CASE REPORT

Disseminated tuberculosis in an HIV-infected child: rifampicin resistance detected by GeneXpert in a lymph node aspirate but not in cerebrospinal fluid

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SUMMARY

A 9-year-old HIV-infected child previously treated with inadequate doses of antitubercular drugs based on weight was admitted 5 months after initial tuberculosis (TB) diagnosis with acute hemiplegia and inguinal lymphadenopathies in a rural hospital in Tanzania. He was diagnosed with TB meningitis and lymphadenitis using Xpert *Mycobacterium tuberculosis*/rifampicin (MTB/RIF) assay. Rifampicin resistance was detected in the lymph node aspirate but not in the cerebrospinal fluid. His TB therapy was optimised based on available medications and antiretroviral treatment was initiated 6 weeks later. Despite these efforts, the clinical evolution was poor and the child died 12 weeks after admission.

BACKGROUND

This case exemplifies the importance of HIV screening for all children with tuberculosis (TB) in sub-Saharan Africa; the possible consequences of inappropriate dosage of antitubercular drugs; the need to formulate new fixed-dose combination tablets for children; and some of the challenges that clinicians in rural African settings might face with the roll-out of the Xpert *Mycobacterium tuberculosis*/rifampicin (MTB/RIF) assay and the treatment of resistant TB. Indeed, this is the first documented case of discordant rifampicin resistance detected by Xpert in different biological samples of the same patient.

CASE PRESENTATION

In May 2013, a 9-year-old boy was diagnosed with miliary TB through the outpatient department of a referral hospital in rural Tanzania. The child presented with weight loss, fatigue and night sweats. The diagnosis was based on these symptoms and on the findings in the chest X-ray (figure 1); he was unable to produce sputum and, thus, initial microbiological confirmation was not possible. No index case was identified. His body weight then was 17 kg. He was started on rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg and ethambutol 275 mg per day, using the available fixed-dose combination tablets (1 tablet/day) for 2 months followed by one tablet of rifampicin 150 mg and isoniazid 75 mg daily to complete 6 months of anti-TB treatment. Even though recommended by the national TB and leprosy guidelines, HIV screening was not performed at TB diagnosis. The adherence to TB medication was optimal as was the initial clinical response. According to his caregivers, the

child improved clinically during the intensive phase of TB treatment, gaining weight, recovering functionally and returning to school. However, since the continuation phase with rifampicin and isoniazid was initiated in July 2013, he presented progressive deterioration with increasing fatigue and weight loss. In October 2013, he was admitted to the paediatric department of the Saint Francis Referral Hospital in Ifakara, southern Tanzania, due to acute left hemiplegia, inguinal lymphadenitis and severe malnutrition. The hemiplegia presented progressively during the 2 days prior to admission. At admission, the patient was ill looking and wasted. His body weight was 16 kg, height was 117 cm and mid-upper arm circumference 11.2 cm. The vital signs were: temperature 35.9°C, heart rate 110 bpm, respiratory rate 28 breaths/min, oxygen saturation 97% and blood pressure 90/50 mm Hg. He presented with left faciobrachiorural hemiplegia. The pupils were symmetric and reactive. Kernig's and Brudzinski's signs were negative. He had two tender, enlarged inguinal lymph nodes and extensive oral candidiasis. The rest of the physical examination was unremarkable.

INVESTIGATIONS

At admission, a rapid antibody test revealed HIV infection, with CD4 counts of 1 cell/ μ L (0%). Haemoglobin was 7.4 g/dL and liver and renal function tests were normal. A cryptococcal antigen lateral flow assay (CRAG LFA) in plasma was negative. A chest radiography showed resolution of the

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Figure 1 Chest radiography, May 2013.

Figure 2 Chest radiography, October 2013.

miliary pattern but a new interstitial infiltrate in the right upper lobe (figure 2).

CT scan is not available in our hospital, and we had to balance the risks and benefits of performing a lumbar puncture. Of note, the patient had symmetric pupils and no signs or symptoms of raised intracranial pressure. Therefore, given the possibility of reaching an aetiological diagnosis, and aiming to avoid the prescription of several long empiric antimicrobial treatments with potential interactions and side effects, a decision was taken to perform the lumbar puncture. The cerebrospinal fluid (CSF) opening pressure was normal and the CSF analysis revealed low glucose (1.1 mmol/L), qualitative low protein and 50 leucocytes/ μ L. TB microscopy smear, Gram's stain and CSF CRAG LFA were negative.

The CSF and a lymph node aspirate were both analysed with Xpert MTB/RIF assay version G4 (Cepheid, Sunnyvale, California, USA) to detect MTB and test for resistance to rifampicin. MTB was detected in both samples with discordance in the rifampicin resistance result, being rifampicin resistant in the lymph node sample and rifampicin susceptible in CSF. Since *Mycobacteria* culture is not available in our hospital, we could not confirm these diagnoses through drug-susceptibility testing. However, repeated samplings of the lymph node and CSF were obtained 48 h later and retested with consistently discordant rifampicin-resistant results between specimens.

The diagnoses reached after the investigations were: (1) HIV infection, WHO stage 4, (2) disseminated TB with rifampicin-susceptible TB meningitis and rifampicin-resistant TB lymphadenitis and (3) severe malnutrition.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute hemiplegia in an HIV-infected child with very low CD4 counts includes primarily: TB meningitis with intraparenchymal tuberculoma(s) or cerebral infarct, cerebral toxoplasmosis, central nervous system lymphoma and cryptococcal meningitis with intraparenchymal cryptococcoma(s). CT scan is not available in our setting. Therefore, we could only reasonably exclude cryptococcal meningitis by having a negative CRAG LFA in plasma and CSF. The positive Xpert test in CSF was confirmatory of TB meningitis but both toxoplasmosis and lymphoma were still possible aetiologies of hemiplegia in this severely immunocompromised child.

TREATMENT

Treatment of multidrug-resistant TB (MDR-TB) in Tanzania is centralised in only one health facility and, as a result, none of the recommended drugs (amikacin, kanamycin, ofloxacin, levofloxacin, pyrazinamide, ethionamide, cycloserine) are available at our regional referral hospital. However, the patient could not be transferred due to his clinical instability and the lack of medicalised transport. Thus, TB treatment was optimised as far as possible with the available drugs by restarting the fixed-dose combination tablets at proper doses, 1.5 tablets/day (rifampicin 14 mg/kg/24 h, isoniazid 7 mg/kg/24 h, pyrazinamide 37.5 mg/kg/24 h and ethambutol 26 mg/kg/24 h), and adding streptomycin 31 mg/kg/24 h and ciprofloxacin 16 mg/kg/12 h. Since cerebral toxoplasmosis could not be ruled out and cotrimoxazole has shown to be effective to treat *Toxoplasma gondii*¹ as well as having antituberculous activity,² high doses of cotrimoxazole (20 mg/kg/day of trimethoprim component) were prescribed for 6 weeks followed by prophylactic doses for *Pneumocystis jirovecii*. In addition, intravenous dexamethasone (0.15 mg/kg/6 h) was administered, followed by oral prednisolone. Four weeks after the reinitiation of TB medications, given the impossibility of transferring the patient and getting the appropriate second-line antitubercular drugs, metronidazole was added (12.5 mg/kg/6 h), due to its documented potential antituberculous activity and good central nervous system penetration.² The initiation of antiretroviral treatment was delayed until 6 weeks after the TB drugs were restarted to minimise the risk of immune reconstitution inflammatory syndrome, which is associated with a high mortality when the central nervous system is involved. The patient was initiated on tenofovir, lamivudine and efavirenz.

OUTCOME AND FOLLOW-UP

Despite an initial mild recovery of the hemiplegia, the clinical evolution was poor and the child died 12 weeks after admission.

DISCUSSION

The WHO estimates that HIV prevalence among children with TB in countries with moderate-to-high prevalence ranges from 10% to 60%.³ The estimated rate of TB among children with HIV-infection also varies widely due to the difficulty of reaching a definitive diagnosis. Therefore, the WHO endorses molecular testing through the use of Xpert MTB/RIF assay. Xpert offers a new rapid diagnostic tool with increased sensitivity compared to the acid-fast bacilli smear, along with the additional benefit of testing for rifampicin resistance, which is considered a reliable indicator of MDR-TB in high-burden settings. However, as this test is being rolled out in sub-Saharan Africa, cases such as the one we present pose additional challenges to clinicians, with results difficult to interpret.

In 2010, WHO reviewed TB treatment in children, and higher doses of isoniazid were recommended. WHO now recommends a 2:3 ratio of isoniazid:rifampicin (ie, 10 mg/kg isoniazid with 15 mg/kg rifampicin) instead of the previous recommended 1:2 ratio of isoniazid:rifampicin.⁴ These evidence-based recommendations have resulted in a significant challenge for implementation due to the lack of available fixed-dose combination tablets matching these new, higher recommended isoniazid doses for children.⁵

MDR-TB has become a significant public health problem in many countries, hindering effective global TB control and complicating the clinical management of TB. Those at higher risk of MDR-TB are patients in whom prior treatment failed, cases of

relapse, defaulters and contacts with MDR-TB. HIV co-infection is also an important risk factor for the development of MDR-TB, by potentially decreasing the absorption of anti-TB drugs. In this view, TB treatment in children co-infected with HIV in resource-limited settings is extremely challenging.⁶

The most recent data on drug resistance from Tanzania are from 2006, with a reported prevalence of MDR-TB among new TB cases at 1.1% and among retreatment cases at 3.1%.⁷ The treatment of these cases is centralised in one hospital in the country, Kibong'oto National TB hospital, where all MDR-TB cases should be transferred and admitted for a minimum of 6 months. Kibong'oto hospital is 1050 km away from our centre and sometimes the clinical instability of the patient precludes referral without medicalised transport.

The case we present illustrates the risk of delaying HIV diagnosis in a child with TB. Also, this case brings up the question of whether MDR-TB was present at initial diagnosis in May 2013 or whether it developed after exposure to inadequate doses of anti-TB drugs. We believe that the child initially presented a disseminated rifampicin-susceptible MTB infection and developed resistance after being treated with low-for-weight doses of antitubercular drugs combined with the malnutrition, and probable malabsorption. In this case, the initial weight-based dosing of anti-TB therapy was too low at 8.8 mg/kg of rifampicin and 4.4 mg/kg of isoniazid, and likely further exacerbated as the child initially improved and probably gained weight with initial therapy. In our opinion, the mistake prescribing the TB drugs was due to the suboptimal knowledge of most health workers dispensing paediatric medications in rural Tanzania, a concern that has been raised in other African settings.⁸

The discordance in detection of rifampicin resistance by Xpert test is also interesting. There are three possible reasons for the non-detection of resistance in CSF. The first possibility is that, due to a lower burden of MTB in CSF, the Xpert assay

was not able to detect the resistance. The sensitivity of the Xpert test to detect rifampicin resistance in CSF has not been reported; however, if we presume that the sensitivity is similar to that reported in sputum (94.4%),⁹ this first explanation is unlikely. The second possibility is that, due to the low bacillary burden in the central nervous system, typical of TB meningitis, resistance failed to develop despite the initial underdosing of anti-TB therapy. The third possible explanation is that the rifampicin CSF levels were too low to induce resistance. Whatever the scenario, it is clear that this child could not receive the optimal anti-TB treatment and could neither be transferred safely nor promptly to the national MDR-TB hospital. This case raises concern about the need for a more swift and flexible system to manage MDR-TB cases in Tanzania and similar African countries. This is particularly relevant in light of the progressive roll out of Xpert in peripheral hospitals of these settings. New strategies to either improve the transfer of severe cases to the referral facility or to decentralise the accessibility to second-line anti-TB drugs need to be envisaged and tested.

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Contributors AG attended the patient and wrote the manuscript. AJN performed all the laboratory analysis and reviewed the final manuscript. MB reviewed the final manuscript. EL contributed to the writing of the manuscript and its final review.

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REFERENCES

- 1 Dediocat M, Livesley N. Management of toxoplasmic encephalitis in HIV-infected adults (with emphasis on resource-poor settings). *Cochrane Database Syst Rev* 2006; (3):CD005420.
- 2 Alsaad N, Wilffert B, van Altena R, *et al*. Potential antimicrobial agents for the treatment of multidrug-resistant tuberculosis. *Eur Respir J* 2014;43:884–97.
- 3 World Health Organization: Global HIV/AIDS response. Progress report 2011. http://whqlibdoc.who.int/publications/2011/9789241502986_eng.pdf
- 4 WHO Rapid Advice: treatment of tuberculosis in children, 2010. <http://apps.who.int/medicinedocs/documents/s19925en/s19925en.pdf>
- 5 WHO Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2014. http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748_eng.pdf
- 6 Trehan I, O'Hare BA, Phiri A, *et al*. Challenges in the management of HIV-infected malnourished children in sub-Saharan Africa. *AIDS Res Treat* 2012;2012:790786.
- 7 Operational guidelines for the management of drug resistant TB in Tanzania, Ministry of Health and Social Welfare, National Tuberculosis and Leprosy Programme, United Republic of Tanzania. 2012. www.moh.go.tz
- 8 Oshikoya KA, Ojo OI. Medication errors in paediatric outpatient prescriptions of a teaching hospital in Nigeria. *Nig Q J Hosp Med* 2007;17:74–8.
- 9 Boehme CC, Nicol MP, Nabeta P, *et al*. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet* 2011;377:1495–505.

Learning points

- ▶ Screening all children with tuberculosis (TB) for HIV and vice versa is vital to improve outcomes.
- ▶ Proper dosage of antitubercular drugs is crucial to treat childhood TB cases, and further challenging as children gain weight.
- ▶ There is a need to formulate new fixed-dose combination tablets of antitubercular drugs that match the latest WHO recommended doses to treat TB in children.
- ▶ Cases such as presented here need to be reported while the Xpert *Mycobacterium tuberculosis* rifampicin (MTB/RIF) test is rolled out to help clinicians interpret challenging results.
- ▶ The management of multidrug-resistant TB cases in rural Africa requires a more swift and flexible system to allow decentralisation, and to ensure broader coverage.

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