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Case report

Multidrug-resistant tuberculosis (MDR-TB) and multidrug-resistant HIV (MDR-HIV) syndemic: challenges in resource limited setting

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SUMMARY

Tuberculosis (TB) is common among persons living with HIV. This public health concern is aggravated by infection with multidrug-resistant organisms and adverse effects of polypharmacy. There are few published cases of multidrug-resistant tuberculosis (MDR-TB) in multidrug-resistant HIV (MDR-HIV) infected patients. We report a case of a 29-year-old Filipino man with HIV on zidovudine (AZT)-containing antiretroviral therapy (ART) but was eventually shifted to tenofovir due to anaemia. He presented with left flank tenderness, which was found to be due to an MDR-TB psoas abscess, and for which second-line anti-TB treatment was started. HIV genotyping showed MDR-HIV infection susceptible only to AZT, protease inhibitors and integrase inhibitors. Subsequently, he developed neck abscess that grew *Mycobacterium avium* complex and was treated with ethambutol and azithromycin. ART regimen was revised to AZT plus lamivudine and lopinavir/ritonavir. Erythropoietin was administered for recurrent AZT-induced anaemia. Both abscesses resolved and no recurrence of anaemia was noted.

BACKGROUND

The tuberculosis (TB) and HIV coinfection is a global syndemic that increases morbidity and mortality from both diseases. It jeopardises disease control efforts, especially in developing countries like the Philippines.¹ Complicating the scenario is the emergence of drug resistance in both disease entities. Despite the advent of new diagnostic tests to detect resistance, there have been only few published cases of multidrug-resistant tuberculosis (MDR-TB) and multidrug-resistant HIV (MDR-HIV) coinfection.² Additional challenges faced are infection with other non-tuberculous mycobacteria (NTM) and unavailability of other classes of antiretroviral therapy (ART) drugs in resource-limited settings. Triple coinfection (TB, HIV, NTM) complicates clinical management with regard to antimycobacterial and ART choices, adverse drug events and compliance issues. We report a complicated case of multiple coinfections and the dilemmas encountered in the course of management.

CASE PRESENTATION

A 29-year-old Filipino man with HIV presented with fever and left flank tenderness. He was diagnosed with HIV infection 1 year prior to his

symptoms with a baseline CD4 count of 246 cells/mm³. Workup for active TB which included chest radiographs, direct sputum smear microscopy for acid-fast bacilli (AFB) and sputum GeneXpert MTB/Rif were all negative. Tuberculin skin test (TST) to screen for latent TB infection (LTBI) was not done. We started him on isoniazid preventive therapy (IPT), consisting of isoniazid 300 mg tablet once per day for 6 months. On diagnosis, we started him on an ART regimen consisting of lamivudine (3TC), zidovudine (AZT) and nevirapine (NVP). Baseline HIV genotyping test is not routinely performed in our setting. Baseline and repeat HIV RNA viral load after 2 months of ART initiation were not done as it is not part of local treatment guidelines. Six months after ART initiation, he developed AZT-induced anaemia. We discontinued AZT and shifted to tenofovir (TDF).

One year after HIV diagnosis, the patient experienced persistent low back pain with radiation to the left flank area, associated with high-grade fevers. A working diagnosis of a psoas abscess was made. He had no previous history and treatment for TB and other opportunistic infections. He was subsequently admitted for further workup.

INVESTIGATIONS

On admission, ultrasound revealed a fluid collection in the left psoas area. Whole abdominal CT scan confirmed the diagnosis, showing a left paravertebral hypodense collection in the left psoas muscle, consistent with abscess formation (figure 1). A CT-guided aspiration biopsy was done. Microbiological workup of the abscess fluid showed no organism on Gram stain but showed AFB on Ziehl-Neelsen stain. Xpert MTB/Rif detected *Mycobacterium tuberculosis* (MTB) with rifampicin resistance. Routine bacterial culture did not grow any organisms. Mycobacterial culture (BACTEC 460 TB system, Beckton Dickinson, Maryland, USA) with drug-susceptibility testing (DST) eventually grew MTB, resistant to all first-line anti-TB drugs (including rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin).

Six months after the TB diagnosis, he developed a left lateral neck mass. Ultrasound revealed an ill-defined hypoechoic focus measuring 4.6×5.5×4.8 cm with an approximate volume of 83 mL. CT scan confirmed the neck abscess (figure 2). Aspiration was done. Gram stain showed

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Figure 1 A contrast-enhanced abdominal CT scan showing a 12.8×2.9×3.5 cm left psoas abscess (pointed by the yellow arrow).

5–10 polymorphonuclear cells/high power field (hpf) and 0–1 cocci in pairs/hpf. The Ziehl-Neelsen stain showed the presence of AFB. No pathogens were isolated on bacterial culture, while the mycobacterial culture grew *Mycobacterium avium* after 11 days of incubation. However, DST for *M. avium* was not done due to limited patient funds.

Due to the occurrence of these opportunistic infections, CD4 count was repeated, showing a decrease from 246 to 37 cells/mm³ despite good self-reported adherence to ART (3TC+N-VP+TDF). HIV-1 genotyping was done, revealing circulating recombinant form 01_AE (CRF01_AE) subtype. K101E, Y181C and Y181I/V mutations were found conferring resistance to all non-nucleoside reverse transcriptase inhibitors (NNRTIs); as well as M184V and K65R mutations indicating resistance to all locally available nucleoside reverse transcriptase inhibitors (NRTIs) except AZT. The virus remained fully susceptible to

Figure 2 A contrast enhanced neck CT scan showing a 4.6×5.5×4.8 cm abscess (pointed by the yellow arrow) with an approximate volume of 83 cc on the left lateral neck.

protease inhibitors (PIs) and integrase strand transfer inhibitors (INSTIs).

TREATMENT

Following confirmation of the susceptibility of the MDR-TB psoas abscess, the patient was started on the following regimen: levofloxacin 750 mg tablet once per day; cycloserine 200 mg tablet, 2 tablets once per day; prothionamide 250 mg/tablet, 3 tablets once per day; and kanamycin 750 mg intramuscularly per day. The patient experienced adverse drug reactions from the regimen, including occasional nausea, vomiting and dizziness, for which metoclopramide was given. We managed the *M. avium* neck abscess with azithromycin 500 mg tablet every other day and ethambutol 400 mg tablet, 2 tablets per day, for 1 year.

Based on the patient's HIV genotyping test, the virus was resistant to all NNRTIs and NRTIs except AZT and remained susceptible to all PIs and INSTIs. However, due to the unavailability of INSTIs in our setting, we shifted back ART to 3TC-AZT-based regimen and the addition of ritonavir-boosted lopinavir (LPV/r). After a few months on the new ART regimen, AZT-induced anaemia ensued, necessitating repeated blood transfusions. We then provided the patient with ferrous sulfate 325 mg tablet once per day and erythropoietin (EPO) alpha 4000 units subcutaneously given two times per day to prevent anaemia recurrence.

OUTCOME AND FOLLOW-UP

Despite the adverse effects from antimycobacterial medications and ART, the patient was able to complete treatment for *M. avium* for 12 months and MDR-TB treatment for 24 months. Neck and abdominal CT scan after treatment revealed resolution of the abscesses. There was no recurrence of anaemia while on EPO and ferrous sulfate. His most recent CD4 count was 778 cells/mm³ and HIV viral load was 192 copies/mL.

DISCUSSION

TB-HIV coinfection is a public health threat. Prevalence of MDR-TB among HIV-infected individuals is highly variable, ranging from 0.6% to 76%,^{3,4} and this coinfection is associated with higher mortality and morbidity.³ However, very few have reported on the outcomes of patients with MDR-TB and MDR-HIV coinfection.² This patient is one of a handful of documented cases of MDR-TB and HIV coinfection, and its management revealed some therapeutic challenges.

Current guidelines recommend that ART be started in all persons living with HIV (PLHIV) regardless of CD4 count.⁵ However, ART can cause a range of adverse reactions that may be acute and life-threatening or chronic and insidious.⁶ Our patient developed AZT-induced anaemia a few months after starting ART. This occurs in 14.6% of patients on AZT-containing regimen.⁷ Management includes shifting to another NRTI, such as TDF. Anaemia usually resolves within 2 weeks after discontinuation of AZT.⁸

HIV infection is the leading risk factor for the progression of LTBI to active disease.⁹ Initiation of IPT is recommended after ruling out active TB. In our patient, active TB was ruled out after an unremarkable chest radiograph, negative bacteriological tests for TB and absence of constitutional symptoms. A meta-analysis has shown that the absence of cough, weight loss, fever and night sweats has a negative predictive value of 98% against the diagnosis of active TB.¹⁰ TST is not required for initiating IPT among PLHIV as recommended by WHO.¹¹ It is also important to note that NTM infections and previous bacillus Calmette-Guérin vaccination may cause false-positive TST among the

HIV-infected population but this should not prevent IPT initiation.¹² In addition, the sensitivity of TST for detecting LTBI is reduced for PLHIV.¹³ Despite the recommendations to use a lower cut-off values for positive TST result for PLHIV (5 mm diameter instead of 10 mm diameter induration),¹⁴ interpretation of the TST remains to be difficult since skin test anergy is common among PLHIV and is associated with low CD4 count.¹³

Fever in PLHIV is associated with an extensive list of infectious and non-infectious aetiologies. In settings where TB-HIV coinfection is common, TB should always be considered and prompt workup should be instituted.¹⁵ In this case report, our patient presented with an indolent fever, constitutional symptoms and low back pain, which was caused by a tuberculous psoas abscess. TB psoas abscess formation is not unusual among PLHIV.^{16 17} Its management involves aspiration of the abscess and starting appropriate anti-TB drugs. In our case, second-line TB drugs were initiated due to the presence of AFB in the abscess fluid, positive Xpert MTB/Rif (MTB detected/rifampicin resistance detected), and DST. Some studies have shown that the presence of rifampicin resistance is a marker of MDR-TB in areas with high burden of infection.¹⁸ However, Xpert MTB/Rif may not be an optimal stand-alone test for the diagnosis of extrapulmonary TB and should be interpreted with caution. Mycobacterial culture with DST should be included in the workup of an HIV-infected patient suspected to have TB for the following reasons: higher prevalence of MDR-TB among HIV-infected, NTM coinfections, and serve as guidance in the targeted management of MDR-TB.^{19 20}

NTM infection, particularly *Mycobacterium avium* complex (MAC), is seen in 2% of HIV-infected patients^{21 22} especially among those with CD4 count <50 cells/mm³. Various case reports have discussed MTB and NTM coinfection among patients with HIV, and there are even reports of coexisting MTB-NTM in a single abscess site such as the brain¹⁹ and lymph nodes.²³ Treatment of NTM is commonly empiric since most of the existing drugs were not specifically developed for the treatment of NTM. Drug activities are usually extrapolated from MTB treatment.²⁴ Azithromycin and ethambutol were added to this patient's MTB treatment regimen to cover for MAC. Randomised controlled trials have shown efficacy of azalides (azithromycin or clarithromycin) combined with ethambutol in treating disseminated MAC.^{25 26} Susceptibility studies have shown that azithromycin and ethambutol remain a good option for MAC treatment. However, it is still recommended that drug susceptibility test be performed for all known NTM isolates.²⁷

Drug-resistance testing (DRT) through HIV genotyping detects clinically significant mutations in the HIV genome, and is a useful tool for assessing resistance among the commonly used ART drugs, particularly NRTIs and NNRTIs.²⁸ The downward trend in our patient's CD4 count and the occurrence of opportunistic infections raised the suspicion of possible resistance. Although not routinely done in resource-limited settings, HIV viral load and (if not suppressed) genotyping is recommended in a patient on ARTs who develops new opportunistic infections, a protracted infection course despite appropriate treatment, or recurrence of a previously resolved infection. However, the utilisation of this test on a larger scale is limited by its availability, accessibility and relatively high cost in resource-constrained settings. Underutilisation of DRT may lead to inadequate investigation of HIV resistance and under-reporting of cases. This may be the reason behind the dearth of published cases of MDR-TB/MDR-HIV coinfection.

The greatest challenge in the management of this case was weighing the HIV genotyping result against the risk of recurrence

of a documented adverse drug reaction. In our setting, ART is currently limited to NRTI (3TC, AZT), NNRTI (EFV, NVP) and PI (LPV/r). The current Philippine HIV epidemic is driven by the predominance of the CRF01_AE subtype^{29 30} in contrast to the predominance of subtype B in the Americas, Western Europe and Australasia,³¹ and subtype C in Africa.³¹ Infection with CRF01_AE has been associated with rapid progression to AIDS and possibly higher mortality,^{31 32} thus ART classes that rapidly suppress HIV viral load are essential. INSTIs comprise a key drug class that has been shown in randomised controlled trials to be more effective in rapidly decreasing HIV viral load within 12 weeks when compared with the standard NNRTI and NRTI combinations,³³ and this effect is similar across most INSTIs.^{33 34} Reports have shown an increasing numbers of pretreatment NNRTI resistance among ART-naïve patients^{35–37} and can be >25% among those experiencing ART failure.³⁸ In our case, HIV genotyping revealed mutations in K101E and Y181C, causing resistance to EFV and Y181I/V mutations causing resistance to NVP, efavirenz and rilpivirine. These transmitted drug resistance (TDR) patterns were reported to occur in 2.2% in a patient cohort in Malawi.³⁵ On the other hand, NRTI mutations are less prevalent, ranging from 1.6%³⁸ to 4%³⁹ among ART-experienced and ART-naïve, respectively. In the Philippines, overall HIV-1 TDR by conventional Sanger-based sequencing is 9.7% overall (NNRTI: 6.2%, NRTI: 1.8% and PI: 2.7%) and was even higher on next-generation sequencing at 5% minority variant cut-off (19.5% overall, NNRTI: 13.3%, NRTI: 2.7%, PI: 4.4%, INSTI 1.8%).⁴⁰ In our case, the patient had M184 mutations conferring resistance to 3TC, emtricitabine (FTC), didanosine (ddI) and abacavir (ABC), while K65R causes intermediate to high-level phenotypic and clinical resistance to TDF, ddI, ABC and d4T and low level to intermediate phenotypic and

Learning points

- ▶ The rarity and complexity of multidrug-resistant tuberculosis and multidrug-resistant HIV coinfection pose a great challenge to all healthcare professionals providing care to persons living with HIV.
- ▶ The rule of parsimony is usually the basis of good clinical judgement, but this case showed that opportunistic infections can coexist in the setting of HIV infection.
- ▶ With the increased use of molecular diagnostic methods, appropriate diagnostic tests should be requested and interpreted with caution, especially when dealing with multidrug-resistant organisms.
- ▶ In resource-limited settings, the choice of antiretroviral therapy (ART) drugs is limited to older classes of nucleoside reverse transcriptase inhibitor, non- nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor that are associated with many adverse effects. Physicians should be familiar with the pharmacokinetics of ART drugs, their expected adverse effects and possible interactions with other drugs.
- ▶ In the setting of increasing HIV resistance to standard ART recommended by the WHO, integrase strand transfer inhibitors (INSTIs) are preferred and should be made widely available given their better tolerability profile and their ability to rapidly reduce viral load.
- ▶ In the absence of INSTIs, baseline drug-resistance testing should be performed due to increasing transmitted drug resistance, particularly to NNRTIs.

clinical resistance to 3TC and FTC. Drug resistance surveillance of CRF01_AE subtype in a Chinese cohort experiencing ART failure reported occurrence of M184V and K65R mutations at 64.98% and 15.97%, respectively, among treatment failures.³⁸ The M184 mutation is not a contraindication to a continued treatment with 3TC or FTC, thus 3TC remained a part of our patient's ART regimen. Studies have shown that the presence of M184V mutation is not associated with virological failure even if 3TC or FTC were continued, as long as other active drugs are present.⁴¹

In our setting where new ART classes remain unavailable, there was a risk in resuming AZT, which previously caused profound anaemia in our patient. Weighing the benefit over the risk, control of the HIV infection was paramount, and the anaemia was managed through blood transfusions as needed. AZT-induced anaemia is postulated to occur due to low levels of endogenous EPO, unresponsiveness to the usual endogenous concentrations, or compounded by HIV infection.⁴² EPO administration in patients with AZT-induced anaemia has been shown to improve mean haematocrit levels and decrease frequency of blood transfusions.⁴³ PIs remain the preferred second-line ART in resource limited setting.⁵ Baseline DRT should be routinely performed as NNRTI resistance increases, and if not done, PIs should be considered as part of the initial ART regimen due to its high genetic barrier for resistance.⁴⁴ However, PIs are associated with metabolic complications including dyslipidemia, hyperglycemia and lipodystrophy.⁴⁵ INSTIs may be a better option since they are potent, well tolerated and have less adverse effects.⁴⁶

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