

# Multicentric Reticulohistiocytosis Treated Successfully with Etanercept

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**Abstract:** Multicentric reticulohistiocytosis (MRH) is an uncommon systemic disease of unknown aetiology, which is characterized by the presence of papulonodular lesions, and is caused by the proliferation of histiocytes associated with arthritis. There are only just 200 cases described in the scientific literature. It can behave like a paraneoplasia and may be malignant in a quarter of the patients. We would like to add our patient to those described in the literature. Our patient was a 68 year-old male stonemason who was diagnosed of multicentric reticulohistiocytosis and was previously unsuccessfully treated with classical immunosuppressants. The patient did, nonetheless, develop favourably with etanercept, with remission of the clinical and articular lesions.

In our opinion we feel that new treatment hopes will emerge for the treatment of inflammatory diseases where tumoral necrosis factor (TNF)-alpha and other cytokine production by monocytes and macrophages will play an important role.

**Keywords:** Multicentric reticulohistiocytosis, TNF-alpha, etanercept.

## INTRODUCTION

Multicentric reticulohistiocytosis (MRH) is an uncommon systemic disease of unknown aetiology, which is characterized by the presence of papulonodular lesions, and is caused by the proliferation of histiocytes associated with arthritis. The term MRH was first used by Goltz and Laymon in 1954 [1] to distinguish it from cutaneous solitary reticulohistiocytosis [2], for describing patients showing destructive polyarthropathy and multiple cutaneous nodules. MRH is an uncommon condition with only 200 cases being described in the literature. It can behave like a paraneoplasia and can be malignant in a quarter of the patients. It occasionally gets better spontaneously.

## CASE REPORT

The case is of a 68-year-old male patient with multiple nodular lesions, which gradually appeared over a 4 year period, and which were accompanied by pruritus in the hands, arms and face. Multiple nodules were also observed on the right elbow and oedema in the left elbow. On the face we observed a nodule on the nasal pyramid (Fig. 1) and other smaller nodules in the nasal mucous membrane. The oral mucous membrane was free from lesions. Facial rash with xanthelasmas was observed; as well as sequels of predominantly bilateral polyarthritis, in the hands which caused their deformity (Fig. 1). Blood tests revealed GSR: 16; glucose: 121; uric acid: 3.1; PCR: 21; polyclonal hypergammaglobulinemia and FR: negative. Thoracic CAT revealed reticulohistiocytosis with a predominance of mean and upper fields, perilymphatic millimetric nodules, which caused retr-

action of the pulmonary architecture and fibrosis at the apexes. Pathological anatomy revealed a diffuse infiltrate of the dermis by histiocytes and giant multinucleate cells eosinophil pale, fine and granular cytoplasm. The cytoplasm of our cells was PAS positive (Figs. 2, 3). The patient was treated with various anti-inflammatory and anti-mitotic drugs, with scarce and intermittent improvement with the latest treatment regime being a combination of 40 mg of oral methylprednisolone, omeprazol and weekly shots of 20 mg of metotrexate. In previous studies and *via* immunohistochemical techniques the presence of histiocytes of monocytic-macrophagic origin and abundant cytokines was demonstrated, such as the TNF-alpha [3, 4]. This led us to use etanercept at a dose of 25 mg twice a week, and, later, 50 mg weekly. The doses of the earlier drugs were progressively reduced. The patient's clinical cutaneous and articular symptoms are, at present, in the process of remission (Fig. 4). The improvement was particularly noteworthy from the fourth dose onwards.

## DISCUSSION

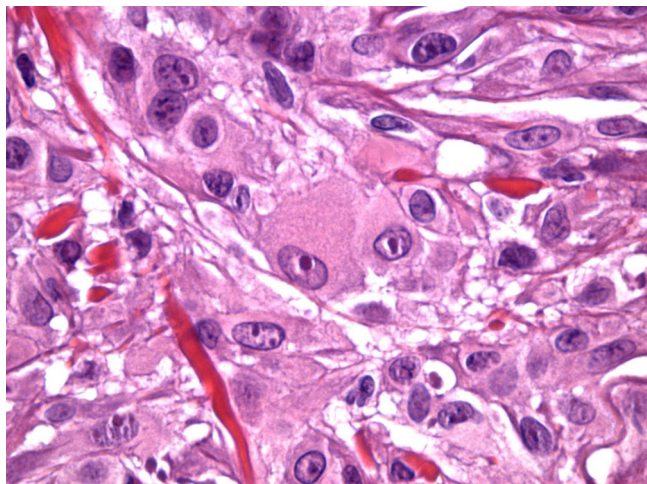
The initial form of presentation in half the patients is of a polyarthritic type. Cutaneous lesions are common, in a quarter of the patients with papules and nodules. Another quarter part of the patients developed articular and cutaneous lesions at the same time. The cutaneous lesions are asymptomatic.

A third of the patients showed pruritus. Almost a third of the patients suffered constitutional symptoms such as weakness, weight loss and fever. The disease rapidly spreads at first, later diminishes and finally disappears. The cutaneous lesions are, in general, red or yellow-brown. The size may vary between papules of 1-2 mm till nodules of various centimetres in diameter. The lesions may be isolated or grouped, giving a cobble-stoned appearance. Thus they may coalesce into plates. In a third of the patients xanthelasma may develop, but this is not clearly related to MRH. Growth of the

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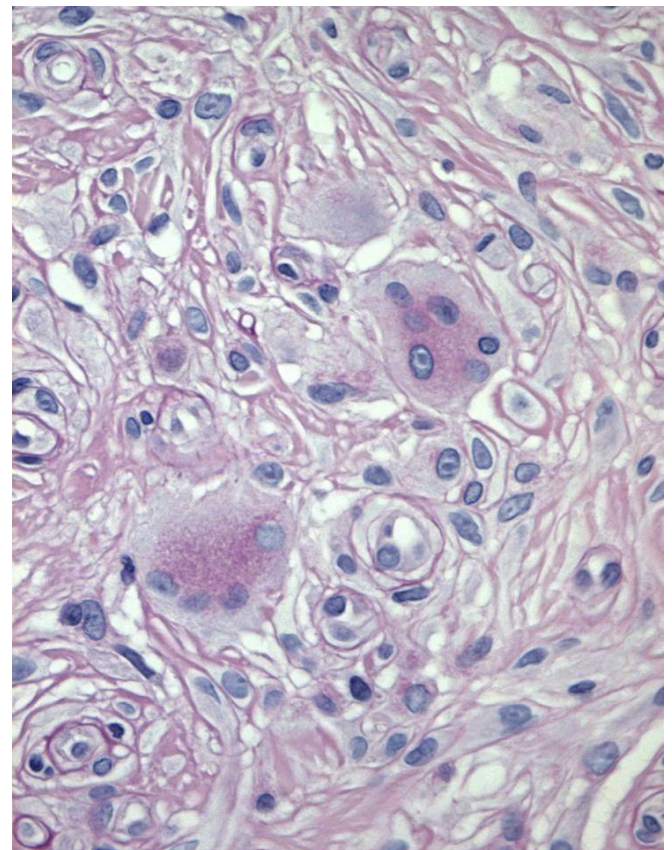
**Fig. (1).** Appearance of the hands with typical nodular lesions before treatment with anti-TNF-alpha.



**Fig. (2).** Infiltrate composed of polygonal cells with wide cytoplasm, eosinophil “in polished glass” and oval nucleoli (Haematoxylin-eosin, x100).

nodules is slow and rarely leads to ulceration. The phenomenon of Koebner has been described in this disease. It is a weakening disease, which does not threaten the patient’s life, except in those cases where it is associated with neoplastic processes. This is the same case as observed in spontaneous regression in a few isolated cases [5, 6]

MRH is histologically characterized, in the skin, by a dense infiltrate in the dermis made from histiocytes and giant multinuclear cells. Both have dense finely granular eosinophil cytoplasm “in polished glass”. Secondary alterations of the epidermis, principally hyperkeratosis, and flattening of the epidermal crests. Histochemically cellular cytoplasm stains uniformly with PAS-diastase. In the immunohistochemical study positive macrophage markers were observed (CD68, NAM 56, MAC 387) and negative markers for Lang-



**Fig. (3).** The cytoplasm of our cells was PAS positive and sensitive to diastase digestion (x40).

herans cells (CD1a, S100). We are dealing with a cellular proliferation of monocytic-macrophagic stock. Langerhans granules were not perceivable under the electron microscope [7, 8].



**Fig. (4).** Appearance of hands after one and a half years treatment with etanercept.

With regards to the laboratory study, half the patients, as occurred with our patients, had high sedimentation rates. Some were suffering from anaemia, diabetes, positive cryoglobulins, dyslipemia or hypergammaglobulinemia. This last anomaly was found in our patient. With regards to image studies, radiography revealed severe destruction of the cartilage and affected articulations. Typical lesions consisted of slight osteopenia and marked reabsorption of sub-chondral bone. Development of the lesions may be rapid and may even provoke mutilating arthritis. Radiological changes are often observed in the proximal and distal inter-phalangeal articulations. Osteoporosis is either minimal or absent. Neither sub-chondral sclerosis nor periosteal reactions have been observed.

Etanercept is a recombinant fusion protein of the soluble receptor of the TNF. It joins and is neutralized competitively and reversibly in both soluble TNF and when joined to the cellular membrane. It also neutralizes alpha lymphotoxin. Recently published papers provide MRH cases successfully treated with etanercept [9-12]. Nonetheless, results are controversial, since other authors such as Sellam *et al.* did not observe the expected improvement in these patients, to whom infliximab was also administered [13].

## CONCLUSIONS

We believe that, with the arrival of biological therapies, new treatment hopes for inflammatory diseases in which TNF-alpha production and other cytokines by monocytes and macrophages play an important role, will emerge. TNF-alpha is found in the synovial fluid of patients suffering from

rheumatoid arthritis and in severe forms of inflammatory arthritis, as well as in patients with MRH. The notable improvement that appeared during the development of our patient, who was only treated with etanercept, reveals the efficacy of this medicine in this type of pathology on its own, and without judging it as a helper for other immunosuppressors. This makes it the preferred treatment for patients suffering from MRH with severe cutaneous manifestations whom have been seen to be resistant to treatment with classic immunosuppressors.

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