

Observation clinique

Successful treatment of recalcitrant oral pemphigus vulgaris with mycophenolate mofetil

Denis Selimovic^{1,2,*}, Martine Soell^{2,3}, Ahmed Feki¹

¹ Département de Médecine buccale et Chirurgie buccale, UF 8601, Hôpitaux Universitaires, Strasbourg, France

² INSERM Unité 977, 11 rue Humann, Strasbourg, France

³ Département de Parodontologie, Hôpital de Hautepierre, Faculté de Chirurgie Dentaire, Strasbourg, France

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Abstract – Oral pemphigus vulgaris (OPV) is an intraepithelial autoimmune bullous disease with circulating autoantibodies against desmoglein 3. The disease is difficult to treat and in some cases may be fatal. Mycophenolate mofetil (MMF), a new immunosuppressive drug which selectively inhibits cytotoxic lymphocytes and antibody production by B-lymphocytes was originally used to treat acute graft rejections in renal transplanted patients. The objective of this trial was to assess the therapeutic efficacy of MMF on OPV. One 61 year-old male patient with oral pemphigus confirmed via histopathology, direct and indirect immunofluorescence, was treated with MMF. After the confirmation of the diagnosis, MMF was administered orally in a dose of 2 g daily. Routine laboratory studies and other recommended laboratory tests for MMF were performed at regular intervals. The patient responded very well to the therapy and all lesions healed completely within 4 months. Under a maintenance therapy of 200 mg MMF per day no relapse of the disease occurred for a follow-up period of 3 years. No side-effects were observed. MMF is a safe and effective therapy for oral OPV. More clinical double-blind studies should be performed to confirm our result.

Oral pemphigus vulgaris (OPV) is an intraepithelial autoimmune bullous disease characterized by circulating autoantibodies against desmoglein 3, a cadherin-like structure [1]. This leads to blister formations and erosions that can become life-threatening. Literature shows strong genetic background to pemphigus with linkage to HLA class II alleles. Certain ethnic groups, such as Ashkenazi Jews and those of Mediterranean origin, are especially liable to pemphigus [2]. This disease is potentially lethal and before the introduction of corticosteroids in the 1950's about 75% of the patients with OPV died one year after the diagnosis was confirmed [3]. Therefore early diagnosis is of utmost importance due to a good prognosis. The dentist has a unique opportunity to recognize the oral presentation of OPV and contribute to an early diagnosis and, therefore, an improved treatment outcome [4].

Hereby the dentist has a special burden of responsibility to have the knowledge about such autoimmune diseases in order to be able to send the patient to a specialist for further treatment. The mortality rate has been lowered down to 30% since the use of corticosteroids and the prognosis of OPV has been improved since the adjuvant therapy with immunosuppressants (e.g. azathioprin, cyclophosphamide) as

corticosteroid-sparing agents was established as a new therapeutic regimen. Nevertheless the new therapeutic advances in the treatment of this disease mortality rate still ranges at about 5% often caused by hazardous and unpredictable side-effects of immunosuppressive agents [5].

Saha et al. reported that pulsed therapy with intravenous methylprednisolone and cyclophosphamide indicates an effective treatment option, but there are currently few data on its use in patients who have failed to respond to conventional immunosuppression therapy [6].

Japanese dermatologists use different regimen for OPV: these include plasmapheresis, steroid pulse therapy, intravenous immunoglobulin (IVIG), various immunosuppressive agents (such as azathioprine, cyclophosphamide, ciclosporin, mycophenolate mofetil and mizoribine) as well as anti-CD20 monoclonal antibody (rituximab). Adjuvant therapies like these bear the risk of severe infections, except IVIG therapy. In the most intractable cases, a combination of these adjuvant treatments may be used [7].

Mycophenolate mofetil (MMF) has been reported to be an effective adjuvant to systemic steroids. It helps in increasing the immunosuppressive effect and minimizing the toxicities by steroid sparing effects. However, its efficacy in refractory

* Correspondence: Denis.Selimovic@t-online.de



Fig. 1. Ulcer on the left margin of the tongue before treatment.



Fig. 2. Left buccal ulcer before treatment.

cases of OPV is not well documented. The lowest possible dose with satisfactory therapeutic efficacy and least side effects is known. MMF offers an effective adjuvant with minimal side-effects in the treatment of resistant OPV [8].

Here we present a case of recalcitrant oral OPV resistant to previous therapies with prednisolone combined with ciclosporin as well as prednisolone and methotrexate. The patient has been successfully treated with MMF for a follow-up period of 3 years.

Observation

A 61 year-old man presented with a two years history of erosions and ulcerations of oral and nasal mucosae. Clinical examination revealed areas of desquamation with associated erythema on soft and hard palate as well as on the lower lip. Two ulcers of 5 mm and 15 mm respectively were present on the left margin of the tongue and left buccal mucosa (Figs. 1 and 2). Hemorrhagic crusts of the nasal mucosa were

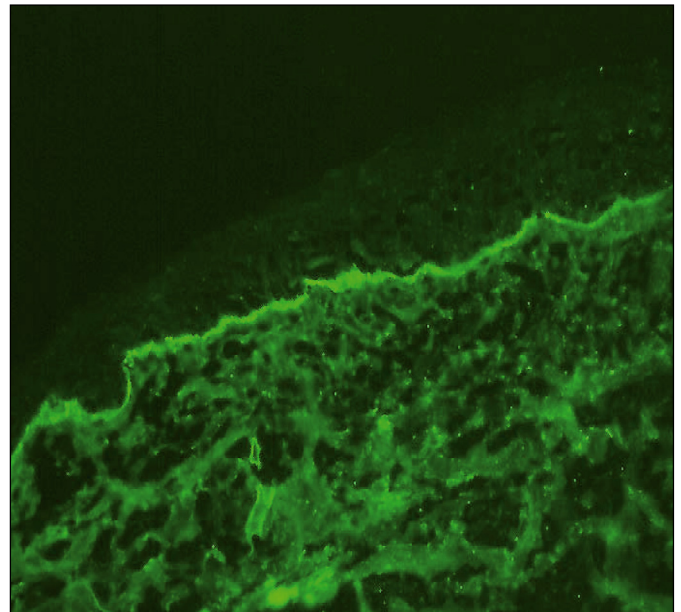


Fig. 3. IgG autoantibodies directed against desmoglein 3 show a typical picture of its intercellular deposition.

seen on examination. Direct immunofluorescence with the patient's skin showed deposition of intercellular IgG (Fig. 3). Indirect immunofluorescence revealed circulating antiepithelial cell surface IgG. A therapy with prednisolone (120 mg daily) and ciclosporin (150 mg daily), as well as prednisolone (120 mg) and methotrexate (25 mg) was not successful. We decided to treat the patient with MMF based on previous experience in autoimmune bullous skin diseases [8]. MMF was administered orally in a dose of 2 g daily. The patient responded very well to the therapy and all lesions healed completely within 4 months (Figs. 4 and 5). Under a maintenance therapy of 200 mg MMF per day no relapse of the disease occurred for a follow-up period of 3 years. Routine laboratory studies and other recommended laboratory tests for MMF were performed at regular intervals. No side-effects were observed. For the time of writing the abstract the daily dose of MMF was reduced to 200 mg. Up to date no relapse of the disease has been observed.

Discussion

Before the introduction of corticosteroids in the 1950's, the vast majority of patients with OPV died [9]. But the well-known side effects of systemic corticosteroids like diabetes, osteoporosis, striae cubis distensae, infections, gain of weight and gastrointestinal ulcers limit their use and demonstrate the requirement of alternative therapies [10]. Moreover high dosages of prednisolone like they are often being required, lead to a higher morbidity of patients compared to those receiving a lower dosage in direct dependency of time duration. In some patients, immunosuppressive agents are not



Fig. 4. Healing of the ulcer on the left margin of the tongue after 4 months of treatment.



Fig. 5. Left buccal ulcer after 4 months of treatment.

effective or even contraindicated. In those cases alternative treatment modalities are needed. Meanwhile a few more treatments in OPV apart from corticosteroids have been described.

Immunoglobulins are said to be helpful in OPV unresponsive to conventional treatment [12, 13]. They appear to have a steroid-sparing effect and even as a monotherapy a positive effect on the course of the disease could be shown. Even though immunoglobulins are said to be relatively safe, they still bear the risk of transmitting infectious agents as well as thromboembolic events or even renal failure. The response to immunoglobulins is rather slow which does not make them recommendable as a first-line treatment of OPV [13]. The administration of immunosuppressive agents like azathioprine may cause side-effects which in some cases can even end lethally [14]. Topical azathioprine in the treatment of oral autoimmune vesiculo-ulcerative lesions might allow control of oral lesions with lower systemic dosing, but it has to be further investigated [15].

As for topical treatment modalities, it has to be mentioned that in contrast to the integument the oral cavity is a

localisation not really eligible for local treatment. Rituximab, an anti-CD 20 monoclonal antibody, was described to have an improving effect in refractory erosive stomatitis secondary to CD20+ follicular lymphoma-associated paraneoplastic pemphigus, but its effect on oral OPV still has to be investigated [16].

A review by Yeh *et al.* focuses on the therapeutic uses of dapsone, methotrexate, MMF, chlorambucil, dexamethasone-cyclophosphamide pulse therapy, immunoablative therapy with cyclophosphamide, plasmapheresis, and extracorporeal photochemotherapy. Among the oral agents, dapsone may be considered a first-line agent. Recently, the use of IVIG therapy, with a defined protocol, has been reported to be beneficial. The adverse effects caused by IVIG therapy are minimal [17]. On the other hand, it has been reported that patients subsequently develop a deep venous thrombosis under IVIG therapy [18].

The combination of MMF and prednisolone turned out to lead to a much better response than a monotherapy with prednisolone in resistant OPV [18].

This trial focuses on the therapeutic management of a patient with recalcitrant OPV of the oral cavity who had a complete remission of all lesions within four months under the administration of MMF in a dosage of 2 g per day. Remission could be maintained by a therapy of 200 mg MMF per day. There were no adverse events to be reported. By inhibiting inosinmonophosphatase dehydrogenase, MMF is a selective inhibitor of cytotoxic lymphocytes and antibody production by B-lymphocytes. It has been successfully used to prevent acute graft rejections in renal transplanted patients [19]. It combines an excellent immunosuppressing effect with a low incidence of side-effects, compared to steroids which have a high rate of negative side-effects when given in a dosage leading to a similar effect as well as other immunosuppressive agents.

The upon described case is to show that MMF seems to be a promising new therapy for recalcitrant oral OPV which is often resistant to other therapies. The problematic localisation of oral OPV limiting the use of topical agents has been claiming for an effective, but not aggressive therapy for a long time. MMF is a promising drug in dermatological disorders, especially autoimmune diseases [20].

Further studies with more patients are required for the investigation of the long-term safety of MMF as well as to determine the period of time the treatment has to be performed to prevent relapse of the disease.

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