Hidradenitis Suppurativa

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ABSTRACT

Background. Hidradenitis suppurativa (HS) is a recurrent, suppurative disease manifested by abscesses, fistulas, and scarring.

Methods. We reviewed the literature to identify reliable information regarding epidemiology, pathogenesis, clinical manifestations, evaluation and differential diagnosis, treatment, complications, and prognosis.

Results. Hidradenitis suppurativa usually affects young women, with a prevalence of 0.3% to 4% in industrialized countries. Once considered to be “apocrine acne,” HS is actually a defect of terminal follicular epithelium. Obesity, chemical irritants, or hyperandrogenism are not consistently associated; bacterial involvement is secondary. Hidradenitis suppurativa should be suspected in young adults with recurrent, deep furuncular lesions in flexural sites, especially when such lesions respond poorly to antibiotic therapy. Clindamycin and isotretinoin may be useful, though wide excision with healing by granulation is considered most efficacious. Anemia, arthropathy, and squamous cell carcinoma are potential complications.

Conclusions. Since spontaneous resolution is rare and progressive disability the rule, early definitive surgical treatment of HS is advisable.

HIDRADENITIS SUPPURATIVA (HS) is a chronic, suppurative, and cicatricial inflammatory disease, affecting apocrine gland-bearing areas. Because of the variable clinical features and many sites potentially involved, patients affected with this disorder may come to family physicians, general internists, gynecologists, urologists, infectious disease consultants, and dermatologists. The axilla is most often involved, followed by the anogenital region. Uncommon sites include the areola of the breast, the submammary fold, periumbilical skin, the scalp, the zygomatic and malar areas of the face, the buttocks, the thighs, and the popliteal fossa.1 Hidradenitis suppurativa has several synonyms, all of which are not commonly used, including apocrinitis, hidradenitis axillaris, and acne inversa.2,3 Unfortunately, HS is a disease that continues to be characterized by chronicity and misdiagnosis, leading to both patient and physician frustration.4-5

BACKGROUND

In 1839, Velpeau6 described a peculiar inflammatory process with superficial abscess formation, affecting tissues of the axillary, mammary, and perianal regions. It was not until 1854 that the suppurative process became associated with sweat glands by Verneuil7 and was given its current name. In 1922, Schiefferdecker8 classified sweat glands as eccrine or apocrine and subsequently localized HS to the apocrine glands. Brunsting,9 in 1939, noted that HS, dissecting cellulitis of the scalp and neck, and acne conglobata commonly occur in the same person. He noted that the central pathogenic event in all three was a tendency toward follicular hyperkeratinization with secondary bacterial infection.10 This group was thus categorized as the follicular occlusion triad, with pilonidal sinus later added to form a tetrad.11

EPIDEMIOLOGY

Although the exact prevalence of HS is unknown, it has been estimated at 1:300.12 Elsewhere, the reported prevalence is similar to that of other major dermatoses (eg, psoriasis) in the adult population.13 Jemec et al14 reported a point prevalence of 4.1%, based on objective findings in a younger adult population; however, this may be falsely elevated by studying a select (at-risk) age range.
The peak onset of HS is between ages 11 and 30, which coincides with postpubertal increase in androgen levels. The disorder rarely occurs before puberty. However, the occasional onset in neonates and infants may reflect the relatively hyperandrogegenic state in the first year of life. In women, HS may persist into the climacteric, but onset after menopause is rare.

Hidradenitis suppurativa occurs more frequently in women, yet the reason for this preponderance is unknown. Women are also prone to have axillary involvement. Other commonly affected areas in women include the inguinal and mammary regions. In contrast, men tend to have perianal or anogenital involvement.

Many authors believe that HS is more frequent in blacks, yet others report no racial predilection. Hidradenitis suppurativa has a worldwide distribution, though hot, humid environments tend to favor its development.

ETIOLOGY AND PATHOGENESIS

Several reports in the literature link HS to a single gene transmission. Fitzsimmons et al studied three families with a total of 21 affected members. They reported that the pattern of transmission and the number of affected individuals were consistent with autosomal dominant inheritance. Later, Fitzsimmons et al studied the families of 26 patients with HS. In all, 62 people were affected by this disorder. Eleven families showed evidence of a single dominant gene while three other families had histories of genetic transmission. In nine families, no pattern of disease transmission could be found. However, both psychosocial issues and problems of ascertainment may have been responsible for falsely negative family histories. In this study, both men and women were affected with vertical transmission through several generations, consistent with autosomal dominant inheritance.

Traditionally, HS has been considered a disorder of apocrine glands. This theory was supported by the experimental model of Shelley and Cahn, which induced poral occlusion by manual skin depilation and application of atropine impregnated tape. The resultant changes included initial keratinous obstruction, with subsequent dilatation, inflammation, and bacterial invasion of the apocrine duct. However, Shelley and Cahn were only able to achieve occlusive results in 25% of the experimental lesions, and the resultant acutely occlusive lesions did not progress to the characteristically chronic condition of HS. More recent studies have identified HS as a disorder of follicular rather than apocrine occlusion. For example, Yu and Cook compared skin samples from HS with controls and found no significant morphologic abnormalities of the apocrine glands. In one third of the cases, they found inflammatory changes involving the apocrine glands but only when the inflammation extensively involved other structures, such as the eccrine glands and hair follicles. Attanoos et al also studied the skin biopsies of HS and reported a consistent finding of follicular occlusion in all specimens when compared with controls, regardless of disease duration. They agreed with Yu and Cook that inflammation of the apocrine glands did not occur in the absence of an adjacent folliculitis. Thus, apocrine gland involvement is only incidental or secondary to the primary developments that involve the terminal hair follicle. Therefore, HS is best considered as a disorder of terminal follicular epithelium within apocrine gland-bearing skin.

The exact etiology of HS remains obscure. Morgan and Hughes studied the size, distribution, and density of apocrine glands in patients with HS and found no significant differences from that of controls. Chemical irritants such as deodorants, mechanical irritation, depilation, and shaving have been considered as factors by many. However, Morgan and Leicester retrospectively compared 40 patients who had HS with 40 age-matched controls and found no significant difference in the use of these items. Obesity is another commonly cited etiologic factor. Several authors have suggested a clear relationship between androgens and HS. Hidradenitis suppurativa is rarely present until after the onset of puberty. Many women describe a worsening of the condition with menses, while others report alleviation with pregnancy, followed by postpartum flaring. Hidradenitis suppurativa is not present in eunuchs or eunuchoids. Also, androgens tend to enhance keratin production, and animal
studies have shown that follicular occlusion can be increased by systemic androgen administration. There have been several case reports linking HS to androgens. One case cites HS as the presenting feature of premature adrenarche in a 7-year-old girl. Another report details seven women with HS after starting oral contraceptive use, which improved after stopping or changing the oral contraceptive to a higher estrogen/progesterone ratio. Some authors dispute the association of androgens and HS, citing no supporting evidence for biochemical hyperandrogenism. Although some suggest enhanced peripheral conversion of androgens by apocrine glands as a critical part in the pathogenesis of HS, found equivalent activity of three peripheral androgen-converting enzymes in axillary apocrine glands of patients with HS compared with those of controls. According to anecdotal reports in the literature, antiandrogen therapy has been effective for a few patients, while remaining ineffective for most others. Thus, hormonal influence remains controversial.

When considering immunology, neither primary cellular nor humoral abnormalities can be found. Dvorak et al reported that patients with HS have normal phagocytosis, chemotaxis, and intracellular killing of bacteria. Abnormal laboratory values associated with HS may include an increased erythrocyte sedimentation rate, leukocytosis, decreased serum iron, and changes in the serum electrophoresis pattern; such changes can be considered due to the chronic inflammatory process.

CLINICAL MANIFESTATIONS

The disease onset is insidious, with early symptoms of pruritus, erythema, and local hyperhidrosis. Later, a firm, pea-sized nodule appears and may rupture spontaneously, yielding a purulent discharge. The lesion then heals with fibrosis, with eventual recurrence adjacent to the original area. Over time, multiple abscesses and sinus tracts develop a subcutaneous honeycomb. Occasionally, the involvement extends into the underlying fascia and muscles. Fibrosis, hypertrophic scarring, and induration ultimately develop. Multiple open comedones (blackheads) may be obvious. Adenopathy is rarely associated and, with advanced disease, destruction of most glands causes a decrease or absence of apocrine sweating.

Bacterial involvement of HS is not a primary pathogenic event, but is secondary to the disease process. The flora of microorganisms is not constant and may change unpredictably. Various bacteria can be isolated from the sinuses, particularly staphylococci, streptococci, and gram-negative rods. With perianal disease, there is an increased incidence of Escherichia coli, Klebsiella, and Proteus as well as anaerobes. Brenner and Lookingbill reported frequent isolation of Bacteroides fragilis and Bacteroides melaninogenicus and suggested treatment with clindamycin to decrease the malodorous sinus drainage. Several other authors have implicated Streptococcus milleri as a major "pathogen" in perineal HS. Streptococcus milleri is an organism that frequently colonizes the gastrointestinal and female genital tracts. Highet et al reported that the presence of S milleri significantly correlated with disease activity. However, S milleri was subsequently sought in 32 patients participating in another study and was never recovered. The course of HS is characterized by exacerbations and remissions; with gradually increasing extent of affected skin. Recurrent, foul-smelling discharge from multiple draining sinuses may cause extensive soiling of clothes, forcing the individual to limit social contact and forfeit employment. Attendant physical discomfort may preclude sexual intercourse or even walking.

HISTOPATHOLOGY

Early lesions show hyperkeratosis of the terminal hair follicle with subsequent occlusion and dilatation. Eventually, inflammatory changes develop in the form of a perifolliculitis with an infiltrate composed of neutrophils, lymphocytes, and histiocytes. Abscess formation occurs, leading to the destruction of the pilosebaceous unit and eventually of the other adnexal structures. Histologically, chronic lesions show a dermis, with an inflammatory cell infiltrate, granulation tissue, giant cells, subcutaneous abscesses, and sinus tracts. Extensive fibrosis may also be seen late in the disease course.

EVALUATION AND DIFFERENTIAL DIAGNOSIS

The physician should suspect HS in any pubertal or adult patient with a tender, abscess-like process in an apocrine gland-bearing area. The diagnosis is primarily clinical, based on the presence of multiple sinuses and abscesses. These lesions often respond poorly to conventional antibiotics and tend to recur. Diagnosis rarely requires biopsy, especially in well-developed lesions. Mortimer rec-
ognized that early cases of HS were more responsive to treatment, yet harder to identify. Thus, he studied the presenting features in 70 patients and proposed these clinical criteria for early diagnosis: recurrent deep boils for >6 months in flexural sites, onset after puberty, poor response to conventional antibiotics, strong tendency toward relapse or recurrence, comedones in apocrine gland-bearing skin, routine cultures of pus from boils revealing no pathogens, personal or family history of acne or pilonidal sinuses, and exacerbation of boils premenstrually in women.

Since the disease begins with recurrent inflammation and abscess formation of only a few follicles, it is often misdiagnosed and treated with repeated incision and drainage or antibiotics. This unfortunately delays definitive treatment. Hidradenitis suppurativa should be differentiated from furuncles, carbuncles, granulomatous disease, infected epidermoid cysts, tuberculosis cutis, actinomycosis, tularemia, and carcinoma. With perineal or inguinal involvement, granuloma inguinale and lymphogranuloma venereum should also be considered, though both of these sexually transmitted diseases are rare in the United States. If the involvement is perianal, HS may be confused with perirectal abscesses, anal fistulae, pilonidal cysts, and Crohn’s disease. The differentiation of HS and Crohn’s disease merits special attention. Perianal lesions are the initial presentation in 5% of all Crohn’s cases and, at times, these two diseases may be clinically indistinguishable. Evaluation of perianal lesions includes proctoscopy to assess any involvement of the anus or rectum. Inspection of all apocrine gland-bearing areas should also be done to look for distant involvement of HS and Crohn’s disease. Several authors have reported the comorbidity of HS and Crohn’s disease. Church et al retrospectively reviewed 61 patients with HS and found 38% to have a concomitant diagnosis of Crohn’s disease, the latter typically preceding the development of HS. Tsianos et al speculated that HS appears to be another cutaneous manifestation of Crohn’s disease. However, this remains to be verified.

As HS becomes more chronic and characteristic, the diagnosis is typically apparent to the physician who is familiar with the disease. No other process produces recurrent abscesses and sinus tract formation with a characteristic distribution in apocrine gland-bearing skin.

**TREATMENT**

Surgery is the sine qua non of successful treatment, especially in the case of chronic disease. However, because of the extensive nature of such treatment, patients are often first given medical therapy. Patients may have symptomatic relief with a long-term course of antibiotics. Clindamycin, in particular, has been favored in the literature. Clemmensen treated 30 patients with either topical clindamycin or placebo in a double-blind trial and reported significant improvement without side effects. Buckley and Sarkany reported a case of severe HS that cleared dramatically after systemic clindamycin, having failed to improve on other antibiotics. In general, after withdrawal of antibiotic treatment, relapse of HS is almost inevitable. Although antibiotics are not curative, they may diminish odor and discharge, and reduce pain. Several reports support the use of antiandrogen therapy in women with HS. Sawyers et al reported on four women with chronic HS who responded within 2 months to treatment with cyproterone acetate and ethinyl estradiol. When the cyproterone acetate was reduced to half its original dosage, three of the four patients exhibited deterioration. After discontinuing therapy, two of the four women maintained the same level of improvement for several months. Mortimer et al executed a double-blind, controlled, cross-over trial comparing ethinyl estradiol/ cyproterone acetate with ethinyl estradiol/ norgestrel treatments in 24 women with HS. Both regimens produced significant improvement in disease activity. Results included seven patients free of disease at 18 months, five patients improved, four patients unchanged, and two worsened. The remaining six patients withdrew because of side effects or disease exacerbation. Overall, patients with more extensive involvement had less response to therapy.

Because isotretinoin has been successful with acne, it has also been considered for the treatment of HS. However, the literature reveals equivocal results with optimal benefit occurring in 3 to 4 months. Isotretinoin has anti-inflammatory activity and has been reported to enhance immune function. Several authors consider it useful as an adjunctive treatment to reduce inflammation, suppuration, and edema before and after surgery.

Radical surgery is considered by many to be the only “cure” for HS, though “cure” can only
be achieved for the particular area excised. Incision and drainage of abscesses offers only transient benefit, since they almost inevitably recur. Unroofing and marsupialization of the sinus tracts may be of value, but recurrences do occur. Wide excision of the involved areas down to soft, normal tissue with margins well beyond the clinical borders of activity is considered to be most effective. Controversy exists about closure of the skin defect. Primary closure and rotation flaps are rarely used because of the extensive nature of the excisions. This method has a high recurrence rate, presumably because it is associated with insufficient excision. However, primary closure is reported to be more effective with axillary excisions in women because of the extra skin available in the lateral mammary area. Split-skin grafting, either immediate or delayed, has the advantage of rapid healing with complete wound healing, often in 2 to 3 weeks. Grafting is also most successful with axillary disease. Disadvantages include an unsightly cosmetic result and the discomfort and poor cosmesis associated with the donor site. In addition, the affected limb must be immobilized for several days. Grafting is associated with high-failure rates in the perineal and perianal areas and is also not advised for closure of the anal canal. Grafts in this area may contract, leading to anal stenosis. Mustafa et al. reported a preference for a 1-week delayed skin graft to avoid missing any retained sinus tracts not completely excised.

Healing by granulation (secondary intention) is associated with a predictable result that is as good or even superior to that obtained by skin grafting. However, complete wound closure may take up to 2 to 3 months. Silastic foam dressing allows patients to manage their own wounds at home and continue with their daily routine during the healing period. A study by Morgan et al. of patients with bilateral axillary involvement compared granulation on one side with grafting on the other. Most patients preferred the granulation with Silastic foam dressing. In another study, subjects reported minimal inconvenience or interruption from daily activities and minimal analgesic requirements, after healing by secondary intention; wound closure was uncomplicated with unrestricted, stable, and cosmetically acceptable scars. Hospital time and costs were also decreased.

Carbon dioxide laser treatment with secondary intention healing has recently been presented as a rapid, efficient, and economical treatment of HS. As a tissue-sparing procedure, laser excision decreases the risk of contractions. The total procedure time is <20 minutes in most cases, including local anesthesia. Laser treatment is suitable for mild-to-severe disease with no need for hospitalization. Finally, the heat of the laser is bactericidal, which prevents the spread of microorganisms to adjacent tissue or into the bloodstream. In a study of 24 patients by Lapins et al., more than half of the patients returned to their usual routine in <3 days, and the range of complete healing time was 3 to 5 weeks. Finley and Ratz treated seven patients with carbon dioxide laser excision and reported a healing time of 4 to 8 weeks. They considered the advantage of laser treatment to be improved hemostasis, which affords better visualization and therefore more complete removal of the affected tissue. Dalrymple and Monaghan treated six patients with the carbon dioxide laser. One to four sessions were needed to completely eradicate the affected areas, and half of the patients had new disease in remote areas, which was similarly treated. The patients reported less scarring and pain than that of previous surgeries or the disease itself.

Regarding perianal surgery, some authors prefer the use of a colostomy to prevent fecal contamination of the wound. However, many others, including us, consider it unnecessary if a thorough mechanical bowel preparation is done preoperatively, bowel activity is suppressed postoperatively, and local hygiene is aggressive during healing. Bhatia et al. reported that transient soiling of the wound followed by prompt cleansing did not interfere with the healing process in patients with perianal excisions.

Local recurrence after surgery usually indicates inadequate excision of the affected area, and re-excision is indicated. A study by Harrison et al. reports the following rates of recurrence in 82 patients treated with 118 radical excisions: axillary, 3%; perianal, 0%; inguino-perineal, 37%; and submammary, 50%. In this study, recurrence appeared from 3 to 72 months after surgery, with a median of 24 months. Because of the poor success with submammary disease, some authors no longer recommend formal surgical excision for this region. Recurrence can occur in remote or untreated regions, since HS may affect any apocrine gland-bearing area, and patients should be cautioned in this regard.
COMPLICATIONS

Complications of HS include local and systemic infections due to the spread of microorganisms and, in rare cases, septicemia.\textsuperscript{12,27} Restricted mobility of the limbs due to marked fibrosis and scarring may also occur, particularly with axillary disease.\textsuperscript{105} With perianal disease, anal, rectal, or urethral fistula formation may occur.\textsuperscript{2,18,91} Anemia, either normochromic or hypochromic, may be associated with HS.\textsuperscript{51,50} Squamous cell carcinoma is a rare but serious consequence of chronic HS. Most cases occur in the anogenital region, perhaps because this site is more easily neglected and prone to advanced disease before treatment is sought. The vast majority of these cases occur with a history of HS for 10 or more years.\textsuperscript{92,96} Squamous cell carcinomas that arise in chronically scarred and inflamed skin tend to be more aggressive than those resulting from chronic sun damage and are associated with local invasion or recurrence after excision, distant metastasis, and high mortality.\textsuperscript{2,11,94,97,98}

Arthropathy associated with HS may present with variable clinical features, ranging from asymmetrical pauciarticular arthritis to a symmetrical polyarthritides/polyarthralgia syndrome.\textsuperscript{99,100} Arthropathy typically involves larger joints of the upper or lower extremity, particularly the knee.\textsuperscript{101-103} The axial skeleton may also become involved, yet it is often asymptomatic.\textsuperscript{102} In many instances, the arthropathy worsens during flares of HS and, conversely, improves after surgical excision of the HS.\textsuperscript{101,102} Rosner et al\textsuperscript{103} did a battery of rheumatologic laboratory tests and reported that the findings of arthritis associated with HS and acne conglobata were characteristic of those seen in other spondyloarthopathies, except for the lack of association with HLA-B27. The treatment for this type of arthropathy consists of oral nonsteroidal anti-inflammatory drugs and excision of underlying HS.\textsuperscript{102}

PROGNOSIS

If untreated, HS typically progresses to total involvement of the affected area without remission.\textsuperscript{2} Although spontaneous resolution may occur, this is rare.\textsuperscript{18} More commonly reported is the decline of severity in women at or after menopause.\textsuperscript{26} Cure rates with surgery are associated with the extent of disease involvement; clinical cure is almost certain with early cases, while it is difficult or almost impossible with extensive involvement.\textsuperscript{2,18} This reinforces the need for early recognition and treatment of this potentially disabling disease.

References