Treatment of Multicentric Reticulohistiocytosis With Tocilizumab

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Abstract: Multicentric reticulohistiocytosis (MRH) is a rare multisystem, granulomatous debilitating disease. It affects the skin with a nodular diffuse dermatitis and the joints with a severe, potentially deforming, and handicapping arthritis. No standardized therapy exists, it is a disease with heterogeneous severity, and therefore, a diversity of therapeutic responses has been published.

Current experience with anti–tumor necrosis factor agents in disease-modifying antirheumatic drug–refractory MRH cases is encouraging, and other agents such as bisphosphonates have proven effective as well. Histological analysis of the granulomatous inflammatory lesions have shown the presence of cytokines including tumor necrosis factor α, interleukin 1, and interleukin 6; the presence of the latter makes tocilizumab a plausible alternative.

In this article, we report a 35-year-old woman with MRH refractory to a combined scheme of prednisone and methotrexate, both at high doses, and who received tocilizumab achieving remission on both cutaneous and articular symptoms. Our patient markedly improved by the second infusion (8 mg/kg monthly), and after 9 infusions, she remained asymptomatic; no toxicity was detected. Tocilizumab could be an alternative for disease-modifying antirheumatic drug–refractory MRH.

Key Words: tocilizumab, multicentric reticulohistiocytosis, biologic therapy

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Multicentric reticulohistiocytosis (MRH) is a chronic inflammatory disease of unknown origin. Its hallmark is the presence of spontaneous inflammatory nodular lesions that grow in the skin and in the synovial membrane.

It is often associated with arthritis, which may be severe, deforming, and handicapping (~60%); indeed, a mutilans variant is even more frequently observed (~45%) than in psoriatic arthritis.

Approximately 25% of MRH cases are paraneoplasic syndromes that have been linked to a diversity of neoplasms, including carcinomas (cervix, breast, lung, gastrointestinal, prostate, and others), leukemia, lymphoma, and melanoma.

The disease is often limited to the skin and joints; however, cases with notable systemic involvement affecting the lungs, heart, and kidney have been described as well.

Cases of MRH mimicking or coincidental with defined connective tissue diseases such as systemic lupus erythematosus,[1,2] Sjögren syndrome,[3,4] polymyositis, and anticitrullinated-positive rheumatoid arthritis (RA)–like disease[5] have also been published, unveiling yet undefined relation.

Multicentric reticulohistiocytosis is a rare disease, with no standardized therapy; methotrexate (MTX) induces significant improvement or remission in some MRH patients according to several reports.[6,7] Cyclophosphamide,[8] leflunomide,[9] azathioprine,[10] and cyclosporin[11] have also proven effective; aside for immunosuppression, in several trials, bisphosphonates[12–14] have also induced remission.

However, some reports present patients who were refractory to disease-modifying antirheumatic drugs, opening a door for alternative strategies such as biologic agents. Current experience includes cases successfully treated with etanercept,[15,16] infliximab,[17–20] or adalimumab[21] as anti–tumor necrosis factor (anti-TNF) agents. To our knowledge, no MRH patient treated with tocilizumab (TCZ) has been reported.

In correlation with the presence of activated, committed macrophagic cells in the MRH nodules, interleukin 1 (IL-1), TNF-α, and IL-6 are overexpressed, and these could be related to the clinical presentation and also contribute to disease pathogenesis.

The intricate relationship between TNF-α and IL-6 creates redundant loops or signaling cycles where blocking either of them results on similar effects over inflammation.[18] The blockade of IL-6 has successfully followed anti-TNF therapy in some of its indications.

Interleukin 6 is overexpressed in the rheumatoid synovium and other inflamed tissues from diseases where TCZ has proven effective; IL-6 was expressed in the MRH inflammatory infiltrate of our patient, in the giant multinucleated cells (GMCs); therefore, TCZ was proposed as a specific immunomodulator to treat this refractory patient.

In this article, we report the case of a 35-year-old woman with MRH, who was refractory to corticosteroids and MTX at top doses and who eventually received TCZ and achieved sustained remission.

CASE PRESENTATION

On September 2009, the patient presented with general malaise, progressive weight loss (15 kg/6 months), mild evening hyperthermia, and diffuse myoarthralgias. A primary care physician prescribed diclofenac; early symptoms initially improved, but in the upcoming months they got worse.

Eventually, an additive polyarthritis started and settled in, presenting itself as a RA in its pattern. It affected both wrists, metacarpophalangeal and proximal interphalangeal (and distal interphalangeal) on both hands and also on both elbows, knees, ankles, and metatarsophalangeal, but it was more severe than

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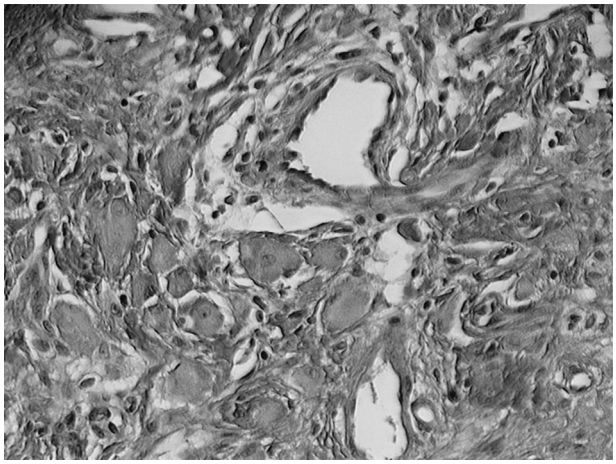

FIGURE 1. Hematoxylin-eosin stain micrograph (original magnification ×100) showing the inflammatory infiltrate and multinucleated cells from one of the patient's nodules. Available in color online at www.jclinrheum.com.

that observed in an average RA patient; indeed, the patient's functional status plunged to functional class IV within days.

Concurrently, multiple vivid erythematous papular lesions appeared on the fingers' dorsa (periungual initially, as coral beds); they were neither painful nor pruriginous, and later on, they extended and raised up to become consistent, gummy nodules ranging in size from some millimeters up to 3 cm.

Nodules spread along the hands, forearms, feet, and forelegs, and in the upcoming weeks, they initially spread on the papulae, and shortly after, nodules were seen on the nose; the eyelids and ears were later involved.

The patient's referral to the hospital explained more the severity of the arthritis than by the notorious dermatitis. Multicentric reticulohistiocytosis was inferred at admission and confirmed with a biopsy days later (Fig. 1). Physical examination was unremarkable aside from joints and skin. No fever was detected; chest and abdomen showed neither abnormalities nor visceromegalies.

We scanned the patient looking for possible neoplasia; chest and abdomen computed tomographic scan, serology (CA-125 and carcinoembryonic antigen), and gynecologic assessment (breast and genitourinary tract) turned out negative, as the esophagogastroendoscopy did. Laboratory results included erythrocyte sedimentation rate of 47 mm/h; C-reactive protein, 16 mg/dL; rheumatoid factor, 1:160; negative anti–nuclear antibody and anti–cyclic citrullinated peptide antibody; hemoglobin, 9.6 g/dL; and normal liver function tests.

Our patient received 3 methylprednisolone IV pulses (1 g/d); afterward, oral prednisone (20 mg/d) and oral MTX (20 mg/wk) were prescribed. Dermatitis partially improved, but arthritis barely changed. One month after, the patient remained in functional class IV; prednisone was increased progressively up to 50 mg/d, achieving some improvement in the arthritis; but just as the dose was tapered down, intense relapse followed on 3 different attempts. Methotrexate dose was adjusted to 25 mg/wk without benefit. Multicentric reticulohistiocytosis is a potentially destructive disease; thus, aside from the handicapping picture, we were further concerned by the potential of structural damage.

After 4 months on top doses of MTX and prednisone with mild improvement, an alternative treatment was essential. Sadly, our patient had neither health insurance nor coverage for anti-TNF drugs, so these were not an option. Fortunately, a lot of TCZ was available with no cost for 1 patient (likely with RA) as a donation for our hospital. The clinical picture of our patient was so desperate that we proposed to our authorities their approval to use the TCZ in our MRH patient. As a strategy to support the use of TCZ, immunofluorescence targeting IL-6 was performed on the nodule biopsy before the onset of the therapy (vide infra). It turned out positive.

After an initial approval, we submitted our petition to the ethics and research committee (it was clear in the submission that it was an off-label use); it was accepted. Finally, it was proposed to our patient, and she agreed. Initially, a 3-month treatment was permitted, and further use was reevaluated as by the results.

We screened the patient for latent tuberculosis with PPD testing and chest x-ray; eventually, a computed tomographic scan (vide supra) showed no evidence of prior or actual Tb infection.

Because the arthritis was so intense and refractory, we selected a high dose for TCZ (8 mg/kg). The patient was flawlessly infused, and after 2 weeks, a very significant improvement was observed in the dermatitis, and by the second dose, a complete absence of nodules was achieved (Fig. 2).

Arthritis improved promptly and sustainedly; at the end of the first month, the patient was on functional class II and basically asymptomatic before the third dose. The MTX dose remained stable; prednisone was tapered in an unfixed, monthly

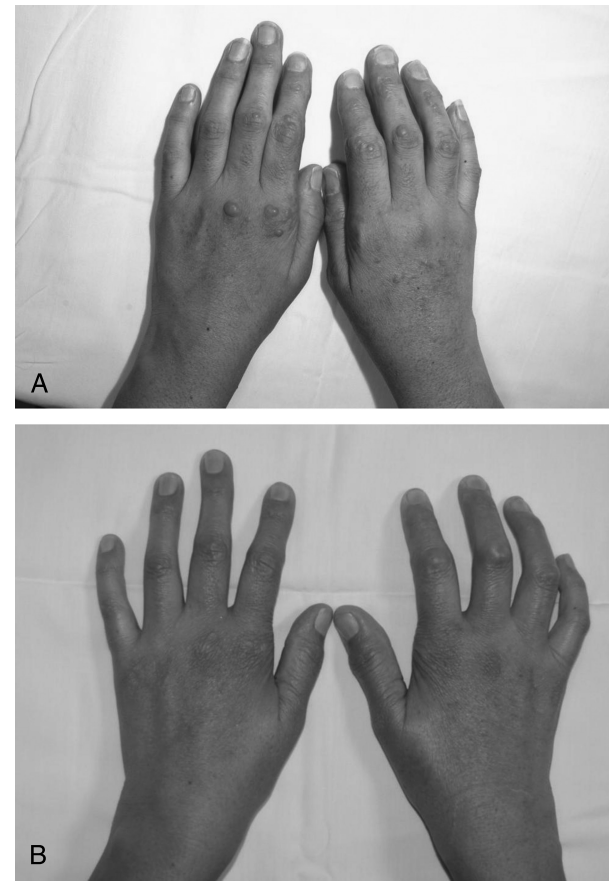

FIGURE 2. A, Patient's hand before starting TCZ (but after prednisone and MTX) showing incomplete resolution of dermatitis. B, Patient's hand after 4 months of treatment. Available in color online at www.jclinrheum.com.

reviewed scheme down to 7.5 mg/d; by the third dose of TCZ, neither cutaneous nor arthritic relapses occurred.

No adverse effects were observed throughout the course of the treatment, and laboratory results (including liver tests and complete blood count) remained unaffected; rheumatoid factor switched negative after the third month, and acute-phase reactants became normal after the second infusion. After 9 monthly infusions, the patient remained asymptomatic on skin and joints.

To carry out the IL-6 immunofluorescence staining, the slides were blocked for 1 hour at room temperature with phosphate-buffered saline at pH 7.4 (bovine fetal serum 10% and skimmed milk 5%). The blocking solution was removed, and approximately 100 μL of the primary antibody in a 1:200 dilution was used to cover the tissue, for an overnight reaction at 4°C in a humid chamber, a negative control including everything in the solutions but the primary antibody, and was run in parallel. After incubation, slides were washed on phosphate-buffered saline, and a secondary antibody (fluorescein isothiocyanate–labeled goat anti–mouse antibody) was added in a 1:1000 dilution and incubated for an hour at room temperature.

The slides showed a positive detection of IL-6 in a variety of cells within the infiltrate (Fig. 3); of particular interest, GMCs showed an intense reaction. Negative control rendered only weak-background, nonspecific immunofluorescence. After the positive detection for IL-6, additional staining with macrophage (anti-CD68) and dendritic cell (anti-CD83) markers was done to further characterize GMCs. Those slides were reviewed under confocal microscopy. In both cases, these markers colocalized with IL-6–positive GMCs, suggesting a dendritic cell of monocyte origin lineage (Fig. 3). A fibroblast marker (ER-TR7) was used as a control and stained no GMCs. All antibodies used in the reactions came from Santa Cruz Biotechnologies (Santa Cruz, CA), and the previously described protocol was used.

DISCUSSION

Pathogenesis of MRH is yet to be understood. Skin nodules and synovial membrane typically show an inflammatory infiltrate, with GMCs sparsely mixed with small histiocytes (indeed, MRH is a histiocytosis). This infiltrate includes also primed T cells (CD8 mainly) and B cells.

The lineage of the multinucleated cells (which resemble foreign-body type) has been debatable. Either a T cell, dendritic, or a monocyte lineage has been proposed, being this latter supported the most by current evidence, because morphologic and functional parallels link GMCs to osteoclasts.[12,22]

The expression of markers for other lineages is, however, inconstant; that is, in the paper from Adamopoulos et al,[22] GMCs were negative for CD3, CD20, and S100, excluding T cell, B cell, and dendritic lineage, respectively, but other cases with positive S100 GMCs have also been detected.[23] In our patient, markers for both macrophagic and dendritic cell lineages were present, suggesting a dendritic cell of macrophagic lineage.

These GMCs consistently express macrophage markers such as CD68, CD45 and are positive for tartrate-resistant acid phosphatase, Mac387, CD15, and others; frequently they express CD14.[24]

The GMCs present a ground-glass aspect and contain deposits of an unspecific accumulation of neutral lipids (probably phospholipids)[24]; this has been deducted based the staining affinity for this material rather than specific chemical characterization.[25] Images from electron microscopy[26] suggest that these lipid vacuoles (likely liposomes) result from a degenerative process more than from abnormal storage.

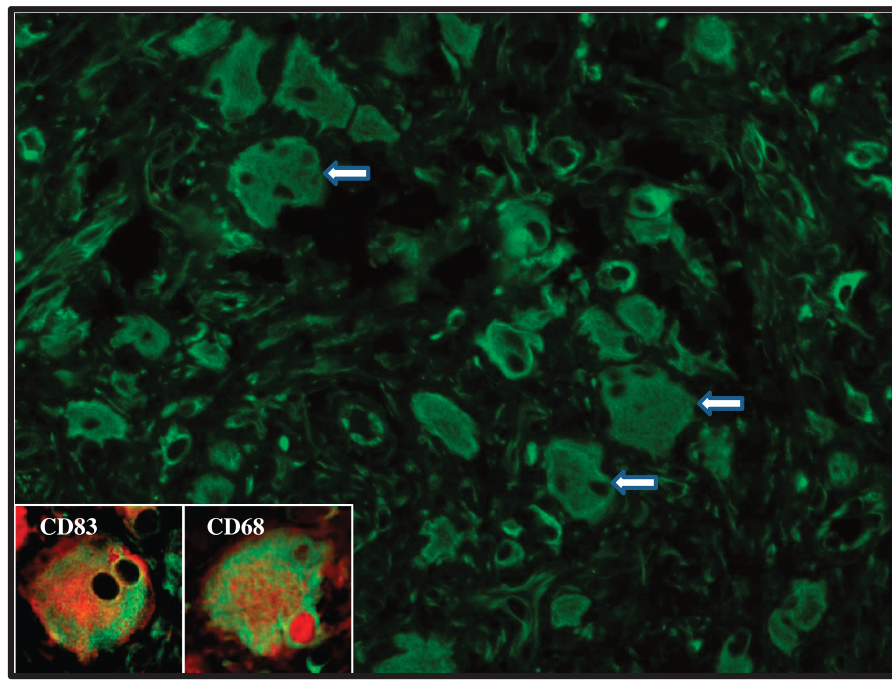

FIGURE 3. Immunofluorescence micrograph (original magnification ×100) of a nodule biopsy stained with an anti-IL6 monoclonal antibody, showing a positive detection in a variety of cells in the infiltrate including GMCs (arrows). Corner: Confocal microscopy (original magnification ×100) showing the positive detection of CD68, CD83, and its colocalization with IL-6 in GMCs.

Interleukin 6 is a pleiotropic cytokine and plays a role as a B-cell differentiation factor, induces T-cell expansion and differentiation to cytotoxic subsets, increases proliferation of hematopoietic precursors, induces macrophage differentiation at their terminal stages, and stimulates synthesis of acute-phase-response proteins (such as C-reactive protein) in hepatocytes.

Interleukin 6 causes fever because it is able to cross the blood-brain barrier and stimulates hypothalamus to raise the body temperature. Interleukin 6 transgenic mice exhibit polyclonal hyperglobulinemia, splenomegaly, adenomegaly, and disperse inflammatory infiltrates. Some symptoms in MRH patients may be explained by the increased secretion of IL-6: fever, weight loss, arthritis, and bone resorption, and although the role for IL-6 as a trigger or nodule formation is not defined, its stimuli over macrophages could account for proliferation, activation, and differentiation.

Interleukin 6 may indeed play a role in the inflammatory structure of the nodules and account for some destructive features of MRH including osteoclastogenesis.[27] In our patient, IL-6 is clearly expressed in the cutaneous inflammatory nodule in a variety of cells including local histiocytes and GMCs. Interleukin 6 blockade with TCZ markedly improved her clinical picture.

Several bone-invasive neoplasms activate osteoclasts via IL-6,[27] which is expressed in stromal cells (mostly fibroblasts) within bone-tumor interface ,and its expression correlates with that of RANKL (also in fibroblastic cells), conforming an osteoclastogenic environment in which bone invasiveness is the resultant.

Synovial fluid mononuclear cells from MRH arthritic patients are osteoclast precursors. The synovial fluid in patients with MRH contains a higher concentration of TNF-α (5 times) and lower concentrations of osteoproteregin if compared with samples from osteoarthritis patients. In presence of TNF-α, RANKL is induced on osteoblasts and fibroblasts. Osteoclast differentiation among precursors is feasible.[22]

In skin nodules, GMCs also express osteoclast surface markers, such as coincidental tartrate-resistant acid phosphatase and cathepsin K,[28] and interestingly, GMCs from MRH patients (in contrast to those from sarcoidosis, RA, and other granulomatous diseases) express CD10, a potential marker predicting its destructive and invasive nature; this marker is also known as neutral endopeptidase (among others) and is a zinc-dependent metalloproteinase present in the active invasive areas of several carcinomas (including lung and prostate).

Tocilizumab is a humanized immunoglobulin G1 antibody against IL-6 receptor (both soluble and membrane-attached) and blocks IL-6 proinflammatory actions. In 2009, TCZ was approved in Europe for moderate to severe RA and more recently in different countries.

Several trials have established the safety and efficacy of TCZ for MTX-refractory[29] anti-TNF–refractory[30] and naive early-RA patients, and aside from its efficacy to improve disease activity, long-term follow-up[31] confirms a preventing effect on radiographic progression comparable to that of anti-TNF agents.[32,33]

Tocilizumab represents a promising alternative and is currently being tested for additional indications (following anti-TNF trend); current reports include systemic lupus erythematosus and[34] spondylarthritis.[35,36] Successfully treated case reports include patients with polymyositis,[37] renal amyloidosis,[38] polymyalgia rheumatic,[39] graft-versus-host disease,[40,41] and Takayasu disease.[42,43]

In this report, we describe the positive effect of TCZ in the skin and joints of a patient with MRH who was refractory to a combination of MTX and high-dose prednisone. Although previous experience with anti-TNF agents in MRH is encouraging, the potential role of TCZ as an alternative agent is welcome especially in patients with contraindications to anti-TNF.

Further experience is required to ascertain the consistency of our findings.

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