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CASE REPORT

Minocycline for the treatment of sarcoidosis: is the mechanism of action immunomodulating or antimicrobial effect?

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Abstract A 47-year-old female was diagnosed to have pulmonary, ocular, and nodular-type muscular sarcoidosis. Seven years later, nodules developed in all limb muscles. She received minocycline 200 mg daily, which resulted in an obvious reduction of the muscular sarcoidosis with a significant decrease in the serum angiotensin-converting enzyme level. Nine months later, the minocycline was discontinued, thus resulting in a rapid recurrence of the disease. The immediate readministration of minocycline again resulted in a prompt improvement. We detected *Propionibacterium acnes* within the granulomas in the affected muscle by an immunohistochemistry. More interestingly, we found a decrease in the circulating levels of interleukin-12 p40 and interferon-inducible protein-10 during the minocycline therapy. The minocycline therapy may be effective for sarcoidosis and the fact that the disease rapidly relapsed after discontinuation of the minocycline administration suggests that the mechanism of action in this case may be immunomodulating but not antimicrobial effect.

Keywords Chemokine · Minocycline · *Propionibacterium acnes* · Sarcoidosis · Treatment

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Introduction

Minocycline has been used as an antimicrobial agent, and recently its anti-inflammatory activities were applied to several kinds of inflammatory diseases. Some authors indicate the effectiveness of minocycline for the treatment of cutaneous sarcoidosis [1] and ocular sarcoidosis [2]; however, the mechanism of action and the long-term efficacy of minocycline therapy have not been fully understood.

Here, we report a patient with pulmonary, ocular, and muscular sarcoidosis developing in all limb muscles. The patient received 200 mg daily of minocycline, which achieved a partial improvement of muscular sarcoidosis, but she experienced a rapid relapse of the disease with the discontinuance of the drug.

Case report

A 47-year-old woman complained of hazy vision and she was diagnosed as having uveitis in 1997. One year later, she noted a palpable nodule in her right leg and therefore she was admitted to our hospital for further evaluation. The chest X-ray film showed bilateral hilar lymphadenopathy (BHL). The diagnosis of sarcoidosis was made on the basis

of uveitis, BHL, lymphocytosis with an increase of CD4/8 ratio in bronchoalveolar lavage fluid and the detection of noncaseating epithelioid cell granulomas by muscle biopsy. At that time, the levels of angiotensin-converting enzyme (ACE) and lysozyme were low with values of 13.1 IU/l (normal, <21.6 IU/L) and 9.7 μg/ml (normal, <10.1 μg/ml). Magnetic resonance image (MRI) showed a nodular bright signal on T2-weighted images, which was enhanced by gadrinium injection. ^{67}Ga citrate scintigraphy showed intensely increased nodular activity in the right leg.

Then, palpable nodules gradually increased and developed in all limb muscles by 7 years. Serum levels of ACE, lysozyme, and soluble interleukin-2 receptor (sIL-2R) rose to 74.6 IU/l, 46.0 μg/ml, and 3,924 U/ml, respectively. Nevertheless, she complained of expansion in her legs without muscle weakness. We observed diffuse accumulation in both upper and lower extremities in ^{67}Ga scintigraphy and numerous intramuscular nodules of high signal intensity on MRI of both legs. The levels of creatine kinase, aldolase, and myoglobin were normal at 76 IU/l, 5.4 IU/l, and 10 ng/ml, respectively. The peripheral white blood cell count was 4,400/mm^3, with 70.1% neutrophils, 13.7% lymphocytes, 10.3% monocytes, and 1.6% eosinophils. Serum level of aspartate transminase was 19.5 IU/l, alanine transminase 11.2 IU/l, lactate dehydrogenase 227 IU/l, blood urea nitrogen 9.5 mg/dl, calcium 9.34 mg/dl, and C-reactive protein 0.02 mg/dl. Chest X-ray showed mild BHL but not pulmonary infiltrates. Cardiac examination by electrocardiogram and echocardiogram was normal.

As she refused an administration of corticosteroid, therapy was initiated with minocycline 200 mg daily. Four months later, her muscle symptoms were reduced and the levels of ACE, lysozyme, and sIL-2R significantly decreased. Nine months later, because the ACE level appeared to reach a minimum value, minocycline was discontinued. In a month, she again felt muscle expansion in her limbs with an increase of serum ACE, lysozyme, and sIL-2R. Minocycline was therefore readministered, resulting in prompt improvement of symptoms and decrease in ACE, lysozyme, and sIL-2R levels. After the second course of minocycline therapy, bright signals on MRI images were diminished (Fig. 1a,b) and Ga scintigraphy revealed decreased activity. During a long-term therapy with minocycline, there were no serious symptoms and laboratory abnormalities although the patient noticed hyperpigmentation in her nails.

To examine the presence of *Propionibacterium acnes* in the granulomatous lesions, the muscle biopsy specimens were served for immunohistochemistry with a specific monoclonal antibody against *P. acnes*, which detected numerous small particles within granuloma macrophages and giant cells (Fig. 1c). We also measured circulating cytokine and chemokine levels during the course of minocycline therapy. Levels of interleukin-12 (IL-12) p40 and interferon-inducible protein-10 (IP-10), which are associated with T helper type 1 (Th1) response, were elevated before minocycline administration and decreased during the therapy. In contrast, levels of thymus- and activation-regulated chemokine, Th2-associated chemokine, were kept elevated during the course of minocycline treatment.

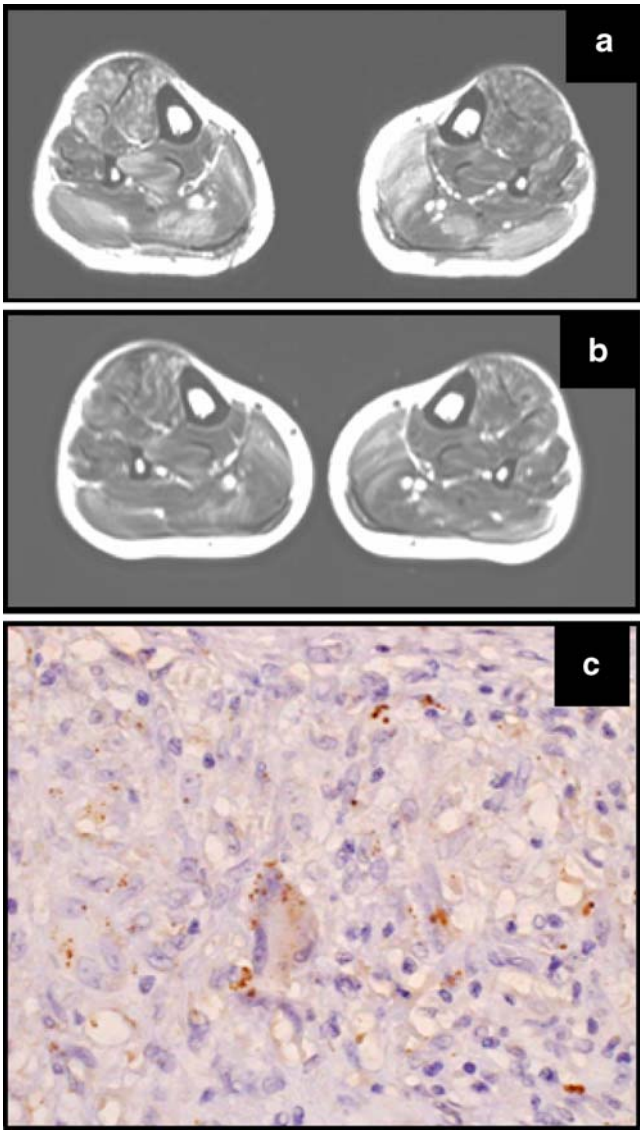

Fig. 1 Magnetic resonance image of the right leg shows multiple bright signals on T2-weighted images (**a**), and after minocycline therapy, the bright signals are decreased (**b**). **c** Immunohistochemical staining with a specific monoclonal antibody against *P. acnes* detects numerous small particles within the granuloma macrophages and giant cells

Discussion

We found during the minocycline treatment a regression of nodular lesion of muscular sarcoidosis with a decrease in levels of ACE, lysozyme, and sIL-2R. Because serum

levels of ACE reflect granuloma load, significant decrease of the serum marker indicated diminished granulomatous inflammation caused by minocycline. Thus, the effectiveness of minocycline for muscular sarcoidosis in this case was confirmed when a prompt response to the minocycline therapy was repeatedly observed.

The mechanism of action in the minocycline therapy remains controversial. In the previous study, ribosomal RNA fragments of *P. acnes* were detected in most lymph-node specimens from sarcoidosis patients [3]. The presence of *P. acnes* within the sarcoid granuloma was detected by an immunohistochemistry in this case; therefore, someone may consider that clinical improvement might be due to the antimicrobial effect of minocycline. However, the fact that the disease rapidly relapsed after discontinuation of minocycline in this case suggests that the mechanism of action is immunomodulation and not antimicrobial effect. It was unfortunate that we could not examine for the presence or absence of *P. acnes* after the therapy because the patient refused to allow a repeat biopsy.

Minocycline suppresses in vitro granuloma formation by monocytes exposed to dextrin beads [4] and also has potency to inhibit T-lymphocyte activation and proliferation [5]. Recent report demonstrated that minocycline therapy suppressed the expression of T-lymphocyte-associated chemokines and chemokine receptor CXCR3 which exists on Th1 cells [6]. During the minocycline therapy for our patient, we found a decrease of serum levels of IP-10, a ligand of CXCR3, as well as IL-12p40. Both IL-12 and IP-10 are generated by granuloma macrophages at the inflamed sites and moved into blood stream, thus reflecting disease activity of sarcoidosis [7, 8]. Given the relationship between minocycline administration and the changes in circulating levels of IP-10 and IL-12p40 in this patient, minocycline therapy might suppress IP-10 and IL-12p40 production by granuloma macrophages at the sites of inflammation.

The present case may also suggest the limitation of minocycline single therapy because minocycline failed to achieve a complete remission and more importantly discontinuing minocycline induced a recurrence. Bachelez et al. [1] previously treated 12 patients with cutaneous sarcoidosis with minocycline over a median period of 12 months. With a median follow-up of 26 months, the authors noted complete and partial responses to treatment in eight and two patients, respectively. They also mentioned that recurrence occurred in three of seven patients after discontinuing the drug. Further studies including randomized controlled trials are needed to assess the long-term efficacy of minocycline for sarcoidosis.

Disclosures None.

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