Multi-Organ Sarcoidosis Treatment with Fumaric Acid Esters: A Case Report and Review of the Literature

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Abstract
Sarcoidosis is a rare, systemic disease that is characterized by the formation of granulomas in various organs, including the skin. As the etiology remains unknown, the treatment of sarcoidosis is challenging. We present a 47-year-old female patient with progressive, multi-organ sarcoidosis who had a complete clinical improvement of the skin lesions, a moderate reduction in pulmonary opacities on chest X-ray, a marked subjective improvement in general status and pulmonary efficiency and a marked reduction in serum angiotensin-converting enzyme and soluble interleukin-2 receptor after 6 months of therapy with fumaric acid esters. The present case and similar reports in the literature highlight the probable efficacy of fumaric acid esters in the treatment of sarcoidosis and other non-infectious, granulomatous diseases.

Case Presentation
A 47-year-old female patient presented with a history of multi-organ sarcoidosis. The disease began acutely 13 years ago as Löfgren syndrome with fever, joint pain, especially in the ankles, and disseminated erythema nodosum. Concomitantly the patient reported vertigo and disturbance of equilibrium, while a left anterior uveitis was diagnosed. Since initiation a chronic, progressive course was seen with lung, lymph node, joint, ocular and skin manifestations, the latter with disseminated plaque-type lesions. While bihilar lymph node enlargement and minor infiltrates in the right upper lung lobe were only detectable 1 year after initiation of the disease, additional progressive disseminated fibrotic changes in the entire parenchyma of both lungs and multilocular confluent peribronchovascular and peribronchial granulomatous infiltrates were reported 6 and 9 years later. The right hilum was elevated and the fibrotic lesions were most prominent in the right upper lung lobe. Before initiation of FAEs treatment, fibrotic changes at the left upper lung lobe were confirmed. The patient was treated several times with systemic corticosteroids up to the duration of 1 year. Cortico-
Steroids had to be discontinued 1 year before presentation to our departments due to adverse effects, namely weight gain, glaucoma and bilateral cataract.

On physical examination, disseminated reddish-brownish plaques on the forehead, chest, abdomen, buttocks, both upper arms and forearms as well as lower limbs were found (fig. 1). Thorax X-ray showed bihilar lymph node enlargement, peribronchial granulomatous infiltrates and parenchymal fibrosis of the middle und upper lobes of both lungs (fig. 2).

After detailed patient information and signed informed consent, oral treatment with FAEs was initiated and performed over 6 months. FAEs dosage was done according to the standard therapy regimen for psoriasis patients. In brief, the dosage of low-strength FAE tablets (Fumaderm® Initial) was increased weekly from one up to three tablets daily. After the third week of therapy, high-strength tablets (Fumaderm®) were administered. Fumaderm® was increased weekly from one tablet up a maximum dose of three tablets daily. During the last month of treatment the daily dose was reduced to two tablets. The patient was regularly monitored for clinical efficacy, adverse effects and clinical and laboratory parameters, including chest X-ray, body plethysmography, gas exchange assessment, white cell count and serum urea, creatinine, angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R). Clinical and laboratory parameters were determined at baseline and at monthly intervals.

Under the therapy with FAEs there was a considerable improvement of skin appearance and slight to moderate pulmonary changes. Complete remission of the skin plaques with disappearance of the newer skin plaques on the face (fig. 1) and pale erythematous scar remnants only at older skin lesions were seen. Chest X-ray examination revealed a slight to moderate reduction in peribronchial and parenchymal granulomatous infiltration (fig. 2). The residual lung volume, which had been continuously increasing before treatment (from 56 to 137%) was reduced to 118% after 6 months of treatment. There was an impressive subjective improvement in the patient’s general status and pulmonary efficiency. ACE, a follow-up marker for overall sarcoidosis activity, decreased from 214 U/l immediately before therapy to 98.9 U/l (normal 12–68 U/l) after 6 months of treatment (fig. 3). sIL-2R (which reflects the de-
gree of activation of T lymphocytes, is increased in around 80% of patients with systemic sarcoidosis and is the laboratory parameter with the highest sensitivity) was reduced from 4,370 U/ml to 1,714 U/ml (normal 158–623 U/ml) (fig. 3). On the other hand, the already reduced lymphocytes before treatment (312/μl) initially increased to 586/μl under treatment with Fumaderm®. Initial to continuously diminish under Fumaderm® up to 255/μl at 6 months of treatment (fig. 4).

A follow-up of 2 months after treatment discontinuation did not reveal any clinical change.

Discussion

Treatment with FAEs has been reported to be effective in small case series and case reports of patients with sarcoidosis [5, 6, 11–14], while marked to complete remission of skin and pulmonary lesions has been reported (table 1). Dümmel et al. [11] presented 2 patients with cutaneous sarcoidosis treated with FAEs. In one patient a remarkable improvement after 4 months of treatment was observed. The other patient showed a slight therapeutic response after 2-month therapy. Nowack et al. [12] reported 3 patients with recalcitrant cutaneous sarcoidosis who were treated with FAEs. After treatment for 4–12 months, complete clearance of skin lesions was achieved in all patients. The side effects included flush, minor gastrointestinal complaints and lymphopenia. Gutzmer et al. [13] demonstrated a 61-year-old female patient with cutaneous sarcoidosis treated with FAEs. After 12 months of therapy, lesions were markedly improved and treatment was discontinued. 18 months later, the cutaneous lesions recurred and a chest X-ray demonstrated pulmonary involvement. Therapy with FAEs was started again. The skin showed improvement after 2 months and completely cleared within 17 months, ACE levels normalized within 4 months and radiologic changes markedly resolved within 10 months. Breuer et al. [5] retrospectively analyzed the therapeutic efficacy and side effects of FAEs in 32 patients with non-infectious granulomatous diseases, including 11 with sarcoidosis (5 with systemic and 6 with cutaneous disease). One patient with cutaneous sarcoidosis discontinued treatment within 4 weeks because of side effects. Of the remaining 10 patients, 2 patients with systemic and 1 with cutaneous disease presented marked improvement to complete clearance, slight to moderate improvement was detected in 3 patients, and 5 patients with cutaneous sarcoidosis did not respond. In the 2 patients with systemic sarcoidosis, the pulmonary changes improved in parallel with the skin, the maximum effect being observed after 12 months. Side effects were usually mild and resolved spontaneously.
Upon dose reduction or discontinuation of the therapy, Klein et al. [6] treated 10 patients with non-infectious granulomatous diseases with FAEs, among them a 43-year-old male with cutaneous sarcoidosis who only exhibited initial partial response. Finally, Wolter et al. [14] presented a 43-year-old male with systemic sarcoidosis whose cutaneous and pulmonary lesions markedly responded after 6 months of FAEs treatment and almost completely cleared after 11 months of FAEs treatment.

Accordingly, we observed complete remission of the skin plaques, with scar remnants only, in our patient after 6 months and improvement of her long-lasting pulmonary disease. In particular the most current skin lesions on the face completely disappeared (fig. 1). The rapid improvement in general status and pulmonary symptoms correlated with the reduction in ACE and sIL-2R levels.


