

Severe inverted acne associated with *pyoderma gangrenosum* and complicated by sepsis

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Abstract

Inverted acne and pyoderma gangrenosum are both rare inflammatory skin conditions that are associated with systemic inflammatory diseases. *Acne inversa* is a chronic or relapsing scarring disease, manifested by recurrent formation of abscesses, fistulating sinus and scarring of the axillae, groins and perineum occurring predominantly in women, with onset at puberty. The association with Crohn disease, psoriasis and pyoderma gangrenosum, as well as the seronegative arthropathies, suggests common immunopathogenesis. All patients required multiple therapeutic agents because their diseases (*acne inversa* and *pyoderma gangrenosum*) were often poorly responsive to standard therapies. We describe the case of a 53-year-old man because of severe *acne inversa* with *pyoderma gangrenosum* complicated by sepsis.

Key words: *acne inversa*, *pyoderma gangrenosum*, sepsis.

Introduction

Inverted acne (*acne inversa*) and pyoderma gangrenosum are chronic diseases with inflammatory aetiology. It is believed that the role here is played by the dysregulation of patient's immune system and the production of pro-inflammatory cytokines, mainly tumour necrosis factor α (TNF- α), interleukin 8 (IL-8), IL-16, IL-1 β .

Acne inversa is a disease of sebaceous glands and hair follicles, and not, as it was previously thought, of apocrine glands (former name *hidradenitis suppurativa*). In its course, lesions generally occur in unusual places, such as buttocks, groins, armpits, genital area and the scalp. The skin lesions have the form of lumps and inflammatory infiltrates, leaving numerous raised and stretched scars and fistulas with massive leakage of purulent secretion. Bacteriological examination shows mixed flora or no bacterial flora. Laboratory tests demonstrate elevated OB levels, elevated leukocytosis and other markers of the chronic inflammatory process [1–3].

Population studies have shown that obesity and smoking are risk factors that cause lesions of the *acne inversa* type.

Pyoderma gangrenosum is characterised by the presence of well-secluded, painful ulcerations, often located on the lower limbs. Similarly as in the case of *acne inver-*

sa, patients' markers of the inflammatory process are elevated including OB, C-reactive protein (CRP) and leukocytosis. The aetiology takes into account an over-reactive inflammatory response to various factors (presence of the so called patergy symptom). However, the relationship with an underlying disease is most often described, namely inflammatory bowel diseases (mainly Crohn disease), liver diseases (HCV, immune hepatitis), rheumatic and hematologic diseases (monoclonal gammopathies, leukaemias). Cases of post-traumatic pyoderma gangrenosum (including those in surgical scars) and *pyoderma gangrenosum* associated with sarcoidosis, solid tumours, HIV/AIDS, conglobated acne and inverted acne are also reported [4–6].

Cases of *acne inversa* associated with *pyoderma gangrenosum* are relatively rarely described in the literature.

We present the case of co-existence of a severe form of inverted acne and *pyoderma gangrenosum*, complicated by sepsis.

Case report

The patient was 53 years old. The first skin lesions in the form of painful lumps, with a tendency towards disintegration, cicatrisation and fistula formation, localised on the buttocks and the inner surface of the thighs,

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occurred at the age of 21 years old (1974). Due to the lack of correct diagnosis, the patient underwent multiple surgeries. The skin lesions were cut out and drained without any permanent improvement. The patient was also repeatedly prescribed oral antibiotics. The patient did not take any medication permanently for any other reasons, and did not suffer from other chronic diseases. He had been smoking cigarettes for 30 years, about one pack a day.

In 1992, for the first time the patient was referred to the Outpatient Dermatology Clinic, where he was diagnosed with inverted acne. However, the patient did not attend the visits regularly. In 1994, the patient was operated on for numerous perianal fistulas, in the Surgical Department, where an artificial anus was established. In 1996, the artificial anus was closed. In the nuclear magnetic resonance (NMR) of the pelvis minor, performed at that time, no pathology was demonstrated. The colonoscopy showed the characteristics of a chronic colitis and inflammation of the anus (confirmed by histopathological examination).

In 1998, in the area of both front lower legs there appeared ulcers, quickly spreading peripherally. In the histopathological examination of the edge of the lesion on the left lower leg, features of vasculitis with massive leukocyte infiltrates, presence of plasma cells, histiocytes and giant cells were found. The whole picture implied *pyoderma gangrenosum*.

In the Dermatology Clinic, dapson was initially introduced into the therapy, which, however, was discontinued due to the high level of methemoglobin. Then, cyclosporine A was applied at the maximum dose of 250 mg/day, which the patient took, with minor interruptions, until 2003. During that period, the inverted acne lesions were mild and treated externally only. However, the ulcers in the area of the lower legs were almost completely healed. Since 2000, the patient continued this treatment under

the supervision of a GP practice, and did not visit the Outpatient Clinic.

In October 2004, because the lesions in the course of both diseases worsened, the patient was hospitalized in the Dermatology Clinic again. For 3 months, the temperature of his body remained elevated (37-38°C), which was accompanied by the weight loss of about 8 kg. On admission, the patient was recognised to be in a medium-severe condition. The temperature was 39°C. The patient complained of a very severe pain.

On the skin around the buttocks, perineum and scrotum, numerous raised and stretched scars and fistulas with a massive leakage of purulent secretion were observed. The surrounding skin was red, swollen and excessively warm.

There were ulcers on both lower legs. On the side surface of the right lower leg – there were oval ulcers 10 cm × 8 cm, with undermined rolled edges and the bottom covered with large amounts of purulent secretions and necrotic tissues. On the medial posterior surface of same lower leg – there was ulceration 6 cm × 4 cm of similar nature. On the left lower leg – ulceration 4 cm × 6 cm and the characteristics as above. Within the left hallux – oval, deep ulcer measuring 2 cm × 3 cm, with the bottom covered with necrosis and purulent content. The skin surrounding the whole ulcer is red, too warm, with features of inflammation. Peripheral lymph nodes were not enlarged. Mucous membranes were free from lesions (Figures 1-5).

Laboratory tests: ESR 95, glucose 8,00 mmol/l, full blood count, electrolytes, asparagine aminotransferase (AspAT), alanine aminotransferase (AlAT), gamma-glutamyltransferase (GGTP), bilirubin, creatinine, urea, general urine test, electrophoresis, CPK, aldolase, Latex-R, Waaler-Rose's reaction – normal. Tumour markers: CEA, CA 125, total PSA were within the norm. Imaging – X-ray of the chest, ultrasonography of the abdomen and com-



Figure 1. Patient, 53 years, cicatrization and fistula formation, localised on the buttocks



Figure 2. Patient, 53 years, cicatrization and fistula formation, localised on the buttocks – lateral view



Figure 3. Patient, 53 years, cicatrisation and fistula formation, localised on the buttocks – back view



Figure 4. Patient, 53 years, deep ulcer located on the toe

puted tomography (CT) of the head were normal. Bacteriology examination (changes on the buttocks): *Escherichia coli*, *Corynebacterium species*, *Staphylococcus aureus*. Mycology – negative.

During the stay in the Clinic, clofazimine was applied at the dose of 2×100 mg, cefuroxime at the dose of 2×1.5 g i.v. for 10 days and, due to the characteristics of urinary tract infection, ciprofloxacin 2×0.5 g for 10 days.



Figure 5. Patient, 53 years, ulcers on both lower legs

After his local and general symptoms improved, the patient was transferred to the district Dermatology Department in order to continue treatment.

After 2 weeks of the patient's stay in the Dermatology Department, his local and general condition worsened further. The temperature was again 39-40°C. The blood culture, obtained 3 times at the top of the fever, was negative. In the therapy, the following were introduced: ampicillin 4×1.0 g i.v., metronidazole 3×0.5 g and amikacin 1.0 g. Clofazimine was also continued 2×100 mg.

In December 2004, the patient was again admitted to the Dermatology Department, where the above treatment was continued. Laboratory tests: ESR 120, iron 3.9 mmol/l, full blood count: red blood cell (RBC) 3.4 T/l, haemoglobin (Hb) 6.1 mmol/l, hematocrit (HCT) 29%, white blood cells (WBC) 8.8 G/l, PLT 412 G/l, electrolytes, AspAT, AIAT, GGTP, bilirubin, glucose, creatinine, urea, general urine test, electrophoresis, CPK, aldolase, Latex-R, Waaler-Rose's reaction – normal.

Due to progression of the lesions and lack of complete response to the treatment, the diagnostics was extended in the direction of paraproteinemia. The levels of IgM, IgA were elevated, while IgG was within the normal range. Elevated levels of kappa light chains and lambda heavy chains. Bence Johns Protein – negative. Immunoelectrophoresis – present polyclonal immunoglobulins. X-ray of the skull – bones of the skull cap unchanged.

Myelogram examination (obtained from the breastbone) – hyperfollicular and hypercellular bone marrow. Plasmocytes present in an increased amount, including the di- and tri-nucleated ones.

Haematological consultation on the basis of the above plasmacytoma was excluded. Elevated levels of IgA, IgM correspond to the polyclonal response to infection. Similarly, plasmocytes visible in the bone marrow biopsy have the nature of reactive response to a chronic infection. Iron formula supplementation was also introduced.

After a 2-week stay in the Clinic, and the therapy used, there was subsequent improvement of the local and general condition of the patient. The patient did not have fever. Antibiotic treatment was gradually withdrawn and, due to the lesions of *acne inversa* type, isotretinoin was introduced at the dose of 30 mg/day (the patient was also taking clofazimine 2 × 100 mg). After a month of hospitalisation, and the local and general condition of the patient stabilised, he was discharged home. A follow-up appointment was scheduled at the Outpatient Dermatology Clinic, which the patient did not attend. On the basis of the documentation received, it was stated that the patient died in the course of sepsis and multiple organ failure at the regional Department of internal medicine.

Discussion

The aetiology of both inverted acne and *pyoderma gangrenosum* is unclear. In both diseases we deal with regulation disorders of the inflammatory process, which may explain the cases of co-existence of both of the entities. Studies of the role of cytokines in etiopathogenesis of these diseases are important for the development of new methods of treatment, which were not used in the period when the patient described by us was ill.

An inflammatory infiltration in the course of inverted acne compared with healthy skin contains a much higher expression of Toll-like 2 (TLR2) receptors. In the infiltration, macrophages CD 68+, dendritic cells CD 209+ and lymphocytes T CD3 dominate. This picture is similar to the lesions observed in *acne vulgaris*, which justifies the current opinion that *acne vulgaris* is also a chronic inflammatory dermatosis [7].

Van der Zee *et al.* [3] described elevated levels of TNF- α , IL-1 β and IL-10 (anti-inflammatory cytokine!) on the skin of patients with *acne inversa*. Skin biopsies were performed on the lesions and on the surrounding skin. Also a correlation of the levels of pro-inflammatory cytokines TNF- α , IL-1 β was noted, with an intensification of the disease process. Wolk *et al.* [8] demonstrated lowered levels of IL-22 and IL-20 in the patients with inverted acne. It also concerned the receptors for these cytokines. Simultaneously, elevated concentrations of inhibitors IL-22 were observed in the patients. Kamp *et al.* [9] evaluated the number of sebaceous glands in hair follicles of the patients with inverted acne and in a healthy control group. The conducted histopathological examination showed fibrosis, obliteration and reduction in the number of sebaceous glands in the patients with *acne inversa*.

In 77% of slices of the skin of the patients with *acne inversa*, intensified epithelial hair follicles hyperplasia was demonstrated. In 43% of the cases, psoriasis-like epidermal hyperplasia was also observed, and in 78% of the slices – intra-follicle and supra-epidermis inflammatory infiltration: CD 3, CD 4, CD 68, CD 79 and CD8. The

described factors are believed to be the early markers of creation of lesions of *acne inversa* type [10].

Both in case of *pyoderma gangrenosum* and inverted acne, the described risk factors are smoking and obesity. In the case described by us, the patient was a long-time smoker. As per Cesko *et al.* [11], 96% of the patients with inverted acne smoked over 20 cigarettes, and 50% were diagnosed with obesity.

The cases of co-existence of *acne inversa* and *pyoderma gangrenosum* are quite rarely described in the literature. In all the cases, the disease which appeared first (similarly as in the patient described by us) was the inverted acne. However, data of such a severe and fatal course were not found in any communication.

Hsiao *et al.* [1], in the retrospective study of the references, found 11 cases of co-existence of inverted acne and *pyoderma gangrenosum*. Ten of the cases involved obese women. In all the patients, the occurrence of lesions of the *pyoderma gangrenosum* type was preceded by a long *acne inversa* history. But on average it was preceded by 2.5 years, which means the time was much shorter than in our own communication (24 years). All the patients were treated with multiple well-known methods of therapy with the inhibitors TNF- α and receptor antagonists for IL-1 (anakinra). Improvement of the local condition was achieved in 75% of the patients. It should be noted here that the TNF- α inhibitor type medications were not available in Poland at the time when our patient was treated.

García-Rabasco *et al.* [12] described a patient, whose *pyoderma gangrenosum* developed in the course of a 20-year history of inverted acne. However, in the case of that patient, full remission of the *pyoderma gangrenosum* type lesions was obtained, with an improvement in the treatment of acne after the therapy used (cyclosporine A, isotretinoin). Ah-Weng *et al.* [6] presented 3 women and 3 men with *pyoderma gangrenosum* and inverted acne type lesions, and also in that case, in all the patients, pyoderma occurred after quite a long time from the occurrence of acne – on average after 20 years. In one patient, as in the case described by us, there was a serious shortage of iron.

The case of simultaneous occurrence of *pyoderma gangrenosum*, seronegative arthritis, conglobated acne and inverted acne in a 42-year-old man was described by Shenefelt [13]. The treatment included the use of minocycline in combination with sulphasalazine, with a good effect.

Treatment of the chronic inflammatory dermatoses described by us is difficult and long. Studies on aetiology made it possible to introduce new medications, which in the early 21st century were not used in treatment of *acne inversa* and *pyoderma gangrenosum*.

In therapy of inverted acne, surgical treatment is used, as well as pharmacological oral retinoids (isotretinoin, acitretin), antibiotics, dapson, inserts of corticosteroids,

TNF- α inhibitors (etanercept), monoclonal antibodies (infliximab, adalimumab), as well as light therapy and photodynamic therapy [4, 14-18].

Treatment of *pyoderma gangrenosum* includes, among other things, general corticosteroids, dapson, clofazimine, cyclosporine A, tacrolimus, mycophenolate mofetil, intravenous immunoglobulin, TNF- α inhibitors, monoclonal antibodies [4, 14, 15].

Numerous medications are used successfully in treatment of both diseases.

In the 1970s, mainly surgical and antibiotic treatments were used in our patient. Later on, cyclosporine A was also introduced (used with a good effect for almost 5 years), dapson, clofazimine and, due to the features of a generalized infection, often antibiotics. However, despite the treatment, the patient died in the course of sepsis and multiple organ failure at the beginning of 2005.

Retinoids have been used to treat *acne inversa* for many years. In this form of acne, however, efficiency is valued differently. Isotretinoin is the most frequently introduced medication. It was also used in the case of our patient, but the therapy is hard to evaluate, as the patient died after one month of treatment.

Boer and Nazary [17] evaluated the effectiveness and tolerance of the *acne inversa* therapy in 12 patients treated with acitretin for 9-12 months. No recurrence during 6 months was observed in 9 patients. However, permanent remission > 5 years concerned only 1 patient.

Surgical treatment is a recognized method in the therapy of inverted acne. The methodology, however, is changing, and often this form of treatment is associated with the others.

Bieniek *et al.* [19] drew attention to the effectiveness of surgical treatment of inverted acne. During 10 years surgical treatment was used in 57 patients. In over 77% of the patients, a good therapeutical effect was achieved. Complete resolution of lesions in the 2-year period of observation was achieved in almost 60% of the patients treated. The effect of the treatment was influenced by the duration of the disease and the number of occupied areas of the body. Walls *et al.* [20] presented a 46-year-old patient, in whom a good therapeutic effect was achieved by the use of negative pressure wound dressings, both before and after the surgery.

Ozdemir *et al.* [21], for a change, used with good effect a hyperbaric chamber in the postoperative treatment of lesions in the course of inverted acne. In recent years, research on inflammatory aetiology of inverted acne and *pyoderma gangrenosum* led to an attempt to introduce biological treatment in these patients. It is, however, the so-called "off-label" use. Reddick *et al.* [2] have described a good effect of treatment of co-existing *pyoderma gangrenosum* and inverted acne, with the use of adalimumab (monoclonal antibody against the TNF- α) in the patient, in whom there was no observed improvement after the infliximab therapy (medication of the same

group). Poulin [22] achieved a full remission of *acne inversa* for a period of 24 months, after an infliximab therapy, in a 25-year-old patient, in whom etanercept (TNF- α receptor protein) treatment did not bring benefits. Moschella [23] successfully applied infliximab in 3 cases of inverted acne, and in 1 case of co-existence of *pyoderma gangrenosum* and *acne inversa*. In 1 case, infliximab was used before surgical treatment of inverted acne.

Recently, the social stigma of patients with inverted acne has also become a subject of interest. In all the communication, a significant reduction in the quality of life of those patients and the frequent need for additional psychological support is highlighted. Esmann and Jemec [24] evaluated the quality of life (interpersonal relationships, emotional responses to odour of the skin lesions, the feeling of lack of control of the disease) in 12 patients with *acne inversa*. A significant deterioration of the quality of life and stigmatisation of this group of patients was demonstrated. Matusiak *et al.* [25] also studied the psychological aspects of *acne inversa*.

The study was conducted through questionnaires, in a group of 54 patients with an active, stable disease process. Similarly, as in other reports, a significant negative impact of the disease on the patients' quality of life was observed.

The patient described by us died as a result of a severe complication of long-term *acne inversa* and *pyoderma gangrenosum* lesions, being the sepsis. In the references, we did not find any communication describing an after-effect of such type. However, the cases presented refer to the emergence of tumours on the ground of long-term skin lesions.

Vogelaar and Willems [26] described a case of a 42-year-old woman with long-term history of inverted acne in the area of armpits, in whom squamous cell carcinoma developed on the ground of the disease lesions. Grewal *et al.* [27] also presented 3 cases of the development of squamous cell carcinoma in patients with *acne inversa* (the so called "Marjolin ulcer"). The lesions also involved the area of armpits. In the patient of Obredor *et al.* [28], squamous cell carcinoma developed on the ground of long-term inverted acne, localised in the perianal area.

We have presented the case of co-existence of the severe forms of inverted acne and *pyoderma gangrenosum*, which ended in death of the patient in the course of sepsis and multiple organ failure, despite many years of therapy. It should be noted that at present we know much more about the aetiology of both disorders, than we knew when we treated the patient, which allows for the use of other methods of therapy, such as biological medications, in this group of patients.

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