

Diagnostic Utility of Sago-Like Nodules on Gross Thoracoscopic Appearance in Tuberculous Pleural Effusion and Their Correlation with Final Histo-Microbiologic Findings

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Abstract

Background: Distinguishing tuberculous pleural effusion (TPE) from other causes of exudative effusion is often challenging. Delay in treatment initiation can occur while awaiting histo-microbiologic confirmation owing to the paucibacillary nature of the disease. Sago-like nodules are the most common visual finding on gross thoracoscopic appearance. The primary objective was to determine the diagnostic utility of the presence of sago-like nodules on gross thoracoscopic appearance in TPE to help justify early initiation of tuberculosis (TB) treatment based on their finding while awaiting final histo-microbiologic confirmation. Secondary objective was to study the correlation between the presence of sago-like nodules and the final histo-microbiologic findings in pleural biopsy specimens. **Methods:** This was a retrospective-descriptive study of all patients with exudative pleural effusion who underwent diagnostic medical thoracoscopy (MT) at Hamad General Hospital during an eight-year period (from January, 2008 to December, 2015). **Results:** The presence of sago-like nodules on gross thoracoscopic appearance of the pleural surface had a sensitivity of 58%, a specificity of 89% and a positive predictive value of 97% for TPE with a diagnostic accuracy of 62%. There is significant association between the presence of sago-like nodules and demonstration of granulomatous inflammation in pleural biopsy specimens ($P = 0.000$). There is no association between sago-like nodules and positive TB smear and culture in biopsy specimens. **Conclusion:** The presence of sago-like nodules on gross

thoracoscopic appearance has a high specificity and positive predictive value for TPE and significantly correlates with the presence of granulomatous inflammation. Patients from TB prevalent areas with exudative pleural effusion and sago-like nodules on gross thoracoscopic appearance may be commenced on TB chemotherapy while awaiting final histologic confirmation.

Keywords

Tuberculous Pleural Effusions, Medical Thoracoscopy, Sago-Like Nodules

1. Introduction

TB poses a major global public health problem for both developing and developed countries. It is the ninth leading cause of death worldwide and the leading cause from a single infectious agent. In 2016, there were an estimated 1.3 million TB deaths among Human Immunodeficiency Virus (HIV)-negative people and an additional 374,000 deaths among HIV-positive with an estimated 10.4 million people fell ill with TB in the same year [1]. Prompt and accurate diagnosis of TB, followed by provision of treatment in line with international standards does not only prevent deaths and limit ill-health among people who develop the disease but also prevents further transmission of infection to others [1]. TPE is the second most common form of extrapulmonary TB worldwide and the most common cause of exudative pleural effusion in endemic TB areas [2]. TPE typically presents as an acute or subacute illness with fever and unilateral exudative pleural effusion with predominant lymphocyte count in the pleural fluid [2] [3] [4]. Nevertheless, such clinical presentation and initial fluid analysis results can be seen in other diseases such as malignancies, sarcoidosis and some rheumatologic disorders [5]. The gold-standard for the diagnosis of TPE remains the detection of *Mycobacterium tuberculosis* (MTB) in pleural fluid or pleural biopsy specimens, either by microscopy and/or culture, or the histological demonstration of caseating granulomas in the pleura along with acid fast bacilli (AFB) [4]. Nevertheless, major challenges encountered in confirming the diagnosis of TPE are the failure to detect AFB on microscopic examination in more than 90% of cases and the long time for AFB to grow on culture (more than 8 weeks) [4]. This can lead to a significant delay in diagnosis and treatment initiation. As a result, the demonstration of AFB has been dropped as an absolute requirement for making the diagnosis of TPE and the presence of caseating granulomas in high burden settings is considered adequate to make the diagnosis [4] [6]. Considering the above challenges in diagnosing TPE, there has been an interest in utilizing the gross thoracoscopic visual appearance of the pleural cavity in making quick diagnosis of TPE in order to initiate the treatment while awaiting final microscopic or histologic confirmation. However, the currently available evidence supporting this approach is limited [7]. We have shown in a previous study from this country that sago-like nodules to be among the most common

findings on gross thoracoscopic appearance of TPE cases (seen in 51% of cases) [8]. Similar results have also been reported by other investigators [7]. To the best of our knowledge the diagnostic utility of the presence of sago-like nodule on gross thoracoscopic appearance in making TPE diagnosis is seldom reported in literature. The primary objective of this study was to determine the diagnostic utility of the presence of sago-like nodules on gross thoracoscopic appearance in TPE in order to justify early initiation of TB treatment based on finding of these nodules while awaiting final histo-microbiologic confirmation. Secondary objective was to study the correlation between the presence of sago-like nodules and the final histo-microbiologic findings in pleural biopsy specimens.

2. Materials and Methods

This was a retrospective-descriptive study of all patients with exudative pleural effusion who underwent diagnostic MT at Hamad General Hospital (The only tertiary government hospital performing MT in the State of Qatar) during an eight-year period (from January, 2008 to December, 2015).

2.1. Definition of TPE

In this study, we defined TPE in a patient with clinical presentation suggestive of TB and exudative pleural effusion by the presence of one or more of the following criteria: 1) positive AFB smear or culture in the pleural fluid or pleural biopsy, 2) presence of caseating granulomas in pleural biopsy; 3) presence of non-caseating epithelioid granulomas in pleural biopsy, in absence of other causes of non-caseating granuloma and favorable response to anti-tuberculous medications.

2.2. Definition of Sago-Like Nodules

Sago-like nodules (also called sago grain-like nodules) are fairly small less than 5 mm solid or caseous seeding of the pleural surface resembling sago grains obtained from palm stems (**Figure 1**).

2.3. MT Procedure

MT at Hamad General Hospital is conducted in the bronchoscopy suite under conscious sedation and local anesthesia using a rigid thoracoscope. The position of the patient varies according to site of effusion, but an anterolateral thoracic approach in the 5th or 6th intercostal space is employed in the majority of patients. Following a 1 - 2 cm incision, a blunt dissection is done with an artery forceps. A trocar with inner diameter of 8 mm is then inserted through a cannula, followed by insertion of the thoracoscope. After achieving clear visualization, the pleural cavity is thoroughly inspected and usually 4 - 5 biopsies are taken from the abnormal areas on parietal pleura by a lateral “lift and peel” technique. Multiple biopsies are taken if no gross abnormalities are noted. All samples are submitted for histopathology and mycobacterial culture. After thoracoscopy, a 24 French chest tube connected to an underwater seal is routinely inserted for

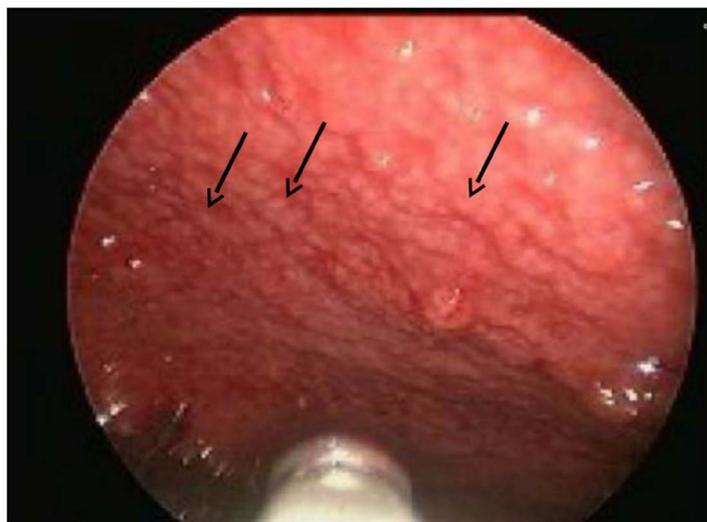


Figure 1. Thoracoscopic image of sago-like nodules on parietal pleura.

drainage of iatrogenic pneumothorax and the tube is removed once pneumothorax has resolved.

2.4. Data Collection

Medical records (both paper and electronic) of all patients with exudative pleural effusion who underwent MT during the study period were analyzed. Demographic data of subjects, pleural fluid characteristics, pathological and microbiological details were recorded in a structured data collection sheet. Details of the MT procedure including gross visual thoracoscopic findings and complications were obtained from the electronic as well as the paper health records and recorded in the structured data collection sheet.

2.5. Statistical Analysis

Categorical and continuous values were expressed as frequency (percentage) and mean \pm SD or median. Descriptive statistics were used to summarize demographic and all other clinical characteristics of the study subjects. Associations between two or more qualitative variables were assessed using the chi-square test or Fisher Exact test as appropriate. Relationship between two quantitative variables was examined using Pearson's correlation coefficients. All P values presented are two-tailed, and P values < 0.05 were considered statistically significant. All Statistical analyses were done using statistical packages SPSS 22.0 (SPSS Inc. Chicago, IL). The accuracy of gross thoracoscopic findings was expressed as sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy.

2.6. Ethical Approval

The research protocol (RP#14422/14) was approved by the Medical Research Center at Hamad Medical Corporation.

3. Results

Among the 407 subjects with exudative pleural effusion who underwent MT during the study period, 344 were diagnosed with TPE based on the criteria mentioned above. Characteristics of subjects with TPE are shown in **Table 1**. Sago-like nodules (**Figure 1**) were observed in 58% (198/344) of TPE cases and in 11% (7/63) of non-TB cases of exudative pleural effusion (**Table 2**). The presence of sago-like nodules on gross thoracoscopic appearance of the pleural surface had a sensitivity of 58%, a specificity of 89% and a positive predictive value of 97% for TPE with a diagnostic accuracy of 62% (**Table 3**). Among the 7 patients with non-tuberculous pleural effusion who had sago-like nodules, 4 had metastatic adenocarcinoma, 1 had lymphoma, 1 had para-pneumonic effusion and 1 had lupus pleuritis. The histopathologic examination of pleural biopsy revealed necrotizing granuloma in 76% (**Figure 2**), and non-necrotizing granuloma in 12% of cases (**Table 4**). Positive AFB smear was observed in 26% of the pleural biopsy specimens and positive MTB culture in 53% (**Table 5**). The presence of sago-like nodules on gross visual appearance during MT is significantly associated with the finding of granulomatous inflammation in pleural biopsy specimens ($P = 0.000$) (**Table 5**). However there was no association between sago-like nodules and positive AFB smear and TB culture in biopsy specimens.

Table 1. Characteristics of subjects with TPE.

Demographics variables	N (%) (Total 344)
Age	
Mean age	30.8 ± 9.5 years
<20 years	14 (4.1)
20 - 50 years	310 (89.1)
50 - 64 years	16 (4.7)
>65 years	4 (1.2)
Gender	
Male	301 (87.5)
Female	43 (12.5)
Ethnicity	
Indian subcontinent	267 (77.6)
Philippines	24 (7.0)
Middle east	11 (3.2)
African	33 (9.6)
Other	9 (2.6)
Occupation	
Unskilled	180 (64.3)
Semiskilled	64 (22.9)
Skilled	24 (8.6)

Continued

Others	12 (4.3)
Risk factors & Comorbidities	
Smoking	64 (18.9)
Alcohol	34 (10)
Diabetes Mellitus	9 (2.6)
Hypertension	8 (2.3)
Coronary Artery disease	3 (0.9)
Average length of hospital stay (days)	4.2

Table 2. Gross thoracoscopic findings in TPE.

Finding	N (%)
Normal	11(3.2%)
Hyperemic pleura only	11 (3.2%)
Hyperemia with adhesions	101 (29.4%)
Sago-like nodules with hyperemia	198(57.5%)
Hyperemia with non-Sago like nodules/plaque like lesions	8 (2.3%)
Missing info	15(4.4)

Table 3. Diagnostic value of sago-like nodules for TPE.

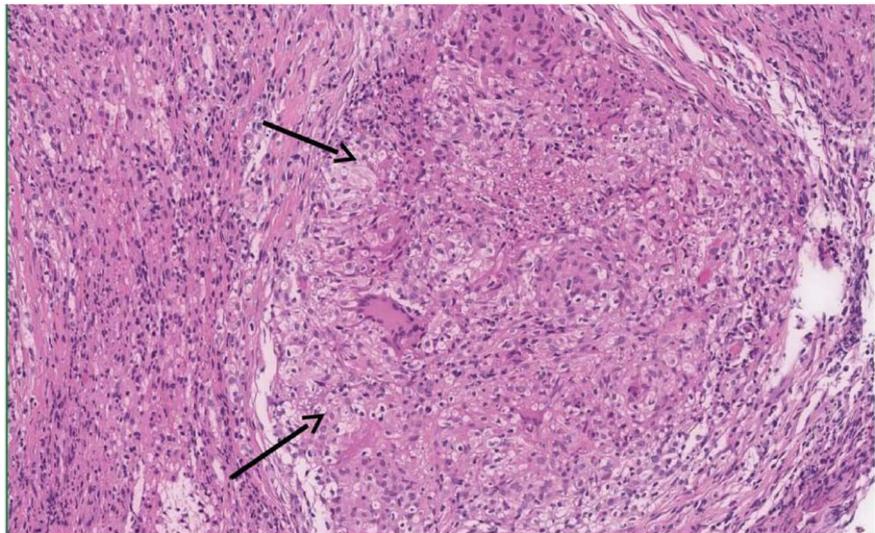
Sago like nodules in TPE	
Sensitivity	58%
Specificity	89%
Positive Predictive value	97%
Negative predictive Value	28%
Positive Likelihood Ratio (LR+)	5.2
Negative Likelihood Ratio (LR-)	4.8
Diagnostic accuracy	62%

Table 4. Histo-Microbiologic findings in pleural biopsy specimens in TPE.

Histopathology	N (%)
Necrotizing Granuloma	262 (76.2)
Non Necrotizing Granuloma	41 (12)
Non Specific Inflammation	31 (9)
Normal	4 (1.1)
Inadequate	6(1.7)
Microbiology	N (%)
Positive AFB stain of pleural Biopsy (N = 336)	88 (25.5)
Positive Tb culture of pleural Biopsy (N = 209)	114 (53.1)

Table 5. Association between the presence of Sago-like nodules on gross thoracoscopic appearance and presence of granuloma, positive AFB smear and positive TB culture.

Outcome		Sago-like nodules present on thoracoscopy	Sago-like nodules absent on thoracoscopy	P value
Granuloma in pleural biopsy	Granuloma present	183	100	0.000
	Granuloma absent	22	57	
AFB smear in pleural biopsy	AFB smear positive	51	33	0.424
	AFB smear negative	150	119	
TB culture in pleural biopsy	TB culture positive	64	45	0.102
	TB culture negative	56	61	

**Figure 2.** Necrotizing granuloma in tuberculous pleuritis showing a peripheral rim of epithelioid histiocytes surrounding the central necrotic region (H & E, 400×).

4. Discussion

Pinpointing the cause of exudative pleural effusion in a patient poses a diagnostic challenge, particularly in distinguishing TPE from other causes of exudative effusion. Because the conventional investigations done on pleural fluid are not always helpful, more invasive procedures are usually needed to confirm the diagnosis and exclude other diseases that cause exudative effusion [9]. MT has gained widespread acceptance in the diagnosis of exudative pleural effusion as it allows direct visualization of the pleura and biopsy from abnormal sites. In many institutions where facilities for MT are available, it replaces second-attempt thoracentesis and closed needle biopsy for patients with exudative effusions of unclear etiology [10]. The visual features are the first and most direct findings on

MT. As histological verification usually takes 5 - 7 days in many hospitals [7], visual features on MT can afford physicians the early impression about the diagnosis, help them pursue the management of patients and minimize delay in treatment and possibly length of hospital stay [7]. Studies conducted on peritoneal TB proved that visual diagnosis on laproscopic examination was very accurate in making the diagnosis of this type of TB. Such studies recommended the initiation of TB chemotherapy on the basis of visual laparoscopic appearances alone [11] [12]. Nevertheless, the evidence on utility of thoracoscopic visual appearance in the diagnosis of TPE is limited by the scarcity of studies. In the current study, sago-like nodules along with hyperemia was the most common gross thoracoscopic finding in TPE. Similar results have also been reported by other investigators. In a study of 46 patients with TPE who underwent MT, Casalini *et al.* reported that presence of small nodules on the parietal pleura as the most frequent endoscopic picture at thoracoscopy in 56.5% of cases [13]. Similarly, Wang *et al.* reported small pleural nodules as the most common gross thoracoscopic finding in 69.4% of cases [14]. In this study also, we demonstrated the high specificity and positive predictive value of sago-like nodules in diagnosing TPE. In an agreement with this finding, Kong *et al.* in a retrospective study from China evaluated 91 patients who underwent MT for suspected TPE and reported a sensitivity and specificity of the presence of diffuse miliary nodules on pleural surface as 64.47% and 86.67% respectively with a positive predictive value of 96.08% [7]. An interesting end point in the current study is investigating the correlation between the presence of sago-like nodules and the final histologic findings on pleural biopsy. The presence of sago-like nodules was significantly associated with the demonstration of granuloma formation in pleural biopsy but not with positive AFB smear or culture. To the best of our knowledge this correlation is seldom reported in previous studies. Granulomas are the hallmark of MTB infection and thus sit at the center of TB immunopathogenesis. They are compact, organized aggregates of immune cells consisting of blood-derived infected and uninfected macrophages, foamy macrophages, epithelioid cells (uniquely differentiated macrophages), and multinucleated giant cells (Langerhans cells) surrounded by a ring of lymphocytes. The granuloma's main function is to localize and contain MTB while concentrating the immune response to a limited area [15] (**Figure 2**). In the current study granuloma formation in pleural biopsy was observed in 88% of cases while positive AFB smear in 25% and positive AFB culture in 53%. This finding confirms the previous recommendation that demonstration of MTB bacilli in biopsy specimens is not an absolute requirement for making TPE diagnosis and the presence of caseating granulomatous inflammation in high burden sittings is considered adequate [4] [6] [16]. In the State of Qatar, TB is a common health problem with an incidence of 40/100,000 populations per year and is the most common etiology of exudative pleural effusions accounting for 84.5% of cases [8]. About 97% of TB patients are expatriates (mostly from Asian countries with high TB prevalence) [17]. Due to the high

burden of TB, most patients with exudative pleural effusions are admitted to the hospital for isolation until sputum results are proved negative for AFB and MT is usually performed in hospital. These factors could have attributed to the high average length of stay associated with MT procedure in the current study. Following MT procedure, waiting for histologic confirmation (can take up to one week) may further result in substantial delay in initiating TB chemotherapy. The high specificity and high positive predictive value of sago-like nodules may thus justify the initiation of TB chemotherapy while awaiting final histological confirmation. Besides being among the first studies reporting the diagnostic utility of sago-like nodules in making TPE diagnosis and elaborating on the correlation with final histologic findings, a point of strength in the current study is the relatively large number of recruited patients compared to previous studies investigating the role of MT in diagnosing pleural effusion. Furthermore, the current study confirmed the results of previous studies regarding the prevalence and diagnostic utility of sago-like nodule in TPE. Nevertheless, besides the retrospective nature, important limitation of this study is the lack of study of the impact of operator (performing physician) experience on the visual thoracoscopic findings in TPE. Furthermore, because estimation of adenosine deaminase (ADA) level in pleural fluid is not performed in our institution, we could not study the correlation between ADA level and the presence of sago-like nodules.

5. Conclusion

In conclusion, the presence of sago-like nodules on gross thoracoscopic appearance has a high specificity and positive predictive value for TPE and significantly correlates with the presence of granulomatous inflammation. Patients from TB prevalent areas with exudative pleural effusion and sago-like nodules on gross thoracoscopic appearance may be commenced on TB chemotherapy while awaiting final histologic confirmation.

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Conflicts of Interest

This manuscript is an original one. It has not been published or considered for publication elsewhere. None of the authors has financial or otherwise any conflict of interest from publishing this manuscript. The manuscript has been seen and agreed upon by all authors.

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