Case Report

Pre-XDR Tuberculosis Acquired by Probable Occupational Transmission

Tuberculose pré-XDR adquirida por provável transmissão ocupacional

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ABSTRACT

Occupational transmission of tuberculosis is a significant part of its importance to public health, including the possibility of healthcare professionals acquiring resistant forms of the disease in situations of high exposure, such as aerosol-generating procedures. This report describes the case of a healthcare professional who developed primary pulmonary tuberculosis with an extensive pre-resistance profile. The diagnosis was confirmed by molecular and phenotypic tests, and treatment involved bedaquiline, linezolid, clofazimine, and terizidone for a total period of 18 months, with good clinical response. This case highlights the need for precise identification of potential resistance levels in tuberculosis and underscores the importance of administrative, environmental, and individual measures to reduce occupational risks.

Headings: Tuberculosis, Multidrug-Resistant. Occupational Diseases. Bronchoscopy. Tumor Necrosis Factor Inhibitors. Case Report.

RESUMO

A transmissão ocupacional da tuberculose é parte do cenário de sua importância para a saúde pública, incluindo-se neste contexto a possibilidade de profissionais de saúde adquirirem formas resistentes da doença em situações de elevada exposição como procedimentos geradores de aerossóis. O presente relato descreve o caso de uma profissional que desenvolveu tuberculose pulmonar primária já com perfil de pré-resistência extensiva. O diagnóstico foi confirmado por testes moleculares e fenotípicos, tendo o tratamento sido à base de bedaquilina, linezolida, clofazimina e terizidona por um período total de 18 meses, com boa resposta clínica. Este caso reforça a necessidade da identificação precisa dos possíveis níveis de resistência da tuberculose e nos remete às medidas administrativas, ambientais e individuais que se fazem necessárias para a redução dos riscos ocupacionais.

Descritores: Tuberculose multirresistente; Doença ocupacional; Broncoscopia; Inibidores de TNF; Relato de caso.

INTRODUCTION

Tuberculosis remains the leading cause of death from infectious agents worldwide, with an estimated 1.25 million deaths in 2023. Given an incidence of over 10 million new cases in the same year, approximately 400,000 corresponded to different forms of resistant tuberculosis, of which less than half received adequate diagnosis and treatment[1].

Occupational transmission of tuberculosis to healthcare professionals is part of this scenario, especially in situations where

there is a delay in the identification and isolation of bacilliferous patients, and in high-risk environments due to aerosol generation and inadequate ventilation, such as emergency departments, intensive care units, and the often-overlooked rooms where respiratory endoscopy examinations and procedures are performed[2-4].

We report a case of pulmonary tuberculosis with extensive pre-resistance acquired by a healthcare professional who worked in a bronchoscopy service, an unusual and potentially serious situation that, fortunately, resulted in a cure. Its diagnostic and therapeutic implications, however, deserve to be discussed and provide a valuable educational opportunity to reinforce concepts and prevention strategies.

CASE REPORT

This is the case of a 35-year-old female healthcare professional who developed daily fever in March 2023, accompanied by persistent dry cough and malaise for over 15 days. She had a history of Crohn's disease, which had been treated with infliximab for about two years; she reported having undergone tuberculin skin tests before starting and after one year of using this medication, both negative. A computed tomography (CT) scan of the chest showed consolidation in the lingula associated with centrilobular nodules in a "tree-in-bud" pattern in the upper left lobe (Figure 1). As the patient did not present spontaneous expectoration, bronchoscopy was performed with bronchoalveolar lavage (BAL), whose direct bacilloscopy was negative, but the rapid molecular test (GenXpert MTB/RIF®) identified *M. tuberculosis* DNA (low detection) with indeterminate rifampicin resistance. Tuberculosis treatment began with the standard regimen of rifampicin, isoniazid, pyrazinamide, and ethambutol (RHZE) pending culture and sensitivity testing, and infliximab was suspended. There was partial improvement in symptoms, but the results released about 40 days later identified resistance of the mycobacterium to all first-line drugs (RHZE plus streptomycin) by the automated macrodilution technique (Bactec 960®). The patient was then referred to a tuberculosis reference outpatient clinic, where a new collection of respiratory samples was requested, and the sensitivity test of the first sample was supplemented for second-line drugs. Using the indirect proportion method, additional resistance to levofloxacin while sensitivity to linezolid and amikacin were found. The second sample (sputum collected with the aid of respiratory physiotherapy) also showed negative bacilloscopy, but this time the molecular test (using the GenXpert Ultra® kit) detected rifampicin resistance. When subjected to line probe assay (LPA) hybridization, this second sample also allowed the identification of mutations in the katG, rpoB, and gyrA genes (associated with resistance to isoniazid, rifampicin, and levofloxacin, respectively). No resistance mutations were detected for amikacin, kanamycin, and capreomycin. Given the diagnosis of tuberculosis with an extensive pre-resistance profile, the RHZE regimen was replaced by bedaquiline 400 mg/day for two weeks (followed by 200 mg three times a week), terizidone 750 mg/day, linezolid 600 mg/day, and clofazimine 100 mg/day. Bedaquiline was suspended after six months (end of the intensive phase), while terizidone, clofazimine, and linezolid were maintained (at these same dosages) for another year – until December 2024. It was not possible to collect a new sputum sample for control, but there was progressive clinical and radiological improvement, documented by a new CT scan performed three months after the start of the second therapeutic regimen (Figure 2). Currently, the patient remains asymptomatic, including regarding Crohn's disease, without the reintroduction of infliximab. For didactic purposes, we summarized the main clinical and therapeutic milestones in a timeline presented in Figure 3.

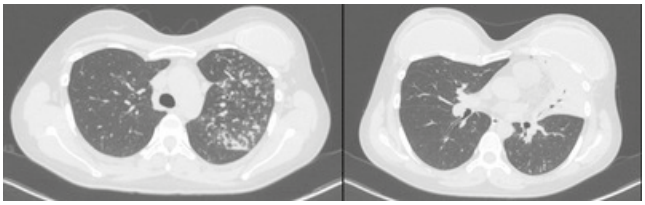

Figure 1. Initial chest computed tomography (axial cuts, pulmonary window) showing consolidation in the lingula and multiple centrilobular nodules in a "tree-in-bud" pattern in the upper left lobe.

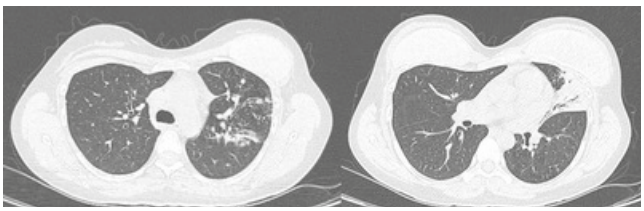

Figure 2. Chest computed tomography after three months of treatment with the pre-XDR tuberculosis regimen demonstrating partial reduction of consolidation and regression of nodular opacities in the left lung.

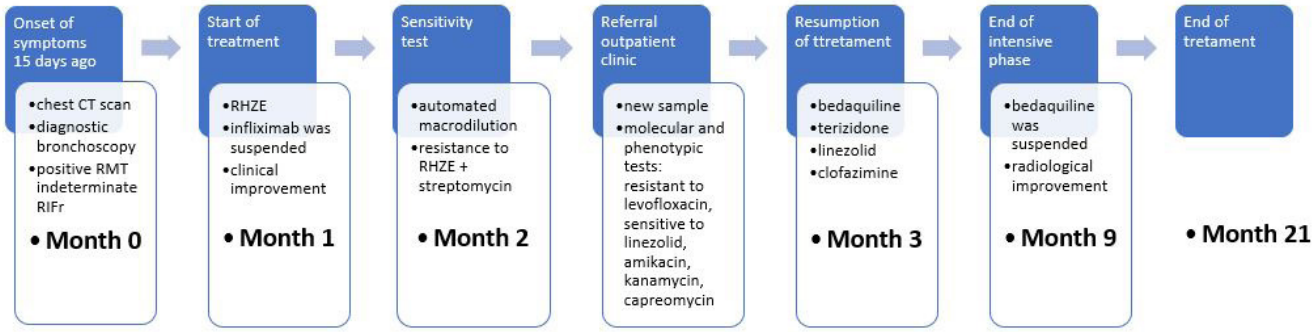

Figure 3. Timeline (between 2023 and 2024) with the main clinical events related to the diagnosis and treatment of a case of occupationally acquired extensively pre-resistant tuberculosis (pre-XDR TB).
Legend: CT: computed tomography; RMT: rapid molecular test for *M. tuberculosis* detection; RIFr: rifampicin resistance; RHZE: rifampicin + isoniazid + pyrazinamide + ethambutol.

It is worth noting that, as a healthcare professional, the patient was aware of the high risk of occupational exposure in her work routine, which included, among other activities, prolonged periods in an endoscopy room where respiratory examinations (bronchoscopies) were performed. She affirmed routine and consistent use of N95 masks during procedures but could not recall any specific case that could have been the source of transmission of this tuberculosis with such an impacting resistance profile. Active screening among household contacts and colleagues was carried out as soon as the initial diagnosis of tuberculosis was obtained, but all showed negative tuberculin tests and no clinical and/or radiological evidence of active disease. Finally, the patient's work routine and workplace were restructured.

DISCUSSION

Healthcare professionals have an increased risk of infection with *M. tuberculosis* compared to the general population, and screening for latent tuberculosis infection (LTBI) is an important strategy in this context. A recent systematic review estimated the prevalence of LTBI in 28% of these professionals, with the highest rates observed in countries where the incidence of tuberculosis in the community is already higher[5]. In Brazil, studies report a prevalence between 27% and 59.7%, which varies according to each professional category and the level of healthcare[6,7]. Among the highest-risk categories are nursing professionals (3 to 20 times higher risk than the general population), clinical pathologists (6 to 11 times), bacteriology laboratory technicians (2 to 9 times), healthcare students (4 to 8 times), and respiratory medicine specialists (6 times)[4]. It is recommended that LTBI screening (which involves directed anamnesis, imaging exams, and tuberculin skin test) be performed upon hiring any healthcare professional and repeated annually to detect possible conversions that require specific treatment[4,8,9]. However, this was not the case for our patient, as her two tuberculin skin tests were performed in the context of immunomodulatory treatment with a tumor necrosis factor (TNF) inhibitor therapy and not as part of an institutional occupational health program. Indeed, the use of infliximab to treat Crohn's disease certainly contributed as a concomitant factor to her illness[10], but this had no relation to the resistance profile of the acquired tuberculosis.

Multidisciplinary and multi-professional care, most directly involved in healthcare situations where there is a greater generation of aerosols, includes maneuvers such as airway aspiration, sputum induction, endotracheal intubation, and, as in this report, bronchoscopies. These procedures invariably provoke coughing, making it imperative to comply with administrative, environmental, and individual measures to mitigate the consequent higher occupational risk[2,4,8]. Administrative measures include early identification of respiratory symptomatic individuals and their immediate isolation, signaling of more vulnerable hospital areas, and definition of clear diagnostic flows, in addition to clinical management protocols, therapeutic follow-up, and continuous training of teams[4,8]. Regarding environmental control, interventions should be adjusted according to the type of procedure and patient profile, with the aim of diluting and removing contaminated air, as well as controlling the pattern and direction of airflow from a clean to a contaminated environment, and not the opposite way around[8]. According to the Brazilian standard (NBR)

7256:2022 from the Brazilian Association of Technical Standards (ABNT), bronchoscopy rooms must operate under negative pressure relative to adjacent areas, with a minimum of 12 air changes per hour (ACH); the temperature must be maintained between 20 and 24°C, and the relative humidity of the air must be less than or equal to 60%[3]. Air recirculation must not occur in these environments, requiring total exhaust to the exterior, taking into account additional safety criteria such as the minimum distance from public circulation points[3]. Furthermore, the Brazilian Ministry of Health recommends the use of HEPA filters in the exhaust and minimum re-entry intervals, calculated by the ACH required to remove more than 99% of suspended particles (23 to 35 minutes for rooms with 12 ACH)[8]. The use of personal protective equipment (PPE), in turn, is regulated in Brazil by the Ministry of Labor, which stipulates, among other things, that companies must provide their employees with appropriate PPE in good condition and free of charge, whenever collective measures do not offer total protection against the risk of accidents or work-related diseases[11]. Regulatory Standard (NR) no. 32 defines the N95 respirator (designated PFF-2 by Brazilian health authorities) as the recommended PPE for tuberculosis prevention, with employees responsible for its regular use and maintenance[11].

Conceptually, rifampicin and isoniazid resistance defines multidrug-resistant tuberculosis (MDR-TB); resistance to these two drugs plus resistance to a fluoroquinolone characterizes pre-extensively drug-resistant tuberculosis (pre-XDR-TB); and resistance to rifampicin, isoniazid, a fluoroquinolone, and linezolid and/or bedaquiline defines extensively drug-resistant tuberculosis (XDR-TB)[12]. Despite the pre-XDR profile reported here, the case corresponds to primary resistance tuberculosis, by definition, due to its direct acquisition by the patient, without her having received any specific prior treatment[4]. This fact reiterates the circulation of multidrug-resistant strains in Brazil, albeit infrequently[13]. In the occupational context, it represents an even greater potential for severity due to the real risk of healthcare professionals being exposed to already pre-resistant strains.

Early identification of tuberculosis resistance level also emerges as a priority strategy. Widely used, rapid molecular tests like GenXpert MTB/RIF® are capable of detecting not only the presence of *M. tuberculosis* complex mycobacteria in biological samples but also mutations in the rifampicin resistance-determining region (RRDR) of the *rpo*B gene[14]. The sensitivity of the method, however, can be suboptimal in paucibacillary samples, which could explain the indeterminate rifampicin resistance result in our patient's first sample collected by BAL. The Ultra® version of this same product incorporates two new molecular targets (IS6110 and IS1081) and the use of nested PCR, thereby reducing the detection limit of the test[14]. These combined factors result in significant gains in diagnostic performance, as occurred with the second sample (sputum). However, both kits are limited to possible detection of exclusive rifampicin resistance. The line probe assay (LPA), in turn, complements these tests by evaluating other genes associated with resistance to different classes of drugs – the Brazilian Ministry of Health, however, prioritizes its use in situations of greater clinical and epidemiological relevance, such as retreatment, symptomatic contacts of drug-resistant cases, detection of rifampicin resistance by rapid molecular test, or therapeutic failure of the basic regimen[15]. First-line LPA analyzes the *rpo*B, *kat*G, and *inh*A genes (rifampicin and isoniazid), while second-line LPA evaluates the *gyr*A/*gyr*B (fluoroquinolones) and *rrs/eis* (aminoglycosides) genes[14,15].

Despite the speed and accuracy of all these molecular methods, they can still fail (especially in cases of rare mutations), which maintains phenotypic tests as a still fundamental part of resistance assessment in tuberculosis[14]. Phenotypic tests, however, depend on culture isolation, a time-consuming process. In solid media, results take an average of 3 to 4 weeks, while automated cultures in liquid media reduce this interval to about 10 to 14 days, with another one or two weeks needed to obtain additional sensitivity test results[4,14]. It is worth recalling the administrative measures already mentioned to mitigate the risks of nosocomial tuberculosis transmission, which include, among others, the definition of efficient intersectoral flows to maintain continuous and effective communication between the laboratory and the clinical team[16].

The therapeutic approach in this case was based on the technical note from the Brazilian Health Ministry in effect at that time, between 2023 and 2024[17]. The incorporation of pretomanid into the Brazilian Unified Health System (SUS) only occurred in January 2025, which is a current option that, when associated with linezolid and bedaquiline ("BPaL" regimen), offers advantages such as lower toxicity, lower abandonment rates, and higher success rates, reducing the total treatment time to six months[14,18,19].

Finally, active screening among household and occupational contacts in our report did not

identify cases of active or latent tuberculosis, but the complexity of the topic warrants reflection: if any LTBI case had been diagnosed, there would be no available treatment due to the pre-XDR profile, recommending only clinical follow-up for at least two years for early detection of symptoms[4]. If a contact with active disease were identified, initial treatment should be guided by the index case's profile, reassessing the conduct after the results of their own culture and sensitivity testing[19].

CONCLUSION

Although it is a rare situation in Brazil and the patient fortunately recovered, this case of pre-XDR pulmonary tuberculosis acquired by a healthcare professional in a high-risk occupational setting reinforces the importance of adopting the necessary biosafety measures that extend beyond individual precautions such as the "simple" use of PPE. Awareness and compliance with these measures align with national and international guidelines, seeking to offer comprehensive practices for prevention, diagnosis, and treatment of nosocomial tuberculosis transmission in high-complexity services.

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