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CASE REPORT

**Yoshinori Katada · Yoshinori Harada · Naoto Azuma
Kengo Matsumoto · Haruko Terada · Eriko Kudo
Masaru Ishii · Hiroyuki Yamane · Suguru Yamamoto
Shiro Ohshima · Toru Mima · Toshio Tanaka
Yukihiko Saeki**

Minocycline-induced vasculitis fulfilling the criteria of polyarteritis nodosa

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Abstract A 47-year-old man who had been taking minocycline for palmoplantar pustulosis developed fever, myalgias, polyneuropathy, and testicular pain, with elevated C-reactive protein (CRP). Neither myeloperoxidase- nor proteinase-3-antineutrophil cytoplasmic antibody was positive. These manifestations met the American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. Stopping minocycline led to amelioration of symptoms and normalization of CRP level. To our knowledge, this is the second case of minocycline-induced vasculitis satisfying the criteria. Differential diagnosis for drug-induced disease is invaluable even for patients with classical polyarteritis nodosa.

Key words Drug induced · Minocycline · Polyarteritis nodosa · Adverse effects

Introduction

Minocycline, a semisynthetic antibiotic derived from tetracycline, has antimicrobial spectra of activity against a broad range of organisms, including *Rickettsia*, *Chlamydia* and *Mycoplasma*. It is widely used for bacterial diseases of a variety of organs, such as pharyngitis, bronchitis, pneumonia, and acne vulgaris. Minocycline is also employed for the treatment of rheumatoid arthritis as a synthetic disease-modifying antirheumatic drug (DMARD).[1] While its antimicrobial effect is exerted by the inhibition of protein synthesis, its presumed anti-inflammatory effects are mediated by unknown mechanisms.[2] Side effects of minocycline can be directed to various organs including the gastrointestinal, dermatological, renal, or hematological systems. These rather frequent side effects are usually not so serious. Among the rarer side effects of minocycline, vasculitis primarily affecting skin has been reported.

In general, vasculitides are divided into various categories by the predominant type and size of affected vessels.[3] They include a number of diseases, such as Takayasu's aortitis, Temporal arteritis, classical polyarteritis nodosa, microscopic polyarteritis, and Goodpasture's syndrome. In patients with drug-induced vasculitis, the affected lesions are often restricted to the skin, manifesting as small-vessel vasculitis.[3] Generally, about 10% of cases of acute cutaneous vasculitis are attributable to drugs, although only a small portion of adverse drug reactions present the systemic form of vasculitis.[4]

Drug-induced systemic polyarteritis nodosa is extremely rare. Here, we present a case of vasculitis that meets the criteria of classical polyarteritis nodosa caused by minocycline.

Case report

A 47-year-old man with a diagnosis of polyarteritis nodosa was admitted to our hospital in August 2004. He had a 30-year history of palmoplantar pustulosis and had been taking minocycline (100 mg/day) for 3 years with some benefit. Six months before admission, he had suffered a persistent subfever, generalized myalgias, arthralgias, and malaise. Two months before admission, he began to have intermittent spiking fevers, paresthesia in the lower limbs, and per-

Y. Katada (✉) · Y. Harada · N. Azuma · K. Matsumoto
Division of Allergy and Clinical Immunology, National Hospital Organization, Osaka-Minami Medical Center, 2-1 Kido-higashi, Kawachinagano 586-8521, Japan
Tel. +81-721-53-5761; Fax +81-721-53-8904
e-mail: kataday@omh.hosp.go.jp

H. Terada · H. Yamane · S. Yamamoto
Division of Respiratory Disease, National Hospital Organization, Osaka-Minami Medical Center, Kawachinagano, Japan

E. Kudo · M. Ishii · T. Mima
Division of Rheumatology, National Hospital Organization, Osaka-Minami Medical Center, Kawachinagano, Japan

S. Ohshima · Y. Saeki
Division of Clinical Investigation, National Hospital Organization, Osaka-Minami Medical Center, Kawachinagano, Japan

T. Tanaka
Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Medical School, Suita, Japan

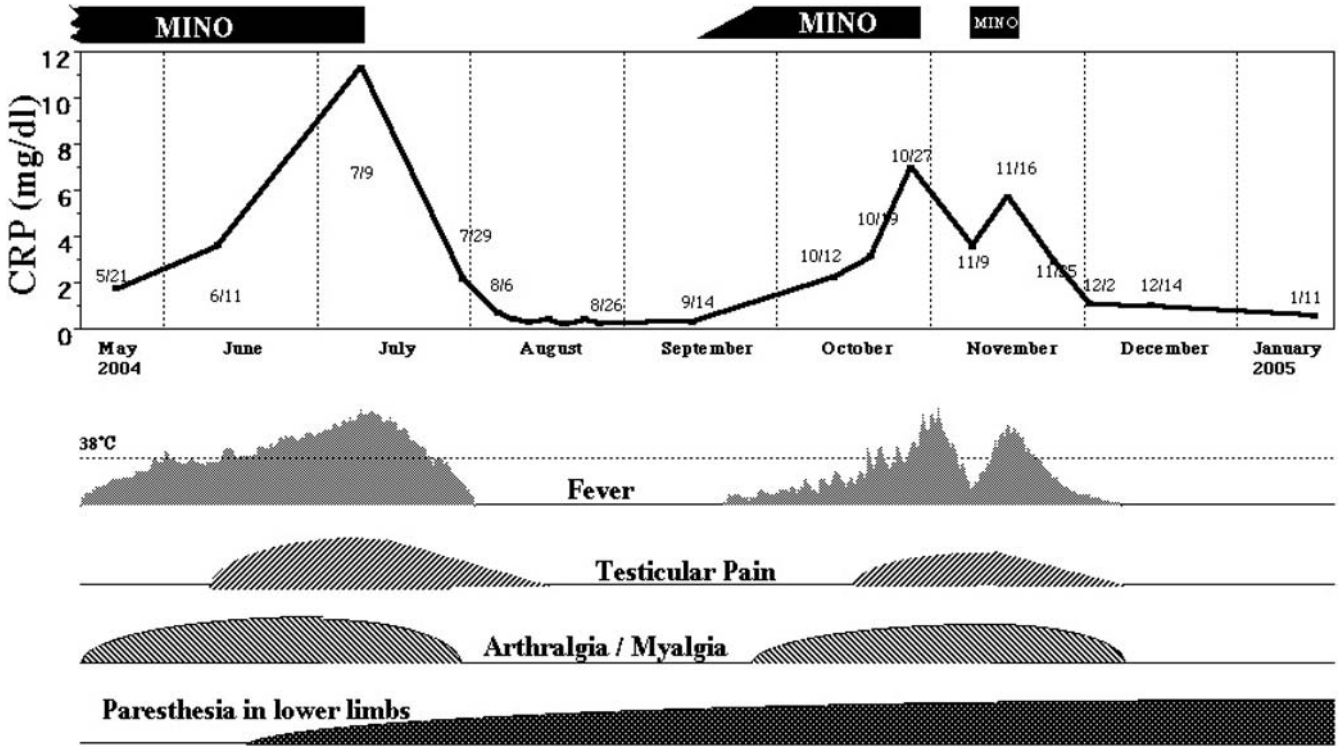

Fig. 1. Clinical course of the patient. All symptoms except polyneuritis deteriorated during his taking minocycline, while they ameliorated in the absence of the drug. *CRP*, C-reactive protein; *MINO*, minocycline

sistent testicular pain. He went to see a doctor at a municipal hospital, where he was diagnosed with bilateral sural nerve neuropathy as a result of nerve conduction velocity test and with some inflammatory disease. Data at the hospital included an elevation of C-reactive protein (CRP) (5–10 mg/dl), increased erythrocyte sedimentation rate (50–60 mm/h), and positive antinuclear antibody (×80, homogeneous and speckled). Neither myeloperoxidase- nor proteinase-3-antineutrophil cytoplasmic antibody (ANCA) was positive. Antibody against hepatitis B virus surface antigen was absent. The major clinical course since then is illustrated in Fig. 1. One month before admission, he was referred to our hospital. He had lost 3 kg of weight in a month (72 down to 69 kg). The symptoms met the American College of Rheumatology (ACR) 1990 criteria[5] for the classification of polyarteritis nodosa (at least 3 out of the 10 parameters). Minocycline, the only drug he had been taking at that time, was discontinued at that point because it might be a causative agent. After the cessation of minocycline, his symptoms gradually ameliorated and laboratory data improved (Table 1). On admission, serum CRP level was decreased to 0.69. The patient was not hypertensive. Studies of muscle biopsy, skin biopsy, and abdominal aortography were done after normalization of serum CRP level, showing no sign of angitis. Urological examination revealed neither infectious agent nor trauma that might cause testicular pain and tenderness. Computed tomography revealed moderate splenomegaly without dilatation of splenic vein. Addition of minocycline into in vitro culture of his peripheral blood mononuclear cells did not cause their enhanced proliferation. He was discharged without symptoms or signs of disease except remaining paresthesia of bilateral lower limbs. Several months after discharge, he voluntarily took minocycline again for aggravation of palmoplantar pustulosis. Serum CRP re-elevated from negative to 6 mg/dl and the same symptoms began to recur. He then stopped using minocycline again, resulting once again in recovery.

Discussion

Although we could show neither histological evidence for arteritis nor angiographic changes, the manifestations of our patient definitely fulfilled the ACR 1990 criteria[5] for the classification of polyarteritis nodosa (at least 3 out of the 10 parameters): (1) testicular pain and tenderness, not due to infection, trauma, or other causes; (2) diffuse myalgias, weakness, and tenderness of leg muscles; and (3) development of polyneuropathy. Although weight loss of only 3 kg per month did not satisfy one of the other parameters of the criteria, the patient was likely to have lost more than 4 kg, in case he would have continued to take minocycline, fulfilling one more parameter.

His severe symptoms prevented us from conducting a minocycline challenge test. However, contrary to our recommendation, the patient voluntarily took minocycline again after almost complete recovery, resulting in recurrence of the same symptoms, with laboratory data corresponding afresh to systemic classical polyarteritis nodosa.

Table 1. Laboratory data around the time of admission

Hematology and coagulation
WBC 4510 (/μl)
[Neu 66.5%, Ly 21.3%, Mo 7.1%, Eo 7.1%, Ba 0.7%]
RBC 4 280 000 (/μl), hemoglobin 10.0 (g/dl), hematocrit 32.2%
[MCV 76.2, MCH 23.4, MCHC 31.1]
Platelets 194 000 (/μl)
aPTT 43.4 (s), PT-INR 1.16 (PT 78.5%)
Fibrinogen 398 (mg/dl), Dd-dimer 0.9 (mg/l)
Clinical chemistry
AST 15 (IU/ml), ALT 13 (IU/ml), LDH 167 (IU/ml)
ALP 406 (IU/ml), γ-GTP 47 (IU/ml), total bilirubin 0.51 (mg/dl)
Amylase 38 (IU/ml), CK 19 (IU/ml)
Total protein 7.7 (g/dl)
[Albumin 55.1%, α1 3.8%, α2 9.5%, β 11.2%, β 20.4%]
BUN 9.2 (mg/dl), creatinine 0.71 (mg/dl), uric acid 5.2 (mg/dl)
Na 143 (mEq/l), K 4.5 (mEq/l), Cl 105 (mEq/l)
Immunology
CRP 2.18 (mg/dl)
IgG 2000 (mg/dl), IgM 55 (mg/dl), IgA 244 (mg/dl)
CH_{50} 45, C3 141 (mg/dl), C4 52 (mg/dl)
ANA ×80 [homogeneous, speckled]
Anti-DNA Ab (–), anti-SSA Ab (–), anti-Jo-1 Ab (–), anti-RNP Ab (–),
anti-Scl-70 Ab (–), PR3-ANCA (–), MPO-ANCA (–)
Infection
HBs Ag (–), HBs Ab (–), HCV Ab (–), RPR (–), TPHA (–), ATLA (–), HIV Ab (–)
Urinalysis
pH 7, protein (–), sugar (–), occult blood (–)

WBC, white blood cells; RBC, red blood cells; aPTT, activated partial thromboplastin time; PT, prothrombin time; CRP, C-reactive protein; Ig, immunoglobulin; CH_{50}, 50% hemolyzing dose of complement; ANA, antinuclear antibody; Ab, antibody; PR3-ANCA, antineutrophil cytoplasmic antibody to proteinase 3; MPO-ANCA, antineutrophil cytoplasmic antibody to myeloperoxidase

This sequence of events convinced us that minocycline was the causative agent for his symptoms.

Minocycline has not only the classical antibiotic effect against microorganisms but also antirheumatic activity.[2] Although the precise mechanisms are still unclear, it has recently been shown to have biologic actions affecting inflammation, proteolysis, angiogenesis, and apoptosis.[6] Possible mechanisms include reducing enzymatic activity of metalloproteinases, phospholipase-A2 and caspase-3, suppression of neutrophil function, and reduction in T-cell proliferation. It is of interest whether these unique immunomodulating mechanisms are related to the aforementioned adverse reactions of minocycline to cause vasculitis.

Drugs that have been implicated in vasculitis include antibacterial agents such as penicillins, aminopenicillins, sulfonamides, and quinolones; foreign proteins, such as streptokinase, cytokines, and monoclonal antibodies; and other drugs such as allopurinol, thiazides, pyrazolones, retinoids, hydantoins, and propylthiouracil. Of these drugs, propylthiouracil and hydralazine appear to cause ANCA-related vasculitis.[3] Besides these drugs, in the 1990s minocycline was perceived to be able to cause vasculitis associated with p-ANCA, especially in the skin.

Elkayam et al.,[7] reviewing 82 cases that appeared in the American and European literature, classified minocycline-induced autoimmune syndromes into four categories: serum sickness, drug-induced lupus, autoimmune hepatitis, and vasculitis. They reported that drug-induced lupus and hepatitis were the most common events, and that the autoimmune syndromes manifested after protracted use (mean, 25.3 months), excluding serum sickness, which presented shortly after starting minocycline treatment (mean, 16 days). The long interval coincided with a 3-year history of taking minocycline before the onset of vasculitis in our case. The long period of taking minocycline also contrasts with the rather short period of taking other drugs that induce vasculitides usually within 1–3 weeks after initiation of therapy.[3]

Although cases of cutaneous polyarteritis nodosa with antineutrophil cytoplasmic antibodies have been sporadically reported,[8–11] drug-induced polyarteritis nodosa is extremely rare. To the best of our knowledge, this is the second case of drug-induced vasculitis that clearly meet the ACR criteria of polyarteritis nodosa. Schrodt and Callen[12] reported the first case of minocycline-induced polyarteritis nodosa that satisfied the ACR criteria.[5] They reported a 15-year-old girl who was treated for 9 months with minocycline for acne vulgaris developed fever, livedo reticularis, myalgias, and arthralgias. Skin biopsy revealed small and medium-sized vasculitis. Erythrocyte sedimentation rate was 98 mm/h. Neither p-ANCA nor antinuclear antibody was detected. The findings met 3 out of 10 parameters of 1990 ACR criteria[5]: livedo reticularis, diffuse myalgias and arthralgias, and biopsy-proven small and medium-vessel neutrophilic vasculitis. Discontinuance of minocycline and prescribing 40 mg of prednisone daily resulted in rapid improvement of her systemic symptoms and normalization of laboratory values. The steroid was tapered and stopped in the subsequent 3 months, without recurrence. The period of

treatment was very brief compared with that for classical polyarteritis nodosa.

In our case, cessation of minocycline alone was sufficient to induce resolution of clinical manifestations, obviating potential harmful immunosuppressive therapy with a large quantity of adrenocorticosteroid and immunosuppressant. Thus, differential diagnosis between naturally occurring and drug-induced disease is invaluable even for patients with classical polyarteritis nodosa.

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