Review Article

Recent advances in the management of pulmonary tuberculoma with focus on the use of tubeless video-assisted thoracoscopic surgery

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Abstract: Pulmonary tuberculoma are benign solitary pulmonary nodules representing up to 25% of all resected solitary pulmonary nodules. However, the differentiation between pulmonary tuberculoma and lung cancer, as well as between active tuberculoma and inactive tuberculoma remains a clinical challenge. The present review summarizes the recent advances in the management of pulmonary tuberculoma, including radiological findings, the response to anti-tuberculosis treatment and surgical treatments. Application of the novel tubeless video-assisted thoracoscopic surgery (VATS) technique in both the diagnosis and treatment of pulmonary tuberculoma has been found to be safe and feasible and leads to less surgical trauma, which results in reduced length of hospitalization and better post-operative quality of life.

Keywords: Pulmonary tuberculoma; video-assisted thoracoscopic surgery (VATS); anti-tuberculosis treatment

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Introduction

Only a few decades ago, pulmonary tuberculosis was the leading cause of death in China. However, the incidence and mortality of pulmonary tuberculosis decreased drastically worldwide during recent years, including in China. This was primarily due to the introduction of effective anti-tuberculosis chemotherapy. However, the incidence and prevalence of pulmonary tuberculosis varies worldwide. Among the 9 million incident cases of tuberculosis in 2013, 56% were found in Asia and only 7% were found in Europe and America combined. In China, the incidence of tuberculosis remains as high as 918,000 cases per year (1). The clinical presentation of tuberculosis varies between patients, and typical radiological findings include miliary tuberculosis, exudative pleuritis, tracheobronchial tuberculosis and tuberculoma (2).

Tuberculomas are spherical, avascular and granulomatous tumors of tubercles that are most commonly found in the lungs and central nervous system. Tuberculomas are primarily observed in healed primary tuberculosis infection but can occasionally also exist in post-primary tuberculosis. Pulmonary tuberculoma develop in approximately 7–9% of tuberculosis patients (3). Inoculation of the *M. tuberculosis* bacteria in the bronchioles causes a complex immunological reaction that is orchestrated by the local alveolar macrophages, leading to granuloma formation.

These granulomas can grow into tuberculomas by increasing in size and becoming encapsulated with connective tissue with caseous necrosis in the center. Calcification is found in 20–30% of tuberculomas, and small satellite lesions are often observed in the immediate vicinity of the main lesion (2).

Pulmonary tuberculomas usually present as a solitary pulmonary nodule (SPN). SPNs are defined as single, round or oval nodules with well-defined boundaries that are smaller than or equal to 30 mm. SPNs can be either benign (such as pulmonary hamartoma, hemangioma, inflammatory pseudotumor, lymph node hyperplasia and tuberculoma) or malignant (such as squamous cell carcinoma, adenocarcinoma and bronchioloalveolar carcinoma). The larger the size of the nodule, the greater the risk for malignancy (4). Some reports have shown that up to 25% of all resected SPNs have been identified as tuberculoma, making it the most common type of SPN (3). However, the percentage of tuberculoma among SPNs varies greatly depending on the incidence of tuberculosis in the area. In areas where tuberculosis is rare, the risk of the SPN being malignant is substantially higher. The incidence of cancer in patients with SPN ranges from 10% to 70% globally (4). Differentiation between active tuberculoma and primary or metastatic lung cancer remains a clinical challenge. Resection of benign SPNs, including tuberculoma, is performed using pulmonary wedge resection. However, the resection technique is very different for malignant SPNs, which require radical surgery with lobectomy and systemic lymph node dissection (5).

The present review summarizes recent advances in the management of pulmonary tuberculoma, including clinical considerations, radiological characteristics, response to anti-tuberculosis treatment and indications for surgical treatment, with special focus on the novel tubeless video-assisted thoracoscopic surgery (VATS) technique in both the diagnosis and treatment of pulmonary tuberculoma.

Clinical considerations

Pulmonary tuberculoma can coexist with multi-drug-resistant tuberculosis. Wang *et al.* (6) studied the efficacy and safety of surgical resection in the treatment of 56 patients with multi-drug-resistant tuberculosis. An analysis of disease-free survival (DFS) using the Kaplan-Meier survival curve revealed that the four patients with pulmonary tuberculoma in this study had 100% DFS, making their prognosis the best among all of the included patients.

The coexistence of pulmonary tuberculoma with primary or metastatic lung cancer is not uncommon, especially in the aging population. However, this coexistence is often difficult to identify. On contrast-enhanced dynamic computed tomography (CT) and high-resolution CT, these lesions are sometimes in the same lesion but can also appear in different locations in the same lobe or in different lobes (7). The pathogenic mechanisms behind this remain not completely known. Rizzi *et al.* reported that patients who were medically treated for tuberculosis may later develop scar cancers in the same area of the lung (8). These patients may present with atypical clinical and radiographic findings, such as a lack of improvement despite adequate medical treatment, which often leads to the need for surgical intervention.

It is also important to note that not all tuberculomas are small. Tuberculoma with sizes as large as 10–11 cm in diameter have also been reported (9).

Radiographic findings of pulmonary tuberculoma

It is important to differentiate active pulmonary tuberculoma from inactive ones. Active tuberculoma has a central mass of epithelioid cells with Langhans type giant cells and varying degrees of caseation, and inactive tuberculoma is primarily composed of acellular caseous material and fibrosis (10). Ongoing active infectious processes can be detected by ^{18}F-fludeoxyglucose (^{18}F-FDG) positron emission tomography-CT (PET-CT) (11), contrast-enhanced dynamic CT (12) or nest polymerase chain reaction (13) *etc*. Visual and quantitative analysis of double phase PET-CT (11,14,15) with both early and delayed images have been reported to successfully differentiate between active and inactive pulmonary tuberculoma. The active nodules are presented as centrilobularly distributed satellite nodules with FDG update on both early and delayed images visualized by non-enhanced CT. This is difficult to differentiate from lung cancer. The inactive nodules have spiculated margins without FDG updates on both early and delayed images. Statistically significant differences between several quantitative indices are observed between active and inactive tuberculoma on double phase ^{18}F-FDG PET. Additionally, some researchers reported that PET can be used to evaluate the efficacy of anti-tuberculosis treatment. Biopsy-confirmed tuberculoma decrease in maximal standardized uptake value (SUV) on PET scan upon effective anti-tuberculosis treatment.

In 2002 (12), a paper in the *Chest* journal studied the use of contrast-enhanced dynamic CT parameters in the

diagnosis of active pulmonary tuberculoma. Subjects with active tuberculomas had significantly higher peak height values than inactive ones. The specificity was 96.4% and sensitivity was 77.1%. Additionally, the relative flow values were significantly higher among subjects with active tuberculomas than inactive ones. The specificity was 88.8% and sensitivity 68.5%. Several characteristics of pulmonary tuberculoma can be found on contrast-enhanced dynamic CT. While pulmonary tuberculoma were most commonly presented with peripheral enhancement patterns, other patterns, such as central curvilinear enhancement, homogeneous enhancement and partial enhancement, can also be observed. These patterns on contrast-enhanced CT images may reflect the histologic background. The histology of pulmonary tuberculoma display different images depending on the inflammatory phase of this disease. During the first phase of granuloma formation, pulmonary tuberculoma is patchy due to multiple microscopic foci. During the second necrotic phase, the tuberculoma presents with a large necrotic core surrounded by multinucleated giant cells and epithelioid histiocytes. Fibroblasts start to show up during the third proliferative phase to form a dense fibrotic capsule at the periphery of the necrotic core, keeping the tuberculoma in a stable inactive state. Although nested polymerase chain reaction can also be used to detect mycobacterium tuberculosis in solitary pulmonary nodules with good sensitivity (87.5%) and specificity (96%), it cannot differentiate active pulmonary tuberculoma from inactive tuberculoma (13).

Response to anti-tuberculosis treatment

Pulmonary tuberculoma respond poorly to anti-tuberculosis treatment and often requires long-term treatment. In 2004, a retrospective study (16) published by the *European Respiratory Journal* assessed the response to anti-tuberculosis treatment in 45 cases of pulmonary tuberculoma. After a mean treatment duration of 11.5±3.6 months, only 40% of patients showed a reduction in tuberculoma size (>25% reduction in area versus its initial area) after 3 months of treatment, while 55.6% remained unchanged, two patients had an increased tuberculoma size (>25% increase in area versus its initial area). However, the enlargement is transient during the early phase of treatment. The response rates improved drastically after 12 months of treatment with 76.2% showing a size reduction.

The diagnosis of pulmonary tuberculoma often requires invasive procedures such as percutaneous fine needle biopsy or VATS. A correct diagnosis is important because pulmonary tuberculoma may be accompanied by lung cancer in rare cases. It is therefore essential for the clinician to be aware of the various responses of pulmonary tuberculoma to anti-tuberculosis treatment. The natural progression of pulmonary tuberculoma commonly includes three phases: a progressive period, a steady period (most common, 30–50% of all affected patients) and a regression period. Auerbach *et al.* found that after the administration of anti-tuberculosis medical treatment, there was a greater reduction in the perifocal reaction surrounding tuberculosis foci (17) and a greater thinning of the capsule surrounding the necrotic foci (18). Cases of SPN containing both tuberculosis and tuberculoma have been reported, and lung cancer misdiagnosis can occur. If the size of pulmonary tuberculoma increases with medical treatment, surgical resection may offer the most appropriate solution.

Surgical treatment of pulmonary tuberculoma

The indications for surgical treatment of tuberculoma are the following: long-lasting subfebrile temperature, tuberculosis intoxication, diameter >3 cm, positive sputum culture, lung parenchymal destruction, multiple tuberculomas in one lobe, and suspected primary or metastatic lung cancer. In 1997, Perelman *et al.* (19) reported 161 surgical pulmonary tuberculoma cases. The choice of operation, wedge or lobectomy, was dependent on the anatomy of the tuberculoma. Peripherally located tuberculomas are operated with pulmonary wedge resection, but multiple tuberculoma in one lobe or large tuberculoma near the hilus are operated with lobectomy. Perioperative complications were very low (no specific data), and no deaths were reported.

The development of modern thoracic surgery techniques, especially VATS, enables the effective treatment of patients with pulmonary tuberculoma. Complications of pulmonary tuberculoma that are unresponsive to conventional anti-tuberculosis treatment can also be treated with VATS. Notably, surgical procedures are not only aimed to cure the patient but also to prevent the development of tuberculosis infection in other people. Treatment should be individualized, and excessively long periods of anti-tuberculosis treatment are rarely advisable.

Although radiological parameters can provide some clues regarding the nature of the SPN, surgical resection of the nodule remains the gold standard of diagnosis and is performed to exclude primary and metastatic lung

cancer. Resection is also valuable to help determine further treatment strategies and decrease the duration and dose of anti-tuberculosis treatment. In many cases, bronchoscopic or needle biopsy are not practically possible, and VATS is therefore a good minimally invasive option (20). Authors from Taiwan (21) reported 53 cases of tuberculoma that underwent VATS. The procedure was found to be associated with few side effects. No perioperative mortality was found, and only two patients had prolonged air leakage (>7 days); two others had minor wound infections that recovered after anti-tuberculosis treatment or antibiotic treatment. Anti-tuberculosis treatment for 6 to 12 months was routinely administered postoperatively. VATS can also be applied in the diagnosis or treatment of various tuberculosis diseases, such as pleural effusion, single or multiple nodules, or cavitary lesions (22). Anti-tuberculosis treatment is not necessary preoperatively and is usually administered postoperatively (23).

VATS can also be carried out without intubation. Non-intubated uniportal VATS is a novel procedure. It is technically feasible and safe for selected patients and a less invasive alternative in managing indeterminate peripheral SPNs. The benefits of non-intubated uniportal VATS include short anesthetic induction, minimal postoperative pain, rapid recovery after the operation, and satisfaction regarding the surgical incision in the patient. As many as 97% of patients were very satisfied or satisfied with the resulting scars at 1 month (24). There are both awake and sedation states in the uniportal procedure. Under the completely awake condition, when a frozen section shows primary lung cancer, the surgical procedure may be significantly prolonged because of additional margin resection and lymph node dissection, which increases the physical discomfort and psychological tension of the patients. The second is a targeted sedation that is monitored by the bispectral index value, which can show whether the patients tolerated the surgical procedure well and allowing a total operating time of up to 213 minutes.

One study (24) included 32 patients with indeterminate peripheral SPNs who underwent uniportal VATS without tracheal intubation using a combination of intercostal nerve block and intrathoracic vagal block, as well as target-controlled sedation. A definite diagnosis was obtained in all 32 cases. A wedge resection was performed in 31 patients and a lobectomy in only 1 patient. Conversion to non-intubated multiple VATS was required in 4 patients. Among those, 3 patients had primary lung cancer requiring further resection for the adequacy of margins and in only 1 patient converted due to difficulty in identifying the small nodule. Conversion to the intubated VATS requires lung ventilation because of very vigorous mediastinal movement.

The increasing popularity of high-resolution CT in lung cancer screening has led to increasing numbers of peripheral indeterminate pulmonary nodules being identified. For reasonable surgical candidates, a minimally invasive surgery with a combination of a simple anesthetic method and small incision is a good choice. Rocco *et al.* (25) reported that the resection of peripheral pulmonary nodules with the awake uniportal VATS technique in selected patients is not only safe but also feasible. The length of hospitalization is also reduced, which further cuts costs. Utilizing uniportal VATS in an awake patient could help solve the clinical challenge of undetermined SPNs.

Tubeless VATS

Tubeless VATS is a special type of non-intubated VATS that is not only carried out under non-intubated spontaneous respiratory anesthesia but also without the use of a urinary catheter or a chest drainage tube. By forgoing the use of the tubes, all minor complications and pain associated with tracheal intubation, chest tubes, muscle relaxants, discomfort at the site of incision, and urinary catheters are avoided. The most prominent desire of patients and surgeons is less surgical trauma, which results in faster recovery and better post-operative quality of life. The benefit of tubeless VATS can be observed in the incredibly fast post-operative discharge and recovery. Tubeless VATS can be used for a number of pulmonary conditions, even including major pulmonary resections (26,27). Among 91 patients undergoing tubeless VATS for sympathectomy, bullae resection or mediastinal tumor resection, only 2 patients had their operation aborted for some reason. Compared to patients who underwent intubated VATS, the tubeless group showed advantages in the postoperative fasting time, the mean duration of the postoperative hospital stay, and postoperative pain scores (28). In SPN, a study on 34 patients in China (29) showed that tubeless VATS provided definitive diagnosis for all patients and was well-tolerated in the 5 weeks follow-up time, with no need of conversion to endotracheal intubation and no need for re-intervention with chest drain or urinary catheter. Another study comparing 30 patients who underwent non-intubated uniportal VATS with 30 who underwent tubeless VATS found that patients in the tubeless group reported less postoperative pain and had on the average 1.3 days shorter hospital stay (30).

The increasing adoption of tubeless VATS has been observed worldwide and continues to gain popularity. With increased training of both surgeons and anesthesiologists for the complete surgical procedures and the indications, tubeless VATS may at some point be applied in more than 50% of thoracic surgical procedures. This would translate to more than 1 million patients benefitting from a faster recovery or fewer days of post-operation recovery each year.

Conclusions

Pulmonary tuberculoma is difficult to differentiate from primary or metastatic lung cancer. Misdiagnosis and loss of diagnosis is common. Treatment of pulmonary tuberculoma should follow the multiple disciplinary team model, including the thoracic surgeon, tuberculosis department, pulmonary department, radiographic department, clinical nutritional department and others. Establishing a system of non-intubated uniportal VATS or tubeless VATS for the diagnosis and treatment of pulmonary tuberculoma may be necessary.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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