Clinical and laboratory profile of patients with tuberculosis/HIV coinfection at a national referral centre: a case series

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مُرْتَسَم سريري ومختبري لمرضى العدوى المشتركة بالسل مع فيروس العوز المناعي البشري في مركز وطني للإحالة: سلسلة من الحالات

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الخلاصة: تصف هذه السلسلة من الحالات المُرْتَسَم السريري والمختبري لخمسة عشر مريضاً بالعدوى المشتركة بالسل مع فيروس العوز المناعي البشري ممَّن استُقبلوا في مركز للإحالة بجمهورية إيران الإسلامية. وكانت غالبية المرضى من الذكور (13 مريضاً)، مع متوسط عمري بلغ 36.9 عاماً. وانتقل المرض في الذكور كافة عن طريق المخدَّرات حقناً، وعن طريق العلاقة الجنسية في سيدتين، كما سبق لاثنَيْ عشر منهم دخول السجون. وكان جميع المرضى مصابين بالسل الرئوي، و13 منهم إيجابيّ اللطاخة، كما كان لدى الجميع، باستثناء مريض واحد تظاهرات شعاعية لا نموذجية. وقد حدث التهاب الكبد بفعل العقاقير في ثلاثة مرضى، كما كانت هنالك عدوى مشتركة مع فيروس الالتهاب الكبدي "سي" في 12 مريضاً منهم. وقد توفي خمسة مرضى، وكان متوسط تعداد اللمفاويات التائية CD4 في المم^3 229.2 (مع انحراف معياري قدره 199.5)، في حين كان تعداد اللمفاويات التائية CD4 في المم^3 في 78.6٪ منهم أقل من 350. ويبدو أن مرض السل قد يعمل بمثابة الكاشف عن الإصابة بمرض الإيدز في هذا البلد.

ABSTRACT This case series describes the clinical and laboratory profile of 15 patients with tuberculosis (TB) HIV coinfection admitted to a referral centre in the Islamic Republic of Iran. Most of the patients (13) were male; the mean age was 36.9 years. Intravenous drug use was the route of transmission for all males and heterosexual intercourse for the 2 females; 12 patients had a history of imprisonment. All patients had pulmonary TB; 13 were smear-positive and all except 1 had atypical radiological presentation. Drug-induced hepatitis occurred in 3 patients and 12 had hepatitis C coinfection. Five patients died. The mean CD4 count was 229.2 (SD 199.5) cells/mm^3 and 78.6% had CD4 count < 350. TB may be an AIDS-defining illness in this country.

Profil clinique et biologique de patients présentant une co-infection par la tuberculose et le VIH dans un centre national spécialisé : série de cas

RÉSUMÉ Cette série de cas décrit le profil clinique et biologique de 15 patients atteints simultanément de tuberculose et d'infection à VIH qui avaient été admis dans un centre spécialisé de la République islamique d'Iran. La plupart des patients (13) étaient des hommes ; la moyenne d'âge s'élevait à 36,9 ans. La toxicomanie par voie intraveineuse était le mode de transmission pour tous les hommes et les relations hétérosexuelles pour les deux femmes ; 12 patients avaient connu la prison. Tous les patients étaient atteints de tuberculose pulmonaire ; 13 avaient un frottis positif et tous, à l'exception d'un, présentaient une image radiologique atypique. Trois patients avaient eu une hépatite médicamenteuse et 12 étaient contaminés par le virus de l'hépatite C (VHC). Cinq patients sont décédés. Le nombre moyen de CD4 était de 229,2 (écart type 199,5) cellules/mm^3 et 78,6 % avaient moins de 350 CD4. La tuberculose peut être une pathologie indicatrice du sida dans ce pays.

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Introduction

Tuberculosis (TB) remains one of the most important causes of mortality and morbidity in the world [*1*]. According to World Health Organization (WHO) estimates the total number of new TB cases in the year 2000 was 8.3 million, of which 9% were associated with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) [*1,2*]. In the same year, a total of 1.8 million people died because of TB, with 12% (226 000) of them suffering from both TB and HIV [*3*]. As the counterpart to this, HIV has resulted in a significant rise in TB cases in different regions of the world [*4*] and HIV/AIDS is thought to be associated with a high risk of transformation of TB infection to TB disease; in other words, the rate of TB reactivation is 5%–15% per year [*1*]. These patients are at high risk of acquiring new disease, probably due to the unbalanced secretion of cytokines from their lymphocytes [*5,6*].

During the process of HIV infection, multiple opportunistic infections occur, with TB being the most important. Also, in contrast to other diseases, TB can occur throughout the course of HIV infection [*7*]. Meanwhile, during the course of TB disease, both the virus burden and viral heterogeneity increases [*7*]. The close relation between HIV and TB and associated poverty leads to a complex situation that makes the implementation of TB control programmes very difficult [*8*]. The evidence suggests that cooperation is needed between national TB and HIV control programmes worldwide. Recognition of this fact has led WHO to adopt the motto of "2 diseases, 1 patient" and to renew efforts to fight TB [*9*].

In this article we describe the clinical and laboratory evaluations from a case series of patients with TB/HIV coinfection, in order to obtain a better picture of the clinical profile of these patients.

Methods

Setting

Masih Daneshvari hospital, Tehran, acts as the reference unit for the national tuberculosis programme (NTP) and is the only tertiary centre for the treatment of TB patients in the Islamic Republic of Iran. It is a WHO collaborative centre in the Eastern Mediterranean Region (EMR). This hospital has various diagnostic and therapeutic facilities, such as the mycobacteriology reference laboratory and bronchoscopy, pathology, radiology and thoracic surgery departments. Annually 600 patients with TB are admitted to the hospital, of whom approximately 3% are HIV positive.

Sample

All patients registered in the TB/HIV registry at Masih Daneshvari hospital during 2002–03 were enrolled in the study. The inclusion criteria were: standard serological confirmation of HIV infection [2 positive samples by enzyme-linked immunosorbent assay (ELISA) test and a single positive sample of Western blot test] and clinically and radiologically confirmed TB disease (more than 3 weeks coughing and other pulmonary symptoms compatible with TB) with further pathological and/or standard microbiological confirmation.

Data collection

A special questionnaire was designed to collect the necessary clinical and paraclinical data.

Sputum smear by Ziehl–Nielsen staining method was performed in our laboratory, which is a referral laboratory for the country. Meanwhile sputum culture was performed in Lowenstein–Jensen medium and the sensitivity test was conducted by the proportion method [*10*].

Flow cytometry was carried out with 2 cm^3 of peripheral blood and conjugated

dual colour antibody panel with fluorescein isothiocyanate and phycoerythrin colour (PE) (Becton Dickinson). The cluster of differentiation (CD) antibodies used were: CD3/CD4, CD3/CD19 and CD3/CD16+56. Using simulation software and fluorescence activated cell sorting, cellular counts were analysed by the flow cytometry technique. Based on CD4+ counts the patients were divided into< 200, 200– < 350, 350– < 500 and ≥ 500 cells/mm^3.

The white blood cell (WBC) counts of the patients were classified into 2 groups: < 4000 and 4000–8000 cells/mm^3. The erythrocyte sedimentation rate (ESR) was classified into: < 30, 30–60, 60–100 and > 100 mm/h. The normal haematocrit levels of the female and male patients were 36.1–44.3 and 40.7–50.3 mg/dL respectively.

Serological tests for hepatitis B (Diagnostic Automation) and C (Dia-Pro) were performed in our laboratory using the ELISA method. Positive cases of anti-hepatitis C virus (HCV) were further confirmed by polymerase chain reaction in the blood transfusion organization (the reference laboratory for HIV diagnosis).

The chest X-rays of the patients were reported by the radiologist of our centre and were divided into typical and atypical groups. Typical manifestations were when the lesions with postprimary or reactivation characteristics consisted of infiltrative or fibrocavitary opacities occurring in the superior lobe of the lung (apical or posterior segments). Atypical manifestation included: opacities in the middle and inferior lobes of the lung, opacity in the anterior segment of superior lobe, hilar adenopathy, mediastinal adenopathy, pleural effusion and diffuse interstitial nodular opacities. Sometimes normal chest X-ray was seen.

Analysis

The findings were analysed using *SPSS* for Windows, version 11. Means and standard deviation (SD) were calculated. Central indices for quantitative variables were calculated. Nominal variables were measured by the chi-squared test and when needed Fisher's exact test was applied. For variables with an abnormal distribution pattern, the Mann–Whitney U test was performed.

$P < 0.05$ was considered statistically significant.

Results

A total of 15 patients were enrolled in the study: 13 males (87%) and 2 females (13%). All were Iranian and resided in urban areas of the Islamic Republic of Iran. The mean age was 36.9 (SD 5.87) years, range 24–46 years. With regard to marital status, 11 were married, while 4 were unmarried. The route of transmission of HIV was intravenous drug use in 13 (87%, all the male patients) and heterosexual intercourse in 2 (all of the female patients).

Regarding their past history: 12 (80%) had a history of imprisonment, 13 (87%) had a history of smoking, 13 (87%) had dependence on intravenous heroin and 8 (53%) were alcohol dependent. None of the patients reported any previous illnesses. All of them suffered from pulmonary TB. In 2 patients (14%) extrapulmonary TB occurred simultaneously with pulmonary TB; 1 had tuberculous empyema and 1 had tuberculous pericarditis.

Sputum smear and culture were positive for acid-fast bacilli in 13 (87%) and 9 (60%) patients respectively. In 4 of the cases, the sputum culture was unknown. Antiobiotic sensitivity tests were performed for 9 of them; in 8 patients there was sensitivity to 4 drugs while 1 patient had isolated resistance to rifampicin.

The laboratory findings are summarized in Table 1. Anaemia was detected in 73% of patients, while white blood cell counts were

Table 1 **Laboratory findings for 15 HIV/AIDS patients with tuberculosis**

Parameter	Mean	SD	Range
Leukocyte count (cells/mm^3)	5 797.3	2 657.1	3 000–10 600
Haemoglobin (mg/dL)	10.5	1.7	7.8–13.6
Haematocrit (%)	32.5	5.5	26–41
Platelet count (/mm^3)	161 600	88 620	2 100–280 000
ESR (mm/h)	69.9	33.6	19–126
CD4 count (cells/mm^3)	229.1	199.5	8–627

SD = standard deviation.
ESR = erythrocyte sedimentation rate.

in the normal range in 75% (4000–8000 cells/mm^3). In 75% of the cases ESR was > 30 mm/h. The mean total CD4+ T-cell count was 229.15 (SD 199.45) cells/mm^3 with a range of 8–627 cells/mm^3.

Table 2 shows the distribution of CD4 counts among patients. In 50% of the cases the CD4 count was < 200 cells/mm^3, while in 79% it was < 350 cells/mm^3.

HCV was detected in 12 patients (80%) and the serology of HCV was unclear in 3. In all of the 10 patients with known serological evidence of hepatitis, there was no report of active hepatitis B. However, all were positive for anti-HBc [antibody to hepatitis B core antigen].

The following features were seen on radiology: 53% patients had adenopathy, 27% suffered from pleurisy and in only 1 patient cavitary lesions were observed. Upper and middle lower lobe involvement was seen in 47% and 73% of patients respectively. Reticular patterns and consolidation were observed in 47% and 27% of the patients respectively. Bronchiectasis (13% of cases) and pleural thickening (20%) were also noted.

Only 1 patient had a normal chest X-ray. In 40% of the cases there was bilateral involvement of the lungs. Regarding the radiological pattern, 1 case had typical manifestations of TB and the rest (14 patients) demonstrated atypical manifestations. In the 1 case with typical manifestations, the CD4 count was 240 cells/mm^3.

There were 3 patients (20%) who developed drug-induced hepatitis. The prevalence of opportunistic infections were: oral and pharyngeal candidiasis (60% of patients), toxoplasmosis encephalitis (1 patient), diffuse cytomegalovirus infection (1), cryptosporidiosis diarrhoea (1) and cryptococcal meningitis (1). One of the female patients suffered from moderate cervical neoplasia (stage CIN2).

Of the patients 13 received the standard 6 months therapy: 2 months isoniazid (IHN) + rifampicin (RIF) + ethambuthol (BMB) + pyrazinamide (PZA) and 4 months IHN + RIF. One patient with drug-induced hepatitis received INH and ETB for 18 months.

Table 2 **Frequency of CD4 counts for 14 HIV/AIDS patients with tuberculosis (1 patient had no CD4 count)**

CD4 count (cells/mm^3)	No. of patients	%
< 200	7	50
200–< 350	4	29
350–< 500	1	7
≥ 500	2	14

Another patient with resistance to RIF received treatment with PZA, ETB and INH for 12 month, and 3 patients (20%) had anti-retroviral treatment.

Improvement was seen in 10 (67%) while 5 (33%) patients died, including 1 who was receiving antiretroviral therapy. The causes of deaths were: unknown (2 patients), cryptococcal meningitis (1), cytomegalovirus diffuse infection (1) and myocardial infarction (1). There were no relapsing cases during follow-up; the mean length of follow-up was 6.5 months, minimum 4 months, maximum 1 year.

Comparing the patients with CD4+ counts < 200 and ≥ 200 cells/mm^3, statistical analysis showed significantly more men in the ≥ 200 CD4+ group ($P < 0.05$). No significant statistical differences were observed between the 2 groups with regard to the following variables: age, marital status, education, anaemia, opportunistic infections, haematological variables, ESR, serum adenosine deaminase, positive sputum smear and sputum culture. There was also no significant difference in the mortality rate of TB/HIV patients with CD4 counts < 200 and ≥ 200 cells/mm^3.

Discussion

After the detection and recognition of HIV in 1983, the declining curve of TB infection started to show a sudden rise during the 1990s [*11,12*]. At present, diagnosis and treatment of TB/HIV coinfection requires specialist and well-equipped dialogistic facilitates [*12,13*]. Anticipating the rising incidence of TB in the next 2 decades [*8,14*] diagnosis and treatment of this disease requires special attention. Unless and until HIV is controlled, and the poverty that is associated with TB is overcome, TB control and management will be impractical and unattainable [*8,13*].

From the epidemiological point of view our TB/HIV patients differed in some respects from those present in other parts of the world. Similar to other studies, we found that the majority of the patients were males and that all of the cases lived in urban areas [*14,15*]. In our country the major route of transmission of HIV is intravenous drug use, while in many countries the route is heterosexual intercourse [*15,16–18*].

Similar to other research the mean age of our patients was the third decade of life. Most of the patients did not report any previous known disease [*14,16*]. However, it is important to note that a past history of intravenous drug use and imprisonment was observed in nearly all of the male TB/HIV patients, a much higher rate than in other similar research [*14,15*]. Overall this difference could be explained by the pattern of HIV transmission in our country. It is notable that there is no significant dissimilarity between TB/HIV patients and HIV cases [*19*]. TB is the most important opportunistic infection occurring in HIV patients worldwide [*12,16,20–22*], with pulmonary TB being the most common form. However, extrapulmonary TB is much more commonly observed in HIV-positive patients. In our research 14% of the patients suffered from extrapulmonary TB, which is a slightly lower rate compared with other investigations [*23,24*], but is similar to another study [*20*]. None of our HIV patients showed atypical mycobacteria (nontuberculous mycobacteria) which agrees with reports of a low incidence of atypical mycobacteria from other developing countries [*18*].

From the diagnostic point of view, 87% of the patients had smear-positive TB. Despite the presence of a large number of patients with CD4 counts < 200 cells/mm^3, the above-mentioned rate was high compared with other research [*25–27*]. Also, sputum culture was positive in 60% of the cases. In

the remaining patients, reports of sputum culture were not available.

Out of 9 antibiogram reports, only 1 case of isolated resistance to RIF was reported. As seen in our results and other documents, HIV per se could not act as a predisposing factor for drug resistance [*28–32*]. Although there are reports showing a higher incidence of multi-drug resistant TB in HIV patients [*12*], no cases of multi-drug resistance were detected in our research. It is noteworthy that isolated RIF resistance is seen more often in HIV-positive patients; the mechanism of this is unclear [*31,32*].

In laboratory investigations, anaemia was detected in 73% of patients, while white blood cell counts were in the normal range in a majority of the patients. Three-quarters of patients had ESR > 30 mm/h. Similar to other areas of the world in which the major route of HCV transmission is intravenous drug use, our study also showed a high incidence of HCV infection (80%) [*14*]. In 3 of the patients the HCV serology was not clear. Regarding CD4 counts, 50% of patients had counts < 200 cells/mm^3, which agrees with other studies [*16,20,27*]. The incidence of drug-induced hepatitis was 20%, which could be expected because of the common occurrence of HIV and HCV coinfection [*33*].

Taking into account the radiological features, most of the patients had atypical TB presentation. Although adenopathy and pleurisy were observed in half of the patients, cavities were detected in only 1 case. Meanwhile, no major difference in radiological manifestations was detected between patients with CD4 counts < 200 and ≥ 200 cells/mm3, suggesting that there is no direct relationship between cavity formation and fibrotic changes with CD4 counts. The factors which are responsible for the appearance of radiological manifestations have not been fully established [*26*]. However, our study conflicts with the evidence that there are differences in the radiological manifestations of patients with CD4 counts < 200 and ≥ 200 cells/mm^3 [*34,35*]. Further work with larger sample sizes is needed to confirm the findings.

The mortality and morbidity rates in our study were 6 times higher than that of HIV-negative TB cases in our institute. This confirms other studies showing the higher mortality and morbidity rates of TB/HIV-positive patients as compared to HIV-negative patients [*26,27,36*]. Various studies have shown that TB is the commonest cause of death in HIV patients [*19,37*]. In this investigation, 60% of the deaths were due to non-TB causes, while in 2 it was unknown. It has been pointed out in different articles that although early deaths of TB/HIV-positive patients are often due to TB, mortality occurring later is usually the result of non-TB opportunistic infections [*27,33,36,39*]; thus opportunistic infections must be kept in mind [*26,27*]. For this reason, TB with its various types is regarded as an "AIDS-defining illness" [*26,38*]. It has been shown that with anti-TB treatment, the viral load and CD4 count in TB patients do not change significantly [*40*]. Only chemoprophylaxis with cotrimoxazole can decrease mortality and morbidity of these patients by 48% [*37*].

Conclusion

Our case series in a referral hospital in the Islamic Republic of Iran showed a high proportion of TB/HIV patients with low CD4 counts, with 79% having CD4 < 350 cells/mm^3. Also, opportunistic infections such as toxoplasmosis occurred in a number of patients. With further evaluations and larger sample sizes, more accurate statistical data would be obtained.

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Tuberculosis infection and transmission

Left untreated, each person with active TB disease will infect around 10–15 people every year. But people infected with TB bacilli will not necessarily become sick with the disease. When someone's immune system is weakened, the chances of becoming sick are greater. 5-10% of those infected with TB bacilli become sick or infectious at some time during their life. People infected with both HIV and TB are much more likely to develop TB disease.

In 2005, estimated per capita TB incidence was stable or falling in all six World Helath Organization (WHO) regions. However, the slow decline in incidence rates is offset by population growth. Consequently, the number of new cases arising each year is still increasing globally and in the WHO regions of Africa, the Eastern Mediterranean and South-East Asia.

In 2006, WHO launched the new Stop TB Strategy. The core of this strategy is DOTS, the TB control approach launched by WHO in 1995. Since its launch, more than 22 million patients have been treated under DOTS-based services. The new strategy builds on this success, while recognizing the key challenges of TB/HIV and MDR-TB. It also responds to access, equity and quality constraints, and adopts evidence-based innovations in engaging with private health-care providers, empowering affected people and communities and helping to strengthen health systems and promote research.

Source: Fact sheet N°104, available in Arabic, English and French (http://www.stoptb.org/resource_center/fact_sheets.asp).