

# Successful treatment of tuberculosis combined with drug-induced myopathy using corticosteroid therapy: a case report

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Xinke Yuan , Sijia Chen and Yinghong Huang

## Abstract

A 39-year-old woman was admitted to our hospital on 19 January 2019 because of a 10-day history of intolerance to oils in her food, fatigue, and yellowing of the skin and sclera. In December 2018, the patient had been diagnosed with tuberculous pleurisy at a local hospital and received quadruple anti-tuberculosis treatment. Ten days before presentation to our hospital, she had developed anorexia, fatigue, nausea, loss of appetite, cough, and shortness of breath. She visited a local hospital, where she was considered to have drug-induced hepatitis. She discontinued the anti-tuberculosis drugs and liver protection treatment. After 3 days, her symptoms had not substantially improved. She visited the infection department of our hospital for further diagnosis and treatment. After 6 days of treatment, the patient's symptoms were not significantly improved, her liver and muscle enzyme concentrations were further increased, and her limbs had become weaker and more difficult to move. We considered diagnoses of drug-induced hepatitis and drug-induced myopathy. The patient was treated with intravenous methylprednisolone at 40 mg once a day for 16 days and other symptomatic treatments. Her symptoms significantly improved and she was discharged.

## Keywords

Corticosteroid, tuberculosis, drug, myopathy, liver injury, case report

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## Introduction

Drug-induced liver injury is one of the most common and serious adverse drug

Department of Nephrology, the First Hospital of Changsha, Kaifu District, Changsha, Hunan, China

### Corresponding author:

Yinghong Huang, Department of Nephrology, the First Hospital of Changsha, 311 Yingpan Road, Kaifu District, Changsha, Hunan 410005, China.

Email: [hyhhzy@126.com](mailto:hyhhzy@126.com)



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reactions<sup>1,2</sup> and can cause acute liver failure or even death.<sup>3</sup> The clinical manifestations of drug-induced myopathy vary; mild cases only cause symptoms such as muscle pain and joint pain, whereas severe cases can lead to rhabdomyolysis and even myoglobi-nuric acute renal failure, which is life-threatening.<sup>4,5</sup> In clinical practice, the diagnosis and treatment of drug-induced myopathy are unclear. This study was performed to summarize the clinical characteristics of drug-induced myopathy and provide a treatment reference by reviewing one successfully treated case in our department. The reporting of this case conforms to the CARE guidelines.<sup>6</sup> The patient provided written informed consent for treatment and publication. The requirement for ethics approval was waived because of the nature of this study (case report).

## Case presentation

### History

A 39-year-old woman was admitted to our hospital on 19 January 2019 because of a 10-day history of intolerance to oils in her food, fatigue, and yellowing of the skin and sclera. In December 2018, the patient had been diagnosed with tuberculous pleurisy at a local hospital based on the presence of cough, chest tightness, and night sweats, and she received quadruple anti-tuberculosis treatment (isoniazid 0.3 g once daily, rifampicin 0.45 g once daily, pyrazi-namide 1.5 g once daily, and ethambutol 0.75 g once daily) for 35 days. Ten days before presentation to our hospital, she had developed anorexia, fatigue, nausea, loss of appetite, cough, and shortness of breath; however, she had no vomiting, obvious expectoration, chills, fever, or mental or personality changes. She visited a local hospital, where she was considered to have drug-induced hepatitis. She discontinued the anti-tuberculosis drugs and liver

protection treatment. After 3 days, her symptoms had not substantially improved. She had no history of hepatitis or other infectious diseases and no family history of hereditary diseases. She did not drink alcohol and had no special hobbies. She visited the infection department of our hospital for further diagnosis and treatment. Laboratory examination of liver function revealed a low total protein concentration (48.7 g/L), low albumin concentration (28.5 g/L), low albumin/globulin ratio (1.29), high alanine amino-transferase concentration (293 U/L), high aspartate aminotransferase concentration (634.5 U/L), high total bilirubin concentration (120.0 µmol/L), high total bile acid concentration (50.1 µmol/L), high direct bilirubin concentration (90.5 µmol/L), and high indirect bilirubin concentration (38.4 µmol/L). Lung computed tomography (CT) revealed bilateral lung infection and pleural effusion. Chest ultrasound showed left pleural effusion. Pleural effusion examination revealed that the pleural effusion was an exudate, the Rivalta test was positive, a high adenosine deaminase concentration in the pleural effusion (68 U/L), a high lactate dehydrogenase concentration (329 U/L), and a positive tuberculosis spot test.

### Physical examination

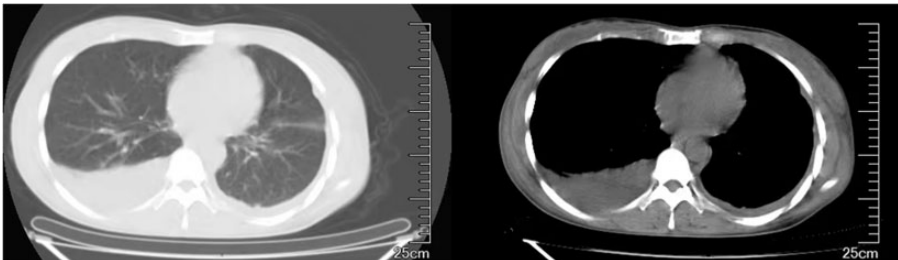
Physical examination revealed a body temperature of 36.5°C, pulse rate of 112 beats/minute, heart rate of 112 beats/minute with a regular rhythm, respiratory rate of 20 breaths/minute, blood pressure of 93/71 mmHg, and severe yellowing of the skin and sclera. The patient had no bleeding points or ecchymoses, palmar erythema, spider naevi, or asterixis. No dry or wet rales and no pleural friction were heard in the bilateral lungs. The abdomen was flat and soft without tenderness or rebound pain, the liver and spleen were not under the ribs, and there was no percussion pain

over the liver and kidneys. The muscle strength of both lower limbs was grade IV, and the lower limbs were slightly swollen.

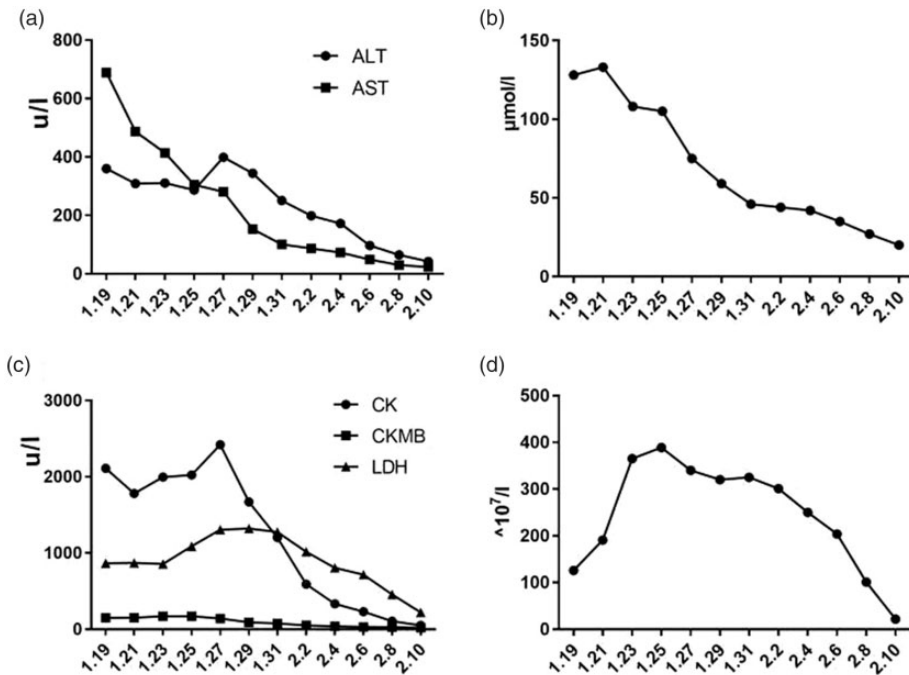
### Laboratory and imaging examinations

Routine blood examination revealed a high red blood cell count ( $5.97 \times 10^{12}$  cells/L), high white blood cell count ( $28.31 \times 10^9$  cells/L), high platelet count ( $339 \times 10^9$  platelets/L), normal hemoglobin concentration (138 g/L), high neutrophil ratio (72.7%), high eosinophil count ( $1.26 \times 10^9$  cells/L), and normal eosinophil ratio (5%). Liver function testing revealed a low albumin concentration (26.4 g/L), high alanine aminotransferase concentration (360 U/L), high aspartate aminotransferase concentration (689.2 U/L), high gamma-glutamyl transpeptidase concentration (162.2 U/L), and high alkaline phosphatase concentration (214 U/L). Among the myocardial enzymes, the patient had a high creatine kinase concentration (2110 U/L), high lactate dehydrogenase concentration (867 U/L), high creatine kinase isoenzyme concentration (148.7 U/L), high myoglobin concentration (273.5  $\mu\text{g/L}$ ), and high troponin I concentration (818 ng/mL); the C-reactive protein concentration and erythrocyte sedimentation rate were normal. With respect to thyroid function, the patient had a low free triiodothyronine concentration (1.99 pg/mL), low total triiodothyronine concentration (0.8 ng/mL), and normal

thyroid-stimulating hormone concentration. Tumor marker measurement revealed a high carbohydrate antigen 125 concentration (96.32 U/mL), high carbohydrate antigen 19-9 concentration (92.79 U/mL), and high neuron-specific enolase concentration (49.61 ng/mL); the alpha fetoprotein, carcinoembryonic antigen, cancer antigen 72-4, and non-small cell lung cancer antigen concentrations were normal. The immunoglobulin E concentration was 1067.9 IU/mL. All autoantibodies were within the normal range, including rheumatoid factor, antinuclear antibodies, anti-double stranded DNA antibodies, anti-extractable nuclear antigen antibody spectrum, and the complete set of hepatitis antibodies (A, B, C, D, and E). Cerebrospinal fluid examination revealed no abnormalities. B-mode ultrasound showed a slightly thickened bright echo spot in the liver parenchyma, indicating mild fatty liver. The gallbladder wall was slightly thick and rough. A small amount of pleural effusion was present on both sides (encapsulated effusion was suspected on the left side) along with a small amount of ascites. Lung CT (Figure 1) revealed a few exudative lesions in both lower lungs, suggesting inflammation. Pleural effusion was confirmed on both sides (more obvious on the right side), and partial compression atelectasis was present in both lower lungs. A small amount of pericardial effusion was also noted on lung CT. An electrocardiogram showed



**Figure 1.** Chest computed tomography image of the patient at admission.



**Figure 2.** Changes in liver function indices, muscle enzymes, lactate dehydrogenase, and eosinophils. (a) Changes in ALT and AST. (b) Change in total bilirubin. (c) Changes in CK, CKMB, and LDH. (d) Change in eosinophils.

ALT, alanine aminotransferase; AST, aspartate transaminase; CK, creatine kinase; CKMB, creatine kinase-myocardial band; LDH, lactate dehydrogenase.

sinus tachycardia. Electromyography revealed myogenic damage of both lower extremities and the right upper extremity accompanied by neurogenic lesions. Bone marrow examination revealed active bone marrow hyperplasia with a high eosinophil ratio.

### Treatment and outcome

After 6 days of treatment in the infection department, the patient's symptoms had not significantly improved, her liver and muscle enzyme concentrations had further increased, and her limbs had become weaker and more difficult to move. On 25 January, she requested a consultation with our department. Physical examination revealed proximal myasthenia as the main

manifestation, and the patient agreed to be transferred to our department for further treatment. We considered primary diagnoses of drug-induced hepatitis and drug-induced myopathy. The following treatments were administered in our department: intravenous methylprednisolone at 40 mg once daily for 16 days; polyene phosphatidylcholine for liver protection; pantoprazole for acid inhibition and stomach protection; anti-tuberculosis treatment consisting of levofloxacin + ethambutol, followed by streptomycin for triple anti-tuberculosis therapy; furosemide diuresis and detumescence after albumin supplementation; oral administration of a calcium supplement (Caltrate; Pfizer, Richmond, VA, USA) and calcitriol to prevent osteoporosis; and maintenance of the fluid

balance. The changes in the liver function indices, muscle enzyme concentrations, lactate dehydrogenase concentration, and eosinophil count after treatment are demonstrated in Figure 1.

After 22 days of treatment, the patient was discharged. Her discharge status was as follows: the yellowing of her skin and sclera had subsided, her lower limb edema had disappeared, and her limb muscle strength had increased to grade V. One month later, a CT scan showed that the exudative lesions in both lower lungs were mostly absorbed, and no pleural effusion was found.

## Discussion

In summary, the main characteristics of this case were as follows.

- A middle-aged woman who had a history of having taken antituberculosis drugs 1 month previously and had no history of taking other special drugs developed acute-onset symptoms.

- Her skin and sclera showed yellow discoloration, and her proximal limbs exhibited symmetrical myasthenia.

- Her eosinophil count and immunoglobulin E concentration were increased.

- Liver function testing revealed high concentrations of transaminases, bilirubin, muscle enzymes, alkaline phosphatase, and gamma-glutamyl transpeptidase.

- Electromyography findings were mainly consistent with myogenic injury.

- Complement, autoantibody, hepatitis antibodies (A, B, C, D, and E), and the liver antigenic spectrum were negative.

- The patient had no history of trauma, excessive exercise, or alcohol drinking.

- The patient had no history of nervous system disease, endocrine disease, or tumors.

- On cerebrospinal fluid examination (lumbar puncture), all routine indices,

biochemical indices, staining results, and culture were normal/negative.

- Electromyography showed myogenic damage of both lower extremities and the right upper extremity accompanied by neurogenic damage.

After considering the above-listed findings combined with the patient's clinical symptoms, we ruled out tuberculous meningitis and peripheral neuritis caused by isoniazid. We then considered the diagnoses of drug-induced hepatitis and drug-induced myopathy. After drug withdrawal, the patient's muscle strength further decreased; however, her condition was then effectively controlled and her muscle strength returned to normal.

In patients with drug-induced myopathy, use of a particular drug induces destruction of the cell membrane structure, cell signal transduction disorder, and cell energy metabolism imbalance; these changes then result in skeletal muscle injury, myalgia, muscle weakness, restless legs syndrome, torsional muscle spasm, and other typical clinical symptoms. Myalgia and muscle spasm are early symptoms of drugs affecting the normal function and structure of skeletal muscle, and myopathy can subsequently develop. As the disease progresses, muscle atrophy can occur.<sup>4,5</sup> A unified diagnostic standard for this disease has not yet been established. It can be clearly diagnosed according to the patient's medication history combined with typical clinical manifestations (such as muscle pain, tenderness, muscle weakness, difficulty in movement, restless legs syndrome, and torsional muscle spasm), electromyography, biochemistry, and other relevant examinations. In the present case, the diagnosis of drug-induced myopathy was clear based on the medication history, typical clinical manifestations, and related examinations.

The pathogenesis of drug-induced myopathy is still unclear, but it is considered to mainly involve an increase in the

intracellular concentration of free calcium. In normal muscle cells, the sarcolemma of striated muscle fibers contains many pumps that regulate the electrochemical gradient of the cells. Under the action of the sodium–potassium pump ( $\text{Na}^+\text{-K}^+$  pump) and calcium pump ( $\text{Ca}^{2+}$  pump), the ion exchange remains normal within the cells. However, when adenosine triphosphate is exhausted (which may occur by many factors), the  $\text{Na}^+\text{-K}^+$  pump and  $\text{Ca}^{2+}$  pump are dysfunctional, leading to an increase in cell permeability to  $\text{Na}^+$ . The accumulation of  $\text{Na}^+$  increases the  $\text{Ca}^{2+}$  concentration. Excessive  $\text{Ca}^{2+}$  then increases the activity of intracellular proteolytic enzymes that degrade muscle cells, resulting in the destruction of muscle cells and the release of large amounts of  $\text{K}^+$ , aldolase, phosphate, myoglobin, creatine kinase, lactate dehydrogenase, and uric acid into the circulatory system, causing drug-induced myopathy (including direct myotoxic myopathy, immune-mediated myotoxic myopathy, and indirect myopathy).<sup>7</sup> The patient described in the present report was considered to have immune-mediated myotoxic myopathy. Generally, this condition does not require treatment, and the symptoms will automatically disappear after drug withdrawal. However, symptomatic treatment can be given if needed.<sup>8–10</sup>

Few reports worldwide have described drug-induced myopathy caused by tuberculosis drugs. Chaouch et al.<sup>11</sup> reported a case of drug-induced myopathy caused by pulmonary tuberculosis treated with isoniazid. After stopping the drug, the patient's muscle strength recovered. Shah and Venkatesan<sup>12</sup> described a 26-year-old man who developed multiple joint pain, generalized myalgia, fatigue, and elevated uric acid and creatine kinase concentrations after standard treatment for tuberculosis. After discontinuation of pyrazinamide treatment, the patient's polyarthralgia and uric acid concentration improved, but his myalgia

and creatine kinase concentration did not. After withdrawal of ethambutol treatment, however, his myalgia and creatine kinase concentration improved. Therefore, drug withdrawal has become an effective treatment for most cases of drug-induced liver injury and drug-induced myopathy. Clinically, the main drugs that can cause drug-induced myopathy are lipid-lowering drugs such as simvastatin and atorvastatin calcium; anti-infective drugs such as azithromycin, voriconazole, entecavir, and adefovir dipivoxil; antipsychotic drugs such as olanzapine and risperidone; anti-tumor drugs such as paclitaxel and cyclophosphamide; nonsteroidal anti-inflammatory drugs such as acetaminophen and ibuprofen; anti-malarial drugs such as quinine and hydroxychloroquine; and other drugs including colchicine and methadone.<sup>13</sup>

The three indications for corticosteroid use in patients with drug-induced myopathy are as follows. First, the symptoms are not relieved after drug withdrawal, indexes are aggravated (jaundice, liver enzymes, muscle enzymes), muscle strength is reduced to a serious degree, and the patient cannot get out of bed. Second, the eosinophil count and immunoglobulin E concentration are significantly increased. Eosinophilia is actually a type of hypersensitivity and autoimmune reaction. In the immune reaction, mast cells, basophils, and neutrophils can release eosinophilic chemokines. Complement fragments and various factors produced by lymphocytes in delayed-type hypersensitivity can cause eosinophils to migrate to the affected tissue and aggregate, which plays an important role in the formation of antigen–antibody complexes. Third, the diagnoses of drug-induced hepatitis and drug-induced myopathy are clear.

The mechanism of corticosteroid therapy for tuberculosis involves antiviral effects, anti-inflammatory effects, and immune suppression. The indications for corticosteroid therapy in patients with tuberculosis are

tuberculous meningitis, miliary tuberculosis, tuberculous exudative pleurisy (pericarditis), tuberculous peritonitis, and an allergic reaction caused by anti-tuberculosis drugs. Notably, treatment for tuberculosis must be combined with corticosteroid therapy based on strong and effective anti-tuberculosis treatment. The purpose is to relieve the symptoms of systemic tuberculosis poisoning as soon as possible, promote the disappearance and absorption of inflammation, and prevent fibrous tissue hyperplasia and adhesion.<sup>14</sup>

In clinical practice, clinicians must pay attention to the risk factors for drug-induced myopathy, mainly drug- and patient-related factors such as the muscle toxicity of the drug itself, combined use of high-risk drugs, the drug dose, the patient's age (especially elderly patients), the presence of multisystem diseases, and the patient's history of drug and alcohol abuse. Before they are treated with any medication, patients should be informed of possible adverse reactions such as muscle toxicity, and their myocardial enzyme concentrations should be measured. During treatment, drugs that can increase the risk of myopathy should be avoided, and relevant indicators should be monitored regularly.

## Conclusion

Anti-tuberculosis drugs may cause drug-induced myopathy, and an autoimmune reaction might be involved in the pathogenesis. Early use of corticosteroid therapy may have a therapeutic effect in patients with drug-induced myopathy.

## Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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## ORCID iD

Xinke Yuan  <https://orcid.org/0000-0002-7804-0315>

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