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Thematic Article

The Role of Thoracic Surgery in Treatment of Lung Tuberculosis

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Abstract

Tuberculosis is a chronic progressive infections caused by acid-alcohol-resistant bacilli *Mycobacterium tuberculosis*. Tuberculosis has many manifestations, affecting bone, the central nervous system, and many other organ systems, but it is primarily a pulmonary disease that is initiated by the deposition of *Mycobacterium tuberculosis*, contained in aerosol droplets, onto lung alveolar surfaces. Contained in aerosol droplets tuberculosis bacillus comes to terminal alveoli, usually subpleural localization, predominantly in the lower parts of the lungs, and is usually implanted only in one place in the lungs. The strength of the host cellular immune response determines whether an infection is arrested or progresses to the next stages. In about 10% of patients, latent tuberculosis infection develops into an active disease, although the percentage is largely dependent on the patient's lifespan and other risk factors. Lung tuberculosis is often suspected based on radiographs of the chest caused by non-specific respiratory symptoms (coughing lasting for three weeks, haemoptysis, chest pain, difficulty breathing), febrile state of unknown etiology, or positive tuberculin skin test. If a person with risk factors for tuberculosis is a radiographic image very characteristic (cavitation in the upper lobe), it is still necessary to examine sputum, but the skin test is often not performed. The finding of acidoalcohol resistant bacteria in the sputum provides a strong assumption that it is tuberculosis, but the final diagnosis requires the cultivation of sputum culture, or a positive rapid molecular test. In immunocompetent patients with pulmonary tuberculosis, which is sensitive to medications, even severe illness and large cavitation are recovered quickly if appropriate treatment is carried out. Drugs for the first choice for the treatment of tuberculosis are: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) and are administered together in the initial phase of treatment. Standard chemotherapy consists of six months of rifampicin and isoniazid, initially supplemented by two months of pyrazinamide and ethambutol.

The successes in the medicament treatment of pulmonary tuberculosis have been influenced by the fact that surgical treatment of this disease is rarely applied today. Therefore, surgical treatment is not an independent method, but it is only one phase in therapy of tuberculosis.

Keywords: *Lung Tuberculosis; Medicament Treatment; Surgical Treatment; Tuberculous Pleural Effusion; Bronchopleural Fistula; Tuberculous Empyema*

Abbreviations

TB: Tuberculosis; HIV: Human Immunodeficiency Virus; INH: Isoniazid; RIF: Rifampicin; PZA: Pyrazinamide; EMB: Ethambutol; ARDS: Acute Respiratory Distress Syndrome; CT: Computerized Tomography; PPD: Tuberculin Skin Test; DNA: Deoxyribonucleic Acid; RNA: Ribonucleic Acid; BCG: Bacillus Calmette-Guerin Vaccine; MDR: Multi-Drug-Resistant; IM Injection: Intramuscular Injection; PAS: Para-aminosalicylic Acid; WBC: White Blood Cell; ADA: Adenosine Deaminase; CRP: C - Reactive Protein; VATS: Video-Assisted Thoracic Surgery

Etiology and epidemiology of pulmonary tuberculosis

Tuberculosis is a chronic progressive infections caused by acid-alcohol-resistant bacilli *Mycobacterium tuberculosis*. Similarly, disease are caused by *Mycobacterium bovis, Mycobacterium africanum* and *Mycobacterium microti*. In addition to these mycobacteria there is a wide range of nontuberculous mycobacteria, many of which are saprophytic and are essential due to the fact that in some conditions such as HIV infection may lead to the incidence of TB with very severe clinical presentation, because these bacteria as a rule, are resistant to conventional medications. Tuberculosis has many manifestations, affecting bone, the central nervous system, and many other organ systems, but it is primarily a pulmonary disease that is initiated by the deposition of *Mycobacterium tuberculosis*, contained in aerosol droplets, onto lung alveolar surfaces. More than 1.7 billion people (about 25 percent of the world population) are estimated to be infected with *M. tuberculosis*, 10 million people fell ill with TB, and 1.6 million died from the disease (including 0.3 million among people with HIV). In the past, when tuberculosis was widespread in highly industrialized countries, it was possible to prove tuberculin testing, the majority of young adults infected with TB, but only a small number of patients (10%) developed the disease. Whether the infection goes into the disease depends on the size of the infective dose and the defence mechanism of the infected person. In some cases, the infection progresses rapidly to disease, in other, the disease can remain latent. Some conditions which lead to a decrease in the defense forces (HIV, malnutrition, old age) can allow the dormant bacilli to multiply and cause disease. Tuberculosis is almost exclusively caused by inhalation of droplets containing *M. tuberculosis*, during speech, coughing, or in other conditions when there is an increased involvement of the respiratory system of a person with active pulmonary tuberculosis, whose sputum contains a significant number of causative agents (typically sufficient to smear positive). People with cavernous form of disease are especially infectious. Also, patients with a direct positive sputum (*Mycobacterium tuberculosis* visible under the microscope) are far more infectious because they cough far more throats than those whose sputum is positive only in culture. The closer a person is to the patient, the higher the dose of *Mycobacterium tuberculosis*, he will likely inhale. Infected urine or stool are theoretically risky, but are much less important because they contain relatively few tuberculosis bacteria.

Pathogenesis of tuberculosis

After inhalation of the tuberculosis bacilli into the tracheobronchial tree, tuberculosis bacteria cause a primary infection, followed by a latent period and in some cases an active disease. In the primary and latent period, disease is not contagious.

Primary infection

Contained in aerosol droplets tuberculosis bacillus comes to terminal alveoli, usually subpleural localization, predominantly in the lower parts of the lungs, and is usually implanted only in one place in the lungs. First contact is with resident macrophages, but it is also possible that bacteria can be initially ingested by alveolar epithelial type II pneumocytes. Dendritic cells play a very important role in the early stages of infection since they are much better antigen presenters than are macrophages and presumably play a key role in activating T cells with specific *M. tuberculosis* antigens. Since dendritic cells are migratory, unlike differentiated macrophages, they also may play an important role in dissemination of *M. tuberculosis*. On entry into a host macrophage, *M. tuberculosis* and other intracellular pathogens initially reside in an endocytic vacuole called the phagosome. Since most macrophage killing of bacteria occurs in the phagolysosome, intracellular pathogens have evolved many ways to avoid this hostile vacuolar microenvironment. It is known that infected macrophages in the lung, through their production of chemokines, attract inactivated monocytes, lymphocytes, and neutrophils, none of which kill the bacteria very efficiently. Then, granulomatous focal lesions composed of macrophage-derived giant cells and lymphocytes begin to form. This process is generally an effective means of containing the spread of the bacteria. As cellular immunity develops, macrophages loaded with bacilli are killed, and this results in the formation of the caseous center of the granuloma, surrounded by a cellular zone of fibroblasts, lymphocytes, and blood-derived monocytes. The strength of the host cellular immune response determines whether an infection is arrested here or progresses to the next stages. This enclosed infection is referred to as latent or persistent TB and can persist throughout a person's life in an asymptomatic and non-transmissible state. In persons with efficient cell-mediated immunity, the infection may be arrested permanently at this point. The granulomas subsequently heal, leaving small fibrous and calcified lesions, such as A Simon focus,

which is a tuberculosis nodule that can form in the apex of the lung or Ghon's complex. Ghon's complex is a lesion consist of a calcified focus of infection and an associated lymph node. However, if an infected person cannot control the initial infection in the lung or if a latently infected person's immune system becomes weakened by immunosuppressive drugs, HIV infection, malnutrition, aging, or other factors, the granuloma center can become liquefied by an unknown process and then serves as a rich medium in which the now revived bacteria can replicate in an uncontrolled manner. At this point, viable *M. tuberculosis* can escape from the granuloma and spread within the lungs (active pulmonary TB) and even to other tissues via the lymphatic system and the blood (miliary or extrapulmonary TB). When this happens, the person becomes infectious and requires antibiotic therapy to survive. Primary extrapulmonary tuberculosis can sometimes manifest at any site in the body without signs of lung involvement. Tuberculous lymphadenopathy is the most common extrapulmonary manifestation, but the greatest danger is tuberculous meningitis, due to high mortality in very young and very old patients.

Active disease

In about 10% of patients, latent tuberculosis infection develops into an active disease, although the percentage is largely dependent on the patient's lifespan and other risk factors. In about 50% to 80% of those patients in whom active disease develops, tuberculosis is reactivated in the first two years, but reactivation of the disease can occur after several tens of years. Each initially affected organ can be a reactivation site, but reactivation usually occurs in the apex of the lungs, where the pressure of oxygen is greatest. Reactivation of Ghon's complex and affected hilar lymph nodes comes significantly less. If a latently infected person's immune system becomes weakened by immunosuppressive drugs, HIV infection, malnutrition, aging, or other factors, the granuloma center can become liquefied by an unknown process and then serves as a rich medium in which the now revived bacteria can replicate in an uncontrolled manner. Tuberculosis damaged tissue via the reaction of delayed hypersensitivity, leading to the production of granulomas with histologically visible caseous necrosis. Changes in the lungs are cavitary. Pleural effusion is less common than in primary progressive tuberculosis but can be caused by direct or hematogenic expansion. Rupture of large tuberculous lesions in the pleural cavity can cause tuberculous empyema pleura, with or without a bronchopleural fistula, and sometimes can occur to pneumothorax. Acute respiratory distress syndrome (ARDS), which is thought to be caused by hypersensitivity to antigen-releasing tuberculosis bacilli, rarely occurs, mainly after hematogenic dissemination, or rupture of a large cavern with dissemination to the lung tissue.

Diagnosis of tuberculosis

Lung tuberculosis is often suspected based on radiographs of the chest caused by non-specific respiratory symptoms (coughing lasting for three weeks, haemoptysis, chest pain, difficulty breathing), febrile state of unknown etiology, or positive tuberculin skin test. In adults, multinodular infiltrate above or behind the clavicle can indicate reactivation of tuberculosis. Infiltrates in the middle or lower lung fields are not specific but should arouse suspicion of primary tuberculosis patients (usually young) whose symptoms or history indicating recent infection, especially if there is pleural effusion.

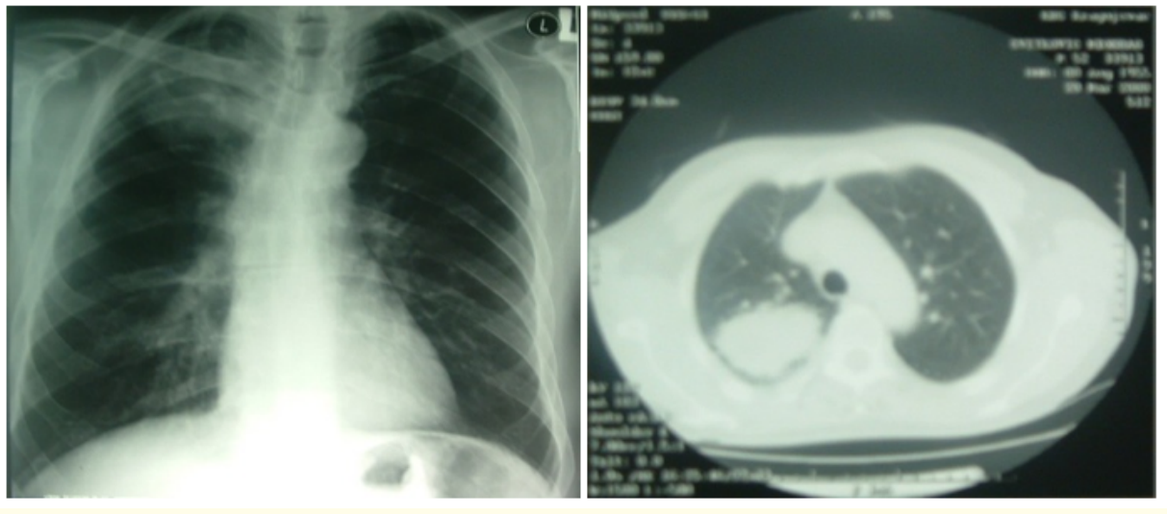

Figure 1: *Tuberculous infiltration of the right upper lobe of the lung (chest X-ray and CT).*

The initial diagnostic procedure in suspected pulmonary tuberculosis are:

- Chest X-ray
- Sputum examination (staining and cultivation in a culture)
- The tuberculin skin test (PPD)

If a person with risk factors for tuberculosis is a radiographic image very characteristic (cavitation in the upper lobe), it is still necessary to examine sputum, but the skin test is often not performed. The finding of acidoalcohol resistant bacteria in the sputum provides a strong assumption that it is tuberculosis, but the final diagnosis requires the cultivation of sputum culture, or a positive rapid molecular test. Molecular techniques have provided quick, sensitive, and specific tests for *Mycobacterium tuberculosis*-such as polymerase chain reaction, DNA and RNA probes, and γ interferon tests-but these are expensive and technically demanding. They are most useful in diagnosing multi-drug resistant organisms quickly and in differentiating *M. tuberculosis* from other, non-infectious mycobacterial species. In positive cultures, resistance to isoniazid, rifampicin, and ethambutol is routinely tested, while along with conventional bacteriological methods, up to eight weeks is required. Patients who cannot spontaneously develop a cough, sputum can be induced by inhalation of an aerosol of hypertonic saline, or fiberoptic bronchoscopy may obtain bronchial washings, which are particularly sensitive method. In case of infiltrative changes in the lungs, transbronal biopsy should also be done and the result should be sent to growing in culture, pathohistological processing and molecular testing. Gastric washings are usually positive, but today they are no longer performed often, except in small children, which usually cannot give a good sputum pattern.

Tuberculin skin testing

Tuberculin testing is helpful in ranking tuberculosis among the differential diagnoses of conditions with symptoms, signs, and radiological changes that would be compatible with pulmonary tuberculosis but where sputum is negative on direct smear or culture. A strongly positive tuberculin test in such a patient who has not previously had BCG vaccination or tuberculosis increases the probability that tuberculosis is the diagnosis. Usually a tuberculin skin test is performed (tuberculin skin test = TST, Mantoux or PPD - purified protein derivative test), although it is a test that proves the infection, latent or active, so there is no diagnostic value for an active disease. The usual dose of 5 units of PPD in 0.1 ml of the solution is injected on to a volar part of the forearm. It is very important to give intradermal injection rather than subcutaneously. A well-formed limited cutaneous flank mass should be created. The induration diameter is measured from 48 to 72 hours after injection. Induction ≥ 10 mm, as a rule, means infection with *M. tuberculosis*, but does not indicate its activity. Sometimes a different margin of susceptibility is more useful in order to improve the sensitivity and specificity of the method. Induration ≥ 5 mm is considered a positive finding in HIV-infected patients, or in people with radiographic evidence of healed tuberculosis, or in people who have been in close contact with TB patients, while in patients without risk factors, the test is not considered positive until the induration. Results may be falsely negative, most commonly in febrile patients, elderly, or HIV infected patients (especially if the number of CD4 + cells is <200 cells / μL) and in severely affected patients, many of whom do not show any reaction to either which skin test (anergy). is> 15 mm.

Prognosis and treatment of tuberculosis

In immunocompetent patients with pulmonary tuberculosis, which is sensitive to medications, even severe illness and large cavitation are recovered quickly if appropriate treatment is carried out. Tuberculosis leads to fatal outcome in about 10% of patients, mainly in patients with reduced resistance to the organism. Disseminated tuberculosis and tuberculous meningitis can be fatal in about 25% of cases, despite adequate treatment. Tuberculosis is much more aggressive in immunocompromised patients and if it is not treated adequately, it can be fatal even within 2 months of the onset of the disease. This is especially the case with MDR (Multi-drug-resistant) - TBC, where mortality is up to 90%. Most patients with uncomplicated tuberculosis and all of the complicated diseases (AIDS, hepatitis, diabetes), adverse reactions to drugs and drug resistance should be referred to the pulmonologist. However, most patients can be treated at home with education on how to prevent the spread of the disease. These measures include staying at home, avoiding visits and covering the face

with a scarf or hand while coughing. Precautions must be continued for several weeks at the hospital or outside. The main indications for hospitalization are the severe clinical picture of the disease, the need for diagnostic procedures and the need for respiratory isolation. All hospitalized patients initially have to be in respiratory isolation, preferably in a room with negative pressure and 6 to 12 air changes per hour.

Drugs for the first choice for the treatment of tuberculosis are: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) and are administered together in the initial phase of treatment. Standard chemotherapy consists of six months of rifampicin and isoniazid, initially supplemented by two months of pyrazinamide and ethambutol.

Isoniazid (INH) is administered per os once a day, well penetrates into tissues, including liquor and is highly bactericidal. It remains the single most effective and cheapest drug for tuberculosis. However, years of uncontrolled use (often as the only drug, i.e., monotherapy) in many countries increased the percentage of resistant tuberculosis strains. Isoniazid is harmless in pregnancy. Side effects are rash, fever, anemia and agranulocytosis. Isoniazid in about 20% of patients causes an increase in aminotransferases and symptomatic (usually reversible) hepatitis in about 1/1000 (more common in people over 35 years of age, alcoholics and chronic liver disease patients). Rifampicin (RIF) when administered orally has a bactericidal effect, it is well absorbed, penetrates well into the cells and fluid, and fast acting. Also destroys dead tuberculosis germs in the macrophages or caseous homes which lead to late recurrence. For this reason, Rifampicin can be applied throughout the entire treatment of tuberculosis. Side effects are cholestatic icterus (rare), fever, thrombocytopenia and renal insufficiency. Rifampicin is non-toxic in pregnancy. Ethambutol (EMB) is administered orally, submitted to the best of all the drugs of first choice. Its main toxicity is expressed as an ocular neuritis, and more often with larger doses and in patients with impaired kidney function. Because both of them are reversible if discovered early, patients should have basic tests of visual acuity and color recognition tests, and they should be monitored every month. If optic nerve neuritis occurs, ethambutol is replaced by another medicine. During pregnancy it can be freely applied. Drugs of the second choice for the treatment of tuberculosis are mainly used for MDR - TBC. The two most important groups are: aminoglycosides and fluoroquinolones. Streptomycin, the most commonly used aminoglycoside, is highly effective and bactericidal. It is poorly penetrating into the liquor, and if other drugs are available, it should not be applied intrathecally. Side effects include kidney damage, vestibular damage, and ototoxicity. The dose is about 15 mg/kg IM (usually 1g for adults, reduced to 0.5g for elderly than 60 years, persons < 45 kg, or those with any degree of renal failure). Patients should be regularly monitored for possible side effects (appropriate balance, hearing and serum creatinine). Allergic reactions are rash, febrile, agranulocytosis and serum sickness. The injection is often accompanied by redness and tingling around the lips, but it quickly retreats. Streptomycin is contraindicated in pregnancy because it can cause damage to the eighth cranial nerve of the fetus. Kanamycin and amikacin can be effective if resistance to streptomycin has developed. Some fluoroquinolones (levofloxacin, moxifloxacin and gatifloxacin) are the most effective and safest medicines against tuberculosis, after isoniazid and rifampicin. Other drugs of the second choice are ethionamide, cycloserine and paraaminosalicylic acid (PAS). They are less effective and more toxic than drugs of first choice but are useful for treatment of MDR - TB. All patients with newly discovered, previously untreated tuberculosis should undergo initial therapy for a period of 2 months, followed by a sustained treatment phase of four to seven months. In the first 2 months, 4 antibiotics were used: isoniazid, rifampicin, pyrazinamide and ethambutol. After two months, the pyrazinamide is terminated and samples for culture and smears are taken. If both culture and smear are negative, regardless of radiographs of the chest, or if the culture or smear is positive but no cavitation is seen on the X-ray, the application of isoniazid and rifampicin continues for another four months (a total of six months). If cavitation is found on the chest radiograph, and culture and smear are positive, the use of isoniazid and rifampicin continues for another seven months (a total of nine months). By any mode of administration, ethambutol is abolished if the antibiogram does not show resistance to any drug in an extended phase of treatment, medication can be administered daily, twice or three times a week. Patients with negative cultures and smears and no cavitation on chest radiography, who are HIV negative, it can be given once a week isoniazid and rifapentine. Both in the initial and in the extended phase of treatment, the total number of doses (calculated by doses/multiplied by the number of weeks) must be applied, and if any dose is skipped, the treatment is prolonged. The procedure for resistant tuberculosis depends on the resistance to the drug. In MDR-TB, prolonged treatment (18 to 24

months) with the remaining first-line drugs (including pyrazinamide, if the cause is sensitive) requires the addition of one or more drugs of another choice (fluoroquinolone and aminoglycoside, or capreomycin). In patients with acute respiratory distress syndrome (ARDS), meningitis, or pericarditis, the use of corticosteroids is indicated. The treatment is continued for two to three weeks. Corticosteroids that are required due to other indications do not pose a risk to those with active tuberculosis who receive adequate anti-tuberculosis therapy.

The role of surgery in the treatment of pulmonary tuberculosis

Proper use of a significant number of drugs in the treatment of pulmonary tuberculosis (tuberculosis) and early detection of the disease allows the cure and extended tuberculous pulmonary lesions. The successes in the medicament treatment of pulmonary tuberculosis have been influenced by the fact that surgical treatment of this disease is rarely applied today. Surgical treatment of pulmonary tuberculosis cannot be used without prior treatment with drugs. Therefore, surgical treatment is not an independent method, but it is only one phase in therapy of tuberculosis. Application of anti-tuberculosis drugs in the preoperative and postoperative phase of treatment allows successful treatment with low postoperative morbidity and mortality. Surgical treatment is indicated when it is estimated that the operation can solve the failure of anti-tuberculosis drug therapy.

The failure of the drug therapy of tuberculosis

The failure of anti-tuberculosis therapy comes extremely rarely in properly treated cases. This can happen when the tuberculosis bacillus primarily resistant to drugs, or when there is a very strong sensitivity to these drugs. However, treatment failure is more likely to occur due to improper or insufficiently long drug use. The failure of treatment is determined on the basis of a positive finding tubercle bacilli in sputum, examining the type, amount, manner and duration of use of drugs and the comparison of chest radiography before and during treatment. Conclusion on the failure of the treatment with drugs can be made only after the expiry of at least six months properly conducted therapy. It is recommended that the decision on a surgical procedure be made only after one year of continuous treatment.

Complications or sequelae of healed pulmonary tuberculosis

In parts of the lungs, where previously there was an active tuberculous process may occur constant purulent (Pyogenic) or fungal infection. The most common reason for the occurrence of such non-specific infections is an incomplete scarring bronchial stenosis (most commonly known as Middle lobe syndrome involving the right middle lobe and/or lingual of the left lung). As a result of chronic infections in these areas can occur massive hemoptysis or being developed suppurative disease of the pleura (empyema), with or without signs bronchopleural, pleurocutaneous and bronchopleurocutaneous fistula. Pulmonary complications are resolved by surgical resection of diseased segments, the lobe or rare and entire lungs. Pleural complications are solved by decortication of the lungs.

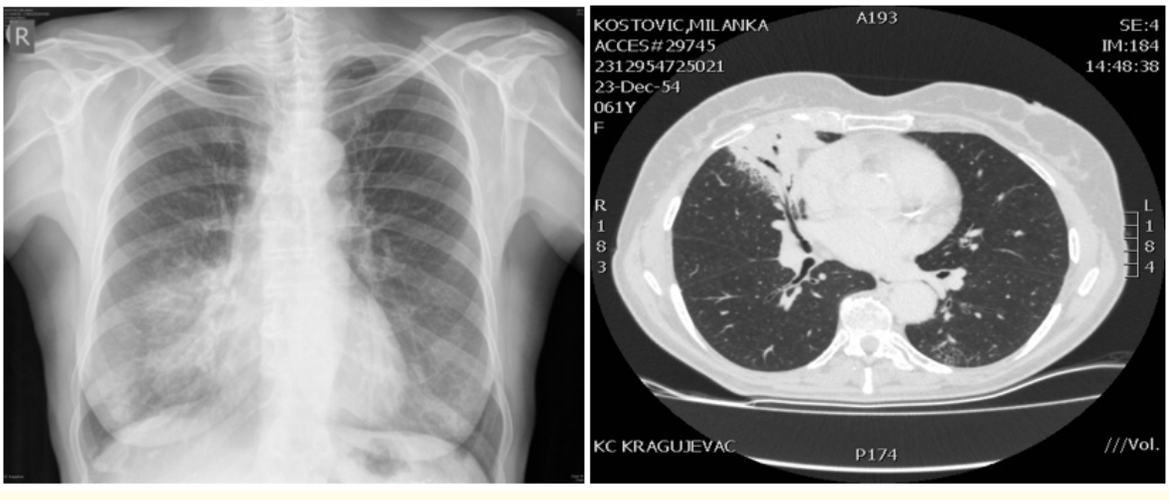

Figure 2: *Middle lobe syndrome (chest X-ray and CT).*

Complications of previously performed surgery for the treatment of pulmonary tuberculosis

In practice, patients who need to solve problems due to previously used so-called collapse methods for the treatment of pulmonary tuberculosis are rarely found. A specific group of patients consists of those who develop complications following pulmonary resection, such as the empyema of the pleura with bronchopleural or bronchopleurocutaneous fistula. In patients treated of lung tuberculosis, or in those who are suspected of this disease, should never forget the possibility of a combined occurrence of tuberculosis and lung cancer. Such a possibility applies especially to those patients with radiographic peripheral nodular lesions, or in whom early inflammatory lesions (fibrotic lesion lesions) are detected, with BK finding negative in the sputum, and the tuberculin test is positive.

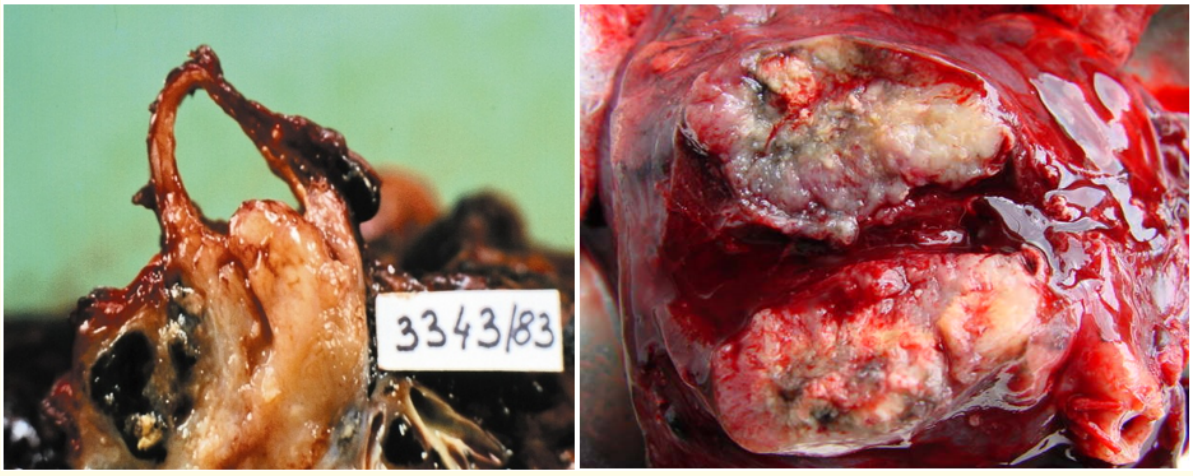

Figure 3: *Lung cancer in the scar of tuberculosis.*

Selection of patients for surgical treatment

The selection of patients for surgical treatment primarily involves estimates that consider the possibilities of preventing further evolution of the disease, or the emergence and development of post-operative complications and estimates that accurately determine the degree of disruption of the respiratory function in relation to the volume and type of surgery.

According to surgical criteria, the chances of success of surgical treatment can be ideal, reduced, or indications are poor.

The ideal indications for the surgical treatment of lung tuberculosis are the unilateral localization of the disease, the complete stabilization of the disease (primarily in the presence of a bacterial infection), the negative finding of a tuberculosis bacilli in the sputum, or an occasional finding without resistance and a good general condition of the patient. Any surgical evaluation for surgical treatment of pulmonary tuberculosis must be taken, inter alia, in relation to a post-mortem findings.

Surgical indications in relation to the pathoatomic finding may be: absolute and relative.

Absolute surgical indications in relation to the pathoatomic finding are: casey hearths (limited to one lobes), tuberculum, filled cavern (closed supply bronchus), primary tuberculosis and enlarged lymph nodes with a predominantly bronchoglandularnom fistula (perforation of casein masses in the bronchial system), bronchial stenosis and distal nonspecific or tuberculous bronchiectasis, a tuberculous process in the lungs with a pleural empyema.

Relative surgical indications refer to conditions that require additional medical treatment, or it is indicated and useful to apply some of the methods of so-called collapsotherapy, and only then assess the justification and the possibility of surgical treatment (first of all, it refers to the use of some of the resection methods, or first resection, and then collapse therapeutic methods). Today, the number of such indications is negligible.

Definitive surgical indications are made on the basis of a pathoatomic finding, assessment of the evolution of the process, assessment of the possibilities and justification of further drug treatment, assessment of the state of the respiratory function, assessment of the possibility of postoperative administration of antitubercular drugs, patient's lifespan, assessment of the prospects for the success of the intended operation.

Contraindications for surgical treatment of lung tuberculosis may be: absolute and relative.

Absolute contraindications are pulmonary emphysema, decompensated cardiac insufficiency, severe respiratory failure, extensive bilateral lung tuberculosis, cachexia, psychosis.

Relative contraindications include: lung tuberculosis in evolution, insufficiently rehabilitated tuberculosis process, fresh bilateralization of the tuberculous process in the lungs, active extrapulmonary tuberculosis, evolutive tuberculosis of the bronchus at the site of the planned resection and suture of bronchi.

In modern conditions indications for surgical treatment of pulmonary tuberculosis refer to cases:

- Primary tuberculosis
- Post-primary tuberculosis
- Sequelae of tuberculosis infection
- Tuberculous pleural effusion
- Tuberculous empyema

Primary tuberculosis

Primary tuberculosis is a rare indication for surgical treatment. The operation is applied to solve the problem of highly pronounced extraluminal compression and threatening acute perforation of enlarged lymph nodes at tracheal or main bronchial levels.

Post-primary tuberculosis

In post-primary tuberculosis, surgery is applied in tuberculomas and cavernous tuberculosis. Diffuse caseous infiltration in the lung without a positive finding of tuberculosis bacilli in sputum localized in a single lobe and without prior evidence of etiology of changes are a rare indication for surgical treatment. Most often such lesions are detected by exploratory diagnostic thoracotomy, which is indicated to exclude the malignant etiology of change.

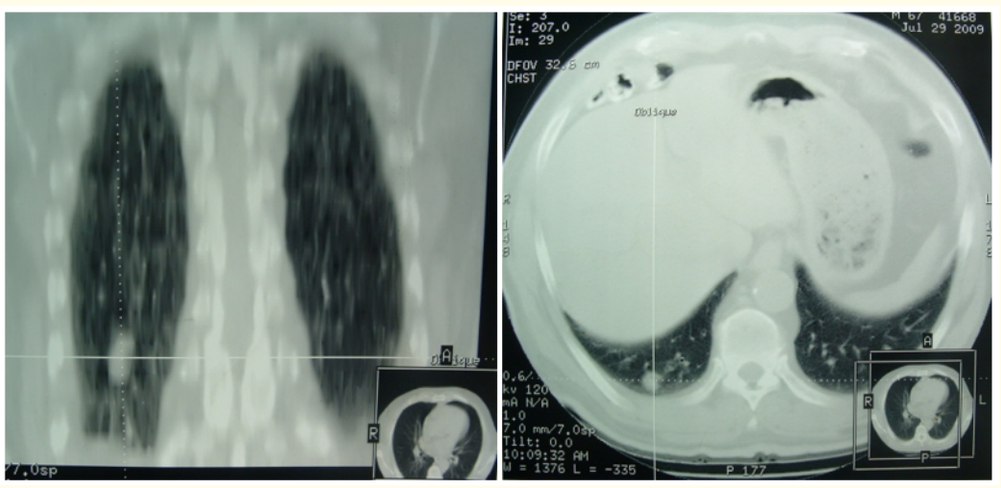

Figure 4: *Tuberculoma of the right lower lobe of the lung (chest X-ray and CT).*

Sequelae of tuberculosis infection

Secondary aspergillosis most commonly develops from three to twelve years of age after the achieved conversion of sputum. It mainly develops in spacious sequelae of previously treated and cured tuberculosis, such as cavities with smooth walls, or in the system of minor cavities in cirrhotic altered lung parts. The reasons for the development of this fungal infection have not been fully clarified, but the development of aspergillosis is considered to be favorable by two groups of factors. On the one hand, these are the general factors of the disorder of the immune defense mechanism of the lungs and the whole organism caused by chronic infection, and on the other hand it is a disturbance of drainage of the bronchial secretion due to metaplasia of bronchial mucosa in the plate-layer epithelium. Bronchial stenosis with secondary bronchiectasis is an indication for surgical treatment only when there is massive haemoptysis and recurrent pneumonia, or when secondary aspergillosis is confirmed. It is known for middle lobe syndrome in the right lung and lingula syndrome in the area of the left upper lobe of the lung. Bronho-esophageal fistula as a tuberculosis sequence meets very rarely, but in clinical practice it is much more common as a complication of lung cancer.

Tuberculous pleural effusion

Tuberculous pleural effusion when it occurs in the absence of radiographically visible tuberculosis of the lungs, may represent a continuation of the primary tuberculous lung infections occurred before 6-12 weeks, or may represent reactivation of tuberculosis. Tuberculous pleural effusion is the result of rupture of subpleural caseous focus localized in the lungs. It is believed that late hypersensitivity plays a major role in the pathogenesis of tuberculous pleural effusion. Mycobacterial cultures of pleural fluid in most patients with tuberculous pleural effusion are negative. T lymphocytes specifically sensitized to tuberculous protein are found in pleural effusion. It is unknown whether the increased percentage of specifically sensitized lymphocytes in pleural fluid caused by their clonal expansion or due to migration PPD - reactive T cells from the blood. When lymphocytes of patients with tuberculous pleural effusion are cultivated with PPD, lymphokines are produced. The level of production of lymphokines is much higher in lymphocytes in pleural fluid than in peripheral blood lymphocytes. Although delayed hypersensitivity to tuberculosis protein is probably responsible for most clinical manifestations of tuberculous pleuritis, many patients who are first examined have a negative PPD skin test. The explanation of this phenomenon may be a combination of two factors. First, in some patients with tuberculous pleurisy, circulating mononuclear adherent cells suppress specific sensitized circulatory T lymphocytes of peripheral blood. Second, there may be sequestration of PPD-active T lymphocytes of the pleural space, including Leu-2 (suppressor/cytotoxic) and Leu -3 (assistant) positive T cells. Tuberculous pleural effusion is enriched by many potentially immunoreactive cells and substances that constitute a strong cell-mediated immune response. In comparison with peripheral blood, pleural fluid is rich in T lymphocytes. The ratio between CD4 (helper/induction) to CD8 (suppressor/cytotoxic) is 3: 4 in pleural fluid compared to 1: 7 in peripheral blood. It has been observed that the pleural fluid lymphocytes of patients with tuberculous pleuritis show a stronger response to PPD than peripheral blood lymphocytes. Some authors believe that tuberculous pleural effusion is a consequence of a late hypersensitivity reaction that increases the permeability of the pleural capillaries to proteins, and an increased level of protein in the pleural fluid leads to the appearance of pleural effusion, while other authors consider that a strong inflammatory reaction of the parietal pleura impairs lymph drainage from the pleural space and leads to the appearance of pleural effusion. It is probable that both of these mechanisms participate in the pathogenesis of tuberculous pleural effusion. In many parts of the world, tuberculosis remains the most common cause of pleural effusion, especially in immunodeficiency patients, in whom the incidence of tuberculous pleural effusion is high. Clinical tuberculosis pleural effusion manifests with dry cough, chest pain, loss of appetite and body weight, difficulty breathing, fever, although normal body temperature does not exclude the existence of tuberculous pleural effusion. Clinical manifestations of tuberculous pleural effusion are more difficult in HIV - positive patients. Systemic signs and symptoms such as night sweats, fatigue, diarrhea, hepatomegaly, splenomegaly and lymphadenopathy are significantly more frequent in HIV-positive patients.

The diagnosis of tuberculous pleurisy is based on chest X-ray, or computerized tomography of the chest, in which the classic picture of the pleural effusion is seen, while the definitive diagnosis is made by pleural punction and the analysis of the pleural punctate. Often, the

level of protein in pleural fluid is above 5 g/dL, and this finding indicates tuberculous pleurisy. In most patients, the leukocyte-differentiated pleural fluid (WBC) reveals more than 50% of small lymphocytes. In patients with symptoms lasting less than two weeks, pleural fluid differentiated by the number of leukocytes may exhibit predominantly polymorphonuclear leukocytes. A useful study to exclude tuberculous pleuritis is the analysis of pleural fluid on mesothelial cells. Four separate studies have confirmed that pleural fluid of patients with tuberculous rarely contains more than 5% of mesothelial cells. Today, the determination of the adenosine deaminase level (ADA) is used for the diagnosis of tuberculous pleural effusion. Adenosine deaminase is an enzyme that catalyzes conversion of adenosine to inosine. ADA is T lymphocytic enzyme and its plasma activity is high in diseases that stimulate cellular immunity. Numerous studies have shown that the level of adenosine deaminase of the pleural fluid is higher in patients with tuberculous pleuritis than in patients with other types of pleural effusion. Another useful test for the diagnosis of tuberculous pleuritis is the level of interferon - gamma in the pleural fluid. Interferon - γ produces CD4+ lymphocytes of patients with tuberculous pleuritis. Patients with tuberculous pleuritis tend to have higher levels of interferon-gamma in the pleural fluid than patients with pleural effusions of another etiology. In recent years, the possibility of diagnosing tuberculous pleural effusion by measuring the level of tuberculous antigens or specific antibodies to tuberculous proteins of pleural fluid has been investigated, but the results of these studies are still not sufficiently reliable. Other chemical analyzes of pleural fluid have limited value in diagnosing tuberculous pleuritis. Although in the past, the level of pleural fluid glucose was thought to be diminished in most cases of tuberculous pleuritis, recent studies show that the majority of patients with tuberculous pleuritis have glucose pleural fluid level above 60 mg/dL. Also, the low level of pH of pleural fluid was once indicative of tuberculous pleuritis, and tuberculous effusion patients had lower pH of pleural fluid than those with malignant effusion, but recent studies suggest that the pH of the pleural fluid has approximately the same distribution in malignant as well in tuberculous pleural effusions. The mean C - reactive protein (CRP) is higher in tuberculous effusion than in other exudative effusions. Measurement of the level of pleural fluid lysosomes was proposed as a useful diagnostic test because it was observed that the mean lysosomal level in the pleural fluid of patients with tuberculous pleuritis is higher than in other exudative pleural effusions. In the last few decades, the diagnosis of tuberculous pleuritis is most commonly established by pleural biopsy, whether it is a percutaneous biopsy of various needles (Abrams, Cope), or video-assisted thoracic surgery (VATS), which today is considered to be a golden standard for the etiology in the case of pleural effusion and tuberculosis. We can say that today percutaneous pleural biopsy is only applied in patients in poor general condition who cannot tolerate general anesthesia, while in most patients, today, video-assisted thoracic surgery (VATS) is applied.

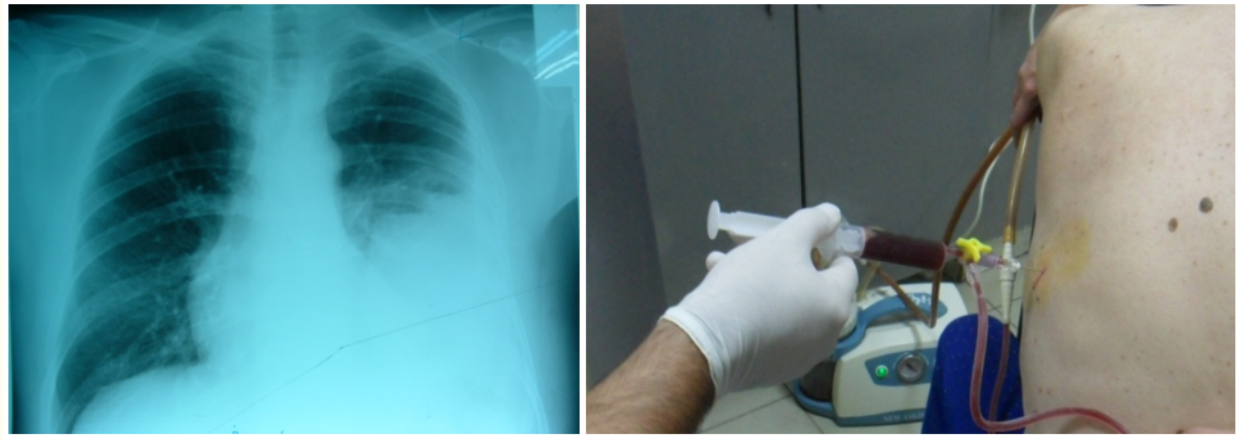

Figure 5: *Left: Tuberculous pleural effusion on X-ray; Right: Thoracentesis.*

Video - Assisted Thoracic Surgery (VATS) is a minimally invasive method for endosurgical instrumental exploration of intrathoracic lesions by access through small intercostal incisions. A camcorder, which is attached to a standard surgical endoscope, allows the surgeon a two-dimensional visualization of the operating field on the monitor. The surgeon directs the videoendoscope and endosurgical instrumentarium directly into the pleural cavity and to the patanoatomic substrate. Video-assisted pleural biopsies are performed in general anesthesia by intubation of patients with a double lumen endobronchial tube, which allows ipsilateral lung collapse for intervention. Ipsilateral lung collapse is necessary in order to be able to perform any surgical intervention. The preparation of the operating field is externally the same as for standard thoracotomy. The patient is in the position of lateral decubitus, as for posterolateral thoracotomy, but with an elevated arm for easier access to space with limited topographic lines of the axillary region. Access to the thoracic cavity is through the intercostal spaces through small incisions in which the thoracoscope, videocamera and additional instruments, pliers, scissors, staplers, needle holders, hood, instruments for retraction of the lungs and other are placed. The material obtained by biopsy of the parietal pleura is sent for analysis, which in most cases sets the diagnosis of tuberculous pleuritis.

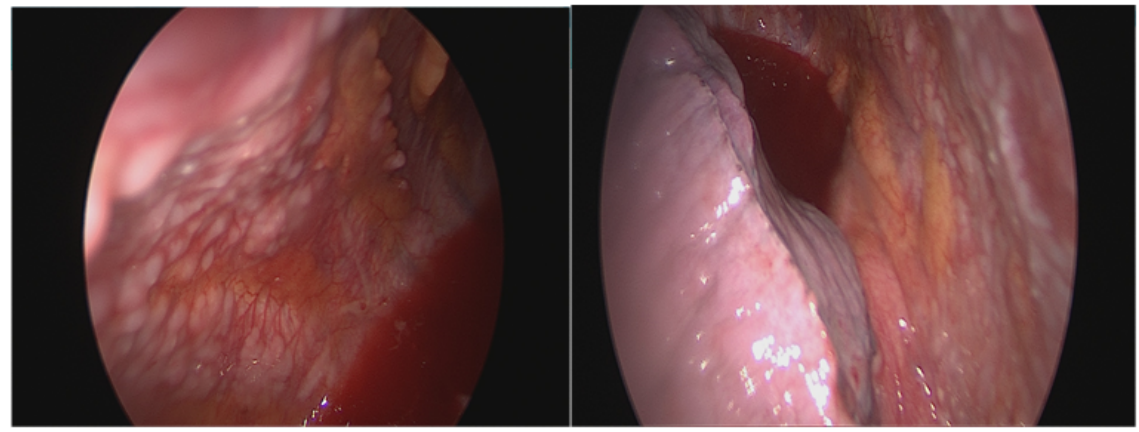

Figure 6: *VATS in the diagnosis of tuberculous pleural effusion.*

The treatment of tuberculous pleuritis has three objectives: to prevent the subsequent development of active tuberculosis, to alleviate the symptoms of the patient and to prevent the development of fibrothorax.

After diagnosis, a six month treatment is started that involves the administration of isoniazid, rifampicin and pyrazinamide for a period of two months, after which the isoniazid and rifampicin are given within the next four months. With this treatment, the symptoms and radiographic signs of tuberculous pleural effusion are gradually withdrawn. The average patient becomes afebrile within two weeks, but high temperature jumps can last up to two months. If the therapeutic thoracentesis is performed at the same time as anti-tuberculous therapy is indicated, most patients become afebrile within five days. Average time for complete resorption of pleural fluid is about six weeks, but can last up to twelve weeks. Patients should be isolated only if their sputum is positive for the mycobacterium. In patients with localized tuberculous pleural effusion, intrapleural administration of fibrinolytic can reduce the degree of pleural thickening. If there is a dyspnea due to a large pleural effusion, thoracentesis should be applied. Surgery should not be included early until a pleural thickening occurs. Although the pleura may thicken when the patient is diagnosed for the first time, the thickening is reduced by treatment, and decortication should not be considered until the patient has undergone treatment for at least six months. After this period of observation, decortication is rarely needed. Decortication should be applied only if the patient's quality of life is diminished by dyspnea.

Tuberculous bronchopleural fistula

Tuberculous bronchopleural fistula is a rare complication of tuberculosis today, because most patients with tuberculosis successfully treated anti-tuberculous therapy. These fistulas are commonly seen in patients with old, healed tuberculosis and especially in patients with previously treated pneumothorax who have never been treated with anti-tuberculous therapy. When such patients develop bronchopleural fistula, sputum production increases, and sometimes bacterial superinfection occurs. The diagnosis is made by finding the level of fluid in the pleural area, especially if the level varies in the serial radiographs of the chest. The fistula can be confirmed by injection of methylene blue into the pleural space, and then it is observed whether the color appears in the sputum or tracheobronchial tree. A definitive diagnosis is made by bronchoscopy. Tuberculous bronchopleural fistula is a very dangerous complication of tuberculosis because communication between bronchus and pleural space allows bacteria to enter the pleural area and cause infection of pleura. Additionally, when a bacterial superinfection occurs, the patient can very often receive fulminant pneumonia caused by the entry of infectious material from the pleural space to the rest of the tracheobronchial tree. This is of particular importance because tuberculous bacilli in the pleural area are most likely to become resistant to anti-tuberculous drugs. Initial treatment of a tuberculous bronchopleural fistula should be the application of appropriate anti-tuberculosis chemotherapy, with the drainage of the pleural space. Thoracic drainage eliminates the risk of contralateral lung contamination by infected pleural fluid and controls the systemic toxicity of bacterial infection. Before attempting to perform definitive surgical procedures, the patient should be administered anti-tuberculous therapy over a period of ninety to one hundred and twenty days, or until the sputum analysis is negative for tuberculosis bacillus. Definitive surgical treatment includes decortication of pleura, which can sometimes be combined with thoracoplasty, because the pulmonary parenchyma is usually so damaged that complete re-expansion of the lungs cannot be achieved. Decortication of the pleura is a serious surgical procedure with a high perioperative morbidity and mortality that can go up to 20%. Thoracoplasty is a surgical procedure that was originally designed to permanently collapse the cavities of pulmonary tuberculosis by removing the ribs from the chest wall. The resection of multiple ribs, allows the apposition of parietal to the visceral or mediastinal pleura.

Tuberculous empyema

Tuberculous empyema pleura is now a rare clinical entity characterized by the presence of pus in the pleural area. Purulent content in the pleural space is abundant with tuberculous bacilli. Tuberculous empyema pleura usually develops in the fibrous scar tissue that occurs as a result of pleuritis, artificial pneumothorax, or thoracoplasty. Usually occurs as a subacute or chronic disease characterized by general weakness and malabsorption, fatigue, subfebrile temperature and loss of appetite and body weight. In some, mainly untreated cases, pus from the pleural space can be ruptured through the chest wall into the outer environment, and then a condition is identified that is designated as empyema necessitates (pleurocutaneous fistula). Radiographically, there may be evident pleural effusion, but often radiographs of the chest exhibit only pleural thickening.

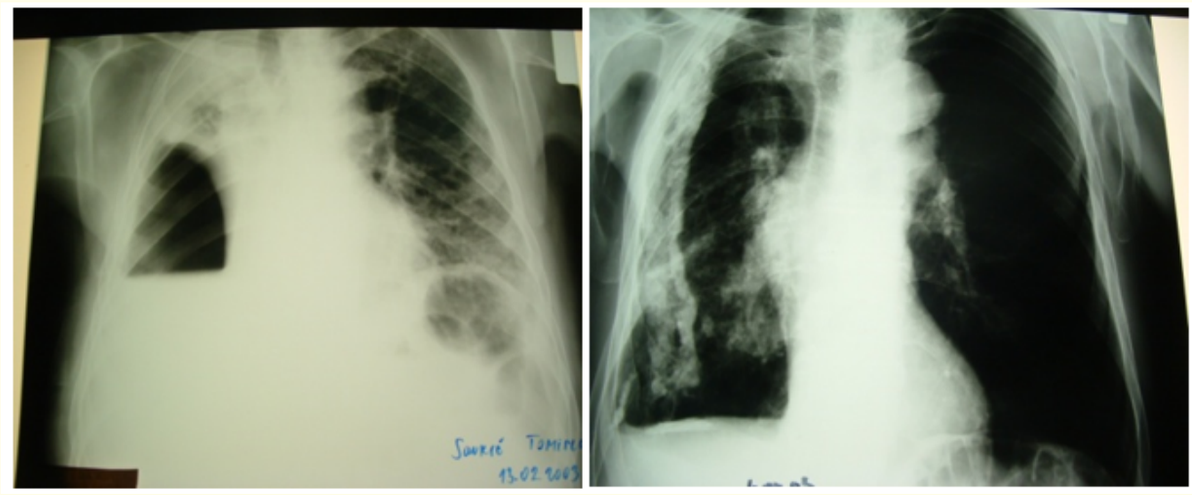

Figure 7: *Left: Tuberculous empyema pleura on chest X-ray; Right: condition after thoracic drainage of the empyema – fibrothorax.*

Computerized tomography of the chest usually shows the thickening or calcification of the pleura, the thickening of the ribs that surrounds the pleural fluid. The diagnosis is made by a thoracocentesis and a finding of thick pus in the punctate in which the tuberculosis bacillus is proven. The treatment of tuberculous empyema is long lasting and it must be persistent. The main goal of the therapy is to control the infection in the empyema cavity, often in the lungs, and to achieve sterilization of the empyema cavity by removing the pus. The ultimate goal of the therapy is that the lungs expand, the empyema cavity is reduced and the obliterate of the empyema cavity is prevented with the eradication of the focal area. In most patients, cure is achieved by the use of thoracocentesis, or by permanent active thoracic drainage. Anti-tuberculosis therapy is continuously applied in all patients, and it continues after the goals of the therapy are achieved. Surgical treatment of the tuberculous empyema is accomplished by the decortication of the lung which is applied in a small number of patients. Decortication removes collections and cavities limited by a thick fibrous layers. Indications for lung decortication are strict and limited. Preoperative evaluation is focused on the condition of the pulmonary lesions in the diseased lung and the functional state of the opposite pulmonary wings. The best results are achieved under the condition that the lungs are healthy and able to fully spread, and the necessary prerequisite for the success of the operation is to be preserved and function of the diaphragm.

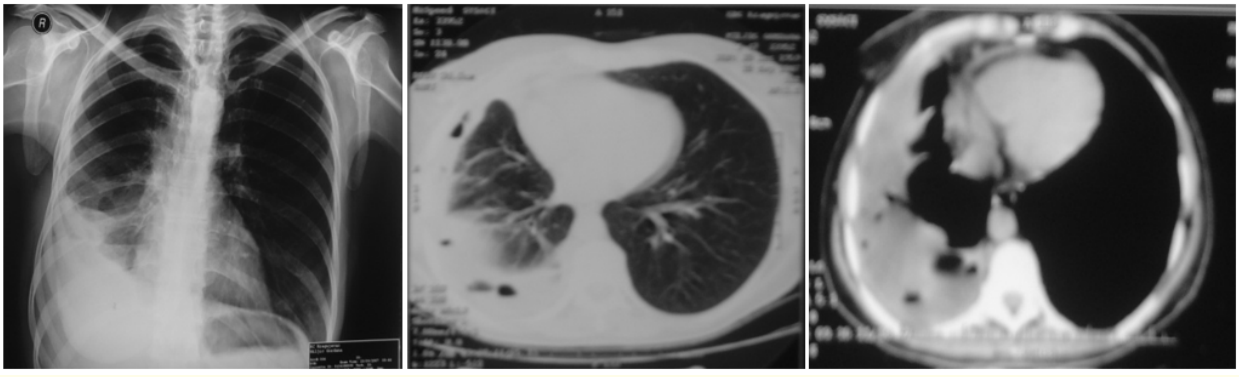

Figure 8: *Tuberculous empyema on chest X-ray and CT.*

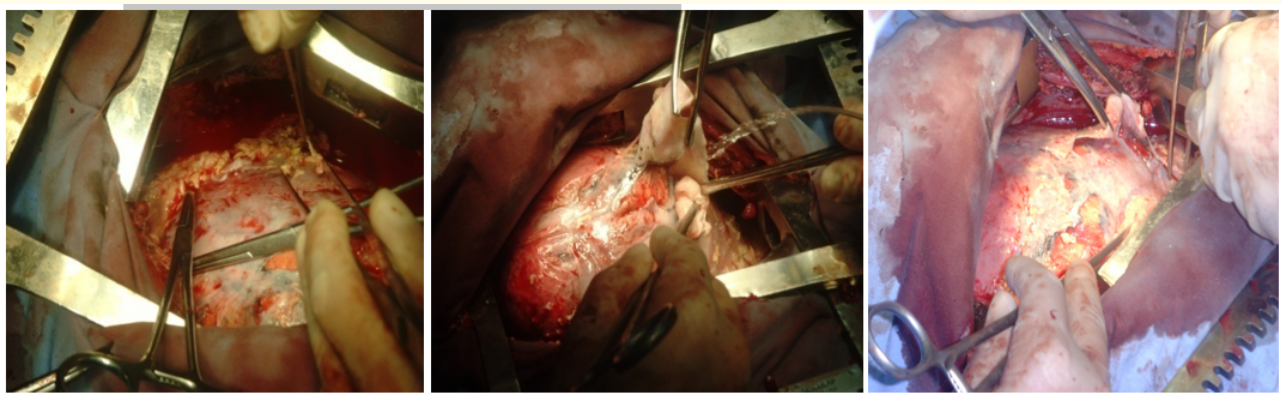

Figure 9: *Lung decortication in patients with tuberculous pleural empyema.*

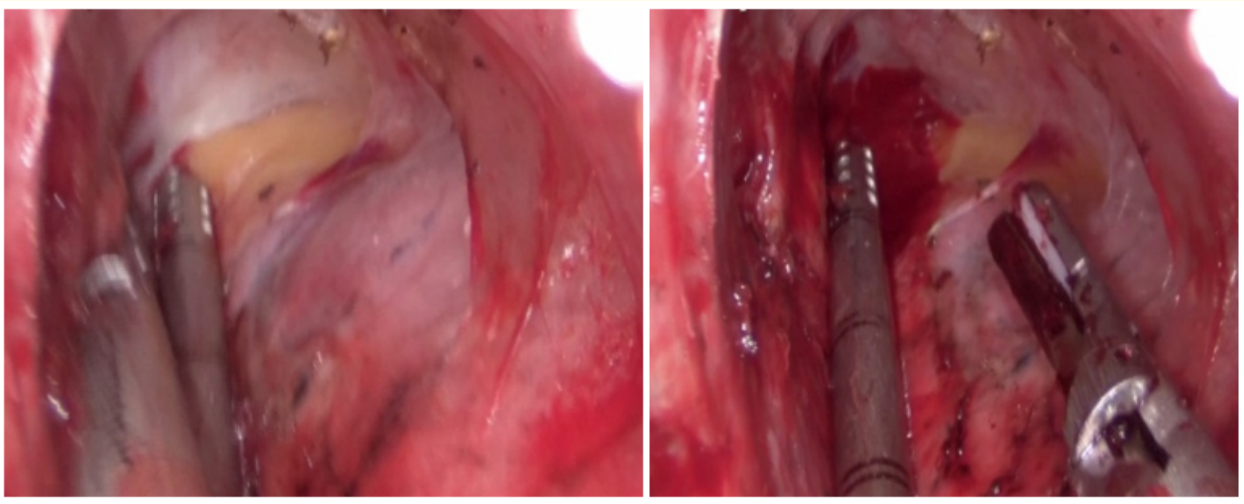

Figure 10: *VATS decortications in patients with tuberculous pleural empyema.*

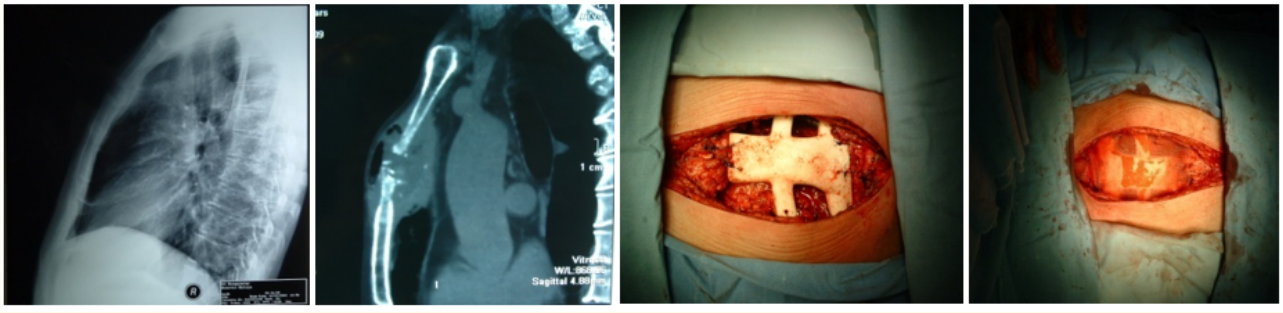

Figure 11: *Tuberculosis of the sternum (chest X-ray and CT), resection and reconstruction of sternum with an anatomic methyl acrylate implant.*

Results of surgical treatment of lung tuberculosis

In the surgical treatment of lung tuberculosis, the resection of diseased lung parts is most often applied. Resection may include a small part of the lung tissue in the extreme peripheral localization and a lesion of diameters up to 2 centimeters (atypical resection), one or two segments (segmentectomy), lung lobe (lobectomy) or the entire lung (pneumonectomy), or pleuropneumonectomy (when resection of the parietal pleura is included). After any resection, a careful bronchial saturation is necessary, regardless of its dimensions. This prevents the formation of bronchomalural fistula. The main goal of each operation is radicality, and to preserve as much as possible functional lung parenchyma. Postoperatively it is necessary to continue controlled treatment with anti-tuberculosis drugs from the first postoperative day. The duration of postoperative therapy depends on the preoperative, intraoperative and postoperative pathohistological and bacteriological findings, and it is recommended that it lasts for at least 9-12 months. The choice of anti-tuberculotics depends on the finding of the resistance of isolated tuberculosis bacilli and later from the resected specimens. Postoperative difficulties following surgery for lung tuberculosis are related to the occurrence of slow reexpansion remaining lung, abundant bleeding, bronchopulmonary fistula development, and postoperative infection. The results of surgical treatment of tuberculosis are good, with a mortality rate below 1%. After sur-

gery, recurrences occur in about 2 - 3% of cases. Surgical treatment of tuberculosis should be applied only when previously correctly conducted anti-tuberculosis therapy remained without effect. Today, surgical treatment of tuberculosis is rarely indicated, but the decision on surgery should not be delayed if there are reasons for its implementation. Occasionally tubercular process in its evolution causes severe cirrhotic changes in the lungs that hinders healing and closure of caverns. Therefore, the effectiveness of treatment with anti-tuberculosis is crucial in the first two months. The goal of the treatment should be rehabilitation of the cavern and prevention of fibrotic transformation of peribronchial and pericavern tissue, as well as prevention of the formation of extensive adhesions in the cavern area. Preserving the elasticity of the pericavern pulmonary parenchy allows rapid collapse and fading of the cavern. This prevents the formation of cavity smooth walls and the possibility of subsequent complications (fungal infection, bleeding). When it is determined the presence of caverns with thick walls that persists over a long period of controlled treatment is not justified to continue further treatment, but to approach surgery. Results of surgical treatment of tuberculosis depend primarily on the selection of patients who will be operated [1-13].

Conclusion

Proper use of a significant number of drugs in the treatment of pulmonary tuberculosis (tuberculosis) and early detection of the disease allows the cure and extended tuberculous pulmonary lesions. Surgical treatment of pulmonary tuberculosis cannot be used without prior treatment with drugs. Application of anti-tuberculosis drugs in the preoperative and postoperative phase of treatment allows successful treatment with low postoperative morbidity and mortality. It is recommended that the decision on a surgical procedure be made only after one year of continuous treatment. The selection of patients for surgical treatment primarily involves estimates that consider the possibilities of preventing further evolution of the disease, or the emergence and development of post-operative complications and estimates that accurately determine the degree of disruption of the respiratory function in relation to the volume and type of surgery. In the surgical treatment of lung tuberculosis, the resection of diseased lung parts is most often applied. The main goal of each operation is radicality, and to preserve as much as possible functional lung parenchyma. The results of surgical treatment of tuberculosis are good, with a mortality rate below 1%.

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