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Permalink
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Journal
Dermatology Online Journal, 19(6)

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Publication Date
2013

DOI
10.5070/D3196018558

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Volume 19 Number 6

June 2013

Review

Diseases associated with hidranitis suppurativa: part 2 of a series on hidradenitis

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Dermatology Online Journal 19 (6): 2

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Abstract

Hidradenitis suppurativa (HS), a pathologic follicular disease, impacts patients' lives profoundly and usually occurs in isolation. Th diseases with the strongest association are obesity, depression, and pain. HS is associated with many diseases including acne conglobata (AC), dissecting cellulitis, pilonidal cysts, and obesity. Pyoderma fistulans sinifica (fox den disease) appears to be the same entity as Hurley Stage 2 of 3 HS. The rate of acne vulgaris in HS patients mirrors unaffected controls. The most common, albei still uncommon, association is with seronegative, haplotype unlinked arthritis (most importantly B27), in particular spondolyarthritis. Crohn disease and HS occur together at a rate that varies from 0.6% to 38% in retrospective cases series. Ulcerative colitis occurred with HS in 14% of patients in one series. The next most common association is with pyoderma gangrenosum, but this association is likely under-reported. Synovitis-Acne-Pustulosis Hyperostosis-Osteitis (SAPHO) syndrome, which is rare, has more than 10 reports linking it to HS. Nine case reports have linked Dowling-Degos disease (DDD) to HS and two reports related HS to Fox-Fordyce disease (FF), but because both occur in the axilla this might be a mere coincidence. HS is rarely associated with ophthalmic pathology. Specifically, more than 5 reports link it to Keratitis-Ichthyosis-Deafness syndrome (KID); greater than10 cases link it to interstitial keratitis and 2 cases are linked to Behçet's disease. The presence of proteinuria and acute nephritis link HS to the kidney, especially since and reports have documented resolution of HS after renal transplant. Florid steatocystoma multiplex, Sjogren Syndrome, and HS have been linked and their reports likely underestimate their coincidence because all these entities involve occlusion (albeit by different mechanisms). Three reports link HS and amyloid, but both share some common genetic underpinnings and thus the coincidence of these diseases is likely underreported. Pyoderma vegetans has been noted in 2 cases of HS and 4 cases o Inflammatory Bowel Disease (IBD) and is likely a clue to the linkage of the pathology of IBD and HS. Pityriasis rubra pilaris, in particular Type VI related to HIV, has a relationship more commonly with acne conglobata, but with HS also. Single case reports of diseases associated with HS include systemic lupus erythematosus, acromegaly, Down syndrome, Bazex–Dupre´–Christol, and prurti ani, but these might be coincidences. Pyogenic Arthritis, Pyoderma gangrenosum, and Acne (PAPA Syndrome) and Pyoderma gangrenosum, Acne, and Suppurative Hidradenitis (PASH Syndrome) are pyodermic-arthritic syndromes that are associated with HS Erythema nodosum and granulomatous lobular mastitis have been reported with HS but the significance of these reports is uncertain. Because of scarring, HS can result in lymphedema including scrotal elephantiasis and verrucous lymphedema. HS is sometimes accompanied by obesity, hypertension, and anemia and can be considered a disease in the spectrum of metabolic syndrome, a skin disease with systemic consequences. HS, like other types of chronic inflammation when long standing in the perianal and perineal areas, can result in squamous cell cancer. A variety of drugs can induce HS. These include lithium, sirolimus, cyclosporine, vemurafenib, and oral contraceptives. Inverse psoriasis or psoriasis vulgaris as a side effect of infliximab therapy may be associated with HS. These associations aside, most cases of HS occur in isolation without coincident morbidity.

Introduction

Hidradenitis suppurativa (HS), is a pathologic follicular disease that impacts patients' lives profoundly. The pathophysiology of HS centers on the hair follicle and involves follicular occlusion and hyperkeratosis. It is likely related to defective innate cellular immunity to coagulase negative Staphylococcus aureus (CONS). This article, which is the 2nd in a series of articles regarding HS fo DOJ, will center on the diseases associated with HS. The first article published in April of 2013 dealt with treatment of HS. When I refer to treatments of HS in this article I refer the reader back to that article [1].

Acne conglobata, pilonidal cysts, and dissecting cellulitis, the other members of the follicular occulsion triad/tetrad will be discussed in brief with the cases noting the triad or tetrad cited in detail. Pyoderma fistulans sinifica (PFS) (fox den disease) appears to be the

same entity as Hurley Stage 2 or 3 HS and reports of PFS are discussed in detail. The discussion will be broken down into the organ systems, (1) the skin (acne and the follicular occulsion tetrad) and other skin conditions that might be joined with HS to make HS a apentad, hexad, or septad, (2) the relationship of psoriasis and HS , (3) the joints (arthritis, SAPHO syndrome), (4) the eye (keratisis, Keratitis-ichthyosis-deafness and other findings), (5) the gastrointestinal system (inflammatory bowel disease), and (6) signs of systemic disease (anemia, kidney disease, wasting, obesity, metabolic sysndrome). (Table 1). I will discuss medications, which indu HS. Lastly, I will review diseases for which only a few reports link them to HS; in these cases the occurrence with HS may be a coincidence.

Table 1 Pathological Associations of Hidradenitis

Strongest associations in order of frequency	Types of Arthritis associated with HS	Physcial Findings With might be added to tetrad	Inflammatory Associations	Weaker Associations	Medication Associations
Acne conglobata	Seronegative Arthritis	Mamillary Fistula	Crohn's Disease	Pachyonychia congenita	Lithium
Pilonidal Cyst	Reactive inflammatory Arthris	Anal Fisulas	Ulcerative Colitis	Natal teeth and steatocystoma multiplex	Sirolimus
Dissecting Cellulitis (Perifolliculitis capitis abscedens et suffodiens)	Osteomyelitis (inflammatory non infectionous)		Interstitial keratitis	Dowling-Degos disease	Cyclosporine
	Spondyloarthropathy		Pyoderma gangenosum	Steatocystoma multiplex	Inverse psoria psoriasis as s of infliximab t
	Sacroiliitis		Behçet's disease	Amyloidosis	Vemurafenib
	Dactylitis		Behcet's disease with psoriasis	Acromegaly	
	Monoarthritis of the hip.		Psoriasis vulgaris	Dowling-Degos disease, hidradenitis suppurativa, and multiple keratoacanthomas.	
	Erosive arthropathy		Pyodermia fistulans sinifica	Prurtis ani	
	Systemic Lupus erythematosus		System Lupus Erythematous	Condyloma like lesions	
			Granulomatous lobular mastitis[315]	Dowling-Degos and multiple epidermal cysts	
			Pyoderma vegetans	Keratitis-ichthyosis-deafness syndrome	
			Sjögren's syndrome	Bazex-Dupre-Christol syndrome	
			Sjögren's syndrome	PAPA syndrome	

			plasma cell panniculitis		
				Erythema Nodosum	
				Down's Syndrome	

I will not speculate as to the etiology of these overlaps or the etiology of HS, which I will save for a future article. Cancer, in particular squamous cell cancer, can develop in long standing severe Hurley stage 2 and 3 HS and will be the subject of a separate article. HS is also painful [2] and can induce or be accompanied by depression and other physical and psychological pathology. This will also be reviewed in a future article on HS, but is summarized briefly in Table 2. Lastly, a variety of inflammatory mediators, suc as the erythrocyte sedimentation rate (ES), which I discuss in greater detail on the etiology of HS, can be altered while HS is active; I summarize some of lab alterations besides anemia in Table 3.

Table 2 Complications associated with hidradenitis suppurativa

Anal, urethral, and rectal strictures and fistulas
Anemia
Contractures and limb mobility limitations
Cutaneous squamous cell carcinoma
Depression
Increased risk of other malignancy
Kidney Disease
Lumbosacral epidural abscess
Metabolic syndrome
Oral ulcers [18]
Pain
Penile ulcers[18]
urethritis,[18]

Table 3 Abnormal Lab value linked to HS

Erythrocyte sedimentation rate (ESR)-elevated
Monoclonal gammopathy-elevated
C Reactive Protein (CRP)
Hypoproteinemia
Soluble interleukin-2 receptor [316] -elevated
Hypergammaglobulinemia -elevated
Circulating immune complexes -elevated
Polyclonal gammopathy-elevated

HS and the Skin

Acne Vulgaris and HS

Acne vulgaris does not seem to be substantially more common in patients with HS versus normal controls [3]. The prevalence of acne, hirsutism, and irregular menses are not more common in HS patients than in controls [4]. In one study that tracked glucose tolerance, lymphocyte populations, and HLA types, 27 patients were studied with untreated hidradenitis suppurativa. Of these, 18 patients had a negative history for acne vulgaris and 9 had a history of acne vulgaris (a rate of 33%) [1]. Among HS patients diagnosed in Olmsted County, Minnesota, between 1968 and 2008, 36.2% carried a diagnosis of acne [5]. These statistics parallel th prevalence of acne vulgaris found in the United States. In the US, 27.5% of people of color have acne [6]. In women in the US, acn is quite common. In one study, 55% of the women studied had some form of acne: 28% had mild acne and 27% had clinical acne, (14% was primarily inflammatory and 13% was primarily comedonal). Acne peaked in the teenage years, but 45% of women aged 2 30, 26% aged 31-40, and 12% aged 41-50 had clinical acne. Women with inflammatory acne were younger than those with comedon acne and postmenopausal women had less acne than age-matched peers. Acne was associated with facial hirsutism, large pores, and sebum excretion. Smokers had more, primarily comedonal, acne than did nonsmokers [7].

Internationally, acne vulgaris seems less common outside the United States. Rates of HS in the US are similar to the European Unio Countries [8, 9, 10]. In the United Kingdom, moderate-to-severe acne affects around 20% of young people and severity correlates wi pubertal maturity. Acne persists into the 20s and 30s in around 64% and 43% of individuals, respectively [11]. In Norway, the prevalence of overweight was 9.5% in girls and 15.4% in boys. The prevalence of acne was 13.1% in girls and 14.0% in boys. Amon those who were overweight or obese (BMI ≥25), the prevalence of acne was 18.5% in girls and 13.6% in boys. Of those considered obese (BMI ≥25), the prevalence of acne was 18.5% in girls and 13.6% in boys [12]. In China, in a study of 17,345 subjects in six cities, the prevalence increased rapidly with age, up to 46.8% in the 19-year-old group [13]. In some studies, only acne vulgaris is studied in relation to HS [14], independent of HS associated with the follicular occlusion triad/tetrad discussed below. It appears tha outside the US, acne vulgaris might be more common in patients with HS, but that requires further definition. Acne fulminans has n been linked to HS [15], whereas it has been linked to the SAPHO syndrome and acne conglobata (AC) [16].

The Classic Follicular Occulsion Triad/Tetrad

Diseases of follicular occulsion in the skin are common fellow travelers with HS. The triad or tetrad of acne conglobata, dissecting cellulitis, hidradentitis, and pilonidal cysts is well reported [17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 3 37,38, 39, 40, 41, 42, 43, 44, 45] and it is likely that reports of the triad or tetrad without complicating factors are no longer being published. Sometimes each of the components of the tetrad can occur in isolation, but such isolated cases will not be discussed herei Acne conglobata occurs after adolescence and most cases are not linked to HS. Moreover, the components of the triad/tetrad can occur simultaneously or at different times. The full tetrad is rare and I have only rarely seen the full tetrad among the more than 400 patients with HS that I have examined since 2006. The most commonly linked condition in the tetrad to HS is acne conglobata, but i is possible that pilonidal cysts might be more common. As stated, in many cases patients have only two of the 4 pathologic conditio of the triad or tetrad.

Dissecting Cellulitis

Dissecting cellulitis (DC) occurs in the scalp as boggy, scarring, flocculent plaques and abscesses, most commonly in black males aged 20-40 [48, 49]. The histology of DC resembles that of HS [50]. It is much less well reported and less common than HS. Because DC is part of the original follicular occlusion triad, it shares some similarities with HS and some differences.

Treatments help define the relationships of HS and DC. Both HS and DC respond to common therapies, such as zinc [51], TNFa Blockers (TNFaB) including adalimumab [52] and infliximab[53, 54], and allitretinoin [55]. Whereas isotretinoin has a role in the treatment of DC [56, 57], isotretinoin does not have a confirmed role in patients with HS. A few reports have claimed cures of DC with ciprofloxin [58], which is not the case for HS. Like axillary HS, removal of all scalp skin either by surgery [59, 60, 61] or radiation [62, 63] can cure DC. Surgery for HS of the female breast has almost a 100% reoccurrence rate. The 1064nm laser has bee used effectively for DC [64] and HS.

HS and DC share certain coincident pathologies. Both HS and DC [65] can evolve into squamous cell carcinoma. DC like HS has been linked to skeletal pathology and arthritis. One report has linked isolated DC to spondylarthropathy [66]. One report [67] noted isolated DC with sternocostoclavicular hyperostosis, a rare rheumatic condition characterized by ossification and erosion of the clavicle and the first rib. Another report linked DC to osteomyelitis [68], which also also been associated with HS. KID syndrome a DC have been linked in two reports, one of which was associated with HS and malignant proliferating pilar tumors [68]. KID syndrome has been linked to the triad as well [69]. DC with interstitial keratitis [70] or rheumatoid arthritis[71] have been noted.

Acne conglobata with and without HS

The etiology of AC and HS likely differs somewhat but AC and HS likely overlap more than the other constituents of the follicular occlusion tetrad. There is no evidence that the sebaceous glands are miniaturized or absent in AC as they are in HS. Interestingly, single nucleotide polymorphisms of toll-like receptor-4 (TLR-4) protects against acne conglobate [72]. Both HS and AC of the buttocks can be aggravated by mechanical and environmental factors [73]; lithium induces both AC and HS [74]. AC [75] and HS both are associated with depression.

Treatment similarities and differences of HS and AC

Treatment helps to define the differences and similarities of HS and AC. Whereas entanercept might ameliorate AC, it is less optima for HS [76]. Treatment of acne conglobata with infliximab has been reported to be effective [77]. Similarly to HS and DC, external beam radiation can abate AC [78]. A randomized controlled study on the treatment of 26 cases of acne conglobata with encircling acupuncture combined with venesection and cupping has noted improvement in AC, but not HS or DC. Acne conglobata has been successfully treated with fractional laser after CO2 laser abrasion of cysts combined with topical tretinoin treatments, but this has not been useful for HS [79, 80]. Treatment with isotretinoin, colchicine, and cyclosporine worked for AC but is a suboptimal mix for HS [81]. Gonadotrophin-releasing hormone analogue has been reported useful for HS and for AC, which responded to buserelin, a gonadotrophin-releasing hormone analogue [82].

Both AC and HS, when longstanding and severe, can evolve into cancer, in particular squamous cell carcinoma. An interesting case c fatal squamous cell carcinoma associated with acne conglobata in a father and daughter is of interest [83].

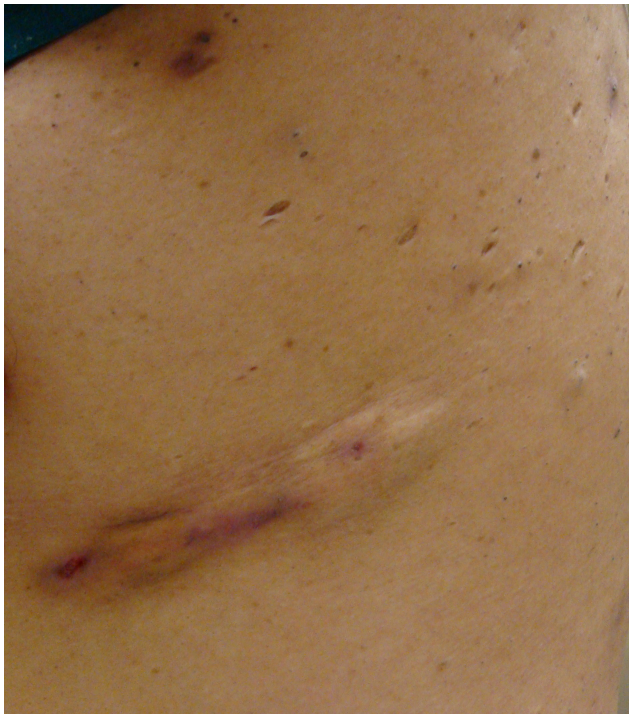

Figure 1. HS and Acne conglobata

I Arthritis and AC

All types of arthritis have been linked to AC independently of HS [84]. Sacroileitis, acne conglobata, and SAPHO have been linked [85]. HIV-associated pityriasis rubra pilaris and acne conglobata have been associated with spondyloarthropathy and ankylosis of the wrists [86]. A case description of 3 patients with acne conglobata and osteoarticular symptoms is reported [87]. Enthesitic talalgia associated with calcaneal osteitis revealing rheumatism with acne conglobata has been noted. Additional case reports have shown associations of ankylosing spondylarthritis with acne conglobata [88] and osteonecrosis in acne conglobata [89]. Multiple hyperostoses with unilateral sacroiliitis, a new spondyloarthropathy associated with AC, has been described [90].

II Renal disease and AC

Renal pathology has been linked to AC and resolution of AC has resulted in improved renal pathology. ANCA-positive vasculitis of the skin and kidneys associated with acne conglobata has been noted [91]. Renal amyloidosis has been related to acne conglobata of the buttocks [92]. Rapid development of renal insufficiency after surgical excision of the suppurative foci of HS was reported [93]. Chronic glomerulonephritis remarkably improved after surgery for and amelioration of acne conglobata [94]. Correction of nephritis has also been shown to preceed improvement of HS. End-stage renal disease in a patient with amyloidosis secondary to acne conglobata has been noted [95].

III Pyoderma gangresonsum and AC

Of all the entities that might be added to the follicular occlusion tetrad the most likely candidate is PG. Cases of PG with AC have been noted. Pyoderma gangrenosum, acne conglobata, and IgA gammopathy appear associated [96]. PG has been linked to AC in other cases [97].

IV Eyes and AC

Ocular pathology has been linked to HS and to AC. Acute anterior uveitis in a patient with sacroiliitis and acne conglobata has been described [98]. The coincidence of Behçet disease and SAPHO syndrome with ophthalmologic findings and recurrent oral and genit aphthous ulcerations with AC have been noted without HS [99]. This relationship of the eye with HS will be further discussed below

V Pitriasis rubra pilaris (PRP) and AC

PRP type VI related to HIV has been associated with AC [100, 101, 102, 103] often with follicular spicules or spines and explosive AC. PRP has been related to HS in two cases. [104].

VI Rare Associations of AC

AC has rare associations. Isolated reports link HS and AC to acromegaly [14, 105]. Unlike HS, AC has been linked to Klinefelter's syndrome [106, 107]. Pyoderma vegetans has been associated with HS. Pyoderma vegetans only in the presence of acne conglobata been reported. Several reports have linked pyoderma vegetans to HS Several reports have linked HS to pyoderma vegetans [108, 109 110]. Acute ulcerative acne conglobata (acne fulminans) with erythema nodosum has been noted [111].

The liver and HS

Almost no reports link HS and the liver. HS is a disease that responds to rifampin, which has many affects on the liver, but any real linkage requires futher investigation. One report notes that the incidence of liver cancer seems to have an increased rate in patients with HS [112], but the significance of this report is uncertain.

Pilonidal cysts

Pilonidal cyts (PC) (pilonidal sinus or disease) and hidradenitis suppurativa are common problems that affect young adults [113, 114, 115]. PC can occur on any body area like HS, but is most common in the sacroiliac region. PC is likely much more common than HS. The surgical management of pilonidal cysts should be tailored to the individual clinical presentation and its goal is the resolution of pilonidal disease with low recurrence and low morbidity. HS manifests with a chronic and relapsing course with frequent flare-ups between quiescent periods. Treatment for both conditions needs to be individualized to the clinical presentation. Like HS, longstanding PC can evolve into squamous cell carcinoma. Hair removal with the 1064 nm laser has a role both in the treatment of HS and PC. The other diseases that coincide with HS, such as arthritis, eye disease, and renal pathology are not commonly present in patients with PC. PC and HS have various common characteristics at the histological and immunohistochemica level. Considering PC as a unilocalized type of HS, risk factors known in the latter should henceforth be evaluated in PS as well [114

In one study [115], cytokeratin (CK) expression in nine cases of PC was studied immunohistochemically using six anti-kerat antibodies. Infundibular-like epithelium contained CK1, 10, and 14, similar to normal infundibulum, but it did not contain CK17. In non-infundibular-like epithelium, CK14, 16, and 17 were detected, similar to that in the normal outer root sheath. CK expression in PC was similar to that in hidradenitis suppurativa, suggesting that sinus epithelium may be fragile, hyperproliferative, and undifferentiated. PC can be classified in a similar category to follicular occlusion diseases based on CK expression. Cytokeratin expression in pilonidal sinus is detailed in a report from 2002 [115].

Mirrors and Mimics of HS in brief

Genetic conditions can be seen to either mimic or mirror HS. Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) syndrome is caused by a mutation in proline-serine-threonine phosphatase-interacting protein (CD2BP1/ PSTPIP1). In some ways th can simulate HS. Finally, infection can mimic HS (e.g. perianal pyoderma) [116, 117, 118], as can squamous cell cancer and even breast cancer. HS can mimic the lymphedematous verrucous changes of SCC [119]. Metastatic Crohn disease (CD) can mimic HS an HS can mimic CD, even with peristomal changes [120].

Pyoderma fistulans sinifica (PFS)

There are 14 articles as of March of 2003 that describe a disease termed PFS or fox den disease. PFS also overlaps with cystic acne, dissecting cellulitis, and pilonidal cysts. In the literature of PFS, 11 of the papers are in the German literature, one is in the Serbian literature, and the other 2 are from American authors [121-134]. I think that stage 2 or 3 HS and PFS are the same disease. Thus, I think when the term PFS is used it is a question of nomenclature. If any distinction is to be made it is that PFS does not have milder variants. The lesions of PFS are, by definition, deep seated and are usually treated with surgery. Like HS, PFS can have an associatic with arthritis of the large joints, ranging from asymmetric pauciarticular arthritis to a symmetric polyarthritis and/or polyarthralgia syndrome and may be part of HLA-B27–negative spondyloarthropathies. Arthropathy worsens during flares of PFS and often improves after PFS resolves. One patient with PFS had an α-1-antitrypsin deficiency [126] and another had cardiac disease [132]. PFS has a variant that looks like giant condylomata of Buschke-Lowenstein that I have seen in patients with HS. It is important to recall that in the groin any disease can take on the appearance of condylomata (e.g. amyloid, HS). PFS can have a fatal outcome, like severe cases of HS [124].

Psoriasis

Interestingly, psoriasis occurs in 1-3% of the general population with no increased incidence in HS patients. In a series of 302 Frenc patients with hidradenitis suppurativa, no patients with psoriasis were noted [135]. That being said, both HS and psoriasis occur in areas of friction and irritation. One certain report [136, 137] and one possible report [138] note psoriasis on the leg of patients with HS (this second report might have been HS alone.) The case of certain HS with psoriasis was treated with resection alone with success. Successful long-term triple disease control by ustekinumab in a patient with Behcet disease, psoriasis, and hidradenitis suppurativa has been noted above [139]. Similarly another patient with HS manifested as recurrent groin and axillary abscesses and cysts, erythematous fissured plaques in his inguinal folds, and well-defined plaques with scale on his trunk and gluteal cleft. The skir of his face and scalp was diffusely erythematous with light scale. There was marked fissuring within a large scaly plaque on his posterior scalp. He had symmetric tenderness of his first interphalangeal joints and small pits were present on his fingernails. Both th HS and psoriasis responded to ustekinumab, dosed 90 mg administered every 8 weeks; at the time of the report the improvement was maintained at 1 year [140].

What is more interesting is that a side effect of infliximab treatment for HS results in the development of psoriasis, in particular inverse psoriasis [141, 142]. I have seen the development of mild to moderate stable plaque psoriasis in a patient treated with infliximab; for insurance reasons this patient could not change to adalimumab. A Japanese report noted psoriasiform and pustular eruption induced by infliximab for Crohn disease [143]. This effect is well documented in the literature on the use of infliximab for rheumatoid arthritis, ankylosing spondylitis, and Crohn disease [144]. The mechanism of this is not understood. Clearly, in skin disease the equipoise of cytokines is as important as the expressed cytokines in defining and promoting the disease state. The literature suggests that infliximab generates more side effects in HS patients than does adalimumab. Therefore, whereas it remains interesting that infliximab can cause psoriasis, it also is able to induce other disease states.

The rapid progression of hidradenitis suppurativa in the lower leg of a patient with psoriasis vulgaris [137] is not unexpected. HS is prone to contiguous areas of spread and I have seen patients who have had numerous surgeries on their thighs and buttocks in which the HS has tracked down the scars of their legs towards their knees.

Panniculitis

The coincidence of panniculitis and HS is rare. One series of 10 patients with HS noted eythema nodum in two patients. A case of Sjögren syndrome plasma cell panniculitis occuring with HS has been noted [145]. These cases are so rare as to represent a coincidence rather than a true association. There is a paucity of reports of panniculits with HS, unlike IBD.

The Skeletal System and HS

Arthritis and HS and the Follicular Occulsion Triad/Tetrad

Among the more common internal associations of HS is arthritis. This is also true of cystic acne and acne fulminans. Interestingly, the arthritis of HS is always B-27 negative. The HLA antigens B16, B17, B27, B39, and Cw6 are associated with psoriatic arthritis but seem to have no link to the arthritis of HS [146]. The matrix metalloproteinases 1 and 3 (MMP1 and MMP3) are thought to be important in the destructive joint changes seen in rheumatoid arthritis (RA) and osteoarthritis (OA), but have not been linked to HS [147]. The HLA-DRB1 allele associated with rheumatoid arthritis HS in Caucasians is not linked to HS and arthritis [148]. A significant susceptibility effect was observed with HLA-DRB1*09, described in other ethnically diverse populations, but not in Caucasians; this was not related to HS. This is true of isolated HS and HS that is part of SAPHO syndrome.

The arthritis of HS can take a variety of forms (like psoriatic arthritis), including rarer ones that include: arthritis isolated to the hip [149, 150], dactylitis [151], seronegative inflammatory arthritis [152, 153, 154, 155, 156], polyarthritis [157], reactive arthritis [158, 159, 160], Dowling-Degos disease, hidradenitis suppurativa and arthritis in mother and daughter[161], and cystic acne, hidradenitis, and arthritis [162].

Several series of patients with HS arthritis have been published. Rosner[15] in a series of 10 HS patients noted the most common locations for arthritis in HS patients in descending order of frequency are the knee, elbow, ankle, wrist, upper extremity metacarpophalangeal, lower extremity metacarpophalangeal, first toe interphalangeal, upper extremity distal proximal interphalangeal,first interphlangeal joint, and distal, first toe interphalangeal joint. In 1994, Bhalla [153] reported 29 cases of arthriti associated with hidradenitis suppurativa and acne conglobata. Of these 29 cases, five had acne conglobata, 11 had hidradenitis suppurativa, 7 cases had both, and 6 had the follicular occlusion triad. The average age at presentation was 35 years of age and more men were affected than women. Most were of African decent and a few were Caucasians. Skin disease antedated the arthritis by 1–28 years. The arthritis had a chronic course with periodic flares. A later study by Rosner [25] of 44 patients with hidradenitis suppurativa and or acne conglobata confirmed this pattern of arthropathy, manifesting with a peripheral inflammatory arthropathy in 29%, an axial arthropathy in 14%, or a combination of both in 57%. Bhalla and Sequeira [153] and Rosner [25] noted that the axial skeleton is invariably involved with the arthritis of HS, even in patients with asymptomatic HS.

Spondyloarthropathy describes any joint disease of the vertebral column. As such, it is a class or category of diseases rather than a single, specific entity. Broadly, the term spondyloarthropathy includes joint involvement of the vertebral column from any typ of joint disease, including rheumatoid arthritis and osteoarthritis. However, the term is often used for a specific group of disorders with certain common features, the group often being termed specifically seronegative spondylarthropathies. They have an increased incidence of negative HLA-B27, as well as negative rheumatoid factor and ANA. Spondyloarthropathy has been linked to HS by a number of reports, but not to any specific haplotype [163, 164, 165, 166]. The association of HS and spondyloarthropathy seems to appear mostly in African American men and equally affects the axial and appendicular joints. HS and spondyloarthropathy often manifest with simultaneous skin and joint flares. In sum, it would seem that the reports underestimate the presence of arthritis with HS; when faced with an HS patient in pain physicians likely do not parse the pain into skin pain from HS and joint pain from the arthritis that accompanies HS. The etiology of the arthritis of HS will be detailed in a future article that discusses the etiology of HS itself.

SAPHO syndrome and HS

SAPHO is an acronym for the combination of synovitis, acne, pustulosis, hyperostosis, and osteitis and is a rare chronic disease that involves the skin, bone, and joints. According to Khan [167] and Chamot [168] there are three diagnostic criteria for SAPHO syndrome: (1) multifocal noninfectious osteomyelitis, with or without skin manifestations; (2) sterile acute or chronic joint inflammation associated with (a) pustular psoriasis or palmoplantar pustulosis, (b) acne, or (c) HS; and (3) sterile mono- or polyosteitis in the presence of one of the aforementioned skin manifestations. Any of these criteria is sufficient for a SAPHO diagnosis. SAPHO and HS have been associated with each other often involving sero-negative, non HLA B-27 related spondylarthropathy [74]. A case of hidradenitis suppurativa related SAPHO associated with spondylarthropathy and proteinuria has been noted [169]. SAPHO accompanied by HS was successfully treated with methotrexate and infliximab [170] and withmethotrexa alone [171]; the HS responded along with SAPHO other clinical manifestations of SAPHO.

In one study [16], 12 patients with SAPHO from three hospitals were analyzed; 7 had HS as part of their syndrome. All required extensive surgery for drainage and antibiotic and non-steroidal anti-inflammatory drug therapy. Of the 7 patients with HS, six were African American, suggesting a possible SAPHO–HS predisposition in that population. In all 7 patents, groin disease occurred and ir 6 patients, axillary disease occurred. Perirectal and neck involvement were described in 2 patients and 1 had affected breasts. Three of the seven patients had pyoderma gangrenosum and HS (suggesting more aggressive SAPHO); 3 patients had life-threatening complications, including gram-negative bacteremia. Two SAPHO/HS patients had a polyclonal gammopathy (associated with dense

plasma cell infiltrates in skin and synovial biopsies). In addition, patients with the most severe HS had more erosive arthropathy. Th it can be concluded that HS in the presence of SAPHO may have more deleterious joint disease than HS alone[172].

The exact relationship of SAPHO and HS remains to be defined. It is not clear whether or not defective innnate cellular immunity ar CONS play as key a role in SAPHO as they do in HS. It should be noted that SAPHO syndrome and psoriatic arthritis exhibit differe immunogenetic profiles [173,174]. This would be in keeping with idea that the arthritis of psoriasis and HS are distinctive as well. Interestingly, the first line treatments for SAPHO can be NSAIDs and bisphosphonate therapy [175, 176] rather than TNFaB or antibiotics; NSAIDs have no effect on HS alone, but they can help with the pain of HS.

The Eye and HS

Interstitial keratitis and other ophthalmic patients in HS without KID syndrome HS is associated with pathology of the eye. The first series of patients with interstitial keratitis (IK) and Hurley Stage 2 or 3 HS was reported in 1967. Bergeron and Stone [177] surveyec 62 HS patient, of which 4 had IK. HS preceded IK by a mean of 7.2 years. The IK in these patients was severe and progressive, ending in corneal destruction. Since that time, a number of reports have linked Hurley Stage 2 and 3 HS to severe IK [178, 179, 180, 181]. The basis for the connection of HS and IK is not certain. Rosner, in his series of 10 patients with HS, noted 2 with xerophtalmia and 2 with conjunctivitis [15]. Three cases discussed below link Sjogrens with HS. Sjogren's often affects the eye, causing dry eye; this association with HS has not been reported extensively in the literature, but might be more common than reports suggest. Mooren's type ulceration associated with severe hidradenitis suppurativa has been noted [179]. Sachs noted HS of the glands of Moll [182]. The incidence of eye issues in HS is likely underestimated because, as is similar to cases of arthritis, when physicians are faced with an HS patient in pain they do not separate the pain into skin pain from HS and ocular discomfort from the ocular complications that accompany HS.

KID syndrome

KID syndrome is a rare genetic disease characterized by keratitis with progressive corneal opacification, ichthyosis, and deafness [184]. KID syndrome is a rare congenital disorder characterized by keratitis, ichthyosis, and neurosensory deafness. Most cases hav been sporadic but autosomal recessive and dominant cases are reported. Like HS, scarring forms of KID can evolve into SCC. The syndrome is caused by missense mutations in the connexin-26 gene, GJB2. Connexin-26 is expressed most commonly on the palms and soles, but also in sweat glands and hair follicles [185]. Skin changes usually develop within the first 3 months of life and are not typical of classic ichthyosis, but rather have features of erythrokeratoderma. The erythematous, nonscaling, verrucous plaques are characteristically located on the forehead, cheeks, perioral area, elbows, knees, and scalp [184]. Hyperproliferative epidermis, resulting from GJB2 mutations may predispose to follicular obstruction, with subsequent cyst formation, rupture, and secondary inflammation. Novel mutations including: Connexin-30 gene (GJB6) mutation [186], GJB2 (N14K) Connexin 26 mutation [187], a novel GJB2 mutation (p.His73Arg) [188], two heterozygous mis-sense mutations (D50Y, D50N0 in the GJB2 resulting in KID syndrome)[189], GJB2 mutation p.Gly59Ser (in which the patient also had atypical Vohwinkel syndrome) [190], a novel heterozygous missense mutation (Ile30Asn) in one patient, a de novo mutation (Asp50Asn) in the GJB2 gene in onepatient [191], a novel nucleotide change, c.263C>T, in exon 2, leading to a substitution of alanine for valine at position 88 (p.Ala88Val) [192], and a GJB2 mutation (G45E) [193] have been reported but these novel mutations have not been linked to KID with HS.

Keratitis-ichthyosis-deafness syndrome is rare and its association with HS is even rarer. One novel muation of GJB2 (G12R) Connexin 26 mutation has been linked to HS in two cases [190, 191]. Another novel mutation in the KID gene, a heterozygous point mutation (C119T) in the gap junction beta2 gene that substitutes a valine for alanine at codon 40 (A40V) in the connexin 26 protein, has been reported in another case [195]. Most cases of KID and HS are in patients who are on the more severe end of spectrum for both diseases (for HS Hurley Stage 2 and 3). Another case linked follicular hyperkeratosis, HS of the groin, progressive developmen of proliferative pilar cysts, and dissecting cellulitis of the scalp; this patient also developed metastatic malignant pilar tumors and was discussed above. Thus, it seems that the particular genetic mutation might matter for KID to be linked to HS and that some mutations of the Connexin 26 gene not do not predispose a KID patient to HS. This, however, remains to be defined.

Sjogren's Syndrome, Lupus and Collagen Vascular Diseases (CVD) and HS

Collagen vascular diseases have seldom been linked to HS. A thorough review of the literature shows that among CVDs, Sjögren syndrome has the most reports linking it to HS [196, 197]. Sjögren syndrome is a systemic chronic inflammatory disorder characterized by lymphocytic infiltrates in exocrine organs. Most patients with Sjögren syndrome present with sicca symptoms, such as xerophthalmia (dry eyes), xerostomia (dry mouth), and parotid gland enlargement. Sjögren's syndrome plasma cell panniculitis and hidradenitis have occurred together [145]. One case report has noted PG in association with hidradenitis suppurativa; one patient had concurrent systemic lupus erythematosus [198]. As both HS and Sjogren syndrome are diseases of occlusion of follicles and glands,

think the association has been under reported. I have been unable to find any reports linking HS to dermatomyositis or sero-positive rheumatoid arthritis. It is likely that the pathologic etiologies that underlie true CVD and HS are wholly different.

HS and Behçet Disease

Behçet disease (BD) is an inflammatory systemic disorder of unknown origin, characterized by recurrent oral apthosis, genital ulcers, uveitis, and skin lesions. The most common skin manifestations of BD are erythema nodosum on the lower legs, pseudofolliculitis, papulopustular lesions, and acneiform nodules on the back. Cutaneous manifestations may include neutrophilic dermatoses such as Sweet syndrome and pyoderma gangrenosum, although these are unusual in BD [199]. Microorganisms might play a role in the development of BD [200]. Interestingly, the ulcerations of BD tend to heal without scarring [201], whereas those in HS almost alway heal with scarring. The first reported link of BD and HS was noted by Sahin in 2007 [202]. The second article to note the linkage of HS with BD and psoriasis noted that successful treatment of all conditions was achieved with ustekinumab [139]. Furthermore, Croh Disease and BD have never been reported to overlap as of the date of the paper in April 2013.

The Gastrointestinal System and HS

Crohn Disease and HS

Crohn disease (CD) is a chronic inflammatory disorder of the gut that can metastastisize to any body area; the etiology of this disease is poorly understood [206]. Epidemiological studies suggest that the disease occurs in genetically susceptible individuals as a consequence of defects in mucosal barrier function and disregulation of immune recognition of commensal gut flora. Of more than 3(genetic loci associated with CD, two genes with important polymorphisms, encoding the intracellular bacterial sensor NOD2/CARD15 and the autophagic regulator ATG16L1, have gained particular importance [203]. Both proteins exert crucial functions in innate immune defense through intracellular bacterial recognition and destruction of bacteria. This function focuses interest on the physiological functions of the protein products of both genes and suggests that innate immune defenses are linked to autophagic processes through recruitment of ATG16L1 by the bacterial sensor NOD2 at sites of microbial infection [204]. However, HS patients do not have CARD15 genetic mutations [205]. Therefore, the basis for the overlap of HS and CD is not clear, but probably has something to do with an immune system that is overactive in response to commensal bacteria.

Crohn disease (CD) is among the most reported associations of HS. It should be kept in mind that CD has a myriad of cutaneous associations, many more than does HS. Interestingly, in a prior report of mine 2001, I did not even list HS as a cutaneous association of CD [206]. Clearly before infliximab became a treatment for both HS and CD, this association was not well recognized. I include with this paper an updated list of the cutaneous associations of CD, which includes HS and other entities not previously linked to CD (Table 4). Few of the conditions linked to CD are linked to HS. It is interesting to note that both CD and HS, diseases that can infrequently overlap, occur primarily in areas rich in bacteria, usually have different histopathologic findings (HS can some time be granulomatous), but share a common treatment--TNFaB. Furthermore, both can affect the eyes and evolve into squamous cell carcinoma. It is interesting that HS can proceed or follow the diagnosis of CD [207].

Several series have tried to define the coincidence of HS with CD and UC (collectively inflammatory bowel disease (IBD). In the largest of these reports, 24 of 61 (38%) HS patients also had a CD diagnosis. In most of these cases, CD affected only the large bowe and its diagnosis preceded that of HS by 3.5 years. The diagnosis of HS preceding that of CD has also been reported [207, 208]. In one study of 158 consecutive patients [209] with inflammatory bowel disease (IBD), the patientswere interviewed about recurrent painful boils in the axillae and/or groin and were shown illustrative clinical pictures of the appearance of HS. Of these patients, 102 (65%) had CD and 56 (35%) had UC. Twenty-five people (16%) responded that they had had or still experienced painful boils in the axillae and/or groin, of whom 17 were patients with CD (17%) and eight were patients with UC (14%). HS affected the perineal and perianal area in all patients and secondary sites in 83%. [209]. In an unpublished study in Jemec's book on hidradenitis, 18 (0.6%) ou of 2926 CD patients presented with HS [210]. The patients affected by CD and HS differ from the others by more frequent colon and perianal involvement and a greater need for immuno-suppression and definitive ileostomy and proctectomy [208]. Other series of IBD have not noted the presence of HS [211, 212, 213].

In order to better understand the relationship of CD and HS, further understanding of HS is needed. CD is more frequent in Americar or European white women, smokers, patients between 20–40 years old, and patients in urban areas. Adding to the epidemiological information, there are a few other factors: CD is associated with the NOD2 gene mutation (CARD15) in 15%–20% of the patients. HLADR1/DQw5, HLAA2, and HLADRB3*0301 carriers are more likely to develop the disease. CD patients have a greater number of intraluminal bacteria, increased intestinal permeability with a deficient tissue repair rate, and show immunoregulation failure (antigen presentation directed to Th1 response rather than suppressor T response). In addition, studies have shown associations of variants in the caspase recruitment domain (CARD)15 gene with CD. These variants are involved in the immune response toward bacterial products. CARD15 seems not only a susceptibility gene, but also a disease modifier gene for Crohn disease. [214, 215, 216]

As noted above, it is interesting to note that both Crohn disease (CD) and HS occur primarily in areas rich in bacteria, have wholly different histopathology, but share a common treatment--TNFaB. Many cases of HS and CD are responsive to infliximab, but the question remains whether solitary HS (or as part of the triad or tetrad without IBD) is a different entity in in terms of the genetic and cytokine basis and response to therapy than HS associated with IBD. The literature is replete with cases of CD and HS that have responded to infliximab [220, 221, 222, 223, 224, 225, 226, 227, 228, 229]. One case of HS and Crohn disease was effectively treate with buried chip skin grafts [230]. Azathioprine (150 mg/d) and methylprednisolone (16 mg/d) combined with isotretinoin (0.7 mg/kg) and periodic administration of antibiotics effectively treated CD with HS, suggesting that HS secondary to CD might have a different course and etiology than HS that occurs alone [231]. Of cases of HS with CD, one complicated by PG, infliximab was an effective therapy [224].

It should be noted that infliximab is not always successful in treating HS [217] and infliximab's effect can wane over time [232]. Or a similar note, I had one patient with Stage 3 HS in the groin who had absolutely no response to adalimumab. Sometimes HS and C can be wholly resistant to infliximab [233], but most cases respond [234]. The other associated morbidities of patients with CD and HS are complex and include spondyloarthropathy [235]. One interesting aspect of CD associated with HS is that HS can be granulomatous [236, 237]. Whether or not the cases of HS that are associated with CD are more commonly granulomatous is not known. In sum, there are some factors that tie CD with HS; both are present in areas with high loads of bacteria, but their exact linkage remains to be defined [238, 239, 240].

Table 4. Common and Episodic Cutaneous Manifestations of Crohn Disease [206]

Common cutaneous manifestations of Crohn's disease[i]	**Episodically reported cutaneous manifestations of Crohn's disease**
"metastatic" Crohn's disease (cutaneous granulomas)	necrobiosis lipoidica diabeticorum
erythema nodosum	lichen nitidus
pyoderma gangrenosum	epidermolysis bullosa acquisita,
rheumatoid arthritis	oral intraepithelial IgA pustulosis
perianal abscesses	deficiency states of niacin, zinc and vitamin C
perianal sinuses	Sweet's syndrome
ischiorectal abscesses	lichen planus
ischiorectal sinuses	porokeratosis
anal fistulae	granulomatosis vasculitis
anal fissures	pyoderma faciale
conjunctivitis	acne fulminans
episcleritis	neutrophilic dermatosis of malar region
uveitis	vitiligo
clubbing	erythema multiforme
palmar erythema	pyostomatitis vegetans (pyoderma vegetans)
phlebitis	psoriasis
aphthous ulcers	vesiculopustular eruption
mucous membrane cobblestoning	erythema elevatum diutinum
perianal skin tags	cutaneous periarteritis nodosa
swelling of oral cavity/labia	cheilitis granulomatosa of the lips
epidermolysis bullosa acquisita	dissecting cellulitis
deep venous thrombosis	hidradentitis supprurativa
thromboembolic disease	
necrotizing vasculitis	

Pyoderma vegetans

Pyoderma vegetans is a rare condition that is clinically characterized by large verrucous plaques with elevated borders and multiple pustules, most commonly on the lips. The etiology of pyoderma vegetans remains unknown. It has been linked to HS in 2 cases. On involved a 24-year-old woman with rapidly evolving pyoderma vegetans with a highly elevated serum IgE level and a history of

hidradenitis suppurativa [109]. Another report of pyoderma vegetans showed association with the follicular occlusion triad and HS [108]. Pyoderma vegetans and IBD have been linked in 4 cases [242, 243, 244, 245] and I think that the underlying etiology of over-reaction of the immune system to normal bacteria underlies the coincidence of pyoderma vegetans in both HS and IBD.

Acanthosis Nigricans

I have found in my practice that acanthosis nigricans (AN) commonly accompanies HS (Figure 2). This makes sense because AN an HS are often accompanied by obesity. However few published reports associate HS and AN [109, 146 245]. Barth [246] noted thirteen patients with the syndrome of acanthosis nigricans and insulin resistance, of which 5 had hidradenitis suppurativa. The patients had raised fasting plasma insulin levels compared with matched normal controls and increased insulin resistance. Insulin resistance correlated with total serum testosterone in these patients. Perhaps the eye of the observer is more struck by the scarring of HS rather than the velvet plaques of AN.

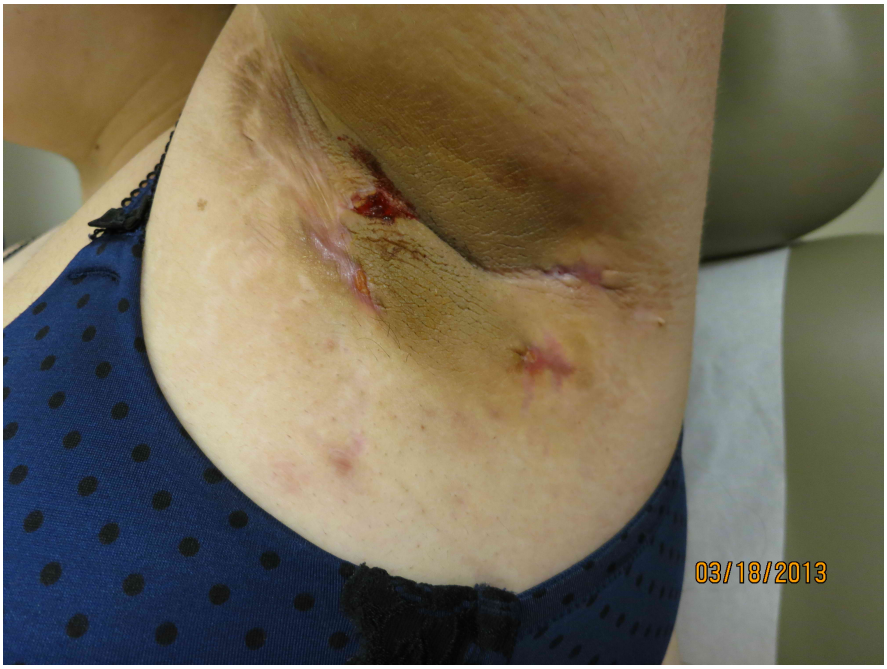

Figure 2 Acanthosis nigricans and HS

Obesity

Studies show that obesity is more common in patients with HS than in matched controls [247, 248]; this association is also demonstrated in case reports [249, 250, 251]. Whether this is causation or correlation is unclear. Harrison [254] found that 77% of males with HS were overweight and 26% were obese, whereas 69% of females with HS were overweight and 33% were obese. A significant association with body mass index in medically assessed HS patients was reported [255]. It is interesting to note, that I have had 6 patients with stage 3 HS associated with wasting who were not obese.

Kidney Disease

The kidney has been linked with a variety of skin diseases that include nephrogenic systemic fibrosis and pseudoxanthoma elasticum [256]. Several patients with kidney pathology have also been noted to have HS. In particular, one patient with nephrotic syndrome had HS [257]. In another with long standing HS, a bout of acute interstitial nephritis was accompanied by a flare of HS that was quieted with high-dose prednisone [258]. A patient with hidradenitis suppurativa related to SAPHO syndrome also had features resembling spondylarthropathy and proteinuria [169]. In other reports, nephrotic syndrome, diarrhea, amyloidosis, and normocytic anemia were noted [259]. Finally, one patient's HS cleared with a kidney transplant. [260]. The significance of these associations is not clear.

Anemia

I found one of the most notable and under reported associations of HS is anemia. It has been noted that HS has been linked to anemi [198], a finding I have encountered myself in a stage 3 HS patient. Rosner and Burg [15] evaluated 10 patients with hidradenitis suppurativa or acne conglobata who developed arthritis. In contrast to patients with acne fulminans and arthritis, all were adults over

22 years of age; nine were black and four were women. Five had chronic anemia. In another series of 42 patient consecutive patient with HS [25], 10 had marked anemia (hemoglobin levels were less than10 gm/100 ml for at least 2 years) and perianal HS. The anemia was hypoferremic and unresponsive to parenteral iron therapy, presumably because of decreased serum transferrin. One observer has noted that in HS, anemia (which can be normochromic-normocytic or hypochromic-microcytic) tends to be present only in stage 2 or 3 perianal HS. In a series mentioned above of 10 patients with pyoderma gangrenosum associated with hidradenitis suppurativa, one had chronic iron-deficiency anemia [15]. Normocytic anemia with HS has been noted in a number of reports [20, 259]. Finally, a case report exists of a 46-year-old man with a twenty-three-year history of painful HS and anemia whose HS and anemia improved with surgery [172]. Whether or not this anemia is an anemia of chronic disease or whether some other factor is at play is not certain. The erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) can track the course of HS and its response to therapy, but I will deal with that in a future paper on biologics and HS. I have summarized some of the abnormal lab values that can accompany HS in Table 3.

Amyloid

Loss-of-function mutations in the γ-secretase genes [135], NCSTN, PSENEN, and PSEN1 have recently been reported to underlie a subset of familial hidradenitis suppurativa (HS) in Chinese, Japanese, and European kindreds [136]. γ-secretase is a multi-subunit protease complex, itself an integral membrane protein, that cleaves single-pass transmembrane proteins at residues within the transmembrane domain. γ-secretase is also critical in the related processing of the Notch protein, which some have suggested is the key to the etiology of HS [261]. Proteases of this type are known as intramembrane proteases. The most well known substrate of γ-secretase is amyloid precursor protein, a large integral membrane protein. When it is cleaved by both γ--secretase and β-secretase it is involved with amyloid formation that occurs in Alzheimer's disease [262]. Amyloid is not a common finding in HS although reports exist of amyloid in HS patients [263, 264]. In other patients with nephrotic syndrome, diarrhea, and HS, the whole colon was permeated by AA amyloid [259]. Because of this common pathogenic mechanism, one might wonder why the two are not more common. However, most sporadic cases of HS lack the mutations mentioned above [265].

Metabolic Syndrome

It has been stated that HS is a disease that can fall under the umbrella of metabolic syndrome, which is associated with metabolic and physiological alterations like central obesity, elevated blood pressure, increased levels of fasting blood glucose, elevated triglyceride (TG), and reduced high density lipoprotein (HDL)-cholesterol. The coincidence of three or more of these abnormalities is called metabolic syndrome. The appearance of the metabolic syndrome is very important because it increases the risk of cardiovascular disorders such as arteriosclerosis. Comparing to controls will be a special challenge because HG patients are often obese and smoke more than controls

A 1998 paper [242] described a hospital-based case-control study in 80 HS patients and 100 age- and sex-matched control participants. The prevalence of central obesity (odds ratio 5.88), hypertriglyceridemia (odds ratio 2.24), hypo-HDL-cholesterolemia (odds ratio 4.56), and hyperglycemia (odds ratio 4.09) in HS patients was significantly higher than in controls. Furthermore, the metabolic syndrome, previously defined as the presence of at least three of the five alterations listed above, was more common in those patients compared to controls (40.0% versus 13.0%; odds ratio 4.46, 95%). This was the first study that stated that HS should be included under the umbrella of metabolic syndrome. A French epidemiology study of HS found that obesity was increased, but not hypertension. It noted increased obesity in HS patients but not higher lipids, hypertension, or diabetes [247]. Of 43 patients with perianal hidradenitis suppurativa at the Lahey Clinic, diabetes was found in 12 percent of HS patients and obesity in 12 percent of HS patients [266].

Other data published in abstract form shows that hypertension, and by extension possible metabolic syndrome, is increased in patient with HS. Crowley [248] studied 147 patients with HS and found that the most common co-morbidities in this population according to self-reported medical history were hypertension (21%), depression(18%), and obesity (15%). According to medical examination, the prevalence of hypertension (self-reported or using hypertension medication) was 22%, morbid obesity (BMI[40 kg/m2) 28%, and depression (PHQ-9 ≥10) 42%. Prevalence of hypertension was similar among patients with severe HS (18%) versus non-severe HS (24%). The prevalence of morbid obesity was higher among patients with severe HS (37%) versus non-severe HS (22%). The prevalence of depression was higher among patients with severe HS (52%) versus non-severe HS (35%). O'Loughlin found that 6 HS patients of 22 patients (22%) had an increased incidence of impaired glucose tolerance [267].

Long standing HS can lead to wasting and to a clinical picture similar to that of patients with long standing debilitating diseases such as cancer or lupus. I have seen cachexia with anemia in stage 3 HS patients and this finding has been noted by others [268, 269].

The conclusions to be drawn form the fact that some HS patients are obese, anemic, and have diabetes (or pre diabetes) is that some patients with HS have metabolic syndrome, but many do not. Furthermore some patients with HS also have symptoms of a chronic disease state with cachexia and wasting, in particular if they have long standing Hurley Stage 2 and Stage 3 disease.

Expansion of Classic Follicular Occulsion Triad/Tetrad

Some have argued that the tetrad should be expanded to include such conditions as mammary fistula, Dowling Degos Disease, pyoderma gangrenosum, and steatocystoma multiplex . Because of the position of these authorities, these conditions will be discussed. Each of these conditions will be discussed separately and in detail. However, because of the large number of reports of th classical triad or tetrad, mammary fistula, DDD, and PG should not be part of syndromic HS of the standard sort i.e. the triad or tetra

A. Mammary-duct fistula

Mammary-duct fistula is a communication between a subareolar duct and skin, usually occurring in the periareolar region. It often occurs spontaneously following underlying periductal mastitis, but can also occur following incision and drainage of a nonlactating breast abscess. It occurs predominantly in younger women, the majority of whom are smokers. Berná-Serna described a case of mammary fistula with the follicular occlusion tetrad and suggested that it be included in the follicular occlusion tetrad [270]. This seems like a tenable rather than a definitive suggestion because mammary fistula has been linked to follicular occlusion [271]. A series of two cases has linked HS with mammary fistula [272]. Still, this remains a rare association and it might be better considered as an associated condition rather as a truly independent entity.

B. Dowling Degos Disease

Dowling-Degos disease (DDD) is a rare genetic disease of the skin, far less common than HS, which presents in adult life with pigmentation, particularly in the folds of the skin. It is also known as "pigmented reticulate anomaly of the flexures." A number of families with classic Dowling-Degos disease and a related condition called Galli-Galli disease (an acantholytic variant of Dowling-Degos disease) have now been studied genetically. All show a gene mutation, which results in a very short keratin 5 molecule that is effectively inactive. One role of keratin 5 is involvement in the transfer of the melanin pigment from melanocytes to keratinocytes. It is likely that the different variants will be related to different mutations in the gene. This has no overlap with genetic linked cases of HS, which show loss-of-function mutations in the γ-secretase genes [273]. As already discussed, NCSTN, PSENEN, and PSEN1 hav recently been reported to underlie a subset of familial hidradenitis suppurativa (HS) in Chinese, Japanese, and European kindreds [274]. This occurs on chromosome 1p21.1-1q25.3 [275]. The histology of DDD is very characteristic, showing dilated follicular, fingerlike projections called rete ridges, with thinning of the suprapapillary plates, resulting in an "antler-like" pattern and increased pigmentation of the basal layer [276]. No cases of Galli-Galli disease have been related to HS. There is no overlap of the genetics of DDD and HS.

Nine reports note DDD and HS occurring in the same patient [245, 277, 278, 279, 280, 281, 282, 283]. A case of DDD associated with squamous cell cancer independant of HS has been noted [284]. Interestingly, several reports have linked DDD, HS, and squamous cell cancer. Whether this is a coincidence or an association has to be explored further. Because DDD commonly occurs in the axilla as does HS, it is not clear if their relationship is one of association or linkage. Loo [277] has claimed that HS with DDD an multiple epidermal cysts is a new follicular occlusion triad, but I find this claim to be more a coincidence than an association. Two o these reports note squamous cell carcinoma with HS and DD, one in the groin [245] and one in the perianal region [282]. Another report describes multiple keratoacanthomas with HS and DDD [281]. Because longstanding HS in the groin and perianal area can tu into SCC and DDD is a condition with an early onset, it is unclear whether DDD itself increases the risk of SCC independently of HS

C. Pyoderma Gangrenosum

Pyoderma gangrenosum is a far more common association with HS than DDD or mammary-duct fistula [24, 285, 286, 287, 288, 289 290]. I have seen PG and HS only once in practice and it was in a patient lymphoma. Hsiao identified 11 cases of PG lesions presenting in patients with HS [287]. The clinical triad of pyoderma gangrenosum (PG), acne, and suppurative hidradenitis (PASH) has recently been described as a new disease entity after bowel bypass surgery for obesity, but it lacks a defined genetic basis [286]. Another interesting report noted Behçet disease with anterior uveitis, arthritis, oral, genital, and cutaneous lesions, pyoderma gangrenosum, hidradenitis suppurativa, perianal fistula, and persisting leukocytosis, which responded to colchicine treatment [291]. Interestingly PG has never been reported to evolve into squamous cell carcinoma.

D. Steatocystoma multiplex and HS

Steatocystoma multiplex is a nevoid sebaceous duct and sebaceous gland tumor, originating from sebaceous follicles, but is not a dermoid tumor [292]. Steatocystoma multiplex is connected to the epidermis by a straight or meandering epithelial cord, the remnant of the follicular infundibulum, which is a more or less solid strand, often containing sebocytes or sebaceous lobule-like structures [292]. A lumen, partly present in a few areas of the cord, is filled with cellular debris of keratinocytes, corneocytes, sebocytes, or trapped hairs [292]. One pilar unit continuously produces vellus hairs, which are trapped in the cystic cavity or in the pilary canal [292].

Steatocystoma multiplex (SM) can occur together with HS. Natal teeth and steatocystoma multiplex complicated by hidradenitis suppurativa has been noted and might be a variation on Jackson-Lawler Pachyonychia congenita [293]. Similiarly, Menter noted familial coincidence of hidradenitis suppurativa and steatocystoma multiplex [294]. Steatocystoma multiplex can present as breast lumps [295] and we can imagine that if this physical process were compounded by an immune response, HS would be the result. It would seem that defects in the follicle that lead to occlusion can result in HS or SM. It is likely that defects in the innate immunity o the skin determine whether SM, which is not an uncommon condition, can evolve or overlap with HS.

SM and HS can have overlapping clinical presentations; the immune system can respond aberrantly to the occlusion, which is involved in SM. Plewig assessed specimens from 25 patients (8 females, 17 males) and described a condition termed "steatocystoma multiplex suppurativum," characterized by spontaneous rupture of the cyst, inflammation, and scarring. It mimics acne conglobata with hidradenitis-suppurativa-like lesions as seen in the acne triad or tetrad [292]. Similarly, Gollhausen noted two patients with a condition that he termed "steatocystoma multiplex conglobatum" that presented as recurrent axillary abscesses, but which had the histology of steatocystoma multiplex [296].

Medication induced HS

Hidradentitis has been reported to be induced by several medications. Unsurprisingly, lithium, which is also an inducer of acne and psoriasis, has also been reported to cause HS in multiple case reports [297, 298, 299]. Sirolimus inhibits the response to interleukin-2 (IL-2) and blocks activation of T and B cells. In contrast, tacrolimus, cyclosporine, and pimecrolimus (calcineurin inhibitors-CIs) inhibit the secretion of IL-2. In one study, of 80 renal transplant patients receiving mycophenolate mofetil and steroids, 74 also were treated with sirolimus. Sirolimus was used as the first immunosuppressive therapy for 36 patients, whereas 44 patients were switched from CIs to sirolimus. Of these patients, 12% developed hidradenitis suppurativa, 46 % developed acne-like eruptions, and 26% developed scalp folliculitis [300]. It does seem that blockage of IL-2 has something to do with the development of HS in patients. In 26 patients with inflammatory skin disease treated with cyclosporine, 2 women developed HS 6 months after use of cyclosporine [301].

Vemurafenib, a BRAF inhibitor used to treat melanoma, has an almost 50% chance of inducing a skin based drug reaction. It appeared to be the cause of HS in one reported patient; the condition remited after the drug was stopped [300]. Ten weeks after starting vemurafenib treatment, the patient presented with follicular-based open and closed comedones and cysts on his cheeks, postauricular ears, and earlobes. Three weeks later, he returned with innumerable hyperkeratotic open comedones on his scalp and painful draining nodules and multiheaded open comedones in his axilla. A month later, he developed increasing hyperkeratotic, follicular-centered papules on his forearms, chest, proximal thighs, lower back, and buttocks. He also developed many nevi on previously unaffected skin. The patient's hidradenitis improved moderately with doxycycline and benzoyl peroxide treatment. The scalp improved with application of tretinoin, 0.025%, cream. Discontinuation of vemurafenib therapy owing to progression of his metastatic melanoma resulted in almost complete resolution of his KP-like eruption, cysts, and HS after 6 weeks. The nevi have persisted.

Hidradenitis suppurativa associated with use of oral contraceptives has been noted in 7 patients [301]. Most were taking (ethinyloestradiol 30 -µg ethynodiol 2 mg), but others were taking ethinyloestradiol 30 µg, levonorgestrel 250 µg. When the HS developed, these patients were all put on an antibiotic of an unspecified type and 3 took or changed to ethinyloestradiol 30/40/30 µg, levonorgestrel 50/75/125 µg. In some cases the HS remained and the patient took ethinyloestradiol 30 µg, levonorgestrel 150 µg. On HS patient who took ethinyloestradiol 30 µg, levonorgestrel 150 µg required 2 axillary surgeries but went into eventual remission. One patient who took 500 µg norethisterone and 35 µg and ethinylestradiol and then 0.15mg levonorgestrel and 0.03mg ethinylestradiol required right groin surgery before her problem was solved. Because there is a hormonal component to HS in some women this is not suprising. Dysregulation of hormonal balance can influence HS. This is the only paper in the literature that has a series of patient who had HS triggered by oral contraceptives. This implies that HS is a disease related to hormonal dysregulation in some cases.

Single diseases with limited reports linking them

Pachyonychia congenital (PC) is an autosomal dominant genodermatosis affecting ectodermal development [304]. Some cases manifest with follicular hyperkeratosis that might be a common feature shared with HS. Todd reported five of six family members with Jackson–Lawler type pachyonychia congenita (JLPC) (which includes natal teeth) and concurrent HS [305]. Another case linking PC and HS was reported that was not responsive to infliximab [306]. Two other reports have linked PC with steatocystoma multipex, a disease related to HS [307, 308].

Pityriasis Rubra Pilaris [309] without HIV infection has been linked to HS. With HS Type VI PRP, the PRP of HIV has been noted t manifest with HS and AC. Sometimes lichen spinulosis is a coincident finding in type VI PRP with HS and AC. Type VI PRP is more common in patients with AC than HS and was discussed above.

Single case reports linking HS with other disease states

Single reports link HS with pruritus ani [310] and complex regional pain syndrome (CRDS). CRDS was previously known a Reflex sympathetic dystrophy (RDS) [311]. One patient who had Bazex–Dupre´–Christol syndrome (and was part of a kindred with Bazex–Dupre´–Christol syndrome) manifested with facial milia, follicular atrophoderma of the cheeks and dorsa of the hands, hypotrichia (since birth), hypohidrosis, and axillary hidradenitis suppurativa. Other family members did not have HS [312]. Roser and Burg [15] noted in their series of 10 patients, two each with urethritis, oral ulcers, and penile ulcers. Borbujo Martínez presented three patients affected by Down's Syndrome who suffered hidradenitis suppurativa in the perianal region with poor response to topica and systemic treatments [313]. Acne vulgaris and hidradenitis suppurativa have been reported as presenting features of acromegaly [14]. Because these are single reports they may merely represent correlation rather than causal links.

Conclusion

HS remains puzzling for dermatologists. Most cases of HS occur in isolation from other pathology. It is likely that HS, in some cases, is a disease within the rubric of a metabolic syndrome [314]. Like psoriasis, it impacts the internal health of those who suffer from it. I have listed the common and episodic cutaneous manifestations of Crohn Disease in Table 1 and only a minority are shared with HS. In table 2, I list pathological associations of HS, which sums up this article in table form. In table 3, I outline laboratory chemistry abnormalities. In a future article I will address the causation of squamous cell cancer in HS, which should also b a diagnostic consideration in long standing (greater than 15 years) perianal and perineal stage 2 and stage 3 HS. HS is seldom biopsied because it is not really a biopsy diagnosis. Therefore, any lesion that looks like an SCC should be biopsied. In addition, the issues of pain and depression will be addressed in a future article. I hope that this article will help dermatologists and patients alike t fit the clinical pieces together when HS alone does not explain the clinical picture and the patients' symptoms.

Table 1 Pathological Associations of Hidradenitis

Strongest associations in order of frequency	Types of Arthritis associated with HS	Physcial Findings With might be added to tetrad	Inflammatory Associations	Weaker Associations	Medication Ass
Acne conglobata	Seronegative Arthritis	Mamillary Fistula	Crohn's Disease	Pachyonychia congenita	Lithiun
Pilonidal Cyst	Reactive inflammatory Arthris	Anal Fisulas	Ulcerative Colitis	Natal teeth and steatocystoma multiplex	Sirolimu
Dissecting Cellulitis (Perifolliculitis capitis abscedens et suffodiens)	Osteomyelitis (inflammatory non infectionous)		Interstitial keratitis	Dowling-Degos disease	Cyclospor
	Spondyloarthropathy		Pyoderma gangenosum	Steatocystoma multiplex	Inverse psoriasis or p effect of infliximz
	Sacroiliitis		Behçet's disease	Amyloidosis	Vemurafe
	Dactylitis		Behcet's disease with psoriasis	Acromegaly	
	Monoarthritis of the hip.		Psoriasis vulgaris	Dowling-Degos disease, hidradenitis suppurativa, and multiple keratoacanthomas.	
	Erosive arthropathy		Pyodermia fistulans sinifica	Prurtis ani	
	Systemic Lupus erythematosus		System Lupus Erythematous	Condyloma like lesions	

			Granulomatous lobular mastitis[315]	Dowling-Degos and multiple epidermal cysts	
			Pyoderma vegetans	Keratitis-ichthyosis-deafness syndrome	
			Sjögren's syndrome	Bazex-Dupre-Christol syndrome	
			Sjögren's syndrome plasma cell panniculitis	PAPA syndrome	
				Erythema Nodosum	
				Down's Syndrome	

Table 2 Complications associated with hidradenitis suppurativa[172]

Anal, urethral, and rectal strictures and fistulas
Anemia
Contractures and limb mobility limitations
Cutaneous squamous cell carcinoma
Depression
Increased risk of other malignancy
Kidney Disease
Lumbosacral epidural abscess
Metabolic syndrome
Oral ulcers [18]
Pain
Penile ulcers[18]
urethritis,[18]

Table 3 Abnormal Lab value linked to HS

Erythrocyte sedimentation rate (ESR)-elevated
Monoclonal gammopathy-elevated
C Reactive Protein (CRP)
Hypoproteinemia
Soluble interleukin-2 receptor [316] -elevated
Hypergammaglobulinemia -elevated
Circulating immune complexes -elevated
Polyclonal gammopathy-elevated

Table 4. Common and Episodic Cutaneous Manifestations of Crohn's Disease[206]

Common cutaneous manifestations of Crohn's diseaseii	Episodically reported cutaneous manifestations of Crohn's disease
"metastatic" Crohn's disease (cutaneous granulomas)	necrobiosis lipoidica diabeticorum
erythema nodosum	lichen nitidus
pyoderma gangrenosum	epidermolysis bullosa acquisita,
rheumatoid arthritis	oral intraepithelial IgA pustulosis
perianal abscesses	deficiency states of niacin, zinc and vitamin C
perianal sinuses	Sweet's syndrome
ischiorectal abscesses	lichen planus
ischiorectal sinuses	porokeratosis
anal fistulae	granulomatosis vasculitis
anal fissures	pyoderma faciale
conjunctivitis	acne fulminans

episcleritis	neutrophilic dermatosis of malar region
uveitis	vitiligo
clubbing	erythema multiforme
palmar erythema	pyostomatitis vegetans (pyoderma vegetans)
phlebitis	psoriasis
aphthous ulcers	vesiculopustular eruption
mucous membrane cobblestoning	erythema elevatum diutinum
perianal skin tags	cutaneous periarteritis nodosa
swelling of oral cavity/labia	cheilitis granulomatosa of the lips
epidermolysis bullosa acquisita	dissecting cellulitis
deep venous thrombosis	hidradentitis supprurativa
thromboembolic disease	
necrotizing vasculitis	

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