Tumor necrosis factor antagonists in the treatment of multicentric reticulohistiocytosis: Current clinical evidence

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Abstract. Multicentric reticulohistiocytosis (MRH) is a rare and debilitating systemic disorder characterized by cutaneous nodules and destructive polyarthritis. Due to its unknown etiology, the treatment of MRH varies with different rates of success, which causes treatment options to be rather independent and empirical. In the present study, a case of a 48-year-old woman with a 12-month history of polyarthralgia and skin nodules was reported. Biopsy samples, which were obtained from her skin eruption exhibited dermal infiltration with histiocytes and multinucleated giant cells. Immunohistochemical staining indicated positivity for CD68. The patient was diagnosed with MRH and treated with a combination therapy of infliximab, prednisolone and methotrexate. Her symptoms improved markedly within 2 weeks. Following the results of this case study, a systematic review of 17 cases of MRH treated with tumor necrosis factor (TNF) antagonists was performed, and the efficacy of anti-TNF treatment in MRH was analyzed.

Introduction

Multicentric reticulohistiocytosis (MRH) is a rare, multisystem inflammatory disease, which is characterized by cutaneous nodules and destructive polyarthritis. It can affect any organs or tissues, however, the most common clinical manifestations are papulonodular eruptions and symmetric inflammatory polyarthritis. It is possible to observe constitutional symptoms, including fever, weight loss and malaise, which may be associated with joint and skin symptoms. There are no specific laboratory tests for the diagnosis of MRH, and its current diagnosis is predominantly dependent on histopathological evaluation (1,2). According to tissue biopsies of the affected areas, ground-glass opacity with increased quantities of periodic acid Schiff-positive materials can be observed, which indicates the infiltration of typical mononuclear histiocytes and multinucleated giant cells (1). In the case of MRH, immunohistochemical analyses are usually positive for CD45, CD68 and HLA-DR, but are negative for S-100, a Langerhans dendritic cell marker, and HHF-35 actin, a fibroblast marker (1,3). In addition, it has been found that serum levels of cytokines, including tumor necrosis factor (TNF)-α and interleukins (ILs), including IL-1β, IL-6 and IL-8, are increased in MRH and decreased upon successful treatment (4). Infliximab is a chimeric IgG1κ monoclonal antibody, which is specific for human TNF-α. It is widely used for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis (5). Previously, following the demonstration of increased levels of TNF-α in patients with MRH, anti-TNF-α treatment has been adopted with promising results (4,6).

The present study reported on a case of a patient with MRH, whose arthralgia and skin eruptions significantly regressed following a treatment regimen combining infliximab, prednisolone and methotrexate (MTX). This outcome demonstrated the effectiveness of anti-TNF-α therapy for MRH. A systematic review of available literature was also performed to evaluate the efficacy of anti-TNF-α agents in the treatment of MRH.

Materials and methods

The present study was approved by the ethics committee of Xiangya Hospital, Central South University (Changsha, China). In 2013, a 48-year-old female diagnosed with MRH, who had a 12-month history of weakness, polyarthralgia, morning stiffness and papulonodular skin eruption was recruited. Her past medical history was unremarkable. According to the results of a biopsy, her skin eruption exhibited dermal infiltration with histiocytes and multinucleated giant cells.

Immunohistochemical staining was performed on samples from the left face cutaneous nodules. Samples were

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fixed using 10% formalin, embedded in paraffin and cut into 0.25-0.30 mm sections. Immunohistochemical staining was conducted at room temperature on a shaker. To enhance tissue penetration by antibodies, sections were incubated with ethanol for 30 min and rinsed with phosphate-buffered saline (PBS) 3 times for 5 min then blocked to prevent nonspecific primary antibody reactions with 10% normal donkey serum (NDS; OriGene Technologies, Inc., Beijing, China). Tissue sections were incubated overnight in anti-S-100 (cat. no. MAB-0697) and CD68 (cat. no. MAB-0041) primary antibodies (OriGene Technologies, Inc.). After reaction completion, tissues were rinsed with PBS (3 times for 5 min), treated with NDS for 15 min, and incubated with goat anti-mouse fluorescein isothiocyanate-conjugated secondary antibody (cat. no. PV-6000; OriGene Technologies, Inc.) for 3 h, rinsed with PBS, and mounted with Vectashield. The dilutions used were optimal, according to the manufacturer's recommendations. Images were acquired using a cooled CCD camera attached to a light microscope The results of immunohistochemical staining indicated positivity for CD68. The patient was treated with combination therapy of infliximab (intravenous infusion of 200 mg and subsequent infusion at weeks 2 and 6, followed by an infusion once every 8 weeks; Cilag AG, Schaffhausen, Switzerland), prednisolone (oral administration; 30 mg/day; Zhejiang Xianju Pharmaceutical Co., Ltd., Zhejiang, China) and MTX (15 mg/week; Shanghai Sine Pharmaceutical Laboratories Co.,Ltd., Shanghai, China).

In addition to the above-mentioned patient, a systematic review was performed on the therapeutic application of anti-TNF-α agents in MRH. This involved the analysis of articles published in the PubMed database (www.ncbi.nlm.nih.gov/pubmed) between January 2003 and April 2014, and additional references cited in these articles were cross-checked. The search strategy involved the use of a combination of key words, including 'Multicentric reticulohistiocytosis', 'Infliximab', 'Etanercept' and 'Adalimumab'.

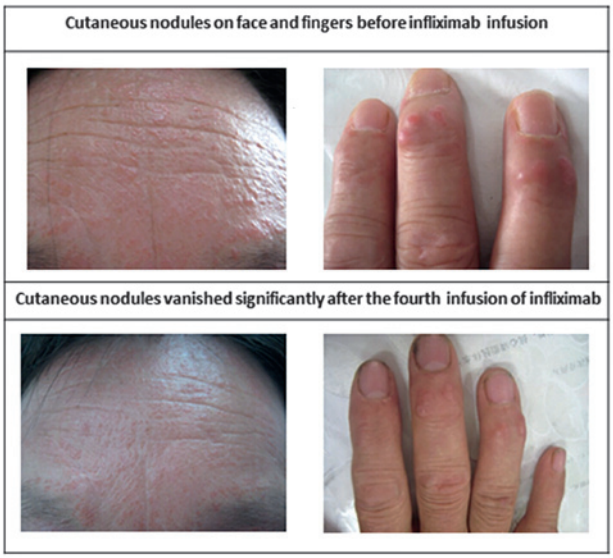

Figure 1. Nodule improvement. Images prior to and following infusion.

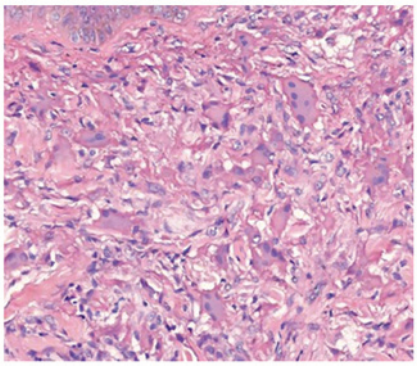

Figure 2. Hematoxylin and eosin staining of left face cutaneous nodules biopsy exhibiting dermal infiltration with histiocytes and multinucleated giant cells (magnification, x400).

Results

Case study. In the case of the female patient recruited in the present study, physical examination revealed an erythematous papulonodular rash, which had developed across her face, anterior chest, back neck, forearms and the dorsum of her fingers, with sizes ranging between 3 and 8 mm in diameter (Fig. 1). Musculoskeletal examination revealed swelling and tenderness at the joints of the patient's hands, elbows and knees. Initial investigations revealed normal full blood counts, blood lipids, C-reactive protein and erythrocyte sedimentation rate. Anti-nuclear antibodies, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, tumor markers [cancer antigen (CA)199, CA125, CA242, CA153, carcinoembryonic antigen, neuron-specific enolase and α-fetoprotein] and tuberculosis antibodies were all negative. In addition, gynecological examination and breast ultrasound were performed to exclude the possibility of gynecological malignancy. Bone marrow aspiration was also performed to rule out the possibility of hematologic neoplasms. Hand X-ray revealed marginal erosions in certain areas of the proximal interphalangeal joints, accompanied with mild osteoporosis and knee osteoarthritis. The chest X-ray findings suggested the possibility of tuberculosis, which was excluded by high-resolution computed tomography scan. Biopsy samples from two of the skin nodules exhibited dermal infiltration with histiocytes and multinucleated giant cells (Fig. 2). Immunohistochemical staining showed suspected positivity for CD68, but negativity for S-100 (Fig. 3). These findings were particularly indicative of MRH.

The patient was initially treated with an infliximab infusion of 200 mg, and subsequent infusions were administered at weeks 2 and 6, followed by an infusion once every 8 weeks. The infliximab infusion was combined with oral prednisolone (30 mg/day), leflunomide (20 mg/day), hydroxychloroquine (HCQ; 200 mg/day), and intravenous MTX (15 mg/week). Diacerein (50 mg/day) was added to the regimen due to osteoarthritis. The patients symptoms improved following treatment for 3 days. Gradual remission of the erythematous papules and nodules were noted prior to the second infusion of infliximab, and polyarthralgia and stiffness were markedly reduced. Following the fifth infusion, the skin signs had regressed markedly (Fig. 1), and symptoms of arthralgia were no longer present.

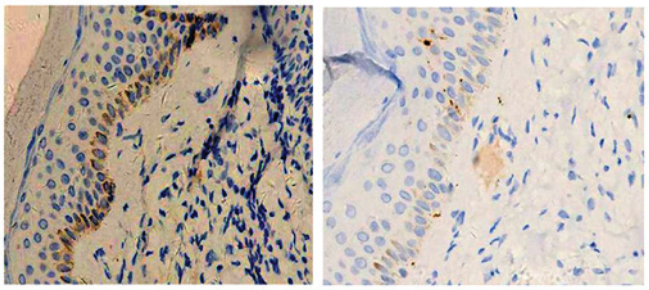

Figure 3. Immunohistochemical staining of cutaneous nodule biopsy demonstrating CD68 (±) and S-100 (-).

Literature review. In the present study, the following key words were used as search terms in PubMed: 'Multicentric reticulohistiocytosis', 'Infliximab', 'Etanercept', 'Adalimumab' and 'Tumor necrosis factor inhibition', from which 16 articles were found. According to the these reviewed articles and the results from the case described above, a total of 17 patients were treated with anti-TNF-α therapy, and none of the cases were excluded due to incomplete data. The present study analyzed the outcomes reported in the reviewed articles, based on the patients' responses to treatment and the reductions in steroid dosage (Table I). The data of these patients are summarized in Table I. The patients comprised 10 (62.5%) women and six (37.5%) men, with a median age of 47.5 years and age range of 3-76 years. All the patients developed arthritis and articular manifestations, as well as a maculopapular rash. Prior to the initiation of treatment with anti-TNF-α agents, the majority of the reported MRH cases had included the use of corticosteroids in their treatment, with the exception of a case reported by Iwata *et al* (7). Combination treatments were administered in 16 (94.1%) patients in the advent of relapse and unmitigated progression of the disease. Therapeutic regimens varied in the different reports due to the absence of standardized treatment protocols. A total of 13 (76.5%) patients received MTX, four (23.5%) received cyclosporine A and eight (47.1%) were treated with HCQ. Cyclophosphamide (CTX) was used in four cases (23.5%) and azathioprine was used in five cases (29.4%). A total of six patients (35.3%) were treated with non-steroidal anti-inflammatory drugs, whereas leflunomide was used in two cases (11.8%), and mycophenolate mofetil was used in one (5.9%) case, as was sulfasalazine (5.9%). A combination of chlorambucil and cariolysine was used in three cases (17.6%). Different treatment modalities were used with little or no success prior to treatment of the patients with anti-TNF-α agents. Alopecia, hypoleucocytosis, pruritus and other side effects appeared following the application of immunosuppressive agents, whereas no adverse effects were reported following the use of anti-TNF-α agents. In the previous literature, anti-TNF-α agents were administered in combination with glucocorticoids in all patients with promising results, with the exception of the single case reported by Iwata *et al* (7). Following the initiation of anti-TNF-α treatment, the number of patients suffering from constitutional symptoms was relatively low. Improvements in skin lesions and arthralgia were observed upon receiving anti-TNF-α treatment, which indicated a positive clinical response. Only minor manifestations were found: Two (11.8%) patients had fever, two (11.8%) patients presented with weight loss, two (11.8%) patients experienced fatigue, one patient (5.9%) presented with night sweats, one patient (5.9%) presented with stiffness and one patient (5.9%) presented with muscle aches.

Among the cases reported in the previous studies, 10 cases included the use of etanercept for the treatment of MRH. Among these, five cases responded well to treatment (8-12), three cases reported the replacement of etanercept treatment with another anti-TNF-α agent, including infliximab and adalimumab. The remaining two cases reported the initiation of etanercept treatment in replacement of adalimumab (13) and infliximab (14).

In the previous literature, eight cases reported the application of infliximab for the treatment of patients with MRH, six of which reported successful treatment with infliximab (5,14,15-18). The remaining two cases reported the replacement of etanercept with infliximab (19,20). In one case, reported by Sellam *et al* (14), there was concern regarding the replacement of infliximab with etanercept.

The use of adalimumab for the treatment of patients with MRH was reported in three cases, and one case was treated successfully. Adalimumab was used in place of etanercept in one case (21), whereas two cases replaced adalimumab with etanercept (13).

Discussion

MRH is a rare and debilitating systemic inflammatory disease of unknown etiology. In the case of MRH, immunohistochemical analysis of synovial tissue shows positive staining of TNF-α, IL-1β, IL-6 and IL-12, suggesting the presence of these inflammatory cytokines in affected areas, as reported by Gorman *et al* (3). In 2010, Tashiro *et al* (22) demonstrated the abundant accumulation of CD10 in the cytoplasm of ground-glass-like multinucleated giant cells in two patients with MRH. Of note, in a case reported by Bennàssar *et al* (4), increases in serum cytokine levels, namely of TNF-α, IL-1β, IL-6 and IL-8, were observed, which decreased following treatment.

TNF antagonists have been widely used for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis (5,23-26). Due to the fact that high levels of TNF-α are expressed in patients with MRH, anti-TNF-α therapy has become a viable option and widely used in the treatment of MRH in previous decades.

TNF-α antagonists are biological agents comprised of fusion proteins or antibodies foreign to the patient. For patients, immunogenicity and sensitization of TNF-α antagonists are of particular concern. The presentation of neutralized antibodies to TNF-α drugs can potentially cause inactivation and increased rates of clearance, thus affecting treatment outcome (27). Therefore, there were no reports pertaining to the presence of antiglobulins towards the anti-TNF-α agents, infliximab, etanercept and adalimumab, among the MRH cases included in the present review. In addition, there are several adverse effects of anti-TNF-α agents, including infusion-associated reactions, allergic reactions, increased susceptibility towards infection, demyelinating diseases and worsening of cardiovascular disease. These side effects are often mild,

Table I. Reported cases of patients with MRH treated with anti-TNF-α agents.

Case (refs.)	Age/ gender	Disease duration (months)	Skin biopsy	Radiography	Clinical features	Laboratory tests	Previous treatment	Anti-TNF agents	Concomitant therapies	Outcome	IHC
Matejicka *et al* (10)	22/F	36	Multinucleated histiocytes; abundant dense pink cytoplasm	Progressive erosions; pencil-in-cup deformities	Erythematous rash; papular lesions; polyarthritis	Normal	GC, CyA, MTX, HCQ, CTX, naproxen	ETA 50 mg/W	GC, MTX, CTX, HCQ	Skin lesions and arthralgia relieved; radiography-no progression	NA
Kovach *et al* (8)[a]	46/M	12	Histocytes and multinucleated giant cells; ground glass cytoplasm; fine PAS-positive granules	Erosive articular damage in hands and right hip	Skin lesions; progressive inflammatory ployarthritis	pANCA positive	MTX, GC, HCQ, chlorambucil	ETA 50 mg/W	GC, MTX, LEF,	Improvement in skin and joint symptoms	NA
Lee *et al* (15)	53/F	2	Densely packed giant cells and histiocytes; Predominantly mononuclear cytoplasm abundant; PAS-positive	No abnormality	Polyarthalgia; Red confluent patches; small erythematous papules	normal	NA	IFN 5 mg/kg	GC, MTX	Rapid regression of papulonodules; no new lesions; arthralgias decreased	CD68 (+) S100 (-) CD1a
Sellam *et al* (14)	37/F	24	Multinucleated histiocytes; abundant dense, pink, cytoplasm	Several erosions	Ployarthritis; red rash, brown -reddish nodules	ANA (1:320)	GC, Cariolysine, HCQ, MTX	IFN	MTX, AZA, NSAIDs	Macular rash/nodule decrease; ployarthritis unchanged;	NA
Sellam *et al* (14)	53/F	42	Typical pattern of MRH	Bilateral erosions	Polyathritis; pruritic rash with nodules	ANA (1:640) ESR (28 mm/h) SSA positive	GC, MTX HCQ, CTX, Chlorambucil, CyA, LEF, AZA	IFN, ETA,	AZA	Skin lesions improved; nodules decreased; ployarthritis unchanged	NA

Table I. Continued.

Case (refs.)	Age/ gender	Disease duration (months)	Skin biopsy	Radiography	Clinical features	Laboratory tests	Previous treatment	Anti-TNF agents	Concomitant therapies	Outcome	IHC
Lovelace *et al* (11)	42/M	24	Nodular interstitial histiocytic infiltrate; multinucleated histiocytes; eosinophilic granular cytoplasms	NA	Red-brown dome-shaped papules and nodules; distal arthritis	NA	NA	ETA, (100 mg/W)	GC	Minimal improvement of pain and skin lesions	NA
Shannon *et al* (6)	37/F	4	Mild hyperplasia of synovial cells; scattered monocytes; occasional giant cells	Symmetric erosion of DIP and first IP joints	Fine flesh-color nodules, clustered; large painful boggy DIP joints	Normocytic anemia ESR (100 mm/h) CRP (33 mg/dl) ANA and RF negative	CyA, MMF, GC, simvastatin, tramadol, NSAIDs	ADA, 40 mg	CyA, MMF, GC	Improved significantly; no evidence of synovitis	CD68 CD3 CD45 (+) S-100 CD1 CD30 (-)
Kalajian *et al* (19)	63/F	12	Histopathologic dermal infiltration; multinucleated giant cells; amorphous eosinophilic ground-glass-appearing cytoplasm varied density of infiltration	NA	Asymptomatic cutaneous lesions; progressively destructive arthritis; purified protein derivative (+); episodic fevers, night sweats, weight loss	CK, CRP ESR elevated; ANCA, ACL RF, ANA, AdsDNA and HCVAb negative	GC, isoniazid, MTX	ETA, IFN	GC, MTX	Condition fluctuations No new cutaneous lesions	NA
Chiba *et al* (16)	76/F	3	Multinucleated giant cells	Marginal erosions	Ployarthritis; red maculopapuplar rash; fever	CRP, ESR RF and CCP negative; ANA (1:320)	NA	IFN	GC, MTX	Erythematous papules; polyarthritis disappeared	CD68 (+) CD68 (+)
De Knop *et al* (17)	47/M	120	Multinucleated giant cells; eosinophilic	Erosions	Symmetric polyarthritis; papulonodular	SSA, SSB, dsDNA, RF and ANA	MTX, SSZ tenoxicam HCQ, CTX,	IFN	MTX	Improved morning stiffness;	

Table I. Continued.

Case (refs.)	Age/ gender	Disease duration (months)	Skin biopsy	Radiography	Clinical features	Laboratory tests	Previous treatment	Anti-TNF agents	Concomitant therapies	Outcome	IHC
			ground-glass cytoplasm		rash	positive; CRP, ESR and CCP negative	GC, AZA			tender and swollen joints	
Chauhan *et al* (12)	74/F	72	Dense histiocytic infiltrate; abundant eosinophilic cytoplasm; multinucleation	Marginal erosive changes	Arthralgias erythematous nodules; papular lesions fatigue weight-loss	ESR elevated; Anemia, RF, ANA and ENA negative; CCP positive	GC, plaquenil	ETA	NA	Skin changes regressed; arthiritic symptoms improved	CD68 (+)
Matiz *et al* (20)	3/F	6	Dome-shaped lesion; foamy histiocyte dermal infiltrate; admixed lymphocytes; CD1a-stained intraepidermis, rare dermal cells; Factor XIIIa-staining of scattered cells	Mild diffuse osteopenia; soft tissue swelling	Papular skin eruption; significant arthralgia	ESR and CRP normal; ANA and RF negative	Naproxen MTX, HCQ GC	ETA, IFN	MTX, GC	Partial initial response to etanercept; all xanthomas disappeared; no further synovitis improvement	CD68 (+) CD1a
Broadwell *et al* (9)[a]	55/M	120	Significant healing of hand erosions	NA	Polyarthritis; multiple skin lesions	NA	MTX, GC	CTX, LEF, ETA	NA	Remained asymptomatic	NA
Iwata *et al* (7)	44/M	8	Infiltration of multinucleated giant cells and histiocytes with eosinophilic ground-glass cytoplasm	NA	Asymptomatic; firm and flesh-colored erythematous cutaneous papules	WBC normal TNF-α MCP-1 elevated	NA	IFN	NA	Skin lesions and arthritis gradually improved	CD68 MCP (+) CD1a S100 (-)
Yeter *et al* (21)	55/M	12	Intradermal histiocytic proliferation;	Chest unremarkable	Red rash, muscle aching and stiffness	CCP, ESR, CRP, SSB, AdsDNA,	MTX	ETA, ADA	MTX, GC, minocycline	Skin lesions significantly Improved shoulder	NA

Table I. Continued.

Case (refs.)	Age/ gender	Disease duration (months)	Skin biopsy	Radiography	Clinical features	Laboratory tests	Previous treatment	Anti-TNF agents	Concomitant therapies	Outcome	IHC
			majority of cells mononuclear; no foam cells		in shoulders, progressed to right hand/ knees/thighs swelling of right wrist	Sm negative; ANA, RF SSA positive				pain, morning stiffness; weaned off steroids; cutaneous manifestiations quiet; arthralgia improved	
Saba *et al* (13)	54/ F	120	Histiocytic infiltration with multinucleated giant cells	Severe diffuse destruction Periarticular osteoporosis; new bone formation	Multiple non-pruritic reddish-brown papulonodular lesions; severe diffuse arthritis	Anemia; CRP elevated ANA RF, CCP normal	Ibuprofen, AzA	ADA	MTX	Symptomatic relief; no resolution of irreversible arthritic deformities	CD68 (+)
Macía -villa *et al* (18)	50/M	48	Non-langerhans cutaneous histiocy-tosis suggests early-phase reticulohistiocytosis subtype; Papular lesions infiltrated by histiocyte-appearing cells with macrophage monocytic features	Marginal erosions in interphalangeal joints; loss of joint space and swan finger deformity; X-rays of feet show hammer toes and joint space narrowing	Symmetrical deforming arthritis of interphalangeal joints, knees and ankles; pruritic brown nodules in both; indurated nodules in hands	Normal RBC WBC, ESR, RF and CRP; C3, C4, anti-CCP, anti-mitochondria; anti-thyroid; ANA, anti-DNA and anti-ENA negative	Prednisone, alendronate, MTX, hydoxychl-oroquin	IFN	Prednisone, alendronate, MTX, hydoxy -chloroquine	Skin lesions improved; complete remission of arthritis and improvement of arthralgia; arthritic deformities failed to resolve	CD68 (+) Factor XIII CD10 (+) S100 (-) CD1a (-)
Zhao *et al* (present)	48/F	12	Dermal infiltration with histiocytes and multinucated giant cells	Marginal erosions; mild osteoporosis; narrowed joint space	Ployarthritis, stiffness and weakness; papulonodular skin eruptions	ESR, CRP RF and ANA normal	Meloxicam, GC	IFN	GC, LEF HCQ, MTX diacerein	Erythematous papules and nodule, and polyarthritis disappeared	CD68 (+) S-100 (-)

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibody; RF, rheumatoid factor; CCP, anticyclic citrullinated peptide antibody; AzA, azathioprine; Mel, meloxicam; GC, glucocorticoids; MTX, methotrexate; LEF, leflunomide; CTX, cyclophosphamide; ETA, etanercept; ADA, adalimumab; IFN, infliximab CyA, cyclosporine; MMF, mycophenolate mofetil; HCQ, hydroxychloroquine; NSAIDs, non-steroidal antiinflammatory drugs; SSZ, sulfasalazine; [a]same patient; IHC, immunohistochemistry; NA, not applicable; F, female; M, male; DIP, distal interphalangeal joint; CK,creatine kinase; ANCA, antineutrophilcytoplasmic antibodies; ACL, anti-phospholipid antibody; AdsDNA, anti-double stranded DNA; WBC, white blood cell; TNF-α,tumor necrosis factor-α; MCP- 1,monocyte chemoattractant protein-1.

self-limiting and often do not necessitate the discontinuation of therapy (28). It is worth noting that observations or reports of these adverse effects were rare when anti-TNF-α treatment was used in the MRH patients in this review.

Matejicka *et al* performed an initial trial involving the application of anti-TNF-α agents in a patient with MRH in 2003. This resulted in the successful treatment of a 22-year-old female college student using a combination of etanercept (25 mg twice a week subcutaneously), MTX, prednisolone, HCQ and CTX. The patient experienced remission of skin lesions and arthralgias 6 weeks following treatment (10). The following year, Kovach *et al* also reported a successful case of treating MRH with the combination of etarnercept, leflunamide and prednisolone (8).

In 2004, Lee *et al* (15) reported an effective combination of infliximab, prednisolone and MTX in treating MRH. Treatment involved the use of infliximab (5 mg/kg/day) in combination with MTX (7.5 mg/week) and prednisolone (30 mg/day) following establishment of the diagnosis of MRH. There was a noticeable regression of dermal nodules following the first infusion, and polyarthralgia were alleviated within 3 months. Several subsequent cases of successful treatment with TNF-α inhibitors have been reported since, as summarized in Table I, which were effective in alleviating symptoms, although there was with disparity in responses to cutaneous and articular manifestations.

According to a review by Kalajian, a trend was noted in treatment modalities comprising TNF inhibition, with prednisolone and MTX having higher success rates (19,29). Among the anti-TNF-α agents, infliximab has been reported to be more efficient than etanercept, which can be explained by the fact that infliximab has a higher association rate and lower dissociation rate, compared with etanercept (30). Infliximab is reported to be able to irreversibly bind to TNF without partial inhibition, thus allowing complete neutralisation of TNF (30). This may also explain the case reported by Sellam *et al* (14), in which no further improvement of symptoms was observed following the replacement of infliximab with etanercept. Based on the reported effectiveness of infliximab in the treatment of MRH, the patient in the present study was treated with infliximab at the beginning of treatment, which was found to be efficacious. As the patient was also receiving treatment with pednisone, MTX, leflunomide and HCQ at the same time, the combination of which has been confirmed to be effective (3,4,29,31), it was not possible to independently evaluate the efficacy of infliximab in this patient (32). Thus, rather than exclusively attributing the success of treatment to infliximab, it was suggested that the inclusion of infliximab in a treatment regimen appears to be a viable option (33-35). As a result of the notable effectiveness of infliximab in treating MRH, according to previous literature, anti-TNF-α agents, particularly infliximab, may be advocated as an efficacious approach for the treatment of MRH.

The present study had certain limitations, predominantly due to the rarity of the disease and the low number of patients reviewed. In addition, the administration of these TNF-α antagonists has often been included in various treatment regiments, however, there has been no systematic comparison between cases, and no independent evaluation of its efficiency. Furthermore, the majority of the case reports focussed partly on favorable responses, and those with poor outcomes have been rarely reported. All these limitations restrict the comprehensiveness of the analysis of anti-TNF-α treatment in the present study. In conclusion, as stated above, TNF antagonists offer a relatively safe and well-tolerated treatment option, and may be recommended in refractory MRH as they induce remission and allow a reduction in steroid dosage. It may be administered in accordance with the sequence of therapy used in the management of rheumatoid arthritis. However, further prospective investigations are required to improve and standardize its application, in terms of dosage and duration, in the treatment of patients with MRH.

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