A), moderate (B), and severe (C), was proposed to help guide treatment.[53] This refined system more accurately reflects disease severity according to patient-reported QoL and physician-assessed Hidradenitis Suppurativa Severity Score Index.[54] There is also a validated HS severity self-assessment tool for survey research that allows patients to report disease severity without being seen by a physician. One study found a 66.7% agreement between physician-determined Hurley stage and self-determined Hurley stage via the HS severity self-assessment tool.[55]

There are multiple HS phenotypes (Table II).[49] These distinct clinical subtypes are not based on disease severity; all 3 Hurley stages can occur in each type. The regular type is the most common, and consists of patients who fulfill the diagnostic criteria for HS but who lack other specific characteristics.[49] The frictional furuncle type features lesions in frictional sites in patients who are overweight.[49] The conglobata type consists of cysts and acne conglobata primarily on the face and trunk in men who are not overweight.[49] The syndromic type features concomitant diseases, such as pyoderma gangrenosum and arthritis.[49] Finally, the ectopic type involves the face.[49] Although these phenotypes do not guide therapeutic decisions, consideration of these phenotypes may help optimize disease management.[56]

COMORBIDITIES AND RISK FACTORS

Key points

- **HS is associated with many comorbidities, most of which are inflammatory in nature**
- **Obesity is the most common comorbidity associated with HS**
- **There is a strong association between HS and tobacco smoking**
- **There is an increased prevalence of HS among psoriasis patients**
- **HS is a component of the follicular occlusion triad/tetrad**

HS patients have an incredibly high comorbidity burden.[57,58] Hypertension, obesity, dyslipidemia, thyroid disorder, arthropathies, psychiatric disorders, and polycystic ovarian syndrome have all been independently associated with HS (Table III).[57] While the exact connection between HS and its comorbidities remains unclear,[59] many associated disorders are also inflammatory.

Adverse cardiovascular outcomes (myocardial infarction, ischemic stroke, and cardiovascular-associated death) and all-cause mortality are significantly increased in patients with HS independent of age, sex, socioeconomic status, smoking, and medications.[60] Atherosclerosis has been associated with increased serum levels of C-reactive protein and tumor necrosis factor−α, which are also elevated in HS.[60]

Metabolic syndrome (MetS), which includes diabetes mellitus, hypertension, dyslipidemia, and obesity, is associated with chronic inflammation[61] and HS.[33,62,63] Hospitalized and nonhospitalized patients with HS have an odds ratio of 3.89 and 2.08, respectively, of being diagnosed with MetS compared with healthy patients.[61] Of the diseases comprising MetS, however, obesity is the most commonly associated: 50% to 75% of patients with HS are overweight

Table I. Hidradenitis suppurativa classification systems

Scoring system		Description				
Hurley score	Stage I	Single or multiple isolated abscesses without sinus tracts or scarring				
	Stage II	Recurrent abscesses with ≥1 sinus tracts and scarring, separated by normal skin				
	Stage III	Diffuse boils with multiple interconnected sinus tracts and no intervening normal skin.				
Modified Sartorius score	Anatomic regions involved	3 points per region: axilla, groin, gluteal, other				
	No. and scores of lesions	1 point for nodule, 6 points for fistula, for each region				
	Longest distance between 2 lesions	1 point if <5 cm; 3 points if 5-10 cm, 9 points if >10 cm. If 1 lesion, use same point system for size of lesion				
	Lesions clearly separated by normal skin	0 points if yes, 9 points if no				
HS Physicians' Global Assessment	Clear: 0	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, 0 noninflammatory nodules				
	Minimal: 1	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, presence of noninflammatory nodules				
	Mild: 2	0 abscesses, 0 draining fistulas, 1-4 inflammatory nodules, OR 1 abscess or draining fistula and 0 inflammatory nodules				
	Moderate: 3	0 abscesses, 0 draining fistulas, ≥5 inflammatory nodules OR 1 abscess or draining fistula and ≥1 inflammatory nodule OR 2-5 abscesses or draining fistulas and <10 inflammatory nodules				
	Severe: 4	2-5 abscesses or draining fistulas and ≥10 inflammatory nodules				
	Very severe: 5	>5 abscesses or draining fistulas				
Hidradenitis Suppurativa Severity Index		No. of sites	Body surface area	No. of erythematous and painful lesions	No. of dressing changes during work hours	Pain (visual analog scale)
	Stage 0	0	0	0	0	0-1
	Stage 1	1	1	1-2	0	0-1
	Stage 2	2	2-3	2-3	1	2-4
	Stage 3	3	4-5	4-5	>1	5-7
	Stage 4	≥4	>5	>5	>1	8-10
Hidradenitis Suppurativa Clinical Response	Hidradenitis Suppurativa Clinical Response achievers	≥50% reduction in the sum of abscesses and inflammatory nodules, no increase in the number of abscesses, and no increase in the number of draining fistulas from baseline				

or obese.[59] Obesity increases the proinflammatory response,[27] and high-BMI patients have higher Hurley scores, more affected areas, and worse self-reported severity compared with low-BMI patients.[64]

There is also a strong relationship between tobacco and HS, although a causal relationship has not been established. The prevalence of smoking in patients with HS is estimated at 70% to 90%,[65] and the odds ratio of a new HS diagnosis increases by 90% among tobacco smokers compared with non-smokers after adjusting for age, sex, race, and obesity.[66] Smoking also appears to correlate with obesity: 75% of tobacco smokers diagnosed with HS are obese.[66]

Psoriasis is also associated with HS. A study of 68,836 patients with psoriasis found that HS prevalence was increased in patients with psoriasis compared with age-, sex-, and ethnicity-matched control subjects (0.3% vs 0.2%).[67] This difference remains statistically significant after adjusting for smoking, obesity, and additional comorbidities. Psoriasis patients with coexistent HS are younger and have a higher prevalence of obesity and smoking.[67]

Table II. Hidradenitis suppurativa phenotypes[49]

Phenotype	Description
Regular	Patients fulfill the diagnostic criteria of HS
	Lack of additional specific characteristics
	Most common type
Frictional furuncle	Overweight patients
	Regular HS plus multiple deep nodules and abscesses on sites exposed to enhanced friction (abdomen, thighs, and buttocks)
Scarring folliculitis	Regular HS plus pustules, cysts, superficial nodules, depressed cribriform scarring, double ended comedones
	These lesions are frequently on buttocks, inguinal region, and pubic region
	Scarring of these lesions typically occurs
	Commonly occurs in overweight patients who smoke
Conglobata	Cyst formation and acne conglobata lesions on the back and the face
	This type is usually familial—initial γ-secretase mutations were found in this group
	Usually more severe (Hurley stage II-III)
	Patients are usually men and are not overweight
Syndromic	Patients have a syndromic constellation
	PASH syndrome
	PAPASH syndrome

HS, Hidradenitis suppurativa; *PAPASH*, pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa; *PASH*, pyoderma gangrenosum, acne, and hidradenitis suppurativa.

Table III. Comorbidities and risk factors for hidradenitis suppurativa[140]

Comorbidity/risk factor	Evidence level, grade of recommendation
Smoking	1, A
Cardiovascular disease	2, B
Metabolic syndrome	
Obesity	
Depression	
Diabetes mellitus	
Hypertension	
Hypertriglyceridemia	
Spondyloarthropathy	
Crohn disease	4, C

Several other conditions associated with a proinflammatory state have also been associated with HS. There is a 3.5% incidence of obstructive sleep apnea in patients with HS versus 2.5% in those without HS.[68] Inflammatory bowel disease (IBD), particularly Crohn disease (CD), also has possible epidemiologic and pathogenic connections with HS.[69,70] Analysis from 4 studies found HS prevalence in IBD and CD patients to be 12.8% and 17.3%, respectively. Inflammatory arthritis also has a higher prevalence in HS populations compared with the general population.[58,71] In a prospective study of 640 patients, 3.7% had comorbid spondylarthritis, and of those patients, HS preceded articular symptoms in >90%.[71]

Some dermatologic diseases share cutaneous pathology with HS. Hyperplasia of the pilosebaceous apparatus, follicular occlusion, and bacterial invasion are etiologic factors in acne conglobata and dissecting cellulitis as well as HS.[72] Together, these conditions constitute the follicular occlusion triad[72]; the addition of pilonidal cyst defines the follicular occlusion tetrad.[73] HS and acne can also be components of autoinflammatory syndromes. Pyoderma gangrenosum, acne, and hidradenitis suppurativa (PASH) is an established syndrome when all three conditions are present. If a patient has PASH with the addition of pyogenic arthritis, it is designated PAPASH.[74] Finally, chronic HS can transform into squamous cell carcinoma. The prevalence of squamous cell carcinoma associated with HS is approximately 4.6%.[75]

PATHOGENESIS

Key points

- **The primary event in HS is follicular hyperkeratosis, leading to rupture of the hair follicle and subsequent inflammation of apocrine glands**
- **TNF-α and interleukin-17 are key cytokines in HS pathogenesis**
- **Levels of TNF-α are higher in the lesional tissue of patients with HS than that of patients with psoriasis**

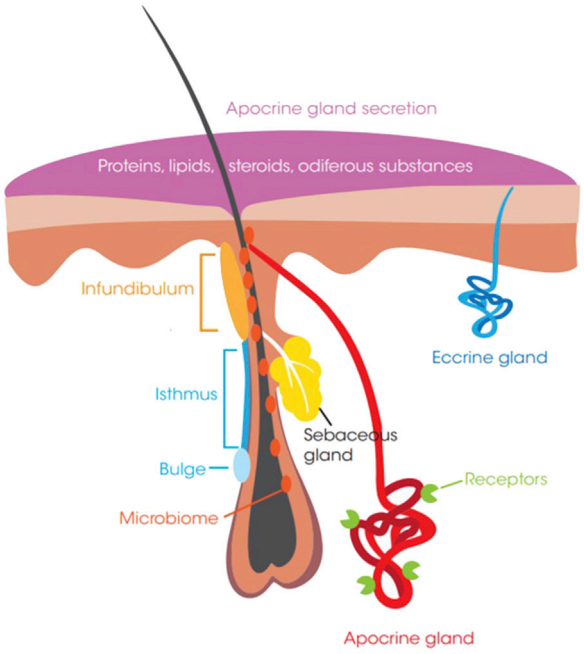

Fig 1. Pilosebaceous-apocrine unit. Adapted from Hoffman et al.[77]

- **Levels of TNF-α in lesional HS skin and serum levels of interleukin-17 correlate with disease severity**
- **The role of sex hormones in HS remains unclear**
- **Thirty percent to 40% of patients with HS have ≥1 family member with the disease, supporting a genetic predisposition**

The mechanism of lesion formation in HS centers around the pilosebaceous–apocrine unit, which contains a hair follicle associated with sebaceous and apocrine glands. Sebaceous glands secrete sebum, a group of complex oils that lubricate the skin.[76] Apocrine glands drain oily sweat through a dermal duct that passes through the hair follicle by a coiled acrosyringium above the sebaceous gland (Fig 1).[77]

Initially, apocrine gland inflammation was proposed as the primary event in HS.[78-80] Newer research suggests that follicular hyperkeratosis occurs first, causing plugging and dilation that results in follicle rupture with subsequent inflammation, abscess, and sinus tract formation (Fig 2).[80,81] Apocrine involvement appears secondary to dermal inflammation.[82] Patients with HS have no change in apocrine gland size, density, or distribution compared with healthy control subjects,[83] but they do tend to have a reduced volume of sebaceous glands.[82,84]

HS immunopathogenesis is complex and still being elucidated, but several cytokines appear to be particularly relevant (Fig 3).

TNF-α

TNF-α is secreted by innate and adaptive immune cells and is elevated in inflammatory diseases including rheumatoid arthritis, IBD, and psoriasis.[85-87] TNF-α is significantly increased in patients with HS compared with healthy control subjects and patients with psoriasis,[88,89] and TNF-α levels increase with increasing HS severity.[89]

The role of TNF-α in HS is multifactorial.[90] First, TNF-α increases the ratio of T_H17 to regulatory T cells, which results in increased production of T_H17 cells' disease-relevant cytokines.[88] TNF-α inhibition in patients with HS decreases this ratio, reduces the polyfunctionality of $CD4^+$ cells, and decreases IL-17–producing T cells, which ultimately reduces IL-22, interferon-gamma (IFN-γ), and IL-2–expressing $CD4^+$ T cells.[88]

Second, TNF-α acts on adipocytes and muscle cells to induce insulin-signaling defects[91] and suppresses the secretion of adiponectin from adipocytes.[92] Adiponectin is an antiinflammatory hormone that regulates glucose metabolism and insulin sensitivity.[93] It is negatively correlated with BMI; decreased circulating levels are associated with diabetes and MetS.[93,94] Adiponectin levels are significantly decreased in patients with HS.[92] Patients with HS have higher fasting serum glucose, insulin levels, and insulin resistance compared with control subjects, suggesting that HS, in part because of elevated TNF-α, might predispose to insulin resistance.[91]

Third, the relationship between smoking and HS is thought to involve TNF-α. Nicotine increases eccrine gland secretion, and nicotine excretion in sweat induces TNF-α release by keratinocytes and T_H17 cells. Nicotine directly stimulates macrophages to produce IL-1β and TNF-α and increases the expression of matrix metalloproteases (MMPs).[95] Nicotine induces infundibular epithelial hyperplasia, causing follicular occlusion and rupture.[66] Notably, nicotine acetylcholine receptors are found on all cells implicated in the pathogenesis of HS, including keratinocytes, sebocytes, mast cells, neutrophils, lymphocytes, and macrophages.[66]

Fourth, the upregulation of Toll-like receptors (TLRs) and MMPs has been observed in HS. TLRs are important for generating innate immune responses. TLR4 helps activate gene expression resulting in production of proinflammatory

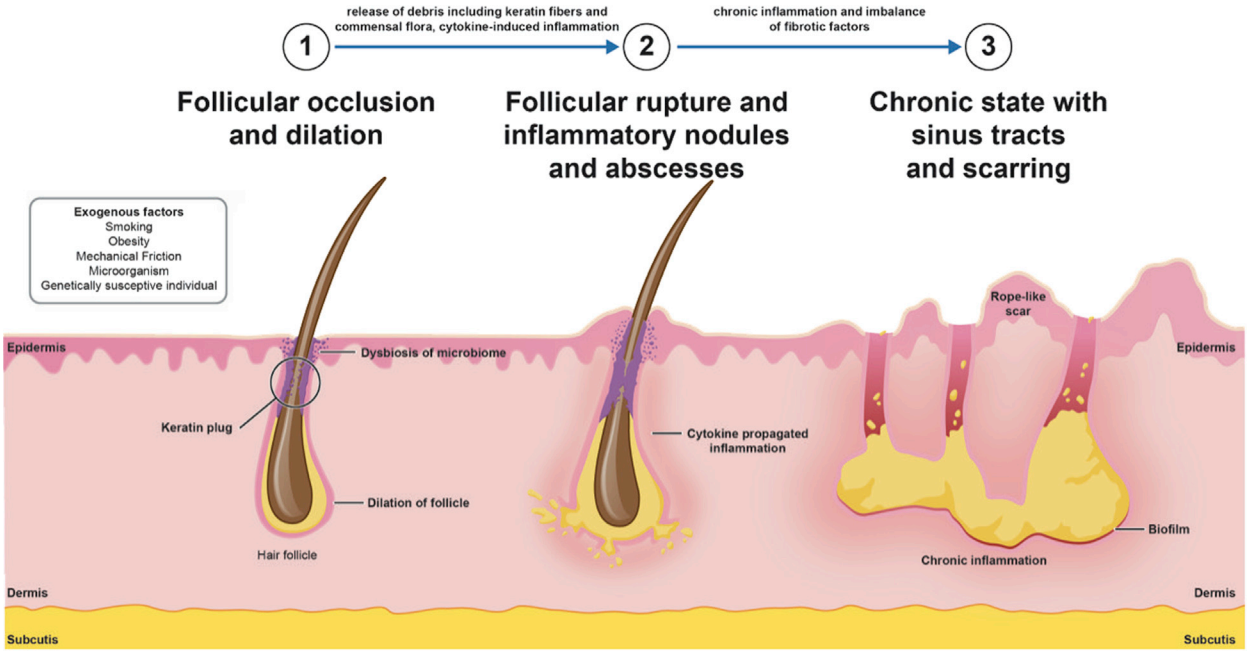

Fig 2. Postulated sequence of events underlying the pathophysiology of hidradenitis suppurativa. The first event is follicular occlusion with subsequent dilation. Endogenous factors in genetically predisposed individuals and exogenous factors (ie, smoking, friction, metabolic changes, and microbiome) contribute to occlusion of the follicular isthmus and early inflammation. The second event is rupture of the dilated follicle, propagation of cytokine-driven inflammation, and the formation of inflammatory nodules and abscesses. The third event is chronic inflammation and an imbalance of fibrotic factors that creates scarring and sinus tracts. Adapted from Vossen et al.[81]

cytokines including TNF-α, IL-1β, and IL-6, as well as antiinflammatory cytokines, such as IL-10.[96] MMPs also activate inflammatory effectors and directly lead to tissue injury.[95] MMP2 is activated by TNF-α, and MMP9 is induced by TLRs, TNF-α, and IL-17. Elevations of these MMPs have been found in HS lesions.[95]

There are still other signaling molecules that interact with TNF-α, though their roles are less well understood. For example, a relationship between TNF-α and mammalian target of rapamycin has been suggested.[97] Mammalian target of rapamycin complexes are major cellular regulators of survival, growth, and proliferation and are dysregulated in inflammatory diseases, including HS.[97] Complement factor C5a is another example. C5a primes overproduction of TNF-α; plasma concentrations of C5a in patients with HS are higher compared with healthy control subjects.[98] Recent data demonstrate a dysregulation of complement-specific differentially expressed genes and proteins in HS lesions compared with nonlesional skin. C5a blood levels were elevated while other factors like C4b, C3, C3b, and iC3b were downregulated in patients with HS. In the skin transcriptome, other complement factors like C1q and C2 were elevated while C7 was decreased. The role of complement dysregulation in patients with HS is still unclear.[99]

IL-17

T_H17 cells develop from IL-23–stimulated $CD4^+$ T cells and are the main producers of IL-17A. T_H17 cells are increased in lesional and perilesional HS skin compared with both autologous uninvolved skin and skin from healthy volunteers.[88] IL-17A levels are increased in patients with moderate-to-severe HS compared with healthy control subjects and correlate with disease severity independent of gender, age, and smoking.[100,101] IL-17 levels are similarly increased in CD and ulcerative colitis,[102] supporting a pathogenic connection between HS and IBD.[103]

IL-17 induces the expression of IL-1β, IL-6, and TNF-α[104] through a mechanism involving the nod-like receptor protein 3 (NLRP3) inflammasome. Inflammasomes are protein complexes in macrophages and neutrophils that detect microorganisms and indicate endogenous stress. They activate caspase-1, which activates proinflammatory cytokines, such as IL-1β and IL-18. IL-1β is a pyrogen

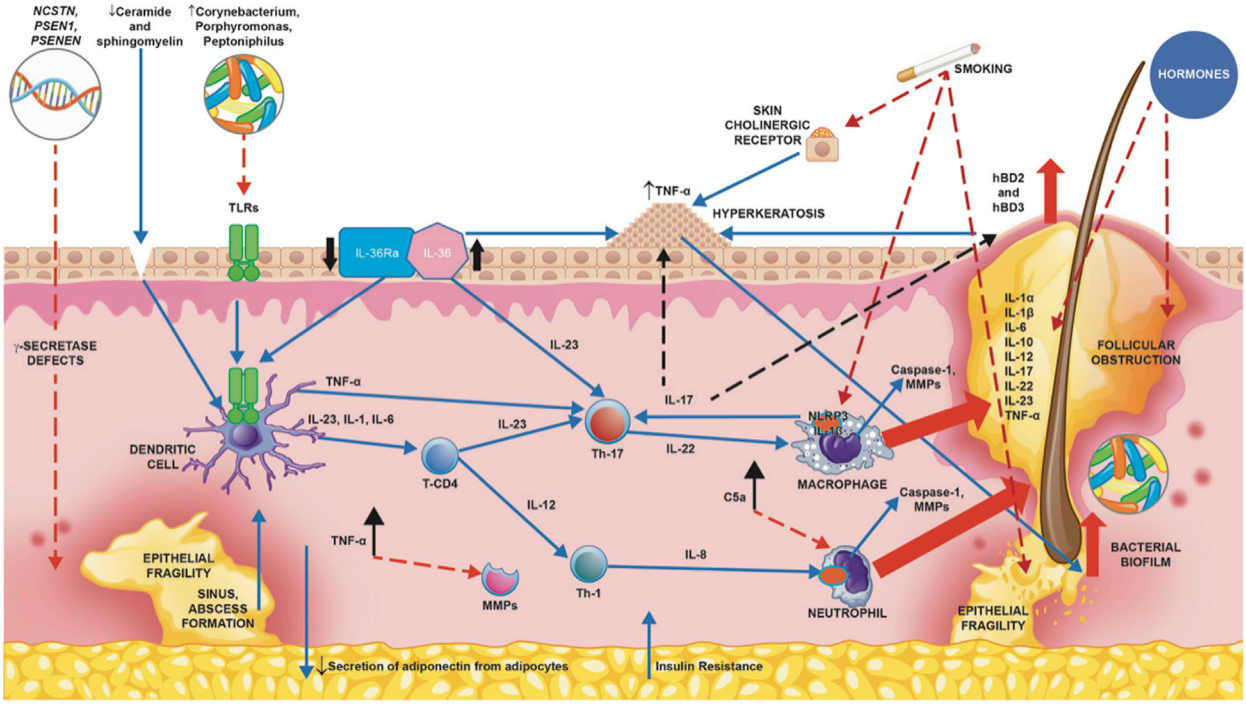

Fig 3. Postulated pathogenesis of hidradenitis suppurativa. Genetic defects affecting γ-secretase subunits result in abnormal immune system function and impaired maturation of hair follicle cells, resulting in an environment predisposed to epithelial fragility. Imbalances in interleukin (IL)-36:IL-36RA along with stimulation of cholinergic receptors from nicotine increase infundibular hyperkeratosis and follicular obstruction. Microbial dysbiosis and biofilm formation stimulate human beta-defensins that enhance follicular obstruction and inflammation. Alterations in sphingolipid composition, overexpression of Toll-like receptors from an altered microbiome, and imbalances in IL-36:IL-36RA stimulate dendritic cells and create a proinflammatory environment. Tumor necrosis factor−α (TNF-α) from keratinocytes and activated dendritic cells induces more hyperkeratosis, decreases adiponectin secretion from adipocytes, and increases the expression of matrix metalloproteases (MMPs). Complement factor C5a increases neutrophil migration and stimulates more production of TNF-α. IL-23 drives T_H17 differentiation and IL-17 overexpression. IL-17 induces expression of the NLRP3 inflammasome in neutrophils and macrophages, resulting in release of more inflammatory cytokines as well as caspases and MMPs into the follicular unit and perilesional skin. Smoking also stimulates NLRP3 expression. Hormones and high insulin levels worsen follicular obstruction and affect cytokine levels. Cytokine-driven feedback propagates and sustains chronic inflammation that results in formation of inflammatory nodules, abscesses, and eventually sinus tract and scar formation. Adapted from Cubilla et al.[139]

and leukocyte-activating factor that further increases T_H17 cell levels.[40] IL-17 in turn increases macrophage production of IL-1β and TNF-α, enhancing the immune response.[95] Elevated IL-1β has been found in HS lesional and perilesional skin,[40,89,90] and is considered a key inflammatory mediator in HS. Keratin fibers and keratinocyte debris also activate inflammasomes, and NLRP3 expression is elevated in HS.[95]

Other cytokines

IL-12 and IL-23 are heterodimeric cytokines that share a common subunit (p40) and play a role in the establishment of chronic inflammation.[105,106] IL-23 is also involved in the development and maintenance of T_H17 cells. IL-23, and to a lesser degree IL-12, are secreted by activated macrophages in the papillary and reticular dermis.[106]

IL-36, primarily expressed from keratinocytes and monocytes, is involved in innate and adaptive immunity.[107] Concentrations of IL-36α, -β, and -γ are significantly higher in HS lesions compared with healthy adults.[107-109] Activity of these proinflammatory cytokines is controlled by natural inhibitors, including the IL-36 receptor antagonist (IL-36RA). IL-36RA is not significantly expressed in HS lesional

skin, so IL-36 signaling might be unopposed.[107,109] Interestingly, IL-36RA is increased in psoriasis, suggesting that an imbalance in the IL-36:IL-36RA ratio might contribute to the differing phenotypes of these conditions.[107]

IL-6 is a proinflammatory cytokine that promotes B cell antibody production and is involved in multiple inflammatory conditions.[110] Elevated levels of IL-6 and its receptor have been detected in HS skin,[95,111] especially in Hurley stage II to III patients compared with healthy control subjects.[112]

Studies regarding the relevance of IFN-γ are inconsistent.[88,113] A pilot study of HS patients and age-matched chronic wound patients demonstrated significantly elevated IFN-γ levels in HS effluent compared with chronic wounds.[113] Increased expression of IFN-γ has also been found in HS lesional skin compared with the skin of healthy donors.[114] An analysis of T cells from HS patient skin and blood, however, found no difference in IFN-γ production between patients with HS and healthy control subjects.[88]

Hormones

Sebaceous glands have 2 types of androgen-converting enzymes: type II 5α-reductase in hair follicles and type I in hair follicles and apocrine glands.[80,115,116] 5α-Reductase converts testosterone (T) to the more potent dihydrotestosterone (DHT). Both T and DHT bind androgen receptors on sebaceous glands, increasing sebum secretion and inflammation. Nonetheless, hyperandrogenism is usually absent in patients with HS[80,117] and T and DHT levels in patients with HS do not differ compared with control subjects,[80,118] suggesting that the effect of androgens in HS, if relevant, is local.[80]

The role of female hormones in HS is also unclear.[119] Up to 43% of female patients with HS experience worsening symptoms around menses.[120] Contraceptives containing progesterone appear to worsen HS, potentially because of their androgen-like effects.[118] Alternatively, spironolactone, which is antiandrogenic, has been shown to decrease HS lesion count, PGA score, and pain.[121]

Sphingolipids

Sphingolipids are membrane lipid signaling molecules. There are 3 main types: ceramides, sphingomyelins, and glycosphingolipids. HS lesional skin demonstrates decreased expression of enzymes that generate ceramide and sphingomyelin as well as increased expression of enzymes that catabolize ceramide.[122] Decreasing ceramide and sphingomyelin levels disrupt the cutaneous barrier and cause immune activation.[122]

Genetics

Thirty percent to 40% of patients with HS have $\geq$1 affected family member.[123,124] *NCSTN*, *PSEN1*, and *PSENEN* genes are involved in γ-secretase production, which is essential for normal immune system function and maturation of hair follicle cells. In families with these mutations, HS follows an autosomal dominant inheritance pattern with incomplete penetrance,[123] and affected members tend to have a more severe phenotype.[125]

Other genetic factors are also important in the pathogenesis of HS. These include the β-defensin gene cluster of chromosome band 8p23.1, which encodes the antimicrobial peptides human beta-defensins-2 and -3.[126] Single-nucleotide polymorphisms at the promoter region of the TNF gene,[96] as well as variations in microRNA expression, have also been correlated with HS.[127,128]

BACTERIAL COLONIZATION

Key points

- **HS patients have a unique skin microbiome**
- **Biofilms are a key feature of lesional skin, but distinct species have also been found**
- **There is a lack of consensus on which bacterial species are most common in HS lesions**

The cutaneous microbiome is significantly different in HS lesional skin, nonlesional skin, and patients without HS.[81] The lesional skin microbiome consists predominantly of Corynebacterium, Porphyromonas, and Peptoniphilus species,[129] while nonlesional skin has predominantly Acinetobacter and Moraxella.[130] Corynebacterium are Gram-positive aerobes that opportunistically infiltrate atypical tissue—like wounds.[131] Porphyromonas are Gram-negative anaerobes that are typically found in the salivary microbiome and thrive as part of a polymicrobial community in inflammatory environments.[132] Peptoniphilus are Gram-positive anaerobes that are commensals of the vagina and gut and that are commonly associated with diabetic skin or infections involving soft tissue, bone, joint, or surgical sites.[133] Porphyromonas and Peptoniphilus species have been associated with chronic wounds and therefore may impact the chronicity of HS.[130]

Propionibacterium acnes is a skin commensal with bactericidal properties against other pathogens

that, along with *Staphylococcus epidermidis*, constitutes the microbiome of healthy adults.[130] *P acnes* is reduced in HS skin, potentially allowing pathogenic bacteria to flourish.[130] *S epidermitis* strains are decreased in HS lesional sites compared with nonlesional sites, too, but within the lesional sites, more strains were cultured from patients on antibiotics, and of those, *S epidermidis* was found to have reduced sensitivity to tetracycline and clindamycin, but higher sensitivity to rifampin.[134] Data involving the presence of *S aureus* in HS are inconsistent.[135] Some groups have observed *S aureus* in HS lesions, but others have not, likely because of the anaerobic nature deep within lesions.[136]

In addition to the dysbiosis inherent in HS, colonization with biofilm-forming bacteria is common in HS, likely because of inflammation and rupture of the innate skin barrier.[114,137,138] Biofilm aggregates occur in 67% to 75% of sinus tracts and infundibula, and are larger in lesional than perilesional skin.[129]

In conclusion, HS is a debilitating condition that stems from follicular hyperkeratosis and apocrine gland inflammation. Patients are frequently smokers, obese, and report pain and a significantly decreased QoL. HS pathogenesis involves immune dysregulation with inflammatory cytokines, specifically TNF-α and IL-17, playing important roles, likely with an underlying genetic predisposition and distinct microbiome. Increased understanding of the immunopathogenesis has paved the way for the development of new targeted treatment options for this disease.

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