CASE REPORT

Drug-induced myopathy in a patient with pulmonary tuberculosis

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Accepted 2 July 2015

SUMMARY

A 26-year-old man, who had started treatment for pulmonary tuberculosis, developed polyarthralgia, generalised myalgia, weakness, and elevated uric acid and creatine kinase levels. His polyarthralgia improved on cessation of pyrazinamide, but the improvement in his myalgia and creatine kinase was delayed. Drug-induced myopathy was considered as there were no clear alternative explanations.

BACKGROUND

Drug-induced myopathy is among the most common causes of muscle disease. The spectrum of disease seen is wide and can range from mild myalgia to chronic myopathy, with severe weakness, or massive rhabdomyolysis with acute renal failure.^{1–4} Several pathogenetic mechanisms are described and include direct toxicity, as is seen in mitochondrial damage caused by zidovudine, immunologically mediated inflammatory myopathy, which can occur with D-penicillamine, and indirect muscle damage, as seen in drug-induced hyperkinetic or dystonic states.^{5–6} We describe a patient with pulmonary tuberculosis who developed myopathy, which improved after cessation of pyrazinamide and ethambutol.

CASE PRESENTATION

A 26-year-old Afro-Caribbean man presented with a 3-month history of being unwell. Three years previously, he had suffered a penetrating gunshot injury to the head, requiring craniotomy and ongoing follow-up. Two years previously, bilateral hilar lymphadenopathy was incidentally noted on a chest X-ray, but the patient was asymptomatic. Five months prior to his presentation, he had a cough with some sputum, and a chest X-ray showed new nodular shadowing in the upper and mid zones, on both right and left sides. A transbronchial biopsy undertaken with endobronchial ultrasound did not retrieve adequate diagnostic tissue. He did not provide sputum for microbiology as requested, but samples for microbiology were also not sent at the time of bronchoscopy. A diagnosis of sarcoidosis was suspected and he was started on prednisolone 30 mg once daily, the dose later being tapered. His condition was initially stable and then for 3 months he had a cough, productive of thick green sputum, and diarrhoea and weight loss totalling 10 kg. Four weeks prior to admission, he took a 7-day course of amoxicillin and clarithromycin, without improvement. By then he was no longer on prednisolone. He took no other prescription or non-prescription drugs.

On admission, he had a temperature of 38.4°C with a regular heart rate of 108 bpm and a blood pressure of 105/65 mm Hg. His respiratory rate was 16 breaths per minute and his peripheral oxygen saturations were 99% inspiring room air. On chest examination, percussion note and breath sounds were normal. A chest X-ray again showed bilateral hilar lymphadenopathy and upper zone nodularity, but he now had right upper zone consolidation with a large cavitory lesion and partial lobar collapse. Sputum samples were smear positive for acid fast bacilli and a diagnosis of pulmonary tuberculosis was performed.

Although born in the UK, he was of Jamaican descent. He had visited Jamaica on several occasions. His uncle and cousin in Jamaica had had tuberculosis, although our patient gave no clear contact history with them at the time of their tuberculous illness.

He was started on quadruple antituberculous treatment according to body weight (rifampicin, isoniazid, pyrazinamide and ethambutol). His fever subsided and his cough and diarrhoea began to settle. He was discharged after a 17-day stay in hospital and was seen again in clinic after 2 weeks. At this point he had started to develop arthralgia, that is, 4 weeks after starting antituberculous therapy. He also complained of generalised muscle aches. On examination, he had a symmetrical polyarthralgia of predominantly large joints but no joint effusions or synovitis. His uric acid level was measured at 636 µmol/L (normal range 220–420 µmol/L). His haemoglobin was 120 g/L (normal range for 130–180 g/L) and C reactive protein was 15 mg/L (normal range 0–10 mg/L). His sodium, potassium, urea and creatinine levels were all normal as were his transaminases, bilirubin and albumin. He was advised to take ibuprofen 400 mg three times a day and was seen again a week later. By this time, his sputum had cultured fully sensitive *Mycobacterium tuberculosis*. There was still no improvement in his debilitating polyarthralgia so his pyrazinamide was stopped.

Three weeks later, his polyarthralgia had settled completely. However, he still complained of generalised muscle aches which were now worse, being weak with difficulty walking and standing. On examination, there was no focal muscle tenderness and his reflexes were normal. He struggled to stand unaided. At this point, his ethambutol was stopped, having completed his first 8 weeks of antituberculous treatment, and he continued on rifampicin and isoniazid. He felt well enough to remain an outpatient.

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To cite: Shah R, Venkatesan P. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-206906

INVESTIGATIONS

At the time of completing 8 weeks of antituberculous treatment, investigations showed raised creatine kinase (CK) of 4786 U/L (normal range 0–170 U/L) and again his renal function was normal. His thyroid function was normal and he had extensive autoantibody testing, which proved negative (table 1). HIV serology was negative.

DIFFERENTIAL DIAGNOSIS

The markedly raised CK indicated the presence of an acquired myopathy. Myopathy is a muscle disease unrelated to any disorder of innervation or the neuromuscular junction. Injury to muscle fibres may be due to trauma, local infection, metabolic disorders, autoimmune disease, toxins or drugs.

Our patient denied any recent seizures or trauma. Tuberculous myopathy is recognised with local infection causing a local muscle problem.⁷ However, our patient had a diffuse myalgia with several muscle groups affected. On investigation, there was no evidence of a metabolic, endocrine or autoimmune disorder. Prior to his admission, he had received courses of amoxicillin and clarithromycin, but his myopathic symptoms started about 8 weeks after finishing these, and at least 12 weeks after completion of prednisolone. His symptoms also improved while continuing on rifampicin and isoniazid, making these unlikely culprits. Isoniazid is associated with a drug-induced lupus syndrome, but the patient was negative for antinuclear antibody and antihistone antibodies, which are characteristic of this condition.⁸ He denied taking any other medications prescribed or otherwise, any recreational drugs, nutritional supplements or herbal remedies. In the absence of other precipitants, we considered the possibility of drug-induced myopathy secondary to either pyrazinamide or ethambutol.

OUTCOME AND FOLLOW-UP

Five weeks after stopping pyrazinamide and 2 weeks after stopping ethambutol, the patient's symptoms were settling and a repeat CK level had come down to 342 U/L. A muscle biopsy was not undertaken in view of the improvement. A biopsy may not have changed our management nor identified the trigger, although it may have provided some pathogenetic insight into the mechanism of the myopathy. The patient completed his anti-tuberculosis treatment without further problems and had good clinical improvement.

DISCUSSION

This patient's story illustrates that delays in investigation for and diagnosis of tuberculosis still occur in low-endemicity areas.

Polyarthralgia with raised uric acid is a well-recognised side effect of pyrazinamide. However, the focus here is the cause of this patient's myopathy. This case was reported to the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK via the Yellow Card scheme.

Pyrazinamide was discovered in 1954, and has been used as part of the first-line multidrug regimen for treatment of tuberculosis for several decades. It is a synthetic pyridine analogue of nicotinamide, and its mechanism of action is still largely unknown. Hepatitis, polyarthralgia and asymptomatic hyperuricaemia are well-recognised side effects caused by pyrazinamide.^{9–10} Our patient's polyarthralgia clearly improved on stopping pyrazinamide. No reports of pyrazinamide associated myopathy are listed by the Federal Drug Administration (FDA) in the USA.¹¹ In the UK, the MHRA have received two reports of myopathy, one of which was reported as rhabdomyolysis, four reports of myalgia, one report of myositis and one report of muscle twitching associated with pyrazinamide. These reports were received between 7 July 1964 and 28 May 2014 and include our case.¹² Adverse effects are more likely to be seen in areas of higher tuberculous endemicity, but even there reports are few. The paucity of reports implies that muscle-related problems with pyrazinamide are rare. As far as we are aware, there have only been two previous published cases of acute myopathy attributed to pyrazinamide, and one of these developed rhabdomyolysis.^{13–15} Fernández-Solà *et al*¹⁴ described a case of acute toxic myopathy due to pyrazinamide in a patient who also had mild renal failure and was on cyclosporine, which can interact with mitochondrial function and thereby potentially cause direct muscle toxicity. A challenge with all drug reporting is distinguishing the effect of an individual drug when a patient is on several agents and has comorbidities. In the case report by Fernández-Solà *et al*,¹⁴ it is mentioned that the patient showed a progressive improvement in muscle weakness and myalgia, and was eventually symptom-free 2 months after pyrazinamide was stopped. However, there is more information in the case report by Namba *et al*.¹³ In this case report CK levels fell 'a few weeks' after cessation of both pyrazinamide and ethambutol, although the latter had been prescribed prior to pyrazinamide, without myopathic problems. Namba *et al* did attempt a 2-week rechallenge with pyrazinamide a few months later, without CK rising above the normal range. Gupta *et al* describe a patient from India with severe bilateral leg cramps following pyrazinamide therapy. In our patient, the myopathic symptoms initially increased after cessation of pyrazinamide and later improved. This was probably a delayed effect.

In our patient myopathic symptoms did settle shortly after stopping ethambutol. Ethambutol was discovered in 1961, and has been the fourth drug in induction treatment for tuberculosis for the past two decades. Ethambutol inhibits arabinosyl transferases involved in the biosynthesis of the mycobacterial cell wall. The major recognised toxicity associated with ethambutol is neuropathy, where retrobulbar optic neuritis is a more common manifestation than peripheral neuropathy. Various possible pathogenic mechanisms have been proposed for optic neuritis.¹⁶ In experimental animal models, axonal swelling is observed and in vitro, at least in rat retinal ganglion cells, there is mitochondrial damage, which may be due to a glutamate mediated excitotoxic pathway.¹⁷ In human fibroblasts, ethambutol can produce a mitochondrial coupling defect, decreased mitochondrial membrane potential and fragmentation of the mitochondrial network.¹⁸ Mitochondrial injury could be a putative mechanism for myopathy.

Table 1 Autoantibody screen

Tests for all of the autoantibodies listed below proved to be negative

Antinuclear antibody (ANA)	Anti-Pyruvate dehydrogenase (PDH)
Antineutrophil cytoplasmic antibody (ANCA)	AMI MI-2
Antihistone RO60	Anti Ku
Anti-centromere	Anti-PL7
Anti-Proliferating Cell Nuclear Antigen (PCNA)	Anti-PL12
Anti-nucleosome	Anti-R052
Anti-ribosomal P	Anti-SCL-70
Double stranded DNA	Anti-Jo-1
Ribonucleoprotein (RNP) antibody	LA antibody
SM antibody	

The FDA lists one report of ethambutol associated myopathy. The MHRA has one reported case of ethambutol associated myopathy. In addition to this, there are three reports of myalgia, three reports of muscular weakness, one report of musculoskeletal pain and two reports of decreased mobility linked to use of ethambutol. The MHRA received these reports between 3 August 1967 and 23 May 2014, our report included. Again, the paucity of reports implies that muscle-related problems with ethambutol are rare. We are aware of one published report of a patient with DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome, who was patch test positive for both celecoxib and ethambutol, and had an eosinophilic polymyositis.¹⁹ In this case, celecoxib was reported as having the major contributory role. Our patient did not develop eosinophilia and did not have features of DRESS syndrome. We have not identified any other publications in which clinical details are provided of myopathy associated with ethambutol. As in the pyrazinamide case reports, it is difficult to distinguish the specific contribution of one drug among several drugs and other disease processes. Rechallenging the patient with pyrazinamide or ethambutol may have been the only definitive way of reaching a diagnosis but was not carried out in order to avoid harm to the patient.

Learning points

- ▶ While polyarthralgia secondary to pyrazinamide is well recognised, there is a clinical need to distinguish arthralgia from myalgia, and to investigate the latter accordingly.
- ▶ Checking the creatine kinase is a simple measure of muscle injury in investigation of myalgia.
- ▶ Iatrogenic problems due to drugs must remain in our differential diagnoses.
- ▶ Full, published clinical reports are rarer than reports to drug registries, and both reporting to and referring to the latter remain important for clinicians.

Contributors RS and PV were both involved in the clinical care of the patient, and were responsible for drafting and revising the manuscript up to its final form.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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