Literature Review

Diagnosis and Management for Pulmonary Tuberculoma

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Abstract

Pulmonary tuberculoma, prevalent particularly in tuberculosis (TB)-endemic regions, often appears as a solitary nodule of less than 30 mm, or a tumor of more than 30 mm on radiological examinations. It may also present with a combination of abnormalities, such as multiple nodules with infiltration or pleuritis. Benign solitary pulmonary nodules represent up to 25% of all resected solitary pulmonary nodules, with approximately 5-24% of these identified as pulmonary tuberculoma post-surgery. This condition is prevalent particularly in TB-endemic regions, and must be considered while determining the diagnosis, especially for patients at high risk for lung cancer. Modalities for diagnosing pulmonary tuberculoma include chest radiography, USG, CT scan, PET scan and bronchoscopy with transbronchial biopsy. The treatments for pulmonary tuberculoma are anti-TB drugs and surgery. Pulmonary tuberculoma responds poorly to anti-TB drugs and requires long-term treatment. Surgery is performed when the diameter of tuberculoma still increases after adequate anti-TB treatment.

Keywords: diagnosis, management, pulmonary tuberculoma

INTRODUCTION

Pulmonary tuberculoma is a prevalent condition, although specific data on its prevalence in Indonesia is not currently available. Clinically, the symptoms and signs of pulmonary tuberculoma do not differ from those of lung cancer, making it challenging to differentiate between the two. The extent and characteristics of the abnormalities play a crucial role in the diagnosis. Pulmonary tuberculoma is often found as a solitary pulmonary nodule on radiological examination. A solitary pulmonary nodule is a single, round, or oval nodule with well-defined margins and a size of ≤ 30 mm. In tuberculosis (TB)-endemic countries, pulmonary tuberculoma is common and must be differentiated from other causes of solitary pulmonary nodules.[1–3]

In countries with low number of TB cases, a solitary pulmonary nodule is a risk of malignancy. Solitary pulmonary nodules can be benign (pulmonary hamartoma, hemangioma, inflammatory pseudotumor, lymph node hyperplasia and tuberculoma) or malignant (squamous cell carcinoma, adenocarcinoma and bronchoalveolar carcinoma). More than 25% of solitary

pulmonary nodules subjected to surgical resection turn out to be pulmonary tuberculomas. Invasive procedures such as transthoracic biopsies and surgery are often required to diagnose and treat pulmonary tuberculoma.[1–3]

Pulmonary tuberculoma is a rare manifestation of pulmonary TB. Approximately 6-9% of pulmonary TB infection develop into tuberculoma. Tuberculomas are commonly found in the form of cavities or calcifications, have well-defined margins and are usually located in the upper lobes of the lungs. Tuberculoma most often occurs between the ages of 17 to 35, with the youngest being 15 years and the oldest 51 years, and are more common in males than females. Most tuberculoma cases do not cause symptoms and are often found during radiological examinations for lung cancer screening in high-risk lung cancer groups. As many as 58% of pulmonary tuberculoma is suspected as primary lung cancer based on radiological examination results.[4–6]

Tuberculosis is included in the ten leading causes of death worldwide. Based on geographical area, the highest number of TB cases in the world are in Southeast Asia (44%), Africa (25%) and the West Pacific (18%). Eight countries with the highest number of TB cases, covering two-thirds of all TB cases in the world are India (26%), China (8.5%), Indonesia (8.4%), Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%). Tuberculosis is the main cause of death from infectious diseases, ranking above Human Immunodeficiency Virus (HIV). In 2019, it was estimated that there would be 845,000 new cases of TB in Indonesia, with 19,000 among them also yield positive HIV results. The death rate among TB patients is 92,000 for patients with negative HIV and 4,700 among the positives.[7,8]

The clinical signs and symptoms of TB may vary between patients. Radiological examination may shows either miliary TB, TB pleuritis, tracheobronchial TB or tuberculoma. Pulmonary tuberculoma is a homogeneous round-shaped opacity, well-defined and caused by Mycobacterium tuberculosis (MTb). Pulmonary tuberculoma is also known as Assmann's focus, solitary or round focus, coinage lesion, tuberculous nodule and caseous nodule. This nodule resembles a tumor and originates from enlarged caseous tubercles in the lung.[2,5,9]

Tuberculoma has a diameter ranging from 1 to more than 10 cm. Tuberculomas are most often found in the lungs and central nervous system. It can be found in primary or post-primary TB cases. The inoculation of MTb in bronchioles causes an immune reaction mediated mainly by alveolar macrophages and forms a granuloma. Granuloma can develop into a tuberculoma by growing in size and covered by connective tissue, with caseous necrosis in the middle.[2,5,9]

PATHOGENESIS OF PULMONARY TUBERCULOMA

The pathogenesis of TB is closely related to the host's immune response and

the number of inhaled droplet nuclei. Only some people exposed to MTb will develop TB disease. Droplet nuclei can reach the respiratory bronchioles and alveoli. The MTb bacteria that enter through the airways will latch onto the lung tissue and form pneumonia nests called primary foci. The primary focus can occur anywhere and causes inflammation of the lymph passages leading to the hilum (local lymphangitis) and then enlargement of the hilar lymph nodes (regional lymphadenitis). The primary focus and regional lymphangitis are known as the primary complex.[8]

Primary complexes will undergo one of several events, including healing without any defects, leaving little scars (such as Ghon nests, fibrous lines and calcification nests in the hilum) or spreading either through *percontinuitatum* spread to the surrounding tissue, bronchogenic spread either on one or both sides of the lung, lymphatic spread to the lymph nodes or hematogenous spread through bloodstream. The severity of hematogenous spread depends on the body's immune resistance and virulence of the bacteria themselves. This spread might cause extrapulmonary TB and result in either recovery with sequelae or death.[8]

Primary TB infection begins with inhalation of MTb into the lungs, then phagocytosis of MTb by alveolar macrophages occurs and infection can progress with or without lung damage. Among 90-95% of healthy individuals will experience a latent infection for several years and potential for reactivation. During the active infection phase, infected macrophages cause an inflammatory response and form granulomas. Activation of the adaptive immune system causes macrophages to become giant cells (Datia Langhans cells), foamy macrophages surrounded by T and B cells. Other macrophages phagocytose dead macrophages.[10]

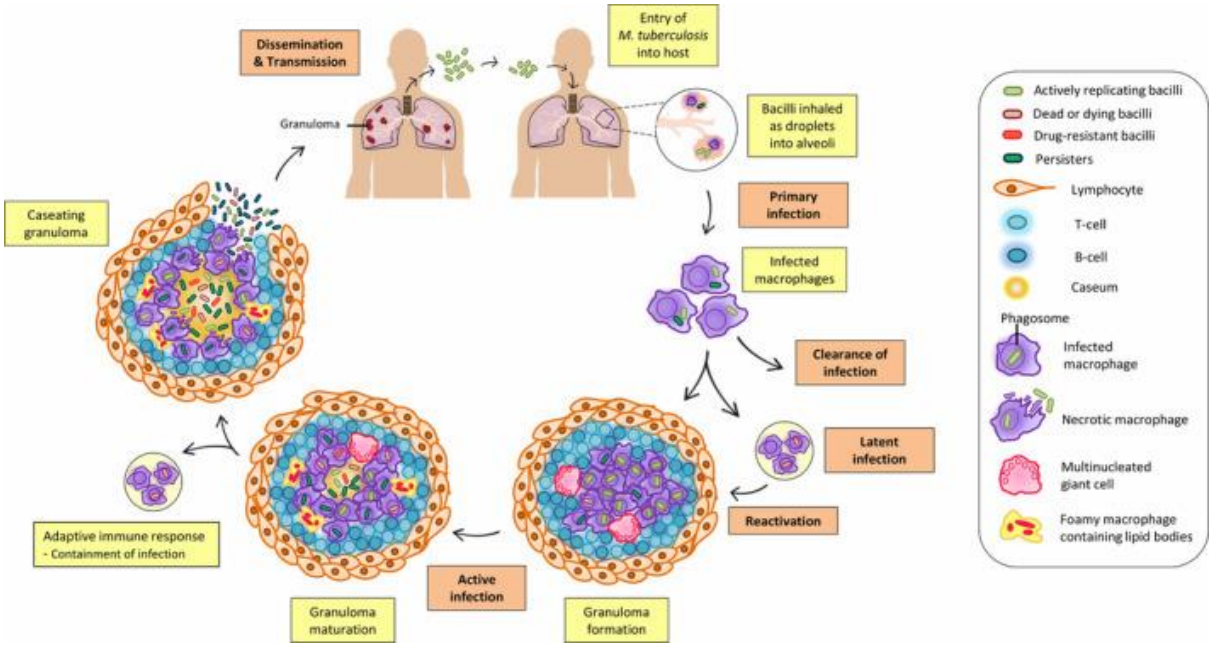

Figure 1. Pathogenesis of tuberculosis[10]

DIAGNOSIS OF PULMONARY TUBERCULOMA

Diagnosis of tuberculoma is challenging, not only because it requires invasive procedures such as needle aspiration or transthoracic biopsy and open thoracotomy, but also because it can be accompanied by cancer in some rare cases. In general, patients with tuberculoma can be asymptomatic. Some cases of tuberculoma can yield symptoms such as chest pain, cough with or without blood, body weakness, decreased appetite or symptoms of TB in general. There may be a history of TB treatment or previous TB contacts. Physical examinations might show no abnormalities.[4,8,9]

Microbiological diagnosis of pulmonary tuberculoma is determined through the findings of acid-fast bacteria (AFB) on microscopic examination or culture of the sputum, AFB from bronchoalveolar drainage samples or positive results in polymerase chain reaction (PCR) testing. Research conducted by Sochocky et al stated that 17 out of 30 tuberculoma cases showed positive results of AFB in sputum culture. The tuberculin test can be performed to rule out the differential diagnosis of lung cancer.[11]

Radiological examinations that can be carried out in the diagnosis of tuberculoma are chest radiography, ultrasonography (USG), thoracic computed tomography (CT) scan and positron emission tomography (PET) scan. Examination of the chest radiography in the posteroanterior position may show a radioopaque lesion, round or oval with flat and smooth edges with diameter around 1.5-8 cm. Tuberculoma nodules are more frequently found in the upper lobes of the lungs, can be solitary or multiple with central necrosis lesion. Other features in chest radiography that might be important in diagnosing and determining prognosis for tuberculoma are satellite nodules, calcifications and cavities. Calcifications are found in 20-30% of tuberculoma cases.[11,12]

Figure 2. A tuberculoma chest radiograph showing a solitary pulmonary nodule in the left hemithorax[12]

Thoracic USG is carried out by administering contrast fluid (4.8 ml of sulfur hexafluoride added to 5 ml of normal saline) intravenously, followed by the examination itself to find patterns of contrast enhancement. A study conducted by Cao et al evaluated 21 tuberculoma patients and found three patterns of contrast enhancement on ultrasound results, namely rim enhancement (only the peripheral parts that enhance contrast but not the central), homogeneous enhancement (homogeneous echogenicity) and heterogeneous enhancement (multiple echoic and hypoechoic areas on ultrasound).[1]

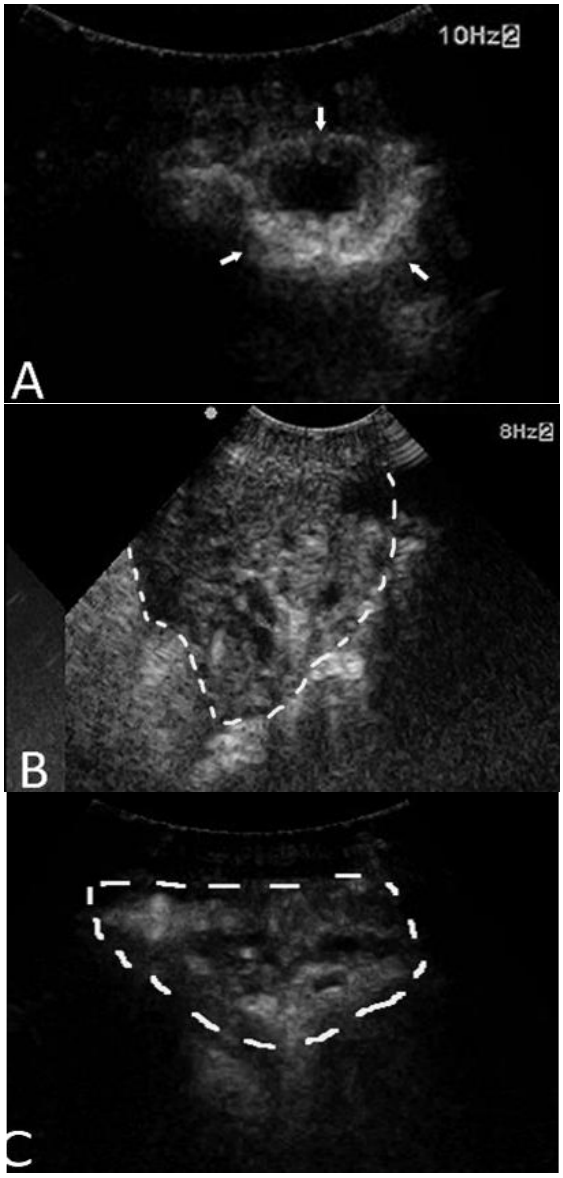

Figure 3. Tuberculoma ultrasound pattern after contrast administration. A) Rim enhancement; B) Homogeneous enhancement; C) Heterogeneous enhancement[1]

Thoracic CT scan with contrast in tuberculoma cases might generate an image similar to lung cancer or tumor metastases in the lung. A study by Totanarungroj et al described that tuberculoma lesions could be found anywhere but were more common in the upper lobes of both lungs. Compared to lung cancer, imaging of tuberculoma more commonly showed multiple lesions, smaller in size (<2 cm), round or polygonal in shape with flat and smooth edges, had satellite nodules, with less nodule enhancement and air bronchogram. Tuberculoma also possessed dense central calcifications and no internal cavities. Bronchovascular invasion also rarely happened.[13] Pulmonary tuberculoma is said to be inactive if the diameter size of the nodule on the CT scan persists for more than three months.[11]

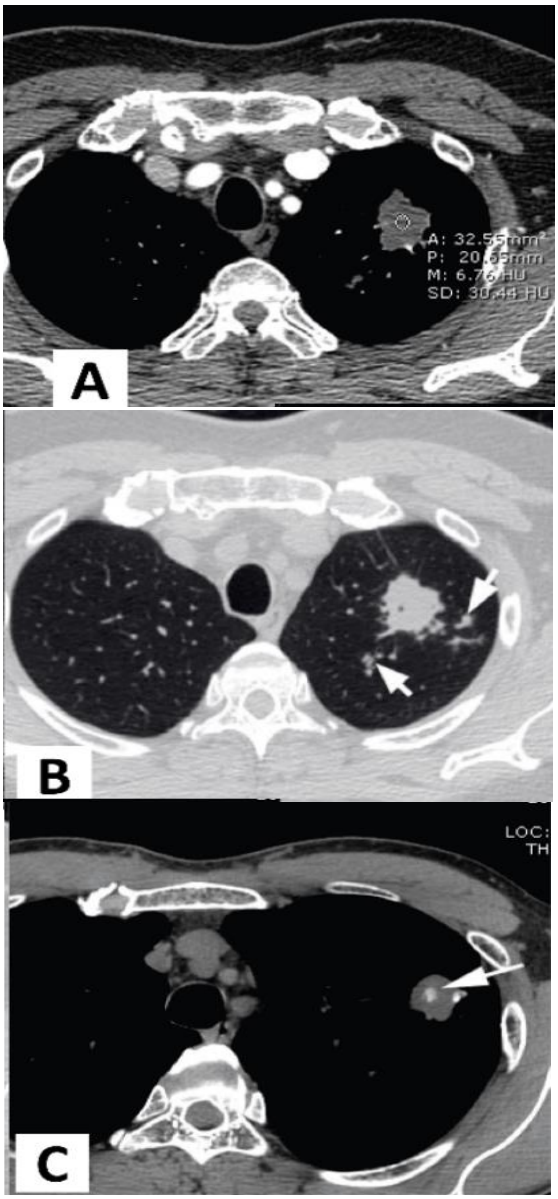

Figure 4. Thoracic CT scans with contrast in a patient with tuberculoma. A. Polygonal, non-enhancing nodule in the left upper lobe. B. Satellite nodule (arrow). C. Central calcification (arrow)[13]

Positron emission tomography is a non-invasive examination. In tuberculoma cases, PET scans are often interpreted as false positives for malignancy. Since active glucose metabolism happens during active granulomatous inflammation, this results in the accumulation of 18F-fluorodeoxyglucose (18F-FDG), similar to lung cancer. One way to differentiate tuberculoma and lung cancer is by using 11C-choline. Choline uptake in tuberculomas is lower than in cancer cells because cancer cells require choline to maintain phospholipid synthesis in cell membranes.[3,14]

Bronchoscopy is important for diagnosing solitary pulmonary nodules, both benign and malignant. The aim of bronchoscopy is to avoid thoracotomy in non-malignant cases and sampling for malignant nodules. Flexible fiber bronchoscopy and transbronchial biopsy are the most frequently performed procedures. The size of the nodule affects the success rate of the procedure.[15]

A study by Lai et al showed that the success rates for diagnosis of nodules sized <2 cm, 2–4 cm and >4 cm in diameter were 35.3%, 64.5%, and 68.8%, respectively. Flexible fiber bronchoscopy, transbronchial biopsy, bronchial brushing and bronchial washing yielded a diagnostic success rate of 40-80% for nodules >2 cm in size. Bronchoscopy findings in tuberculosis cases include granulomatous ulcers, solitary ulcers, hyperplastic lesions and fibrous stenosis.[15]

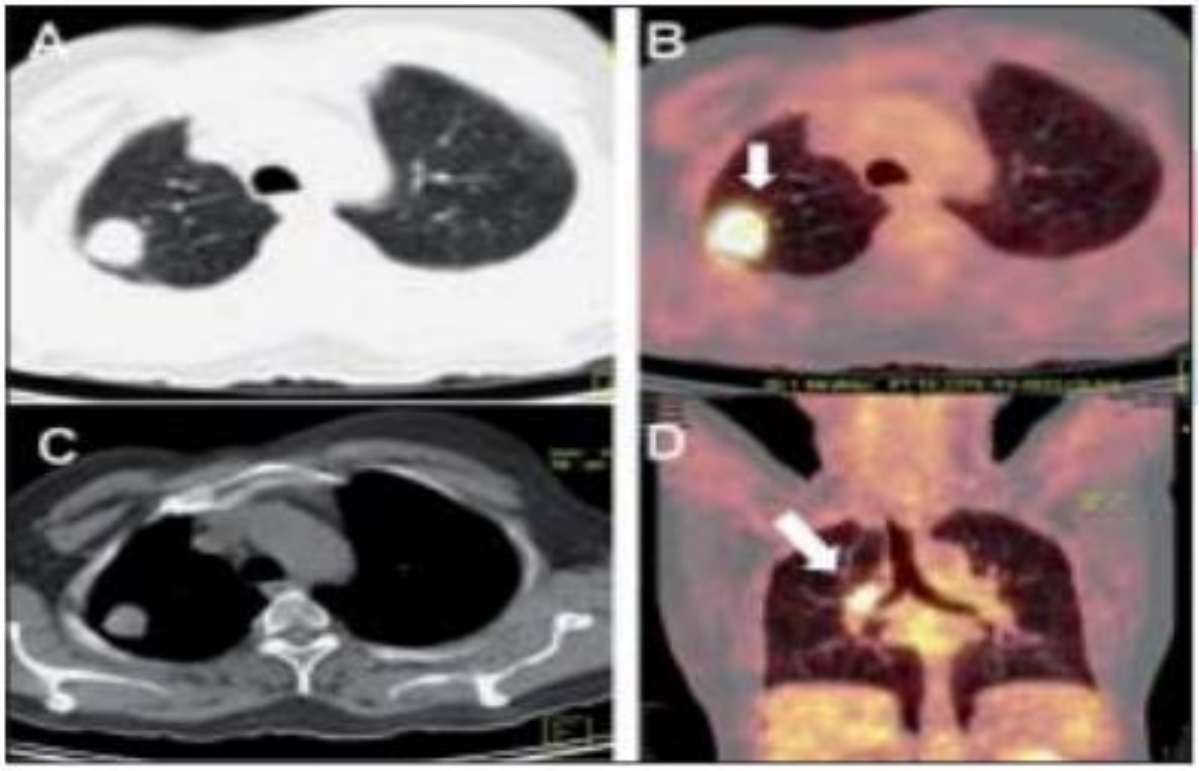

Figure 5. Pulmonary tuberculoma. Axial lung (A) and mediastinal window (C) CT images show a soft tissue density nodule in the right upper lobe of the lung. Axial (B) and coronal (D) PET/CT images reveal intense FDG uptake in the nodule (SUV_{max} of 19.0) and an enlarged right parabronchial node (arrows), suggesting a malignant neoplasm. Wedge resection and histopathologic examination of this solitary pulmonary nodule revealed TB. In TB endemic countries like India, FDG-avid lung lesions need to be interpreted cautiously[16]

MANAGEMENT OF PULMONARY TUBERCULOMA

Antituberculosis Drugs

Anti-TB drugs remains the mainstay of the management of pulmonary tuberculoma. Tuberculoma usually responds poorly to anti-TB drugs and requires long-term treatment. A clinician must be real careful in evaluating the effect of anti-TB drugs in tuberculoma cases because tuberculoma usually shrinks in size after the administration of anti-TB drugs for three months, as described in a study by Lee et al on 45 patients with tuberculoma.[2,4]

In this study, the smallest tuberculoma was found in the diameter of 23.2±10.8 mm, while the largest was 32.1±17.8 mm. Anti-TB drugs were given in the duration of 11.7±3.7 months. There were three kinds of anti-TB regiments given to the subjects, namely combination of rifampin, isoniazid, ethambutol, and pyrazinamide (38 patients), the combination of rifampin, isoniazid, and ethambutol (as many as six patients) and combination of ethambutol, streptomycin, cycloserine and levofloxacin (one patient due to poor liver function).[2,4]

After three months of anti-TB treatment, 18 patients (40%) showed a reduction (>25%) in tuberculoma diameter, while 25 patients (55.6%) experienced no change and two patients (4.4%) showed enlargement. This evaluation was repeated on the 6th, 9th and 12th month of anti-TB administration, which found a decrease in tuberculoma diameter in 24 patients (57.1%), 25 patients (59.5%) and 32 patients (76.2%), respectively. At the end of follow up period (27.0±10.2 months after initial anti-TB administration), there were 37 patients (82.2%) in the decreased group, seven (15.6%) in the no change group and one (2.2%) in the increased group. Continuous administration of anti-TB drugs for a long time wasn't found to be useful if the diameter does not decrease and might cause drug resistance instead. If the size of tuberculoma increases after receiving adequate treatment, lung resection is the treatment of choice.[4,9]

Surgery

Before performing surgery to manage tuberculoma, two things should be considered: the spread of MTb bacteria after surgery and the possibility of bronchopleural fistula. Surgery is performed as both diagnostic and therapeutic measures. Diagnostic surgery should be considered if other modalities have been performed without yielding any satisfactory results, while therapeutic surgery might be useful especially in cases of massive blood coughing.[2,9]

Indications for surgical management include prolonged sub-febrile fever, tuberculoma with the diameter of >3 cm, size of tuberculoma not decreasing after six months of anti-TB drugs administration, positive smear or culture, lung parenchymal damage, multiple tuberculomas in one lobe and suspected lung cancer or metastases.[2,9]

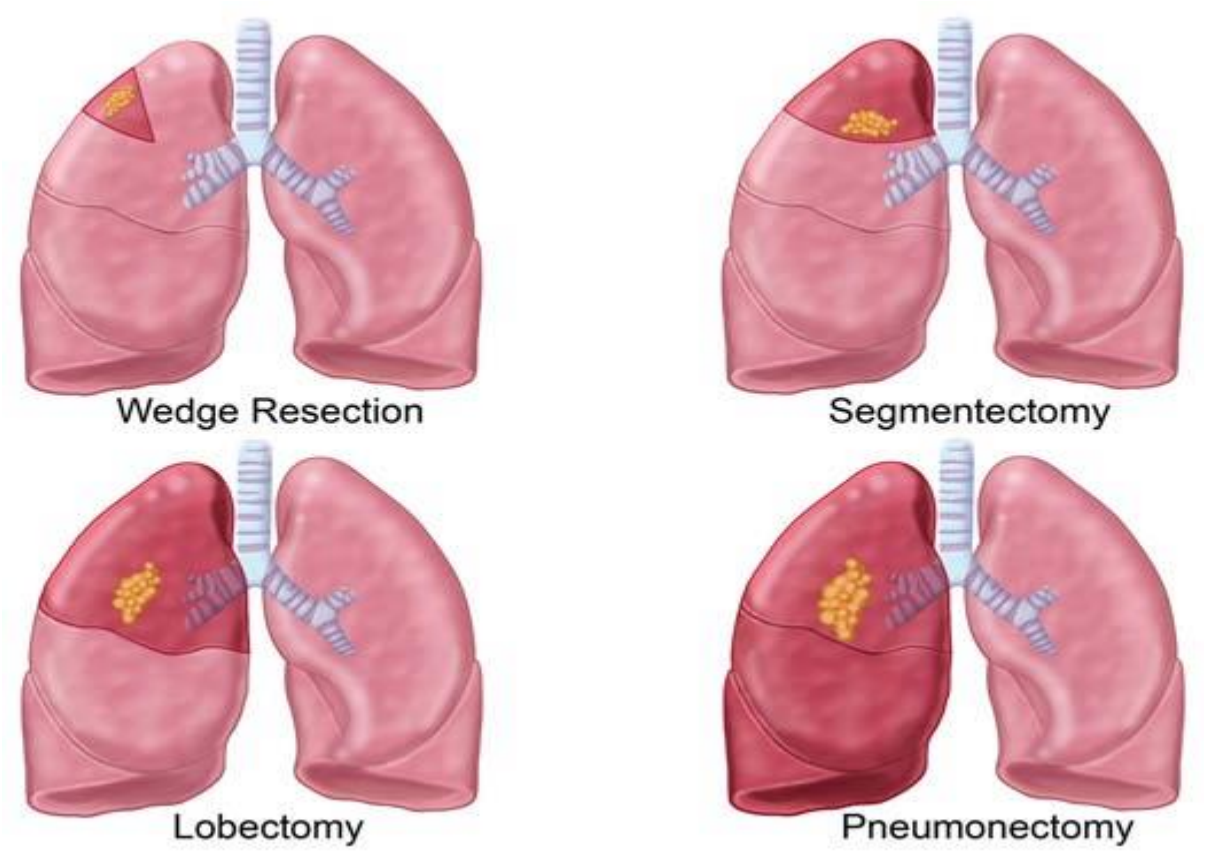

Figure 6. Lung Resection Technique[17]

Surgery might be performed through open lung resection or video assisted thoracoscopic surgery (VATS) with the condition in which no anti-TB drugs resistance is found and anti-TB drugs have been administered at least two months before the procedure.[2,9]

The choice of resection performed is based on the shape and location of the tuberculoma. If the lesion is peripheral, a wedge resection technique can be performed, while lobectomy is preferred if there are multiple lesions in one lobe. Nowadays, a less invasive surgical technique called tubeless VATS has been developed. This procedure was performed with no intubation nor general anesthesia, only using intercostal innervation block and sedation since only one hole incision was made. The advantages of this technique are short anesthetic time, minimal postoperative pain, faster postoperative healing and minimal incision. Anti-TB drugs administration is continued for 6-12 months postoperatively to prevent the progression or recurrence of tuberculosis.[2,9]

CONCLUSION

Pulmonary tuberculoma is often found as a solitary pulmonary nodule on radiological examination. The diagnosis of pulmonary tuberculoma is obtained from the history, physical examinations, laboratory and radiology examinations. Diagnosis modalities include chest

radiography, USG, CT scan, PET scan and bronchoscopy with transbronchial biopsy. The management of pulmonary tuberculoma is anti-TB drugs administration and surgery. Anti-TB drugs are recommended to be given for more than 6 months and surgery is indicated if the size of the tuberculoma does not decrease after administration of anti-TB drugs.

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