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

O Elkayam, M Yaron, D Caspi

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/arthralgia, and livedo reticularis during treatment with minocycline for acne vulgaris. The clinical syndrome was associated with high titre of serum perinuclear anticytoplasmatic antibodies (p-ANCA) and antimielyoperoxidase 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.


Minocycline hydrochloride is a semisynthetic tetracycline used for a variety of infections, and for treatment of acne vulgaris. Several adverse effects have been reported, including nausea, blood eosinophilia, transient vestibular symptoms, photosensitivity, hyperpigmentation, rashes, fever, hypersensitivity pneumonitis, and hepatitis. Few rheumatic manifestations of toxicity have been reported.

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.

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 2
A 20 year old woman presented a six week history of fever, severe fatigue, myalgias, and arthralgia affecting shoulders, hands, and ankles. Her past medical history was unremarkable except for acne treated with minocycline from the age of 17 to 19. Minocycline had been stopped for six months and renewed a few weeks before her current illness. On examination, the patient appeared ill with fever up to 39°C, livedo reticularis on both legs, and symmetrical synovitis of wrists, meta-

Laboratory tests on admission

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tbody>
<tr>
<td>ESR</td>
<td>90</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>ANA</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Anti-DNA</td>
<td>Normal</td>
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<td>Normal</td>
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<tr>
<td>Anti-histone</td>
<td>-</td>
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<tr>
<td>Anti-Ro, La</td>
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<tr>
<td>Anti-cardiolipin</td>
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<tr>
<td>Lupus anticoagulant</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C3 C4</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>1/1280</td>
<td>1/640</td>
<td>1/1280</td>
</tr>
<tr>
<td>Anti-MPOa</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Anti-elastaseb</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>Anti-PR3c</td>
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</tr>
</tbody>
</table>

ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; MPO, myeloperoxidase.

a ELISA, ELIASSVARELISA kit, code 19296.
b Clone system, EL-elastase kit, code 11-1100.
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-
gia persisted. A two week course of treatment
with prednisone, initially 15 mg/d, induced
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
had taken 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-
genic 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 mino-
cycline and recurrently after rechal-
lenge, clearly implicating the drug in causation.
The slow but persistent decline of anti-MPO
autoantibodies during remission further supports
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 Polyarthitis with autoimmune hepatic
itis due to minocycline has also recently been
reported.10 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 antihistone
antibodies), our patients differ in having
marked livedo reticularis, high titre p-ANCA,
and absence of antinuclear antibodies and
antihistones in two cases.

Autoantibodies against cytoplasmatic deter-
minants of neutrophilic 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, ulcerative
colitis, and systemic lupus erythematosus
(SLE), they are usually infrequent and at low
titre.13 High serum levels of anti-MPO have
been found in microscopic polyangiitis and
Churg Strauss syndrome14 and in drug induced
lupus caused by hydralazine and procaina-
mine.15 16 In all six patients with SLE-like
syndrome induced by hydralazine treatment,
amy-MPO autoantibodies were detected and
antielastase in five of them.17 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-
mine, 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 carbima-
зole20 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, chlorpro-
mazine, and propylthiouracil, are possible sub-
strates for myeloperoxidase,22 - 23 their cytoxic
toxic 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


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

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