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CLINICAL PICTURE OF PULMONARY TUBERCULOSIS AT THE END OF THE SECOND MILLENNIUM*

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SUMMARY – Over the last 120 years, a great progress has been made in the diagnosis and treatment of pulmonary tuberculosis. In Western Europe, the incidence of pulmonary tuberculosis was 700/100,000 at the beginning, and 10-20/100,000 at the end of the 20th century. Changes in the epidemiological pattern entailed modifications in the clinical picture of pulmonary tuberculosis over the mentioned period of time, so that at the end of the century (and millennium) four forms of the disease could be defined: 1) active pulmonary tuberculosis in patients with post-tuberculosis sequels; 2) active pulmonary tuberculosis not associated with other diseases; 3) active pulmonary tuberculosis associated with chronic diseases; and 4) active pulmonary tuberculosis in immunocompromised patients. It is emphasized that an increase in the number of group 3 and 4 active pulmonary tuberculosis patients should be expected in the third millennium. The detection and management of these patients are difficult and complex. The detection of pulmonary tuberculosis is relatively late, while the treatment often fails and leads to development of resistant *Mycobacterium tuberculosis* strains. The existent problems encountered in the management of tuberculosis patients could be minimized by the use of DOTS program, recommended by the World Health Organization and also by the Ministry of Health of the Republic of Croatia.

Key words: *Tuberculosis pulmonary, epidemiology; Tuberculosis pulmonary, prevention and control*

Introduction

In the last 120 years, the diagnosis and treatment of pulmonary tuberculosis have seen considerable advancement. This progress has primarily been owing to the leading figures as R. Koch, who discovered *Mycobacterium (M.) tuberculosis* in 1882; K. Röntgen, who discovered x-rays in 1895; Calmette and Guerin, who reported on the discovery of tuberculosis vaccine in 1924; Waksman, who discovered streptomycin in 1944; and Robitzek and Salikof, who reported on the discovery of isoniazid in 1952. These ingenious discoveries have certainly contributed to the decrease in the incidence of tuberculosis in Western Europe from 700/100,000 at the beginning to 10-20/100,000 at the end of the 20th century[1]. In the '80s, a low incidence of pulmonary tuberculosis was recorded in the Western countries, having given rise to hope it would not present a medical and public health problem in the third millennium. Misled by this line of reasoning, the antituberculotic care service was dissolved in the USA in 1985, which turned out to be a mistake. Pulmonary tuberculosis surveillance was soon lost, entailing epidemics in particular cities, especially among HIV infected individuals, with consequential rapid development of resistant myocobacteria[2]. Now, the global situation with pulmonary tuberculosis is by no means good, as one third of the population are infected with *M. tuberculosis,* 50 million of them

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with resistant agents. About 10 million people are affected with, and about 3 million die from pulmonary tuberculosis every year. The number of individuals affected with pulmonary tuberculosis has been anticipated to increase in the next 10 years, primarily due to the rising number of immunocompromised patients such as those with HIV infection, transplanted organs, malignant diseases, on chronic dialysis, and on immunosuppressive therapy[3,4]. Changes in the epidemiological pattern during the last hundred years entailed modifications also in the clinical picture of pulmonary tuberculosis. Thus, the clinical picture of pulmonary tuberculosis at the beginning of the 20th century differed substantially from the clinical picture of the disease observed today, and can be basically classified into four forms: 1) active pulmonary tuberculosis in patients with post-tuberculosis sequels; 2) active pulmonary tuberculosis not associated with other diseases; 3) active pulmonary tuberculosis associated with chronic diseases; and 4) active pulmonary tuberculosis in immunocompromised patients.

1) Active Pulmonary Tuberculosis in Patients with Post-tuberculosis Sequels

This group includes elderly patients who underwent treatment with a collapse method (thoracoplasty, extrapleural pneumolysis, phrenicotomy, artificial pneumothorax) some 50 years ago. At present, their clinical picture is generally predominated by chronic obstructive pulmonary disease (COPD), chronic pulmonary heart, and chronic respiratory insufficiency. In these patients, pulmonary tuberculosis which may not always be easily demonstrable, may reactivate at any moment. Tuberculosis reactivation is clinically manifested with subfebrile body temperature, coughing, excessive perspiration, loss of appetite, emaciation, and general exhaustion. Auscultatory finding is non-characteristic, while laboratory findings may show normal leukocyte count and signs of anemia due to chronic infection. Radiologic diagnosis of reactivated pulmonary tuberculosis is hampered by massive pathomorphological and anatomical changes of pulmonary parenchyma and mediastinum. Therefore, computed tomography (CT) of the thorax may occasionally be required, as it can better differentiate recent changes from previous lesions. Gallium scintigraphy can also be helpful in the diagnosis of pulmonary tuberculosis reactivation, because the radioactive medim is accumulated in recent foci[5]. Reactivation of pulmonary tuberculosis is definitely demonstrated by the finding of *M. tuberculosis* in sputum.

Current treatment of pulmonary tuberculosis includes six-month 2 HRZE/4 HR+ (H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin; Z = pyrazinamide) regimen, with dose reduction in elderly patients (H, 5 mg/kg; R, 450 mg; E, 20 mg/kg; Z, 1.5 g; S, 0.5 g)[6]. The number of tuberculotic patients from this group is small, and they will only sporadically be seen in the third millennium.

2) Active Pulmonary Tuberculosis not Associated with Other Diseases

This group of pulmonary tuberculosis patients prevailed in Europe until the introduction of antituberculotics. In Croatia, their number was relatively high until the late '70s. These mostly were young and middle-aged patients with exudative forms (caseous pneumonia, cavernous disseminated tuberculosis), productive forms (fibroulcerative tuberculosis, fibroproductive tuberculosis), and hematogenous forms (miliary tuberculosis). The exudative and hematogenous forms usually presented with a clinical picture of acute disease (high body temperature, dyspnea, coughing, hemoptysis, emaciation, weight loss, etc.), as differentiated from the productive forms that proceeded subclinically with mild symptoms. Such 'pure' forms of pulmonary tuberculosis have recently been ever less frequently encountered, anticipating their further reduction in the next millennium. In the treatment for these types of pulmonary tuberculosis, the six-month 2 HRZE/4 HR regimen is used. The post-tuberculosis sequels are minimal provided the treatment has been properly performed. However, inappropriate treatment results in chronic BK positivity, frequently with resistant *M. tuberculosis* strains.

3) Active Pulmonary Tuberculosis Associated with Chronic Diseases

This group of patients generally includes elderly individuals with poor socioeconomic status, poor home care and inadequate family concern, in whom two, three or more organic systems have been seriously impaired (e.g., chronic cardiac, renal, hepatic, pulmonary, psychiatric diseases, diabetes mellitus, alcoholism, rheumatism, and stroke). In these patients, the symptoms of pulmonary tuberculosis overlap with the symptoms of other chronic diseases, thus it is no surprise that they are initially managed at internal wards, while the diagnosis of pulmonary tuberculosis is made relatively late. Clinically, they present

general fatigue, subfebrile body temperature persisting for weeks or months, thinning, and of respiratory symptoms coughing and occasionally hemoptysis. The diagnosis is quite difficult to make due to the patient noncooperativity. Radiologic finding is not as characteristic as in the former two groups. The specific pathomorphological substrate may be masked by pulmonary alterations due to other chronic diseases such as chronic cardiac arrest, uremic lungs, rheumatic infiltration, abscessing pneumonia in alcoholics, pleural effusion in cirrhosis, etc. Thoracic CT and gallium scintigraphy may help make the diagnosis[5,7]. The treatment is primarily based on the bacteriologic verification of *M. tuberculosis;* very rarely, antituberculotics are administered *ex iuvantibus* (on the basis of clinical picture and laboratory findings), because the addition of three or four drugs in a chronic patient already taking a number of medicaments means a considerable additional load. In these patients, the antituberculotic therapy is by no means easy to administer, and may sometimes even prove unsuccessful. The patients frequently show low medication compliance or even refuse it on the excuse of being 'heavy'. Side effects and complications may develop requiring therapy discontinuation, which is the easiest way for the development of resistant strains[8]. Attention should especially be paid to the treatment of active pulmonary tuberculosis in patients with hepatic and renal insufficiency.

Pulmonary tuberculosis in patients with liver cirrhosis, hepatitis and icterus is treated with three nonhepatotoxic drugs: streptomycin 1.0 g (0.75 g) *per* day, to a total of 60 g; ethambutol 25 mg/kg/day; and Terizidon 3 capsules a 250 mg. Isoniazid (5 mg/kg) and rifampicin (450 mg) should be introduced as soon as possible, however, if it is not possible due to pathologic liver findings, quinolones are added to therapy (ofloxacin, ciprofloxacin). The treatment is performed for 9-12 months[9].

There still are some controversies concerning the treatment of pulmonary tuberculosis in patients with chronic renal insufficiency. Some authors consider that the dose of antituberculotics should be reduced according to creatinine clearance levels, whereas others suggest that there is no need of dose adjustment, only the drugs should be taken intermittently. This especially holds for nephrotoxic drugs such as streptomycin, pyrazinamide and ethambutol. Rifampicin is excreted by the liver, therefore it should be administered in total dose every day, and isoniazid in a dose of 300 mg/day on five days of the week. Accordingly, the antituberculotic medication schedule in patients with renal insufficiency is as follows:

– isoniazid – 300 mg on 5 days of week for 6 months
– rifampicin – 600 mg (450 mg) *per* day for 6 months
– ethambutol – 25 mg/kg 3x *per* week for 2-3 months
– pyrazinamide – 1.5-2.0 g 3x *per* week for 2-3 months

In patients on chronic dialysis, a total dose of antituberculotics is administered 6 h before dialysis[10].

In chronic cardiac patients with active pulmonary tuberculosis, care should be taken of possible interactions of isoniazid and rifampicin with cardiac agents. Rifampicin diminishes the pharmacologic effect of aminophylline, beta-blockers, calcium antagonists and digitalis; isoniazid increases the level of aminophylline; and propranolol slows down the isoniazid breakdown.

4) Active Pulmonary Tuberculosis in Immunocompromised Patients

This group includes patients with HIV infection and clinical picture of AIDS on long-term immunosuppressive therapy (corticosteroids, cyclosporin, etc.), organ transplantation, rheumatoid arthritis, immunoproliferative diseases, etc.

Patients with inactive pulmonary tuberculosis and subsequent HIV infection soon progress to active pulmonary tuberculosis, while patients with HIV infection and without pulmonary tuberculosis easily acquire *M. tuberculosis* infection from the bacillus expectorating subjects[11]. The reason is the same in both cases. HIV infection impairs immunity and weakens the body's mechanisms of defense, thus allowing for the infection to develop. It is considered that in HIV-infected individuals, the infection with tuberculotic (*M. tuberculosis*) and nontuberculotic mycobacteria (*M. avium/intracellulare* complex (MAC) occurs when the CD4+ count falls below 100/mm^3.[12,13] The clinical picture of pulmonary tuberculosis in HIV-infected patients differs substantially from the usual clinical picture of the disease. Clinically, general symptoms (febrility, thinning, diarrhea, fungal infections, herpes zoster) and generalized lymph node enlargement predominate; miliary tuberculosis is frequently present; and atypical localizations of tuberculous foci such as tuberculoma of the brain, spleen, thorax, etc. are by no means infrequent. Radiologic finding is atypical, regularly showing mediastinal lymphonodi, basal infiltrations tending to migrate, and pleural effusions, while cavernization is rarely observed. The diagnosis of tuberculosis is made on the basis of positive *M. tuberculosis* in the sputum, blood, effusion and other specimens, and histologic analysis of the compro-

mised tissue. The treatment as a rule consists of the six-month regimen with four ATL in the first two months (2 HRZE), followed by two drugs (4 HR) for another four months, or according to some authors for six months postnegativization.

Patients with active pulmonary tuberculosis associated with chronic diseases and HIV infection are highly susceptible to the development of resistant *M. tuberculosis* strains, which may cause complete therapeutic failure[14]. In most cases, it is secondary resistance, rarely natural or primary resistance. Secondary resistance develops during the course of therapy, due to an error made by the physician, patient, or both. In case of monoresistance, antituberculotics to which the causative agent is sensitive are prescribed. The situation is more difficult in polyresistance, and very difficult in multiresistance (MDR)[15]. In these cases, quinolones (ofloxacin, ciprofloxacin), aminoglycosides (amikacin), or macrolides (clarithromycin) should be introduced in therapy[16].

The management of resistant tuberculosis is expensive for the society, painstaking for the patient, and difficult and risky for the medical personnel involved, while the results of treatment are quite poor. In Croatia, there are 2.2% of patients resistant to one or more antituberculotics, 0.5% of them relating to multiresistant strains. Therapeutically and prognostically, multiresistant patients generally fall into the same category with AIDS patients, however, the issue of resistant tuberculosis has by no means been given due consideration as AIDS at the national level, although the two diseases bear an equal life-threatening risk and lethality. Therefore, health care service should be so organized as to prevent the development of resistant *M. tuberculosis* strains, which could be achieved by implementing the DOTS program, recommended by the World Health Organization and Ministry of Health of the Republic of Croatia[17-19].

In immunocompromised patients, beside *M. tuberculosis* infection, infections with nontuberculous human pathogenic ubiquitary mycobacteria may occur, which clinically and radiologically bear great semblance with active tuberculosis. Among nontuberculous mycobacteria, MAC is most commonly reported. These infections are more common in elderly patients. The disease is chronic, manifesting with coughing, expectoration, febrility, and faint auscultation finding of the lungs. Radiologic alterations are similar to those seen in pulmonary tuberculosis, visualized as subpleural and subapical infiltrates with a tendency to disintegration and fibrozation. The diagnosis is made on the basis of bacteriologic verification of MAC in the sputum or blood in case of a disseminated form of disease. MAC infection should be suspected when antituberculotic therapy fails in the presence of clinical and radiologic findings indicative of tuberculosis[20]. The treatment is long-term, performed for at least 12 months with five drugs, including two basic (rifampicin and ethambutol) and three adjuvant (clarithromycin, amikacin, ciprofloxacin, azithromycin, clafamizin) drugs, and can be prolonged for up to 24 months[10].

In conclusion, 'comfortable' management of pulmonary tuberculosis will have been left behind in the second millennium. In the third millennium, the occurrence of pulmonary tuberculosis asssociated with other chronic diseases also in immunocompromised patients should be expected, which will require much patience and good internist knowledge from pulmonologists. We do believe that pulmonologists will find way to manage this new *M. tuberculosis* challenge successfully.

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Sažetak

KLINIČKA SLIKA PLUĆNE TUBERKULOZE NA KRAJU DRUGOG TISUĆLJEĆA

I. Grbac, S. Smolčić, D. Jurman i S. Broz

U posljednjih 120 godina učinjen je velik napredak u dijagnostici i liječenju plućne tuberkuloze. Incidencija tuberkuloze u zapadnoj Europi na početku bila je 700/100.000, a na kraju stoljeća 10-20/100.000. Promjenom epidemiološke situacije kroz navedeno razdoblje mijenjala se i klinička slika tuberkuloze, koja bi se na kraju stoljeća (tisućljeća) mogla definirati u četiri oblika: 1. aktivna plućna tuberkuloza u bolesnika s poslijetuberkuloznim posljedicama; 2. aktivna plućna tuberkuloza bez drugih popratnih bolesti; 3. aktivna plućna tuberkuloza s popratnim kroničnim bolestima; i 4. aktivna plućna tuberkuloza u imunokompromitiranih bolesnika. Ističe se kako u trećem tisućljeću treba očekivati porast bolesnika s aktivnom plućnom tuberkulozom treće i četvrte skupine. Napominje se kako je otkrivanje i liječenje ovih bolesnika teško i složeno. Tuberkuloza se otkriva relativno kasno, liječenje je često neuspješno i brzo dovodi do razvoja rezistentnih sojeva *Mycobacterium tuberculosis.* Primjenom programa DOTS koji preporuča Svjetska zdravstvena organizacija i Ministarstvo zdravstva Republike Hrvatske postojeći bi se problemi u zbrinjavanju tuberkuloznih bolesnika mogli svesti na najmanju moguću mjeru.

Ključne riječi: *tuberkuloza plućna, epidemiologija; tuberkuloza plućna, prevencija i suzbijanje*