Treatment of recalcitrant ulcers in pyoderma gangrenosum with mycophenolate mofetil and autologous keratinocyte transplantation on a hyaluronic acid matrix

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ABSTRACT
Pyoderma gangrenosum sometimes takes a recalcitrant course that is unresponsive to standard immunosuppression with corticosteroids and/or cyclosporin A. In these cases improvement of painful ulcerations is a therapeutic challenge. We report a 17-year-old boy with severe pyoderma gangrenosum treated successfully with mycophenolate mofetil and autologous keratinocyte transplantation using an esterified hyaluronic acid delivery system.

Key words: pyoderma gangrenosum, mycophenolate mofetil, hyaluronic acid, autologous keratinocyte transplantation.

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Introduction
Pyoderma gangrenosum (PG) is a severe, rapidly developing, chronic relapsing, painful neutrophilic dermatosis. The early lesions are small erythematous papules suggestive of folliculitis. Rapid evolution leads to tender pustules, followed by necrosis and characteristic ulcers with ragged undermined violaceous borders and pus-covered centres. Intense pain and depigmented parchment-like scarring bordered by hyperpigmentation are hallmarks of the disease. In about one third of cases PG is associated with bowel inflammation, rheumatoid arthritis, sarcoidosis, myeloma or malignancies. The pathogenesis is not completely understood but disturbances in cellular immunity have been detected.1

The treatments of choice are either cyclosporin A, intravenous steroids or combination treatment. Methotrexate, azathioprine, chlorambucil and cyclophosphamide have been used alone or in combination with steroids. In many cases these treatments are able to improve PG, but some individuals present a recalcitrant 'malignant' course.2–3 Though only 4% of PG cases occur in childhood, these patients are a particular challenge. Infants and children appear to have an unusual distribution of perianal and perigenital lesions not often described in adults.4,5

Case report
A 17-year-old boy was referred to our department because of relapsing painful ulcers on his lower legs. The otherwise healthy boy had suffered from ulcerating tonsilitis in 1995 followed by delayed wound healing. From summer 1996 he suffered from relapsing painful ulcers on the hip and lower legs. He had been hospitalized several times because of these ulcerations. Treatments were performed with antibiotics. Two mesh graft transplants were applied to his lower legs in 1997. Wound healing was delayed and relapses occurred on the transplanted sites.

We found a severely ill youth with two rapidly enlarging, painful ulcers on the lower legs, one along the anterior site of the right lower leg, the other above the left malleolus medialis. A small ulcer was seen on his left hip. The ulcers were covered by pus. The borders were undermined and violaceous. Additionally the youth suffered from painful ulcerations of the throat. The ETN investigation demonstrated necrotizing pharyngitis.

Laboratory investigations showed a markedly increased blood sedimentation rate of 73 mm in the first hour and a C-reactive protein of 109 mg/L. Antinuclear antibodies and ANCA were negative. We could not find either an infectious cause or any evidence of systemic disease. Colonoscopy and
The diagnosis of ulcerative PG was confirmed by skin biopsy which revealed granulocytic pustulation.

**Treatment and course**

Initially intravenous prednisolone (100 mg/d; Prednisolut®, Jenapharm, Jena, Germany) and cyclosporin A (100 mg/d; Sandimmun Optoral®, Novartis, Nürnberg, Germany) were administered with success. After 2 months the boy was free of ulcerations of the skin and mucous membranes. In another hospital the dosage was rapidly reduced in a symptom-free interval because of Cushing-like side-effects. Within 2 days, ulcerations reappeared and developed into the worst during his medical history.

High dosage intravenous steroids (200 mg/d) together with cyclosporin A (100 mg/d) were not able to control the disease during a course of 6 weeks. We changed the immunosuppressant to mycophenolate mofetil (CellCept®, Roche, Grenzach-Wyhlen, Germany) 2 g/d p.o. in combination with 100 mg prednisolone/d i.v. in March. During the next 4 weeks there was partial improvement with diminished inflammation, reduced exsudation and less pain. In April, the lesions were treated topically with hyaluronic acid derivatives (Hyalogran®, ConvaT ech, Munich, Germany). The ulcers became flattened and granulation tissue developed. We decided to perform an autologous epithelial grafting. Two 8-mm punch biopsies were taken, the grafting was performed (fig. 1). On one ulcer (left leg) complete wound closure was achieved.
achieved. On the other ulcer the initial take rate was about 60%, but relapse occurred. Nevertheless, both transplanted ulcers showed marked dermal response to the graft. Granulation was stimulated and pain was reduced. The laboratory investigation in June showed normalized blood sedimentation rate and C-reactive protein. We performed a second graft on the ulcer above the left malleolus medialis leading to stable reductions in wound area and the steroid dosage was reduced to 50 mg/d.

Comments

The course of PG is characterized by chronicity and relapses. While most subjects benefit from either corticosteroids or cyclosporin A, some are or become recalcitrant. The more cytotoxic compounds, such as cyclophosphamide, chlorambucil or methotrexate, have been used in such patients.\(^1\) In this case of a 17-year-old boy, however, we did not prefer these compounds because of the possible tumour induction.

Since the first case report of PG treated with cyclosporin A\(^2\) more than 60 patients have been reported in the literature.\(^3\)–\(^10\) Some patients, however, fail to respond to cyclosporin A. There is one case report in the recent literature about the beneficial action of mycophenolate mofetil in combination with cyclosporin A in a patient with PG.\(^11\) Another observation on mycophenolate mofetil in PG provides further support regarding the efficacy of this drug in refractory cases.\(^12\)

The immunosuppressant mycophenolate mofetil, the 2-morpholinoethyl ester of mycophenolic acid, is a pro-drug, which has been shown to be effective in the suppression of acute allograft rejection. In vitro mycophenolic acid was shown to inhibit cell division selectively for lymphocytes. The action of this drug is mediated through specific non-competitive binding to inosine monophosphate dehydrogenase.\(^13\) Mycophenolate mofetil has been used in steroid resistant disorders known to be associated with PG-like inflammatory bowel disease\(^14\) and rheumatoid arthritis.\(^15\)

In this case, a combination of prednisolone and mycophenolate mofetil provided secondary cyclosporin-resistant PG. This immunosuppressant helped to limit systemic inflammation and facilitate ulcer treatment with autologous keratinocyte grafts. We performed repeated grafting; after initial take the wounds stabilized and showed partial improvement. The boy felt less pain and the exudation diminished.

Classical transplantations were used to cover PG ulcers on the breast. In this case sequential grafting was necessary.\(^16\) For such a purpose, the use of epithelial autografts seems to be advantageous because one biopsy allows several subsequent graftings.\(^17\)

The ulcers were pretreated topically with esterified hyaluronic acid (Hyalogran\(^®\)). Hyaluronic acid is a major component of the extracellular matrix and has been shown to be involved in tissue repair and wound healing; in particular epithelial migration and differentiation are facilitated.\(^18\)–\(^20\) Recently, benzyl esters of hyaluronic acid have been employed as a matrix for keratinocyte transplantation. By such means the take rate of graftings can be improved compared to those of standard techniques.\(^21\)

Some subjects with PG present extraordinary resistance to therapeutic modalities. The aggressiveness of the disease and the type and amount of therapy required varies in individual subjects. Improvements in systemic therapy and local wound management, however, now lead to controlled PG even in the worst cases.

References
