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Review Article

Botulinum toxin type A for the management of hidradenitis suppurativa

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Abstract: Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory skin disease that centers around the hair follicle and occurs as a result of follicular occlusion. HS primarily presents as painful, inflamed lesions that begin during puberty and occur most commonly in areas with numerous apocrine glands. The etiology and pathogenesis of HS involve internal and external factors, including genetic susceptibility, inflammation and immunity, microorganisms, obesity, and smoking. Management of HS is difficult, and the current aim of treatment is to control the frequency and duration of disease flare-ups and improve the quality of life. Medical treatments include antibiotics, retinoids, biologics, immunosuppressive agents, and antiandrogen agents. Adjuvant treatment includes surgery, laser, and light therapy. However, the efficacy of these treatment modalities varies from person to person. In recent years, related reports have shown that injection of botulinum toxin type A has a positive effect in the management of HS. This article reviews the pathogenesis, clinical manifestations, diagnosis, and traditional treatment methods for the management of HS and investigates the use of botulinum toxin type A as a treatment option for this disease.

Keywords: Botulinum toxin type A, hidradenitis suppurativa, research progress

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic inflammatory skin disease that heavily impairs quality of life for patients. It is characterized by recurrent painful nodules, abscesses, and draining sinus tracts in primarily intertriginous areas [1]. The prevalence of HS varies. In European and American populations, the reported prevalence [2-4] is 0.05-4.1%, with a male:female ratio of approximately 1:3 and approximately 30% to 40% of patients reporting a positive family history of the disease [5, 6]. At the same time, the reported incidence of HS in the Asian population is 0.04-0.06%, with a 1.6-2.5:1 male:female ratio [7-9]. This article describes the pathogenesis, clinical manifestations, diagnosis, and traditional management of HS. In addition, this report investigates the use of botulinum toxin type A as a treatment option for HS.

Etiology and pathogenesis

Although the etiology and pathogenesis of HS is incompletely understood, it is generally accepted that genetics, immunity and inflammation, microbes, obesity, and smoking contribute to the development of follicular hyperkeratosis and dilatation, follicular rupture, and inflammation (both acute and chronic) (**Figure 1**). This ultimately leads to permanent structural tissue changes [1].

Recent studies have reported breakthrough discoveries regarding the genetic and immunologic nature of HS. In terms of heredity, gene variations in the three subunits of γ-secretase, presenilin 1, presenilin enhancer 2, and nicastrin have been found in patients with familial HS [10]. The notch signaling pathway and the toll-like receptor (TLR) have also been implicated in the pathogenesis of HS [11].

Levels of tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-1β, and IL-18 are significantly elevated in the skin lesions of individuals with HS [12]. Studies have also found that interferon (IFN)-γ, IL-12, IL-23, IL-32, other type-1 T-helper (Th1) cells, and Th17-related cell factors are contained within these lesions [13, 14].

The main bacteria cultured from the skin lesions of patients with HS are *Corynebacterium*,

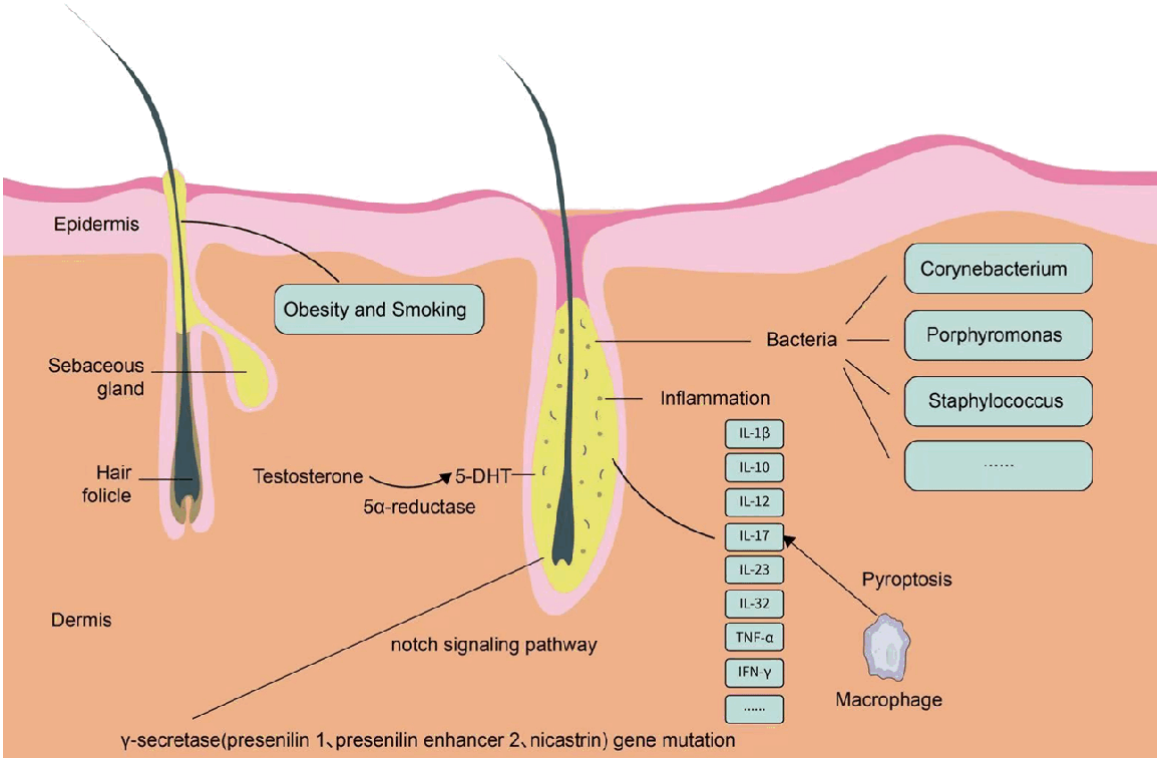

Figure 1. Brief pathogenesis of HS.

Porphyromonas, and *Staphylococcus* species; while populations of *Propionibacterium acnes* are significantly reduced in individuals with HS compared to those without HS [15]. Biofilm formation, which can resist host immune defenses and inhibit antibiotic penetration, may cause HS infections to be more difficult to clear and result in acute exacerbations [16, 17]. This has been detected in 67% of patients with chronic lesions and in the skin surrounding the lesions in 75% of patients.

The role of hormones in the pathogenesis of HS remains unclear, but evidence supports a connection. Progesterone and estrogens may take part in the pathogenesis of HS through their effects on the immune system. Macrophages that are present in HS lesions overexpress IL-12 and IL-23, which induce a Th-17 response [18]. Progesterone may inhibit macrophage TNF production [19]. Furthermore, the pilosebaceous unit is filled with sebaceous and apocrine glands that contain two types of androgen-converting enzymes that are responsible for converting testosterone into 5-dihydrotestosterone (5-DHT), which may bind to androgen receptors on the sebaceous gland and give rise to increased sebum production and inflammation [20].

Risks and trigger factors

Genetics seem to contribute to the development of HS. A positive family history is reported in some 30% of patients with HS [21]. Genetic analysis over several members of Chinese families with severe HS shows that haploinsufficiency of the γ-secretase component gene is the genetic basis for a subset of familial HS [10]. The γ-secretase mutations have not been detected in other sporadic cases of HS, and efforts are being made to identify the genetic predisposition of these patients [22].

Additionally, obesity and smoking serve as risk factors for chronic inflammatory disease. In people with HS and obesity, increased mechanical friction of the skin at the folds (i.e. intertriginous areas), increased sweat retention, or increased secretion of inflammatory cytokines have been documented [23]. Nicotine and benzopyrene in cigarettes may be related to epidermal hyperplasia, hair follicle horn plugs, and inflammation [24].

Clinical presentation

The pathophysiology of HS includes follicular orifice occlusion and inflammation. Occlusion of the follicle leads to dilation and rupture of the follicle ducts, and overflow of follicular contents (i.e. keratin and bacteria) into the dermis; this induces intense chemotaxis of neutrophils and lymphocytes. Inflammatory cell infiltration leads to abscess formation, which eventually leads to the destruction of the hair follicle sebaceous units and other adjacent adnexa [25]. Clinically, HS is characterized by clusters of comedones during the early stage, followed by continuous occurrence of sinus tracts, abscesses, and scars, which represent chronic and often irreversible changes to the skin. Various skin lesions such as nodules, cysts, sinus tracts, and contracture scars exist simultaneously. Skin lesions are most likely to occur in areas rich in apocrine glands, such as the axilla, groin, perianal region, and areola, but they can also occur on the face, neck, and trunk [26]. Patients may have severe acne and acne cysts, and squamous cell carcinoma may occur secondary to long-term chronic inflammation [27]. In 1989, Hurley [28] first divided HS into three stages according to the scope of the lesions and the presence or absence of a scar or sinus tract. Stage I HS is characterized by single or multiple abscesses formed without a sinus tract or scar; Stage II by one or more extensive recurrent abscess with sinus formation and scarring; and Stage III by multiple interconnected sinuses and abscesses throughout the lesion area. HS can have a substantial psychosocial effect on quality-of-life. In terms of the psychosocial impact, among all the skin diseases evaluated, HS is the most detrimental to the quality of life of patients, and it is often accompanied by depression and anxiety [25]. Therefore, HS not only brings physical pain and discomfort to patients, it is also related to varying degrees of psychosocial impairment.

Diagnosis

Preliminary diagnosis of HS can be made according to the age of onset, the location of the lesions, and the coexistence of various types of inflammatory lesions, such as papules, cysts, sinus tracts, and contracture scars, with purulent discharge, and the lack of response to antibiotic treatment alone. Histopathologic examination can be used to assist the diagnosis if the diagnosis is not clear. Histologically, the main manifestations of HS are follicular and perifollicular inflammation, as well as granulomatous inflammation caused by the structural destruction of hair follicles and sebaceous glands [21]. The diagnostic criteria for HS from the European S1 guideline [25] include the following. (1) History of painful or suppurative skin lesions occurring more than two times in 6 months; (2) the presence of skin lesions, clinical nodules (inflammatory/noninflammatory), sinus tracts (inflammatory/noninflammatory), abscesses, or scars; and (3) skin lesions mainly involving the axilla, groin, perineal region, and the breasts.

Conventional treatment

The etiology and pathogenesis of HS are complicated, and the traditional treatment methods are varied and include drug therapy, laser therapy, and surgical management. The initial phase of treatment may include antibiotics, endocrine therapy, retinoic acid, zinc preparations, cryotherapy, radiofrequency therapy, and a short course of either an oral or locally injected glucocorticoids. Phase II treatment may include carbon dioxide laser, immunosuppressive therapy, local excision, radiotherapy, and radiofrequency therapy. Phase III treatment may include radiotherapy, extensive excision, and sinus incision [29]. However, there is no uniform treatment for HS at present. Antibiotic, anti-inflammatory, and anti-proliferative drugs can achieve moderate therapeutic effects in a short period of time, but the probability of recurrence is high, and long-term oral drugs have side effects, including gastrointestinal disturbance, gingival hyperplasia, hypertrichosis, and others. Photodynamic therapy is also an alternative treatment for patients with severe skin lesions [30]. Biologic agents such as adalimumab and infliximab can effectively treat severe HS and improve the quality of life [31], but they are expensive, and long-term monitoring of medication safety is required. In patients for whom drug therapy is ineffective or results in intolerable side effects, surgical management can be considered. Different surgical approaches, include incision and drainage, localized resection and suture, extensive radical resection, and skin transplantation according to the location and extent of the lesions. Radical resection is considered to be the first choice in the surgical management of HS, but there remains a risk of recurrence. A systematic review by Mehdizadeh [32] concluded that

wide excision was associated with lower recurrence rates (overall, 13%; primary closure, 15%; using flaps, 8%; grafting, 6%) compared with local excision (22.0%) or deroofing (27.0%). However, these operations can be disfiguring and despite the removal of significant amounts of tissue, they do not necessarily protect against disease recurrence.

Botulinum toxin A therapy

Botulinum toxin type A (BTX A) is an exotoxin produced and released during the growth and reproduction of *Clostridium botulinum* [33]. It acts selectively on the peripheral cholinergic nerve endings and muscle junctions and inhibits the release of acetylcholine. This results in a chemical denervation or a paralysis of the skeletal muscles. BTX A has been applied in the treatment disorders including intractable headache, chronic migraine, facial spasm, and neurogenic bladder, among others. It is also widely used for cosmetic wrinkle reduction and skin rejuvenation through shallow injection on the face and neck, as well as benign masseter muscle hypertrophy, and simple calf muscle hypertrophy. Additionally, BTX A is now used in the treatment of focal hyperhidrosis; it functions to inhibit oil secretion, narrows pores, and reduces sweat gland secretion [34].

The first report of the management of HS with BTX A was in 2005. O'Reily [35] reported that the application of BTX A in the treatment of one patient with HS achieved a good result. A total of 250 units of BTX A was injected into bilateral axillary skin lesions, and the skin lesions were under good control after 3 months. After a total of four treatments within one year, the lesions were completely resolved with a remission period of up to 10 months. Four years later, in 2009, Feito-Rodriguez [36] presented a case of management of HS using BTX A in a child aged 7 years with bilateral inguinal skin lesions. The child's lesions were resistant to all topical and systemic medication. Forty units of BTX A were injected into the skin of each groin area, and a complete response was achieved at 6 months. After HS recurrence, the 7-year-old patient responded well to retreatment. In 2014, Khoo [37] reported a woman aged 46 years with Grade II HS who received BTX A four times in 3 years; she was treated with 50 units of BTX A for bilateral axillary lesions, and she achieved complete remission for more than 1 year. In 2019, Shi [38] discussed the case of a woman aged 41 years with Grade III HS. She had bilateral axillary and groin lesions with pain and mobility disorders, and had minimal response to traditional treatment methods. BTX A was administered every 3 months for a total of 4 cycles, which greatly relieved her pain and managed the disease. In 2019, Campanati [39] reported another two cases of successful use of BTX A in the management of Grade II HS, with an average complete remission period of 6 to 12 months; the treatment effect was substantial.

The precise mechanism of action of BTX A in the management of HS remains unknown. It is well known that a moist environment can promote the reproduction of bacteria and the development of inflammation, and the reproduction of bacteria can serve as the impetus for scar formation [40]. It was hypothesized that hyperhidrosis could be a comorbidity that contributes to the development of HS. Using cross-sectional data from a collection of research databases, Hua [41] performed age- and sex-adjusted multivariable logistic regression and observed a 3.61-fold (95% CI 2.83-4.61, p<.0001) increased risk of the development of HS in 17 patients with hyperhidrosis, thus showing a novel association between hyperhidrosis and HS. BTX A reduces sweat secretion mediated by overactive cholinergic nerve fibers by blocking acetylcholine release. By reducing sweat excretion, the skin microbiota and its potential to produce a proinflammatory effect are simultaneously diminished [42].

Another hypothesis regarding the therapeutic effect of BTX A is that the toxin may inhibit the secretory function of the entire hair follicle, which includes the sebaceous and apocrine glands. This would prevent the rupture and diffusion of follicular material through the dermis, and could subsequently prevent inflammation and sinus tract formation [36].

Currently, all relevant reports on BTX A injection in the management of HS have shown that this method has a positive therapeutic effect and good patient satisfaction. However, large-scale, prospective, controlled clinical studies are still lacking. In the future, larger studies should be conducted. Future research should also focus on the pathogenesis of HS and the use of BTX A injection therapy for its management. BTX A is

easy to administer, may have fewer side effects than other available treatments, and is considered to have a high safety profile, all of which may support BTX A as a future standard treatment for HS.

Disclosure of conflict of interest

None.

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