CASE REPORT

Rifampicin-induced adrenal crisis in a patient with tuberculosis: a therapeutic challenge

Nicholas Denny, Sarika Raghunath, Praveen Bhatia, Muntasir Abdelaziz

Department of Respiratory Medicine, Tameside General Hospital, Ashton-under-Lyne, UK

Correspondence to

Dr Nicholas Denny,
scat3660@doctors.org.uk

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SUMMARY

A 55-year-old Indian man presented with productive cough and a large left pleural effusion. Pleural fluid culture grew *Mycobacterium tuberculosis*, and he was started on antituberculosis therapy. One week later, the patient presented to hospital with drowsiness, dehydration and hypotension. He was transferred to critical care and only improved after starting hydrocortisone and stopping rifampicin. His short synACThen test subsequently confirmed primary adrenal insufficiency, and a CT of the abdomen showed bilateral adrenal enlargement. Rifampicin is known to accelerate cortisol metabolism. We report the rare case of a rifampicin-induced adrenal crisis as a first presentation of Addison's disease in a patient with tuberculous infiltration of the adrenal glands.

BACKGROUND

Addison's disease or primary adrenal insufficiency has a number of potential causes. Worldwide tubercular infiltration is the commonest cause of Addison's disease.¹ However, with the low prevalence of active tuberculosis in the UK, this complication, which occurs in ~5% of cases,¹ is rarely seen.

An adrenal crisis is a life-threatening manifestation of Addison's disease and may be the first presentation of this condition in about 50% of cases.² In general, an Addisonian crisis is precipitated by an acute trigger, which include infection, trauma, stress and medication adherence.³ Less commonly, medication that interferes with glucocorticoid metabolism may induce an adrenal crisis.

We report a rare case of an adrenal crisis as a first presentation of Addison's disease induced by rifampicin in a patient with tuberculosis. To the best of our knowledge, an adrenal crisis triggered by rifampicin has only been reported in three previous cases.^{4–6} It is important to be aware of this interaction prior to starting rifampicin, to prevent potential life-threatening consequences.

CASE PRESENTATION

A 55-year-old Indian man, with a background of type 2 diabetes controlled with metformin and glizalide, presented with a productive cough and weight loss. His chest X-ray revealed large left side pleural effusion. Investigations during this initial presentation demonstrated an exudative effusion, but other pleural fluid analysis was negative for *Mycobacterium tuberculosis*. Pleural fluid cytology was also negative for malignant cells. Blood tests showed a microcytic anaemia, mild lymphopenia

and hypoalbuminaemia but were otherwise normal at this stage, including a random cortisol. CT thorax, abdomen and pelvis confirmed a left-sided pleural effusion and also showed multiple pulmonary nodules, mediastinal lymphadenopathy and bilateral adrenal attenuation. Bronchoscopy and bronchoscopic samples were normal. His effusion was drained, and in the absence of a diagnosis, he was referred for rigid thoracoscopy. While waiting for this procedure, his pleural fluid culture grew fully sensitive *M. tuberculosis*, and he was started on standard quadruple antituberculosis therapy (ATT), which included rifampicin, isoniazid, ethambutol and pyrazinamide.

A week later after being started on ATT, he presented to hospital with drowsiness and dehydration following a 3-day history of nausea, vomiting and abdominal pain. On examination, the patient appeared unwell, drowsy and in respiratory distress, with a respiratory rate of 40, a SpO₂ of 99% on 15L non-rebreathe, a blood pressure of 85/40 mm Hg, a heart rate of 110 regular and a temperature of 34.5°C. Auscultation of the chest revealed scattered crepitations throughout, reduced air entry bibasally and normal heart sounds. His peripheries were cool with a prolonged capillary refill time, but there was no peripheral oedema. There was minimal urine output in a catheter bag. He was alert to voice, and his blood glucose measurement was 3 mmol/L. His abdomen was generally tender with no evidence of peritonism and normal bowel sounds.

INVESTIGATIONS

Haematological analysis showed a white cell count of $18.6 \times 10^9/L$ ($<11 \times 10^9/L$) with neutrophilia and microcytic anaemia with a haemoglobin of 122 g/L (130–180/L) and an INR of 1.6 (0.8–1.2). C reactive protein was 25 mg/L (<6 mg/L).

Urea and electrolytes showed a stage 2 acute kidney injury with a Cr of 160 $\mu\text{mol/L}$ (54–110 $\mu\text{mol/L}$), a urea of 18.4 mmol/L (2.5–6.5 mmol/L), a sodium of 131 mmol/L (133–146 mmol/L) and a potassium of 5.9 mmol/L (3.5–5.3 mmol/L). Liver function tests (LFTs) were deranged with a mixed cholestatic and hepatitic picture; bilirubin was 42 $\mu\text{mol/L}$ (<21 $\mu\text{mol/L}$); albumin was 18 g/L (31–45 g/L); and alanine transaminase (ALT), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) were all twofold the upper limit of normal.

Arterial blood gas analysis revealed a profound metabolic acidosis with a pH of 6.8, a PaCO₂ of 6 kPa, a PaO₂ of 20 kPa, a base excess of –27, a bicarbonate of 5 and a lactate of 15. Ketones were

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1.1 mmol/L (<0.6 mmol/L). An ECG demonstrated sinus tachycardia, and a chest X-ray showed patchy consolidation in the left upper zone.

A CT of the thorax, abdomen and pelvis showed patchy consolidation in both upper zones, pulmonary nodules and small bilateral pleural effusions. There were also bilaterally enlarged adrenal glands and mesenteric lymphadenopathy as shown in figure 1.

DIFFERENTIAL DIAGNOSIS

There is a broad differential diagnosis for this acutely unwell patient including sepsis secondary to bronchopneumonia, acute coronary syndrome and cardiogenic shock and an Addisonian crisis.

TREATMENT

He was initially treated for severe septic shock secondary to a hospital-acquired pneumonia and given intravenous tazocin and intravenous crystalloid titrated against blood pressure and urine output. His blood pressure only improved transiently in response, and consequently he was intubated and transferred to the intensive care unit (ICU) for invasive monitoring and vasopressor support. Overnight his vasopressor requirement was 10 mL/hour of norepinephrine (320 µg/mL). As the patient remained critically unwell, a trial of intravenous hydrocortisone was carried out. This led to a marked improvement in vasopressor requirements, which fell to 2 mL/hour of norepinephrine (320 µg/mL) over 12 hours. Over the following 5 days, his vasopressor requirement decreased until it was no longer necessary.

During this period, rifampicin was identified as a trigger for an Addisonian crisis in our patient who already had subclinical adrenal insufficiency as a result of tuberculous infiltration. As a result, it was stopped. An alternative approach considered was continuing rifampicin and using a larger dose of corticosteroids to act as adequate replacement therapy. However, our patient developed a progressive mixed cholestatic and hepatic deterioration in LFTs with values of ALT, ALP and GGT over fivefold the upper limit of normal, and in the face of this decline, rifampicin was not restarted. Although our patient's hepatitis may have been secondary to adrenal insufficiency, it is rarely this severe.⁷ Moreover, in spite of 3 days of corticosteroid therapy and cessation of rifampicin, his LFTs continued to worsen. In previous cases of Addisonian hepatitis, LFTs began to normalise

shortly after starting corticosteroids.⁷ Therefore, it was felt that hepatitis secondary to adrenal insufficiency was unlikely, and other hepatotoxic medication was changed; specifically, isoniazid and pyrazinamide were substituted for streptomycin and moxifloxacin. Unfortunately, moxifloxacin also led to an acute transaminitis and was withdrawn. It was only on temporarily substituting ATT that our patient's LFTs plateaued and improved. Isoniazid was eventually re-introduced gradually with close monitoring of LFTs.

OUTCOME AND FOLLOW-UP

After 8 days on ICU, he was extubated and discharged to an inpatient ward where he made an excellent recovery. Cortisol level in the blood taken on admission was 322 nmol/L (250–650 nmol/L). A short Synacthen test, carried out when he had fully recovered, showed an 8 am serum cortisol of 73 nmol/L (250–650 nmol/L) and, 30 min after tetraoctadecanamide administration, a serum cortisol of 179 nmol/L (250–650 nmol/L). This was strongly suggestive of primary adrenal insufficiency, and therefore, he remains on physiological doses of hydrocortisone. He also received 2 months of streptomycin, isoniazid and ethambutol to treat tuberculosis and is currently taking a further 16 months of isoniazid and ethambutol. Fortunately, he has made a full recovery and has not suffered any further complications of ATT.

DISCUSSION

Cortisol metabolism is complex and varies between individuals. Previous studies have shown that 6β-hydroxylase metabolism of cortisol to 6β-hydroxycortisol is a key inducible pathway.⁸ In most individuals, this pathway accounts for a small proportion of cortisol metabolism. However, under certain circumstances, it can be induced 10-fold and may account for 50% of cortisol metabolism.⁸

Rifampicin, a broad spectrum macrocyclic antibiotic first isolated from *Streptomyces mediterranei*, is a potent inducer of the cytochrome P450III_A enzyme.⁸ Ged *et al*⁸ demonstrated that a 5-day course of 600 mg rifampicin orally led to a substantial induction of this hepatic microsomal enzyme. In contrast, patients who did not receive rifampicin poorly expressed this enzyme. Subsequently, Ged *et al*⁵ were able to inhibit 6β-hydroxylase activity in a human in vitro model of cortisol metabolism with an anti-P450III_A antibody. This set of experiments illustrates that the cytochrome P450III_A enzyme has 6β-hydroxylase activity and is induced by rifampicin. Overall, it appears that rifampicin increases cortisol breakdown to 6β-hydroxycortisol by selectively upregulating liver microsomal cytochrome P450III_A and that this can be achieved by clinical doses of rifampicin given orally over 5 days.

Significant biochemical hypoadrenalism occurs in ~50% of patients with pulmonary or disseminated tuberculosis when measured by a conventional short Synacthen test.⁹ However, this is rarely clinically apparent.⁹ Our patient had radiological evidence of adrenal infiltration on his initial staging CT but lacked any symptoms, signs or biochemical evidence to suggest primary adrenal insufficiency. As any adrenal insufficiency was subclinical, he was started on ATT. This unmasked his hypoadrenalism, and 1 week later, he presented with an adrenal crisis. Addison's disease was subsequently confirmed with a short Synacthen test.

In light of his adrenal infiltration, the strong temporal relationship between beginning ATT and our patient's symptoms and a lack of other clear triggers for an adrenal crisis, a diagnosis of rifampicin-induced primary adrenal insufficiency was

Figure 1 Axial CT slice at T12 that shows bilateral enlarged adrenal glands.

made. Consequently, his rifampicin was stopped, hydrocortisone was started, and thereafter he made a full recovery. A rifampicin-induced adrenal crisis in a patient without evidence of clinical Addison's has only been described in a small number of case reports in the past⁴⁻⁶ and a single prospective study.¹⁰ In this study, 1.5% of patients with either pulmonary or extrapulmonary tuberculosis started on standard ATT developed clinical evidence of adrenal insufficiency and required admission for intravenous corticosteroids.¹⁰ As with our case, none of the patients displayed evidence of hypoadrenalism prior to treatment; however, in contrast, all cases were women and diagnoses were not confirmed with a short Synacthen test. In all these previously reported cases, the dose of rifampicin used ranged from 450 to 600 mg and the time from starting ATT to presentation ranged from 9 days to 7 weeks. Our patient presented 7 days after starting 600 mg rifampicin. The difference in duration from starting ATT to presentation may be due to a number of factors, which include the degree of pre-existing adrenal insufficiency and variable effect of rifampicin on liver enzyme expression in each patient.

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In conclusion, adrenal insufficiency is a common complication of tuberculosis infection, is often subclinical and is one of the possible mechanisms for sudden death in this condition.¹ Starting rifampicin in patients with tuberculosis infection, particularly with adrenal infiltration, may precipitate an adrenal crisis as a result of the induction of hepatic 6 β -hydroxylase and the increased breakdown of cortisol to 6 β -hydroxycortisol. As a consequence, we suggest that an early morning cortisol is performed in all patients with active tuberculosis infection, especially if there is radiological evidence of adrenal gland involvement. This will allow clinicians to identify patients at risk of hypoadrenalism prior to starting standard ATT, monitor them more closely and intervene with corticosteroid replacement earlier if needed.

Contributors ND contributed to design of and drafted the initial manuscript. ND and MA were involved in acquisition of the data. All the authors were involved in critical revision of the manuscript and final version for publication.

Competing interests None declared.

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Learning points

- ▶ Rifampicin increases cortisol metabolism and can trigger an adrenal crisis in patients with known pre-existing adrenal insufficiency. More rarely, rifampicin may lead to a first presentation of adrenal insufficiency as an Addisonian crisis. This is a possible cause of sudden death in tuberculosis infection.
- ▶ An early morning cortisol should be considered in patients with tuberculosis infection, especially if there is radiological evidence of adrenal gland infiltration. This should be performed prior to or as soon as the patient starts antituberculosis therapy that includes rifampicin because hepatic enzyme induction can occur within 5 days.
- ▶ Patients with evidence of adrenal insufficiency should have a short Synacthen test and be monitored more closely when starting standard ATT, given the small but serious risk of precipitating an adrenal crisis.

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