Minocycline Induced Autoimmune Disease in Rheumatoid Arthritis: A Missed Diagnosis?

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ABSTRACT. Minocycline is one of the major drugs for acne and is effective in rheumatoid arthritis (RA). We describe the first case of drug induced lupus secondary to the use of minocycline in a patient with RA. The difficulties of making this diagnosis as well as the implications for its pathogenesis are discussed. (J Rheumatol 2001;28:377–8)

CASE REPORT

A 46-year-old man presented in 1974 with a small joint polyarthritis of his hands and feet of more than 12 months' duration. Initial investigations at the time showed him to have a weakly positive rheumatoid factor (RF) and negative ANA with raised inflammatory markers (erythrocyte sedimentation rate 28 mm/h). Radiographs of his feet showed evidence of erosive disease consistent with RA. Initial treatment included different non-steroidal antiinflammatory drugs (NSAID), intraarticular corticosteroids, regular physiotherapy, and local wax treatment to his hands, which were his worst affected joints. Due to the persistence of symptoms and synovitis, sulfasalazine was started as a disease modifying agent. However, this had to be eventually discontinued due to severe gastrointestinal side effects. In 1993 minocycline was started at a dose of 100 mg twice daily, with good clinical and laboratory response. Apart from the development of nodulosis, his RA remained quiescent and he was followed twice yearly.

In November 1998 he presented with an arthritic flare with generalized polyarthritis. Clinical examination revealed synovitis in his left ankle, right knee, and several metatarsophalangeal joints. Of interest, he was also noted to have marked pigmentation of his face, affecting mainly exposed areas such as nose and ears, which on direct questioning he related to a recent holiday. Investigations at this time showed: ANA positive at a titer of 1/640, positive p-ANCA at 1/640 with anti-myeloperoxidase (anti-MPO) antibody specificity. Liver function testing was normal. Despite the presence of clinical synovitis, C-reactive protein (CRP) levels were within normal limits. Antihistone antibodies were not checked. HLA typing showed him to be DR4, DR10. The possibility of drug induced lupus was raised to explain the new flare of synovitis. Minocycline was considered to be the likeliest cause for both the skin pigmentation and the new autoimmune presentation and was therefore stopped.

He was treated with local corticosteroid injections and on review 12 months after withdrawal of the drug his arthritis remains in remission. Skin pigmentation is resolving slowly. Maintenance therapy is with regular NSAID. ANA titer remains elevated and anti-MPO antibodies are now undetectable. Laboratory results are summarized in Table 1.

DISCUSSION

Drug induced lupus is a difficult clinical entity to recognize and although diagnosis is aided by proposed guidelines, specific criteria have not been formally established. Several

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<th>Table 1. Summary of antibody results and evolution over time, pre and post-treatment with minocycline.</th>
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<td>Before</td>
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<td>ANA</td>
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MN: minocycline, ND: not done.
points in our case are worth emphasizing. First, in the context of RA, it is difficult to distinguish a flare of the underlying disease from a drug induced synovitis. In this case, the flare occurred in the context of new serological abnormalities without an accompanying rise in the CRP concentration, favoring drug induced lupus as the cause for the new symptoms. Second, both the clinical and serological abnormalities appeared after longterm exposure to the drug (more than 6 years) and unusually were associated with signs of chronic minocycline toxicity, i.e., skin pigmentation. To our knowledge there have been no previous reports of the simultaneous occurrence of these events. One explanation could be that when an autoimmune process is triggered it occurs rapidly, not allowing sufficient time for dose-dependent drug toxicity to occur. Lastly, our subject is male, and minocycline related lupus occurs more frequently in females (8:1 women to men)\(^8\), suggesting that his sex may have been a protective factor.

Why is minocycline induced autoimmune syndrome not seen more frequently in patients with RA? It is possible that RA may have a protective role for the development of lupus, or alternatively, its development may be masked by overlapping features. With respect to the latter, it is easy to explain an acute arthritic exacerbation in the context of underlying RA without implicating a drug induced event or checking the ANA levels. More interesting is the former possibility, that RA may protect against the development of lupus. In RA there are elevated levels of tumor necrosis factor--\(\alpha\) (TNF--\(\alpha\)), and successful treatment leads to its suppression. Agents such as sulfasalazine, D-penicillamine, or anti-TNF--\(\alpha\) not only reduce TNF levels but increase the risk of drug induced lupus. Data on genetic polymorphisms on TNF confirm that the presence of homozygosity for the TNF2 allele determines an increased production of TNF--\(\alpha\). Interestingly, where a high prevalence of this allele is found, the incidence of systemic lupus is very low\(^9\). Accordingly, high levels of TNF--\(\alpha\) in RA may protect against lupus, making it more likely to occur when circulating serum levels are decreased, such as when the disease goes into remission, as was the case here.

In summary, our case of drug induced autoimmune disease in RA developed after longterm exposure to minocycline. Serology showed positive ANA, p-ANCA, and anti-MPO antibodies, and the patient was found to carry the DR4 allele (reported to be associated with minocycline induced autoimmune disease)\(^5\). Clinical and serological improvement followed cessation of the drug. Physicians should be aware of the possibility of drug induced lupus in patients with RA, particularly when minocycline has been used. If TNF suppression predisposes to this syndrome, then its incidence is likely to increase. We propose that a patient’s ANA status be checked before starting minocycline and when drug induced lupus is suspected.

REFERENCES