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Case Report: Carbapenemase-Producing Enterobacteriaceae in an Asylum Seeker with Multidrug–Resistant Tuberculosis

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Abstract. A Syrian asylum seeker with multidrug–resistant tuberculosis (TB) developed a bronchopleural fistula after pneumonectomy. Although screening tests were negative on admission, carbapenemase-producing Enterobacteriaceae were cultured after a few months of TB treatment. Prevalence of multidrug–resistant organisms is reported to be increased in asylum seekers compared with the general Dutch population. Arduous conditions during transit and interrupted health care delivery in our patient led to multiple-resistant microorganisms that complicated treatment.

INTRODUCTION

The increasing number of asylum seekers trying to enter Europe over recent years, with a peak in 2015, has challenged local health care systems. This trend was also noticed in the Netherlands.[1] Carriage rate of multidrug–resistant organisms (MDROs) in asylum seekers is higher than in the general Dutch population, which impacts hospital infection control strategies and complicates empiric treatment in asylum seekers.[2]

Here, we report a patient who had been admitted to two Greek hospitals and was treated for tuberculosis (TB) before admission to our TB center for multidrug–resistant TB (MDR-TB). The patient developed a bronchopleural fistula after pneumonectomy that was complicated by his carriage of carbapenemase-producing (CP) *Pseudomonas aeruginosa* and CP *Klebsiella oxytoca*.

CASE DESCRIPTION

In September 2015, a 38-year-old male asylum seeker originating from Syria, with a history of an ST elevation myocardial infarction and earlier lost to follow-up treatment of MDR-TB in Greece, was admitted to our TB center. From November 2014 through March 2015, he had been admitted to two Greek hospitals for treatment of MDR-TB with pyrazinamide, moxifloxacin, ethionamide, cycloserine, and amikacin. During his admissions, no screening cultures were taken for MDRO carriage, and the clinical cultures were negative for MDRO. After discharge, he was advised to continue his treatment and revisit the hospital every month. However, he did not return for a follow-up appointment. More than 5 months later, he arrived in the Netherlands where he visited the TB physician at the municipal health center, who referred him to our TB center for further diagnosis and treatment.

At that time, he had complaints of a non–productive cough that was present for 4 weeks and in the 5 days before presentation at the TB center became productive. Furthermore, he had dyspnea on exertion without chest pain, fever, or night sweats. The physical examination showed reduced air entry on the left side. The oxygen saturation was 98%. Radiographic examination showed atelectasis in the left lung and pleural effusion. TB was confirmed by sputum microscopy and later by culture. Polymerase chain reaction (PCR) for TB was positive, and mutations were detected in the *rpo*B gene.

Treatment for MDR-TB was started with amikacin, moxifloxacin, linezolid, prothionamide, clofazimine, and cotrimoxazole[3] while using therapeutic drug monitoring (TDM). A venous access port was placed surgically. In February 2016, drug susceptibility testing showed that susceptibility for rifampicin was at the breakpoint and that the strain was susceptible to rifabutin. Rifampicin in higher dose (15 mg/kg) was started, and TDM was continued. Based on the susceptibility results, rifampicin was switched to rifabutin. Moxifloxacin was stopped because of inadequate serum levels and cycloserine was started.

The Groningen Protocol created at the University Medical Center Groningen indicates that all patients admitted to a foreign hospital in the previous year, or asylum-seeking patients should be screened for MDRO on admission in the UMCG.[4,5]

Screening tests for MDRO were performed on arrival. PCR on a rectal swab sample targeting the carbapenemase genes *KPC*, *NDM*, *VIM*, and *OXA-48* (Check-Direct CPE, Checkpoints, the Netherlands) and culture on selective media showed negative results. Screening tests by culture for rectal and throat carriage of MDRO were repeated every month. In December 2015, 4 months after the admission date, a CP *P. aeruginosa* was detected. Two months later, a CP *K. oxytoca* was cultured, both strains carrying the VIM carbapenemase gene. All strains were found in pooled cultures derived from throat and rectum samples. As a consequence, the patient was nursed in both aerogenic and contact isolation.

Pneumonectomy was performed in July 2016 because of the destroyed left lung caused by the MDR-TB. For perioperative prophylaxis, colistin and aztreonam were administered instead of the routinely used cefazolin to prevent

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infection by the CP microorganisms. The detailed prophylactic antimicrobial regiment is described in Appendix 1.

Postoperative recovery was uneventful except for a bronchopleural fistula radiographically detected 4 weeks after surgery, accompanied only by symptoms of chest discomfort during exercise. Fortunately, the patient did not develop an infection relating to the fistula, and no further interventions were necessary. The patient was discharged 20 weeks after surgery in good condition. At the time of writing this report, well after completion of therapy, the patient is considered cured without relapse 7 months after completion of treatment and with negative sputum cultures for *Mycobacterium tuberculosis*. Also, cultures for MDRO remained negative.

Written consent was obtained from the patient before writing this case report.

DISCUSSION

Drug resistance is a growing threat and limits treatment options. This patient carried MDROs including both MDR-TB and multidrug–resistant (MDR) Gram negatives (GNs), which may be a consequence of arduous conditions during the transit and nosocomial transmission during transit. The risk of MDR-TB is higher among migrants than the general population.[6] Asylum seekers originate from countries that are endemic for multidrug–resistant pathogens, and higher carriage rates of these pathogens among asylum seekers have been previously observed.[7,8] In Germany, a carriage rate up to almost 24% was found for GN with extended spectrum beta-lactamase (ESBL).[2]

The treatment for MDR-TB in the TB center in Groningen is highly successful and has limited treatment failure and minimal loss to follow up.[9,10] However, MDR-TB treatment remains challenging and can be complicated by the carriage of MDRO, as seen in our patient. Nosocomial infections can be caused by multidrug–resistant Enterobacteriaceae (MDRE) like ESBL-producing *Escherichia coli* and *Klebsiella* species. These microorganisms complicate therapy and limit treatment options.[11] We previously raised special attention for MDRO resistance among patients with TB, leading to complications during TB treatment like bacteraemia and sepsis.[12]

This patient illustrates the rationale behind screening for MDRO. The detection of carriage of CP microorganisms resulted in targeted prophylaxis during the surgical intervention and would have resulted in an adapted choice of empirical antimicrobial therapy in the case of infection. Treatment regimens of MDR-TB may include antibiotics such as amikacin, moxifloxacin, and co-trimoxazole that select for MDR GN. In this particular case, the patient remained negative for 4 months, during which time he was treated with numerous different antibiotic agents. This might have altered his intestinal microbiota and presumably increased the load of his MDRO strains under antibiotic pressure. Repeated screening allows for detection of MDR GN in patients who carry low, undetectable loads of bacteria on admission.

After the start of his treatment in a Greek hospital, this patient migrated through Europe before entering the Netherlands. Although the surveillance detection rate of MDRO like CP-producing Enterobacteriaceae (CPE) in the Netherlands is less than 1%,[13] carbapenem resistance has now become endemic in various parts of the world, including Greece.[14] According to European Antimicrobial Resistance Surveillance Network, Greece reports CP *P. aeruginosa* and *Klebsiella pneumoniae* isolates, causing invasive infections in 40.4% and 62.3%, respectively.[15] During the past 15 years, an epidemiological shift has occurred, which led to endemicity of *K. pneumoniae* strains producing KPC or metallo-beta-lactamase type of carbapenemases, and several polyclonal outbreaks have been described.[16,17] The first outbreak caused by OXA-48–producing *K. pneumoniae* strains occurred in 2012.[18] Most data refer to *Klebsiella* strains belonging to *K. pneumoniae* species except one report from Northern Greece describing the epidemiological link between nine health care–associated ESBL-producing *Klebsiella* strains belonging to *K. oxytoca* species, of which two were VIM producing.[19] Moreover, Greece is endemic for *P. aeruginosa* strains harboring the bla_{vim} gene, and numerous outbreaks have been described.[20,21] Specifically, concerning the two Cretan hospitals in which the patient was admitted. Tsioutis et al.[22] documented the frequency in which carbapenem-resistant GNs were isolated from clinical samples, between June 2011 and December 2014. During the particular 4-year period, a total of 1.537 CR GNBs were isolated of which, 510 were *K. pneumoniae* and 445 were *P. aeruginosa.* None were identified as *K. oxytoca*[22]; however, data published on *K. oxytoca* in Greece are very limited, and the prevalence could be underestimated.

Considering Crete's local epidemiology and the fact that no CPE was found among other patients in the TB department that time, we hypothesize that the patient acquired his *P. aeruginosa* strain before admission to our TB center, possibly during his hospitalization in Greece. The *Klebsiella* strain might have been acquired from his country of origin or during his transit through Europe. Plasmid transmission from *Pseudomonas* to *Klebsiella* species is most likely, considering VIM is relatively rare in *K. oxytoca*.

In conclusion, drug resistance is still a threat for the treatment of different infectious diseases. This threat is even more increased in asylum seekers because of poor conditions during the transit, higher chance for infectious diseases, and an increased risk of MDRO carriage from their country of origin or during their transit. Arduous conditions during transit and interrupted health care delivery in our patient led to both MDR TB and MDRO carriage. Screening for carriage on arrival and continuous screening of multidrug–resistant negative organisms are frequently debated. This case shows that screening for MDRO influences not only hygiene precautions but also prophylactic and empiric antimicrobial treatment.

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APPENDIX 1

ANTIBIOTIC PROPHYLAXIS REGIMEN AGAINST GRAM-NEGATIVE BACTERIA

Eight hours before incision: colistin 9 million units + 1 aztreonam 1 gram intravenously

30–60 minutes before incision: colistin 3 million units + aztreonam 1 gram

Eight hours after incision: colistin 3 million units + aztreonam 1 gram

Sixteen hours after incision: aztreonam 1 gram

ANTIBIOTIC PROPHYLAXIS REGIMEN AGAINST GRAM-POSITIVE BACTERIA

Administer linezolid 600 milligrams intravenously before incision 30–60 minutes

Repeat 12 hours after incision