Acne inversa (alias hidradenitis suppurativa)

T Jansen,†* P Altmeyer,† G Plewig‡
Departments of Dermatology and Allergology, † Ruhr-University Bochum and ‡Ludwig-Maximilians-University, Munich, Germany. * Corresponding author: Department of Dermatology and Allergology, Ruhr-University Bochum, Gudrunstrasse 56, D-44791 Bochum, Germany, tel. +49 0234 509 3411; fax +49 0234 509 3409

ABSTRACT

Acne inversa is a recurrent, suppurative disease manifested by abscesses, fistulas, and scarring. Once considered to be a disease of the apocrine glands, it is actually a defect of follicular epithelium. Thus, the term hidradenitis suppurativa is a misnomer and should be abandoned. In cases of familial acne inversa, the pattern of transmission and number of affected individuals are consistent with autosomal dominant inheritance. Aetiological factors such as hyperandrogenism, obesity, smoking and chemical irritants are not consistently associated with the affection. Bacterial involvement is not a primary event in acne inversa, but is secondary to the disease process. Potential complications include dermal contraction, local or systemic infection due to the spread of microorganisms, systemic amyloidosis, arthropathy, and squamous cell carcinoma. As spontaneous resolution is rare and progressive disability is the rule, early definitive surgical intervention is advisable. The surgical procedure of choice in most cases is wide local excision and healing by secondary intention. Pharmacotherapeutic drugs, including synthetic retinoids and antiandrogens, do not prevent progression of the disease.

Key words: acne inversa, arthropathy, hidradenitis suppurativa, hyperandrogenism, squamous cell carcinoma

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Introduction

Acne inversa (alias hidradenitis suppurativa) is a chronically relapsing inflammatory skin disease characterized by recurrent draining sinuses and abscesses, predominantly in skin folds that carry terminal hairs and apocrine glands. The main localizations are the axillae, groins, and perineum, but the mammary folds, genitalia, anal fold, buttocks, nape of the neck, and even the scalp may also be affected (figs 1–3). Healing occurs with substantial scarring. Polyporous comedones are a characteristic feature of previous acne inversa. The disease is probably more common than has been thought, but the diagnosis is frequently ignored or missed, leading to both patient and physician frustration. Although the exact prevalence of the disease is not known, it has been estimated at $1 : 100$, $1 : 300$ or $1 : 600$. Jemec et al. reported a point prevalence of 4.1%, based on objective findings in a younger adult population, although this may be falsely elevated given the select age range. Some authors believe that acne inversa is more frequent in black people, yet others report no racial predilection. Both men and women may be affected, but men have anogenital lesions more frequently, whereas women are more predisposed to axillary lesions. The female/male ratio in most published series is 2–5 : 1.

Historical background

The disease was first described in 1839 by Velpeau who reported a peculiar inflammatory process with superficial abscess formation, affecting the axillary, mammary, and perianal regions. The disease has traditionally been considered a disorder of the apocrine glands, a concept based on a series of articles by Verneuil who named the condition hidrosadénite phlegmoneuse and suggested its association with sweat glands. Kierland wrote an influential comprehensive paper on this entity in 1951. Unfortunately, he also concluded that the target of the disease was the apocrine glands. In 1955, Shelley and Cahn presented an experimental model with poral occlusion induced by manual skin depilation and application of atropine impregnated tape. The resultant changes included initial keratinous obstruction with subsequent dilatation, inflammation, and bacterial invasion of the apocrine duct. However, the authors were able to achieve occlusion in only 25% of the experimental lesions, and these occlusive lesions did not

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progress to the characteristically chronic condition of acne inversa. In 1956, Pillsbury et al. coined the term follicular occlusion triad to encompass acne conglobata, hidradenitis suppurativa, and dissecting cellulitis of the scalp (perifolliculitis capitis abscedens et suffodiens). The latter picture was originally described by Hoffmann in 1907. The authors argued that the central pathogenetic event, as in acne vulgaris, was follicular hyperkeratinization, distension of the infundibulum leading to rupture, and colonization by a variety of pathogenic bacteria. They viewed retention hyperkeratosis as the primary event but again they thought that the vast destruction of tissue was a consequence of the involvement of the apocrine glands. Plewig and Kligman in their textbook on acne added to the original triad another feature, pilonidal sinus (pilonidal cyst), thus creating the acne tetrad as retrospectively all four could be associated with acne. In 1989, Plewig and Steger introduced the term acne inversa based on the follicular origin of the disease. It is now time to flush out all outdated synonyms for this disease, including hidradenitis suppurativa and pyodermia fistulans sinefica, which we now call acne inversa.

Acne inversa is a disease of the follicular epithelium

More recent studies have identified acne inversa as a disorder of follicular rather than apocrine occlusion. For example, Yu and Cook compared skin samples from acne inversa with controls and found no significant morphological abnormalities of the apocrine glands. The one-third of cases presenting inflammatory changes involving the apocrine glands presented extensive inflammation that also involved other structures such as the eccrine glands and hair follicles. Attanoos et al. also studied the skin biopsies of acne inversa and reported a consistent finding of follicular occlusion in all specimens compared with controls and regardless of disease duration. Jemec et al. examined a total of 51 specimens from 11 patients with acne inversa; of these 30 were from synchronous biopsies and 21 from consecutive biopsies. The majority of specimens (44 of 51) contained poral occlusion, sinus tracts or cysts. This pattern was present in 50–85% of the specimens from each individual subject with acne inversa. No primary apocrine involvement was seen. The authors suggested that the homogeneous histopathology of acne inversa supports its classification as a follicular disease. From a series of 27 consecutive patients, Boer and Welterveden collected clinical data and examined the histopathological pattern in biopsies of newly formed nodules. Histopathological findings showed an occluding spongiform infundibulofolliculitis with secondary involvement of apocrine glands. The results of this prospective study confirmed former histopathological studies, indicating that acne inversa is a disease of the follicular epithelium. Thus, apocrine gland involvement is only incidental or secondary to the primary developments that involve the terminal hair follicle. As a
consequence, there is no significant difference in the size or density of the apocrine glands in patients with acne inversa compared with controls, but the apocrine glands of individuals with axillary hyperhidrosis are significantly larger than those of subjects with acne inversa or controls.22

Acne inversa has been reported to coexist with other skin diseases that show poral occlusion, e.g., Fox–Fordyce disease,48 leading to extensive, periodically inflamed lesions that are of follicular hyperkeratosis. Once rupture of the follicular tissue, the apocrine glands are not involved in the earliest stage of acne inversa. The draining sinus is a late complication of acne inversa,22 consistent with autosomal dominant inheritance. Later, they identified a possible immunity disorder underlying the chronic suppurative process,28 and in these cases the favourable response of both pyoderma gangrenosum and acne inversa to cyclosporin A supports this theory. Congenital tyrosinemia deficiency has been anecdotally reported,29 but could not be confirmed in a large case series. Abnormal laboratory values associated with acne inversa may include increased erythrocyte sedimentation rate, leucocytosis, decreased serum iron and changes in serum electrophoresis pattern; such changes can be considered due to the chronic inflammatory process.30

There is evidence that the transmission of acne inversa in some families is consistent with single gene dominant inheritance, and thus it is probable that genetic predisposition is important in this disorder, but to date not enough is known in this regard. In 1984, Fitzsimmons et al.25 studied three families with a total of 21 affected members. They reported that the pattern of transmission and number of affected individuals were consistent with autosomal dominant inheritance in the original study group and the original probands of previously unaffected family members. In the group where a positive family history had been noted previously, 27% of first-degree relatives of affected family members. In the same study, there was a negative family history in nine families and expected a total of 62 affected individuals, 34% of whom were first-degree relatives in 11 families. This fell short of the 50% expected of an autosomal dominant condition. Later, they studied the families of 26 subjects with acne inversa, comprising a total of 62 affected individuals, 34% of whom were first-degree relatives in 11 families. This fell short of the 50% expected of an autosomal dominant condition. In the same study, there was a negative family history in nine families and familial occurrence only in a further three families. However, both psychosocial issues and problems of ascertainment may have been responsible for false negative family histories.

Recently, von der Werth et al.44 tested the reproducibility of an autosomal dominant inheritance for acne inversa in the original study group and the original probands of previously unaffected family members. In the group where a positive family history had been noted previously, 27% of first-degree relatives were definitely affected by the disease. The concept of autosomal dominant inheritance in families from this group was further strengthened by the detection of nine new acne inversa
cases, in seven of whom the disease developed after the previous study. It is difficult to reconcile the female predominance evidenced in most studies with the proposed autosomal dominant inheritance. If acne inversa were a largely genetically determined disease, then one would have to consider the possibility of hormonal influences on gene expression or even the possibility of an X-chromosomal disease. HLA-A1 and HLA-B8 may predispose the affected subject to more severe disease, but further investigations are necessary to confirm this.

Acne inversa has been reported to be associated with overt endocrine disorders, such as Cushing’s syndrome and acromegaly, indicating that hormonal factors play a aetiological part in the development of the disease. In addition, acne inversa has 4 been regarded as an androgen-dependent disorder. There is a female predominance, and the disease usually does not occur before puberty. In women, it may persist into the climacteric, but onset after menopause is rare. In men, it may persist into middle age, and is usually caused by an androgen-dependent disorder.

It has been suggested that enhanced peripheral conversion of androgens by apocrine glands play a critical part in the pathogenesis of acne inversa. However, Barth and Kealey found equivalent activity of three peripheral androgen-converting enzymes in axillary apocrine glands of subjects with acne inversa compared with those of controls.

A relationship between acne inversa and hyperandrogenism is largely based on the finding of an increased free androgen index [testosterone/sex hormone binding globulin (SHBG)] due to a low sex SHBG, but the subjects were not controlled for body mass index (BMI). This finding is compromised, as many subjects are significantly overweight, and SHBG is negatively correlated with BMI. Another study could only demonstrate hyperandrogenism in a subgroup of women who did not experience a premenstrual flare in their disease. Recently, no supporting evidence for hyperandrogenism or suppression of SHBG has been regarded as an androgen-dependent disorder. There is a female predominance, and the disease usually does not occur before puberty. In women, it may persist into the climacteric, but onset after menopause is rare. In men, it may persist into middle age, and is usually caused by an androgen-dependent disorder.

Some investigators have studied the aerobic and anaerobic microbiology of this condition in a retrospective review of the microbiological and clinical data of 17 specimens obtained from axillary acne inversa over a period of 6 years. A total of 42 bacterial isolates were obtained, 12 aerobic or facultative and 30 anaerobic or microaerophilic. Aerobic and facultative bacteria were isolated in six cases, anaerobic bacteria in seven, and mixed aerobic and anaerobic bacteria in four. The predominant aerobic bacteria were Staphylococcus aureus, Streptococcus pyogenes, and Peptostreptococcus aerogenes. The most frequently isolated anaerobic strains were Peptostreptococcus spp., Prevotella spp., microaerophilic streptococci, Peptostreptococcus spp., and Bacteroides spp. sensu stricto. In conclusion, the flora of microorganisms found in acne inversa lesions is not constant and may change unpredictably.

Various bacteria can be isolated from the sinuses, particularly staphylococci, streptococci and Gram-negative rods. With perianal disease, there is an increased incidence of Escherichia coli, Klebsiella and Proteus as well as anaerobic bacteria. Several investigators have found that Streptococcus milleri is a major pathogen in perianal acne inversa. Streptococcus milleri is an organism that frequently colonizes the gastrointestinal and female genital tracts. Hight et al. reported that the presence of Streptococcus milleri significantly correlated with disease activity. However, Streptococcus milleri was subsequently sought

Complications

The chronic inflammatory process may lead to scars and dermal contractures. Swellings of elephantiasis nostras following streptococcal complications may be superimposed on acne inversa lesions leading to monstrous enlargement and distortion of external genitalia.64,65 Urethral fistula and sinus formation is another uncommon complication of the disease.66 The most serious but rare long-term complication is development of squamous cell carcinoma, occasionally with metastases, on the background of the chronic inflammation, mostly occurring in men in the anogenital area.64,65 The time interval between the diagnosis of acne inversa and appearance of squamous cell carcinoma is, on average, 19 years. Bacterial meningitis,73 bronchitis, pneumonia,13 and systemic amyloidosis are other serious and sometimes fatal complications.

A spectrum of articular manifestations has been reported in subjects with acne inversa. The combination of arthritis and acne inversa is rare,73 previous reviews having mostly described arthritis occurring in combination with both acne conglobata and acne inversa rather than acne inversa alone.72 The arthritis described is seronegative, typically asymmetrical, and affects the knee, ankle, and elbow joints most often, and occurs in subjects between the ages of 22 and 46 years with equal sex incidence. Axial involvement, typically sacroiliitis, also occurs. There have been reports describing the arthritis as occurring before the skin condition,72 but in most cases onset of the arthritis follows the skin lesions by 2–25 years. In most cases the arthritis is episodic, oligoarticular, and non-deforming, but a few patients have progressive disease with joint erosions and ankylosis and require aggressive immunosuppressive therapy to control the disease. Rosner et al.77 found no significant HLA association in their study, although there was a suggestion of B27 association with more severe sacroilitis. The presence of HLA-DR or D antigens was not evaluated. Vasey et al.78 reported finding D antigens in 84% of cases of acne inversa. However, there has been no further confirmation of this observation. Analysis of circulating immune complexes when present to find any bacterial antigens may be useful in evaluating the role of bacteria in the pathogenesis of the arthropathy-associated acne inversa. Arthritis associated with acne conglobata and acne inversa is a condition that may fall within the spectrum of SAPHO syndrome (synovitis, acne, palmoplantar pustulosis, hyperostosis, and osteitis) and other HLA-B27-negative spondyloarthropathies.

Differential diagnosis

Acne inversa is often a diagnostic challenge, particularly when it presents with odd variants, in which case one has to search for other signs of the disease from the history and by total-body examination. Acne inversa should be differentiated from foruncles, carbuncles, pyoderma, tuberculosis subcutanea et fistulosa, actinomycosis, and lymphogranuloma inguinale. The differentiation of acne inversa and Crohn’s disease merits special attention. Perianal lesions are the initial presentation in 5% of all cases of Crohn’s disease and, at times, these two diseases may be clinically indistinguishable. Evaluation of perianal lesions includes proctoscopy to access any involvement of the anus or rectum. Several investigators have reported the comorbidity of acne inversa and Crohn’s disease.80–83 Church et al.74 retrospectively reviewed 61 cases of acne inversa and found that 38% had a concomitant diagnosis of Crohn’s disease, the latter typically preceding the development of acne inversa. Tsianos et al.84 speculated that acne inversa appears to be another cutaneous manifestation of Crohn’s disease. However, this remains to be verified.

Treatment

When properly diagnosed and adequately treated, the early stages of the disease can be controlled with medical measures. However, in established acne inversa there is no evidence that treatment other than surgery has any effect on the natural course of the condition.

Topical treatments, including antiseptics, antibiotics, and corticosteroids, are usually only of limited benefit. Clindamycin, in particular, has been favoured in the literature. Clemmensen85 treated 30 subjects with either clindamycin or placebo in a double-blind trial and reported significant improvement without side-effects. Acne inversa shows a much less favourable response to systemic antibiotics than acne vulgaris. In a clinical
study, therapy with systemic tetracycline did not show better results than topical therapy with clindamycin.85 In general, after withdrawal of antibiotic treatment, relapse of acne inversa is almost inevitable. Although antibiotics are not curative, they may diminish odour and discharge, and reduce pain. Systemic or intralesional corticosteroids have been used with variable results, but may be effective in select cases. The concept of acne inversa as an androgen-dependent disease has led to attempts at hormonal therapy. One report details seven women with acne inversa after starting oral contraceptive use, which improved after stopping or changing the oral contraceptive to a higher oestrogen/progesterone ratio.86 Sawers et al.87 reported on four women with acne inversa who responded within 2 months to treatment with cyproterone acetate and ethinyl oestradiol. When the cyproterone acetate was reduced to half the original dosage, three of the four subjects showed worsening. After discontinuing therapy, two of the four subjects maintained the same level of improvement for several months. Mortimer et al.88 carried out a double-blind, controlled, cross-over trial comparing ethinyl oestradiol/cyproterone acetate with ethinyl oestradiol/norgestrel treatments in 24 women with acne inversa. Both regimens produced significant improvement, including seven subjects free of disease at 18 months, five improved, four unchanged, and two worsened. The remaining six subjects withdrew because of side-effects or disease exacerbation. Farrell et al.89 reported the beneficial use of finasteride, a competitive inhibitor of the 5α-reductase type II enzyme, in two cases of severe, long-standing acne inversa. In our experience, antiandrogen therapy has been effective for a few subjects, while remaining ineffective for most others. Treatment using gonadotrophin-releasing hormone agonists in two cases of severe, long-standing acne inversa. In this study, recurrence appeared 3–72 months after surgery, with a median of 24 months. Poor success rates in cases of submammary disease have led some investigators to avoid recommending formal surgical excision for this region.

Radiotherapy has been used in some series but often fails to eradicate the lesions completely; troublesome sinuses and scarring may follow.101

Although incision and drainage and exteriorization of individual lesions may be useful in some instances, radical surgical excision at the earliest recognized stage remains a mainstay of therapy. Various surgical techniques have been employed for treating acne inversa.6-102 The complete excision of all involved skin and tissues is necessary to ensure eradication of the condition. A comparison of techniques is difficult because of the various methods of excision and reconstruction used. Split-thickness skin grafts, fasciocutaneous flaps, and primary closure have been advocated for repairing the surgical defects. Available data indicate that inadequate excision is the main reason for recurrence and that radical excision with healing by secondary intention is the treatment of choice in most cases. Ritz et al.103 examined the extent of surgery in terms of the clinical course of acne inversa. The operative procedures were divided into drainage procedures, limited regional, and radical wide excisions. At a mean follow-up of 72 months, they found developed iatrogenic recurrence of acne inversa in 45% of cases. There was 100% recurrence after drainage, 42.8% after limited, and 27% after radical excision. Acne inversa recurred after a median interval of 3 months for drainage, 11 months for limited excision, and 20 months for radical excision. The disease-free interval continued up to 35 months. A study by Harrison et al.104 reported the following rates of recurrence in 82 subjects treated with 118 radical excisions: axillary, 3%; perianal, 0%; inguinoperineal, 37%; and submammary, 50%. In this study, recurrence appeared 3–72 months after surgery, with a median of 24 months. Poor success rates in cases of submammary disease have led some investigators to avoid recommending formal surgical excision for this region.

Carbon dioxide laser excision is another treatment option for acne inversa.105-108 Finley and Ratz105 treated seven subjects with carbon dioxide laser excision and reported a healing time of 4–8 weeks. They considered the advantage of laser treatment to be improved haemostasis, which affords better visualization and therefore more complete removal of affected tissue. Carbon dioxide laser treatment is a rapid, efficient, and economical treatment of acne inversa that gives good results especially when done by an experienced technician.

Therapeutic interventions in the articular manifestations of acne inversa have centred mainly on anti-inflammatory medications with the presumption that the underlying pathogenesis was immunological. Treatments employed have included non-steroidal anti-inflammatory drugs, corticosteroids, methotrexate, and n-penicillamine.

**Prognosis**

With rare exceptions, surgical intervention is sufficient to stop the disease. Too often precious time is lost with inadequate

treatment, with the consequence that many affected individuals drift away from society, and many subjects develop new lesions at a site not affected at the time of their initial surgery. Although spontaneous resolution may occur, this is rare. This reinforces the need for early recognition and treatment of this potentially disabling disease.

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