Successful treatment of multi-organ refractory sarcoidosis with Adalimumab

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Introduction

Sarcoidosis is a multi-organ granulomatous disorder of unknown etiology that typically affects young adults. Sarcoidosis most frequently involves the lung. Common extrapulmonary sites are the eyes, joints and skin. The illness can be mild and self-limiting but can also lead to progressive multi-organ failure. If treated, systemic glucocorticoids are the most commonly used agents. Several cytotoxic and immunosupressive medications have been reported successful in the treatment of refractory cases.

Tumor necrosis factor-alpha (TNF-α) is important in the pathophysiology of the granulomatous inflammation that exists in sarcoidosis. Specific inhibition of TNF-α with the monoclonal antibody Infliximab has been reported successful in several case reports. A phase II clinical trial showed significant improvement of FVC with Infliximab treatment in stable sarcoidosis patients. Less is known about treating sarcoidosis with other TNF-α inhibiting agents like Adalimumab. To emphasize the clinical usefulness of anti-TNF-α therapy and propose a good alternative to Infliximab, we here report two cases of refractory multi-organ sarcoidosis responding well to treatment with Adalimumab.

Case reports

Case 1

A 55-year old man with a history of Granuloma Annulare (GA), was admitted to the surgical outpatient clinic in our hospital with a facial node on the forehead just above the right eyebrow. An excision of this node showed a granulomatous inflammation with birefringent material on polarization microscopy. A few months later the patient presented with photophobia to the ophthalmologist. An iridocyclitis was confirmed and steroid treatment was started.

The patient had no respiratory symptoms. There was no history of nicotine abuse. He worked as a technical engineer in a hospital. Now and then he had been exposed to chemical agents like solder damps, silicon-spray or formaldehyde resins. His family history showed a twin brother with GA as well. Additional patient characteristics found during the further evaluation of the patient are shown in table 1. It was concluded that our patient suffered from sarcoidosis with hypercalcemia, cutaneous, ocular and pulmonary manifestations. Medical treatment was initiated with Methotrexate 7.5 mg weekly. The urinary calcium level normalized but the iridocyclitis persisted and it was decided to add Adalimumab (first dose 80mg, subsequently 40mg weekly) as a TNF-α inhibiting agent. Consequently, the ocular manifestations disappeared completely. Also the cutaneous lesions showed a very good respons. A new thoracic CT scan showed that all previous pulmonary lesions went into regression (see figure 1). Also laboratory results improved (see table 1). Moreover, the GA considerably improved as well.

Characteristics	Case 1		Case 2	
Age at diagnosis	55		69	
Symptoms	Photophobia		Fatigue, dry cough, compromised vision, arthralgia	
Physical examination *(figure 1)*	Skin lesions on extremities (GA)		Facial skin lesions	
Ocular examination	Iridocyclitis		Posteroir uveitis	
Pulmonary function tests Forced vital capacity *(% of predicted)* Diffusing capacity *(% of predicted)*	75% 68%		112% 70%	
Imaging Chest radiograph stage High resolution computer tomography *(figure 2)*	II Mediastinal/hilar lymphadenopathy, beaded interlobar septa Oberstein score: 13		II Mediastinal/hilar lymphadenopathy, thickened interlobar septa, pleural lesions Oberstein score: 4	
Skin biopsy	Granulomatous inflammation with birefringent material		Granulomatous inflammation	
Laboratory results *(before and after treatment)*	Before	After	Before	After
Calium (mmol/l, 2.1-2.6)	2.6	2.4	2.3	618
Soluble IL-2 receptor (pg/ml, 240-3154)	4241	1207	4093	1
Angiotensin converting enzyme (U/l)	44	21	1	
Urinary calcium (mmol/24u, 2.5-7.5)	11.3			

Table 1. Patient characteristics.

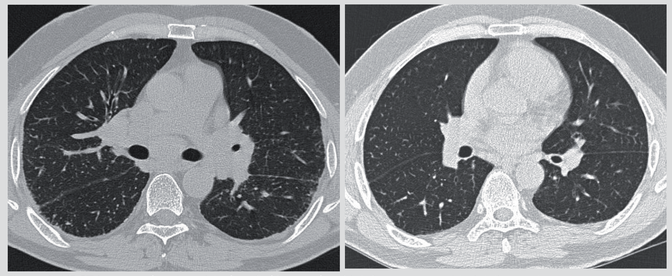

Figure 1. HRCT images of patient 1 before (left) and after (right) treatment with Adalimumab.

Figure 2. Skin lesions of patient 2 before (left) and after (right) treatment with Adalimumab.

Case 2

A 69-year old woman was referred to our hospital, a tertiary referral centre for sarcoidosis. She was diagnosed with the disease elsewhere. A skin biopsy showed granulomas consistent with sarcoidosis. Her medical history showed a type two diabetes, axonal polyneuropathy with neuropathic pain and psoriatic disease.

She suffered from fatigue and a dry cough. She had stopped smoking eight years ago and had no history of pulmonary disease. She used to work in a snackbar on a shipyard.

Further evaluations on the patient are shown in table 1.

It was concluded that also this patient suffered from an active sarcoidosis with pulmonary as well as extra-thoracic manifestations in the skin, eyes and joints. Medical treatment was initiated with Methotrexate 7.5 mg weekly in combination with Adalimumab (first dose 80mg, subsequently 40mg once week). After six months treatment with the above regiment the clinical situation improved significantly. The skin lesions improved dramatically (figure 2) and the pulmonary abnormalities on HRCT stablised. Also the laboratory results improved (see table 1). After two years of treatment she still feels much better.

Discussion

Treatment of chronic sarcoidosis remains controversial. Standard treatment with systemic corticosteroids is often successful. In refractory cases several agents such as Methotrexate, antimalarial drugs and thalidomide have been proven useful but are potentially toxic.

Sarcoidosis is a Th-1 lymphocyte mediated disease in which production of TNF-α plays a central role. It plays a crucial role in the development of the noncaseating granulomas that are the hallmark of sarcoidosis. The anti-TNF-α antibody Infliximab binds to and neutralizes TNF-α, thereby inhibiting its action. Infliximab has been reported successful in treating sarcoidosis. Besides Infliximab, Adalimumab is another TNF-α inhibiting drug. Nevertheless, its contribution in the treatment of refractory sarcoidosis is less well studied. Several case histories report positive effects of Adalimumab treatment on neurologic and cutaneous manifestations, fatigue and cognitive failure from sarcoidosis.

Our two cases indicate the usefulness of Adalimumab in chronic refractory sarcoidosis with GA, uveitis, as well as pulmonary involvement. In both cases pulmonary, as well as cutaneous and ocular manifestations showed dramatic improvement.

There are several potential advantages of treatment with Adalimumab above Infliximab. First of all Adalimumab can be self administered subcutaneously while Infliximab must be given intravenously in hospital. Moreover, the intravenous injection needs medical monitoring, since allergic infusion reactions are described in 9% of cases. Besides these side-effects, anti-Infliximab antibodies may develop in patients who require high doses. However, currently Adalimumab is only reimbursed in patients suffering from uveitis. Studies evaluating the effect of Adalimumab on other manifestations of sarcoidosis are needed.

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