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Case report
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Fatal outcome of Pyoderma gangrenosum with multiple organ involvement and partially responding to Infliximab

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Abstract: Pyoderma gangrenosum is an inflammatory dermatosis of uncertain etiology, often associated with chronic inflammatory bowel or rheumatoid disease. It predominantly affects the skin. A systemic organ involvement caused by aseptic neutrophilic abscesses, however, fundamentally influences the prognosis.

A patient with idiopathic pyoderma gangrenosum insufficiently responded to a conventional immune suppressive therapy and the disease proceeded aggressively. During treatment with Infliximab, partial remission was achieved intermediately. However, a recurring endocarditis, led to a lethal outcome of this patient.

Keywords: Pyoderma gangrenosum, extracutaneous manifestation, cardiac involvement, Infliximab

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1 History

A 14-year-old adolescent developed pharyngeal ulcerations succeeded by a painful, ulcerating tonsillitis for the first time in 1995. The histologic feature following tonsillectomy only showed non–specific inflammation. There were no signs of an underlying bacterial, vasculitis or malignant disease. Since 1996 he has developed ulcerations on both lower legs (Figure 1) and in the gluteale region (Figure 3). Repeated microbial swabs were negative. Further diagnostics excluded a primary disease (especially hypogammaglobulinaemia, a disturbed function of granulocytes, Hyper-IgE syndrome or leukocyte adhesion deficiency type II) as well as a secondary immune defect (e.g. HIV). Morbus Crohn could also be excluded following endoscopic biopsy.

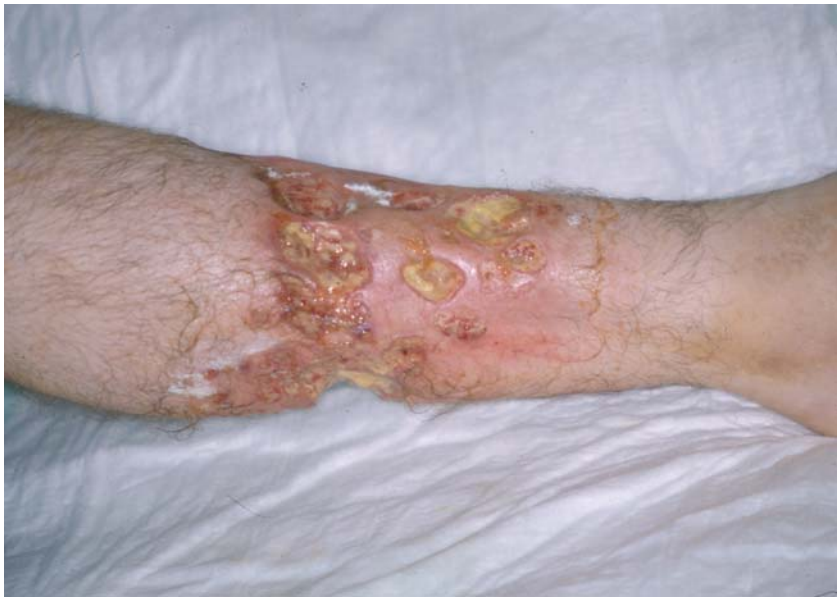

Fig. 1 Ulcerations due to pyoderma gangrenosum of our patient lower left leg (picture performed in April 1998).

The typical clinical course of the disease, positive Pathergy testing and the histology of vasculitis affecting the medium-sized arterioles supported the diagnosis of pyoderma gangrenosum.

Initially a prednisolone pulse therapy (100mg/1x per day) was administered inducing a swift yet only partial remission. However, a dose diminution to 40 mg of prednisolone was soon followed by a relapse. Prednisolone therapy was then combined with Mucophenolate mofetil (2g daily), which also only led to a partial remission. Between 1998 and 2001 weight-adapted therapies with Methotrexate, Ciclosporine, Sulfasalazine and Cylophosphamide showed only short-term effects and were followed by severe relapses.

After an alternative repeated treatment with high doses of immunoglobulines (up to 400 mg/kg body weight over five days) the pharyngeal ulcerations healed though the cutaneous lesions did not.

Further severe relapses, affecting almost entirely both lower legs and feet, led to an

increasing functional loss of the lower extremities. At the same time the patient developed multiple septic temperatures with a positive blood culture (Enterococcus faecalis). These were treated with a systemic antibiotic therapy (Ampicilline, Imipenem) and accompanied by severe serological inflammation parameters (leucocytes 72 Gpt/l, C-reactive protein 335,4 mg/l). We could further exclude a hematooncological systemic disease.

Ultrasound and computer tomography (Figure 2) showed multiple, partly confluating abscesses throughout the spleen (with a size of up to 16x17cm). Additionally a pleural effusion on the left side was diagnosed. The transthoracic echocardiography, on the other hand, was inconspicuous. Treatment was continued with drainage of the spleen abscesses. A microbial pathogen could not be identified. At the same time the systemic therapy was switched to Tacrolimus (up to 8mg daily). The patient also suffered from a decreasing hearing capacity on one and later on both sides in the course of an acute hearing loss. The following treatment with Pentoxyphylline led to a slight improvement only.

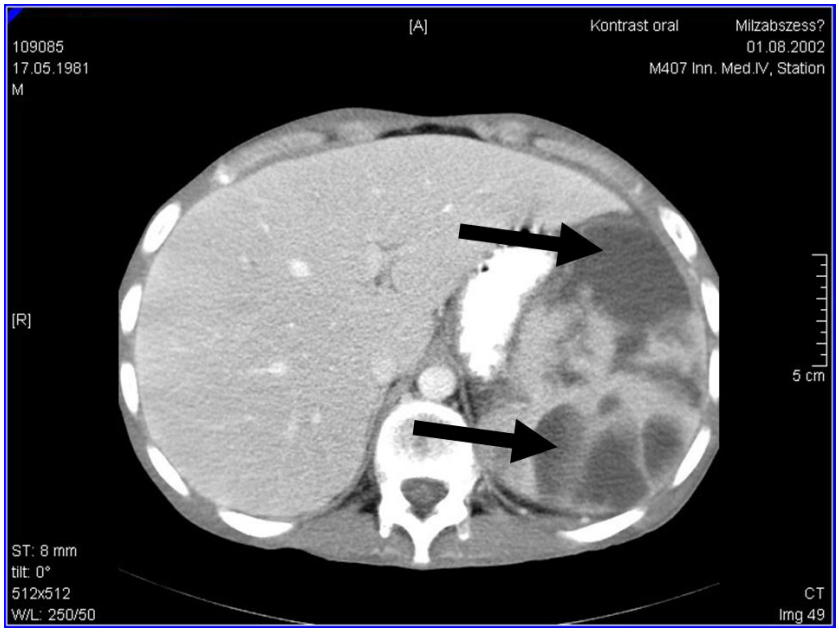

Fig. 2 Spleen abscesses in computer tomography (performed in August 2002).

Despite the elevated serological inflammation parameters (leucocytes 25 Gpt/l, C-reactive protein 150 mg/l), no evidence signalling an underlying systemic disease was detectable except the incomplete unfolding of the intestine with wall disturbances of the terminal ileum, which could be verified in the radiograph of the small intestine performed by Sellink Technique. The biopsies obtained during enteroscopy and gastroscopy were inconspicuous thus a chronic inflammatory bowel disease could not be verified.

Given the continued poor response to the immunosuppressive therapy, anti-TNF alpha treatment with Infliximab (3mg/kg body weight) was indicated.

The week after the induction of therapy the spleen abscesses showed regression. After another four weeks they were no longer observable by ultrasound, leukocyte count was normal and the C-reactive protein level decreased to 85 mg/l. The general condition had

improved considerably during the following three months and the cutaneous ulcerations had healed to a great extent (Figure 4).

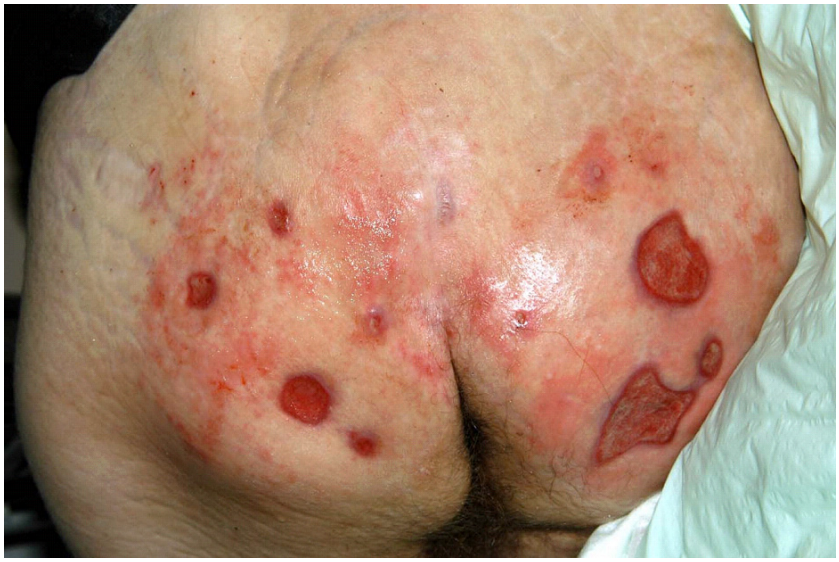

Fig. 3 Gluteal ulcerations of our patient before anti TNF alpha therapy (picture performed in July 2002).

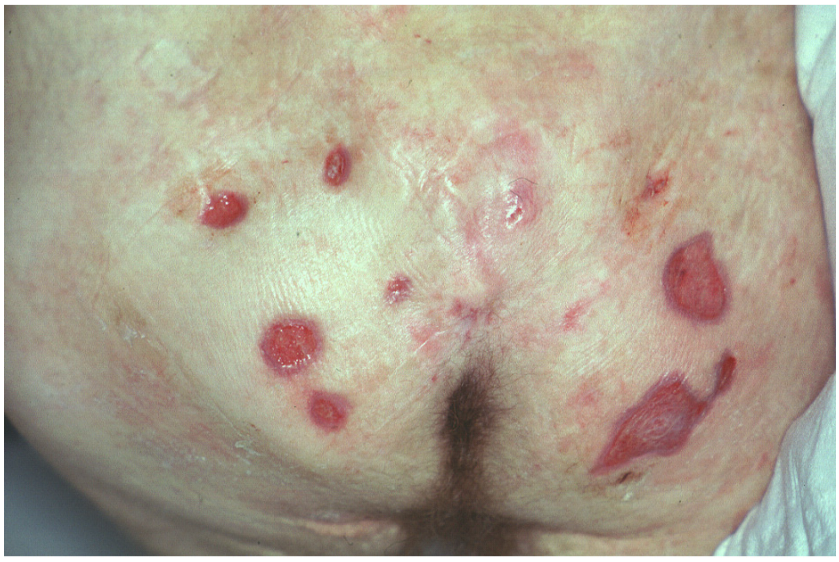

Fig. 4 Amelioration of gluteal abscesses after two months treatment with anti TNF alpha therapy (picture performed in September 2002).

However, five months after the start of the anti-TNF alpha treatment, the patient developed an acute endocarditis accompanied by severe aortic and moderately severe mitralis insufficiency. Therapy with Infliximab was interrupted and an antibiotic treatment with Piperacilline/Tazobactam was initiated. The destroyed aortic valve was replaced by a homograft. Histological investigations showed a bacterial infection of the cardiac valves.

Thus a preceding damage of the endocardium in the course of pyoderma gangrenosum could not be excluded.

After another two months and a temporary remission, the patient was hospitalized with acute dyspnoea. An extreme tricuspidal and aortic valve insufficiency was diagnosed. The histological picture of a bacterial endocarditis was the same as in the first histology. Following reimplantation and uncomplicated wound healing, the Infliximab therapy could be started again with 2 mg/kg body-weight after a six-month interruption.

During a routine investigation of the almost asymptomatic patient, another relapsing endocarditis of the aortic valve as well as an accompanying parasternal sterile abscess was diagnosed. Moreover, an aneurysm spurium of the ascending aorta was diagnosed via computer tomography. With the intention to initiate a third valve reconstruction and surgical treatment of the abscess and the complicating aortic aneurysma, the patient was transferred to the German Heart Centre Berlin. Shortly after hospitalisation the patient complained of increasing retrosternal pain. Echocardiography showed a severely restricted leftventricularly ejection fraction (20%). A new left bundle-branch block appeared on the ECG and troponin was increased up to 11 ng/ml. The patient needed cardio-pulmonal reanimation which did not achieve success.

A post-mortem examination showed the properly implanted homograft prosthesis of the aortic valve, altered by a massive verrucous and polypous thrombo-endocarditis. There were several subvalvular abscesses in the myocardium, the size of which was up to 15mm. The inflammation process secondarily involved the surrounding soft tissue, including the proximal third of the right coronary artery without any indication of a bacterial inflammation. Furthermore, a 10 mm perforation of the ascending aorta was detected.

2 Discussion

Pyoderma gangrenosum is characterized by predominantly involving the skin. However, the prognosis of this disease essentially depends on underlying diseases and manifestations of internal organs [1]. Despite multiple, intensive and substantial diagnostic exploration neither a chronic inflammatory bowel disease nor a hematooncological, immunological or rheumatoid disease could be determined in our patient.

Systemic involvement affects the lung most frequently. A work-up on extracutaneous manifestations of neutrophile diseases (Sweets syndrome, pyoderma gangrenosum, subcorneal pustular dermatosis, erythema elevatum diutinum) revealed suspicious radiographs in each of the 21 evaluated patients. Neutrophile infiltration in six out of seven patients undergoing lung biopsy could be proved. The infiltrations were resistant to antibiotics and disappeared after immunosuppressive therapy. Some patients suffering from pyoderma gangrenosum have died due to the involvement of their lungs [2]. Or patients intermediately showed a pleural effusion, which reduced after the Infliximab therapy.

Simultaneously, in our case sterile spleen abscesses appeared for the first time after about four years and responded to an Infliximab therapy. Such sterile spleen abscesses

were also diagnosed in a patient suffering from chronic myeloic-monocytic leukaemia. In this case the spleen and liver abscesses preceded typical skin lesions for weeks and complicated the diagnosis [3]. Several other patients suffering from pyoderma gangrenosum with spleen and liver involvement were reported [4]. One patient with spleen and psoas abscesses due to pyoderma gangrenosum was successfully treated with Adalimumab and Infliximab [5] .

Moreover, the abscesses in the myocardium confirmed by autopsy have to be seen into the context of pyoderma gangrenosum as well. There were no pathogens identifiable from the abscesses and the surrounding tissue. Histological, the endocarditis showed a morphological picture compatible with bacterial endocarditis. However, the alterations could have been alternatively a result of an organ manifestation of pyoderma gangrenosum with a secondary bacterial infection. During the repeated endocarditis no bacteria could be detected in the blood culture. Cardiac involvement in pyoderma gangrenosum is rare [6].

The aggressive and unusual course of pyoderma gangrenosum in our patient is emphasized by a prominent involvement of the mucous membrane of the oral cavity and the upper parts of the oesophagus. Wegener's disease could be excluded several times. There exist different reports describing patients with prominent oral and nasal manifestation on the mucosa as well as the larynx [7, 8] .

Treatment of pyodema gangrenosum focuses on the systemic application of corticosteroid in connection with immunosuppressiva (e.g. Methotrexate, Ciclosporine, Azathioprine). A new treatment option arises from developing specific antibodies. Infliximab is a chimeric (human/mouse), monoclonal antibody against TNF alpha, consisting of a consistent human and a variable murine IgG-region. The antibody binds to soluble TNF-alpha and blocks membranous localized cytokines. During therapy of pyoderma gangrenosum, Infliximab was most effective if Crohn's disease was diagnosed at the same time. Here, Infliximab also positively influenced the accompanying pyoderma gangrenosum positively [9]. In a recent publication 13 patients with inflammatory bowel disease and simultaneous pyoderma gangrenosum were treated with Infliximab [10]. All patients had a benefit from the therapy as the skin lesions completely healed.

In our patient an inflammatory bowel disease could not be proved. After exhausting all established therapy regimen and due to the severe progression, we opted for a therapy with Infliximab. This led to an impressive improvement of the cutaneous and visceral manifestations of the pyoderma gangrenosum. However, the lethal outcome has to be seen in the context of a long standing severe clinical picture of numerous preceding therapies in case of an extremely aggressive form of pyoderma gangrenosum. From our point of view a therapy with Infliximab presents a good alternative for treating therapy-resistant idiopathic pyoderma gangrenosum.

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