ACNE CONGLOBATA

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Abstract

Acne conglobata is a severe form of acne which is most commonly seen in teenage males, but also in females and into adulthood. *Conglabate* means a rounded shape mass or ball. Acne conglobata is a mixture of comedones, papules, pustules, nodules, abcesses, and finally scars. It can be seen in all main parts of the skin, but especially on the back, buttocks and chest. Comedones often have multiple openings. The inflammatory lesions are mostly large, tender and dusky-colored. The draining lesions may have a foul-smelling serous, purulent, or mucoid discharge. After healing, lesions become an admixture of depressed and keloidal scars. The management of these patients is usually difficult and the effectiveness of treatment is often temporary. Several medications have been used, including intensive high dose antibiotics, glucocorticoids, surgical incision and excision. The use of isotretinoin has produced good results in some of these patients. Some of these lesions may be more ressistant to monotherapies and a concomitant therapy is sometimes needed.

Keywords:

acne conglobata, isotretinoin.

Introduction

Acne conglobata (AC) is an uncommon and the most severe form of acne vulgaris. It presents with interconnecting inflammatory painful nodules, cysts, fistula, abscesses, draining sinus tracts, all leading to severe scarring (1). Disfiguring scars may produce serious cosmetic and psychological impairment in most patients with AC (2).

Epidemiology

Acne conglobata was first described by Spitzer and Lang (3, 4). The disease affects boys and men more frequently than females. It usually starts in late puberty and often persists beyond the third decade of life, but infants may develop this condition as well (5). The peak incidence ranges between 18 and 30 years. Several studies on twins and families have confirmed that a history of acne among first degree relatives – especially mothers – has the strongest impact on severity and treatment success of acne. Familial occurrence of AC has been reported. It occurs frequently in first degree relatives (6, 7). Familial AC is more widespread and aggressive than "ordinary" acne conglobata and involves unusual areas such as the antecubital fossa and ankles (7). Familial cases of AC with hidradenitis suppurativa can also be seen (8).

Etiology and Pathogenesis

Although many factors interact to produce acne conglobata, the primary causes remain unknown. *Propionibacterium acnes* (*P. acnes*) may play an important role in the etiology of AC. Since testos-

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terone is one of the causes, it appears primarily in men. The condition might be caused by androgens and anabolic steroid abuse, androgen-producing tumors, and it may appear following stopping testosterone therapy. Other possible causes include exposure to halogenated aromatic hydrocarbons or ingestion of halogens (*e.g.*, thyroid medication, hypnotic agents). Also, drug-induced AC may be caused by lithium. One patient with hidradenitis suppurativa and acne conglobata induced by lithium has been described (9). Most studies indicate a significant association between high body mass index and severe acne (10, 11). Lesions on the buttocks can be aggravated by mechanical and environmental factors (12).

Genetic Factors

The association of acne conglobata with the chromosomal defects in the XYY syndrome has been reported. Patients with an XYY chromosomal genotype tend to have more severe acne unresponsive to therapy. In contrast, the XXY karyotype of Klinefelter syndrome is believed to exclude severe acne, but one patient with the unusual association of Klinefelter syndrome and acne conglobata has been reported (13). The HLA-A and HLA-B phenotypes were studied in 65 patients with acne conglobata, but any association of this disease with specific HLA phenotypes has not been proven.

Evidence from studies indicates that the novel mutations in γ-Secretase (NCSTN) is a causative factor in AC. Mutations in γ-Secretase proteins lead to epidermal and follicular abnormalities in hidradenitis suppurativa. Nonsense mutation (p.Leu600X) within exon 16 of NCSTN has been reported in families with AC (14).

Recent reports have described that Toll like receptor 2 (TLR-2) and TLR-4 play an important role in the pathogenesis of acne vulgaris (15, 16). TLR-2 and TLR-4 are expressed on normal skin layers and their expression is increased in patients with acne vulgaris. Interstingly, Grech *et al.* found a considerable role of single nucleotide polymorphisms (SNPs) of the TLR-4 gene in the physical course of acne. In fact, carriage of SNPs of the TLR-4 gene has been shown to be related with acne severity. But they also found that carriage of gene SNPs was protective against the development of acne conglobata even in the presence of *P. acnes* (17).

Mutations in proline-serine-threonine phosphotase interacting protein 1 (PSTPIP1) have been found in patients with AC, which is a component of pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA syndrome) (18, 19). CD2 antigen-binding protein 1 (CD2BP1) also leads to PAPA syndrome (20). Braun-Falco *et al.* and Marzano *et al.* reported patients with pyoderma gangrenosum, acne and hidradenitis suppurativa (PASH syndrome), found to be associated with a mutation in the PSTPIP1 gene (21, 22). Pyogenic arthritis, PG, acne and hidradenitis suppurativa (PAPASH syndrome) has also been shown to be associated with a missense mutation in the PSTPIP1 gene (23). Zeeli *et al.* described a patient with a clinical triad of pyoderma gangrenosum, acne and ulcerative colitis (termed PAC syndrome), which was found to be associated with a novel mutation in PSTPIP1 gene (19). Recent reports have shed light on the presence of PSTPIP1 mutations, which predicts a good response to IL-1 blockade (24, 25). PAPA, PASH, PAPASH and PAC syndromes share a possible common aetiology and the same gene mutation and have a good therapeutic response to anakinra, which is an IL-1 signalling blocking agent (19).

Clinical features

Acne conglobata usually presents as numerous comedones, cystic nodules, papules, pustules, interconnecting abscesses and draining sinus tracts (26) (Fig. 1). The comedones often have multiple openings. The inflammatory lesions are large, tender and dusky-colored. The draining lesions discharge serous, purulent, or mucoid material (27). It is also characterized by depressed or keloidal scars (Fig. 2). Deep ulcers may form beneath the nodules leading to disfiguring scars. The lesions are usually found on the face, neck, chest, upper

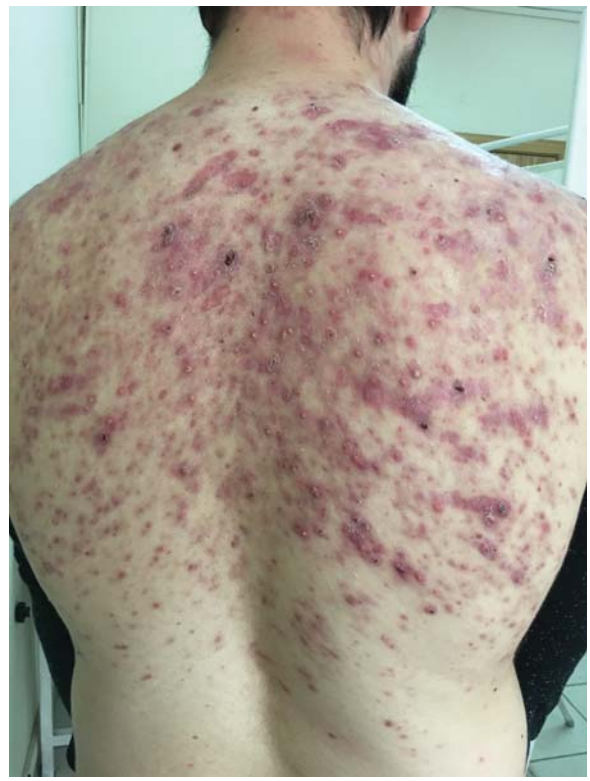

Figure 1. AC usually presents as numerous comedones, cystic nodules, papules, pustules.

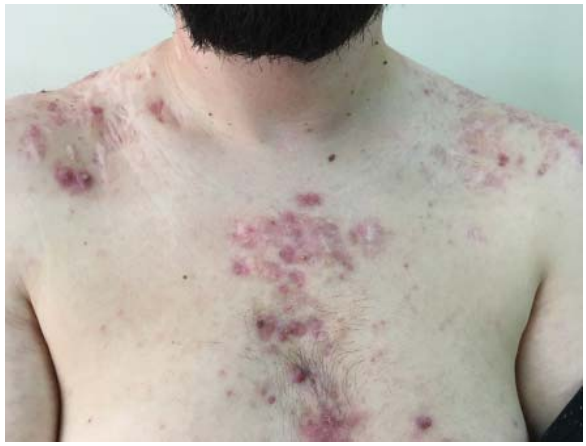

Figure 2. AC is also characterized by depressed or keloidal scars.

shoulders, arms, buttocks and thighs. This disease can have extracutaneous manifestations, mainly polyarthralgia and arthritis (28). It can be seen simultaneously with some diseases, as mentioned in the 'Related Disease' section.

Histopathology

In established lesions, there is a heavy, mixed inflammatory cell infiltrate in the lower half of the epidermis. The appearances are similar to hidradenitis suppurativa, with deep abscesses and mixed inflammation, foreign body granulomas, and discharging sinuses. Comedones are often present. Chronic abscesses are present in active cases and these may connect with sinus tracts leading to the skin surface. The sinuses are usually lined by stratified squamous epithelium in their outer part. They contain inflammatory and other debris (29).

Related Disease

Acne conglobata is part of the follicular occlusion tetrad, along with hidradenitis suppurativa, dissecting cellulitis of the scalp and pilonidal disease, which are also characterized by chronic, recurrent inflammation with follicular occlusion (26).

Acne conglobata also presents as part of systemic inflammatory conditions such as SAPHO, PAPA and PASH syndromes. SAPHO syndrome is characterized by including synovitis, acne, pustulosis, hyperosteosis and osteoitis. Skin manifestations in SAPHO syndrome may be AC, acne fulminans, palmoplantar pustulosis, or hidradenitis suppurativa. Affected patients may suffer from walking difficulty, owing to pain, weakness, and weight loss. The patient should be asked about such symptomps. PAPA syndrome clinically presents with pyogenic sterile arthritis, pyoderma gangrenosum and acne. PASH syndrome, an acronym for pyoderma gangrenosum, acne, hidradenitis suppurativa is distinctly different from PAPA, which does not include arthritis (26, 30). The association of pyoderma gangrenosum, acne and ulcerative colitis is also described as PAC syndrome (19). AC may also be associated with the PASS syndrome, which consists of pyoderma gangrenosum, AC, hidradenitis suppurativa and seronegative spondyloarthritis (31).

Acne conglobata has been reported in association with lichen spinulosus in a man who was seronegative for the human immunodeficiency virus (HIV) (32). Malignant degeneration such as squamous cell carcinoma can develop in long standing lesion of AC (33, 34). Patients who exhibit AC along with sacroileitis have also been found to have anterior uveitis (35). Spondyloarthritis associated with AC, hidradenitis suppurativa and dissecting cellulitis of the scalp has been reported (36). Pyoderma gangrenosum, AC and Ig A gammopathy have been reported in the same patient (37). Renal amyloidosis may accompany C (38, 39).

Differential Diagnosis

The differential diagnosis of AC consists of some disease such as halogenoderma, acne fulminans and hydradenitis suppurativa.

Halogenoderma, especially iododerma and bromoderma, must be considered. The main difference in these lesions is the history of medications with halogens. Iodides are found in many cold and asthma medications, contrast dyes, kelp and combined vitamin-mineral supplements. Bromides are found in sedative, analgesics and cold remedies.

Acne conglobata is different from acne fulminans. But initially, the disease resembles AC with numerous lesions on the back and chest. The distinguishing morphologic feature is the formation of hemorrhagic nodules and plaques which later ulcerate. The onset of acne fulminans is more explosive, nodules, and comedones are less common, ulcerative and crusted lesions are unique. Systemic symptoms and findings such as fever, polyarthralgia, myalgia, hepatosplenomegaly, leukocytosis, elevated sedimentation rates, proteinuria, and anemia are more common in acne fulminans. Osteolytic bone lesions may also accompany acne fulminans (27, 28).

Hidradenitis suppurativa is characterized by inflammation of apocrine glands especially in axillae and anogenital regions. Lesions are usually inflammed nodules and sterile abcess, followed by sinus tracts, fistula and hypertrophic scars. The main difference between hidradenitis suppurativa and AC is the localization of lesions (39, 40).

Acne conglobata may also initially resemble staphylococcal furunculosis, but the latter usually presents central pointing or ulceration usually does not form sinus tracts (40).

Prognosis

The course of AC is prolonged and chronic. AC can cause pronounced scarring. Severe disfigure-

ment produces psychological impairment. Because of the involvement of the face, patients with AC are often ostracized, or they may feel excluded. Acne conglobata has also been responsible for anxiety and depressive moods in many patients (42). Squamous cell carcinoma (SCC) can rarely develop in acne conglobata after a lengthy latent period; prognosis is poor, with a high metastatic rate and fatal outcome. Therefore, the patients affected by acne conglobata should be monitored very carefully, especially when the condition is severe or familial (7, 34).

Treatment

Acne conglobata is a highly inflammatory form of acne that can be difficult to treat with standard acne therapy. Although a variety of therapeutic interventions for AC have been explored, the therapeutic effects are unsatisfactory. Therefore, the combination of several treatments might cause better results than monotherapy for the successful treatment of acne conglobata – both systemic therapy and surgical approaches might be used together.

Systemic Treatment

Oral treatments for acne conglobata include antibiotics, hormones, isotretinoin and occasionally, systemic corticosteroids. Other drugs such as dapsone, clofazimine, colchisine, cyclosporin, oral zinc are rarely used (42-44).

Systemic antibiotics are the mainstay of acne therapy but oral antibiotics (tetracycline, doxycycline, minocycline, azithromycin) alone are usually unsuccessful in the treatment of AC rather than classical acne vulgaris. Although some success can be achived using them in high doses, the results are not very satisfactory becouse of treatment resistance. The treatment period with systemic antibiotic should be as short as possible to reduce the risk of bacterial resistance (45).

Isotretinoin is the first choice of oral treatment in AC. Oral isotretinoin may be used alone or in combination with systemic steroids. Because of their antiinflammatory activity, systemic glucocorticoids may be of benefit. Prednisolone is given 40 mg daily tapered over 3-4 weeks, starting ideally 1-2 weeks before isotretinoin. Systemic isotretinoin is highly efficacious in severe nodulocyctic acne. Although a dose of 0.5-1 mg/kg is the standard of care, usually higher doses than 1.0 mg/kg daily are more effective than standard dose (46). In severe cases, dosages as high as 2 mg/kg/day for a 20 week course may be necessary. Consequently, oral isotretinoin is also has limited success in the treatment of AC.

Dapsone is an alternative treatment strategy for resistant cases of AC. The dosage for dapsone is 50-150 mg per day (47). When monotherapy with isotretinoin or dapsone alone had not been successful, a combination with dapsone and isotretinoin might produce signficant improvement (48).

Patients with AC who do not respond to isotretinoin alone may be alternatively treated with colchisine or cyclosporine. There is a case report in which these alternative therapies were used and some benefits observed (43).

There is limited data on hormones used for AC. The gonadotropin-releasing hormone analogues, such as buserelin, may be useful in the treatment of resistant acne conglobata. These agents are used in the treatment of ovarian hyperandrogenism (49).

There are some alternative therapies such as targeted treatments for refractory AC. They consist of TNFα antagonists. Recent reports showed that TNFα antagonists may be used as an effective therapy for AC (26). Adalimumab was used as monotherapy in a patient with AC who was unresponsive to doxycycline, isotretinoin, prednisolone and dapsone, with an initial loading dose of 80 mg, followed by 40 mg twice monthly. After 4 weeks, the patient had a dramatic response (50). There have been reports of successful treatment for SAPHO syndrome with etanercept, adalimumab and infliximab (51, 52). Anakinra has been reported beneficial in the treatment of PAPA, PASH, PAPASH and PAC syndromes (19).

Radiotherapy

For patients with severe acne conglobata resistant to standart treatments, external beam radition may be an alternative therapy. There are some data about radiation therapy for AC. This limited data observed that a total of 8 doses of 2.5 Gy radiation given in an overall duration of 8 weeks had some benefits on AC lesions (53).

Photodynamic treatment

Photodynamic therapy with topical 5% 5-aminolevulinic acid and red light once every ten days for a month significantly improved acne lesions and reduced scar formation. In this study, photodynamic treatment for AC is associated with high cure rate, short treatment period and few side effects. This was the first report on AC with photodynamic therapy (54).

Carbon dioxide laser

Acne conglobata has been successfully treated with carbon dioxide laser combined with topical tretinoin therapy. Acne conglobata may be treated susccessfully with carbon dioxide laser ablation to remove the top of the sinuses and their tracts. Based on the results in same data, authors proposed that the use of carbon dioxide laser for opening the cysts, combined with topical tretinoin therapy to prevent the appearance of new lesions, might be a powerful treatment option for AC (55).

Alternative treatment

Chinese authors observed the curative effect of encircling acupuncture combined with ventouse and cupping for acne conglobata. They concluded that both acupuncture and medication can effectively promote recovery of the affected skin and lower serum IL-6 level in acne conglobata patients. The effect of acupuncture is stronger than that of Isotretinoin in lowering serum IL-6 content and has fewer adverse effects (56).

Surgery

Surgical removal of involved tissue beyond clinically involved margins and coverage with healthy grefts of split-thickness skin is an effective treatment modality for resistant AC. Surgical excison of interconnecting inflammatory nodules may be beneficial. Post operative recurrence may ocur in some patients (2, 5). Pharmacotherapy and surgical approaches may be combined.

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