Thoracoscopy in undiagnosed pleural effusions

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Objective. To review the indications and accuracy of diagnostic thoracoscopy for pleural effusions of unknown origin.

Design. Retrospective review of consecutive patients referred for diagnostic thoracoscopy over a 5-year period from 1 January 1989 to 31 December 1993.

Setting. Tertiary referral cardiothoracic unit.

Patients. Thirty-four patients referred from either medical or oncology services within a university-affiliated academic complex.

Interventions. All patients had diagnostic thoracoscopy performed under general anaesthesia. Retrospective data were collected in respect of presenting symptoms, gross findings, final pathological findings, amount of drainage, length of hospital stay and complications of the procedure. In 7 patients (21%), iodised talc was insufflated at the same time to create pleurodesis.

Main results. Final diagnoses were: 17 (50%) malignant disease, 6 (18%) tuberculosis and 9 (26%) 'negative' pathology. In 2 (6%), further intervention was required to make a conclusive diagnosis. The diagnostic sensitivity for malignant disease was 89% and the specificity 100%. For pleural tuberculosis both the sensitivity and specificity were 100%. For 'negative' diagnoses the negative predictive value was 82%. A history of fever and sweats had a marked association ($P = 0.002$) with the final diagnosis of tuberculosis. No association could be identified between the gross observations at the time of thoracoscopy and the final diagnosis. The average length of hospital stay was 6.7 (range 1 - 25) days. There was 1 in-hospital death (3%), and 9 patients (26%) had major complications related to the procedure.

Conclusions. Diagnostic thoracoscopy is a useful modality for obtaining a diagnosis in effusions of unknown origin where other methods have failed. The presence of symptoms such as fever and sweats is highly associated with a final diagnosis of tuberculosis.

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Diagnostic thoracoscopy (pleuroscopy) was first introduced by Jacobaeus in 1910,[1] when during the era of pulmonary collapse therapy for tuberculosis it was used to lyse adhesions, thereby facilitating therapeutic atelectasis. With the development of more effective treatment for tuberculosis enthusiasm for and expertise in its use waned. Being relatively invasive it tended to be shunned by the pulmonologist and was at the same time viewed by the surgeon as a minor, unrewarding procedure. The purpose of this study was to evaluate our local experience with diagnostic thoracoscopy for patients with pleural effusion who remain undiagnosed afer preliminary investigations.

Material and methods

Patient population

We retrospectively reviewed 34 consecutive diagnostic thoracoscopies performed for pleural effusion of unknown origin (EUO) over a 5-year period from January 1989 to December 1993 in the Department of Cardiothoracic Surgery at Groote Schuur Hospital. All patients were referred from either the medical or the oncology services within the academic complex.

Procedure description

Thoracoscopy was performed under general anaesthetic in the main operating suite of the hospital. In 18 cases (53%), double-lumen endotracheal intubation was used to facilitate lung collapse and enhance visualisation of the entire pleural space. In the remainder single-lumen intubation with pleural venting and low tidal volume ventilation was utilised. In no patient was CO_2 insufflation used. Examination of the pleural space was enhanced by rolling or tilting the patient to displace the lung during the procedure.

To choose the optimal site of trocar insertion current chest radiographs or computed tomography scans were reviewed at the time of the procedure. The patient was positioned in either a semi-lateral or full lateral decubitus position. After surgical preparation, needle aspiration was performed at the site of proposed trocar insertion and specimens were sent for cytological and bacteriological examination. If the tap was positive, a 9 mm trocar and sleeve were inserted and the pleural space evacuated with a standard suction cannula. The thoracoscope (Karl Stortz GMBH, Germany) was inserted through the trocar sleeve and the entire pleural space visualised. Multiple representative biopsies were taken with optically guided biopsy forceps. Care was taken to avoid direct lung biopsy or areas where intercostal arteries or other vessels could be anticipated. At the end of the procedure an intercostal drain was inserted through the trocar site into the pleural space and attached to an underwater drainage system. The drains were left *in situ* until less than 50 ml drainage per 24-hour period was observed.

In 7 (21%) talc insufflation was administered concomitantly with the thoracoscopy. Two grams of pharmaceutical grade asbestos-free sterilised iodised talc[2] was insufflated into the pleural space using a standard insufflator (Richard Wolf GMBH, Germany). Complete coating of the parietes was confirmed visually before termination of the procedure.

Follow-up

Final diagnoses were obtained from pathological reports and autopsy records or by follow-up notes in cases where no overt pathological cause was identified. Diagnosis was considered to be 'negative' if no pathological cause could be identified or if the patient's eventual course was one of complete resolution of the EUO. The 'working diagnosis' was defined as the presumptive clinical diagnosis recorded by the referral source at the time of admission for the procedure. Patients with 'negative' pathological findings were reviewed at 12 or more months after thoracoscopy to record outcome and confirm diagnostic accuracy.

Statistical and analytical methods

Categorical differences between groups were analysed using Pearson's χ^2 statistic or Fisher's exact test using the SPSS statistical package (SPSS Inc., Chicago, USA). For consideration of diagnostic yield the following formulas were used:

$$\text{Sensitivity} = \frac{\text{True positives}}{\text{True positives} + \text{false negatives}}$$

$$\text{Specificity} = \frac{\text{True negatives}}{\text{True negatives} + \text{false positives}}$$

$$\text{Negative predictive value} = \frac{\text{True negatives}}{\text{True negatives} + \text{false negatives}}$$

Results

The patient profile and summary of results are shown in Table I.

Indications for thoracoscopy

For the 34 patients referred with the problem of EUO the average time from initial medical contact to referral was 25 days (range 1 - 165 days). The most common presenting symptoms were dyspnoea (76%), chest pain (65%), cough (62%), significant weight loss (50%) and fever with night sweats (26%). Fifty-five per cent were current or previous smokers, 18% had previous exposure to asbestos, and in 11% there was a history of previous malignant disease.

Final diagnoses

A final diagnosis of malignant disease was made in 17 patients (50%), tuberculosis was found in 6 (18%) and findings were 'negative' in 11 (32%), of whom 2 (6%) were eventually found to be falsely negative for malignant disease. In the latter the diagnosis was made by open lung biopsy in one (lung carcinoma) and lymph node biopsy (lymphoma) in the other. Comparison of the final diagnosis with the working diagnosis revealed a change in a high percentage of cases (Table II). The most accurate clinical pre-thoracoscopic diagnosis was with a working diagnosis of tuberculosis where thoracoscopy confirmed the suspicion in 85% of cases and the diagnostic specificity was 83%. However for the remainder, mesothelioma (38%), metastatic malignancy (45%) and non-malignancy and non-tuberculosis

Table I. Summary of results

Total patients	34
Race	
Black	10 (29%)
Mixed	16 (47%)
White	8 (24%)
Sex	
Male	31 (91%)
Female	3 (9%)
Ratio (M/F)	10.3:1
Average age (yrs) (range)	53 (20 - 85%)
Final diagnosis	
Malignant	17 (50%)
'Negative'	9 (26%)
Tuberculosis	6 (18%)
False negative (malignancy)	2 (6%)
Diagnostic sensitivity	
Malignancy	89%
Tuberculosis	100%
Diagnostic specificity	
Malignancy	100%
Tuberculosis	100%
Negative predictive value	
'Benign' histology	82%
Chest drain time (range)	58 h (2 - 264 h)
Length of stay (range)	6.7 d (1 - 25 d)
Complications	
Major	9 (26%)
Minor	11 (32%)
Mortality	1 (3%)

Table II. Final diagnosis compared with presumptive clinical diagnosis (working diagnosis) as recorded by the referral source prior to thoracoscopy

	Working diagnosis No. (%)	Final diagnosis* No. (%)	Specificity of clinical judgement
Tuberculosis	13 (38)	6 (18)	83%
Mesothelioma	7 (21)	8 (24)	38%
Metastatic	9 (26)	9 (26)	45%
'Negative'	5 (15)	9 (26)	33%

* Excluding 2 patients (6%) with a false-negative diagnosis of malignant disease.

(33%), the clinical impression was proved wrong in the majority of cases.

Table III shows the relationship between the final diagnosis and the pre-operative symptoms and risk factors. No patient with a final diagnosis of primary or metastatic tumour had a history of previous malignant disease ($P = 0.014$). History of exposure to asbestos was as frequent in patients found not to have mesothelioma as in those who did. All patients with a final diagnosis of malignant disease had a history of smoking. Anorexia and weight loss were frequently seen with the final diagnosis of tumour or tuberculosis but was uncommon with a final diagnosis of 'negative' histology.

The gross thoracoscopic findings in each diagnostic category are displayed in Table IV. There appeared to be no association between these findings and the final diagnosis. In the 9 patients with 'negative' diagnoses, 2 were lost to follow-up, 3 died and in 2 cases autopsy confirmed absence of malignant disease or active tuberculosis. The remaining 4 patients are alive and well and effusion-free at a mean follow-up of 24 months.

Diagnostic efficiency

The average time from initial contact by the referring physician to diagnosis was 28 days (range 1 - 165 days). In only 1 patient (3%) with pleural tuberculosis could an appreciable delay in the diagnosis be identified that might have delayed treatment. Most patients had received pleural taps and/or closed pleural biopsies as part of their diagnostic work-up. Of all patients, 71% had between 1 and 5 aspirations (mean 1.7) and 63% underwent between 1 and 3 closed pleural biopsies (mean 1.4) prior to referral. Four (12%) were referred without either pleural tap or biopsy, 2 (6%) because of a clinical suspicion of mesothelioma that was borne out by the final diagnosis.

Thoracoscopy was found to have a sensitivity of 89% and a specificity of 100% for the diagnosis of malignancy. For the diagnosis of pleural tuberculosis, both sensitivity and specificity were 100%. Where the final result of investigation was 'negative', the negative predictive value was 82%, confirmed at 1 year after thoracoscopy.

Other therapeutic and operative procedures

The average amount of pleural fluid drained at the time of surgery was 1 027 ml (range 0 - 4 000 ml). The average period of time that the intercostal drains were left in was 58

Table III. Relationship between the final diagnosis, risk factors and symptoms

	Incidence of risk factor or symptoms (%)				
Final diagnosis	Fever/ sweats	Anorexia/ weight loss	Smoking	Asbestos exposure	Malignancy history
'Negative'	22	11	44	22	22
Mesothelioma	0	63	63†	25	0
Malignant lung	0	40	100†	0	0
Metastatic other	33	75	100†	25	0
Tuberculosis	83*	83	33	33	17
False negative	50	50	50	0	50

* $P = 0.002$ — clinical history of fever or night sweats v. a final diagnosis of pleural tuberculosis.
† $P = 0.014$ — clinical history of smoking v. final diagnosis of malignant disease (all types).

Table IV. Final diagnosis v. gross observational findings

Findings	No.	Final diagnosis 'Negative'	Mesothelioma	Malignant lung	Metastatic other	Tuberculosis	False negative
Pleural thickening	13	3	2	2	2	4	
Nodules	7	1	2	1	1	1	1
Nodules and thickening	6	2	3	1			
Nonspecific	4	2		1			1
Prolific tumour	3		1		1	1	
Normal	1	1					
Total	34	9	8	5	4	6	2

hours (range 2 - 264 hours). In no case was re-expansion pulmonary oedema documented in the postoperative period. In addition to the diagnostic procedure, 7 (21%) had talc insufflated to stimulate pleurodesis. The indication was presumed malignant disease in all cases; however, this was borne out in only 4 of the 7 patients. The clinical results of this were a complete success in 4, partial success in 2 and no success in 1, where the lung failed to expand satisfactorily. Empyema developed in 3, 1 with metastatic tumour and the other 2 with benign pathological findings. The median length of stay in hospital after the procedure was 6.7 days (range 1 - 25 days).

Complications

Complications of the procedures are listed in Table V. The most common complication was prolonged excessive drainage, which occurred in 9 (26%). One patient underwent drainage for over 10 days, before drains could be removed. Three in this same group developed empyema as a complication. Of note is that all patients who developed empyema had talc pleurodesis.

Table V. Morbidity and mortality

Complication	No. (%)
Prolonged drainage (> 100 ml/day and > 5 days)	9 (26)
Empyema	3 (9)
Incomplete lung expansion	2 (6)
Prolonged air leak (> 3 days)	2 (6)
Respiratory distress	2 (6)
Tumour at insertion site	1 (3)
Death	1 (3)

Nineteen complications occurred in 16 patients, giving an overall morbidity rate of 47%. One post-procedural death occurred, giving a mortality rate of 3%.

Tumour implantation at the site of trocar insertion developed in 1 patient with mesothelioma. This was treated with external-beam radiotherapy and the patient subsequently survived for 14 months. There was 1 in-hospital death, a 54-year-old woman with a history of previous tuberculosis who presented with a large pleural effusion and diffuse bilateral interstitial lung infiltrates. Thoracoscopy revealed a generalised pleural thickening and biopsy was non-diagnostic. Sudden acute respiratory distress manifested on the second postoperative day and the patient died shortly thereafter. Autopsy showed extensive nonspecific pulmonary fibrosis with no evidence of active tuberculosis or malignancy.

Discussion

The success of cytological analysis of pleural fluid by thoracentesis varies widely and is reported to be diagnostic in 45 - 96% of malignant effusions.[3-8] Where mesothelioma is the final diagnosis the diagnostic yield is reduced to approximately 20%.[6,7,8] The diagnostic yield is lower with malignant effusion secondary to primary lung carcinoma compared with metastatic effusions.[10] This may be due to the fact that effusions may occur as a result of lobar collapse, lymphatic obstruction, pneumonitis or severe hypoproteinaemia rather than pleural tumour involvement. A second tap for cytology can increase the yield by 17 - 22%, but further aspirations are unlikely to increase this figure.[5] For pleural lymphoma the diagnostic yield may be as low as 10%.[10] The false-positive rate of pleural fluid cytology for malignancy is less than 1% in most series.[4] The yield from pleural biopsy alone in malignant effusions has a broad reported range of success (30 - 70%).[4,8,10] Prakash[11] reported that in only 7% of patients with non-diagnostic pleural cytology did an additional closed pleural biopsy give a finding of malignancy. Storey *et al.*[10] found a tumour in only 2 of 8 patients (25%) with non-diagnostic cytology. Conversely, in tuberculous effusions the pleural biopsy often plays a significant role. Epstein *et al.*[12] found closed pleural biopsy to be diagnostic in 88% of patients, with EUO subsequently shown to be of tuberculous origin. In a comprehensive review by Tomlinson and Sahn,[8] rates of diagnosis between 60% and 95% are reported. Both non-diagnostic thoracentesis and pleural biopsy do not ensure the absence of serious pathology, as was shown in 81% of the patients in this study.

The diagnostic yield of most series reviewing basic diagnostic modalities for pleural effusions ranges from 87% to 99%.[13] Unfortunately 5 - 27% of patients remain without diagnosis at the conclusion of normal investigations.[10,14-16] With long-term follow-up, approximately 50% of these patients are found to have malignant disease.[6] This percentage varies with the predominant pleural pathology of the cohort, region and institution.[16] In our series, 56% of patients presenting with EUO were subsequently proven to have malignant disease. The 18% of our patients subsequently proven to have tuberculosis is high compared with most Western series and probably reflects the high prevalence of this disease within our local community.

Thoracoscopy offers several advantages over repeated thoracentesis and blind pleural biopsy, viz.: (*i*) potential access to the entire pleural space; (*ii*) direct visualisation and biopsy of pathology; (*iii*) potential for additional lung biopsy if indicated; (*iv*) identification and potential control of

complications such as bleeding and air leak; and (*v*) easy addition of insufflated talc (or other agents) for pleurodesis, if indicated at the same session.

The reported diagnostic sensitivity for thoracoscopy in EUO is high. Menzies and Charbonneau[6] in a prospective study of 102 patients obtained a definitive diagnosis in 94% of 95 patients (42 malignant, 31 benign and 22 idiopathic). Overall, thoracoscopy was 96% accurate, with sensitivity of 91%, specificity of 100% and negative predictive value for pleural malignancy of 100%. These results are comparable to those of open pleural biopsy,[8] with the major advantage being the less invasive nature of the procedure. Publications from the developed world tend to reflect a high incidence of malignancy in EUO and correspondingly high success rates for thoracoscopy.[17-20] Harris *et al.*[13] reported a diagnostic sensitivity of 95% and specificity of 100% for pleural malignancy; after a 6-month follow-up they reported a negative predictive value of 94%. The diagnostic sensitivity for malignancy in our series was 89% and for pleural tuberculosis 100%, with specificities of 100% for both. The negative predictive value for patients not diagnosed with tumour or tuberculosis was 82%.

In our study we found a poor correlation between gross thoracoscopic observations and the final diagnosis and would therefore not recommend that any presumptions be made on the basis of these findings. Of note is that one patient described by the operator as having 'gross tumour', returned the histological diagnosis of tuberculosis. Our observations did not agree with those of Harris *et al.*,[13] who found that age over 50 and a pre-operative history of malignancy were statistically significant as positive predictors of malignancy diagnosed at thoracoscopy. However, our data did show a significant correlation between a history of fever and sweats and the final diagnosis of tuberculous effusion. This is similar to the findings of Marel *et al.*[16] who observed that an elevated temperature was associated with a non-malignant aetiology in 73% of cases. A diagnosis of 'negative' histology was returned in 44% of our patients. Ryan *et al.*[14] found that 61% of patients who underwent a thoracotomy for EUO remained without a diagnosis during a follow-up of 1.5 - 15 years. In many of these patients aetiologies such as viral pleurisy or peri-pneumonic effusion are the probable cause.

It has not been our practice to perform therapeutic thoracentesis prior to the procedures. The rationale proposed is to facilitate anaesthesia and prevent re-expansion pulmonary oedema.[21] No instances of pulmonary oedema occurred in our series despite amounts of up to 4 litres being removed at a single session. Conversely we feel that the presence of an effusion facilitates insertion of the thoracoscopy cannula. The most convincing argument for pre-operative thoracentesis is that it may demonstrate the inability of the lung to expand fully, obviating futile attempts at pleurodesis.[3] Possibly by utilising this approach the incomplete lung expansion noted in 2 (6%) of our patients may have been avoided.

Reported peri-operative mortality rates associated with diagnostic thoracoscopy range from 0% to 10%.[3,20,22] Complication rates between 9% and 20% have been reported[13,23] and vary largely because of definition and completeness of reporting. Our most troublesome complication was failure of lung expansion (6%), which contributed to the development of empyema in 1 patient. One of our patients with mesothelioma developed tumour implantation at the site of trocar insertion. This has been reported in approximately 30% of patients with the final diagnosis of mesothelioma and in 10 - 15% of other tumour types.[8] This complication is usually adequately palliated with external beam radiotherapy, as was the case in our patient.

All of our procedures were performed by thoracic surgeons. Arguably, the simplicity of the procedure allows it to be used by any practitioner with appropriate training and equipment. Iatrogenic injuries associated with the procedure are rare,[13,24] but it would be prudent to argue for thoracoscopy to be performed in institutions with amenities and personnel available for immediate thoracotomy. General anaesthesia provides optimal analgesia and the option of one-lung anaesthesia and manipulation to allow visualisation of the entire free pleural space. Thoracoscopy may be performed under local anaesthetic with a high degree of success.[21] Flexible pleuroscopy has been described[9,25] with limitations being the availability of equipment and the poor quality of biopsy material. It can be performed utilising sterilised standard bronchoscopy equipment.[20] Similarly, rigid thoracoscopy does not necessarily demand specialised equipment and can be adequately performed using the standard Carlens mediastinoscope or a rigid bronchoscope.[20]

It can be argued that the delay in the diagnosis of a malignant effusion is immaterial to the final outcome. Harris *et al.*[13] found that 48% of patients diagnosed with malignant disease by thoracoscopy were dead by 6 months. Irani *et al.*[4] reported a wide variation in survival depending on site of origin, the worst being the pancreas with a 3-month mortality rate of 100% and the best with ovary with a 2-year survival rate of 20%. In the final analysis the need to press on to more invasive measures to secure a diagnosis will depend on: (*i*) strength of the diagnostic impression; (*ii*) the patient's anxiety over the diagnosis; and (*iii*) urgency in identifying potentially treatable pathology. Harris *et al.*[13] found that 73% of patients had further surgery or therapeutic procedures performed, and in 36% the medical management was affected by the findings. In 10% of patients the working diagnoses changed as a result of thoracoscopy.

In conclusion, we feel that diagnostic thoracoscopy is a useful modality for obtaining a diagnosis in EUO where other methods have failed. The presence of symptoms of fever and sweats appears to be associated with a final diagnosis of tuberculosis and empirical treatment should be considered.

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