

Rapid communications

EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS: FIRST REPORT OF A CASE IN IRELAND

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Extensively drug-resistant tuberculosis (XDR-TB) is an emerging global threat. Between 2002 and 2007 sixteen countries in the European Union (EU) reported at least one case of XDR-TB [1]. Infection is characterised by alarming mortality rates in both HIV and non-HIV populations.

We report the first case of XDR-TB in Ireland and describe a successful outcome after 20 months of treatment. We also discuss the implications for public health in our country as well as the international community.

Case report

In January 2005, a 25-year-old Lithuanian female was admitted from the emergency department with a three-month history of productive cough. There was no associated haemoptysis, weight loss or night sweats. The patient denied previous treatment with anti-tuberculous drugs or exposure to patients with active TB.

There was no significant medical history. The patient was an ex-smoker and drank occasionally. She had been living in Ireland for two and a half years.

The patient was afebrile with oxygen saturations of 99% on room air. Respiratory examination was normal. The chest radiograph on admission showed bilateral pulmonary infiltrates and a cavity in the right mid-zone (Figure 1).

Auramine staining of sputum demonstrated acid-fast bacilli. *Mycobacterium tuberculosis* was cultured from sputum. Screening for HIV and hepatitis B/C was negative. Isoniazid 250 mg od, rifampicin 600 mg od, pyrazinamide 1500 mg od and ethambutol 400 mg bd were commenced for presumed pan-sensitive tuberculosis.

In February 2005 preliminary drug susceptibility tests (DST) showed a profile of resistance consistent with MDR-TB. The

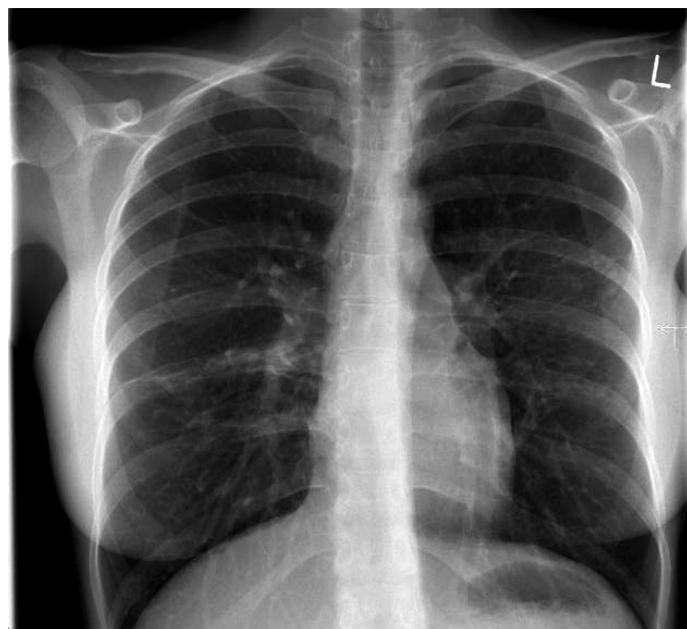
FIGURE 1

Chest X-ray of a patient diagnosed with XDR-TB in Ireland (on admission)



FIGURE 2

Chest X-ray of a patient diagnosed with XDR-TB in Ireland (after treatment)



drug regimen for drug-sensitive TB was stopped. Treatment was recommenced with capreomycin 1g im od, moxifloxacin 400mg od, prothionamide 750 mg bd, cycloserine 250 mg bd and P-aminosalicylic acid (PAS) 4g tds. The patient was placed under directly observed therapy (DOT)

After four months PAS was stopped when the final report of DST demonstrated resistance. The final drug resistance profile is shown in Table 1; this profile is consistent with XDR-TB. No drug susceptibility test was available for Moxifloxacin. No further drugs were added to the regimen as the patient was responding clinically and radiologically.

Sputum culture was negative for TB after 96 days; capreomycin was consequently reduced to thrice weekly administration. Treatment for XDR-TB continued until October 2006 for a total of 20 months. During this time there was no clinical or radiological evidence of disease recrudescence. The final chest X-ray showed bilateral fibrocalcific changes only (Figure 2).

Adverse events were noted. A mild, transient transaminitis (AST 33 □ 82) occurred in the first week. Nausea persisted until the fourth month and required anti-emetics. Bilateral tinnitus developed after eight months; capreomycin was discontinued at this point and an audiogram showed high frequency hearing loss in the right ear (5 db below normal). The final 12 months of the total 20 months of treatment passed without complication.

Once treatment was discontinued the patient failed to attend for follow-up. She did not re-present to our hospital. She is still living in Ireland. Since her treatment was stopped 21 months ago, Ireland has not reported any further cases of XDR-TB.

Discussion

The treatment of patients with multi-drug resistant (MDR) tuberculosis (i.e. resistance to both isoniazid and rifampicin) is a daunting medical challenge. Isoniazid and rifampicin are the most potent anti-tuberculous agents but by definition are ineffective in

MDR-TB. Second line agents replace them but these drugs are less efficacious, more toxic and more costly.

XDR-TB is defined as resistance to isoniazid, rifampicin, any fluoroquinolone and any one of amikacin, capreomycin or kanamycin [2]. In these circumstances therapeutic options are further restricted because of resistance to both first and second line agents. Consequently the XDR-TB treatment regimen often consists of older drugs (i.e. serine analogues, thioamides) that are predominantly bacteriostatic rather than bactericidal.

The poor efficacy of XDR-TB chemotherapy is reflected in the alarming mortality rates. In Western European countries mortality among non-HIV patients has been reported as 36% [3]. Infection in immunocompromised patients is even more devastating; an outbreak of XDR-TB in a HIV positive population killed 52 out of 53 infected patients [4].

Although XDR-TB carries a high mortality rate, our patient had a successful outcome. In this case the patient was treated with an antimycobacterial cocktail of capreomycin, moxifloxacin, prothionamide and cycloserine. Current World Health Organisation (WHO) guidelines recommend treatment of MDR-TB with at least four drugs whose efficacy against the isolate is certain or almost certain [5]. Formulating an appropriate regimen is a crucial component of treating MDR-TB (and XDR-TB). If DST shows susceptibility, pyrazinamide and ethambutol should be included. An injectable agent should also be added i.e. amikacin, kanamycin or capreomycin; if tolerated these agents should be continued for a minimum of six months. Next a fluoroquinolone should be considered e.g. moxifloxacin or levofloxacin. Finally oral second line agents (i.e. PAS, cycloserine or prothionamide) should be added until the drug cocktail consists of four to six drugs to which the isolate is susceptible. Once the regimen has been commenced, patients should be placed on DOT. Treatment should continue for at least 18 months [5].

Drug resistance in TB arises from ineffective TB control programmes. Patient non-compliance, poor quality drugs or incorrect prescribing engender resistant strains. Furthermore resistance cannot be detected if resources for TB culture and drug susceptibility tests are lacking. Thus in the absence of appropriate resources and infrastructure there is improper identification and treatment of resistant cases which ultimately leads to uncontrollable disease.

Although XDR-TB has been recognised since 2000 [6], epidemiological data describing its distribution worldwide only became available in February 2008 [1]. South Africa has so far reported the greatest absolute number of XDR-TB cases worldwide [1]. The vast majority of XDR-TB cases reported in the EU have occurred in Estonia, Latvia and Lithuania [1].

However assumptions that XDR-TB is limited to resource-limited countries are incorrect; all G8 countries have now reported at least one case [1]. The emergence of XDR-TB in industrialised nations may be linked to issues of immigration; 76% of United States cases reported from 2000-2006 occurred in foreign-born persons [7]; 63% of XDR-TB cases in Germany and Italy have occurred in non-nationals [3].

TABLE 1
Results of final drug susceptibility tests, XDR-TB case, Ireland 2005-2006

Drug	Resistant (R) / Sensitive (S)
Isoniazid	R
Rifampicin	R
Ethambutol	R
Pyrazinamide	R
Streptomycin	R
Amikacin	R (highly resistant)
Prothionamide	S
PAS	R (highly resistant)
Cycloserine	S
Capreomycin	S
Ciprofloxacin	R
Rifabutin	R
Clarithromycin	R

In October 2006 the WHO Global Task Force on XDR-TB announced its response to XDR-TB [2]; infection control measures and surveillance systems required strengthening; laboratory facilities must be augmented to improve access to drug susceptibility tests; low-priced, high-quality second-line drugs must be more readily available. A US\$ 2.15 billion plan to implement these recommendations was launched by the WHO and Stop TB partnership in June 2007 [8].

This is the first report of a case of XDR-TB in Ireland. Further cases are likely as immigration from European countries with a high burden of MDR-TB continues. How can the threat be averted? Suspected cases of tuberculosis should be referred for chest X-ray as well as sputum staining and culture. Patients should be isolated until infectivity is excluded. If *Mycobacterium tuberculosis* is cultured, drug susceptibility testing should be performed to detect resistance; MDR-TB or XDR-TB is more likely in patients previously treated for TB or in immigrants from countries with a high burden of MDR-TB. If MDR-TB or XDR-TB is diagnosed, treatment in a specialist centre is advised. Public health authorities should be notified to identify contacts and offer chemoprophylaxis if appropriate.

These measures must be followed carefully; this will ensure that the devastation wrought by tuberculosis in 20th century Europe is not repeated in the modern day.

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