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REVIEW

Successful treatment of multi-focal XDR tuberculous osteomyelitis

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Summary We herein describe the nosocomial transmission of a pre-XDR or MDR case of pulmonary tuberculosis in a HIV-negative health care worker in an area endemic for MDR and XDR tuberculosis. Following inadequate therapy and non-compliance, he presented with extra-pulmonary XDR tuberculosis in the form of multi-focal osteomyelitis and encysted pleural effusion. He was cured after two years of treatment with various anti-tuberculous drugs in addition to interferon gamma.

Contents

Abbreviations: XDR, extensively drug resistant; MDR, multi-drug resistant; MRI, magnetic resonance imaging.

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Case presentation

The case was a 30-year-old Saudi physician who studied medicine for six years in the Ukraine from 1992 until 1997. He denied direct contact with patients who had extensively drug-resistant tuberculosis. He described having indirect contact with these patients in January 2006. These patients were waiting in the radiology department for chest X-rays. In August 1996, he developed a fever and cough that did not respond to one week of treatment with moxifloxacin. His CT chest revealed a right apical cavity. He was admitted to a hospital in Riyadh and was started on isoniazid, rifampin, ethambutol and pyrizinamide for smear-positive tuberculous cavitary pulmonary disease. He did not improve after one month of therapy. Moxifloxacin, amikacin and cycloserine were therefore added. His sputum *Mycobacterium tuberculosis* [isolate A] was sensitive to ethambutol and resistant to isoniazid, rifampin and streptomycin. Second-line drug susceptibility information was not available (Table 1). He improved clinically but his sputum cultures continued to be positive for *M. tuberculosis* in September and October 2006. He returned to the Ukraine in November 2006 and continued on isoniazid, rifampin, ethambutol, pyrizinamide, moxifloxacin and cycloserine for six months. He stopped his therapy in April 2007 and developed a recurrent fever and cough in May 2007. He graduated in July 2007 and returned to Saudi Arabia to be admitted for pleura-pulmonary tuberculosis. His sputum was smear-positive and his pleural effusion was also positive for *M. tuberculosis*. His tuberculous empyema required chest tube drainage. He was re-started on isoniazid, rifampin, pyrizinamide, ethambutol, moxifloxacin, cycloserine and amikacin. In July 2007, second-line drug susceptibility testing was performed by the National Tuberculosis Reference Laboratory, London, UK. His sputum *M. tuberculosis* [isolate B] was resistant to isoniazid (high level resistance), rifampin, ethambutol, pyrazinamide, ofloxacin, streptomycin, amikacin, capreomycin and ethionamide. It was only sensitive to linezolid, clofazimine and cycloserine (Table 1). He had no medical follow-up from September 2007 until July 2008. He sought a second opinion in Jordan. He felt better on alternative medicine and his respiratory symptoms improved. He was receiving moxifloxacin, ethambutol and cycloserine in August 2008 when he experienced left ankle pain, swelling and limitation of movement. MRI confirmed left ankle osteomyelitis (Fig. 1) and he underwent debridement. Bone histopathology showed caseating granuloma with negative acid-fast bacilli. A tissue sample from the ankle bone was emulsified in sterile normal saline using a sterile mortar and pistol. Both samples were inoculated in BACTEC-MGIT TB liquid culture tubes (BD Biosciences, Sparks, MD) and incubated in the BACTEC-MEGIT 960 instrument (BD Biosciences) until there was positive detection by the machine. The isolate was confirmed to be *M. tuberculosis* by PCR using the gene GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA). Sensitivity testing to isoniazid, rifampin, ethambutol and streptomycin were performed on a MEGIT 960 instrument (BD Biosciences) according to manufacturer's instructions. The drug concentrations were as follows: isoniazid 0.4 mg/ml, rifampin 1 mg/ml, ethambutol 5 mg/ml and streptomycin 4.0 mg/ml. The organism was resistant to all first-line drugs. The sample was referred

Table 1 Tuberculosis drug susceptibilities for the three isolates sputum and bone (R: resistant, S: sensitive, NP: not performed).

Tuberculosis drug sensitivities	Isolate A sputum	Isolate B sputum	Isolate C bone
Rifampin	R	R	R
Isoniazid	R	R	R
Pyrizinamide	R	R	R
Ethambutol	S	R	R
Streptomycin	R	R	R
Amikacin	NP	R	R
Capreomycin	NP	R	R
Kanamycin	NP	NP	R
Ethionamide	NP	R	R
Ofloxacin	NP	R	R
Moxifloxacin	NP	NP	R
Linezolid	NP	S	S
PAS	NP	NP	R
Cycloserine	NP	S	NP
Clarithromycin	NP	NP	NP
Clofazimine	NP	S	NP

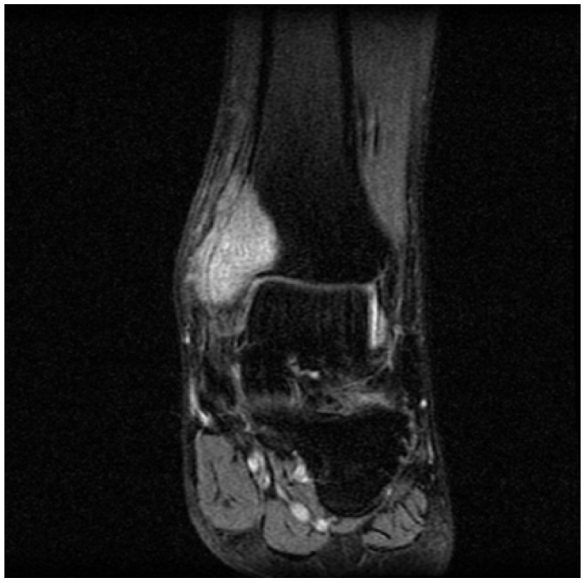

Figure 1 The first MRI of the left ankle showing osteomyelitis of the left fibula.

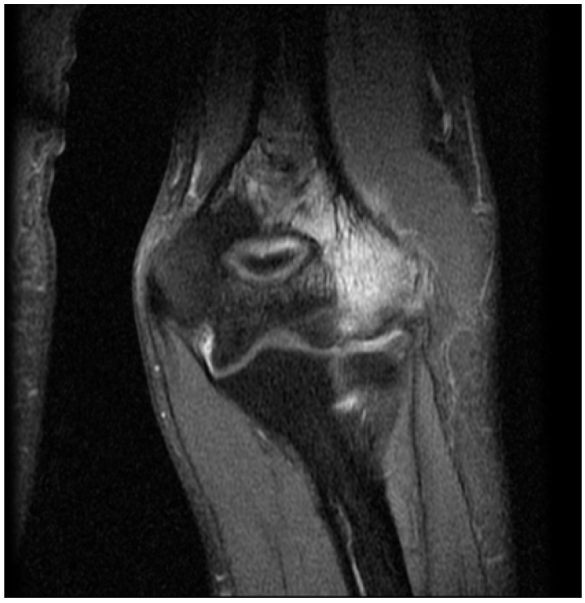

Figure 2 The first MRI of the left elbow showing osteomyelitis of the left humerus.

to the National Tuberculosis Reference Laboratory, London, UK for second-line sensitivity testing. The bone tissue *M. tuberculosis* strain [isolate C] was resistant to isoniazid, rifampin, pyrizinamide, ethambutol, streptomycin, amikacin, capreomycin, kanamycin, ethionamide, para-aminosalicylic acid (PAS), ofloxacin and moxifloxacin. It was only sensitive to linezolid. The sensitivity to cycloserine, clofazimine and clarithromycin was not examined (Table 1). Within two weeks, the patient developed left elbow and knee pain, swelling and limitation of movement, which were confirmed by MRI as left elbow and knee osteomyelitis (Figs. 2 and 3). His chest CT showed right encysted pleural effusion with no cavitary pulmonary disease. At this stage, it was realized that this patient had serious XDR tuberculosis in the form of multifocal osteomyelitis and encysted pleural effusion. We used a combination of clofazimine, linezolid, meropenem, ampicillin-clavulanate, cycloserine, PAS, capreomycin daily, moxifloxacin and clarithromycin for two months. Subsequently, he was continued on PAS, cycloserine, moxifloxacin, azithromycin, clofazimine, linezolid and amikacin every other day (the capreomycin was stopped) for four months. Finally, he received PAS, cycloserine, moxifloxacin, clofazimine and azithromycin for 18 months. He developed intolerable gastro-intestinal upset related to clarithromycin, meropenem and ampicillin-clavulanate and they were stopped after two months of treatment. He developed linezolid-associated axonal neuropathy confirmed by nerve conduction studies, so the linezolid was stopped after six months of therapy. Capreomycin was stopped after two months because it was not available. He was continued on amikacin for four months only in view of its ototoxicity. In summary, he received a total of six months of second-line injectable agents. Pyrizinamide was not given because of the patient's severe polyarthritis. Subcutaneous interferon gamma injections were started after six months of therapy when the linezolid and amikacin were stopped. It was continued for six months with no adverse effects. After two years of therapy, the patient is clinically

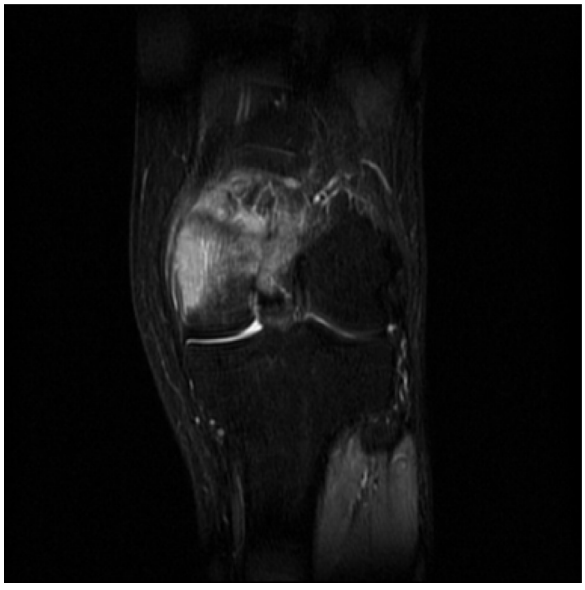

Figure 3 The first MRI of the left knee showing osteomyelitis of the left femur.

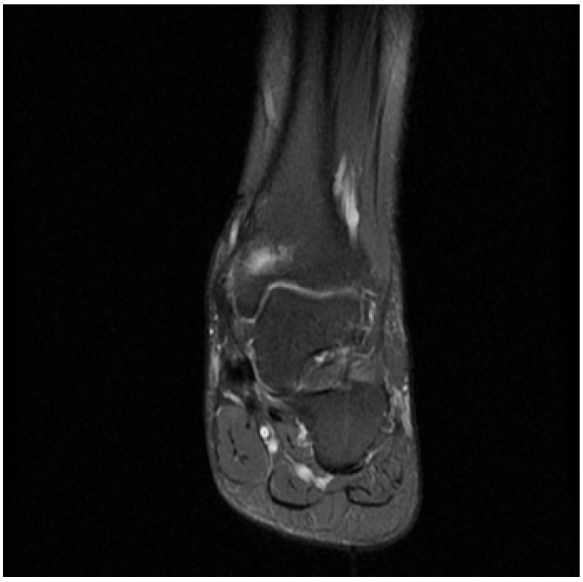

Figure 4 A follow-up MRI of the left ankle after 12 months of treatment showing improvement of the osteomyelitis in the left fibula.

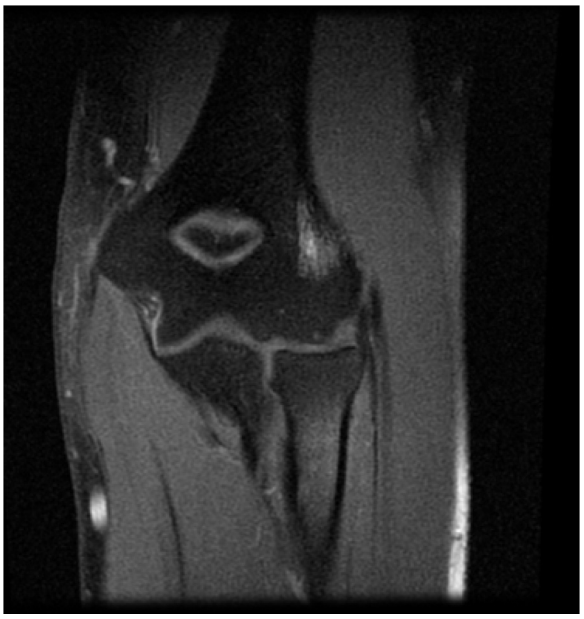

Figure 5 A follow-up MRI of the left elbow after 12 months of treatment showing improvement of the osteomyelitis in the left humerus.

asymptomatic with no residual joint pain, swelling or limitation of movement. His HIV serology is negative. His CRP and ESR, as well as his complete blood count and renal and liver function tests are normal. After one year of therapy, a follow-up MRI of his left ankle, elbow and knee showed 80% improvement of the osteomyelitis (Figs. 4—6) and his CT chest revealed 50% resolution of his encysted pleural effusion. After 18 months of therapy, his left knee MRI showed resolution of the osteomyelitis (Fig. 7). He has been asymptomatic since the discontinuation of his anti-tuberculous medication in March 2011. As he is doing postgraduate studies outside Saudi Arabia at this time, follow-up imaging could not be performed.

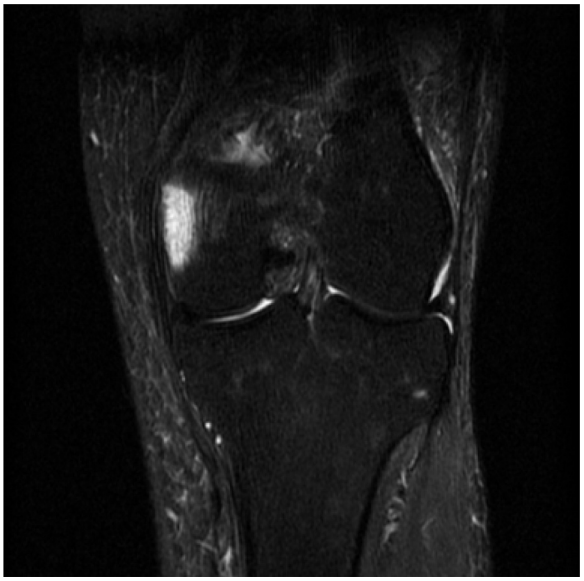

Figure 6 A follow-up MRI of the left knee after 12 months of treatment showing improvement of the osteomyelitis in the left femur.

Case discussion

Our case illustrates the nosocomial transmission of MDR tuberculosis to a health care worker in an area endemic for resistant tuberculosis. The nosocomial transmission of MDR tuberculosis is a real concern in resource-poor settings. It has been estimated that the application of nosocomial infection control strategies could prevent half of XDR tuberculosis cases [1].

It was difficult to determine whether our case was initially an MDR tuberculosis stain or an XDR stain due to the lack of second-line drug susceptibility testing on specimen A. However, the development of secondary ethambutol resistance in specimen B is an indicator of the propagation of resistance. Our case demonstrates the various risk factors for the progression of tuberculosis from MDR to XDR strains. First, our patient was non-compliant with his therapy and did not continue his medical follow-up. In MDR tuberculosis patients with baseline resistance to second-line

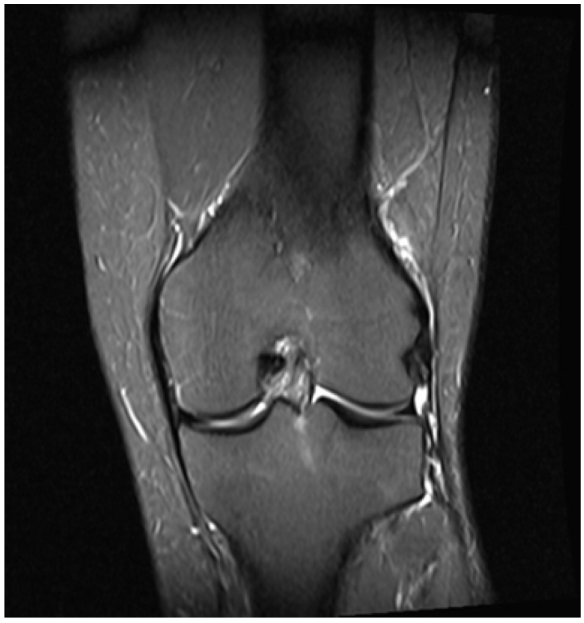

Figure 7 A follow-up MRI of the left knee showing resolution of the osteomyelitis in the left femur after 18 months of therapy.

drugs, it was shown that the risk of XDR tuberculosis increased from 1.4% to 15.9% in directly observed therapy programs, whereas it increased from 3.4% to 60.9% in indirectly observed therapy programs [2]. Second, our case illustrates that the presence of cavitary pulmonary disease is an important risk factor for the amplification of secondary resistance among MDR and XDR tuberculous bacilli. It was previously found that 25% of resected pulmonary cavity XDR tuberculosis cases had additional drug resistance compared to preoperative sputum tuberculous cultures [3]. Third, the extent of resistance to second-line drugs was initially unknown in our MDR tuberculosis case, leading to inadequate therapy and a complicated outcome. It was shown that 2.4% of MDR tuberculosis patients with no baseline second-line drug resistance developed acquired XDR tuberculosis, while 44.1% of those with resistance to three second-line drugs developed acquired XDR tuberculosis [2].

The resistance of our case was confirmed by direct susceptibility testing of sputum and bone tuberculous cultures. The diagnosis of XDR tuberculosis osteomyelitis is challenging. The disease is paucibacillary and requires invasive procedures. The genotype line probe assays for rifampin, second-line injectable agents and fluoroquinolones are promising in respiratory specimens but require further evaluation in non-respiratory specimens [4]. Because they are dependent on the gold standard, slow, direct susceptibility testing, the diagnosis and initiation of effective therapy are delayed for several weeks in cases of XDR tuberculosis osteomyelitis. In addition, follow-up specimens to assess the disease response were lacking in our case, although we clearly demonstrated the radiological improvement of osteomyelitis after adequate therapy in addition to the patient's clinical response.

The optimal treatment for MDR and XDR extrapulmonary tuberculosis is difficult to determine and has not been clearly demonstrated. The guidelines for the management of MDR and XDR extrapulmonary tuberculosis were adopted from the treatment guidelines for MDR and XDR pulmonary tuberculosis. The WHO guidelines for XDR tuberculosis therapy suggested six medications in the induction phase for eight months and four medications in the maintenance phase for 12 months [5].

In our case, we could not adopt the WHO guidelines. The treatment was challenging for several reasons. First, the strain was only sensitive to linezolid and clofazimine and might have been sensitive to cycloserine (the patient was previously exposed to cycloserine). Second, the patient had an interrupted exposure to cycloserine, moxifloxacin and amikacin, which made it more difficult to build an effective drug regimen for him. Third, several medications were not available in Saudi Arabia, such as PAS and capreomycin, and were purchased using personnel efforts and communications. Fourth, the best drug combination to provide effective bone penetration is not known. Fifth, the treatment plan was modified because of drug toxicity and intolerance (pyrizinamide, linezolid, amikacin, clarithromycin, clavulanate and meropenem). We discussed our case with several international XDR tuberculosis experts and we agreed that the therapy should be tailored for the above reasons. The difficulty in building our regimen relied on combining medications with limited benefit to which the patient had not been exposed (meropenem, clavulanate, clarithromycin, clofazimine and linezolid) and adding medications with proven benefit but with known resistance, to which the patient was exposed (cycloserine, moxifloxacin and amikacin). The induction phase was shortened to six months in view of drug toxicity (linezolid and amikacin) and drug intolerance (meropenem, clavulanate, and clarithromycin) with a sequential reduction of medication from nine drugs to five drugs.

In our case, with the limited options available for sensitive drugs, resistant drugs such as moxifloxacin, PAS, amikacin and capreomycin were used. Despite the bacteria being resistant, the

use of moxifloxacin is recommended in XDR tuberculosis to improve the treatment outcome [5,6]. It is not known whether the use of other resistant medications, such as second-line injectable drugs, will lead to a similar outcome. The synergistic effects of resistant anti-tuberculous agents are unknown and need to be evaluated. In addition, with the availability of new drugs for resistant tuberculosis, the best combination therapy with the lowest pill burden and shortest effective therapy needs to be determined in future studies. In the French cohort study that evaluated the efficacy of bedaquiline, 19 out of 35 patients had XDR tuberculosis and one case was osteoarticular tuberculosis. After six months of therapy, all but one of the patients had culture conversion. This cohort study also showed that bedaquiline had a favorable outcome when combined with moxifloxacin, even though the tuberculous strains were resistant to fluoroquinolones [7].

The role of immune modulation and the use of interferon gamma in XDR tuberculosis are controversial and poorly studied [8]. We used interferon gamma injections in our case when our patient developed adverse effects related to linezolid and amikacin and the number of drugs in the induction phase was reduced. Further clinical studies are needed to evaluate its efficacy against XDR tuberculosis. At present it may be considered in refractory cases of XDR tuberculosis despite optimal therapy and in the presence of medication-related side effects.

Our case is unique in the literature in that it is a case of multifocal XDR tuberculous osteomyelitis with a successful outcome. The literature describing MDR and XDR tuberculous osteomyelitis is limited to a few case reports [9—12]. All of the previous cases reviewed were MDR tuberculosis and not XDR tuberculosis. A systematic review summarized 13 case reports, and indicated that six patients had spinal disease and seven patients had extraspinal disease. All of them had a good outcome with medical therapy. Eight of them required surgical intervention [11].

Conclusion

The diagnosis and management of extra-pulmonary XDR tuberculosis remains challenging, particularly because it is endemic in resource-limited countries. With the lack of rapid diagnostics and effective therapy, preventive strategies are crucial. Reliable molecular testing and low-burden treatments are areas that should be addressed in future research.

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Competing interests

None declared.

Ethical approval

Not required.

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