Rifampin-induced flu-like syndrome with shock in a patient with tuberculosis infection

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A 15-year-old girl, born in a country with a high burden of tuberculosis (TB), was in the care of a tertiary care infectious disease clinic for TB infection (TBI) based on a positive QuantiFERON gold test. She had no evidence of TB disease. She had a history of iron deficiency anemia (hemoglobin 97–104 [normal 112–151] g/L) and moderately active systemic lupus erythematosus (SLE), given her symmetric nonerosive polyarthritis, nonscarring alopecia, photosensitivity and Raynaud phenomenon, as well as positivity for antinuclear, anti-Smith and anti-ribonucleoprotein antibodies. Her medications were naproxen (375 mg, twice daily) and hydroxychloroquine (5.5 mg/kg/d); she had not taken corticosteroids for several years. The patient began treatment with 600 mg rifampin (10 mg/kg/d) and tolerated the medication well for 11 days. For the next 3 days, she had chills and myalgias that began a few hours after rifampin ingestion and resolved a few hours later. She stopped treatment for 3 days without symptom recurrence.

After an in-person assessment, with a normal physical examination aside from arthritis in 2 joints, the patient was advised to resume rifampin. Within 1 hour of taking the medication, she developed sudden onset severe neck pain, myalgias, arthralgias, shortness of breath and chest pain. During ambulance transport to the emergency department, she received a fluid bolus for hypotension (80/40 mm Hg). On physical examination, she was febrile (38.3°C), tachypneic (28 breaths/min, 99% saturation) and tachycardic (123 beats/min) with a low-to-normal blood pressure (91/52 mm Hg). Her weight was 60 kg. She had no angioedema, rash, wheezing or gastrointestinal symptoms. She received intravenous fluids and empiric vancomycin and ceftriaxone. Three hours after symptom onset, she became hypotensive again (89/36 mm Hg) and diaphoretic, requiring fluid resuscitation and norepinephrine and epinephrine infusions. She was admitted to the intensive care unit (ICU).

On physical examination, the patient had no rash or mucous membrane involvement. Blood work showed a decreased leukocyte count at admission (2.84 [normal 4.23–9.99] × 10^9/L), which increased to 17.34 × 10^9/L 6 hours later, with low eosinophil counts throughout (0.00 [normal 0.02–0.51] × 10^9/L). Her hemoglobin level decreased to 74 g/L on the second day of admission after fluid resuscitation. Her bilirubin and haptoglobin levels were normal, a direct antiglobulin test was negative and her blood film did not show schistocytes.

Key points

- Rifamycin-based regimens are increasingly used for the management of patients with tuberculosis infection because of lower rates of hepatic adverse drug reactions and higher completion rates than other regimens.
- Rifampin-induced flu-like syndrome is usually a mild illness associated with intermittent dosing regimens (i.e., weekly) but can also occur with low-dose daily administration.
- Mild flu-like symptoms can be managed by short-term, over-the-counter analgesia.
- If treatment is temporarily stopped because of flu-like syndrome, patients can uncommonly have a more severe reaction, including shock, after resuming treatment.
- Patients should be encouraged to resume treatment in a location where medical care is available in case life-threatening symptoms develop.

Inflammatory markers were elevated, with a C-reactive protein (CRP) level of 13.6 (normal < 1.7) mg/L at admission, increasing to 101.8 mg/L about 24 hours later. The patient's aspartate aminotransferase level increased from 71 (normal < 31) U/L to 99 U/L during this time. Her complement C3 level was slightly decreased at 0.76 (normal 0.83–1.52) g/L and her C4 level remained within normal range. Her creatinine kinase level was normal. Given a previous finding of a partially empty sella turcica on magnetic resonance imaging, the patient's cortisol level was tested and found to be increased at 605 nmol/L (normal range 30–254 nmol/L for evening sampling).

Given the presence of severe neck pain, nuchal rigidity and shock, the critical care team suspected sepsis and performed additional investigations. A computed tomography (CT) scan of the head and an echocardiogram were normal; CT angiography of the neck did not show an infected thrombus or edematous retropharyngeal soft tissue but showed localized myositis. A chest radiograph showed mild pulmonary edema attributed to fluid resuscitation, which responded to diuresis; CT imaging of

the lungs showed bilateral increased septal thickening with ground glass opacities. All infectious work-up — including cultures of blood, sputum, throat and cerebrospinal fluid samples, and serology for Epstein–Barr virus, cytomegalovirus and mycoplasma — was negative. The patient was negative for SARS-CoV-2 on polymerase chain reaction.

Because infection was suspected, she received 1 dose of rifampin in the ICU, which led to a decreased blood pressure of 93/39 mm Hg. In response, her vasopressor dose was increased for 6 hours (norepinephrine 0.04–0.06 μg/kg/min). Rifampin was stopped, and the patient was weaned off vasopressors within 30 hours of admission. Our teams became involved after this episode, and we attributed her presentation to a rifampin-induced adverse drug reaction. We started her on isoniazid for TBI and she successfully completed 9 months of therapy. We told her to avoid rifamycin-based medications in the future.

Discussion

Rifampin-induced flu-like syndrome is a type III hypersensitivity reaction that typically develops 1–4 hours after ingestion of a dose, but delayed reactions up to 8–12 hours later have been reported. Symptoms usually last for 8 hours and often include fever, chills, malaise, headache and arthralgias. When treatment is resumed after stopping because of adverse drug reactions, patients may uncommonly develop hypotension and shock, which generally resolve within 24 hours.[1–6] The terminology in the literature is inconsistent; we refer to this severe clinical presentation as rifampin-induced flu-like syndrome with shock.

Rifampin-induced flu-like syndrome has been reported for all rifamycin compounds, the drug class to which rifampin belongs.[1,2,4] The pathophysiology remains unclear, but the occurrence of this syndrome has been associated with the presence of anti-rifampin antibodies. Because patients may be symptomatic in the absence of anti-rifampin antibodies, and antibodies have been found in patients tolerating rifampin, measurement of anti-rifampin antibodies is not helpful in the diagnosis or management of this condition.[1,3] The diagnosis can be made based on a clinical assessment of presenting symptoms, physical examination and available laboratory investigations, and exclusion of other causes.

Female sex and increasing age have been shown to increase the likelihood of rifampin-induced flu-like syndrome.[7] Patients with HIV have been found to have a lower risk;[8] however, SLE or other autoimmune diseases have not been reported as risk factors for the development or severity of rifampin-induced flu-like syndrome.[9] Treatment-specific risk factors include prolonged treatment duration (i.e., > 3 mo), intermittent dosing (i.e., once weekly) and increased dose (although there is no clear definition for what constitutes an increased dose in this context); however, patients can develop the syndrome without these risk factors.[10]

Our patient's presentation was typical for an adverse drug reaction to rifampin, although it was important to consider alternative diagnoses. Infections were excluded, and her clinical presentation was atypical for an SLE flare. She had no signs of pulmonary embolus to explain the hypotension, nor serositis or hemophagocytic syndrome to explain the increased CRP, which is unusual in an SLE flare. Our patient did not have adrenal insufficiency, which can present with hypotension and shock. A Jarisch–Herxheimer reaction that could cause a flu-like syndrome has not been reported in TBI without disease. Although a relatively acute onset of hypotension can suggest anaphylaxis, a pure type I hypersensitivity reaction was unlikely, given the associated symptoms such as fever and raised inflammatory markers. Finally, she had no thrombocytopenia, hemolysis or acute renal failure, which are all uncommon adverse drug reactions to rifamycins.[1,2]

The Canadian TB Standards strongly endorse 2 rifamycin-based regimens as the preferred treatment of TBI, namely daily rifampin for 4 months or 12 weekly doses of rifapentine (a long-acting rifamycin) and isoniazid.[11] These regimens have the advantage of decreasing hepatic adverse drug reactions compared with 9 months of daily isoniazid treatment, and are associated with higher completion rates.[12] Among patients receiving the rifapentine regimen for TBI, around 3.5% develop a flu-like reaction;[12] a minority (0.2%) develop hypotension requiring intravenous fluid therapy and, occasionally, vasopressors. The rate of flu-like syndrome with the daily rifampin regimen is not reported, but it is thought to be rare.[13] Based on the updated treatment recommendations in the Canadian TB Standards, we expect increased usage of rifamycin compounds for TBI in Canada, which will likely result in a higher absolute number of patients with rifamycin-induced adverse drug reactions, particularly rifampin-induced flu-like syndrome. Management guidelines for TBI and TB disease should be updated to provide specific guidance regarding patient counselling and rechallenge with rifamycins.[9,13] We suggest that patients should be advised to speak to their prescribing provider if experiencing a possible adverse drug reaction to a rifamycin-based medication to limit unnecessary treatment interruptions. If treatment is stopped because of an adverse drug reaction, patients should discuss when to restart treatment with their provider. Patients who develop a mild flu-like syndrome on weekly rifapentine treatment may tolerate a daily rifampin regimen.[1,2,5] Patients on daily rifampin treatment who develop mild flu-like symptoms can be treated with over-the-counter anti-pyrectic and analgesic agents. However, the effectiveness of these treatments is not known. If rifamycin-based therapy is resumed after stopping because of flu-like symptoms, there is a very small risk the patient will develop a more severe reaction.[2] Providers should consider the accessibility of appropriate care (e.g., intravenous fluid administration) when planning treatment restart. Intramuscular epinephrine should be considered when intravenous vasopressors are unavailable, although no data regarding its effectiveness are available. For patients who tolerate rifamycin-based treatment upon rechallenge, an observation period of 1 hour appears reasonable based on the available literature. For patients who have had a severe reaction, rifamycin compounds should be avoided. In cases where no alternative treatment is available (e.g., isoniazid drug resistance), rifamycin-based treatment should be resumed under the guidance of a provider experienced in the management of this severe adverse drug reaction. No data are available regarding the success of desensitization for flu-like syndrome.

Given better overall safety and completion rates, rifamycin-based regimens are now the preferred therapy for TBI. It is important that health care providers recognize flu-like symptoms caused by rifamycin compounds, appropriately counsel patients before starting treatment and consider accessibility of appropriate care in case of rechallenge, if the medication has been stopped for this reason.

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