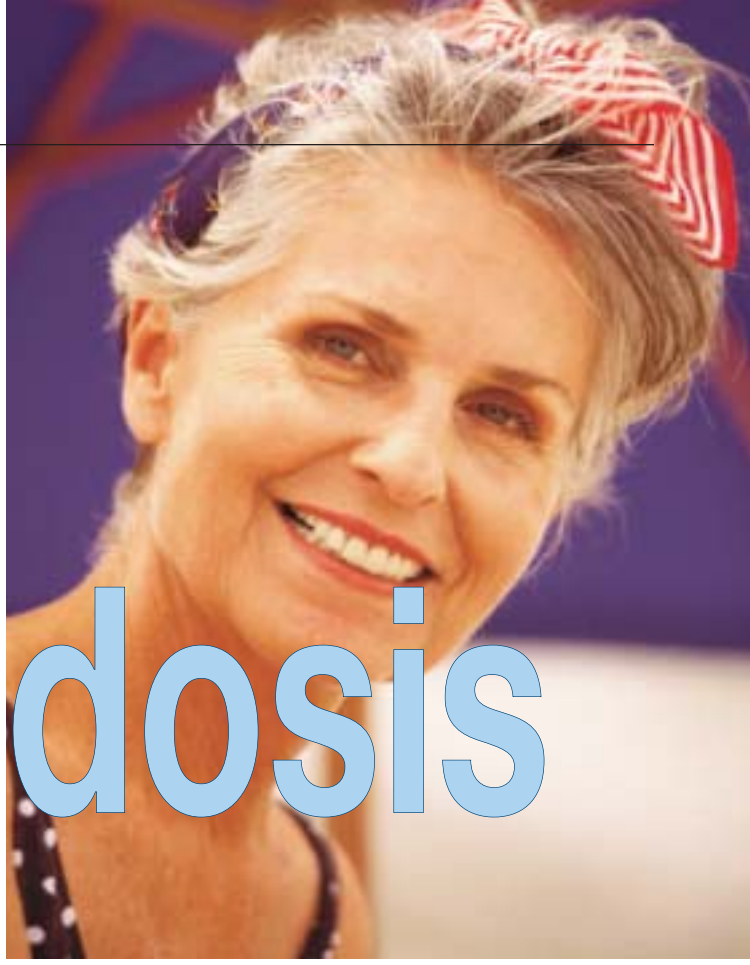
Infliximab in sarcoidosis



By Monique Camerlain, MD, FRCPC

Mrs L.V. is a 65-year-old Caucasian woman and a retired laboratory technician. In 1999, she was diagnosed with seropositive nodular erosive rheumatoid arthritis. She was referred to our clinic in the spring of 2001 because her disease was resistant to methotrexate, 20 mg/week; prednisone, 10 mg/day; and rofecoxib, 25mg/day. As we tried to initiate combination therapy, she developed a severe cutaneous rash to chloroquine. She requested a prescription of infliximab, having read about the new class of remitting agents and being privately insured.

Looking at her history, we discovered Mrs. L.V. received a high dose of corticosteroid therapy for a biopsy-proven pulmonary and cutaneous sarcoidosis in 1998. She recovered fully and her tuberculin test was negative at the time.

Concerned with the possibility of reactivating Mrs. L.V.'s pulmonary disease with infliximab, we reviewed the literature on sarcoidosis in rheumatology and infliximab use in these types of patients.

Infliximab in sarcoidosis

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What is sarcoidosis?

Sarcoidosis is a visceral disease of unknown etiology characterized by non-casealing granulomas (see Figure 1). In 1877, sarcoidosis was first described in a patient with raised purple cutaneous lesions on his hands and feet.[1]

Who gets sarcoidosis?

The prevalence of sarcoidosis in the U.S. is approximately 1 - 40 for every 100,000 people. The incidence is 11/100,000 cases in Caucasians and approximately 3/100,000 in the black population. Sarcoidosis is more severe among blacks and more frequent in women and people under the age of 40.[2]

Common symptoms & diagnosis

The rheumatological manifestations are: arthropathy, bone disease, muscle disease, vasculitis and diverse conditions of the conjunctive tissue.[3] Arthropathy is present in 25% of cases and it can be acute or chronic.

The acute form is characterized by erythema nodosum (see Figure 2), with or without pulmonary hilar adenopathies (see Figure 3). Females are more frequently affected with swelling of the ankles and knees. There is an association with human

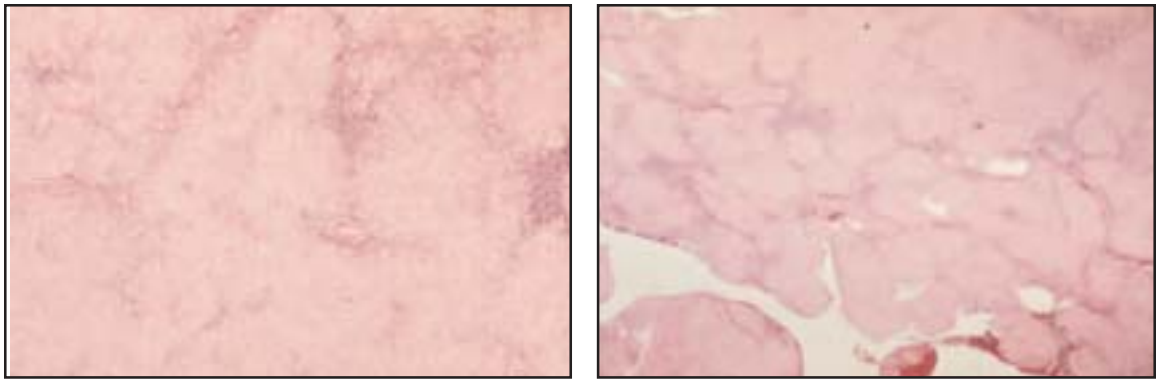


Figure 1: Non-caseating granuloma in adenopathy.

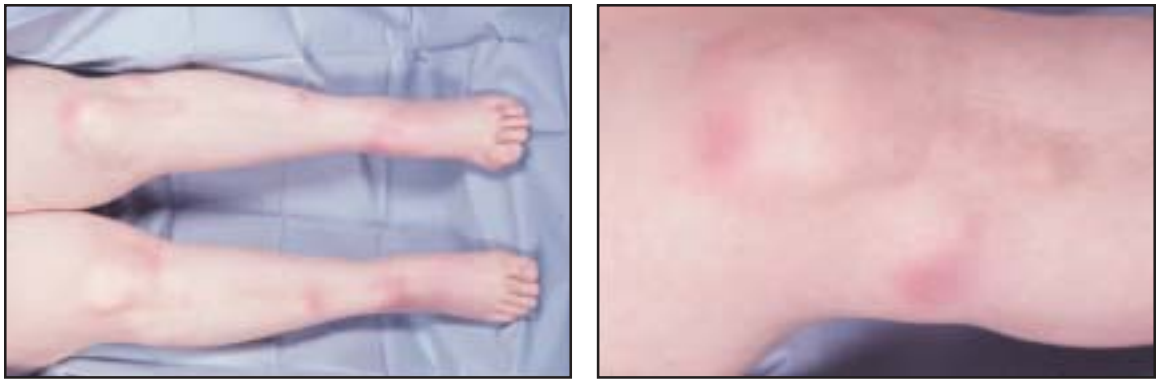


Figure 2: Acute arthritis with erythema nodosum.

lymphocyte antigen (HLA)-Dr 3 typing. The evolution is favorable, with no erosion or deformation.

The chronic form affects the hands, knees and ankles. Chronic arthropathy (Jacoud type, nonerosive with reducible deformity) is associated with pulmonary sarcoidosis and elevated levels of conversion enzyme for angiotensin.

Bone disease is found in 13% of patients. It is generally asymptomatic with lesions of the hands and feet. The lesions are cystic and lytic, and have a reticular lacy appearance on radiographs. Muscular disease is asymptomatic in 80% of cases. It affects proximal ocular and diaphragmatic muscles. The acute form responds well to corticosteroid therapy. Non-caseating granulomas are observed with a biopsy.

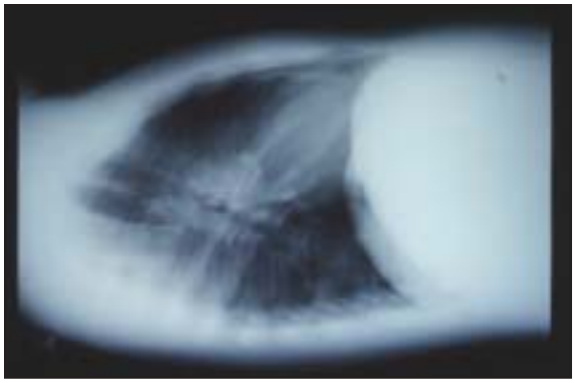
Sarcoidosis can be associated with various autoimmune diseases. It has been described with vasculitis, Sjögren's syndrome, myasthenia gravis, rheumatoid arthritis, primary biliary cirrhosis and antiphospholipid syndrome.

How is it treated?

Discussions on treatment are influenced by the presence of spontaneous remissions of pulmonary involvement in 60% to 88% of Grade I cases, 50% to 60% of Grade 2 cases, and in less than 30% of Grade 3 patients.

The following criteria for treatment have been defined: aggravation of pulmonary symptoms, deterioration of pulmonary functions, progressive of X-ray changes (fibrosis), pulmonary hypertension and important extra-thoracic manifestations.

Corticosteroids are prescribed as the first-line drug, 0.5 mg/kg to 1 mg/kg for three months. Therapy is progressively tapered off to 10 mg to 20 mg every other day for a year. Lower and Borghman have reported treating 50 patients with



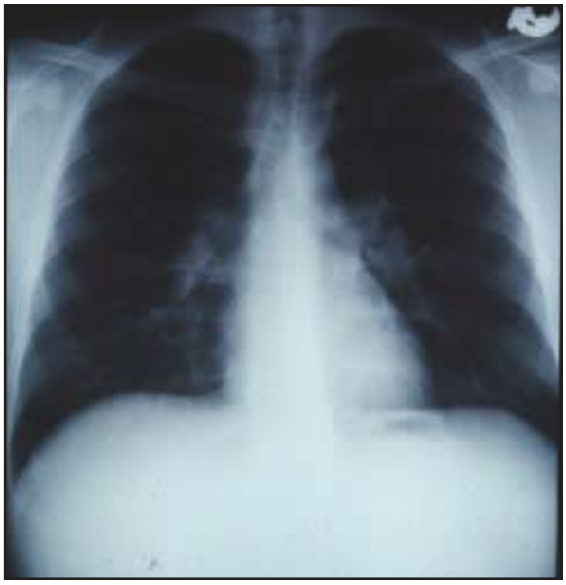


Figure 3: Pulmonary Hilar Adenopathy.

methotrexate as a second-line agent. There was a positive, mainly cutaneous and musculoskeletal, response, in 33 patients.[4]

Other agents have been used, mainly anti-inflammatories, retinoids, chloroquine, azathroprine, chlorambucil and cyclophosphamide.[5,6,7]

Infliximab is a chimeric monoclonal antibody which specifically inhibits TNF-a and has proved useful in treating rheumatoid arthritis, Crohn's disease and psoriasis. Its efficacy was investigated in patients with persistent symptomatic sarcoidosis because TNF-a appears to be an important cytokine in the inflammation of sarcoidosis.

Borghman and Lower treated patients with persistent symptomatic sarcoidosis despite corticosteroids and immunosuppressive agents with infliximab. Patients were treated initially at 2 - 4 weeks and at 12 weeks with 5 mg/kg of infliximab at each treatment. Index lesions which had progressed, despite corticosteroid therapy, were revaluated at 16 weeks. In two of the three patients treated, the index lesion was lupus pernio which improved significantly with infliximab. The third patient had restrictive lung disease. At week 16, there was a 26% improvement in the vital capacity from pre-treatment values. All patients tolerated the treatments well.[8]

Yee and Pochapin treated a 72-year-old woman with sarcoidosis presenting with severe protein-losing enteropathy, hypoalbuminemia and proximal myopathy. She had not responded adequately to corticosteroid therapy and her clinical course was further complicated by acute tubular necrosis and renal failure requiring long-term hemodialysis.[9]

Intravenous infusions of infliximab, 5 mg/kg, were given at week 0 - 2 and at week 6. There was a clinical response of enteropathic and myopathic symptoms and of serum albumin level. The clinical course was complicated by the development of an hypercoagulable state associated with circulating anticardiolipin antibodies which prompted discontinuation of infliximab.

Infliximab therapy appears successful in the treatment of refractory sarcoidosis. It may cause adverse events associated with cytokine cascade manipulation. The U.S. Food and Drug Administration (FDA) Advisory Committee published a summary of worldwide complications associated with TNF-a inhibitors in August 2001.[10]

Case Management

After we reviewed the literature, we prescribed infliximab to our patient, Mrs. L. V,. without fear of reactivating her cutaneous and pulmonary disease. At week 6 of her treatment with 3mg/kg of infliximab, her ACR (American College of Rheumatology) 20 response was positive and she tolerated her treatment. She is now doing well on maintenance therapy. Dx

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Suggested Readings
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