Case Report: Multidrug-Resistant Tuberculosis Complicated by Nosocomial Infection with Multidrug-Resistant Enterobacteriaceae

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Abstract. Treatment of mycobacterial diseases such as tuberculosis (TB) entails long and intense antimicrobial therapy. TB patients are at risk of coinfection with other multidrug-resistant bacteria, such as those from Enterobacteriaceae family, because of antimicrobial selection pressure and nosocomial transmission during prolonged hospital admission. Here, we report on two patients treated for multidrug-resistant TB, who developed severe sepsis due to an extended spectrum β -lactamase producing organism. Diagnostic culture identified the venous access port as source, and upon surgical removal and antimicrobial therapy rapid clinical improvement was achieved. Increased awareness and knowledge on the prevalence of multi-resistant Enterobacteriaceae is needed, notably in TB centers, to provide a safe hospital environment to our patients.

INTRODUCTION

Antimicrobial drug resistance is one of today's major concerns in health care with multiple repercussions on the safety of the hospital environment. Long-duration and intense antibiotic treatment disturbs the gut microbiome and is a major driver of in vivo evolution of drug resistance.^{1,2} *Mycobacterium tuberculosis* resistant to the two first-line drugs rifampicin and isoniazid is defined as multidrug-resistant tuberculosis (MDR-TB) and requires at least 20 months of antibiotic therapy. This lengthy treatment and the current surge of nosocomial, extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae are a problematic combination.³

Here, we describe two patients who were admitted to our TB center for management of MDR-TB and who subsequently developed bacteremia and sepsis due to secondary infection with an ESBL-producing organism.

CASE PRESENTATION

Patient 1. In April 2013, a 30-year-old woman from the Indian subcontinent, diagnosed with pulmonary TB, was referred to our TB center because of MDR-TB. Molecular testing had shown mutations for *kat G*, *InhA*, and *rpoB*. She reported earlier treatment of lymph node TB between 2010 and 2011 in northern India in an outpatient setting. No documents about this treatment, culture results, or resistance patterns were obtainable, though she mentioned that treatment contained rifampicin. Awaiting definite susceptibility testing results, treatment with moxifloxacin, ethambutol, pyrazinamide, prothionamide, linezolid, and kanamycin was started and a venous access port (VAP) was surgically established. Later, moxifloxacin, ethambutol, and prothionamide were stopped as the patient complained of nausea and vomiting; cycloserine as well as bedaquiline under compassionate use were added to her treatment regimen. The first routine throat and rectum

cultures at admission for multi-resistant Enterobacteriaceae were negative. After 1 month, they turned positive for ESBL-producing *Escherichia coli* and in July 2013, cultures yielded ESBL-producing *Klebsiella pneumoniae*. In late July 2013, the patient presented with high fever and chills. The VAP did not appear infected, and meropenem was started with the working diagnosis sepsis of unknown origin in a patient carrying ESBL Enterobacteriaceae. Blood cultures from the VAP and, upon removal, culture of the VAP itself showed the presence of ESBL-producing *K. pneumoniae* confirming the diagnosis of sepsis associated with an intravascular device. She fully recovered without further complications and without the need for intensive care unit admissions.

Patient 2. In May 2013, a 37-year-old woman originating from Eritrea was diagnosed with TB upon positive sputum microscopy in a general hospital in the Netherlands after 4 weeks of nocturnal cough, chest pain, and night sweats. As molecular testing revealed MDR-TB, the patient was referred to our TB center and first-line TB treatment was changed to ethambutol, pyrazinamide, moxifloxacin, linezolid, and kanamycin. A VAP was placed to administer kanamycin. Late July 2013, the routinely performed rectum and throat cultures revealed ESBL-producing *K. pneumoniae*, after two earlier negative cultures. Shortly after, she developed chills, fever, and tachycardia without cough or pain. Serologic testing for respiratory viruses as well as urine tests for *Legionella pneumophila* and *Streptococcus pneumoniae* was negative. The VAP was surgically removed, and meropenem was started. Cultures from blood and the VAP confirmed the diagnosis of *K. pneumoniae* sepsis associated with the intravenous device. Within a few days, she fully recovered and continued her TB treatment.

Written informed consent was obtained from both patients before writing this case report.

DISCUSSION

Gram-negative Enterobacteriaceae such as *K. pneumoniae* are among the most common causes of nosocomial infection.² Infection by strains conferring resistance to β -lactams, the antibiotics mostly used for treatment, and third-generation

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cephalosporins, such as ESBL-producing bacteria results in prolonged hospital admission and increased costs of treatment.³ The impact on the possible mortality of TB patients has not been assessed. A report from South Africa shows that nosocomial infections with ESBL and methicillin-resistant *Staphylococcus aureus* in TB patients contributed to increased mortality.⁴ Especially in countries where TB is endemic, nosocomial infections with MDR organisms have the potential to be fatal due to the absence of routine screening and lack of effective antimicrobial agents for these high-risk organisms.

The admission history of these two patients raises concern about the emergence of resistant gram-negative bacteria in patients with mycobacterial illness. Our two patients received both up to five drugs at any point in time during their treatment and nine different antimicrobial agents in total, as treatment change typically follows as a response to drug susceptibility test results that only become available several months after start of the treatment. The role in selecting resistant bacteria has not been described for all antibiotics prescribed here, yet a direct link between fluoroquinolone use such as moxifloxacin or ciprofloxacin and emergence of ESBL-producing bacteria has been shown.⁵ Apart from high antimicrobial pressure by these antibiotics, horizontal transfer of two resistance mechanisms coexisting on the same plasmid could explain this correlation.⁶ In general, the use of antimicrobial therapy has provided continuous selection pressure of drug-resistant bacteria, such as in the case of carbapenem-resistant Enterobacteriaceae.⁷

Apart from selection of resistant microorganisms due to antimicrobial pressure, these organisms can also be imported from high-prevalence areas around the world. While the prevalence of ESBL-producing Enterobacteriaceae carriage among the Dutch population is low with 5.1%,⁸ a study reports 48% prevalence in northern India, the region of origin of our first patient.⁹ To determine whether the infecting strains were indeed imported or acquired in the Netherlands, typification of the isolates would be valuable. Unfortunately, the clinical isolates of our patients were lost for additional testing.

The prevalence of ESBL-producing organisms is monitored in our TB center, and current policy includes routine screening on admission and for patients with MDR-TB, monthly testing thereafter. This routinely performed screening was introduced after an earlier outbreak of ESBL-producing organisms in our TB unit in 2009. With this report we alert for the prevalence of ESBL-producing Enterobacteriaceae in hospitals and notably TB centers during treatment of MDR-TB.

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