Hidradenitis suppurativa

Key points

- Hidradenitis suppurativa is a chronic relapsing inflammatory condition affecting the skin and subcutaneous tissue
- It manifests as painful deep nodules, abscesses, sinus tracts, comedones and scarring in intertriginous zones, most commonly involving the axilla and inguinal skin
- The disease is probably more common than originally thought due to under-recognition of mild cases. Patients with stage I disease are often misdiagnosed with recurrent boils.
- Early and mild disease may be managed in general practice with topical or oral antibiotics, and hormonal therapy in women
- Incision and drainage is not recommended as lesions frequently recur
- Patients with frequent or debilitating exacerbations despite initial management and risk factor modification should be referred to a dermatologist for consideration of advanced medical management and referral for surgery

Introduction

Hidradenitis suppurativa (HS) is a chronic and potentially incapacitating skin condition characterised by painful and suppurative inflammatory nodules primarily affecting intertriginous areas. In the initial stages the condition is often misdiagnosed as boils or furunculosis. The severe form causes physical and emotional debilitation due to painful deep abscesses, disfiguring scars and malodorous discharge from sinus tracts. Early treatment can mitigate disease severity and prevent complications. Therefore early recognition and appropriate management is imperative.

Epidemiology

Hidradenitis suppurativa is not an uncommon condition. In its milder forms it is probably under-recognised, being treated as recurrent boils in many cases. While epidemiological studies from the Australian population are not available, our experience is consistent with published prevalence rates of 1% to 4%. (Revuz JE, 2008) (Jemec GB, 1996) A recent population-based study in Minnesota suggested the annual incidence is 6 per 100,000 people. (Vazquez BG, 2013)

The condition rarely presents before puberty, with the highest incidence occurring between the ages of 20 to 29 years old. The prevalence is lower in age groups older than 55 years. It is three times more common in women. There is no ethnic predilection. (Alikhan A, 2009) (Revuz JE, 2008) (Jemec GB, 2012)
**Pathogenesis**

HS affects areas of skin that bear apocrine sweat glands. Thus it was originally thought that it was caused by apocrine sweat gland dysfunction, as implied by its name. More recent research suggests the primary problem is occlusion of the follicular portion of the pilosebaceous unit. According to this theory, proliferation and failed keratinocytes shedding in the follicular duct may be hormonally induced. Follicular hyperkeratosis and plugging ensues, followed by expansion of the follicular duct and apocrine gland stasis. This causes inflammation (perifolliculitis) which may lead to rupture of the follicular duct and destruction of the pilosebaceous unit, in turn releasing proinflammatory contents such as keratin, sebum, hair and bacteria. The ensuing influx of inflammatory cells results in abscess formation, providing a nidus for secondary infection. A chronic inflammatory process results in sinus tract formation and fibrosis. (Alikhan A, 2009) (van der Zee HH L. J., 2012)

Several factors are currently under investigation to elucidate the primary cause of follicular occlusion. These include abnormal molecular response to hormones, nicotine, anoxia and mechanical stress; defective follicular walls predisposing to plugging, rupture and sinus tract formation; and immune system dysregulation. (Melnik BC, 2013) (Danby FW, 2013) A familial tendency with an autosomal dominant pattern of inheritance has been observed although a common candidate gene is not yet clear. (Von der Werth JM, 2000) (Alikhan A, 2009) Current studies are focused on genes encoding proteins involved in the Notch pathway of normal skin functioning as well as tumour necrosis factor (TNF) pathways. (Melnik BC, 2013) Other factors recognised to exacerbate or that are clinically associated with HS are summarised in Table 1.

It is important to note that the contribution of bacteria as a causative agent is controversial. Sinuses and old ruptured lesions typically demonstrate a wide variety of bacteria including staphylococci (most commonly coagulase-negative staphylococci), corynebacterium, streptococci, Gram-negative rods and anaerobic bacteria. However acute and unruptured lesions may be sterile or colonized by skin commensals, indicating secondary infection and colonization may be more likely than primary infection. (Alikhan A, 2009) (Collier F, 2013) (van der Zee HH L. J., 2012) Nevertheless persistent bacterial colonization may promote the ongoing inflammatory process. (Lapins J, 1999) (Sartorius K K. H., 2012) (van der Zee HH v. d., 2010)

**Clinical presentation**

**Distribution**

HS predominantly affects intertriginous areas of skin such as the axillae, inguinal, perianal and perineal areas, inframammary folds and gluteal cleft. It can also affect
the inner thighs, breasts, buttocks, pubic area, scrotum, vulva and chest. It has been reported to affect the scalp, eyelid and retroauricular skin. (Alikhan A, 2009) The distribution of the disease is influenced by sex. (Vazquez BG, 2013) The most commonly affected sites in men and women are presented in Table 2.

**Lesions**

The primary lesions of HS are deep inflammatory nodules ranging in size from 0.5cm to 2cm in diameter (Figure 1). Patients may initially experience erythema, burning, pruritus, local warmth and hyperhidrosis associated with painful, often solitary nodules. (Alikhan A, 2009) (Jemec GB, 2012) At this stage the condition is commonly misdiagnosed as boils. However, unlike furuncles, HS nodules are deep-seated and round-topped rather than pointed. Acute nodules can resolve in days to months, or cause recurrent episodes of acute inflammation, before progression to an abscess containing purulent or serosanguineous fluid. Walking, sitting or limb movement may be impaired due to pain. Abscesses may drain to the skin surface spontaneously or after manipulation. Pain is often relieved by drainage. (Jemec GB, 2012) Patients often report the presence of at least one painful nodule at a time, with a median of two nodules a month. (Von der Werth JM, 2000)

Over time recurrent nodules at an anatomic site may interconnect, forming sinus tracts (Figure 2). Patients often experience intermittent haemoserous or seropurulent discharge which may be malodorous. Secondary infection can be problematic. Open comedones are a sign of long-standing HS, reflecting end stage damage to the pilosebaceous unit at the openings of old nodules and sinuses. Fibrotic, atrophic or keloidal scarring represents end-stage disease process, but may be mixed in with active lesions in the same region (Figure 2). (Alikhan A, 2009) (Jemec GB, 2012) Table 3 summarises the morphological characteristics of the lesions involved in HS.

**Complications**

Severe chronic HS can result in debilitating complications affecting physical and mental health as listed in Table 4. (Alikhan A, 2009) Particular emphasis should be placed on the high prevalence of depression in patients with HS. Recent studies show the prevalence of depression in HS patients is 40%. (Vazquez BG, 2013). Furthermore quality of life and self-reported general health is significantly reduced in HS. (Matusiak L, 2010) (Wolkenstein P, 2007) Some of the psychosocial consequences of HS include embarrassment and humiliation due to unpredictable malodorous discharge and disfigurement, social isolation and relationship breakdown, increased sick leave and loss of employment, and feelings of worthlessness and low self-esteem.

**Diagnosis and staging**
The diagnosis is usually made clinically, based on lesion morphology, location, and a history of recurrent symptoms lasting longer than 6 months. Associated factors should be sought on history-taking, especially with a view to identifying modifiable risk factors. A full skin examination should also be performed to assess extent and severity. Investigations are usually unnecessary although the tests outlined in Table 5 may be warranted in certain circumstances. (Jemec GB, 2012) The most useful test in the primary care setting is a swab for microscopy, culture and sensitivities. Tests for immunodeficiency are generally unnecessary unless clinical suspicion is high, such as in the case of recurrent pyogenic skin infections at sites atypical for HS. (Collier F, 2013) Differential diagnoses are presented in Table 6.

The Hurley system of staging is a useful clinical tool to determine disease severity at each site of involvement and to guide management options. Approximately 1% of patients progress to stage III disease. (Jemec GB, 2012) The Hurley system is summarised in Table 7.

Associated conditions

HS is one of four conditions that comprise a group of associated diseases, called the follicular occlusion tetrad, that often occur together and share an aetiology of follicular occlusion. The tetrad consists of HS, acne conglobata, dissecting cellulitis of the scalp and pilonidal disease. Other conditions that occur more commonly in patients with HS include acne vulgaris, Crohn’s disease, polycystic ovarian syndrome (PCOS), metabolic syndrome and seronegative arthritis. (Alikhan A, 2009) (van der Zee HH v. d., 2010) (Vazquez BG, 2013) (Collier F, 2013) HS has also been observed in conjunction with the rare auto-inflammatory syndromes PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis), PASH (pyoderma gangrenosum, acne, and suppurative hidradenitis) and SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis). (Marzano AV, 2013) (Braun-Falco M, 2012)

Management

The aims of treatment are to allow healing of inflammatory lesions while preventing formation of new lesions, prevent complications of infection, remove chronic sinuses and limit scar formation. Unfortunately large-scale randomized controlled trials to guide treatment choices are lacking. In addition HS often demonstrates unpredictable and variable responses to therapeutic options, and relapse after cessation of therapy. Nevertheless a therapeutic ladder compiled from existing data is presented below and summarised in Table 7.

General measures
The first important step in treatment of HS is to reassure the patient by dispelling myths that the condition is contagious or caused by poor hygiene. Important lifestyle measures include smoking cessation (Simonart, 2010) and weight loss in cases of obesity. Patients should be advised to wear light loose clothing and avoid traumatizing or manipulating lesions including with cleaning products. (Jemec GB, 2012) Gentle cleansing (without loofahs or cloths) using a pH neutral triclosan wash may help by reducing bacterial colonization. Dietary avoidance of dairy products and foods with high glycaemic loads may be beneficial. (Melnik BC Z. C., 2013) Psychosocial support is central to management in all patients. Analgesia may be required during acute flares.

**Topical therapies**

Topical 1% clindamycin applied twice daily to affected areas in mild cases may be effective. This can also be used in combination with benzoyl peroxide. Empirical evidence has shown that a series of up to three intraleisional triamcinolone injections of dose 1-5mg using a 30-gauge needle at monthly intervals to individual lesions can expedite resolution of nodules. (Jemec GB, 2012)

**Oral medications**

In mild disease, acute flares can be treated with a 7-10 day course of oral antibiotics, typically doxycycline or minocycline (50-100mg twice daily), clindamycin (300mg twice daily) or amoxicillin/clavulanate (500mg-1000mg every eight hours). Longer term antibiotic courses, for several weeks or months, are reserved for stage II disease. They may be effective due to their anti-inflammatory action. Long-term regimes lasting three to six months include doxycycline or minocycline (50-100mg twice daily), or clindamycin with rifampicin (300mg twice daily and 600mg daily, respectively). (Jemec GB, 2012) (Gener G, 2009). Erythromycin (500mg twice daily) is also used in clinical practice. (Collier F, 2013) There is some evidence that dapsone (25-150mg) reduces disease severity in mild to moderate cases. Regimes of rifampicin (300mg twice daily, moxifloxacin (400mg daily) and metronidazole (500mg twice daily) has also been suggested. (Join-Lambert O, 2011)

Hormonal anti-androgen therapy is a suitable option for women. Combined oral contraceptive pills (COCPs) containing anti-androgenic progestagens have been shown to beneficial in high doses, such as cyproterone 50-100mg daily, over a six month period (Sawers RS, 1986) (Mortimer PS, 1986). In Australia anti-androgenic COCPs include cyproterone acetate 2mg (in combination with ethinyl-oestradiol 35mcg), drospirenone 3mg (with ethinyl-oestradiol 20mcg or 30mcg), desogestrel 150mcg (with ethinyl-oestradiol 30mcg) and dienogest 2mg (with ethinyl-oestradiol 30mcg). Cyproterone 50mg is also available in Australia. There are occasional reports of the use of spironolactone to control HS (Joseph MA, 2005), (Scheinfeld, 2013), but in practice it is frequently used at a dose of 25-200mg daily. Off-label use of finasteride in men reduces inflammation and promotes healing of active lesions.
Due to their efficacy in acne vulgaris, retinoids have been used as a treatment option in HS. Studies show isotretinoin has only limited effect, possibly due to its effect primarily on sebaceous glands rather than follicular occlusion (Blok 2013) (Collier F, 2013). On the other hand acitretin showed promising results in a small retrospective study, although it is only suitable for men or women of child-bearing potential due to its teratogenicity. (Boer J, 2011) (Blok 2013)

There is interest in using systemic immunosuppressants and immunomodulators to treat HS but evidence is currently lacking. Prednisolone is not recommended due to its adverse effects, but is occasionally utilized in a short course for acute severe attacks in the absence of infection. Methotrexate has also shown to be ineffective, (Jemec, 2002) however in our experience it is often beneficial at a dose of 15-20mg weekly. There are a few reports of improvement with a course of cyclosporine lasting several weeks to months, but duration of treatment is also limited by the potential for adverse effects. Colchicine has been suggested but one trial showed only modest effect. The use of azathioprine or tacrolimus (topically or systemically) has been proposed but not yet investigated. (van der Zee HH L. J., 2012) (Scheinfeld, 2013) (Blok JL, 2012)

High dosage zinc treatment in the form of zinc gluconate (30mg three times daily) has been suggested for its anti-inflammatory and anti-androgenic properties. (Collier F, 2013) (Scheinfeld, 2013)

**Biological agents**

Emerging understanding regarding the inflammatory aetiology and dysfunctional local immunity of HS has led to a growth in interest in biological immunomodulating agents. Various studies have demonstrated efficacy with few adverse effects from TNF-alpha inhibitors infliximab, adalimumab and etanercept. Current evidence suggests that infliximab is probably the more effective agent, although disease progression often follows cessation of therapy. (Blok JL, 2012) (Chinniah N, 2014) Ustekinumab, an IL (interleukin)-12/IL-23 pathway inhibitor, has shown a positive response in a small number of patients but requires further investigation. (Blok JL, 2012) (van der Zee HH L. J., 2012) Expense and access to biological agents is usually prohibitive except for the most severe cases.

**Surgical intervention**

Surgical procedures may be useful for localized disease or in cases which are non-responsive to medical therapy alone. The purpose of surgical intervention is to
control active HS by eliminating the nidus for inflammation and to remove sequelae such as sinus tracts and scarring. In some cases it can lead to at least local cure of the disease. Any of the aforementioned medical therapies are utilized in conjunction with surgical measures to reduce the extent and severity of inflammation, with the aim of reducing the extent of surgery and minimizing the risk of disfigurement and recurrence.

Minor surgical procedures include punch debridement and deroofing of sinus tracts. Incision and drainage should be avoided as it provides only short-term relief, may result in sinus formation, and lesion usually recur. (Ellis, 2012) Punch debridement is a minor procedure using a 5-7mm punch biopsy to remove the acutely inflamed pilosebaceous unit in an inflammatory nodule, followed by digital or curette debridement. A pilot study into this technique is currently underway. Deroofing and exploration of nodules and sinus tracts is performed by an experienced surgeon to either individual lesions or on an entire affected area with the aim of removing inflammatory material while leaving the floor of the lesion intact for rapid healing. However recurrence is common, probably due to incomplete removal of affected tissue. (Ellis, 2012) (Jemec GB, 2012)

For severe disease radical wide excision well beyond the clinical margins of affected tissue is advocated as potentially curative. Wide excision results in lower recurrence rates compared to local excision. (Alikhan A, 2009) However wound healing can be problematic. Closure by primary intention has higher relapse rates due to the potential for burying active disease foci. On the other hand healing by secondary intention may take months due to the size of tissue removal required. Flap and split-thickness grafts and vacuum-assisted closure (VAC) techniques have been used with better outcomes than primary closure. (Ellis, 2012) (Alikhan A, 2009) Risk of recurrence is greater in inguinal areas compared to axillary disease, and also in the context of obesity and smoking. (Collier F, 2013)

Other physical therapies
Carbon dioxide laser techniques are used under local anaesthetic to achieve deroofing and ablation of inflamed lesions. A few small series showed good results. The use of neodymium:yttrium-aluminum-garnet (Nd:YAG) laser excision has also been demonstrated in one randomized controlled trial. (Jemec GB, 2012) (Collier F, 2013) Other treatment modalities that have shown mixed results in small case series include photodynamic therapy using aminolevulinic acid, botulinum toxin injections and resorcinol peels. (Ellis, 2012)

Referral

Patients with stage I disease can be effectively managed in the primary care setting. Early referral to a dermatologist should be considered for patients with recurrent exacerbations despite adequate first-line treatment, or who show evidence of scarring (stage II disease). (Collier F, 2013) HS requires a multi-disciplinary team
approach involving general practitioners, dermatologists and surgeons; and potentially psychologists, psychiatrists, infectious disease and sexual health specialists and gynaecologists.

Future directions

Given the disease prevalence and paucity of evidence-based information guiding treatment of HS, there is significant interest in furthering the knowledge base. Current research is mainly aimed at existing therapies and pathogenic mechanisms with the intention of providing improved treatment options.

Although follicular occlusion appears to be a major factor in the pathogenesis of HS, the primary trigger is still unknown. A genetic predisposition is inevitable, and genetic studies including genome wide scanning should shed light on genetic susceptibility to HS. Different genes may be involved in different presentations of HS. Therefore defining phenotypic subtypes of HS may help to identify candidate genes. (van der Zee HH L. J., 2012)

The role of endogenous and exogenous environmental factors is also under investigation. Some researchers suggest the initial stimulus for follicular hyperkeratosis is abnormal hormonal response. Others predict HS is an autoinflammatory disease caused by dysregulated innate immunity, possibly with an abnormal response to commensal skin bacteria as the triggering factor. Research into the molecular events occurring in HS, as well as the role of skin flora, smoking, mechanical friction and obesity, should contribute to elucidating the enigmatic cause of HS and therefore inform treatment strategies. (van der Zee HH L. J., 2012)

Current treatment options as discussed above are largely empirically-based as there are very few randomized controlled trials comparing treatments for HS. Studies with sufficient follow-up time of at least 6 months are required to compare durations of antibiotic regimes, monotherapies with combination therapies, and hormonal or antibiotic therapies with immunosuppressants. (Jemec GB, 2012) Currently available immunomodulators such as acitretin, methotrexate, cyclosporine and azathioprine have been effective in either small case series or clinical experience, but larger studies are required to prove their utility. The use of biological agents is a point of interest, with many recent studies investigating the efficacy and safety of TNF-alpha antagonists infliximab, adalimumab and etanercept. Further research with greater patients numbers is required (Blok JL, 2012). Given the probable role of interleukin (IL)-1, IL-17 and IL-23 the interest in biological therapies will extend to anakinra and ustekinumab. (van der Zee HH L. J., 2012) There is also a lack of evidence guiding physical therapies. Studies exploring the effect of physical therapies such laser hair depilation on prevention of flares would be useful to guide practice. So far, surgery has provided the only cure for the disease, and only in some circumstances. Research comparing surgical techniques such as laser ablation, local excision, wide excision, and closure techniques such as primary closure, skin grafting or flaps will inform best surgical practice. (Jemec GB, 2012) (Ellis, 2012)
Conflicts of interest

None to declare.

Works Cited

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