Acne inversa

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Keywords
- acne inversa
- hidradenitis suppurativa
- apocrine acne
- pyoderma fistulans sinifica
- follicular retention tetrad

Summary
Acne inversa is a chronic inflammatory skin disease featuring cutaneous and subcutaneous nodular inflammation, fistula formation and discharge of foul-smelling secretions. The disease can lead to functional impairment and psychological problems. There is inflammation of the terminal hair follicles in intertriginous regions, especially perianal, axillary and inguinal areas. Less often there is submammary, periumbilical, retroauricular or nuchal involvement. Without treatment the disease is chronic and progressive. The causes of acne inversa are multifactorial and pathogenesis is still not well understood. Besides a positive family history, obesity and cigarette smoking are trigger factors. Early diagnosis and therapy of acne inversa saves the patient years of suffering. The most effective treatment is undoubtedly the radical wide excision of the affected areas. Local measures such as radiotherapy, photodynamic therapy and cryotherapy have provided little benefit; the same is true for systemic antibiotic treatment or hormonal therapy with anti-androgens. TNF-alpha antagonists seem to have a promising influence on the disease. Further studies investigating the effect of these substances on acne inversa are warranted.

1 Historical background
The Paris surgeon Velpeau described an unusual inflammatory process with formation of superficial axillary, submammary and perianal abscesses in 1839 [1]. His colleague Verneuil, also working in Paris, coined the term “hidrosadénite phlegmoneuse” 15 years later [2]. This name reflects the former pathogenetic model of acne inversa, which considered inflammation of sweat glands as the cause of the disease. This concept was followed by a variety of authors for many decades. In 1922 Schiefferdecker suspected a pathogenic association between acne inversa and apocrine sweat glands [3]. In 1956 Pillsbury et al. [4] postulated follicular occlusion as cause of acne inversa, which they grouped together with acne conglobata and perifolliculitis capitis abscedens et suffodiens (dissecting cellulitis of the scalp) as acne triad. For the first time, it was discussed that the pathogenetic mechanism of acne vulgaris and acne inversa are similar. Plewig and Kligman added another entity to acne triad, pilonidal sinus [5]. In 1989 Plewig and Steger introduced the term acne inversa which is in use today, indicating a follicular source of the disease [6] and replacing older terms such as Verneuil disease, hidradenitis suppurativa, apocrine acne and pyoderma fistulas sinifica (Table 1).

2 Definition
Acne inversa is a chronic inflammatory skin disease with cutaneous and subcutaneous nodular inflammation, fistulas and discharge of a foul-smelling secretion and capable of causing severe physical and mental impairment. Pathogenetically, it is an inflammation of terminal hair follicles manifesting in intertriginous skin at perianal, inguinal and axillary sites. In addition to familial occurrence, smoking and obesity are contributing factors to the disease. Treatment of choice is the radical excision of affected regions.

3 Epidemiology
The exact prevalence of acne inversa is unknown and has been estimated at 0.3 % [7]. Jemec et al. [8] report a point prevalence of 4.1 % in a collective of young adults. The average age of these
patients was 42 years for men and 39 years for women. In a study from 1996 Jemec found a clear predominance of women. He studied the incidence of acne inversa in a collective of 507 patients. Anogenital lesions are significantly more frequent in women than in men (odds ratio 4.6), while axillary lesions were equally distributed among the genders [8]. Further, Jemec et al. studied the prevalence of acne inversa in an unselected collective of 793 randomly selected individuals; 3 women and 3 men with acne inversa were found [5]. A higher proportion of women was confirmed by Barth et al. He observed 10 men and 36 women who were admitted as inpatients for surgical treatment of acne inversa [9]. The disease is quite rare before puberty [10]. In the fifth decade of life, the incidence decreases. In women, the disease can continue into menopause, new manifestations after menopause are rarities.

4 Pathogenesis

4.1 Exogenic factors

The exact etiology of acne inversa is not known. Smoking is without doubt associated with the development of acne inversa. A series of studies has confirmed a significantly larger proportion of smokers in patient collectives with acne inversa in comparison to control groups. The proportion of patients with acne inversa who smoke regularly is reported in control groups between 23–46 %. In a study from 1996 Jemec found a prevalence of acne inversa who smoke regularly is reported [11]. The pathogenetic mechanism by which smoking leads to acne inversa is unknown. Smoking induces chemotaxis in neutrophilic granulocytes. This mechanism possibly plays a role in the etiology of palmoplantar pustulosis [12] and may be involved in the development of acne inversa. We presume that stopping smoking has a positive effect on the course of the disease but prospective studies are lacking. Obesity is probably not directly involved in the development of acne inversa, but maceration and occlusion in the body folds lead to follicular hyperkeratosis and thus worsen the disease [13]. In 45 % of patients with acne inversa sweating and heat; in 35 %, stress and exhaustion; and in 16 %, wearing tight clothing leads to deterioration of the disease [14]. A variety of factors is blamed with a causal relationship in the pathogenesis of acne inversa. Included is use of deodorants and depilatory products or shaving of the involved sites. In a retrospective study done by Morgan et al. comparing 40 patients with acne inversa with 40 healthy subjects, no significant difference regarding the factors mentioned above could be found [15]. We assume that these factors at most play a secondary role in the development and aggravation of acne inversa.

4.2 Endogenous factors

4.2.1 Hormonal factors

Essential for the pathogenesis of acne inversa is the effect of androgens in the formation of terminal hair follicles in the axillae and anogenital regions, as acne inversa is primarily an inflammatory disease of terminal hair follicles and not, as presumed in the past, a disease of apocrine glands. This is also exemplified by the fact that terminal hair follicles on the scalp are not connected with apocrine glands, but clinical manifestations such as perifolliculitis capitis abscedens et suffodiens (dissecting cellulitis of the scalp) do occur. This no longer can develop in the face of androgenetic alopecia. With the onset of puberty, the secretion of androgens begins and thus the enlargement of hair follicles.

The course of the disease, onset only after puberty, improvement after menopause and during pregnancy all suggest an influence of sexual hormones. Most patients with acne inversa have normal androgen levels [9]. Case reports do exist of successful therapy with anti-androgens [16].

4.2.2 Genetic factors

Acne inversa often occurs in a familial fashion, so that generic factors probably play a role. The first study on a possible hereditary pattern was performed by Fitzsimmons et al. in 1984. Three families with 21 family members affected by acne inversa were examined. In one of the three families studied, family members in three generations were affected, in the other two families; two generations each with acne inversa were reported [17].

One year later the authors expanded their study and examined 26 patients with acne inversa and their families. Information on family history could be obtained from 23 patients. Among 14 patients a total of 37 further affected family members were found. In nine families the patients were the only clearly affected family member [7].

In 2000 the working group of Werth et al. studied the reproducibility of the autosomal dominant inheritance postulated by Fitzsimmons et al. using the same study group as then. Here, 14 surviving persons and their families were examined. Of these, 7 had stated a positive family history in the previous study, two, on the other hand, had stated a negative or only possible family history. In the patient collective with a positive family history, 27 % of first-degree relatives were affected by the disease. Additionally, seven newly affected persons, who were not yet affected in the previous study, were found. An analysis of the pedigrees [17] shows that the disease is transmitted through several generations of a family with acne inversa and affects both genders.

4.3 Microbiologic data

The role of bacterial colonization and/or infection in the pathogenesis of acne inversa is discussed controversially. For a long time it was presumed that contamination or infection by specific microorganisms belong to the triggering factors of the disease [19]. Lapins et al. described

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### Table 1: Historical view.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>Velpeau [1]</td>
<td>1839</td>
<td>First description of the disease</td>
</tr>
<tr>
<td>Verneuil [2]</td>
<td>1854</td>
<td>Hidrosadénite Phlegmoence</td>
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the presence of *Staphylococcus aureus* and coagulase-negative streptococci [20]. In a retrospective review of data, Brook and Frazer studied the microbiologic spectrum of 17 samples from axillary lesions of patients with acne inversa. A total of 42 cultures were performed. The most common aerobic organisms were *Staphylococcus aureus, Streptococcus pyogenes* and *Pseudomonas aeruginosa*. The most common anaerobes found were peptostreptococci, Prevotella and fusobacteria [21]. Hight et al. found *Streptococcus milleri* in three cases of severe acne inversa in the anogenital region. This is a bacterium often found in the gastrointestinal tract and the female genital tract and is presumed to correlate with disease activity of acne inversa [19]. It is unclear at present if bacterial colonization and infection are primarily or secondarily included in the developmental process of acne inversa. Obviously, a very heterogenous spectrum of pathogens exists, so that the development of advanced stages of the disease is not bound to the presence of a specific pathogen.

5 Clinical features

5.1 Course
Clinical manifestations in early stages of the disease include giant comedones and firm palpable nodules. In the further course these can coalesce deeply and form large abscesses and sinus tracts (Figure 1). Additionally, darkly colored, infiltrated inflammatory plaques are seen. Pressure can cause secretion of pus, sebum or a foul-smelling secretion. At a later point in time the disease is characterized by numerous scarred areas as the result of burned out inflammatory lesions (Figure 2).

5.2 Clinical spectrum
Clinical forms of manifestation of acne inversa are diverse. In addition to typical clinical presentations in the above-mentioned sites of predilection, acne keloidalis nuchae, folliculitis abscedens et suffodiens (dissecting cellulitis of the scalp) as well as the rarely observed cutis verticis gyrate-like acne inversa belong to the broad spectrum of clinical presentations. The latter is a form of scalp involvement with folds resembling sulci and gyri of the brain, sinus tracks and discharge of secretion [22].

5.3 Complications
5.3.1 Reduced mobility
Healing of areas affected by acne inversa with scarring can lead to contractures and greatly limit the mobility of the limbs. This is especially true for axillary manifestations of the disease.

5.3.2 Fistulas
Anogenital disease is frequently accompanied by anal, rectal or urethral fistulas [23].

5.3.3 Development of malignant tumors
The most severe complication of acne inversa of the anogenital region is the development of squamous cell carcinoma on the basis of chronic inflammation. A series of case reports exists in the literature, but they do not allow for an estimation of the incidence of malignant tumors in acne inversa. Usually long-term presence of acne inversa for about 20 years is a prerequisite for the development of squamous cell carcinoma [24]. Men are predominantly affected.

5.3.4 Chronic lymphedema
In the course of the disease recurrent infections, for example with streptococci, as well as the formation of elephantiasis-like swellings mainly in the genital region can occur [25].

5.3.5 Anemia
Due to chronic inflammation anemia has been reported in patients with acne inversa [26].

5.4 Disease burden
Subjectively patients complain about limited mobility and pain. In severe cases the patients are in reduced general health. Due to feelings of shame, the disease causes a great mental burden resulting in social withdrawal. In a study by Werth a distinctly reduced quality of life in patients with acne inversa was measured using the Dermatology Life Quality Index (DLQI). A total of 114 patients, 16 men and 98 women, were examined. The DLQI score correlated significantly with the number of inflammatory lesions. In comparison to patients affected by other skin diseases, the quality of life of patients with acne inversa was lowest with an average DLQI score of 8.9 [14].

6 Histology
Published studies on histopathologic changes have contributed greatly to understanding the disease acne inversa. Plewig and Steger view the hyperkeratosis of the follicular infundibulum with subsequent bacterial superinfection and rupture of the follicle (Figure 3) and the resulting inflammation of connective tissue (Figure 4) as primary events. Histologically, the apocrine and eccrine sweat glands are not involved primarily, but secondarily [6]. Yu et al. examined 12 histological samples of patients with acne inversa and found cysts and sinus tracts lined by epithelium in the dermis in 10. About one-half of the sinus tracts
contained free hair shafts. In about one-third of the samples inflammation of the apocrine sweat glands with simultaneous inflammation of the eccrine sweat glands and hair follicles was found [27]. In a study by Jemec et al. the majority of samples (44 of 51) revealed occlusion of the tracts and cysts and follicles. Primary inflammation of apocrine glands was not seen [28]. Boer and Weltvreden were also able to demonstrate a primary inflammation of the follicular infundibulum and secondary involvement of apocrine sweat glands (Table 2) [29]. On the other hand, inflammation of the hair follicle without involvement of the associated apocrine sweat glands is often seen [6]. The inflammatory reaction is quite mixed consisting of an unspecific lymphohistiocytic infiltrate, plasma cells, mononuclear cells and neutrophilic granulocytes.

Histological features are quite unequivocal and allow making differential diagnoses which are clinically difficult and rule out entities such as furunculosis, irritated sebaceous gland retention cysts, perianal Crohn disease or multiple sweat gland abscesses.

7 Differential diagnoses/associated diseases
In initial stages of acne inversa differential diagnosis includes furuncles and carbuncles caused by staphylococci and streptococci. At the initial visit other pathogen-induced diseases such as deep fungal infections, actinomycosis and sporotrichosis should be excluded. In the groin or anogenital region, lymphogranuloma venereum and granuloma inguinale are additional considerations. Further differential diagnoses are granulomatous diseases such as tuberculosis cutis colliquativa or cutaneous fistulas in Crohn disease (Table 3).

Clinical differentiation from Crohn disease can be particularly difficult, as in 5% of all cases of Crohn disease perianal lesions are the initial manifestation [28]. In a study by Church et al. 38% of patients with acne inversa examined had simultaneous Crohn disease (n = 61 patients). The diagnosis of Crohn disease preceded acne inverse by 3.5 years on average [30].

8 Treatment
8.1 Surgical treatment
Treatment method of choice is the total excision of affected skin areas.

<table>
<thead>
<tr>
<th>Table 2: Dermatohistological view.</th>
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</thead>
<tbody>
<tr>
<td><strong>Author</strong></td>
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</table>
| Plewig et al. [6] | 1989 | Initial hyperkeratosis of the follicular infundibulum  
Bacterial superinfection and follicle rupture  
Granulomatous inflammatory reaction of the connective tissue  
Apocrine and eccrine sweat glands secondarily involved |
| Yu et al. [27] | 1990 | Cysts and sinus tracts lined with epithelium, in part with hair shafts  
Inflammation of apocrine sweat glands only if eccrine sweat glands and hair follicles are also inflamed |
| Boer et al. [29] | 1996 | Primary inflammation of the follicular infundibulum  
Apocrine sweat glands secondarily involved |
Table 3: Differentiation points.

<table>
<thead>
<tr>
<th>Differential diagnoses</th>
<th>Clinical criteria</th>
<th>Diagnostic criteria</th>
</tr>
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<tbody>
<tr>
<td>Furuncle/carbuncle</td>
<td>Follicular nodule, rapid enlargement, fluctuation and possible spontaneous discharge of pus</td>
<td>Bacteriologic identification of Staphylococcus aureus; Diagnosis is made clinically</td>
</tr>
<tr>
<td>Deep fungal infection</td>
<td>Inflammatory lesions with pustules, follicular abscesses</td>
<td>Identification with direct microscopy and culture</td>
</tr>
<tr>
<td>Actinomycosis</td>
<td>In the neck and mandibular region, painful, firm indurations</td>
<td>Histologic identification of drusen, Gram stain, anaerobic culture</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>Often subcutaneous nodes occurring on the arms, spread along lymphatic vasculature</td>
<td>Histologic identification of cigar-like yeast cells in the PAS stain, Culture at 37 °C (yeast colonies) and at 25 °C (colonies of hyphal fungi)</td>
</tr>
<tr>
<td>Lymphogranuloma venereum</td>
<td>Initially, primary papule, after 2–3 weeks lymph node enlargement and rupture; Livid rope-like adherent swelling in the groin</td>
<td>Occurrence in endemic regions (East Africa, East Asia); Direct identification with FITC labeled monoclonal antibodies, PCR, culture on McCoy cell line (inclusion bodies)</td>
</tr>
<tr>
<td>Granuloma inginale</td>
<td>Papules in the genital or anal region followed by ulceration</td>
<td>Direct identification of pathogen in a tissue biopsy, Giemsa stain (Donovan body), Culture on McCoy cell line</td>
</tr>
<tr>
<td>Tuberculosis cutis</td>
<td>Often clavicular, submandibular and cervical location</td>
<td>Diascopy: “apple jelly”-colored infiltrate; Positive sound phenomenon</td>
</tr>
<tr>
<td>Cutaneous manifestations of Crohn disease</td>
<td>Clinical features similar to acne inversa, no comedones</td>
<td>Often perianal or periorificial location</td>
</tr>
</tbody>
</table>

Unfortunately only few studies on surgical results and recurrence rates of acne inversa after surgical treatment exist. The largest study which we are aware of reports the following recurrence rates 3–72 months after radical surgical excision: axillary 3 %, perianal 0 %, inguinal and perineal 37 %, submammary 50 % [31]. Here, pseudorecurrences must be differentiated from true recurrences. The former is the new manifestation of acne inversa in an untreated hairy border area of the surgical field. It was shown that the recurrence rate after surgery correlated primarily with the extent of surgery [32]. This was confirmed in a study by Ritz et al. Here, the long-term results of three differing surgical procedures were followed up to 72 months postoperatively. The comparison revealed a recurrence rate of 100 % in patients treated with incision and drainage, a recurrence rate of 42.8 % in patients treated with narrow excision of the lesions as well as a recurrence rate of 27 % in patients with wide excision of lesions in healthy tissue [33]. For axillary lesions postoperative difficulties are slight, but the recurrence rate is higher for primary wound closure than for secondary intention healing [34]. Varying statements on the extent of excision, which correlates with recurrence rates, exist. The tissue block to be excised should include not only lateral but also deep safety margins. Furthermore, although the healing process is more rapid with a split-thickness graft, patients usually prefer healing by secondary intention. Advantages of secondary intention healing are a shorter hospital stay, more rapid return to work as well as less limitation of mobility immediately after surgery [35].

In our clinic radical excision of affected areas with secondary conditioning of the wound or split-thickness grafting after adequate granulation to prevent scar strictures with the resulting limitation of mobility are standard (Figures 5–9). In patients with mild acne inversa who have only few inflammatory nodules and fistulas in a small area, we perform excision and primary wound closure with adapting sutures. We do not perform surgery on more than two extensively affected sites in one session. Antibiotic therapy is administered only in case of postoperative bacterial wound infection or preoperatively only in particularly severe and active acne inversa.

8.2 Conservative treatment
Treatment of choice for acne inversa is without doubt the surgical procedure described above. Due to the extent of this procedure and the incurable significant surgical trauma, there has been a continual search for conservative treatment options.

A small study on cryotherapy exists. Here, marked improvement could be realized in 8 of 10 patients. In addition to considerable pain, in almost each case complications such as infection and/or...
ulceration were observed. No data on recurrence rates were provided [36].

On the basis of knowledge on induction of acne inversa by androgens [37], substances with antiandrogenic properties were therapeutically tried. In a double-blind randomized study published in 1986 treatment with ethinyl estradiol/cyproterone acetate and ethinyl estradiol/norgestrel showed improvement in 18 of 24 women treated over a follow-up period of 18 months [16].

The administration of 5-α–reductase type II inhibitors for therapy of benign
prostate hyperplasia as well as male androgenetic alopecia suggested use for acne inversa as well. In an open trial at a dose of 5 mg daily a positive effect was observed in six of seven patients treated (follow-up 8–24 months) [38]. The important role of bacterial contamination and infection especially for signs and symptoms of the disease such as odor, inflammation and suppuration particularly in advanced stages of the disease suggests primary or additional antibiotic therapy. A retrospective evaluation of 14 patients with long-term antibiotic therapy is representative. Clindamycin (2 x 300 mg daily) and rifampicin (2 x 300 mg daily) were administered for a 10 week period. In 10 patients complete healing occurred [39]. Case reports on the administration of cyclosporine exist. In all cases improvement of the condition at doses between 2 and 6 mg/kg body weight daily could be observed. Due to the spectrum of side effects of cyclosporine, it does not appear suitable for the necessary long-term treatment required [40].

Due to clinical, histologic and pathogenetic similarities between acne inversa and Crohn disease, it has been attempted to administer pharmacological agents proven efficacious for Crohn disease for acne inversa, too. Methotrexate therapy of three patients did not lead to the desired effects [41]. In 2001 an open study on therapy with dapsone was published. Due to positive treatment results in acne conglobata, effects in acne inversa could also be expected. A good response to treatment could be documented in all five patients treated [42], but this treatment could not prevail in clinical routine. Based on the known efficacy of retinoids in other forms of acne and other skin diseases accompanied by hyperkeratosis [43] several publications on treatment with isotretinoin as well as acitretin have appeared. Due to the fact that the main mechanism of action of isotretinoin is the inhibition of seborrhea, this treatment appears inappropriate for acne inversa, as no relevant seborrhea exists here. The publications on isotretinoin are thus controversial. A case report exists on successful treatment with isotretinoin (initial dose 20 mg daily increased to 60 mg daily), but in combination with prednisolone (20 mg daily) [44]. An open study showed a response to therapy (follow-up 2 months) in five of eight patients [45]. In a retrospective study (follow-up 4–6 months) on isotretinoin, these positive effects could not on the whole be documented [46]. Great hope in the development of conservative treatment modalities have been raised by the introduction of TNFα antagonists. TNFα as a proinflammatory cytokine plays a key role in the development of severe, chronic inflammatory reactions. Based on positive results in treating Crohn disease with infliximab, the first case report of successful administration of this monoclonal chimeric IgG TNFα antibody for acne inversa was published in 2003 [47, 48]. An excellent response was achieved with doses of 5 mg/kg body weight administered as a short infusion with up to 3 repetitions (week 0, 2, 6). In the first case control study on this therapy, also published in 2003, Sullivan et al. report an excellent response to treatment in all five patients treated. Significant improvement was already seen after one or two therapy cycles, while it must be taken into consideration that in some cases parallel treatment with other anti-inflammatory agents such as prednisolone and cyclosporine were being administered [49]. Cusack and Buckley reported in a first case series on 6 patients treated with etanercept, a fusion protein with soluble TNF receptor function. An initial response to treatment was observed after (on average) 16 days at a dose of 25 mg 2x weekly. About 2–3 weeks after the end of treatment, recurrence occurred [50]. The administration of TNFα receptor antagonists in patients with acne inversa is an off-label use. In summary, available data on conservative treatment of acne inversa does reveal some innovative approaches, that might possibly avoid surgery or perhaps can be performed preoperatively resulting in less extensive or less complicated surgery.

Conflict of interest
None.

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