Netherlands
The Journal of Medicine

CASE REPORT

Interstitial pneumonia and hepatitis caused by minocycline

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ABSTRACT

A 28-year-old patient is described who presented with progressive dyspnoea and jaundice due to interstitial pneumonia and hepatitis. The most likely cause is a drug-related reaction to minocycline. We discuss the different kinds of drug-related reactions that are most likely involved.

INTRODUCTION

Minocycline is a semisynthetic tetracycline widely used for the treatment of acne vulgaris and for treatment of infections. A variety of mild adverse reactions have been described. Among these, light-headedness in women is most prominent. In addition, photosensitivity, various rashes, fever, hyperpigmentation, nausea and weakness have been reported.
More serious immunological adverse reactions include serum sickness-like syndrome and other hypersensitivity reactions, drug-induced lupus, autoimmune hepatitis, pneumonitis and vasculitis.[1-4]
We describe a patient who developed hepatitis and severe dyspnoea while on treatment with minocycline for severe acne vulgaris.

CASE REPORT

A 28-year-old Caucasian man was admitted to our hospital because of progressive dyspnoea and jaundice. He had a six-week history of abdominal symptoms after a flu-like episode with gradual onset of jaundice. After one week, progressive dyspnoea developed. He complained of severe exertional dyspnoea and orthopnoea. He suffered from a weight loss of 16 kg in a six-week period. There was no history of fever, rash or arthralgia. The patient denied intravenous drug abuse, although he admitted to occasionally using speed, cocaine and XTC. There was no history of changing sexual contacts, nor had he received a blood transfusion. He had lived in the Caribbean for three years, until five years ago. There was no history of recent travel. The medical history revealed an infectious mononucleosis years ago and acne vulgaris, for which the patient had been taking minocycline 100 mg once a day for the last two years.
On examination we saw an ill-looking, weakened and deeply jaundiced patient with a respiratory rate of 40-45/min, temperature 37.8°C, pulse rate of 72 beats/min and BP 110/80 mmHg. Chest auscultation revealed crackles over the lower lung fields. There were no palpable masses in the abdomen. A chest radiograph revealed diffuse small sized consolidations in both lungs (*figure 1*). Abdominal ultrasonography revealed a normal liver with no signs of portal thrombosis; the spleen was slightly enlarged at a length of 12 cm.
Laboratory evaluation showed a WBC of 7.4 x 10^9/l with 0.2 x 10^9/l eosinophils. Liver function tests were abnormal: alanine transaminase 523 U/l (normal <25); aspartate transaminase 311 U/l (normal <20); γ-glutamyl transferase 109 U/l (normal <45); alkaline phosphatase 156 U/l (normal 30-90); total bilirubin 161 umol/l (normal <16); conjugated bilirubin 123 umol/l (normal <4.5). The prothrombin time (PT) and activated partial thromboplastin time

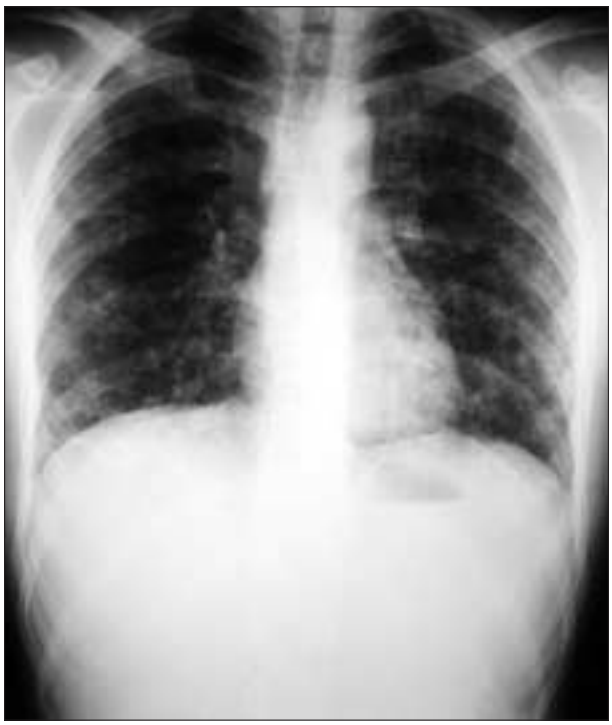

Figure 1
Chest radiograph on admission with diffuse small sized consolidations in both lungs

(APTT) were normal. The erythrocyte sedimentation rate was 22 mm/h with a C-reactive protein of 12 mg/l. The kidney function was normal. The test for antinuclear antibody (ANA) was negative. The antineutrophil cytoplasmatic autoantibody (ANCA) test showed an atypical pattern with no antibodies against proteinase 3 and myeloperoxidase. Complement studies showed a normal C3 and slightly increased C4 of 489 (normal 120-360 mg/l). There were negative serological test results for hepatitis A, B, C, EBV and CMV. The HIV status was negative. Serological tests against *Legionella* species, influenza virus, parainfluenza virus, RS virus, *Mycoplasma pneumoniae*, adenovirus, coxsackie B5, *Chlamydia psittaci* and *Coxiella burnetii* were also negative.
On admission arterial blood gas analysis without oxygen showed a pO_2 of 57 mmHg, pCO_2 of 35 mmHg, pH of 7.45, HCO_3 of 24 mmol/l, a base excess of 1.1 and an oxygen saturation of 91%. Because of the unclear diagnosis and the severe clinical condition of the patient, we decided to perform an open lung biopsy under anaesthesia; thereafter, the patient was transferred to the intensive care unit for further ventilatory support for six days. Cultures from the lung biopsy material were negative for viruses, including CMV, and bacteria, including *Mycobacterium tuberculosis*, *Legionella* species, *Mycoplasma* and *Pneumocystis carinii*. Histology revealed a diffuse interstitial dense infiltration with lymphocytes, but no eosinophils, with thickening of

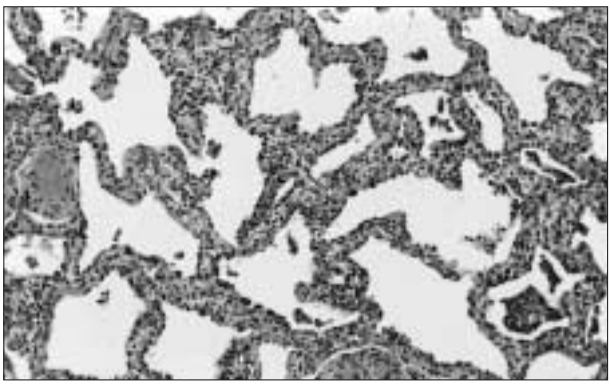

Figure 2
Histology of lung biopsy: interstitial infiltration of lymphocytes with thickening of the alveolar septa

the alveolar septa by oedema. Some fibroblast plugs, macrophages and foam cells were observed. No granulomas were seen. Furthermore there were some signs of organising pneumonia, as can be seen in association with a bronchiolitis obliterans organising pneumonia (BOOP) (*figure 2*).
After having excluded a variety of infectious causes, we concluded that the most likely diagnosis was a hypersensitivity reaction possibly related to the minocycline. There were no signs of malignancy, nor was another toxic agent likely to be responsible. The drug was stopped on admission. The patient was treated with prednisolone 60 mg iv once a day and was switched to prednisolone 60 mg orally once a day after three weeks. Within one month there was a gradual recovery with resolving of the dyspnoea and normalisation of the liver tests and arterial blood gas analysis. The chest radiograph was unchanged with interstitial infiltrates still present. On discharge the prednisolone dose was 40 mg daily and was thereafter slowly tapered. During his stay on the ward the patient suffered from hallucinations for a short period of time, which recovered after medication prescribed by the psychiatrist.

DISCUSSION

Serious adverse effects, as in this patient, have been described with minocycline. These usually concern young, otherwise healthy people to whom minocycline is prescribed because of acne vulgaris. Our patient suffered from hepatitis and severe dyspnoea due to pulmonary infiltrates.

Various forms of minocycline-induced hepatic injury have been described. One form is a direct dose-related hepatotoxic effect, also described with tetracycline.[5] On liver biopsy, it looks like microvesicular steatosis. A second

form is fulminant hepatic failure as part of an allergic idiosyncratic reaction, requiring liver transplantation.[6] A third form is considered an autoimmune hepatitis, which is characterised by fever, arthralgia, rash, elevated transaminases, positive ANA antibodies and elevated immunoglobulins. Liver biopsy shows chronic active hepatitis.[7-9] Our patient did not have a history of rash or arthralgia, nor did he have positive ANA antibodies. Although a direct hepatotoxic effect is possible, resolution of the damage with glucocorticoid therapy would not be expected. A liver biopsy would have made the diagnosis more accurate, but was not performed.
Hepatic injury due to minocycline has also been described due to a hypersensitivity reaction, which usually occurs two to four weeks after the start of minocycline treatment. It is characterised by fever, rash and internal organ involvement, usually hepatic injury, although pulmonary, haematological, or renal impairment may occur. This reaction may be life-threatening and is thought to be caused by a reactive metabolite of minocycline.[1,4,10]

Severe dyspnoea and bilateral pulmonary infiltrates may also occur as part of the same hypersensitivity reaction. It is accompanied by blood eosinophilia and/or pulmonary eosinophilia, although in some cases as our patient, the eosinophilia is absent. In most cases there is also an elevated IgE level. On chest radiography it typically gives biapical subpleural opacities, but infiltration can develop anywhere.[11-15] T lymphocytes are thought to play an important role in the pathogenesis of drug-induced hypersensitivity pneumonitis.[16] Alternatively, pulmonary infiltrates can be caused by minocycline-induced lupus, but in our patient there were no antinuclear antibodies.[17,18]

Our patient was on treatment with minocycline for two years when he first developed jaundice followed by severe progressive dyspnoea. It is tempting to speculate about an immunological pathogenesis of the hepatitis and pulmonary infiltrates. The prolonged exposure to minocycline or a metabolite may have been the trigger. The patient did not fulfil the criteria of drug-induced lupus and it is unclear whether there was a response to steroids. The combination of liver and pulmonary involvement would fit a hypersensitivity reaction. This is more commonly seen after a short period of minocycline treatment, although reactions have developed after a more prolonged period.[14]
Severe drug-related reactions may pose a difficult diagnostic problem especially in patients under treatment for a longer period of time. Recognition of the drug-related reaction and adequate management are essential for such a potentially life-threatening event.

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