

Pyoderma Gangrenosum after Bone Marrow Transplantation for Leukocyte Adhesion Deficiency Type 1

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Leukocyte adhesion deficiency type 1 is a rare congenital defect in beta-2 integrins resulting in abnormal leukocyte migration [1]. This rare autosomal recessive condition was first described in 1980 and the mutation is found on chromosome 21q22.3 [2] (genetic testing is available). Paucity or absence of CD11/CD18 neutrophils by flow cytometry is diagnostic. If less than 1% of neutrophils have CD11/CD18 markers, the prognosis is poor; the average life span is 10 years. The only known therapy is bone marrow transplantation.

Pyoderma gangrenosum, first described in 1930 [3], is an uncommon ulcerative cutaneous lesion of uncertain

etiology. It has been associated with systemic disease in at least 50% of patients. To date, few cases of PG and LAD-1 have been reported [4,5], while the combination of PG and recurrent LAD-1 has not been described. We present, to the best of our knowledge, the first such case.

PATIENT DESCRIPTION

A 14 year old girl was admitted with a necrotic lesion of the left thigh. Her medical history revealed that at age 12 months she underwent successful allogeneic (haploidentical, from her father) bone marrow transplantation for LAD-1. Until one year prior to the present admission she had been completely healthy. During the previous year she suffered recurrent painful lesions on her legs; these were treated successfully with topical therapy comprising a combination of antibiotics, antimycotics and steroids. Pyoderma gangrenosum was ultimately diagnosed clinically and later confirmed by biopsy. No family member or close contact had a similar problem.

On physical examination she was not in distress. Her vital signs were normal. A painful, ulcerated nodule 3 cm in diameter [Figure A], with violaceous undermined borders was present on her left thigh. A similar, smaller nodule with a central ulcer was located on her forehead. The rest of her physical examination was within normal limits.

Laboratory studies revealed white blood cells $16 \times 10^3/\text{mm}^3$ with polymorphonuclears 81%, 13% lymphocytes, hemoglobin 10.3 g/dl and platelets $247 \times 10^3/\text{mm}^3$. Blood chemistry results were entirely within normal limits.

She was treated with intravenous cloxacillin for 5 days, but there was no improvement in her condition. Biopsy of the lesion revealed a necrotic inflammatory lesion characterized by small blood vessels with fibrinoid deposits and a perivascular infiltrate composed of lymphocytes, few neutrophils and nuclear dust, supporting the diagnosis of pyoderma gangrenosum. Bacterial and fungal cultures were negative. Flow cytometry revealed 1% CD11/CD18 neutrophils. The reappearance of LAD-1 was diagnosed. A repeat bone marrow transplantation was performed and she is currently doing well.

COMMENT

Leukocyte adhesion deficiency type 1 is a rare congenital defect of leukocyte migration [1]. Clinical presentation includes delayed separation of the umbilical cord for > 1 month, leukocytosis, periodontitis and early loss of primary and then secondary teeth, and recurrent infections of the skin, gastrointestinal tract, genitalia and respiratory tract by enteric gram negative bacteria – *Staphylococcus aureus*, *Candida* and *Aspergillus* spp. Skin lesions heal slowly and are characterized by a paucity of leukocytes. Diagnosis is obtained by flow cytometry, which shows lack or paucity of CD11/CD18

Ulcerated nodule 3 cm in diameter on the left thigh



PG = pyoderma gangrenosum

LAD-1 = leukocyte adhesion deficiency type 1

neutrophils. Confirmation by genetic testing is available.

If less than 1% of neutrophils display CD11/CD18 markers, the prognosis is poor, with an average life span of 10 years. If the CD11/CD18 markers are positive in 1–10% of polymorphonuclear leukocytes, the approximate life span is 40 years [5]. Treatment includes bone marrow transplantation for severe deficiency, prophylactic antibiotics, usually with trimethoprim-sulfamethoxazole, and broad-spectrum antibiotics for significant acute infections.

Pyoderma gangrenosum is an uncommon ulcerative cutaneous disease of uncertain etiology. It is commonly associated with inflammatory bowel disease [3] (either ulcerative colitis or Crohn's disease), polyarthritis that is usually symmetric (either seronegative or seropositive), and hematological disorders (such as leukemia or preleukemic states, predominantly myelocytic or monoclonal gammopathies, primarily immunoglobulin A). Less common associations include other forms of arthritis (such as psoriatic, osteoarthritis, or spondyloarthropathy), hepatic diseases (including hepatitis and primary biliary cirrhosis), and immunological diseases (such as lupus erythematosus and Sjögren syndrome).

Diagnosis is based on clinical and histological findings after ruling out infec-

tious etiologies. The main typical histological findings are edema, superficial perivascular lymphocytic infiltration, and massive deep dermal neutrophilic infiltration, necrosis, hemorrhage, and abscess formation. In addition, thrombosis of small and medium sized vessels may be seen.

Treatments for pyoderma gangrenosum are topical or systemic. Topical treatments include corticosteroids, cromolyn sodium 2% solution, and tacrolimus. Systemic treatment includes corticosteroids, cyclosporine, mycophenolate mofetil, azathioprine, dapsone, tacrolimus, cyclophosphamide, chlorambucil, thalidomide, tumor necrosis factor-alpha inhibitors, and nicotine [3].

The lesions that appeared during the year prior to re-diagnosis were either PG or skin infections, since they resolved spontaneously or following administration of topical antibiotics and steroid therapy. Most probably, PG was the first sign of recurrent LAD-1.

PG is a known phenomenon in autoimmune and other inflammatory conditions. It may be an indicator of severe decline of CD11/CD18 neutrophils. A review of the English-language medical literature yielded only a few case reports of PG with LAD-1 [4,5]. Recurrence of LAD-1 after bone marrow transplantation has not been described before. It

may be due to remaining native leukocytes deficient in CD11/CD18 that proliferated over time while transplanted leukocytes from the patient's father declined; the leukocytes were later confirmed on flow cytometry as having only 1% positive CD11/CD18. The occurrence of PG in a patient after bone marrow transplantation for LAD-1 may be an indication for reevaluation and may suggest the reappearance of LAD-1.

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