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Pulmonary tuberculosis in the immunocompromised patients

Plućna tuberkuloza imunokompromitovanih bolesnika

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Abstract

Background/Aim. During the last few decades, immunocompromising diseases led to an increase in the number of tuberculosis cases. The aim of this study was to examine the influence of immunocompromising diseases on the course of tuberculosis. **Methods**. The research included two groups, each consisting of 40 subjects with tuberculosis, who were treated at the Institute for Pulmonary Diseases of Vojvodina during 2010 and 2011. The first group had no immunocompromising diseases (the kontrol group), whereas the second group contained patients with accompanying immunocompromising diseases. The data from the patients' medical history, from the Center for Microbiology and from the Radiology Center were used. The two groups were compared according to the following characteristics: age, sex, bacteriological status, radiological presence of the disease, presence of adverse effects of drugs, presence of resistance to drugs, duration of the therapy regimen and the duration of hospitalization. **Results**. The group of immunocompromised patients was older in average than the control group and included a higher percentage of males. The immunocompromised group had statistically important longer average time required for the sputum smear conversion ($p = 0.000$) and for the conversion of sputum cultures to *M. tuberculosis* ($p = 0.010$), more frequent presence of cavity ($p = 0.030$), longer average therapy regimen duration ($p = 0.000$) and higher average number of hospital days ($p = 0.000$) compared to the control group. The most frequent localization of changes in the immunocompromised patients was in all lobes of both lungs (32.5%) whereas the changes in the control group were mostly localized in the upper lung lobes (62.5%). There was no statistically important difference in the finding of sputum smear positive acid-fast bacilli on direct micoscropy, the presence of adverse effects of drugs and *M. tuberculosis* resistance to drugs between the two groups of patients. **Conclusion**. The immunocompromising diseases change the course of tuberculosis, primarily by affecting bacteriological status, radiological presentation, the length of therapy regimen and the duration of hospitalization.

Key words:
tuberculosis; immunocompromised host; prognosis.

Apstrakt

Uvod/Cilj. Imunokompromitujuće bolesti su tokom poslednjih decenija dovele do porasta broja obolelih od tuberkuloze. Cilj rada je bio da se ispita uticaj imunokompromitujućih bolesti na tok tuberkuloze. **Metode**. Ispitivanjem su obuhvaćene dve grupe od po 40 bolesnika obolelih od tuberkuloze koji su lečeni u Institutu za plućne bolesti Vojvodine tokom 2010. i 2011. godine. Prva grupa nije imala imunokompromitujuće bolesti (kontrolna grupa), dok su u drugoj grupi bili bolesnici sa pridruženim imunokompromitujućim bolestima. Korišćeni su podaci iz istorija bolesti, podaci Centra za mikrobiologiju i Centra za radiologiju. Dve grupe su poređene prema sledećim karakteristikama: starost, pol, bakteriološki status, radiološki nalaz, prisustvo neželjenih efekata lekova, prisustvo rezistencije *M. tuberculosis* na lekove, trajanje terapijskog režima i dužina hospitalizacije. **Rezultati**. Grupa imunokompromitovanih bolesnika je bila starija od kontrolne grupe i sa većom zastupljenošću muškog pola. Grupa imunokompromitovanih je imala statistički značajno duže prosečno vreme potrebno za direktnu konverziju sputuma ($p = 0,000$) i konverziju kultura sputuma na *M. tuberculosis* ($p = 0,010$), značajno češće prisustvo kaverne ($p = 0,030$), prosečno duže trajanje terapijskog režima ($p = 0,000$) i prosečno veći broj bolničkih dana ($p = 0,000$) u odnosu na kontrolnu grupu. Najčešća lokalizacija promena kod imunokompromitovanih je bila u svim režnjevima oba plućna krila (32,5%) dok su u kontrolnoj grupi promene bile najčešće lokalizovane u gornjim plućnim režnjevima (62,5%). Nije bilo statistički značajne razlike u nalazu mikobakterija u sputumu direktnom mikroskopijom, prisustvu neželjenih efekata lekova i prisustvu rezistencije na lekove između dve grupe bolesnika. **Zaključak**. Imunokompromitujuće bolesti menjaju tok tuberkuloze, prvenstveno utičući na bakteriološki status, radiološku prezentaciju, dužinu terapijskog režima i dužinu hospitalizacije.

Ključne reči:
tuberkuloza; imunokompromitovan domaćin; prognoza.

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Introduction

After human immunodeficiency virus (HIV) infection, tuberculosis is the second most frequent cause of death among infectious diseases in the world. Annually, 8–10 million people are infected, and around 2 million people die [1]. One person with active tuberculosis infects 10–15 individuals per year. It is believed that one third of the entire human population is infected with *Mycobacterium tuberculosis* (*M. tuberculosis*) [2]. The epidemiological situation of tuberculosis has changed during recent years, primarily due to an increasing number of patients with immunocompromising diseases (the patients with transplanted organs, patients undergoing immunosuppressive therapy, people infected with HIV, people suffering from malignant diseases, diabetes mellitus, liver cirrhosis, renal insufficiency, alcoholism) that change the course of tuberculosis infection [3, 4]. An increase in the number of these patients can be expected in the future [5].

Aquired cell mediated immunodeficiency is the most common kind of immunodeficiency and it is very important in pathogenesis of tuberculous infection. The patients who have impared cell mediated immunity are predominantly susceptible to infections caused by intracellular microorganisms including *M. tuberculosis* inside alveolar macrophages [3].

Individuals suffering from immunocompromising diseases with latent tuberculosis infection (LTBI) have an increased risk of developing active tuberculosis.

LTBI is a complex clinical condition where the exact biological status of *M. tuberculosis* is not sufficiently known. It is believed that during LTBI the bacteria persist in a subclinical state with minimum replication, and, therefore, do not cause a clinically manifested disease. It is believed that 5%–10% of individuals with LTBI have a risk of developing active tuberculosis. The greatest risk of LTBI developing into active tuberculosis occurs in the first two years when a half of the infected individuals become ill. The tuberculin test and the more recent interferon-gamma release assays (IGRA) tests are used for LTBI screening. The limitation of the tuberculin test is based on the fact that the test is a mixture of different antigens that are not specific for *M. tuberculosis*. Therefore, it cannot be determined whether the positive result comes from the response to the Bacillus Calmette-Guerin (BCG) vaccine *M. bovis*, *M. tuberculosis*, or non-tuberculosis *mycobacteria*. Unlike the tuberculin test, the IGRA test detects the presence of cellular immune response to antigens specific to *M. tuberculosis* so that the results of this test do not depend on the previous BCG vaccination or non-tuberculosis *mycobacteria* infection. Therefore, the application of IGRA tests has an advantage in the BCG vaccinated population [6]. In the immunocompromised individuals, the IGRA tests do not distinguish between latent or active tuberculosis. They play a role within the entire risk assessment for LTBI which entails insight into the epidemiological data, risk factors, radiogram, and tuberculin test. Following this assessment, if a patient is determined to be in a risk of developing active tuberculosis, chemoprophylaxis is administered [1]. The aim of this study is to point out the influence of immunocompromising diseases on the course of tuberculosis.

The HIV infected patients have dominantly impared cell immunity with lower number of CD4+ lymphocites. If these patients suffer from latent tuberculosis infection, they have 20–30 times higher risk to develop active tuberculosis then the immunocompetent persons. The HIV positive patients exhibit more frequent occurrences of disseminated and extrapulmonary forms of tuberculosis, more frequent occurrence of sputum smear negative pulmonary disease, and an atypical radiological presentation of changes in the patients with CD4+ lymphocyte number lower than 200 cells/uL. The adverse effects of drugs are also more frequent. Hepatotoxicity is connected to the overlapping of adverse effects of antituberculotics, antiretroviral therapy, antibiotics and antimycotics that are used simultaneously [7, 8]. It should be noted that rifampicin affects the metabolism of protease inhibitors by inducing cytochrome P450 enzyme system in the liver [7].

The patients with liver cirrhosis have increased risk to develop tuberculous infection due to the multifactorial process, dominantly reticuloendothelial system dysfunction. These patients more frequently exhibit extrapulmonary forms of tuberculosis with predominant peritoneal localization of the disease. The tuberculosis treatment regimen must be modified in accordance with the level of damage to the liver functions. Considering that the basal function of the liver is often disturbed, the most common adverse effect during the treatment is hepatotoxicity. Three out of four of the first-line antituberculotics are potentially hepatotoxic. Pyrazinamide is considered to be the most frequent cause of hepatotoxicity, followed by isoniazid, and thirdly by rifampicin. According to the recommendation of the World Health Organization (WHO), the larger extent of damage to the liver function, the smaller number of the hepatotoxic drugs can be used [9].

The patients with chronic renal failure have 10–15 times higher incidence of tuberculosis mostly due to impaired cellular immunity [10]. In those patients, tuberculosis is usually diagnosed later on, because of unspecific clinical signs and due to 50% more frequent occurrence of extrapulmonary form of the disease, especially with peritoneal localization. Mortality rate in the patients on hemodialysis who develop tuberculosis is two times higher compared to the patients without tuberculosis. The tuberculosis treatment regimes usually last six or nine months. Duration of treatment is individual reflecting the different clinical circumstances, immunosuppression level, or the spread of disease. Usually, the standard doses of antituberculotics are used and they are administered daily or in an intermittent therapy regimen, depending on the drug metabolism and creatinine clearance. Hemodialysis eliminates most of the antituberculotics, therefore they are administered after hemodialysis. The adverse drug effects are observed in a majority of cases, the most common being neurotoxicity, hepatotoxicity, and optic neuropathy [10, 11].

Systemic diseases are connected with the increased risk of tuberculosis infection. It remains unknown whether that risk is linked only to the use of immunosuppressive therapy or to the immunologic disease itself as well. The cases of ac-

tive tuberculosis were reported in the patients who used corticosteroid therapy in doses of 15–20 mg of prednisone or equivalent for a month or longer [12]. The cases of active tuberculosis following the usage of methotrexate and cyclophosphamide were also reported [13]. Recently, a biological therapy has been successfully applied in rheumatoid arthritis which entails the use of tumor necrosis alpha (TNF-alpha) inhibitors. TNF-alpha is an important proinflammatory cytokine which plays an important role in the tuberculosis granuloma formation. There is an increasing amount of data that suggests that the use of these drugs is linked to the risk of developing active tuberculosis [14, 15].

In the patients with malignancies, the increased risk of developing tuberculosis occurs due to the drop in immunity conditioned by the local or systemic effect of the tumor mass itself, or as a consequence of chemo- and radiotherapy [16].

The patients with transplanted organs require the application of immunosuppressive therapy with the aim of preventing the rejection of organs which significantly increases the risk of active tuberculosis [3, 4, 11].

Alcohol is the most commonly abused substance throughout numerous countries [17]. The chronic alchocolics have impaired the neutrophils function and the impaired alveolar macrophage phagocytosis and superoxide production. T cells of the alchoholics show the impiared delayed type hypersensitivity responses. It has been proven that individuals who use more than 40 g of alcohol per day are three times more likely to develop active tuberculosis [17–20].

Diabetes mellitus is predisposing factor for developing tuberculous infection. The frequency of tuberculosis is four times higher in diabetics then in nondiabetics [21]. The diabetic patients show the neutrophil and macrophage disfunctions which includes: impared chemotaxis, adherence, phagocytosis and ability to kill the phagocyted microorganisms. These patients show alternations in the T lymphocyte subsets. Tuberculosis incidence among the diabetics increases proportionally with the duration of the diabetes and the increase of insulin doses required for glucoregulation [22, 23]. If diabetes is well-regulated, the course of tuberculosis and the response to the antituberculotics therapy shows no significant difference compared to the individuals without diabetes, whereas poorly-regulated diabetes has a negative impact on the course of pulmonary tuberculosis [24].

Methods

The research included two groups, each consisting of 40 subjects with recently diagnosed pulmonary tuberculosis who were treated at the Institute for Pulmonary Diseases of Vojvodina during 2010 and 2011. The first group consisted of patients with pulmonary tuberculosis without accompanying immunocompromising diseases whereas the other group contained the patients with pulmonary tuberculosis with accompanying immunocompromising diseases, including: diabetes mellitus (27 patients), use of alchohol (9 patients), liver cirrhosis (2 patients) and malignancy (2 patients). The HIV positive patients were not included in the examined sample. The patients were analyzed and the two groups were compared according to the following characteristics: age, sex, bacteriological status, radiological presentation of the disease, presence of adverse effects of drugs, presence of resistance to antituberculotics, duration of the therapy regimen in months and the duration of hospitalization. The data from the patients' medical history, from the Center for Microbiology and from the Radiology Center of the Institute for Pulmonary Diseases of Vojvodina were used.

The collected data were analyzed on the level of descriptive statistics by the measures of central tendency (arithmetic mean) and measures of variability (standard deviation), as well as on the level of percentage representation of certain variable categories. On the level of inferential statistics, the significance of the research hypotheses was tested by using the χ^2 test and the Student's *t*-test. The statistical data were processed by using the statistical program package SPSS 16.0.

Results

As seen in Table 1, the group of patients suffering from tuberculosis with accompanying immunocompromising diseases was older in average than the group of subjects suffering from tuberculosis, but without accompanying immunocompromising diseases. While the group of patients with tuberculosis without accompanying immunocompromising disease had slightly more women (52.5%), the group of tuberculosis patients with accompanying immunocompromising diseases had significantly more male patients (77.5%). In the group of patients with accompanying immunocompromising conditions, diabetes mellitus was the most common, followed by the use of alcohol. The number of patients with liver cirrhosis and malignancies was significantly smaller (Table 1).

By analyzing the frequency of presence or absence of finding sputum smear positive acid-fast bacilli on direct microscopy between the tested groups of subjects, no statistically significant difference was found (χ^2 = 0.457; p = 0.499). By using the *t*-test, a statistically significant difference was determined between the average length of time required for the sputum smear conversion (t = -7.532; p = 0.000) and the average length of time required for the sputum culture conversion (t = -6.403; p = 0.010) between the two groups of patients. In both cases, the group of patients with immunocompromising diseases had longer average time required for the sputum conversion to *M. tuberculosis* (Table 2).

By analyzing the frequency of presence or absence of cavities, a statistically significant difference could be noted between the groups, where a significantly higher number of patients with cavities was observed among the patients with tuberculosis and accompanying immunocompromising diseases (χ^2= 4.713; p = 0.030). A statistically im significant portant difference between the two groups of patients was also present in relation the affected area of the lung lobes. In the group of patients without accompanying immunocompromising diseases, only the upper lobe was affected in the majority of patients; on the other hand, in the group of patients with immunocompromising diseases, all lobes of both lungs were affected in the majority of patients (χ^2= 16.358; p = 0.006) (Table 3).

Table 1

Distribution of patients according to age, sex, and accompanying immunocompromising diseases

Sample description	Tuberculosis without accompanying diseases (n = 40)	Tuberculosis with accompanying diseases (n = 40)
Age (years), mean ± SD (range)	51.87 ± 18.83 (19–84)	61.55 ± 12.13 (25–83)
Sex, n (%)		
males	19 (47.5)	31 (77.5)
females	21 (52.5)	9 (22.5)
Immunocompromising conditions, n (%)		
diabetes mellitus		27 (67.5)
alcohol abuse		9 (22.5)
liver cirrhosis		2 (5.0)
malignancy		2 (5.0)

SD – standard deviation.

Table 2

Mycobacteriological status of the patients

Parameter	Patients without accompanying diseases (n = 40)	Patients with accompanying diseases (n = 40)
Sputum smear positive, n (%)		
no	6 (15.0)	4 (10.0)
yes	34 (85.0)	36 (90.0)
Time required for sputum smear conversion (days), mean ± SD	20.91 ± 6.70	40.64 ± 13.80
Time required for the *M. tuberculosis* culture conversion (days), mean ± SD	32.37 ± 8.12	47.67 ± 12.74

SD – standard deviation.

Table 3

Radiological presentation of pulmonary tuberculosis

Parameter	Tuberculosis without accompanying diseases (n = 40)	Tuberculosis with accompanying diseases (n = 40)
Cavity, n (%)		
no	17 (42.5)	8 (20.0)
yes	23 (57.5)	32 (80.0)
Affected lobes, n (%)		
only upper	25 (62.5)	8 (20.0)
only middle	1 (2.5)	1 (2.5)
upper and middle	6 (15.0)	12 (30.0)
lower and middle	1 (2.5)	4 (10.0)
lower and upper	0 (0.0)	2 (5.0)
all lobes of both lung	7 (17.5)	13 (32.5)

Table 4

Drug susceptibility, adverse drug reactions and length of tuberculosis treatment

Parameter	Tuberculosis without accompanying diseases (n = 40)	Tuberculosis with accompanying diseases (n = 40)
Resistance to drugs, n (%)		
no	40 (100.0)	38 (95.0)
yes	0 (0.0)	2 (5.0)
Adverse drug effects, n (%)		
no	28 (70.0)	29 (72.5)
yes	12 (30.0)	11 (27.5)
Length of hospitalization (days), mean ± SD	38.98 ± 11.44	58.00 ± 17.03
Length of treatment (month), mean ± SD	6.25 ± 0.67	6.75 ± 0.98

SD – standard deviation.

Between the examined groups, no statistically significant difference was recorded in the frequency of presence of adverse effects of drugs (χ^2= 0.061; p = 0.805) as well as in resistance to drugs (χ^2= 2.051; p = 0.152). In both groups, a significantly higher number of patients did not have the adverse effects of antituberculosis drugs, nor resistance to the drugs. In the group of patients with accompanying immunocompromising diseases, there were two patients with drug resistant tuberculosis. In the first case it was monoresistance to isoniazid, and in the second case polyresistance to isoniazid and streptomycin. By using the *t*-test, a statistically significant difference between the two groups was determined in terms of the average length of hospitalization (t = -5.864; p = 0.000) where the group of patients with accompanying

immunocompromising diseases exhibited longer hospitalization time compared to the group without accompanying immunocompromising diseases. A statistically important difference between the two groups of patients was also determined in terms of the average length of treatment expressed in months (t = -2.663; p = 0.000). In this case as well, the group of patients with accompanying immunocompromising diseases exhibited longer average length of treatment (Table 4).

Discussion

The group of tuberculosis patients with accompanying immunocompromising diseases in this study was mostly comprised of diabetics (67.5%) and a significantly lower number of patients who abuse alcohol (22.5%), the patients with liver cirrhosis and patients with malignancies (5% in both cases). A majority of published results refer to the course of tuberculosis in diabetics and the HIV positive individuals (the latter were not included in the examined sample), while considerably less data can be found on the influence of other immunocompromising conditions on the course of tuberculosis [25]. For this reason, the obtained results were mostly compared to the results of the authors who researched the influence of diabetes on the course of tuberculosis infection.

The results of this study showed that the group of patients with accompanying immunocompromising diseases was older in average and consisted of a substantially higher percentage of males than the control group. These results coincide with the results of other authors. In a study conducted by Perez-Guzman et al. [26], the group of tuberculosis patients with diabetes was older in age than the group of patients with tuberculosis in the control group. A study done by Singla et al. [27] also showed that the group of tuberculosis patients with accompanying diabetes was considerably older with a higher percentage of males. The individuals who abused alcohol were exclusively males which coincides with the results of other authors. This was probably conditioned by some social prejudices towards female alcoholics because of which women are less likely to admit that they have an alcohol abuse problem[18].

In terms of bacteriological status, the results of this study pointed to a slightly higher frequency of sputum smear findings on direct microscopy and statistically significantly longer time required for the sputum smear conversion and the conversion of sputum cultures to *M. tuberculosis* in the group of patients with immunocompromising diseases. The acquired results were probably linked to the higher frequency of cavity occurrence in this group of patients (although results of some studies are opposite, denying the role of cavities on sputum positivity). In studies that were conducted earlier, different results were reached in terms of the bacteriological status of patients. Yurteri et al. [21] proved that there was a lower number of patients with positive sputum smear among diabetics. In their study, Jabbar et al. [28] reached a different result that showed a higher number of patients with positive sputum smear among diabetics, and a longer time required for the conversion of *M. tuberculosis* sputum cultures. Singla et al. [27] also proved that diabetics require longer time for the conversion of sputum cultures to *M. tuberculosis*. In a study conducted in North Carolina, Fiske et al. [29] proved that there was a higher frequency of patients with positive sputum smear among the individuals who used alcohol excessively.

In terms of radiological presentation of pulmonary changes, this study proved that there was a statistically significant higher occurrence of cavities and atypical radiological presentation of pulmonary tuberculosis in the group of patients with immunocompromising diseases. These results were in concordance with the results of certain authors. Yurteri et al. [21], Perez-Guzman et al. [26] and Singla et al. [27] published that the occurrence of cavities was significantly higher among diabetics. On the other hand, in a study conducted by Jabbar et al. [28] a more rare occurrence of cavities among diabetics was proven. Bacakoglu et al. [30] proved that there was no difference in the frequency of cavity occurrence between the diabetics and individuals without diabetes. In their study, Kiyan et al. [25] reached results that showed no significant difference in the frequency of cavity occurrence between the immunocompromised individuals (who are not HIV positive) and immunocompetent individuals, whereas Fiske et al. [29] proved that there was a higher frequency of cavity occurrence among the alcoholics. Perez-Guzman et al. [26], Jabbar et al. [28] and Singla et al. [27] published results showing that the majority of diabetics had radiological changes in lower lobes. On the other hand Yurteri et al. [21] published that the atypical radiological presentation of tuberculosis was present only in a minor number of patients with tuberculosis and accompanying diabetes.

This study found no statistically important difference in the presence of adverse antituberculotics effects between the two groups of patients. The percentage of patients who showed the adverse effects in both groups matched the results of other authors [31]. In a study conducted by Kumar et al. [9], the patients with liver cirrhosis demonstrated hepatotoxicity in 17% of the cases, but there was no statistically important difference compared to the patients without liver cirrhosis.

This study found no statistically important difference in the presence of resistance to antituberculotics between the two groups of patients. The obtained result was in accordance with the fact that the examination included newly-diagnosed tuberculosis cases and that the therapy regimen of the majority of patients were not interrupted due to the demonstrated adverse effects of antituberculotics. Furthermore, the examination did not include the patients with multiresistant tuberculosis. According to this facts, two patients who had drug resistant tuberculosis probably were initially infected with drug-resistant strains of *M. tuberculosis* (transmitted or primary drug resistant tuberculosis) [32]. The results of other authors differ to a great extent among themselves. Bashar et al. [33] proved a significantly more frequent occurrence of multiresistant tuberculosis among diabetics. Contrary to their results, Yurteri et al. [21] found multiresistant tuberculosis in few diabetics only. Singla et al. [27] proved the resistance to antituberculotics was significantly rarer among diabetics, while there was no significant difference in the oc-

currence of multiresistant tuberculosis between the two groups of patients.

This study proved that a statistically significant longer therapy time was required in the group of immunocompromised patients which coincided with the results of certain authors [23, 24]. The result is probably a consequence of the longer time required for the sputum smear conversion and the conversion of sputum cultures to *M. tuberculosis*, and the slower radiological regression in immunocompromised patients as well. Results published by Singla et al. [27] confirmed that diabetes did not affect the duration of therapy regimen, while other authors published opposite results.

This study proved that the group of immunocompromised patients had a statistically significant higher average number of hospital days. This result is linked to more frequent cavity presence and longer time required for the sputum smear conversion and the conversion of sputum cultures to *M. tuberculosis* [26, 28].

Conclusion

Immunocompromising diseases affect the course of pulmonary tuberculosis. This primarily refers to the bacteriological status (meaning longer time required for the sputum smear conversion and the conversion of sputum cultures to *M. tuberculosis*), radiological presentation of the disease (more frequent cavity occurrence and atypical localization of changes), duration of the therapy regimen (longer duration in the immunocompromised patients), and the duration of hospitalization (the immunocompromised patients have more hospital days). There is no significant difference between the two groups in exhibiting the adverse effects of antituberculotics and exhibiting the resistance to antituberculotics.

The results of this study may be useful during diagnostics and treatment of tuberculous patients with accompanying immunocompromising diseases.

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