Pyoderma gangrenosum in a patient with common variable primary immunodeficiency

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Abstract
Pyoderma gangrenosum is a rare inflammatory skin condition that is associated with systemic inflammatory diseases. It is characterised by the presence of well-secluded, painful ulcerations, often located on the lower limbs. Similarly as in the case of acne inversa, patients’ markers of the inflammatory process are elevated; including OB, C-reactive protein and leukocytosis. The aetiology takes into account an over-reactive inflammatory response to various factors (presence of the so-called pathergy symptom). Common variable primary immunodeficiency (CVID) is a disease that is rather often recognized and affects about 1/10,000-100,000 individuals. It is a heterogeneous group of disorders of combined B-and T-cell dysfunction. The case is described of a 22-year-old man with pyoderma gangrenosum that coexisted with CVID.

Key words: pyoderma gangrenosum, immunodeficiency, inflammation.

Introduction
Pyoderma gangrenosum is a chronic disease with inflammatory aetiology. It is believed that the role here is played by the dysregulation of the patient’s immune system and the production of pro-inflammatory cytokines, mainly tumor necrosis factor-α (TNF-α) and interleukin 8, 16, and IL-1β (IL-8, IL-16 and IL-1β) [1, 2].

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 inversa, patients’ markers of the inflammatory process are elevated; including OB, C-reactive protein and leukocytosis. The aetiology takes into account an over-reactive inflammatory response to various factors (presence of the so-called pathergy symptom). However, the relationship with an underlying disease is most often described: inflammatory bowel diseases (mainly Crohn’s disease), liver diseases (HCV, immune hepatitis), rheumatic and hematologic diseases (monoclonal gammopathies, leukaemias). There are also reports of 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 [3].

Common variable primary immunodeficiency (CVID) is a disease that is rather often recognized and affects about 1/10,000-100,000 individuals. It is a heterogeneous group of disorders of combined B-and T-cell dysfunction. Some cases could be asymptomatic, but in most patients severe clinical manifestations occur, such as recurrent sinusitis, recurrent pneumonia, bronchiectasis, lymphadenopathy and an increased lifetime risk of lymphoma and autoimmune disease. For diagnosis, marked reduction in serum levels of IgG (or IgG subclasses) +/-IgA deficiency is typical. Approximately 50% of patients have also associated IgM deficiency. In treatment, the replacement therapy with intravenous immunoglobulin every 3-4 weeks is used [4].

The cases of pyoderma gangrenosum that coexist with immunodeficiency are relatively seldom presented.

Case report
The patient is 22 years old. The first skin lesions in the form of a quickly spreading peripherally ulcer on the left lower leg occurred a year ago. Since he was one, the patient has been under control of the Department of Allergology and Immunology due to recognised common primary variable immunodeficiency. He has also suffered from recurrent infection of the upper and lower respiratory tract. Recur-
rent sinusitis and bronchiectasis were also diagnosed. In treatment, replacement therapy with intravenous immuno
globulin every 3-4 weeks has been used. The patient also
took antibiotics several times. The patient did not take any
medication permanently for any other reasons, and did not
suffer from other chronic diseases. In the family history,
no immunodeficiency was diagnosed.

In 2011, 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, his-
tiocytes and giant cells were found. The whole picture was
not diagnostic.

At that time the patient was treated in the outpatient
clinic. It was only local treatment. Because of no improve-
ment and massive overgrowth of the granuIatio that could
suggest neoplastic transformation, the man was referred to
the Department of Dermatology, Silesian Medical Uni-
versity.

On admission there was an ulcer on the left lower leg.
On the medial posterior surface of the left lower leg there
was an oval ulcer of 10 cm × 15 cm, with undermined rolled
edges and the bottom covered with large amounts of puru-
1ent secretions, necrotic tissues and granulatio. The skin sur-
rounding the whole ulcer was red, very warm, with features
of inflammation. Peripheral lymph nodes were not enlarged.
Mucous membranes were free from lesions (Figure 1).

Laboratory tests: ESR 35, CRP 11.3, WBC 10.9, glucose,
full blood count, electrolytes, AST, ALT, GGTP, bilirubin, cre-
atinine, urea, general urine test, electrophoresis, CPK,
aldolase, Latex – R, Waaler-Rose’s reaction were normal.
Protein of the complement: C3 172 mg/dl (N), C4 – 61 mg/dl
(10-40), IgA – 6 mg/dl (70-400), IgG – 655 mg/dl (700-1600),
IgM – 13 mg/dl (40-230). Tumour markers: CEA, CA 125, total
PSA were within the norm. Imaging: X-ray of the chest, left
lower leg, ultrasonography of the abdomen were normal.

Mycology – negative. Histology – an edge of the ulcer – pyo-
derma gangrenosum. Proliferatio reactiva epithelli plani; the
bottom of the lesion – necrosis et granulatio. Vasculitis.

Immunological consultation – without contraindication to
cyclosporine, but this kind of therapy needs higher dos-
es. Because of the result of immunological consultation and fast improvement of the local stage, we stopped using cyclosporine. After his local and general symptoms improved, the patient was trans-
ferrred to the Department of Allergology and Immunology
in order to continue treatment with immunoglobulin. Der-
matological treatment is continued at the Outpatient Clin-
ic of Dermatology, where healing of the ulcer is observed
and the dose of methylprednisolone is slowly tapered.

Discussion

The aetiology of pyoderma gangrenosum is unclear. It
is believed that dysregulation of the patient’s immune sys-
tem plays a role here and that is why it could coexist with
the immunology diseases. However, the cases associated
with immunodeficiency (especially congenital) are relatively
rarely described in the literature [5]. The relationship with
an underlying disease is most often described: inflam-
matory bowel diseases (mainly Crohn’s disease), liver dis-
eses (HCV, immune hepatitis), rheumatic and hematologic
diseases (monoclonal gammapathies, leukaemias) [1, 6].

Therapy of pyoderma gangrenosum, regardless of its
aetiology, is difficult. In treatment we can use general glu-
corticosteroids, dapsone, clofazimine, cyclosporine A,
tacrolimus, mycophenolate mofetil, intravenous immu-
oglobulin, anti-TNF inhibitors and monoclonal antibod-
ies [1]. The therapy of our patient, because of his basic dis-
 ease, had some limitations.

Neiderer et al. [7] presented a 76-year-old male patient
with a history of rheumatoid arthritis and recalcitrant pyo-
derma gangrenosum. After 9 months of treatment with
local wound care, steroids, and topical tacrolimus, the
wound had increased in size. At that time, he was on a reg-
imen of five applications of a bioengineered cell-based pro-
duct with twice-weekly mechanically powered negative
pressure device changes and 40 mg of prednison. The
wound was completely healed after 16 weeks. Also Frac-
calvieri et al. [8] described a good medical result of treat-
ment of pyoderma gangrenosum with a negative pressure
device.

Andrisani et al. [10] suggest the efficacy of infliximab
(inhibitor TNF-α) in the treatment of pyoderma gangre-
nosum in the case of a patient with ulcerative colitis and
an ulcer localized on the left breast. Also in a patient of Moo-
ji et al. [11] pyoderma gangrenosum was treated with inflix-
imab with good results. Biological treatment (etanercept) was also used by Kim et al. [12].

Pyoderma gangrenosum could often be difficult to diag-
nose and could be suspected of neoplastic changes. Spinocellular carcinoma was also suggested in the case described by us. However, histopathological examination confirmed the diagnosis of pyoderma gangrenosum.

Wolfe et al. [13] described a case of atypical pyoderma gangrenosum of the dorsal hand in a patient who presented with the histopathologic and clinical diagnosis of squamous cell carcinoma (SCC). Atypical pyoderma gangrenosum is a rare variant of pyoderma gangrenosum that occurs on the upper extremities, presenting as a cutaneous ulcer. The correct treatment is nonsurgical, and surgical intervention often results in trauma-induced expansion of lesions.

As mentioned, the cases of pyoderma gangrenosum that coexist with immunodeficiency are relatively seldom presented. More often some patients with HIV are pre-

presented. Miksimovic et al. [14] presented a 53-year-old male treated since 1989 for HIV infection who had been pre-

senting two neutrophilic diseases, that could be connected with immunodeficiency: erythema elevatum diutium and pyoderma gangrenosum. Kreuter et al. [15] described a pa-

ient with pyoderma gangrenosum and psoriasis also in the course of HIV infection.

Since he was one, our patient has been under control of the Department of Allergology and Immunology because of recognised primary variable immunodeficiency. However, in treatment, replacement therapy with intravenous immu-

noglobulin every 3-4 weeks is used in our patient, and we observed progression of skin changes. Differently from the patient of Nord et al. [16] – a 31-year-old Caucasian male with leukocyte adhesion deficiency type I and a 20-year history of pyoderma gangrenosum, where upon completion of six courses of intravenous immunoglobulin, ulcerations had nearly healed for the first time in a decade.

Hinzé et al. [17] reported an 11-year-old boy with a leu-

kocyte adhesion deficiency type 1 and longstanding history of recurrent pyoderma gangrenosum. This article empha-

sizes the importance of considering immunodeficiencies in the differential diagnosis of patients with recurrent skin ulcers. Ellenberg et al. [18] presented a patient with pyoder-

ma gangrenosum after bone marrow transplantation for leukocyte adhesion deficiency type 1. Bedlow et al. [19] described a 5-year-old girl with a history of recurrent bac-

terial infections since early childhood who developed necrotic skin ulcers – pyoderma gangrenosum and a per-
sistent circulating neutrophilia. Histologically, the lesions showed deep ulceration with a diffuse lymphohistiocytic infiltrate, but with a relative scarcity of neutrophils. Sub-

sequent investigation revealed a complete absence of CD11a/CD18 beta 2 integrins on the surface of the patient’s neutrophils, confirming the diagnosis of LAD type 1.

Paller et al. [20] presented two children with congeni-
tal immunodeficiency in whom pyoderma gangrenosum developed. In a 60-year-old patient of Carsuzaa et al. [21] with a history of low IgA gammopathy, pyoderma gan-

grenosum developed on both knees, following vesiculob-

ullous lesions. Similarly, Choulou and Saint Martin [22] described pyoderma gangrenosum in a patient with low IgA syndrome.

In a bit older references, Sánchez Yus et al. [23] showed a case of pyoderma gangrenosum with myeloma IgA lambda and deficiency of cellular immunity and Bar-

rièr et al. [24] presented a child with congenital hypogam-

maglobulinemia and pyoderma gangrenosum.

We have presented a case of co-existence of primary variable immunodeficiency and pyoderma gangrenosum, which despite typical history, was not recognized for more than a year. In our patient, despite difficulties with ther-

apy, we reached improvement of skin changes and prob-
ably it would be completely cured.

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