CASE REPORT

Urine trouble: genitourinary tuberculosis and subsequent DRESS syndrome

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SUMMARY

A 40-year-old woman with HIV (CD4 270, viral load undetectable) from Zambia presented with fevers, urinary tract infection symptoms, sterile pyuria and haematuria. She was found to have genitourinary tuberculosis (TB) via mycobacterial culture of urine and ascites, and treated with rifabutin, isoniazid, pyrazinamide and ethambutol. She later had multiple episodes of asymptomatic transaminitis, triggering changes to both TB and HIV regimens. The patient then presented with diffuse rash, fevers, transaminitis and eosinophilia concerning for drug reaction with eosinophilia and systemic symptoms (DRESS). After initial improvement on discontinuation of likely responsible medications and completion of corticosteroid therapy, the patient returned with acute liver failure. This new episode was felt to be severe organ dysfunction due to DRESS, and she was treated with a prolonged corticosteroid taper and changes to her TB regimen. She has since completed therapy for TB, has improving CD4 counts and is without evidence of liver dysfunction.

BACKGROUND

Genitourinary tuberculosis (TB) is infrequently seen in the developed world, but the diagnosis warrants consideration in immunocompromised patients. Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, severe syndrome characterised by haematological changes and organ dysfunction. Both diagnoses are challenging to recognise and manage, which warrants additional exploration of these topics. Here, we present a clinical case of a HIV-positive pregnant patient diagnosed with genitourinary TB and subsequent DRESS syndrome complicated by acute liver failure. There are few case reports of this type and severity of drug reaction to tuberculosis or HIV medications during the peripregnancy period.^{1 2}

CASE PRESENTATION

A 40-year-old G3P2 woman at 15 weeks estimated gestational age presented to the emergency room with 1 week of fevers, headache, dry cough, dysuria and dyspnoea on exertion. She was diagnosed with HIV infection 8 years prior (most recent CD4 270 cells/mm³, viral load undetectable) and had been previously treated with nevirapine and lamivudine/zidovudine. A few months prior to presentation, lamivudine/zidovudine was replaced with emtricitabine/tenofovir disoproxil fumarate. She had a history of latent tuberculosis treated with 9 months

of isoniazid 4 years prior, sickle cell trait, glucose-6-phosphate dehydrogenase (G6PD) deficiency and stage 1 chronic kidney disease. She emigrated from Zambia to the USA 6 years prior to presentation.

Eight days prior to presentation, the patient received nitrofurantoin and phenazopyridine from her obstetrician after a screening urinalysis showed haematuria and pyuria. A follow-up urine culture was negative. On admission to the hospital, her examination was significant for scleral icterus, tachycardia to 108 beats per minute and fever of 101°F (38.3°C). The patient was otherwise haemodynamically stable, and fetal status was within normal limits. Chest roentgenogram was unremarkable, and obstetrical ultrasound was notable only for abdominal and pelvic ascites. A basic metabolic panel was remarkable for blood urea nitrogen (BUN) and creatinine of 19 mg/dL and 1.9 mg/dL, respectively, which is above the patient's baseline of 11 mg/dL and 1.3 mg/dL. Complete blood count was significant for haemoglobin of 7.8 g/dL and haematocrit of 23.2%, down from her baseline of 12.8 g/dL—no leucocytosis was noted. Active haemolysis, most likely secondary to the combination of G6PD deficiency and nitrofurantoin, was confirmed via elevated lactate dehydrogenase (LDH) and decreased haptoglobin.

The patient received transfusions, supportive care and 1 day of ceftriaxone; however, she remained febrile with dysuria and suprapubic discomfort through day 9 of hospitalisation. Review of prior clinical history indicated that the patient had presented with intermittent dysuria, pyuria and haematuria, but negative urine cultures on multiple occasions. Abdominal ultrasound revealed ascites, loculated collections at the right flank and lower pelvis, a hyperaemic right adnexal region mass and a right kidney with dilated calyces filled with debris (figure 1). These findings were interpreted as xanthogranulomatous pyelonephritis versus TB. Given ascites and potential genitourinary TB, paracentesis was performed yielding 1.5 litres of fluid, 4.150×10^9 leucocytes/L (50% polymorphonuclear leucocytes, 39% lymphocytes), 1.750×10^9 erythrocytes/L, glucose 60 mg/dL, protein 4.3 g/dL, albumin 2.0 g/dL and LDH 317 U/L. At the time of paracentesis, serum values were as follows: albumin 3.0 g/dL, protein 5.9 g/dL and LDH 355 U/L. Given findings consistent with exudative ascites with elevated lymphocytes in an immunosuppressed woman from an endemic region, empiric therapy for TB was initiated with rifabutin, isoniazid, pyrazinamide and ethambutol. The patient began to

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Figure 1 Abdominal sonogram of right kidney in sagittal plane demonstrating dilated calyces filled with debris. Radiology interpreted these findings as genitourinary tuberculosis versus xanthogranulomatous pyelonephritis.

defervesce soon after initiation of therapy and was discharged from hospital on day 13 after three negative sputum acid-fast bacteria (AFB) smears.

After discharge, mycobacterial cultures of urine and ascites grew pan-sensitive *Mycobacterium tuberculosis*. Despite clinical improvement with anti-TB therapy, the patient experienced a spontaneous abortion 17 days following discharge. Pathology demonstrated placental abruption due to chorioamnionitis and fetal sepsis with negative AFB smears. A month after discharge, CD4 was noted to be 179 cells/mm³ with undetectable HIV viral load. The patient continued anti-TB therapy for 6 weeks, but developed transaminitis to the 400s. All anti-TB therapy was then stopped. After transaminases improved, only ethambutol and levofloxacin were restarted to avoid hepatotoxicity. Rifampin was then added to the regimen, but was discontinued after 1 week due to another elevation in transaminases. Five days after discontinuation of rifampin, nevirapine was replaced with raltegravir out of concern for possible contribution to hepatotoxicity. Despite myalgias and arthralgias, the patient's liver function tests (LFTs) remained stable, and 25 days after changes to the antiretroviral regimen, isoniazid was reintroduced to augment anti-TB therapy. One week later, diffuse pruritic rash and elevated LFTs were noted, prompting discontinuation of isoniazid and replacement of raltegravir with lopinavir/ritonavir. Dermatological and musculoskeletal symptoms subsequently improved. During this time, CD4 count was 429 cells/mm³ and viral load remained undetectable.

INVESTIGATIONS

One week after the last antiretroviral regimen change, the patient presented to the emergency room for fever and worsening rash. She was found to have a temperature of 101.5°F (38.6°C), tachycardia to 100 beats per minute, but was otherwise haemodynamically stable. Examination was notable for diffuse, pruritic, erythematous, maculopapular rash sparing extensor surfaces of both arms, oral mucosa and upper abdomen. Creatinine was

2.1 mg/dL and BUN 30 mg/dL. Urinalysis was negative except for trace blood. Laboratories were significant for eosinophil count 1.33 k/μL (reference range 0.0–0.4 k/μL), total bilirubin 1.2 mg/dL, direct bilirubin 0.7 mg/dL, alkaline phosphatase 267 U/L, aspartate aminotransferase (AST) 192 U/L, alanine aminotransferase (ALT) 322 U/L and protein 6.6 g/dL. Notably, she was HLA-B*57:01 negative. Chest roentgenogram, three sputum AFB smears, one AFB urine smear and urine mycobacterial culture were negative. Hepatitis B, C, cytomegalovirus (CMV), Epstein-Barr virus (EBV) serologies, stool for ova and parasites, and *Schistosoma* serology were negative for active infection. Given transaminitis, eosinophilia, rash and fever in setting of recent changes to medication regimen, 60 mg oral prednisone was started for presumed DRESS syndrome. A decrease in eosinophilia and transaminases was noted immediately, as well as improvement of rash and resolution of fevers. Due to clinical improvement, the patient was discharged 4 days later on 40 mg oral prednisone daily and instructed not to resume HIV or TB medications until allergy testing could be completed. Given resolution of rash, and concerns for immunosuppression, the prednisone taper was discontinued at an outpatient appointment the day after hospitalisation.

Eight days later, the patient presented to the emergency room on advice of her primary care provider for AST 3736 U/L and ALT 3129 U/L. The patient noted no use of any HIV or TB medication, alcohol or herbal remedy since the last hospitalisation. She admitted to fatigue, xerotic and pruritic skin, 1 day of scleral icterus and new onset right upper quadrant pain. On examination, the patient had a xerotic, hyperpigmented rash, scleral icterus and tender hepatomegaly. The patient was afebrile and haemodynamically stable. She was found to have an eosinophil count of 1.31 k/μL (reference range 0.0–0.4 k/μL), albumin 4 g/dL, total bilirubin 19.9 mg/dL, direct bilirubin of 13.5 mg/dL, alkaline phosphatase of 454 U/L, AST 2466 U/L, ALT 2881 U/L, total protein 606 g/dL, prothrombin time (PT) 17.5 s and partial thromboplastin time (PTT) 42.1 s. Intravenous

N-acetylcysteine (NAC) infusion was started, but within 1 hour, she complained of severe headache, flushing and palpitations. Blisters were noted over antecubital intravenous sites bilaterally, and the NAC infusion was discontinued immediately. Hepatic ultrasound showed mild hepatomegaly with steatosis. She was initiated on 80 mg oral prednisone daily per allergy consultant recommendations for suspected DRESS syndrome complicated by acute liver failure. The following serologies/laboratories were negative: anti-mitochondrial antibody, anti-smooth muscle antibody, anti-nuclear antibody, rheumatoid factor, hepatitis C virus PCR assay (PCR), hepatitis B PCR, hepatitis E virus antibody and PCR, herpes simplex virus PCR and serology, CMV PCR and IgM, EBV PCR and IgM, varicella IgG and PCR, adenovirus PCR, strongyloides IgG, trichinella IgG and leptospira antibody panel. Skin biopsy of rash showed superficial perivascular and perifollicular inflammation and post-inflammatory pigmentary alteration, which were interpreted either as old drug reaction or viral exanthem.

TREATMENT

With supportive care and corticosteroids, the patient's PT, PTT and LFTs improved. Prednisone was tapered by 10 mg per week. She completed a 2-year course of ethambutol and levofloxacin for genitourinary TB with consistently negative urine AFB smears and mycobacterial cultures.

OUTCOME AND FOLLOW-UP

Currently, the patient has not been seen by allergy/immunology consultants for further testing, but is doing well on abacavir/lamivudine and rilpivirine, which were chosen for tolerability and minimisation of secondary effects. She has completely normal LFTs, a CD4 count of 735 cells/mm³, an undetectable HIV viral load, and BUN and creatinine of 19 mg/dL and 1.8 mg/dL, respectively.

DISCUSSION

In summary, we present a case of genitourinary TB followed by DRESS syndrome complicated by acute liver failure likely related to TB or HIV therapy. Extrapulmonary TB should be suspected in patients, especially those immunocompromised, with likely TB exposure or history of latent infection presenting with unexplained fever. In genitourinary TB, urinary urgency, frequency, dysuria, back pain and haematuria are common presenting symptoms.³ A suspected diagnosis of genitourinary TB can be assessed in a variety of ways; the most sensitive include imaging studies (abdominal CT or sonogram), mycobacterial urine culture or urine mycobacterial PCR.³

DRESS syndrome is a rare, idiosyncratic drug reaction with eosinophilia, systemic symptoms and organ dysfunction, often presenting with fever, lymphadenopathy, rash, eosinophilia, atypical lymphocytosis, leucocytosis, facial oedema, thrombocytopenia and multi-system organ dysfunction.⁴ European and Japanese groups have both put forth diagnostic criteria based on expert consensus; however, neither have been validated prospectively.

The pathogenesis of DRESS is yet to be fully elucidated. It may include contributions from genetic polymorphisms in human leucocyte antigen types, alterations in drug metabolism, drug-specific CD4 and CD8 lymphocytes producing a pro-inflammatory cytokine cascade, and even herpesvirus reactivation.⁴ HIV itself induces a hyper-allergic state,⁵ predisposing to increased rates of drug rashes. This immune hyper-reactivity associated with HIV infection may be related to increased oxidative stress, differences

in drug metabolism and changes in cytokine profiles.⁶ Notably, a study of individuals undergoing tuberculosis therapy found that adverse skin reactions were more prevalent in those coinfecting with HIV.⁷ Recent evidence also suggests that pregnancy is independently associated with an increased risk of severe skin reactions (including DRESS) in patients with HIV on antiretroviral therapy.⁸ These associations are theorised to be due to changes in immune function in the pregnant state, given the multitude of effects sex hormones have on this delicate interplay.⁹

In our patient's case, we suspect that her postpartum status, HIV infection and her combination of new medications all contributed to the development of DRESS syndrome. Given the literature above on viral reactivation contributing to DRESS syndrome, the patient was checked for EBV and CMV infection. She was previously exposed to EBV and CMV based on positive IgG titres, but did not have evidence of active infection. Human herpesviruses 6 and 7 have also been implicated in DRESS; unfortunately, we do not have serological results on which to report. Of note is the immediate reaction to the NAC infusion without previous known exposure, which perhaps speaks to a hyper-reactive immune state induced by the factors we describe above. However, anaphylactic-type reactions including rashes are a known secondary effect of NAC infusions, occurring in up to 10% of patients receiving the agent.¹⁰

There are few confirmed DRESS cases from rifampin, isoniazid, nevirapine, raltegravir, ethambutol and levofloxacin.^{11–16} Unfortunately, as the patient did not undergo allergy testing, we cannot definitively state the agent responsible for this episode. She underwent multiple medication changes in the months prior to presentation, and given that DRESS syndrome can start days to months after the last dose of medication, identifying a causative agent is challenging.⁴ This difficulty is compounded as the patient took multiple drugs that are known hepatotoxins during this period.

As isoniazid was the last medication challenge before the initial rash, we suspect that this is the most likely cause. Although she previously tolerated isoniazid for a latent tuberculosis infection, the agent was now in combination with a variety of other medications, and she was recently pregnant, which may be contributing factors. Because the patient had previously tolerated nevirapine for years prior to presentation, this is less likely the causative drug. Nevirapine-associated hepatitis usually occurs within weeks of initiation with systemic hypersensitivity,⁵ although, rarely, nevirapine-associated hepatitis may occur after months of therapy without other systemic symptoms.⁵ However, neither syndrome mirrors our patient's course. Rifampin and rifabutin were also less likely since they were used for short periods without associated skin changes. The patient was on raltegravir for approximately 1 month with joint pain starting after initiation. However, this symptom, which is a known side effect of raltegravir, resolved with discontinuation of the medication. As the patient took ethambutol and levofloxacin before and after the episode, we do not believe these agents to be responsible. Abacavir is also an unlikely suspect as the patient is HLA-B*57:01 negative.

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Learning points

- ▶ Consider tuberculosis in the setting of fever of unknown origin, immunosuppression and possible tuberculosis exposure or history of latent tuberculosis infection.
- ▶ Recognise genitourinary TB as a cause of urinary symptoms with pyuria and/or haematuria with negative bacterial urine culture.
- ▶ Recognise the clinical picture of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: new medication exposure, systemic symptoms (fever, tachycardia), haematological abnormalities (eosinophilia, atypical lymphocytosis), diffuse rash and multi-organ dysfunction, among others.
- ▶ Consider the side effect of hepatotoxicity of rifampin and isoniazid while monitoring patients actively on TB therapy, and be aware that almost all TB medications have been implicated in DRESS syndrome.
- ▶ Avoid prescribing sulfa drugs, and other agents known to cause hemolysis, for G6PD deficiency patients.

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