Netherlands
The Journal of Medicine

CASE REPORT

Successful treatment of myelodysplastic syndrome-induced pyoderma gangrenosum

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ABSTRACT

We report successful treatment of a refractory myelodysplastic syndrome-associated pyoderma gangrenosum with the combination of thalidomide and interferon-α2a in a single patient. A non-healing wound developed on a 40-year-old woman's left thumb after minor trauma. Massive ulcerovegetative lesions developed after reconstruction surgery. Histopathological examination of the bone marrow and cytogenetic studies revealed an atypical myeloproliferative/myelodysplastic syndrome. The skin lesions resolved dramatically after two months of thalidomide and interferon-α2a combination therapy and the haematological status improved.

KEYWORDS

Melodysplastic syndrome, pyoderma gangrenosum, thalidomide, trisomy 8

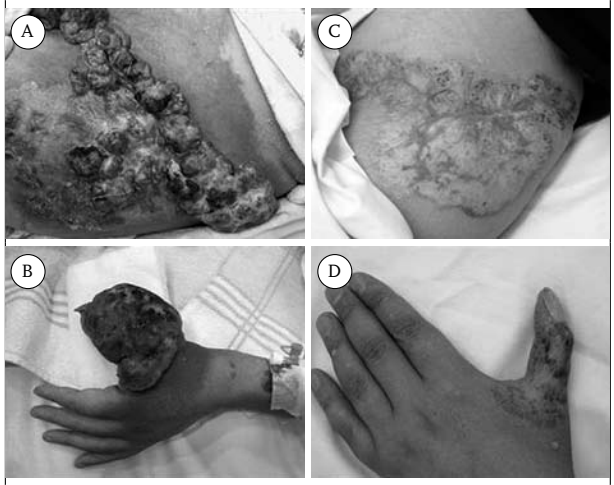
INTRODUCTION

Pyoderma gangrenosum is a painful, noninfectious, ulcerovegetative skin disorder which may be associated with myelodysplastic syndromes (MDS).[1] Angiogenesis and immunobiological abnormalities are among the key events sticking the pathological pieces of MDS and pyoderma gangrenosum together.[1-3] Clinical management of both pyoderma gangrenosum and MDS represents a great challenge.[1,4-5] We report here the successful treatment of a refractory MDS-associated pyoderma gangrenosum with the combination of thalidomide and interferon-α2a in a single patient. This combination of antiangiogenic, immunosuppressive, and biological response modifier drugs resulted in the resolution of massive ulcerovegetative lesions of pyoderma gangrenosum and the dyshaematopoiesis and cytopenias of MDS.

CASE REPORT

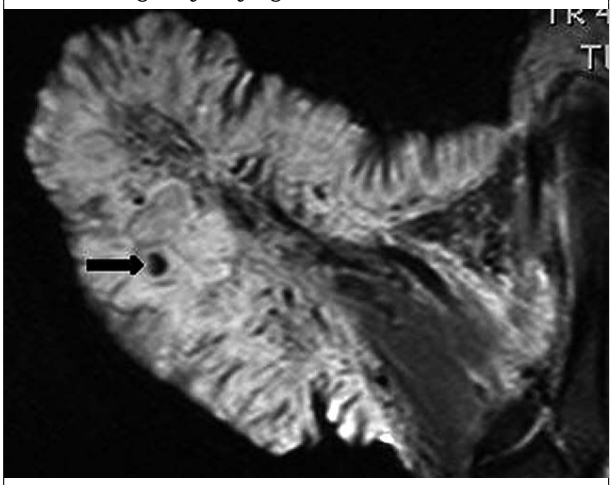
A 40-year-old woman with documented antiphospholipid syndrome (APS) associated with a history of recurrent abortions was admitted to a rural hospital complaining of non-healing wounds. Three months before the admission, she had sustained a minor knife cut on her left thumb which had not healed. A graft from her left inguinal region was implanted to the wound on her hand in the rural hospital. After the surgery, massive ulcerovegetative lesions developed both in the graft region and on her thumb. She was then admitted to the Department of Plastic Surgery in our hospital. During this admission, her left thumb and left inguinal region were oedematous with numerous verrucous papules and purulent discharge (*figure 1*). The lesions, which were compatible with pyoderma gangrenosum, were situated from the pubis to the anterior iliac spine. Magnetic resonance imaging revealed a villous hyperintense lesion surrounding the first finger (*figure 2*). Multiple biopsies were taken from the lesions and anti-infective therapy with amoxicillin/clavulonic acid was started as her body temperature was over 38.7°C. Biopsy of the lesion demonstrated multiple pyogenic granulomas.
Haematological laboratory investigations revealed leukemoid reaction and normochromic normocytic anaemia (white blood cells (WBC) 58,000/mm^3, haemoglobin 7.0 g/dl and peripheral blood smear: 20% promyelocytes, 8% myelocytes, 12% band, 60% polymorphonuclear leucocytes with normal erythrocyte morphology and platelets). The leucocyte alkaline phosphatase (LAP) score was increased. Bone marrow aspirate was hypercellular and morphological analysis disclosed

Figure 1. *Lesions before and after treatment*



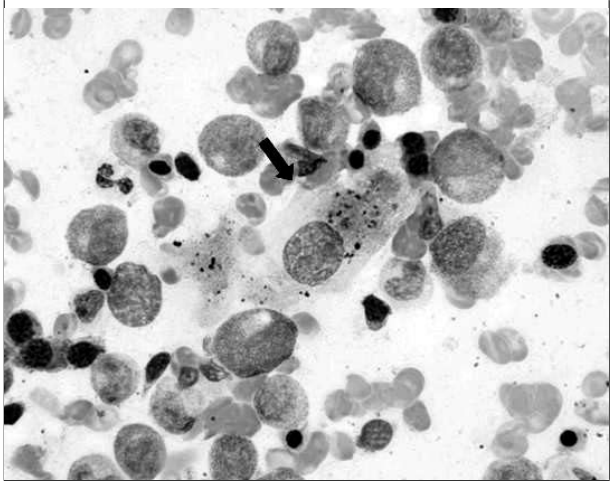
Verrucous papules with purulent discharge on inguinal region (A) and the oedematous left thumb with a similar lesion on admission (C). Marked improvement of lesions on the inguinal region (B) and on her left thumb after treatment with IFN and thalidomide (D).

Figure 2. *Coronal T2 weighted image with fat saturation reveals a villous hyperintense lesion surrounding the first finger*



The lesion demonstrates low intensity foci representing flow void.

Figure 3. *Bone marrow aspirate showing sea-blue histiocytes (arrow) and dysplastic changes in erythroid precursors*



prominently increased atypical hypergranular promyelocytes (42%) with granulocytic hyperplasia, dysplastic suppressed erythropoiesis, and increased atypical megakaryocytes. A small number of sea-blue histiocytes were also seen (*figure 3*). On the histopathological examination of the bone marrow biopsy, increments in the myeloid/erythroid ratio (8/1), reticulin fibres, megakaryocytes and iron store were noted. Cytogenetic studies revealed clonal trisomy 8 abnormality. All of those findings were found to be compatible with an atypical myeloproliferative/myelodysplastic syndrome presenting as a leukemoid reaction in the presence of pyoderma gangrenosum. During her follow-up, deep vein thrombosis also developed in her left superficial femoral and popliteal vein, which was successfully treated with low-molecular-weight heparin.

High-dose intravenous methylprednisolone as a 1 gram pulse and oral prednisone 60 mg/day was started for the treatment of pyoderma gangrenosum and MDS. *E. coli, K. pneumonia* and *E. feacalis* were isolated from the wound cultures. Bacterial infections were controlled with amikacin and imipenem treatments. After the steroid therapy, haemoglobin values reached 10 g/dl without transfusion. Erythrocyte sedimentation rate decreased from 143 mm/h to 34 mm/h. WBC counts were between 5000/mm^3 and 11,000/mm^3 but no marked improvement in the lesions could be achieved.

The patient underwent palliative surgery one month after admission for lesions in the left inguinal region. However, the operation failed to be completed because of bleeding from the giant vegetative lesions. Postoperative interferon-α2a was initiated at a dose of 5 MU/day as a biological response modifier. However, no improvement in the lesions was evident. Thalidomide was started at the dose of 200 mg/day as an antiangiogenic drug three weeks later. The steroid dosage was reduced slowly and discontinued in four weeks. The massive ulcerovegetative skin lesions resolved dramatically after four months of interferon-α2a plus thalidomide combination therapy (*figure 1*), and the haematological status of the patient improved (WBC 8500/mm^3, haemoglobin 12.8 g/dl, platelets 125,000/mm^3 and peripheral blood smear findings consistent with dysplastic changes especially in granulocytes). Thalidomide was withdrawn after 14 months following the healing of all the lesions with scarring.

DISCUSSION

In this report, successful treatment of massive ulcerovegetative lesions of pyoderma gangrenosum and the dyshaematopoiesis and cytopenias of MDS with a combination of thalidomide and interferon-α2a was described. Neutrophilic dermatoses, including

ulcerovegetative necrotic pyoderma gangrenosum, may be associated with myelodysplasia in transition to leukaemia. The distinctive cutaneous symptoms sometimes precede MDS.[6] Pyoderma gangrenosum presented initially as a 'leukemoid reaction' in our MDS patient. Moreover, our patient also had APS, which was associated with recurrent abortions. Skin manifestations have been described in lupus anticoagulant (LA) positive patients. A report on 33 LA-positive patients indicated that three patients developed pyoderma gangrenosum-like ulcers.[7] Laboratory investigations failed to demonstrate antiphospholipid antibodies in our patient during the last clinical presentation of pyoderma gangrenosum and MDS.

The combination of antiangiogenic, immunosuppressive, and biological response modifier drugs was successful in the clinical management of our patient. There are currently no guidelines for the treatment of pyoderma gangrenosum but high-dose corticosteroids are usually the first choice.[5] Immunosuppressive drugs such as cyclosporine A, azathioprine, cyclophosphamide, chlorambucil, sulphasalazine, dapsone, minocycline, clofazamine and thalidomide are used in steroid-refractory cases, alone or in combination with steroids.[5] Autoimmune manifestations of MDS and pyoderma gangrenosum frequently respond to immunosuppressive agents and occasional haematological responses to steroid therapy have been reported in MDS.[3] Daily wound oxygenation increases collagen production by fibroblasts to support capillary angiogenesis in pyoderma gangrenosum.[8] Surgical procedures could have precipitated the generation of pyoderma gangrenosum lesions[9] as in our patient. Thalidomide is used in pyoderma gangrenosum for its antiangiogenic and anti-inflammatory effects.[5] Many successful anecdotal treatments of pyoderma gangrenosum with thalidomide have been reported.[10-12] Two of these patients had pyoderma gangrenosum associated with Behcet's disease.[10,11] Thalidomide is also effective in treating mucocutaneus lesions of Behçet's syndrome.[13] Several immunomodulatory mechanisms of action of thalidomide have been suggested, such as inhibition of TNF-α, chemotaxis of monocytes and leucocytes, and inhibition of phagocytosis by neutrophils.[14] It affects human keratinocyte viability, proliferation and migration, which is critical for the re-epithelialisation of skin wounds.[15] Thalidomide is also effective in the management of MDS.[4] Haematological improvement usually occurs after a median of two months of treatment,[4] as in our patient. It exerts heterogeneous biological effects on haematopoiesis in MDS. Some recent clinical trials have confirmed that thalidomide may improve anaemia and less frequently other cytopenias in some younger patients with low-risk MDS (11-56%, on intention-to-treat analysis). How thalidomide acts in MDS is not clear. Some data suggest several mechanisms possibly involving stimulation of erythropoiesis through activation of physiological compensative mechanisms and reduction of apoptosis.[4]

In summary, distinct pathobiological pathways comprised the challenging clinical course of APS, pyoderma gangrenosum, leukemoid reaction, and MDS in our cytogenetically handicapped patient. Nevertheless several drugs affecting distinct molecular crossroads of inflammation, neoplasia, angiogenesis, cytokine response, and cellular events have served to provide a successful clinical outcome.

NOTE

A written informed consent was taken from the patient for the photographs.

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