Therapeutic Vignette: Old and New Drugs in Mixed Connective Tissue Disease

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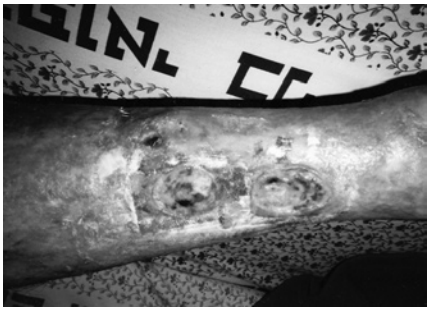
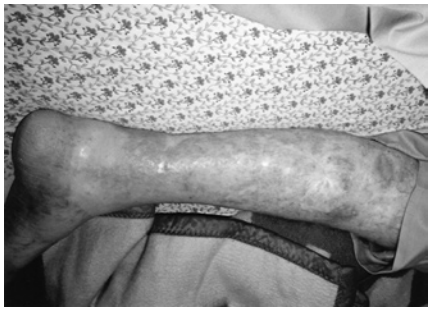
Mixed connective tissue disease is an overlap syndrome combining features of systemic lupus erythematosus, systemic sclerosis and polymyositis, together with the presence of antibodies to U1-RNP. While there is no specific treatment for MCTD, one of the original claims in support of its being a "distinct clinical entity" was its purported favorable prognosis and its unusually good responsiveness to treatment with steroids, when compared to its constituent entities. It is now generally agreed that the treatment of MCTD depends entirely on each patient's clinical involvement, requiring only symptomatic treatment in mild disease to high dose corticosteroids often combined with immunosuppressive drugs in the presence of severe manifestations [1]. We describe a patient with MCTD with various evolving end-organ complications: necrotizing cutaneous vasculitis treated with an "old drug," potassium iodide, and later presentation of a severe intractable polyarthritis treated with a "new drug," an anti-tumor necrosis factor agent. This clinical picture was then further complicated by malignant lymphoma and a rapid demise.

Patient Description

A 59 year old previously fit white man was diagnosed with MCTD when presenting with Raynaud's phenomenon of recent onset, polyarthritis, telangiectasia and myositis with laboratory studies remarkable for high creatine phosphokinase and acute-phase reactants, elevated globulins, positive rheumatoid factor, antinuclear antibody and anti- U1-RNP. Anti-Sm, anti-DNA, anti-topoisomerase I(Scl -70), anti-centromere and anti-Jo were negative. Other investigations ruled out coexisting infections and malignancy.



[A] Severe ulcers on the leg before potassium iodide therapy



[B] Complete remission after 3 months of potassium iodide

The patient was treated with low doses of corticosteroids, methotrexate 7.5 mg per week, folic acid and hydroxychloroquine 400 mg daily. The muscle and joint symptoms resolved. Four years later, the patient complained of Raynaud's phenomenon exacerbation in the hands and several ulcers on the left calf [Figure A]. A biopsy revealed necrotizing granulomatous cutaneous vasculitis.

Chest X-ray, echocardiogram and echo-Doppler of the legs were normal. Autoantibodies RF, ANA and U1-RNP remained positive with new high immunoglobulin M anticardiolipin level, 53 u/ml (normal range 0–10). The patient was treated with high dose corticosteroids (1 mg/kg), methotrexate 25 mg/week, intravenous iloprost, cilazapril and antibiotics. Since there was no improvement, pulse methylprednisolone, alternate antibiotics, and then hyperbaric oxygen and skin grafting were administered but 6 months of these efforts failed to heal the open skin lesions. There was no involvement of a major internal organ (heart, lung, kidney or gastrointestinal tract) and so potential cyclophosphamide toxicity was felt to outweigh its possible efficacy in this setting.

An "old therapy" from the 19th century, potassium iodide, 300 mg orally three times a day, was started [2]. A good response was seen after 1 month, and complete resolution of the skin ulcers was noted after 3 months of therapy [Figure B]. Since there were no side effects or reactivation of the lesions, potassium iodide was stopped after 6 months.

For the next 3 years the patient felt well, with maintenance prednisone of 5 mg/day, methotrexate 10 mg/week, folic acid and hydroxychloroquine. There was a mild relapse with a small skin ulcer on the left ankle malleous, which resolved

MCTD = mixed connective tissue disease

RF = rheumatoid factor
ANA = antinuclear factor

again with a short course of potassium iodide.

The patient had no pulmonary complaints but routine two-dimensional Doppler-echocardiography and computed tomography of the chest revealed evidence of pulmonary hypertension with enlarged central pulmonary arteries and estimated pulmonary arterial pressure 51 mmHg (normal range < 30 mmHg). Cardiac right and left catheterization confirmed pulmonary hypertension with normal coronaries arteries. No cardiac shunt was noted. He was treated with intravenous iloprost, angiotensin-converting enzyme inhibitor and selective alpha-1 blocker while azathioprine 100 mg/daily was added to methotrexate and corticosteroids.

Six months later the patient was hospitalized due to flare of the polyarthritis, exacerbation of Raynaud's phenomenon, appearance of new subcutaneous nodules on the elbows and very high acute-phase reactants. After pulse i.v. steroids, infliximab (3 mg/kg) was initiated and continued along with the azathioprine 100 mg/day and methotrexate 15 mg/week. There was good clinical improvement, equivalent to an American College of Rheumatology 70 response, C-reactive protein down to 0.8 mg/dl (normal < 0.5). After a full year of therapy with infliximab, the patient was admitted for fever of unknown origin. A mass 4 x 4 cm was noted retrocarinally on chest CT, not present on re-review of a previous chest CT obtained 14 months earlier. On excision, the histology of the mass was consistent with a malignant lymphoma, diffuse, large cell B type. A few days after the tumor resection, the patient succumbed to sepsis and died with multiple organ systems failure.

Comment

The long-term outcome in MCTD is generally good. Burdt et al. [3] reported a favorable long-term, 15 ± 8 year, outcome in 62% of patients. The remaining 38% had continued active disease or died, pulmonary hypertension being the most frequent disease-associated cause of death.

We describe a patient with a relatively late onset of MCTD who presented two disabling complications of non-major organ targets within 10 years of disease onset. The first was an extensive intractable necrotizing cutaneous vasculitis with ulcers, possibly related to newly acquired anticardiolipin antibodies, which was successfully treated with potassium iodide. This "old drug" is well known by dermatologists and, we suggest, should be better known by rheumatologists. Our experience with the successful treatment of intractable livedoid vasculitis with this modality has been reported previously [4]. In the present case, the evolution of MCTD was further marked by severe polyarthritis, unresponsive to combinations of disease-modifying antirheumatic drugs, and so the patient was treated with the biologic anti-TNF agent infliximab, theoretical concerns for the development of a lupus-like syndrome notwithstanding. The patient subsequently developed a malignant lymphoma, diffuse, large cell B type.

There is a well-appreciated increased risk of lymphoma in rheumatoid arthritis, SLE and methotrexate therapy with a possible but controversial additional contribution by anti-TNF agents in rheumatoid arthritis [5], but no such association with lymphoma has been established in MCTD. In the present patient there was no evidence of lymphoma on CT of the lung before initiation of infliximab and thus there is a time-related association to TNF-blocking therapy and the development of this malignancy in this case. To the best of our knowledge this is the first reported case of lymphoma developing with anti-TNF therapy in MCTD. Thus, the above described case illustrates the use of both "old" and "new" modalities in the management of complex disease entities.

TNF = tumor necrosis factor
SLE = systemic lupus erythematosus

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