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Hidradenitis suppurativa/Acne inversa – etiopathogenesis, clinical presentation and therapeutic options

Hidradenitis suppurativa/Acne inversa – etiopatogeneza, obraz kliniczny i możliwości terapeutyczne

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Summary

Hidradenitis suppurativa/acne inversa (HS) is a chronic recurrent inflammatory skin disease affecting mainly the intertriginous areas. Cutaneous nodules, abscesses, subsequent widespread deep inflammation, sinus tract and fistulas formation with foul-smelling purulent discharge are the main clinical features of the disease. Etiology of HS is believed multifactorial and not clear, but the cigarette smoking and obesity are the established triggering factors.

Pathogenesis is not well understood yet. The primary event is a follicular occlusion with secondary inflammation, infection and destruction of the pilosebaceous unit and extension of inflammation to the adjacent subcutis. Treatment depends upon the clinical stage of the disease. There are various therapeutic options known, including antibiotics, antiandrogens, retinoids, systemic corticosteroids, TNF inhibitors, immunosuppressive/anti-inflammatory agents, all of them used with limited results. The most effective treatment is the radical wide excision of the affected area. Due to its chronicity, recurrent character and specific multifocal embarrassing location HS is physically, psychologically and socially disabling condition with considerable impairment of the quality of life.

Key words: hidradenitis suppurativa, Acne inversa, etiopathogenesis, treatment

Streszczenie

Hidradenitis suppurativa/Acne inversa (HS) jest przewlekłą nawrotową zapalną chorobą skóry zajmującą głównie okolice wyprzeniowe. Zasadniczymi klinicznymi objawami choroby są skórne guzki, ropnie, prowadzące do rozlanego głębokiego stanu zapalnego, powstawanie zatok/kanałów i przetok uwalniających cuchnącą ropną wydzielinę. Etiologia HS jest wieloczynnikowa i niejasna, a palenie papierosów i otyłość są uznanymi czynnikami prowokującymi. Patogeneza nie została całkowicie wyjaśniona. Pierwotnym zjawiskiem jest okluzja mieszków włosowych z wtórnie rozwijającym się zapaleniem, infekcją i zniszczeniem jednostki włosowo-łojowej oraz rozprzestrzenieniem zapalenia na otaczające tkanki. Leczenie zależy od klinicznego stadium choroby. Znane są różne metody terapeutyczne, w tym antybiotyki, retinoidy, leki przeciwandrogenowe, ogólne kortykosteroidy, inhibitory TNF, leki immunosupresyjne/przeciwzapalne, wszystkie przynoszą tylko ograniczoną poprawę. Najskuteczniejszą metodą leczenia jest rozległe radykalne wycięcie chirurgiczne całej zmienionej okolicy. Z powodu przewlekłego, nawrotowego charakteru i szczególnej, kłopotliwej dla pacjenta lokalizacji, HS jest chorobą fizycznie, psychologicznie i społecznie upośledzającą, ze znacznym pogorszeniem jakości życia.

Słowa kluczowe: hidradenitis suppurativa, trądzik odwrócony, etiopatogeneza, leczenie

Hidradenitis suppurativa/Acne inversa (HS) is a chronic recurrent, inflammatory skin disease affecting mainly the intertriginous areas. The disease involving the apocrine – gland – bearing skin areas may be mild and limited or severe, causing widespread deep infection and resulting in abscesses, sinus tract formation, fistulas releasing malodorous discharge and subsequently in excessive scarring (1-4). Due to its chronic-

ity, recurrent character and specific multifocal location of the lesions, HS is a physically, psychologically and socially disabling condition associated with considerable impairment of the quality of life (5).

EPIDEMIOLOGY

There are some controversies about the epidemiology of HS. Despite the common opinion of HS being

a rare disease, the exact prevalence is uncertain and probably different in various populations and groups of age. Literature data report the prevalence rate ranging between 0.03-0.06 and 4%, but most authors suggest 1% in general population (1, 2, 4, 6). The onset of the disease is usually observed between 11 and 30 years of life (1, 4). Postmenopausal onset is rare, its prevalence among the subjects older than 55 years of age is about 5 times lower than in younger patients (1, 2, 4). What is interesting, some locations have distinct sexual predisposition, thus the perianal HS seems to affect male more than female patients (1, 7). Although the disease occurs in all human races, a higher prevalence is observed in black people than in Caucasians (1, 2).

Genetic background is being taken into consideration, although genetic studies conduce to conflicting results (4, 8). Clinical data, indicate that, 30-40% of HS patients have a family history, but the HLA association seems to be not significant (4, 8). An autosomal dominant pattern has been suggested with locus for the disease on chromosome 1p21.1-1q25.3, but a specific gene was not identified (1, 4).

ETIOPATHOGENESIS

Understanding of the HS pathogenesis has changed considerably over time, but still remains unclear. Due to the specific anatomical distribution of the disease, HS was initially believed to be a disorder of the apocrine glands (1, 2, 4). It is well known, that the apocrine sweat glands, mainly distributed in the axillary and anogenital skin, are evolutionary analogues of an odour-producing organ found in lower animals (2). Early data suggested that the apocrine gland involvement is the primarily event leading to the development of the widespread inflammation in the skin and subcutis (1). In 1955, Shelley and Cahn evidenced that the primary event was a keratinous plugging of the apocrine sweat duct leading to the follicular occlusion, which eventually resulted in inflammation of the apocrine glands and neighbouring periglandular tissue (1). Further data suggested that inflammation of apocrine glands is not basic to HS pathogenesis, being only the secondary phenomenon (1). Pillsbury et al confirmed follicular occlusion as cause of HS, and what is more, the authors included this disease, together with acne conglobata and perifolliculitis capitis abscondens et suffodiens/dissecting cellulitis of the scalp, to so called "acne triad" or "follicular triad" (6). From this time, the similarity between the pathogenic mechanisms of acne and HS is being discussed. Plewig and Kligman added pilonidal sinus to "acne triad" and coined the term "acne tetrad" (9). In 1989 Plewig and Steger introduced the term "acne inversa" for the hidradenitis suppurativa, emphasizing a follicular origin of the disease (10).

The results of histologic study published by Yu and Cook in 1990 considerably influenced the contemporary understanding of the HS pathogenesis (1). The researchers showed that follicular occlusion and the dilated follicles were the most constant and probably

primary feature and concluded that HS was a disease of follicular epithelium rather than a disease of apocrine glands.

Hidradenitis suppurativa is currently considered as an inflammatory disease of terminal hair follicles manifesting in intertriginous skin sites (2, 8). The accepted belief is that the initiating event is occlusion of the follicular ducts by keratinous plugging, leading to ductal dilatation and stasis in the pilosebaceous unit (1, 2, 3, 11). Bacteria entering the apocrine gland through the hair follicle, are entrapped under the keratinous plug and multiply rapidly (2). Subsequent follicular rupture leads to extrusion of follicular contents, into the dermis inducing a chemotactic inflammatory response (1). The resulting influx of neutrophils, lymphocytes and histiocytes lead to inflammation of the surrounding tissue and abscess formation (1, 2). Bacterial infection results in further local inflammation, suppuration, tissue destruction and skin damage (1, 2). Numerous recurrences and presence of ruptured epithelium lead to development of sinus tracts and fistulas (1, 2).

Last years studies have brought new data concerning the extent of skin inflammation in HS. In 2011 van der Zee et al (12) investigated the cytokine profile in lesional and perilesional HS skin and have shown that TNF- α , IL-1 β and IL-10 levels are elevated in HS skin. Moreover, it was also demonstrated that HS inflammation extend beyond the visibly affected inflammatory lesions, and that likely can be the cause of recurrences. These results are in agreement with those obtained earlier by Matusiak et al. (13), who evidenced the elevated TNF- α level in the peripheral blood of HS patients. Recently, alterations in leukocyte subsets in normal-appearing perilesional skin and in HS lesions have been found (14). Moreover, psoriasiform hyperplasia, follicular plugging and mild mixed infiltration consisted of T cells, plasma cells dendritic cells and mast cells, was observed in perilesional "normal" skin (14).

A variety of etiologic factors is suspected of a causal relationship in the pathogenesis of HS. First of all, the role of hormones, especially androgens in HS is still being investigated, but with conflicting results provided by many studies (1). Some researchers present opinion of the disorder being androgen dependent in adults, but others believe that hyperandrogenism probably does not play a role in HS (2). It is worth to stress, that the influence of androgens on the formation of terminal hair follicles in the axillae and anogenital regions may be important in the development of HS, as it is primarily an inflammatory disease of terminal hair follicles (8). A relationship between onset of hidradenitis and androgen levels is strongly suggested by clinical observations of the disease occurring with puberty and its persisting in females up to menopause, rarity of onset thereafter (1, 2). What is more, HS may decline substantially following menopause, also suggesting a hormonal role (1, 8). However, there is no substantial evidence to support hyperandrogenism in women with HS (2). No change in the peripheral blood

hormone levels, including testosterone and dehydrotestosterone was observed in HS patients (1, 4). Revuz considering the etiopathogenesis of HS stresses that some important facts concerning the role of androgens remain still unexplained, among them the high female prevalence, the frequent improvement during pregnancy, and the termination of the disease in post-menopausal women (4).

Bacterial infection was suggested as a important etiologic factor contributing to HS pathogenesis. Various aerobic and anaerobic species have been cultured from samples taken from the HS lesions, among them *Streptococcus viridans*, *Staphylococcus aureus*, *Staphylococcus milleri*, *Staphylococcus epidermidis*, *Peptostreptococcus* spp., *Bacteroides melaninogenicus* and *Bacteroides corrodens*, coryneform bacteria (1, 4). In perineal and perianal locations of HS the Gram-negative bacteria are more commonly found, such as *Escherichia coli*, *Klebsiella*, and *Proteus* (1, 4). Very heterogeneous spectrum of pathogens indicates that the disease is not associated with the presence of a specific pathogen because no single species is dominant (1, 8). Most researchers believe that the bacteria implicated in HS are the secondary colonizers, which may exacerbate the disease, but should not be regarded as the primary etiologic factors (1, 4, 8).

The possible role of numerous exogenous factors in HS development are also taken into consideration. Among them, the mechanical and chemical irritation of the local skin in the areas typically involved, especially caused by shaving and friction (1, 2, 4). The use of chemical irritants, such as deodorants, depilatory chemicals, antiperspirants, talcum powder have been suggested as triggering or exaggerating factors (1, 2, 4, 8).

The role of pharmacological agents is also being considered and it seems that it can not be completely ruled out as yet. Onset or exacerbation following lithium therapy has been reported (1, 4). The suggested mechanism is not only the known lithium ability to induce inflammation but also to facilitate follicular plugging through its direct effect on follicular keratinocytes (1).

Results of many studies indicate smoking and obesity as the established risk factors of HS. High prevalence (70 – up to 90%) of heavy cigarette smokers among patients with HS suggests that cigarette smoking can be a major triggering factor (1, 2, 4, 6, 15). Revuz et al (4, 6) showed a strong association with current smoking in HS patients, but they failed to observe this association for ex-smokers. Much stronger relationship than with smoking exists between obesity and HS (2, 4, 6, 8). It is worth to stress that a significant association with body mass index in HS patients was found (4, 6, 7). Some authors have observed above 75% of HS patients to be overweight and obese (1). Moreover, there is dose/effect relationship between the overweight/obesity and severity of HS (6, 7). Obesity may affect disease not only through the sweat reten-

tion, maceration, and occlusion in the skin folds but also through its connection with the abnormal hormonal metabolism, including changed production and activity of the sex hormone binding globulin, estrogens and androgens, resulting in the relative androgen excess (1). It is believed that this androgen surplus may be involved in coarsening of the hair shaft with further follicular plugging (1).

Considering the chronic, inflammatory course of HS, defects in the immunological response mechanisms are suggested as a possible etiologic factors (1, 12). Some studies do not confirm any abnormalities of the immune system (1). Other investigators, however, have found the defected neutrophilic function, decreased percentage of NK cells with the progression of the disease, and lower monocyte responses to bacterial compounds (4, 16). Moreover, the increased expression of Toll-like receptors 2 within infiltrating macrophages and dendritic cells of the HS inflammatory lesions has been observed (16, 17).

CLINICAL PRESENTATION

HS often begins insidiously with non-specific early symptoms, such as pain, burning, erythema, pruritus, local warmth and hyperhidrosis (1, 2, 4).

The primary lesions are single firm palpable nodule or few solitary painful nodules which are deep-sited and rounded (1, 2, 8). Approximately 50% of all patients have above mentioned subjective prodromal symptoms 12-48 h before consecutive nodule recurs (4). The subcutaneous nodules may persist for weeks with recurrent episodes of inflammation, or may spontaneously rupture after 7-15 days or coalesce into deep, painful abscesses (1, 4). Spontaneous resolving of the single nodule is possible, but the most frequent evolution observed is to form abscesses with an external rupture and draining purulent discharge (1, 2, 4). The numerous recurrences of inflammatory nodules may lead to the development of chronic secondary lesions. Multiple abscesses release purulent malodorous material due to the anaerobic colonization (1, 4, 8). Formation of sinus tracts results with generating deep interconnected network and progressive tissue inflammation and destruction which may extend deep into muscles and fascia (1, 2). Healing occurs with extensive fibrosis and hypertrophic scars making the rope-like dermal contractures (1, 2, 4, 11). The double or multiporous giant comedones can be often observed and are regarded as characteristic feature of HS (1, 4, 8). What is interesting, despite the chronic extensive inflammation, there is no regional lymphadenopathy (4).

The affected areas in HS exhibit distinct distribution pattern. The lesions are observed usually in the intertriginous apocrine gland-bearing areas of the inguinal, perineal, perianal, axillary, submammary, inframammary, buttock, pubic, scalp, retroauricular and eyelid areas (1, 2, 4). Rarely, waist, abdomen, specially periumbilical region, chest may be also involved (4). These sites are along so called “milk line”, which means the

embryonic location of apocrine and mammary tissue in the mammals (1, 4). What is very important, the affected sites have relation also to location of terminal hair follicles dependent on low androgen concentrations in humans (1). It is worth to notice, that several sites may be symmetrically simultaneously affected (2, 4). However, distinct differences are observed between female and male patients, thus groin and submammary region are most commonly affected in women; buttocks and perianal area in men (4, 7). Clinical observations indicate that perineal and anogenital HS is associated with a higher possibility of recurrence and with more debilitating course and outcomes than located in axillary region (1, 2, 7).

Canoui-Poitrine et al (7) analysed the possible factors associated with disease severity and evidenced that the presence of atypical locations, personal history of severe acne and the absence of family history of HS are independently associated with more severe HS. In the Polish population, Matusiak et al (15) found that extreme severity of clinical manifestation was more frequently associated with male subjects.

In 2009, the Congress of the Hidradenitis Suppurativa Foundation in San Diego has proposed the diagnostic criteria which have been subsequently accepted and are applied in clinical practice (18).

There are 3 criteria that had to be fulfilled for the HS diagnosis:

1. typical lesions, i.e. deep-seated painful nodules: blind boils in early lesions; abscesses, draining sinus, bridged scars and giant open comedos in secondary lesions.
2. typical location, i.e. axillae, groin, perineal and perianal region, buttock, infra- and intermammary folds.
3. chronicity and recurrences.

Another discussed problem is the possibility to reliably assess the severity of HS. Well known classification of Hurley defines 3 severity grades for each area involved (19) (tab. 1).

Table 1. Hurley's classification system for hidradenitis suppurativa severity (1, 7, 19).

Stage I	Abscess formation, single or multiple lesions without sinus tracts and cicatrization
Stage II	Single or multiple widely separated recurrent abscesses with sinus tract formation and cicatrization
Stage III	Multiple interconnected tracts and abscesses throughout an entire anatomic area

This clinical staging system based mostly on the presence of sinus tracts and cicatrices is regarded as simple and still useful for clinicians (1, 4). In 2003, Sartorius and al proposed a more developed scoring system that included four additional factors: anatomic region involved, number and types of lesions, longest distance between two lesions and the presence of normal skin clearly separating lesions (20). Many authors strongly suggest that, other measures including patient scoring of pain, the DLQI and the number and intensity

of painful episodes per year should be added for the assessment of the HS severity (1, 4, 7, 21).

HS COMPLICATIONS

Chronic and recurrent character of severe inflammation leads to variety of possible complications. Among them, the anatomical deformations due to excessive scarring are the typical consequences (1, 4, 8). In addition, anogenital location of the disease is frequently connected with formation of the urethral, anal, rectal, or perineal fistulas, and scrotal or vulvar lymphedema (1, 4, 8). The most severe HS complication of the anogenital and buttock region is the development of squamous cell carcinoma mostly in men (1, 4, 8).

TREATMENT

Numerous treatment modalities are known and used but the effects are not stable enough to prevent the recurrences. Considering the proved role of smoking and obesity in the HS pathogenesis, the smoking cessation and weight loss should be first of all strongly recommended to patients (1, 2, 6, 9, 11).

Antibiotic therapy for HS is widely used, being administered as the initial therapy for HS and especially before the planned surgical treatment (1, 4, 11, 21). Among the systemic antibiotics, amoxicilline, cephalosporine, tetracycline, minocycline, erythromycin and clindamycin are used for chronic treatment of HS (1, 4, 11). It is observed that the combination of clindamycin and rifampicin during a 10-week course may be effective (2, 4, 11, 22). Although antibiotics can induce a temporary remission, there is lack of evidence that long-lasting antibiotic therapy alters the natural course of HS (2).

Another therapeutic approach, the use of retinoids is based on the suggested relationship between HS and acne (2, 11). However, in contrast with their highly efficacious use in acne, the results in HS have not been encouraging (2, 4). Good effects of HS treatment with dapson within 4-12 weeks have been reported, probably due to the well known anti-inflammatory properties of this agent (1, 4, 11).

Despite the controversy considering the androgen abnormalities in HS development, some improvement of HS due to use of antiandrogens has been observed (2, 4, 11, 23). **The most frequently examined agents are cyproterone acetate and finasteride.** Cyproterone acetate administered in a dose of 50 or 100 mg daily caused improvement in disease activity but HS relapsed when the therapy was finished (1). The use of finasteride in a dose of 5mg daily in 7 patients produced complete healing of the lesions or reduction in suppuration and inflammation (23). It is worth to stress, that finasteride due to its fast elimination is believed as safer than retinoids for women (23).

Beneficial effect of immunosuppressive and anti-inflammatory agents, such as cyclosporine, azathioprine, tacrolimus, mycophenolate mofetil, has been observed in HS patients receiving these compound due to the

associated chronic inflammatory diseases with the immune abnormalities, including pyoderma gangraenosum, Crohn's disease, chronic granulomatous disease (1, 24). No improvement was achieved in HS patients treated with methotrexate for up to 6 months (1).

There are some controversies concerning possible advantages of using corticosteroids in the treatment of HS. The role of this therapeutic agents is difficult to assess, because they are frequently used in combination with other medications (1). Corticosteroids in the HS patients are administered either intralesionally or orally with varied dosing regimens (1, 2, 25). It is worth to stress, that even dramatic improvement may be seen initially, but it recedes shortly after the discontinuation of the treatment (1).

Moderately good results have been noted using the TNF inhibitors both in the HS alone and in the HS with associated inflammatory diseases, among them Crohn's disease/inflammatory bowel disease (1, 2, 25). However, although HS patients were quite satisfied with the effects of treatment with infliximab, which was demonstrated by improvement in the DLQI, in fact the clinical responses were various and adverse events were observed (1, 11, 26). Since these first observations further studies have described the positive effects of infliximab, etanercept and adalimumab in patients with HS without concomitant diseases (1, 2, 5, 21, 27, 28). In contrast, the results of the open-label clinical trial did not demonstrate significant improvement in 10 HS patients treated with adalimumab for 12-weeks period (29). It seems that much more information that currently available is needed to assess the true risk of TNF inhibitors used in HS patients.

Among other, less frequently administered modalities, encouraging results of the botulinum toxin use for the treatment of HS were reported, believed due to the reduction of the apocrine glands secretion (1). Usefulness of cryosurgery has been examined with overall poor results and severe complications were observed, including infections and ulcers (11). Variable results were observed using the photodynamic therapy (1, 4, 11, 21).

Carbon dioxide laser therapy and focused mode laser therapy have been administered relatively successfully in HS for moderate to severe cases (1, 2, 21).

Surgery is regarded as the most effective treatment or even the only effective treatment for severe HS (1, 2, 4, 8, 21). Clinical classification of the disease defined by Hurley is helpful in deciding between pharmacological or surgical options (4). There are also other factors taken into consideration, including the patient's assessment of pain and the physician severity assessment based on the frequency of flares during a year period (4). Surgical intervention may be carried out within a more limited or a wider scope. Incision of the painful fluctuating abscess is frequently done as the emergency surgical procedure in order to evacuate purulent discharge and to immediately alleviate pain (4, 11, 21). However, it is common opinion that

the simple incision can not change the course of HS and should not be regarded as the treatment method (2, 4, 21). Wide radical excision of all involved tissue and the underlying sinus tracts down to soft normal tissue is proved to be the most effective treatment for the patients (1, 2, 4, 8, 21). Data indicate that the recurrence rate after surgical procedures is generally over 50% and is proportional to the extent of resection (2). Various methods of the wound closure after surgical excision are in use, among them the primary closure, skin flaps, grafts and second intention healing, and some new techniques are worked out lately (1, 4, 30).

Taking into consideration, that there is no sufficiently satisfactory treatment for patients with HS, Alikhan et al have suggested a treatment algorithm based mostly upon the Hurley's classification (1). Thus, for the Hurley's stage I, antibiotics are regarded as a useful first line therapy (1). Limited nodular lesions can be injected with corticosteroids and short courses of systemic corticosteroids can be administered to stop the flares. As a second line, zinc compounds or antiandrogen therapy may be suggested. Lack of the sufficient response following these treatment methods should induce to try one of the options intended for the more severe (Hurley's II) stage of disease.

HS patients who have failed above mentioned first line therapeutic approach and those with the Hurley's stage II, need more intensive treatment (1). For them, the prolonged immunosuppressive treatment or one of the minor surgical options, including the limited excisions or the opening of sinus tracts may be recommended (1).

Patients with the Hurley's stage III need the large radical excisional surgery, because other therapeutic options, both pharmacological and surgical, can not be helpful (1).

It is worth to notice, that some authors regard the wide excisional surgery as intended only for the severe Hurley's III stage (4), but recently there is an opinion presented that this surgical procedure should be employed early to cure the current lesions and what is more to prevent the further development of this debilitating disease (30).

In conclusion, hidradenitis suppurativa is a complex and chronic inflammatory disease affecting a significant number of people. Not all aspects of HS pathogenesis are sufficiently elucidated yet, some of them are still investigated and discussed. Although a variety of treatment options are available and surgical procedures are more efficient than pharmacological agents, it should be considered, that the disease is characterized by recurrences regardless of the treatment modality used. Due to the deeply frustrating and devastating character of this disease, early diagnosis and early administration of the optimal therapy is essential for patients. Large controlled studies are needed to reliably assess the advantages and disadvantages of the currently used treatment methods and to identify the most efficient modalities.

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received/otrzymano: 22.08.2012

accepted/zaakceptowano: 28.09.2012

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