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Fluoroquinolone resistant tuberculosis: A case report and literature review

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ABSTRACT

Despite the advancements made in medicine and treatment of tuberculosis over the last century, it remains a significant healthcare challenge. It remains the leading cause of death from a single infectious agent and the ninth leading cause of death worldwide. A 23-year-old male with a history of tuberculosis treated in Nepal seven years prior, presented to the emergency department with one week of hemoptysis, fever, chills, night sweats and weight loss. A CT scan of the chest showed multiple cavitary lesions at the superior segment of the left lower lobe. He had persistent massive hemoptysis and required blood transfusions. He underwent bronchial artery embolization followed by lobectomy. He was ultimately diagnosed with fluoroquinolone-resistant tuberculosis, and required a prolonged intensive care unit with transfer to a regional tuberculosis center to successfully complete treatment.

1. Introduction

In developed countries, *Mycobacterium tuberculosis* (TB) still remains a health care challenge due to immigration from endemic regions. It is one of the leading causes of death from a single infectious agent and the ninth leading cause of death worldwide in 2016 [1]. It is estimated that nearly one-third of the world population is affected by either latent or active TB [2]. The 2017 Global Tuberculosis report has estimated approximately 600,000 new cases worldwide of drug resistant TB [1]. Depending on the region, the risk of reactivation of latent TB is 5%–10% in people without comorbidities. Half of the reactivations occur in the first 2–3 years after latent infection [3]. The *Mycobacterium* establishes itself in the lungs by inhalation of droplets from the infected host. Hemoptysis is one of the most common but dangerous presenting symptoms in patients with active TB. The bleeding is usually small volume, frequently presenting as blood streaked sputum. Massive hemoptysis, defined as greater than 300 mL of blood in 24 hours, is now a rare complication. Prior to effective antibiotics, massive hemoptysis accounted for approximately 5% of TB-related deaths [4]. Thoracic surgical intervention was the mainstay in treatment prior to the introduction of streptomycin [5]. Here we present a patient with recurrent TB, complicated by massive hemoptysis and multidrug resistance who required early surgical intervention and specialized antibiotic selection.

2. Case report

A 23-year-old man with a medical history of treated TB presented to the emergency department with hemoptysis for one week. His symptoms started with a dry cough that progressed from blood-tinged sputum to frank blood over three weeks. He had associated fever, chills, night sweats and subjective weight loss. His previous symptoms had completely resolved and he moved to the United States from Nepal one year prior to the hospital admission.

On physical examination, the patient was afebrile, hemodynamically stable with a generalized cachectic appearance and diffuse rhonchi bilaterally on pulmonary auscultation. His labs were notable for a normal leukocyte count, a hemoglobin of 11.7 g/dL, and normal chemistries. The chest x-ray, Fig. 1, had a lucency in the left suprahilar region and bilateral peribronchial thickening of the upper lobes. A follow up CT scan, Fig. 2, showed multiple cavitary lesions at the superior segment of the left lower lobe.

On hospitalization day 2, a microscopic smear of his sputum showed many acid-fast bacilli that was later identify in cultures as *Mycobacterium tuberculosis complex*. He was started on a 5-drug regimen with rifampin, isoniazid, pyrazinamide, ethambutol and moxifloxacin due to his prior history of possible resistant TB. He continued to have persistent hemoptysis and worsening anemia requiring a transfusion due tachycardia and dyspnea, suggesting massive hemoptysis. Four

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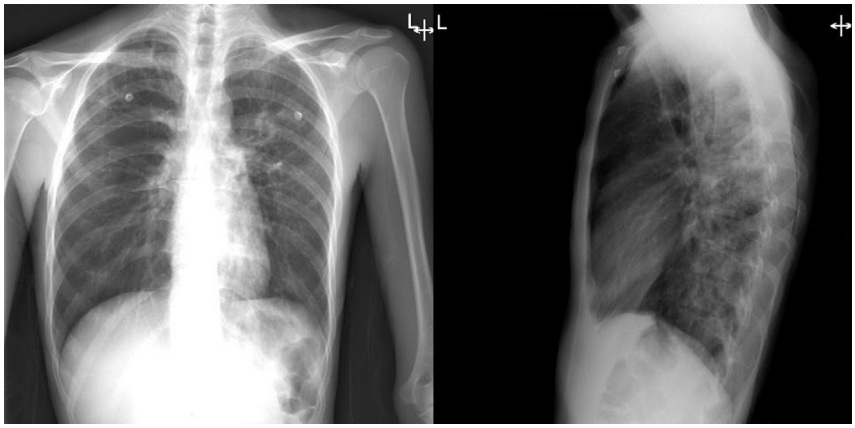

Fig. 1. Posteroanterior and lateral chest roentgenography showing left suprahilar lucency.

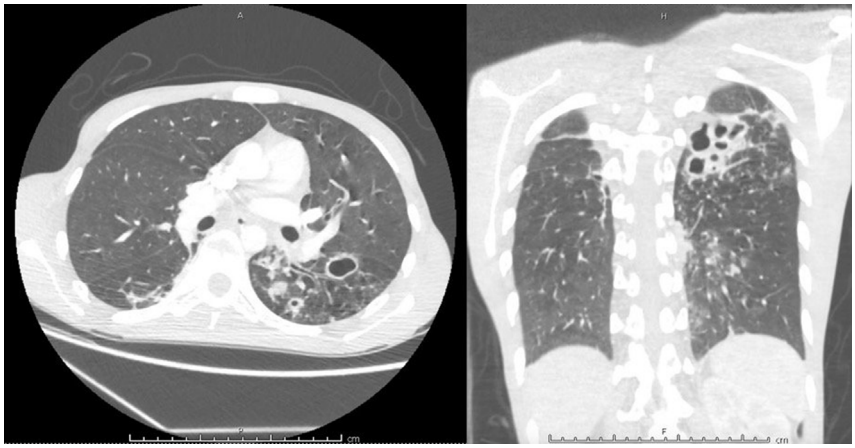

Fig. 2. Transverse and coronal CT chest showing multiple cavitary lesions.

days after the anti-tuberculosis medication was initiated, he developed respiratory distress and was transferred to the medical intensive care unit and was placed on non-invasive positive pressure ventilation but did not improve. Thus, he underwent an urgent bronchoscopy, revealing a significant burden of blood clots in the left main bronchus that did not allow for a complete survey of the airway. As a result, an endobronchial blocker was placed and the patient was evaluated by interventional radiology. He underwent urgent left bronchial artery angiography with embolization of two abnormally hypertrophied left bronchial arteries.

The following day, he underwent repeat bronchoscopy that showed persistent clot burden in the left main bronchus. Given his active tuberculosis, difficulty with oxygenation, and multiple cavitary lesions, the decision was made to proceed with left lower lobectomy. On gross examination, the lobe of lung was severely congested weighing 645 g (normal weight of a complete left lung: 395 g). There was widespread consolidation with nodules containing caseous material, Fig. 3A. It corresponded to necrotizing nonsuppurative granulomas with a peribronchial and subpleural distribution in a miliary pattern, Fig. 3B. The granulomatous inflammation extended around medium sized vessels causing destruction of the vasa vasorum and secondary obliterative endarteritis, Fig. 3C. Numerous cavities developed in relation to necrotizing granulomas with suppuration and hemorrhage, Fig. 3D. Round foreign particles were deposited in the arterial lumina, consistent with a prior embolization procedure. Intra-alveolar hemorrhage emerged after bleeding into the cavitating granulomas due to destruction of vessel walls, Fig. 3E and F. Few acid-fast organisms consistent with *L*-shaped mycobacteria were identified on FITE stain, Fig. 3G–I. Other special stains including Kinyoun cold procedure, auramine-rhodamine staining, and mycobacterium immunostaining, were negative for acid fast bacilli.

On hospitalization day 6 the patient's family, who was previously unable to contacted, arrived at the hospital and the team was able to provide additional history regarding his previous TB therapy. He was diagnosed with multidrug resistant (MDR) TB seven years prior to admission and treated for 18 months with rifampin, isoniazid, pyrazinamide, ethambutol, moxifloxacin and an injectable medication, the name of which they could not recall. The following day, the Health Department confirmed fluoroquinolone-resistant tuberculosis by nucleic acid amplification testing (NAAT). Rifampin, isoniazid, and moxifloxacin were discontinued and the patient was started on amikacin, linezolid, meropenem, clavulanate, *para*-aminosalicylic acid and ethionamide. Bedaquiline was requested from the Centers for Disease Prevention and Control (CDC). After his lobectomy, he required persistent intensive care unit monitoring because he would not tolerate extubation trials along with multiple episodes of mucous plugging, which required multiple bronchoalveolar lavages. He was successfully extubated on hospitalization day 14. The patient was transferred to the regional TB center of Florida on hospitalization day 21.

After an additional two months of being monitored and treated at the regional tuberculosis center, the patient was discharged to the community and continued his treatment under directly observed treatment through the department of health.

3. Discussion

Despite the advent of effective anti-TB chemotherapy, this disease still remains a global burden. Poverty, human immunodeficiency virus

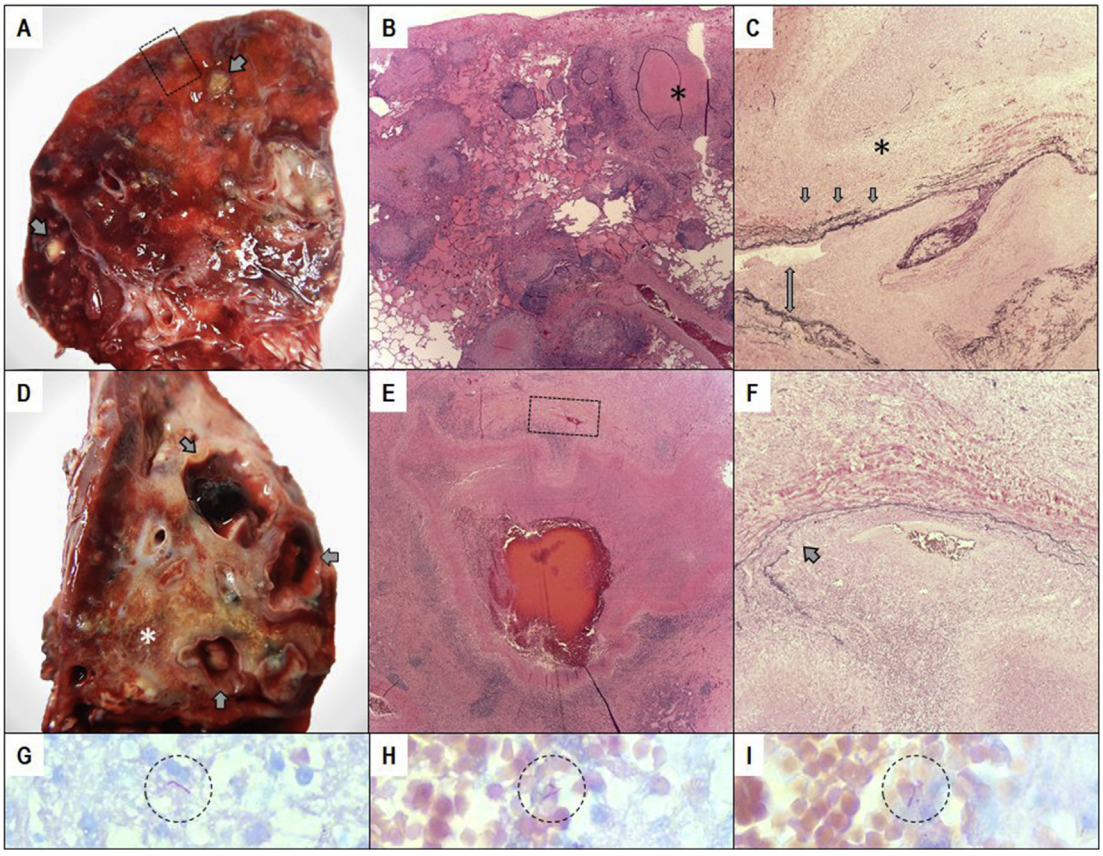

Fig. 3. Pathology of pulmonary TB involving the left lower lobe. **A-B**. Necrotizing non-suppurative granulomatous and chronic inflammation in a miliary pattern (arrows and asterisk: caseous necrosis, dashed frame: area displayed on B, H&E stain, 25x). **C**. Obliterative endarteritis (Verhoeff elastic stain, 100x). Granulomas (asterisk) disrupted the wall and elastic fibers of an artery (small arrows) inducing a reactive intimal proliferation (two headed arrow). **D-F**. Granulomas complicated with parenchymal necrosis (asterisk, D), cavitation (arrows, D) and hemorrhage due to vascular erosions (dashed frame: area displayed on F, Verhoeff elastic stain, 200x; arrow: duplication of inner elastic lamina of an artery). **G-I**. *L*-shaped mycobacteria on FITE stain, 600x.

Table 1
Overview of genetic mutations that lead to drug resistance.

Antibiotic	Mechanism of Action	Gene Mutation	Effect of Mutation
Rifampin	Binds to RNA polymerase	*rpoB*	Alters the β-subunit of RNA polymerase
Isoniazid	Inhibits mycolic acid synthesis	*katG*	*katG* mutation prevents activation of INH
		inhA	*inhA* mutation prevents INH from inhibiting cell wall synthesis
Pyrazinamide	Converted to pyrazinoic acid	*pncA*	Decreases synthesis of pyrazinamidase preventing activation of pro-drug
Ethambutol	Inhibits cell wall synthesis	*embB*	Overwhelms EMBs ability of inhibit cell wall synthesis
Streptomycin	Inhibits mRNA translation	*rpsL*	Alters ribosomal structure
		rrs	
FQ	Inhibits DNA gyrase	*gyrA*	Causes amino acid changes in DNA gyrase
		gyrB	
Ethionamide	Inhibits peptide synthesis	*inhA*	Prevents ethionamide from inhibiting cell wall synthesis
Injectables	Inhibits protein biosynthesis	*rrs*	Alters rRNA binding site
		eis	

FQ: Fluoroquinolone, EMB: Ethambutol, INH: Isoniazid, Injectables: amikacin, capreomycin, or kanamycin.

(HIV), and drug resistance are some of the major contributors to its resurgence, especially in developing countries [6]. A high index of suspicion is required for quick diagnosis and early isolation. Our patient presented with a three-week history of cough with hemoptysis and a remote history of TB treatment, allowing the clinicians to strongly consider TB as a diagnosis and have the patient provide sputum samples on admission. Understanding the patient's social and medical history of MDR-TB factored into choosing the initial antibiotic regimen to empirically include moxifloxacin prior to a full susceptibility report.

Based on the limited history that we were able to obtain from the patient we had a high suspicion that his previous TB diagnosis was at the very least rifampin resistant. It was not until the treatment team was able to obtain corroborating history from his family that a suspicion for MDR-TB was made. Our institution does not have a method of rapid resistance testing, so the results of the nucleic acid amplification test (GeneXpert® MTB/RIF) took five days from the time of sputum collection on admission until the results were reported to us by the local Health Department. From there it took another five days for the CDC to confirm the degree of resistance.

In the era before effective anti-TB antibiotics, surgery was one of the few treatment modalities available for TB. When TB was discovered to be an aerobic organism, different surgical techniques were introduced with the goal of decreasing the oxygen tension in the alveoli. These techniques which included iatrogenic pneumothorax, plombage, and

phrenic nerve ligation would lead to atelectasis of the diseased lung [5].

The discovery of streptomycin in the late 1940s shifted the treatment of TB from surgical to medical and soon after the advent of rifampin in the 1960s, antibiotics became the mainstay of treatment and the need for surgery decreased. However, the use of antibiotics also led to resistance by means of drug-imposed selective pressures. Adaptive mutations and incomplete treatment are factors involved in the induction of resistant mycobacteria (Table 1). In addition, *L*-form transformation, as shown in Fig. 3G–I, is the morphological expression of cell-wall deficient mycobacteria that is thought not only to contribute to the resistance of several antimicrobial agents, but also confers marked resistance to the host immune system [7–10]. From a public health perspective, social-network analysis showed the primary mode of resistance transmission comes from direct transmission [11]. Direct transmission from patients with MDR and XDR spreads resistant strains of TB and suggest the importance of social programs that promote comprehensive therapy.

Given the high risk of direct transmission, hospital policies and protocols for the prevention and control of tuberculosis is important to consider. General isolation practices and principles along with special consideration for all respiratory equipment involved in the care of the patient led to no transmission of the patient's tuberculosis to any healthcare provider or support staff at our facility. Standard precautions should be observed with all patients cared for in a hospital setting which assumes every person is potentially infected or colonized with an organism that could be transmitted. Standard precautions include proper hand hygiene and the use of personal protective equipment, such as gloves, when providing direct patient care or handling any bodily fluids [12]. In a patient with tuberculosis, these precautions are augmented with the use of airborne precautions. Airborne precautions observed at our institution include training for early recognition of patients suspected to be infected with an organism transmitted person-to-person via airborne route. Patients are placed in a negative-airflow room that removes more air than is allowed in and thus creates a pressure gradient for air to be regularly exchanged. These special rooms are tested daily with visual indicators such as smoke tubes or tissue test to prove airflow is towards the door. Along with visual indicators, each room has a pressure monitoring device (manometer). Any person entering the room is required to wear an approved N95 respirator as an addition to standard precautions [13]. An effort is made to minimize transporting patients with airborne precautions. If medically necessary to transport for testing, a proper facial barrier is placed to prevent direct transmission. The patient developed respiratory distress and the use of a non-invasive positive pressure ventilation device and ultimately a ventilator was used. These devices use high-efficiency particulate air (HEPA) filters throughout the circuit to theoretically trap mycobacterium and prevent contamination [14]. These respirator devices also undergo regular manufacture suggested maintenance to thoroughly clean the circuit and prevent cross contamination. In addition to respiratory devices, the patient required multiple fiberoptic bronchoscopies. Once used, each bronchoscope undergoes a pre-cleaning and cleaning procedure. The pre-cleaning procedure includes the use of a dual enzymatic cleaner for the outer sheath as well as internally using the suction capability. The scope is then taken to be sterilized using the manufacturer protocol. After our patient was transferred to the regional TB center, the room he occupied, and its contents, were thoroughly cleaned using a medical grade quaternary ammonium disinfectant that also had tuberculocidal properties.

Once TB is resistant to rifampin and isoniazid, it is known as multidrug-resistant TB (MDR-TB). MDR-TB has an increased morbidity and mortality with higher likelihood of treatment failure. Fluoroquinolones are commonly used as second line medications for the treatment of MDR-TB, the main mechanism of action of which is inhibition of DNA gyrase (topoisomerase II). The injectable medications used in TB treatment work by inhibiting protein biosynthesis and include kanamycin, amikacin and capreomycin. The TB strain isolated from the patient described above harbors mutations in the *rpoB, katG, embB* and *gyrA* genes. If a TB strain is resistant to only a fluoroquinolone, then the strain is known as fluoroquinolone-resistant TB or formerly pre-XDR TB [15]. Fluoroquinolone-resistant TB became a class of its own as researchers found they had similar poor outcomes as patients with extensively drug resistant (XDR) TB [16,17]. When a TB isolate is resistant to rifampin, isoniazid, a fluoroquinolone and an injectable antibiotic (amikacin, capreomycin, or kanamycin), the isolate is known as XDR-TB [18]. XDR-TB carries the highest mortality risk and risk of treatment failure.

Bedaquiline is an antibiotic approved by the FDA for the treatment of MDR-TB. It is an oral diarylquinoline with bactericidal anti-tuberculous activity. In 2018, Schnippel et al., reported the findings of their retrospective cohort study comparing regimens containing bedaquiline to a standard regimen without bedaquiline in patients with varying degrees of drug resistant TB. They found that the group which had bedaquiline included in their regimen experienced a risk reduction in all-cause mortality for both MDR-TB and XDR-TB [19]. In the same year, Ahmad, et al., reported their findings of a meta-analysis exploring which medications were associated with higher rates of treatment success and found that bedaquiline, in combination with linezolid and levofloxacin or moxifloxacin showed a lower rate of treatment failure. This is reflected in the 2019 WHO guidelines [20,21].

The WHO guidelines also include recommendations for surgical evaluation in the treatment of MDR-TB. The increase in drug resistant strains of TB renewed interest in surgical options. The operative mortality risk between lobectomy and lung carcinoma are similar at 3.3% [22]. Current indications for surgical evaluation include persistently positive sputum cultures after four to six months of treatment regardless of resistance, XDR that is unlikely to respond to therapy alone and the presence of serious complications such as massive hemoptysis or persistent bronchopleural fistula [18,20,23–25]. Patients who undergo lung resection surgery have been found to have increased treatment success rates and decreased poor outcomes [18,23,24].

The 2019 update to the World Health Organization guidelines on the management drug resistant strains of TB outline that the recent body of evidence supports a longer duration of treatment of at least 18 months. They also recommend against the routine use of an injectable agent and instead prefer a fully oral regimen. The guideline development group recommends that all three group A agents (fluoroquinolones, bedaquiline, and linezolid) be given priority in addition to at least 1 group B agent (clofazimine, cycloserine or terizidone) [20]. This new recommendation comes after a meta-analysis including more than 12,000 adults with MDR-TB showed a lower mortality rate with fully oral regimens when compared to regimens containing an injectable.

In a patient with XDR-TB or, such as our patient, fluoroquinolone resistant TB, an initial regimen containing five agents should be implemented [20]. The specific details on the duration and composition of the treatment regimen are beyond the scope of this discussion, but it is important to note that treatment decisions should be made in conjunction with the department of health or a clinician experienced in treating drug resistant TB.

Our patient had massive hemoptysis as suggested by signs of hemodynamic instability and a significant drop in hemoglobin without other sources of bleeding or dilution that led to the need to control bleeding. It is recommended that rigid or flexible bronchoscopy be performed prior to surgery to localize the hemorrhage [22]. Bronchoscopy also allows for adequate airway protection by implementing unilateral lung ventilation with an endobronchial blocker or balloon tamponade if needed. Bronchial artery embolization has been shown to be effective in controlling hemorrhage from massive hemoptysis temporarily while patients are stabilized [26]. However, there are large variances in the reported recurrence of hemoptysis in patients undergoing bronchial artery embolization. Recurrence can occur in 10%–45% of the cases and higher in patients with chronic lung disease,

including TB [27]. The patient described above had persistent clots visible on bronchoscopy after embolization. Along with a worsening of his anemia, the decision was made for lung resection surgery, which most likely stabilized the patient enough to tolerate anti-TB therapy.

Many factors led to the survival of our patient. A proper history and physical exam raised the suspicion of TB and even drug resistant TB high enough that he was promptly placed in isolation and early efforts to obtain adequate sputum samples were made. There was consistent communication between the Department of Health and the treating team which led to early initiation of second line chemotherapy with their guidance and assistance in obtaining the medications. There was a comprehensive healthcare team actively involved in the patient's care, including critical care, pulmonology, infectious disease, CT surgery, pharmacy, and interventional radiology. Given the already high mortality risk with drug resistant strains of MTB, early surgical intervention was critical in not only controlling his hemorrhage, but also decreasing the pathological burden in his lung tissue, thus decreasing his risk of treatment failure. There is still much research that needs to be done with regards to the role of surgery in drug resistant TB patients. Nevertheless, these factors allowed the patient have an increased chance of treatment success.

Declaration of conflict of interests

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