

## Refractory multicentric reticulohistiocytosis treated by infliximab: two cases

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### ABSTRACT

We report the effect of infliximab, a monoclonal anti-TNF $\alpha$  antibody, in two patients with refractory cutaneous and articular multicentric reticulohistiocytosis (MRH).

One 37-year-old woman and one 53-year-old woman with polyarthritis, facial rash and nodular lesions on the hands related to MRH were refractory to multiple agents: cariolysine, corticosteroids, hydroxychloroquine and cytotoxic agents. Infliximab at 3 mg/kg which was then increased to 5 mg/kg in combination with methotrexate or azathioprine was effective on cutaneous manifestations of the disease but not on polyarthritis. A switch to etanercept did not improve polyarthritis in the second patient.

Some data suggest that TNF $\alpha$  is involved in MRH, but based on our cases anti-TNF $\alpha$  therapy needs further evaluation in patients with refractory MRH.

### Introduction

Multicentric reticulohistiocytosis (MRH) is a rare systemic disorder of unknown etiology characterized by destructive polyarthritis and skin nodules. Multiple therapies have been proposed. Complete or partial remission have been described with dexamethasone pulse (1), alkylating agents (2), methotrexate associated with hydroxychloroquine (3), prednisone (4-6), cyclosporine (7), corticosteroids, cyclophosphamide (8), and recently etanercept (9) and alendronate (10). We report two patients with MRH refractory to multiple agents whom we treated with infliximab.

### Case reports

#### Case 1

A 37-year-old woman with diabetes mellitus since 1999 and Hashimoto's thyroiditis presented in March 2000 a polyarthritis involving the proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, elbows, knees, ankles and hips. Simultaneously she developed a red maculopapular rash on the perinasal zone and brown-reddish nodules on the hands (Fig. 1). Laboratory studies showed a normal erythrocyte sedimentation rate (ESR)

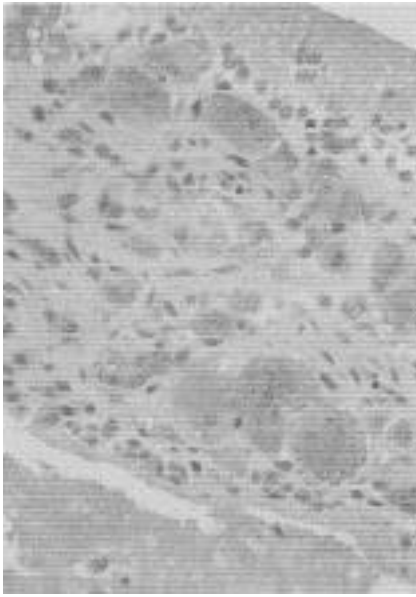
(2 mm/1st hr) and C-reactive protein level (CRP), positive rheumatoid factor (100 UI, normal < 20) and antinuclear antibodies (ANA) (1/320). Joint radiographs showed no erosions. A skin biopsy revealed the dermis to be filled with multinucleated histiocytes with abundant, dense, pink cytoplasm, consistent with the diagnosis of MRH.

Topical corticosteroids were started; topical cariolysine and oral hydroxychloroquine (400 mg/day) were added because of skin flares. Worsening and extension of skin lesions led us to switch hydroxychloroquine to methotrexate (15 mg weekly) in November 2000, with transient efficacy. In February 2002 the nodules had extended and polyarthritis was still active (28 tender and 9 swollen joints) despite administration of an intravenous (iv) methylprednisolone pulse (500 mg). Synovial knee biopsy revealed a typical pattern of MRH (Fig. 2). On hands radiograph several erosions appeared.

Infliximab, a monoclonal antibody against tumour necrosis factor- (TNF-) at a 3 mg/kg dosage was started on March 2002 with methotrexate (10 mg/week), and given at 0, 2 and 6 weeks and then at 8-week intervals. After the third infusion, skin lesions improved but not polyarthritis (17 tender, 8 swollen joints). In May 2002, methotrexate was changed to azathioprine.



**Fig. 1.** Typical diffuse brown-reddish nodules involving both hands, localised on the lateral and dorsal sides of all the fingers.



**Fig. 2.** Synovial membrane cellular infiltrate mainly composed of histiocytes with multinucleated giant cells exhibiting eosinophilic cytoplasm (hematoxylin and eosin stained).

prine (100 mg/day) because of cytopenia. After increasing the dosage of infliximab to 5 mg/kg then 8 mg/kg and administering 8 infusions, the macular rash and nodules decreased in size and number but polyarthritis was unchanged (24 tender and swollen joints). Infliximab was stopped; she received only azathioprine and NSAIDs. Eight months later, cutaneous disease was still in remission with active polyarthritis (15 tender and swollen joints). During the next 6 months, skin lesions did not relapse and arthritis improved with only 6 tender and swollen joints at the last control.

#### Case 2

In April 1999 a 53-year-old woman with essential hypertension presented a polyarthritis with 40 tender joints (wrists, knees, elbows, shoulders, PIP, distal interphalangeal and MCP joints), 4 swollen joints (wrists and knees) and a pruritic papular rash with nodules on her face, scalp, upper limbs and hands. ESR was increased (28 mm/1st hr) with normal CRP, positive ANA (1/640) and positive anti-SSA antibodies. Hands radiographs revealed bilateral erosions on the third and fourth DIP joints. A skin biopsy revealed a typical pattern of MRH.

Oral prednisone (0.5 mg/kg/day), intramuscular methotrexate (20 mg/week), hydroxychloroquine (400 mg/day) and topical corticosteroids were instituted but no improvement was seen after 4 months. Methotrexate and hydroxychloroquine were then substituted for iv cyclophosphamide (1000 mg/month). The rash and nodules decreased but a flare occurred after 6 infusions and the arthritis remained unchanged. After 10 infusions, cyclophosphamide was replaced by chlorambucil (0.1 mg/kg/day) with topical caryolysine. Chlorambucil was stopped because of a seizure. Cyclosporine (300 mg/day) was begun, but quickly stopped because of inefficacy and a rise in serum levels of creatinine. Leflunomide (20 mg/day) was stopped after 3 months because of inefficacy and alopecia. With azathioprine (100 mg/day) cutaneous lesions and the joint disease worsened.

Infliximab at a dosage of 3 mg/kg and then 5 mg/kg after the second infusion, was added to azathioprine in October 2002. After 5 infliximab infusions (weeks 0, 2, 6, 14 and 22), cutaneous lesions improved, pruritus disappeared and the number of nodules dramatically decreased. However, the effect on the joint disease was mild: 4 swollen and 21 tender joints. A switch to etanercept (25 mg twice weekly) was tried, but 6 months later the clinical symptoms were unchanged (stable cutaneous lesions, active polyarthritis).

#### Discussion

Case reports and open-label studies have revealed promising results of anti-TNF therapy in rare inflammatory disorders (11); moreover the role of TNF in the pathogenesis of MRH has been suggested in several studies. Gorman *et al.* (12) reported positive staining for TNF in macrophages of the synovial lining layer and around the blood vessels in a synovial biopsy of a patient with MRH, and suggested that this cytokine could be involved in the disease process. Nakamura *et al.* (13) have reported that TNF was detected immunohistochemically in hip synovium in a patient with MRH, TNF was present in culture supernatant of the synovial cells. Based on these results, it

could be hypothesized that anti-TNF therapy might be effective in MRH. One MRH patient with refractory articular and cutaneous involvement was treated by etanercept, and a dramatic improvement in both manifestations was seen (9), but no cases of infliximab treatment have been reported.

In our first case, steroid treatment was interrupted because of diabetes and poor efficacy, but methotrexate alone failed to obtain a long-term improvement. Infliximab resulted in an improvement of the cutaneous manifestations of the disease, but only a transient stabilization of joint disease with a flare-up of polyarthritis after 54 weeks of follow-up. In the second case, inefficacy or side effects of the drugs were observed and, as in the first patient, infliximab led only to an improvement in cutaneous manifestations.

In conclusion, our two cases did not confirm the results observed with etanercept in a single patient (9). Anti-TNF therapy in MRH needs controlled studies. At the present time, based on our experience, we feel that infliximab could be used in cutaneous MRH and included in the therapeutic tree of Liang *et al.* after the failure of methotrexate, prednisone and alkylating agents (8).

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