Minocycline induced arthritis associated with fever, livedo reticularis, and pANCA

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Abstract

Objective—to describe a novel iatrogenic immunological reaction produced by minocycline.

Case reports—The clinical course and laboratory results of three women who presented with similar rheumatological manifestations after a prolonged exposure to minocycline are described. All three presented a unique reaction manifested by fever, arthritis/arthritis and livedo reticularis during treatment with minocycline for acne vulgaris. The clinical syndrome was associated with high titre of serum perinuclear anticytoplasmonic antibodies (p-ANCA) and antitymelyperoxi-dase antibody (anti-MPO). Symptoms resolved after stopping the drug and recurred promptly after rechallenge in all three patients.

Conclusions—Minocycline, which is widely used in the treatment of acne, often without adequate supervision, may induce arthritis and livedo vasculitis associated with anti-MPO.

Laboratory investigations are reported in the table. Treatment with naproxen 500 mg twice daily partially relieved her symptoms and rendered her afebrile. During the next 10 months—while taking minocycline intermittently—she suffered relapses which retrospectively could be related to her self administered courses. Her livedo reticularis worsened and a skin biopsy revealed perivascular inflammatory infiltrates. The patient herself raised the possibility of a connection between minocycline and her symptoms. Minocycline was discontinued with resolution of her fever within days. Two weeks later, the patient was rechallenged with a single tablet of 100 mg minocycline. She developed fever up to 39°C and severe arthralgia within 24 hours, resolving completely after a few days. Although the patient has been asymptomatic ever since, serum p-ANCA remains positive 12 months later, but its titre is progressively decreasing (from 1/1280 at the beginning of the disease to 1/160).

Case reports

Case 1

A 19 year old woman presented a two month history of fever, under 38°C in the first seven weeks, rising to 39°C in a constant diurnal pattern the week preceding admission. She also complained of exhaustion and bilateral ankle pain. Her only past medical history was acne, treated with minocycline 100 mg daily from the age of 15 to 18. Three months before admission, she had renewed regular minocycline. On examination, she had fever of 39°C, acrocyanosis of hands and feet, livedo reticularis of the legs, and mild swelling and exquisite tenderness of both ankles.
carpophalangeal joints, proximal interphalan-
geal joints, and ankles. Laboratory tests are
reported in the table. Stopping minocycline
induced a complete resolution of fever and
improvement in her arthralgias within days.
Rechallenge with a single tablet of minocycline
two weeks later provoked fever of 39°C and
synovitis of both hands and ankles. Within 24
hours, fever resolved completely while arthral-
gias persisted. A two week course of treatment
with prednisone, initially 15 mg/d, induced a
complete resolution of symptoms. Nine
months later, the patient remains asympto-
matic with a slowly decreasing P-ANCA titre.

CASE 3
A 22 year old woman presented a three week
history of fever, severe fatigue, myalgias, and
pain in her elbows, ankles, and wrists. Since
adolescence, she had suffered from acne and
did not have minocycline from the age of 17 to
20. Minocycline was renewed a few weeks
before her current symptoms.

On examination, she had fever of up to
38.5°C, livedo reticularis on both legs, sym-
metrical synovitis of elbows and tenderness of
both ankles. Laboratory tests are summarised
in the table. Withdrawing minocycline induced
complete resolution of fever within 24 hours
and of the musculoskeletal symptoms within
two weeks. Rechallenging with minocycline
promptly reproduced fever, myalgia, and
arthralgia within hours. This resolved after
stopping the drug.

Discussion
We report three women with a common iatro-
getic clinical picture of marked pyrexia, severe
fatigue, polyarthritis, and livedo reticularis,
associated with acute phase response and anti-
MPO in the serum. All had used minocycline
for prolonged periods. Common to all three
was renewal of the drug after a variable period
(12-24 months) of withdrawal, and symptom
onset within just a few weeks of restarting the
drug. Symptoms resolved after stopping minoc-
cycline and recurred promptly after rechal-
lenge, clearly implicating the drug in causation.
The slow but persistent decline of anti-MPO
autoantibodies during remission further sup-
ports a cause-effect relation. Although there are
only three patients, it seems the more
prolonged the exposure to minocycline after its
renewal the more severe the clinical course.
A serum sickness-like syndrome with
urticaria, fever, lymphadenopathy, and joint
symptoms has been reported with minocy-
cline.9 Polyarthritis with autoimmune hepatis-
tis due to minocycline has also recently been
reported.9 Minocycline has been associated
with acute drug induced lupus syndrome with
positive antinuclear antibodies in five young
women taking minocycline for years. In four of
these, clinical features disappeared shortly after
stopping minocycline, whereas in one case the
illness persisted and required treatment with
corticosteroids. Resolution of serological
abnormalities in these patients occurred more
slowly than the clinical symptoms.11 Although
our third patient presents some similarities to
those cases (antinuclear and antihistidine
antibodies), our patients differ in having
marked livedo reticularis, high titre p-ANCA,
and absence of antinuclear antibodies and
anitihistones in two cases.

Autoantibodies against cytoplasmatic deter-
minants of neutrophil granulocytes are
important diagnostic markers in systemic
vasculitis. Circulating antibodies against
myeloperoxidase, elastase, cathepsin G, lactof-
errin, and lysozyme have been identified as
causes of the p-ANCA phenomenon.12 Though
MPO-ANCA have been detected in several
non-vasculitic chronic inflammatory condi-
tions like rheumatoid arthritis, juvenile
rheumatoid arthritis, Felty syndrome, ulcera-
tive colitis, and systemic lupus erythematosus
(SLE), they are usually infrequent and at low
titre.10 High serum levels of anti-MPO have
been found in microscopic polyangiitis and
Churg Strauss syndrome13 and in drug induced
lupus caused by hydralazine and procaina-
mide.1516 In all six patients with SLE-like
syndrome induced by hydralazine treatment,
anti-MPO autoantibodies were detected and
antielastase in five of them.14 We believe that
case 3 may indeed represent drug induced
lupus in which p-ANCA is found at a very high
level.

In addition to hydralazine and procaina-
mide, propylthiouracil has been found to be
associated with vasculitis, positive ANCA, and
antibodies against human neutrophil elastase,
proteinase 3 and myeloperoxidase in six
patients. Following withdrawal of the drug,
clinical symptoms resolved completely and
ANCA concentrations decreased though they
persisted even after one year of follow up.17

Crescentic glomerulonephritis induced by
penicillamine,18 hydralazine,19 and carbi-
mazole20 associated with ANCA have also been
reported. Likewise, interstitial nephritis due to
omeprazole has been linked with serum p-
ANCA.21

All major classes of drugs that induce a
lupus-like syndrome, such as hydralazine, pro-
cainamide, isoniazid, quinidine, chlorprom-
azine, and propylthiouracil, are possible sub-
strates for myeloperoxidase,2223 their cytotoxic
properties depending on the fact that
neutrophil myeloperoxidase is implicated in
the conversion of these drugs into toxic
metabolites.24 Those data and the
experience with hydralazine, procainamide,
penicillamine, omeprazole, and antithyroid
drugs, and the present report on minocycline,
suggest that ANCA, beside being a useful marker in
the detection of drug induced connective tissue
disease, is involved in the pathogenesis of the
iatrogenic disease.

We believe that minocycline may induce a
characteristic vasculitic reaction manifested by
fever, fatigue, arthritis/arthralgia, and livedo
reticularis in the presence of positive
immunofluorescent p-ANCA and anti-MPO.
Minocycline is widely used by young female
patients and awareness of this reaction is thus
important. Prompt suspicion and discontinua-
tion of minocycline will usually result in
resolution.
Minocycline induced arthritis


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