THE CHALLENGING MANAGEMENT OF GENITOPERINEAL HIDRADENITIS SUPPURATIVA

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Summary

Verneuil's disease or hidradenitis suppurativa (HS) is a chronic inflammatory cutaneous condition affecting primarily the areas of the body abundant in apocrine glands, most commonly the axillary, inguinal, as well as the anogenital regions. The frequent relapses and the overall chronic course of the disease is believed to greatly impact the quality of life, with a pronounced influence on the social and professional activity of the patient. Since the response to treatment and the progression of HS are different depending on the area affected, in this review, we aim to summarize the management of genitoperineal HS.

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1. Introduction

Verneuil's disease or hidradenitis suppurativa (HS) is a chronic inflammatory cutaneous condition affecting primarily the areas of the body abundant in apocrine glands, most commonly the axillary, inguinal, as well as the anogenital regions [1]. It is considered that it affects approximately 1% of the global population [2]. The onset of hidradenitis suppurativa is usually after puberty, particularly in the second or third decade of life and it appears to have a slight predominance in women [3]. HS is a multifaceted affliction in which environmental factors such as obesity and cigarette smoking may trigger the disease in a genetically predisposed individuals [4]. The frequent relapses and the overall chronic course of the disease is believed to greatly impact the quality of life, with a pronounced influence on the social and professional activity of the patient [5].

A review from 2021 by Weigelt MA et al. on the psychosocial impact of hidradenitis suppurativa showed that the most significant drivers of a poor health-related quality of life were depression, anxiety and the financial strain of the patients [5].

Since the response to treatment and the progression of HS are different depending on the area affected, in this review, we aim to summarize the management of genitoperineal HS.

2. Mechanisms involved in the development of hidradenitis suppurativa in the genitoperineal area

The pathophysiology of HS in the genitoperineal area is complex and numerous factors are thought to contribute to its development [6]. The main physiopathologic event is represented by the occlusion of the hair follicle in the inguinal and perineal region [1].

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This particular mechanical factor, along with a dysregulation in both the innate and the adaptative immune processes are believed to be fundamental for the onset of HS [1]. The occlusion of the hair follicle leads to dilation followed by rupture and discharge of the follicular contents such as keratin and bacteria in the adjacent dermis, thereby inducing an intense inflammatory reaction mediated by neutrophils and lymphocytes causing an abscess and, finally, damaging the pilosebaceous unit [7]. It is well established that HS is a follicular disease, rather than an infectious one. However, bacterial dysbiosis with *Staphylococcus lugdunensis* (the most abundant microorganism in the HS abscesses and nodules), followed by polymicrobial anaerobic microflora such as *Porphyromonas* and *Prevotella* spp., plays an important part in the pathophysiology of the disease [8]. Furthermore, keratinocyte-mediated products, with both pro-inflammatory – tumor necrosis factor-alpha (TNF-alpha), interleukin 17 (IL-17), interleukin 23 (IL-23) and interleukin 1β (IL-1β)- and anti-inflammatory cytokines such as interleukin 10 (IL-10), are broadly considered to contribute to the inflammatory cascade responsible for the development of HS [9-11]. It has been found that both the HS lesions, as well as the perilesional skin are abundant in these mediators [9-11]. The resulting intense inflammatory reaction leads to tissue destruction and the accumulation of macrophages and dendritic cells through toll-like receptors, which further increases the amount of the pro-inflammatory mediators, notably TNF-alpha [12].

In a review from 2017 by Shah A et al., TNF-alpha was positively correlated with the disease severity in patients with HS [12]. The inflammatory events lead to a vicious circle which clinically translates into formation of painful nodules and abscesses, of sinus tracts, discharge of purulent secretions, tissue destruction and, finally, scarring [1].

3. Clinical aspects of hidradenitis suppurativa in the genitoperineal area

The presence of both tender nodules and abscesses in the genitoperineal area, sometimes developing into fistulas and extensive scarring are the hallmarks of HS [13]. The diagnosis of HS is based on clinical criteria: morphology of the lesions - the presence of nodules, abscesses and tunnels which may, sometimes, discharge a malodorous secretion; location of the lesions - the involvement of an intertriginous area, such as the genitoperineal area and disease progression, with two recurrences within the last six months or persistent lesions for more than three months [14, 15].

The Hurley classification is used to stage the progression of the disease [14]. Stage I is represented by the presence of an isolated or multiple abscesses without fistulas or scarring in a particular intertriginous area, in stage II recurrent abscesses and sinus tract formation may be present among the normal skin, while in stage III there is a broad involvement with interconnected sinus tracts and diffuse scarring which may replace all the normal skin in the anatomic area [14].

The prevalence of HS is 2.4-fold higher in women than in men [16]. It has been found that women have a more pronounced disease activity in the inguinofemoral region, which may require special considerations due to the unique challenges concerning menstruation and pregnancy [17, 18]. Nevertheless, it seems that male patients develop more commonly sequelae in the perineal, perianal and buttock regions [17].

The differential diagnosis of genitoperineal HS mainly includes furuncles, carbuncles, abscesses (triggered by infectious agents and responsive to systemic antibiotic therapy), intergluteal pilonidal disease, perianal Crohn disease and sexually transmitted diseases, among others [15].

4. Medical management

The management of patients with genitoperineal HS is challenging and consists in a combination of both conservative and surgical approaches in order to obtain the best therapeutic outcomes [14].

4.1. Topical and intralesional therapy

Topical and intralesional therapy in patients with HS refers to the use of skin cleansers, topical

antibiotics, as well as corticosteroid injections [19]. A skin cleanser containing chlorhexidine, zinc pyrithione or benzoyl peroxide is usually recommended [20, 21].

Regarding the topical antibiotic therapy, there is evidence that clindamycin 1% solution reduced pustules in patients with HS stage I and II; however, there was no anti-inflammatory effect on nodules and abscesses [22].

A double-blind, comparative study of 46 patients with mild to moderate disease conducted by Fisher AH et al. in 2017 showed that patients using topical clindamycin are more likely to develop clindamycin-resistant *Staphylococcus aureus* (*S. aureus*) strains compared to those not using antibiotic therapy (63% vs 17%; P = 0.03) [23]. Benzoyl peroxide may reduce the risk of growing resistant *S. aureus* [24].

In a multicentre, prospective case series from 2016 by Riis PT et al, the authors aimed to assess the efficacy of intralesional triamcinolone acetonide for the management of acute flares of HS with painful nodules [25]. It seemed that intralesional triamcinolone acetonide 10 mg/mL reduced pain after one day, as well as the signs of inflammation, approximately seven days after the procedure [25].

4.2. Pain management

Pain is a major contributor to reduced quality of life in patients affected by HS. It is considered that, in HS, pain is both nociceptic, as well as neuropathic [26]. Nociceptic pain is a consequence of the signalling molecules found at the sites of tissue injury, while the neuropathic pain is caused by the peripheral neurologic changes and central sensitization due to the chronic inflammation associated with HS [27, 28]. Pain management in patients with HS is based on expert opinion and general pain guidelines [29].

Acute flares of HS are associated with a sharp pain which may be treated with oral acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), which are considered first-line therapeutic agents [29]. Because the maximal analgetic and anti-inflammatory effect may not be quickly reached, incision and drainage of inflammatory nodules may be required as a rapid solution for pain relief [29].

The chronic continuous phase of HS faces a different approach of the associated pain [29, 30].

First-line options to treat nociceptive pain is represented by acetaminophen and NSAIDs (ibuprofen, naproxen, celecoxib) administered in the normal dosages [29]. Acetaminophen seems to provide pain alleviation by blocking a nitric oxide pathway and, consequently, elevating the pain threshold [29]. NSAIDs, on the other hand, suppress inflammation and provide pain relief by inhibiting the prostaglandin synthesis [29].

Second-line options for the management of nociceptive pain are represented by opiates, anticonvulsants, such as gabapentin and pregabalin, as well as second-generation tricyclic agents and serotonin and norepinephrine reuptake inhibitors (SNRIs) [29].

4.3. Wound care

Local hygiene is crucial for proper wound management in patients with HS, therefore, cleansers are the first step [20]. The appropriate cleanser may decrease bacterial colonization, especially if used in combination with antiseptics [20]. Isotonic normal saline and sterile water are suitable options for wound hygiene since they have low cytotoxicity [20]. Concerning antiseptics, silver and iodine are recommended for those patients with chronically colonized wounds [20].

In HS, chronic, relapsing, painful and draining wounds may be present [31]. According to a review from 2018 by Kazemi A et al. on the optimal management for HS wound care, an appropriate dressing should be conformable to the anatomical location of HS lesions, highly absorbent, easily accessible and easily self-applied, it should have an atraumatic adhesion, as well as antimicrobial properties [31]. The authors provide insight on the optimal dressing for each type of HS lesion [31]. For sinus tracts or a high drainage nodule, first line recommendation is represented by the use of regular gauze, while second line options include hydrofiber with silver and calcium alginate with silver dressings [31]. Concerning painful wounds or postoperative wounds after HS surgery, a silver-impregnated foam is considered suitable [31].

4.4. Negative pressure dressings

In the last ten years, negative pressure wound therapy (NPWT) has proven to be a valuable therapeutic adjunct to radical surgical excision in patients with perineal HS [32-34]. NPWT refers to a vacuum-type system which ensures a symmetrical mechanical pressure over the lesion [32, 35]. NPWT aids in reducing wound contamination, while, at the same time, promotes granular tissue formation and angiogenesis [35]. Moreover, in genitoperineal HS, NPWT improves the effectiveness of a primary delayed closure or a posterior surgical closure with aids (synthetic matrix or grafts) [32]. In a case report from 2015 by Jianbing T et al. on the use of NWPT in HS patients with genitoperineal involvement, the authors shed a light on the importance of a few key points which should be taken into consideration when opting for NPWT as a therapeutic adjunct [36]:

- Concomitant diseases which may affect healing, such as adrenal insufficiency or diabetes mellitus should be treated prior to NPWT [36].
- The dressing should be changed every 72 hours in order to avoid bacterial infection and sponge hardening [36].
- To prevent the blockage of the NPWT tube from the necrotic tissue, the use of saline irrigation is recommended [36].

4.5. Antibiotics

Oral antibiotics are chosen more for their immunomodulatory rather than antimicrobial effects in the treatment of HS [37]. The combination of oral clindamycin with rifampicin is recommended by European guidelines as a first-line treatment in moderate-to-severe hidradenitis suppurativa [38]. In five retrospective series and two prospective cohorts, the association of Clindamycin, 300 mg twice daily, and Rifampicin, 300 mg twice daily, for 10 to 12 weeks, proved to be very effective and made it possible to achieve prolonged remission [39-43].

A small randomized controlled trial of patients with mild to moderate HS showed that tetracycline, 500 mg twice daily for three months, has not been proven to show any difference in the assessment of overall effect, soreness, nodules, or abscesses compared to topical clindamycin [44]. The alternative use of doxycycline (100 mg daily) is also reported [45].

4.6. Retinoids

Acitretin can be started as the treatment in the early stages of HS as well as the chronic stage of the disease with sinus tracts and scarring, according to the European guidelines. The recommended dose is 0.25 to 0.88 mg/kg/d with a duration ranging from three months to one year [30]. It has been evaluated in three cohort studies and in a small randomized controlled trial - in total 46 patients, mostly in stages 2 and 3, receiving 0.5-0.6 mg/kg/day for an average period of 3 to 12 months. 63% of patients showed significant improvement [46-49]. However, it is not recommended for women of childbearing age, as they should not conceive for 3 years, even after stopping treatment [50].

Alitretinoin has a similar pharmacological action to acitretin, but its shorter lifespan (only a few weeks) makes it more attractive to women of childbearing age. A series of 14 patients was reported in 2015 showing an improvement in the Sartorius score in 78.5% of cases after 24 weeks of treatment at a dose of 10 mg/day [51].

4.7. Biological therapy

Subcutaneous adalimumab, a TNF-α blocker, received approval from the United States Food and Drug Administration and the European Medicines Agency for the treatment of moderate to severe hidradenitis suppurativa [52, 53]. Two recent RCTs, Pioneer I and II, showed higher clinical response rates at week 12 in patients receiving adalimumab (160 mg on day 1, 80 mg on day 15, and a 40 mg injection every week from week 4 onwards) as compared to placebo groups [54]. According to Zouboulis et al., the adalimumab treatment should not be continued in non-responders at week 12 (less than 25% improvement in abscesses and inflammatory nodules) [55].

A small placebo-controlled trial evaluating infliximab 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks with an open crossover, reported the efficacy and safety of infliximab in HS [56]. Other biologics including etanercept, anakinra, ustekinumab, canakinumab, and secukinumab need more evidence in HS [57].

5. Surgical management

Surgical treatment may be performed in any Hurley stage of disease, from punch debridement, incision and drainage on individual inflammatory nodules or sinus tracts, up until wide excision in severe cases typically reserved for Hurley stage III disease [58, 59]. There are no clearly established surgical recommendations. The choice of the appropriate operative approach depends on the acute or chronic nature of the disease, the affected site, the severity and extent of the lesions, and patient's comorbidities [39].

5.1. Punch debridment

This procedure, also called mini- unroofing, is recommended to treat acute inflammatory nodes typically in patients with mild or moderate HS. The objective of this approach is to remove the acutely inflamed folliculo-pilosebaceous unit within the inflammatory nodule with a small amount of surrounding tissue, and, more importantly, to remove the "bulge" area (containing the stem cells) of the follicular unit, to eliminate the risk of recurrence of the lesions [38, 57, 59, 60].

5.2. Incision and drainage

Incision and drainage can be used as a treatment modality in acute cases with tender fluctuant nodules/abscesses with pus accumulation. This procedure is undisputedly beneficial in relieving acute pain and suffering. However, this approach does not remove the folliculo-pilosebaceous unit; as such, it provides only short-term relief and is associated with a high risk of recurrence of up to 100% [61-63].

5.3. Wide surgical resection

There is overall agreement that radical wide excision of all involved skin and tissue is the only curative approach in Hurley stages II and III [30]. It is defined by complete excision of the lesion area with a lateral margin of healthy skin of 1 to 3 cm associated with a deep margin of healthy tissue, if necessary, specified by a preoperative magnetic resonance imaging or ultrasound to assess the depth of the sinuous tract [30]. Alternatively, intraoperative injection of methyl violet, iodine starch or hydrogen peroxide into the fistulous tracts can be used to define the lateral and deep margins of the surgical excision [64-67]. A multidisciplinary surgical approach (urologist, visceral/proctologist, gynaecologist, plastic surgeon) is essential due to the presence of sphincters and the long-term risk of retractile scars responsible for vulvar gaping, stenosis, or anal incontinence. The recurrence rates on the treated area are the lowest here, between 0 and 15% depending on the series [68].

6. Suitable reconstruction techniques

Several reconstructive modalities after surgical excision have been described, including primary closure, healing by secondary intent, split-thickness skin graft (STSG), and flap closure [69].

Despite the many available surgical and reconstructive techniques, there is still no general consensus on the optimal surgical technique [68, 70, 71]. In the inguinal and anogenital areas, secondary intention healing is favoured by some authors [72, 73]; the advantages mentioned are immediate mobilization of the patient, acceptable scarring, rapid integration into everyday life, and a low risk of recurrence and complications [34, 67]. According to a systematic review by Mehdizadeh et al., recurrence rates after wide excision are 15% in primary suture, 8% in flaps, and 6% in grafting. The study notes also that healing with secondary intention had much lower recurrence rates [68].

Squamous cell carcinoma, perianal fistula formation, pubogenital lymphedema have been reported in the scientific literature as the most serious complications of HS [74, 75].

7. Conclusions

In conclusion, genitoperineal HS is a debilitating disease that requires a multidisciplinary (dermatology, plastic surgery, urology, gynaecology, infectious disease, microbiology specialists) and multimodal approach (medical and surgical management). Although the medical community strives towards long-term remission, the emergence of new therapies is mandatory to offer such results.

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Conflict of interest
NONE DECLARED

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