PNG SUPPLEMENT

Tuberculosis treatment unmasking leprosy: management of drug-resistant tuberculosis and leprosy co-infection

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Co-infection with tuberculosis (TB) and leprosy is thought to occur infrequently, but has been reported in settings highly endemic for both infectious diseases. We report for the first time a case where treatment for multidrug-resistant TB (MDR-TB) led to the 'unmasking' of clinically silent leprosy through the precipitation of a type-1 immunological reaction. Current treatment regimens for MDR-TB may contain a number of drugs, such as levofloxacin and clofazimine, which also have activity against *M. leprae*. A treatment regimen containing drugs active against both mycobacterial species may be used to achieve cure. Individual considerations on drug-drug interactions, potential additive toxicities and other comorbidities should be taken into account.

SETTING AND CASE REPORT

We report the case of a 25-year-old man, living on Daru Island, Papua New Guinea (PNG), who presented with cough, fever, night sweats and right axillary lymphadenopathy with suppurative discharge. This occurred in the context of known close contact with two patients with multidrug-resistant tuberculosis (MDR-TB). Apart from the axillary lymphadenopathy, examination was otherwise unremarkable, with specifically no evidence of neurological abnormalities of his upper or lower limbs. He had no other medical comorbidities and no previous history of TB or leprosy.

A diagnosis of MDR-TB was made on a fine-needle aspirate specimen from the axillary lymph node, which was smear-negative for acid-fast bacilli (AFB), but positive for *Mycobacterium tuberculosis* DNA on Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA). In addition, genotypic resistance to rifampicin (RMP) was detected, consistent with the contact history, and culture of lymph node tissue was later positive for *M. tuberculosis*. Drug susceptibility testing (DST) using MGIT™ (BD, Sparks, MD, USA) culture revealed the isolate to be resistant to RMP, isoniazid, streptomycin and ethionamide and sensitive to pyrazinamide (PZA), ethambutol, ofloxacin, amikacin, kanamycin (KM), capreomycin and cycloserine (CS). Testing of sputum was negative and baseline chest X-ray was unremarkable.

The patient was commenced on treatment (before the availability of DST results) according to his weight with a regimen of once-daily levofloxacin (LVX) 750 mg, KM 600 mg, PZA 1500 mg, CS 500 mg, clofa-

zamine (CFZ) 100 mg, linezolid (LZD) 600 mg and pyridoxine 100 mg.

After 2 weeks of treatment, the patient began to develop symptoms of hearing impairment and progressive numbness of his feet and hands. KM was suspended due to concerns of ototoxicity, with substitution for bedaquiline, and CS and LZD were withheld due to concerns of progressive peripheral neuropathy, with the addition of para-aminosalicylic acid.

On subsequent clinical review, 2 months into his treatment for MDR-TB, the patient was noted to have changes consistent with multibacillary leprosy with loss of eyebrows, a palpable thickened ulnar nerve of his left hand with reduced grasping power, a small depigmented skin lesion with anaesthesia on his left arm (Figure) and bilateral partial foot drop. A slit skin smear taken from the patient's ear lobe was positive for AFB.

A diagnosis of multibacillary leprosy co-infection was made according to PNG national guidelines,¹ with ulnar and likely bilateral peroneal nerve neuritis secondary to a type-1 leprosy immunological reaction. He was immediately commenced on oral prednisolone 20 mg daily. He was also commenced on multidrug therapy (MDT) for leprosy with RMP 600 mg once monthly (12 months) and dapsone 100 mg once daily (12 months) added to the CFZ and LVX he was already taking for MDR-TB.

On review 1 month later, the foot drop had largely resolved and the weakness of his left hand had dramatically improved. He is planned to have 12 months of MDT treatment for leprosy and 20 months of MDR-TB treatment. No significant drug reactions to the once-monthly RMP and the current MDR-TB treatment regimen are anticipated.

DISCUSSION

We feel that this case represents a type-I immunological reaction to clinically silent leprosy, resulting in bilateral ulnar and peroneal nerve neuritis precipitated by MDR-TB treatment. The TB treatment regimen used had a number of drugs known to be active against leprosy—CFZ is part of the standard multibacillary MDT regimens for leprosy,² and LVX is highly bactericidal against *M. leprae*³ and is recommended as a second-line agent for leprosy treatment.² It is therefore likely that CFZ and LVX caused the death and breakdown of *M. leprae* organisms, which in turn precipi-

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FIGURE A depigmented skin lesion with anaesthesia on the left arm of a patient with MDR-TB and leprosy co-infection. MDR-TB = multi-drug-resistant tuberculosis.

tated an immunological reaction. Alternatively, immunological recovery that occurs with MDR-TB treatment may have precipitated the reaction, similar to immune reconstitution reactions seen in the treatment of patients co-infected with human immunodeficiency virus (HIV) and TB.⁴ A recent study reported leprosy diagnosed in a 31-year-old Brazilian man following the development of a type-1 immunological reaction after 4 months of MDT for drug-susceptible TB.⁵

The recommended treatment for type-I reactions is prednisolone for at least 3 months.² Our patient was administered a dosage of 20 mg prednisolone daily with good clinical response, although higher doses of 40–60 mg daily are more typically used. Recognised as a medical emergency, failure to do so can result in nerve damage with subsequent loss of sensation, paralysis and deformity.⁶ Prednisolone appeared to be effective in our case with rapid resolution of the symptoms and signs of the nerve palsies. It is important for clinicians to be aware that there are potential risks in a context such as PNG, where there are high rates of co-existent infections such as TB or strongyloidiasis whose outcomes can be worsened by prednisolone if not specifically treated.^{7,8} Testing and/or empirical treatment for strongyloidiasis should be considered in endemic settings to reduce the risk of hyperinfection syndrome with corticosteroid use.

Daru Island in Western Province is highly endemic for both TB and leprosy.¹ This case illustrates the potential in such settings for

patients to be co-infected with *M. tuberculosis* and *M. leprae*.⁹ Although it is thought to occur infrequently, the interactions between leprosy and TB and their effects on each other's incidence remain controversial. Some experts argue leprosy predisposes one to TB via immune anergy, while others argue that it protects against TB due to cross-immunity.⁵ There were 658 cases of leprosy registered in PNG in 2015,¹⁰ with approximately 100 cases a year registered at Daru General Hospital (DGH) over the last 3–4 years. Leprosy and MDR-TB co-infection has been diagnosed in five patients at DGH from January 2015 to September 2018, representing approximately 1% of all MDR-TB cases and 1% of all leprosy cases enrolled at DGH across this time period. Rajogopala et al. have reviewed 156 confirmed cases of leprosy-TB co-infection published between 1968 and 2012 and reported TB co-infection rates in leprosy patients of 2.5–13.5% in endemic areas.¹¹ In this review, leprosy was diagnosed before TB in 90% of the cases, and most TB cases were pulmonary. Reported mortality of co-infection was high, at 37.2%.

In cases of co-infection, the World Health Organization recommends that anti-tuberculosis treatment and MDT leprosy treatment be given together.² Although this was done in our case, it is likely that this mainly applies to drug-susceptible TB cases where, apart from RMP, the other anti-tuberculosis drugs have no activity against *M. leprae*. However, it is probable that dapsone can be withdrawn from MDR-TB treatment regimens containing a fourth generation fluoroquinolone and CFZ, as in our case. In our case, the combination of monthly RMP for 12 months, plus 20 months of LVX and high-dose CFZ (100 mg daily for TB compared with the recommended 50 mg daily for leprosy) would achieve leprosy cure, although this needs to be confirmed in further studies. In addition, this would avoid the potential toxicity of dapsone, including haemolysis, when screening for G6PD deficiency in settings such as ours is not available.

CONCLUSION

We have described for the first time a case involving the unmasking of *M. leprae* co-infection via an immunological reaction in a patient being treated for MDR-TB. Clinicians treating MDR-TB in leprosy-endemic areas need to be aware of this potential co-infection during anti-tuberculosis treatment.

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Il est considéré que la co-infection tuberculose (TB) et la lèpre est peu fréquente, mais elle a été signalée dans des milieux très endémiques pour les deux maladies infectieuses. Nous signalons pour la première fois un cas de traitement de la TB multirésistante (MDR-TB) 'démasquant' la lèpre cliniquement silencieuse par précipitation d'une réaction immunologique de type 1. Les schémas thérapeutiques actuels pour la MDR-TB peuvent contenir un certain

nombre de médicaments, comme la lévofloxacine et la clofazimine, qui ont également une activité contre *M. leprae*. Un régime de traitement contenant des médicaments actifs contre les deux espèces mycobactériennes peut être utilisé pour obtenir la guérison. Les considérations individuelles sur les interactions médicamenteuses, les toxicités additives potentielles et les autres comorbidités doivent être prises en compte.

Se considera que la coinfección por tuberculosis (TB) y lepra es infrecuente, pero se han informado casos de concomitancia en entornos con alta endemicidad por ambas enfermedades infecciosas. En el presente artículo se comunica por primera vez un caso de tratamiento de la TB multirresistente (MDR-TB) que desenmascaró una lepra asintomática, tras desencadenar una reacción inmunitaria de tipo 1. Las pautas actuales de tratamiento de la MDR-TB pueden

comportar un cierto número de fármacos como la levofloxacina y la clofazimina, que tienen también actividad contra el *Mycobacterium leprae*. Con el objeto de alcanzar la curación, se puede utilizar un esquema terapéutico que contenga fármacos activos contra ambas especies de micobacterias. En cada caso, es importante tener en cuenta los aspectos de las interacciones medicamentosas, la posible toxicidad acumulada y otras afecciones concomitantes.