

Case report

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Successful treatment of recalcitrant cutaneous sarcoidosis with fumaric acid esters

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Abstract

Background: Sarcoidosis is a multisystem disease of unknown origin characterized by the formation of noncaseating granulomas, in particular in the lungs, lymph nodes, eyes, and skin. Systemic treatment for cutaneous sarcoidosis can be used for large disfiguring lesions, generalized involvement, or recalcitrant lesions that did not respond to topical therapy.

Case presentations: We report three patients with recalcitrant cutaneous sarcoidosis who were treated with oral fumaric acid esters (FAE). Three female patients presented with cutaneous sarcoidosis that have proved to be refractory to various therapies, including corticosteroids and chloroquine. We treated the patients with FAE in tablet form using two formulations differing in strength (Fumaderm[®] initial, Fumaderm[®]). Dosage of FAE was performed according to the standard therapy regimen for psoriasis patients. After treatment with FAE (4–12 months), a complete clearance of skin lesions was achieved in the three patients. The side effects observed in this trial correspond to the well-known spectrum of adverse effects of FAE (flush, minor gastrointestinal complaints, lymphopenia).

Conclusions: On the basis of our findings FAE therapy seems to be a safe and effective regimen for patients with recalcitrant cutaneous sarcoidosis. Nevertheless further investigations are necessary to confirm our preliminary results.

Background

Sarcoidosis, a multisystem disorder of unknown aetiology characterized by the formation of noncaseating granulomas, may involve any organ of the body, but the most common sites of predilection are the lungs, lymph nodes, eyes, and skin. The predominance of activated T helper cells in affected sites may account for many of the immunologic aberrations observed in sarcoidosis. The production of macrophage chemotactic substances by T cells may be the initial stimulus for the formation of granuloma.

The clinical variants of cutaneous sarcoidosis (CS) are micronodular-disseminated, macronodular, subcutaneous-nodular, cicatricial sarcoidosis, and mucosal/nail sarcoidosis. Histopathologically, sarcoidosis is characterized by accumulation of T lymphocytes and mononuclear phagocytes that induce the formation of noncaseating epithelioid granulomas with secondary derangement of normal tissue. The prognosis of sarcoidosis is usually good, in particular, if it affects predominantly or solely the skin [1–4].

In about 50% of patients, CS resolves spontaneously without leaving significant residues. In other cases, the disease persists for years, results in considerable cosmetic damage, and requires effective therapy. In cases in which surgical or topical therapeutic approaches fail, systemic therapies are applied – corticosteroids are the "drugs of choice" for this purpose. It is recommended that corticosteroids should be administered primarily in symptomatic and progressive parenchymal lung disease, or when critical or disabling extrathoracic sarcoidosis is present [1–5].

In recent years, the efficacy of fumaric acid esters (FAE) has been proved in controlled clinical trials and a defined mixture of FAE has been registered for the treatment of psoriasis. In experiments using psoriatic and normal keratinocytes it has been demonstrated that FAE have immunomodulatory effects, including inhibition of T lymphocyte, keratinocyte, and fibroblast proliferation as well as inhibition of pro-inflammatory granulocyte cytokines and modulation of monocyte cytokine production. Because of the immunomodulatory effects of FAE, we hypothesized that this treatment may be beneficial in sarcoidosis in which T cells seem to play a crucial pathogenetic role [6,7]. We report three patients with recalcitrant CS who were successfully treated with oral FAE.

Case presentations

Patient 1

A 36-year old female patient presented with a five-year history of sarcoidosis of the lungs and the skin. The diagnosis was radiographically and histopathologically confirmed five years ago. No therapy was indicated for the asymptomatic lung involvement. The disfiguring cutaneous lesions were previously treated with topical corticosteroids and oral chloroquine. However, the lesions did not respond to these therapies. Physical examination revealed multiple reddish-brownish nodules on the cheeks (Fig. 1). Thoracic X-ray showed bilateral lymphadenopathy and mild pulmonary infiltrates (stage II). Pulmonary function tests were unremarkable. Laboratory investigations, including differentiate blood count, angiotensin-converting enzyme, and soluble interleukin 2-receptor, were within the normal range.

Patient 2

A 25-year old female patient presented with a eight-year history of cicatricial sarcoidosis that had developed after acupuncture in the periauricular region. Despite excision of the lesions sarcoidosis relapsed within a few weeks. Treatments with intralesional corticosteroids as well as oral chloroquine were unsuccessful. On examination, she had bilateral reddish-brownish papules on the helices and pre-auricular region. A skin biopsy specimen was consistent with the diagnosis of CS. Complete work-up, including differentiate blood count, angiotensin-converting



Figure 1

Reddish-brownish lesions on the left mandibular region before FAE therapy (patient no. 1).

enzyme, thoracic X-ray, and abdominal sonography, did not reveal evidence for systemic involvement (this case report has been presented on the 70. Meeting of the North-German Society of Dermatology, 29.-31.08.1997, Göttingen, Germany).

Patient 3

A 33-year-old female patient presented with a five-year history of sarcoidosis of the skin, lungs, and parotid glands. Whereas involvement of the lungs and parotid glands had almost completely resolved after a three-month therapy with oral prednisolone, CS was proved to be refractory to oral corticosteroids and chloroquine. On physical examination there were disseminated reddish-brownish papules and plaques on the upper and lower limbs (Fig. 2). Clinical diagnosis of CS was histopathologically confirmed. Complete work-up, including differentiate blood count, angiotensin-converting enzyme, and abdominal sonography, did not reveal pathological findings. Magnetic resonance tomography of the lungs was unremarkable, with the exception of a slightly enlarged hilar lymph node on the left side (stage I).

Treatment with FAE

The patients were treated with FAE in tablet form using two formulations differing in strength (low strength tablets: 30 mg dimethylfumarate, 67 mg monoethylfumarate Ca salt, 5 mg monoethylfumarate Mg salt, 3 mg monoethylfumarate Zn salt; high strength tablets: 120 mg dimethylfumarate, 87 mg monoethylfumarate Ca salt, 5 mg monoethylfumarate Mg salt, 3 mg monoethylfumarate Zn salt), supplied as Fumaderm® initial and Fumaderm® (Fumedica GmbH, Herne, Germany) [6]. Dosage of FAE was performed according to the standard therapy



Figure 2
Disseminated reddish-brownish papules and plaques on the legs before FAE therapy (patient no. 3)

regimen for psoriasis patients; in brief, dosage of low strength tablets Fumaderm® initial was weekly increased from one up to three tablets daily. After the third week of therapy, high strength tablets Fumaderm® were prescribed. Fumaderm® was weekly increased from one tablet up a maximum dose of six tablets daily. After complete remission, the dosage was gradually reduced to one tablet Fumaderm® daily. The patients were regularly monitored for an overall assessment of clinical efficacy, for subjective adverse effects, and for laboratory parameters, including white cell differential count, blood urea, and serum creatinine. Laboratory parameters were determined at baseline, at monthly intervals for the first six months, and bi-monthly thereafter. Therapy outcome of the patients is detailed in Table 1 and Figures 3 and 4.



Figure 3
On follow-up 12 months after discontinuation of FAE hypopigmented slightly hypothyrophic scars. No relapse of disease (patient no. 1)



Figure 4
Clearance of CS after 12-months therapy (patient no. 3)

Table 1: Results of three patients with cutaneous sarcoidosis (CS) treated with fumaric acid esters (FAE)

Patient (no.)	Duration of treatment (months)	Adverse effects	Complete remission	Follow-up after discontinuation of FAE
1	18	flushes, slight lymphopenia	after 12-month therapy	12 months in remission
2	6	slight lymphopenia	after 4-month therapy	12 months in remission
3	18	flushes, gastrointestinal complaints, moderate lymphopenia	after 12-month therapy	9 months in remission

Discussion

The indication for treating CS is disfigurement. External therapies reported for limited CS have included potent corticosteroids, intralesional triamcinolone, and laser therapy. Besides, surgical approaches have consisted of excision or dermabrasion. Systemic therapies for CS can be employed for large disfiguring lesions, generalized involvement, or lesions that did not respond to topical treatments. Anecdotically reported systemic therapies that have been successful with CS include methotrexate, allopurinol, thalidomide, isotretinoin, psoralen plus ultraviolet-A, and chloroquine. Nevertheless, corticosteroids are considered the first-line treatment for disfiguring and recalcitrant CS [1]. Corticosteroids act rapidly, but cannot be used as long-term therapeutics due to the well-known corticosteroid-induced side effects. Although the exact mechanism of action of corticosteroids for CS is unclear, corticosteroids probably restore the balance between locally produced Th1 and Th2 cytokines and immunoglobulin isotypes to normal levels in skin [8]. Similar immunomodulatory effects may be mediated by FAE.

Previous investigations in psoriasis patients have repeatedly demonstrated a persistent decrease in the lymphocyte count during treatment with FAE. Based on these studies it has been suggested that there is a shift towards Th2-like cytokine secretion induced by FAE. The experimental data published so far reveal a complex mechanism of action of FAE in psoriasis, targeting predominantly on T lymphocytes (e.g., inhibitory activity on cell proliferation and cytokine production) and keratinocytes [7,9,10]. Furthermore, Asadullah and co-workers [11] have found that FAE therapy is followed, despite initial pro-inflammatory effects (TNF- α), by a subsequent counter-regulatory expression of anti-inflammatory cytokines (e.g., IL-10) with consecutive anti-psoriatic effects. Consequently, a cytokine-mediated down-regulation of the antigen-presenting capacity of monocytes and macrophages has been suggested.

T lymphocytes seem to play a key role in the pathogenesis of sarcoidosis. Okamoto [12] performed histological studies on 62 CS lesions and found lymphoid cells in the epidermis in 50 cases (81%), expressing among other

markers CD3. The development of noncaseating granulomas is thought to be the result of the local presentation of a – still unknown – antigen by macrophages to CD4+ cells. These cells mediate the recruitment and retention of monocytes for granuloma formation. The monocytes gathered in this way then change into epithelioid cells and secrete angiotensin-converting enzyme, collagenase (e.g. lysozyme), vitamin D3, and fibroblast-activating factors. The latter process may lead to cicatrization of the granulomas from the outside to the inside [2,4].

FAE therapy has recently proved to be effective in patients with disseminated granuloma annulare which is closely related to sarcoidosis [13–15]. Previously, Dümmler et al. [16] reported two patients with cutaneous sarcoidosis who were treated with FAE. In one of the patients, the authors observed a remarkable improvement after 4 months of treatment. The other patient showed a slight therapeutic response after 2-months therapy. Accordingly, we observed a complete remission of CS in our patients after 4–12 months. Low-dose maintenance therapy from 2 to 6 months was performed to prevent relapse. Since the patients had long-standing and recalcitrant CS we do not assume that the therapeutic effect was due to spontaneous remission. Notably, patient 1 had CS with co-existing slight lung involvement that did not radiographically change after FAE therapy (data not shown). The side effects observed in our study correspond to the most frequently noted adverse events associated with FAE therapy: flush, gastrointestinal complaints, and lymphopenia. The latter adverse effect is the most frequently laboratory finding in long-term users (> 6 months) [17]. In accordance with the guidelines for therapeutic use of FAE, patients should be regularly monitored during the course of treatment.

The results of our case-based study indicate that FAE therapy is an effective and safe treatment regimen for patients suffering from recalcitrant CS. However, our preliminary results have to be confirmed in large controlled studies. We suggest that FAE are a promising therapeutic option which should be investigated in patients with systemic sarcoidosis as well.

List of abbreviations

CS: cutaneous sarcoidosis

FAE: fumaric acid esters

Acknowledgment

Written consent was obtained from the patients for publication of the patients' details.

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