Multiresistent tuberculosis: the third pandemic?

F. Maltez*, J. Machado*, A. Morgado**, R. Proença***

Abstract

The authors describe their recent experience with single and multidrug resistant tuberculosis, associated with HIV infection. They emphazise particularly, the scope and severity of this issue both in health institutions as Public Health.

Key words: HOV, tuberculosis, multidrug resistance, nosocomial transmission.

Introduction

Tuberculosis is reemerging at the end of this century in areas of high prevalence of infection by the human immunodeficiency virus. According to reports from various institutions, this increase has been accompanied by the occurrence of resistant strains and outbreaks of multi-resistant tuberculosis, characterized by high morbidity and high mortality.[1,2,3,4,5,6] In Portugal too, since 1994, there has been a resurgence of tuberculosis, with reports of multi-resistant strains in several hospitals,[7,8,9,10] raising some doubts, if not disbelief.

The authors present here their hospital experience, summarizing the main clinical, epidemiological, and bacteriological characteristics of 144 male patients co-infected with HIV and Mycobacterium tuberculosis, hospitalized in Service 1 (Infectious Diseases) of the Hospital de Curry Cabral over a 24-month period (1995 and 1996). For logistical reasons, only cases in the male ward are presented, which has 24 separate and isolated beds, as opposed to female patients and the other medical units of the service, located in other buildings. Eighty patients (55.2% of the total) had multi-resistant tuberculosis. The severity of the problem justifies alerting the authorities of the Public Health System, in terms of promoting important preventative measures and urgently advocating an epidemiological intervention that will clarify the situation.

Epidemiological considerations

It is estimated that, today, about 2 billion people are infected by Mycobacterium tuberculosis worldwide, of whom 8 million are co-infected with HIV. Tuberculosis is responsible today for about 2.5 million deaths annually. Depending upon the geographical area, between 10 and 67% of cases of tuberculosis occur in people already infected by HIV or, to put it another way, 5 to 50% of those infected with HIV will develop tuberculosis at some stage of their disease. Considered together with other factors like alcoholism, poverty, or malnutrition, infection by HIV has taken over as the main risk factor for contracting tuberculosis, and as such, has increased in areas where HIV is prevalent, emerging as the main cause of morbidity and the principal opportunistic infection in patients with AIDS, behaving like a second pandemic.[11]

Portugal is, today, one of the European countries with the highest number of cases of AIDS determined by tuberculosis,[9,10,12,13] and our case series bears witness to this in that in recent years, among the male population, the frequency of tuberculosis has surpassed that of other opportunistic infections (*Fig. 1*); in 1996 it was responsible for around 64.2% of all cases of AIDS and accounted for ± 70% of the occupied beds in our ward, of an average occupancy of 100%.

The problem

The reciprocal influence of the two infections has been well studied and while, on one hand, the possibility of tuberculosis stimulating the progression of

*Hospital Assitant in Internal Medicine

**Head of the Internal Medicine Service

***Director of the Medicine Service I of the Hospital Curry Cabral

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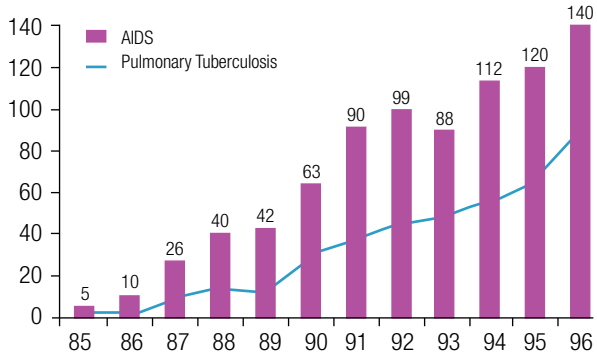

Acquired immune deficiency syndrome. Pulmonary tuberculosis. Annual incidence.

FIG. 1

TABLE I

Tuberculosis and HIV: natural history

- Small inoculum and/or short period of exposure sufficient to infect these patients
- Rapid progression of repeat infections
- Increased risk of reactivation of latent infection
- Possible frequent reinfection

the HIV infection needs to be confirmed, regulating viral replication by means of a tumor necrosis factor, on the other hand, the influence of HIV on the natural history of Mycobacterium tuberculosis (*Table I*) seems clear, leading to greater ease of acquisition of the bacillus, more rapid progression of the infection, and a greater risk of reactivating a previous infection. In four months or less, an individual can progress from infection to active disease. Also, the probability of reactivation of a latent infection is thirty times higher than in the general population, and re-infection with different strains is also more frequent.

Due to these conditions, people co-infected by HIV and Mycobacterium tuberculosis are at high risk of acting as repositories for future cases of tuberculosis. If we also add poor absorption and poor adherence of these patients, and occasionally, incorrect therapeutic or prophylactic regimens (*Table II*), the prerequisites for the emergence of resistant strains are present, and a strain of Mycobacterium tuberculosis could become resistant to various drugs within just a few months,

TABLE II

Nosocomial outbreaks of multi-resistant tuberculosis

Predisposing factors
for
Resistance: Poor adherence
Poor absorption
for
Nosocomial Transmission: Diagnostic and therapeutic delays
Prolonged infectiousness
Lack of environmental control measures

TABLE III

TUBERCULOSIS AND HIV

n = 144*

- Sensitive tuberculosis – 53 (36.8%)
- Resistant tuberculosis – 91 (63.2%)
- Multi-resistant tuberculosis – 80 (55.2%)

BACTEC TB	ANTIBIOGRAMS
• To 2 drugs - 8	INH + RMP - 8
• To 4 drugs - 40	INH + RMP + PZA - 4
• To 5 drugs - 6	INH - RMP + SM - 17
	INH - RMP + SM + PZA - 3
	INH + RMP + SM + EMB + PZA - 6
	INH + RMP + SM - EMB - 35
	INH + RMP + SM + PZA - 2
	INH + RMP + EMB - 5

* 144 patients co-infected with HIV and M tuberculosis
Service 1 (Infectious Diseases)
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which in turn, is passed on to other people who develop tuberculosis that is resistant from the onset. There is also a possibility of the occurrence of larger bacillary populations in patients, resulting in a higher probability of resistance to antibacillary antibiotics.

Delays in the diagnosis and recognition of these resistances, leading to prolonged infectiousness, despite chemotherapy, and repeated delays in the implementation of measures to prevent transmission in our hospitals, create the environment necessary for

TABLE IV

Epidemiological characteristics. n = 80*

Average Age	32 yrs	(20-67)	
Race	White	74	(92.5%)
	Black	6	(7.5%)
HIV (ELISA and W. Blot)	1	76	(95%)
	1 + 2	3	(3.75%)
	2	1	(1.25%)
Risk Behavior			
	Drug addicts	58	(72.5%)
	Homo/Bisexuals	16	(20%)
	Heterosexuals	6	(7.5%)
CD4 Lymphocytes/mm3			
	< 50 /mm3	62	(77.5%)
	> 50 /mm3	18	(22.5%)
Mantoux	Total Anergy	80	(100%)
Patients with opportunistic infections and previous hospitalizations in 95 and 96		42	(52.5%)
Patients with other previous visits in 95 and 96 (Outpatient Clinic/Appointment)		?	(%?)

80 patients co-infected with HIV and multi-resistant M. tuberculosis
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the occurrence of nosocomial outbreaks. Eighty percent of nosocomial outbreaks of tuberculosis reported worldwide involve multi-resistant tuberculosis.[14,15,16]

Our case series

During 1995 and 1996, we studied 144 patients, admitted to the men's unit of our Infectious Diseases Department, who were HIV-positive and diagnosed with tuberculosis.

In all cases, serum positivity was affirmed by ELISA and confirmed by W. Blot. In all the patients, the tuberculosis diagnosis was made through the detection and identification of Mycobacterium tuberculosis in one or more samples of sputum, gastric juice, blood, and/or cerebrospinal fluid, using the radiometric Bactec TB method. For the respective antibiograms, performed by the same method, isoniazid, rifampicin, streptomycin, ethambutol, and pyrazinimide were used.

Ninety-one patients had resistant strains (*Table III*), i.e. 63.2% of the total, of which eighty had an equal number of multi-resistant strains (defined by resistance to at least isoniazid and rifampicin); 55.2% of the total. Of these, the most frequent pattern was resistance to four antibacillaries. Twenty-seven strains were resistant to three, five were resistant to two, and six were resistant to five antibacillary antibiotics. *Table IV* shows the main epidemiological characteristics of the eighty patients with multi-resistant tuberculosis.

Present-day polymorphic analysis techniques (DNA fingerprinting) enable us to establish connections between the strains, leading to the detection of an index case and the possible confirmation of nosocomial transmission of tuberculosis, if it exists, both between patients and from patients to health workers. It also shows that patients treated for one strain of Mycobacterium tuberculosis can be re-infected with a different strain.

It was the results of a study conducted in London using this technique, and to which seventeen cultures of Mycobacterium tuberculosis from patients hospitalized at the H. de Curry Cabral were initially sent, that confirmed the suspicion of the existence of a chain of nosocomial transmission of multi-resistant tuberculosis among the patients of our Department (*Tables V and Fig. 2*).[1,2,3]

Diamantino S., 33 years of age, HIV_1-positive, under observation in our Department, was diagnosed in September 1994 with lymph node tuberculosis, identified as sensitive Mycobacterium tuberculosis in a lymph node, and began traditional therapy. He immigrated to England six months later and went to the Chelsea and Westminster Hospital with a fever and hepatomegaly. The chest x-ray, when compared to previous x-rays, showed resolution of mediastinal lymphadenopathies and a liver biopsy showed non-

TABLE V

Clinical case

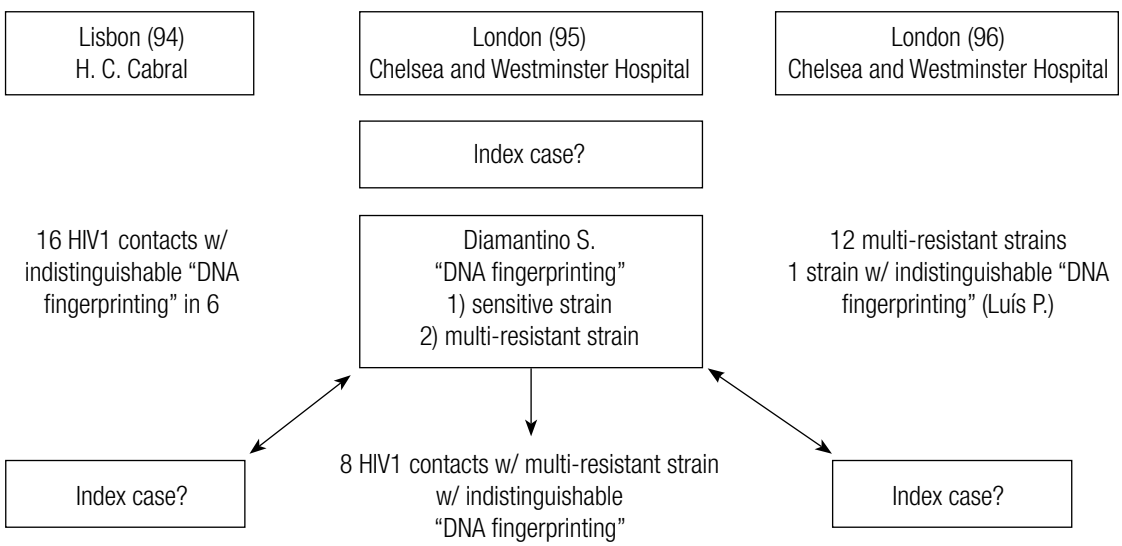
Diamantino S., 33 years of age, White, Homosexual, HIV1,	
Lisbon	8/94 – Pulmonary aspergillosis
(H. Curry Cabral)	Kaposi sarcoma
	9/94 – Lymph node tuberculosis
	AST without resistance to
	INH + EMB + RIF + PZA
London	3/95 –Fever and hepatomegaly
(Chelsea and	CD4 – 8 cells/mm3
Westminster Hospital)	Liver biopsy – granulomas and AFB
	Bronchoscopy w/ LBA – direct examination
	Atypical mycobacteriosis?
	Clarithromycin + Amikacin
	4/95 –Expectorated sputum - AFB
	Liver biopsy – M. tuberculosis
	TSA - resistance to INH, RIF, PZA, CLOF, RIFAB, ETH.
	Immediate prevention measures
	6/95 –Deceased

caseating granulomas and AFB which, when considered together with his profound immunodepression and the fact that the original strain of Mycobacterium tuberculosis was sensitive, led to a probable diagnosis of atypical mycobacteriosis. He resumed his previous treatment with clarithromycin and amikacin, improved, and was discharged, following a bronchoscopy, of which direct examination of the LBA was negative.

His condition worsened, and he was readmitted for fever and cough. Mycobacterium tuberculosis resistant to INH, RIF, PZA, CLOF, RIFAB and ETH were isolated in both expectorated sputum via AFB and in the original liver biopsy. Recommended preventative measures were immediately taken.

However, prior to his isolation, he had moved freely around the ward and the outpatient clinic of the English hospital. He died two months later from miliary tuberculosis.

Eight English HIV-positive patients,



Tuberculosis: trans-european transmission.

FIG. 2

TABLE VI

Tuberculosis and HIV: evolution (n = 144*)

Resistant Tuberculosis	91 patients	
Deceased		74 (81%)
Multi-resistant Tuberculosis	80 patients	
Deceased		67 (83%)
Average survival		3 months

*144 patients co-infected with HIV and M tuberculosis
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who had been in contact with the presumed index case, in the ward and in the outpatient clinic in London, developed pulmonary tuberculosis. The TSA was identical in all of them. DNA fingerprinting was performed for the Portuguese patient (Diamantino S.) and for the eight contacts infected in London, as well as for sixteen strains of multi-resistant Mycobacterium tuberculosis in an equal number if patients in our Department in Lisbon. This technique identified two genetically distinct strains of Mycobacterium tuberculosis in the index case (Diamantino S.), indicating that the patient had acquired a second infection with a multi-resistant strain.

All the multi-resistant strains of the eight patients infected in London and of six of our patients in Curry Cabral were indistinguishable, showing that he had contracted the second strain in Portugal. It should be pointed out that this was the first nosocomial outbreak of multi-resistant tuberculosis reported in the United Kingdom.

From January to June, 1996, twelve more cases of multi-resistant tuberculosis were identified in that unit in London. One of the strains, while not related temporally to the outbreak referred to above, had DNA fingerprinting that was indistinguishable from the nine cases involved. This strain was found in another Portuguese HIV-positive patient (Luis P.), who had been diagnosed with pulmonary tuberculosis in 1994 in our hospital.

Preliminary results of the ongoing epidemiological study point to the probable existence of identical strains in 1993 in some of our patients, with the index case of our nosocomial outbreak as yet undetermined.

These chains of transmission justify the fact that the preoccupation, in our wards of accidentally contracting HIV has given way to the fear of contracting tuberculosis, especially multi-resistant forms. Effectively, nosocomial outbreaks of multi-resistant tuberculosis have been documented and are now a worldwide problem, reported in various hospitals, especially in Europe and the USA, affecting mainly patients infected with HIV and characterized by high morbidity and mortality.[5,6,7,15,16]

TABLE VII

Prevention

Resistance	Transmission
Correct therapy and prophylaxis	Rapid diagnosis and treatment
	Environmental control
Direct observation of treatment	Monitoring and screening of Heath workers

Among the eighty previously mentioned patients admitted to our Department with multi-resistant tuberculosis, the mortality rate was 83%, with an average survival, following diagnosis and the beginning of treatment, of ± 12 weeks, not including several patients (6), who were lost to follow-up (*Table VI*).

Prevention and conclusions

While new therapeutic areas are being explored, all efforts should be focused on early recognition of infection, often based only on supposition, either because the patient comes from an area of prevalence or due to a history of recent exposure. The treatment is under direct observation, which is probably the most effective means for ensuring successful treatment and preventing resistance. It is also recommended that doctors, at the beginning of treatment, have a good knowledge of the epidemiological data relating to the people and the communities they are treating. However, this effort will only be effective if accompanied by a careful epidemiological investigation and the implementation of environmental control measures, considered capable of preventing this carnage[14,17,18,19,20] (*Table VII*), bearing in mind, among other things, the need to use masks, negative pressure isolation rooms, ventilation systems, etc.; in short, the various means of controlling airborne transmission recommended by our Directorate-General of Health since April, 1994.

A new attitude in Public Health is desired, together with a careful study by epidemiologists in the hospital wards, in order to end with all doubts.

Tuberculosis, even in the HIV patient, if treated promptly and correctly and provided the patient adheres to the treatment, is treatable just as in HIV-negative patients. But if these conditions are not present, and given the current inadequacy of measures used to control transmission, nosocomial tuberculosis can become unstoppable and who knows, by the end of this millennium we could find ourselves on the brink of a third pandemic. ■

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