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Original Article

Role of Cryobiopsy in Diagnosis of Pleural Tumors

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Abstract

Background: Rigid thoracoscope is considered the gold standard procedure for diagnosis of pleural malignancies, but sometimes forceps biopsies are insufficient for diagnosis, the main aim of this study is to assess the diagnostic yield of pleural cryobiopsy and the safety of the procedure in cases with undiagnosed exudative pleural effusion.

Methods: The study was a prospective one and was done on 30 patients with an exudative pleural effusion that has not been yet diagnosed by the standard investigations. They underwent thoracoscopic pleural cryobiopsy, 6 of them were excluded as they were proved to be of inflammatory origin as revealed by histopathological results, While the remaining 24 patients with malignant pleural pathology were included in the study.

Results : Histopathological results of cryobiopsy was 100 % diagnostic, the most common result was mesothelioma (70.8%). In (83.3%) of cases there were fat cells in the biopsy reflecting the good depth of cryobiopsies. There were no crush cells in all biopsies reflecting the good quality and preserved tissue of cryobiopsies. As regard the complications there were mild controllable bleeding and post procedural pain that was controlled by simple analgesics.

Conclusions : Thoracoscopic pleural cryobiopsy has a high diagnostic yield with good depth and high quality and it is an effective procedure with mild controllable complications.

Keywords : Cryobiopsy, thoracoscopic, pleural, effusion, pleural tumors

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Introduction

Even after thoracocentesis or closed pleural biopsy, we are unable to diagnose 25% of pleural effusion cases.(1) requiring either medical or surgical thoracoscopy (VATS). Pleuroscopy is a less invasive, and cost-effective maneuver with a good diagnostic yield.(2)

Cryotechnique has been used since a while in the therapeutic management of endobronchial tumors. There was no recorded high risks or complications with it.(3) Despite thoracoscopy is a well recognized maneuver used for the diagnosis of malignancies of the pleura, recently the cryobiopsy is used in pulmonary medicine. Cryotechniques play an important role as a hemostatic, analgesic, and anti-inflammatory tool.

Using cryobiopsy in pleuroscopy gives the opportunity of higher diagnostic yield with large and well preserved tissues.(4)

The aim behind this study is to evaluate the diagnostic efficacy and safety of pleural cryobiopsy in the undiagnosed exudative pleural effusion.

Patients and methods

This prospective study included 30 patients with undiagnosed exudative pleural effusion that underwent thoracoscopic pleural cryobiopsy, 6 of them were excluded as they were proved to be of inflammatory origin as revealed by histopathological results, while the remaining 24 patients with malignant pleural pathology were included in the study. The study was done from July 2019 to October 2022 after approval from the Ethical Committee at our institute. An informed written consent was obtained from the patients.

Cases with bleeding tendency, hypoxemia, transudative effusion, pleural thickening with no effusion, or cardiac issues were excluded.

All patients were subjected to history taking including chest pain evaluation, dyspnea evaluation according to (mMRC) dyspnoea scale (from 0 to 4) [5] before and after the procedure, local examination and investigations, including blood count , s.albumin and creatinine, bleeding tendency analysis, and examination of the pleural fluid. Chest computed tomography was done before medical thoracoscopy.

Equipment Rigid thoracoscope (KARL-STORZ by Germany) in a thoracoscopy unit with its instruments, including, light source, trocar, rigid telescope, and cold light source with camera attached to the telescope.

Cryo-machine (ERBE by Germany) contains console, flexible cryoprobe (length 900 mm) and cryogen which is Carbon dioxide at (−78°C).

Technique

Local anesthesia (lidocaine 2%) was used in all patients and pethidine 100 mg as analgesic. The patient lies down in a lateral decubitus, with the affected side up. The fifth intercostal space mid axillary line was the site of puncture. Skin incision of 1 cm was made then dissection of the intercostal muscles to the costal pleura. The trocar was introduced then withdrawn, and we introduce the thoracoscope inside it.

Then the cryoprobe was introduced through the thoracoscope and approached to the suspicious area of pleura. After freezing for 10s, the pleura in contact with the cryoprobe was iced. The cryoprobe with the tissue adherent to it was pulled together with the thoracoscope. Then the samples were thawed in normal saline. 3 to 5 biopsy samples were obtained from suspicious areas in the parietal pleura. Then a chest tube with an underwater seal was inserted in place. The samples were fixed in formalin 10% and examined by a histopathologist.

Bleeding severity assessment:

Bleeding severity was classified according to this scale: **none; mild bleeding**: (self-limiting bleeding); **moderate bleeding**: (use of any intervention such as APC or electrocautery); ***severe bleeding***: (intravenous resuscitation and surgical or radiological interventions required).(6)

Statistical analysis

Data were coded by the researcher, and analysed using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA). Descriptive statistics were means, standard deviations, medians, ranges, frequency.

Results

Demographic data of the studied cases shows a range of age from 30 to 70 years old with Mean ± SD was (57.50 ± 8.1). 13 (54.2%) cases were males, while 11(45.8 %) cases were females. As regard

smoking status 8 (33.3%) cases were current smokers and 8 (33.3%) cases were ex-smoker while 8 (33.3%) cases were non-smokers. As regard the diagnosis, the diagnostic accuracy was 100%. 17 (70.8%) cases were diagnosed as mesothelioma, 6 (25%) cases were metastatic adenocarcinoma and 1 (4.2%) case was Non-Hodgkin's Lymphoma. **Table1**

Table 1: Baseline demographic characteristics, spectrum of histopathological diagnoses.

		N = 24
Age/years		57.50 ± 8.1
Sex	**Female**	11 (45.8%)
	Male	13 (54.2%)
Smoking status	**Current**	8 (33.3%)
	Ex-smoker	8 (33.3%)
	Non smoker	8 (33.3%)
Diagnosis	**Mesothelioma**	17 (70.8%)
	Adenocarcinoma	6 (25%)
	Non-Hodgkin's Lymphoma	1 (4.2%)

As regard chest CT findings, 13 (54.2%) cases were presented with moderate pleural effusion, 10 (41.7%) cases with massive effusion, 4 (16.7%) cases had mediastinal lymphadenopathy, and there was pleural thickening in 9 (37.5%) cases. During medical thoracoscopy we found a pleural mass in 2 (8.3%) cases, pleural nodules in 16 (66.7%) cases, while there was only pleural thickening in 6 (25 %) cases. **Table 2**

Dyspnea scores and chest pain improved significantly after the procedure (P-value <0.001) **Table 3.**

Table 2: CT findings and thoracoscopic findings:

	Moderate effusion	13 (54.2%)
	Massive effusion	10 (41.7%)
	Mediastinal LN	4 (16.7%)
	Pleural thickening	9 (37.5%)
Thoracoscopic Pleural Findings	Pleural Mass	2 (8.3%)
	Pleural Nodules	16 (66.7%)
	Pleural Thickening	6 (25%)

Table 3: Clinical Symptoms before vs after thoracoscopy and pleural cryobiopsy in studied patients:

				N = 24
		Before	**After**	**P**
Chest Pain		19 (79.2%)	8 (33.3%)	< 0.001*
Dyspnea Score	0	0 (0%)	11 (45.8%)	< 0.001*
	1	3 (12.5%)	10 (41.7%)	
	2	11 (45.8%)	3 (12.5%)	
	3	7 (29.2%)	0 (0%)	
	4	3 (12.5%)	0 (0%)	

As regard the depth of the biopsy, fat cells were present in 20 (83.3%) biopsies while no fat cells in 4 (16.7%) biopsies. No crushed cells appeared in the biopsies in 24 (100%) cases. The mean surface area of the biopsies was 0.3377 cm² (±0.24708 cm² SD), ranging from 0.06 to 0.9 cm².**Table 4**

Table 4: Depth of biopsy, tissue viability and surface area:

Depth of the biopsy	Fat cells	20 (83.3%)
	No fat cells	4 (16.7%)
Tissue viability	Crushed cells	0 (0%)
	No crushed cells	24 (100%)
Surface area of biopsy	Mean	0.3377 cm^2
	Range	0.06 cm^2 to 0.9 cm^2
	SD	0.24708 cm^2

As regard the complications during procedure, there was minor bleeding in 9 (37.5%) cases that required no intervention, 19 (79.2%) cases complained of postprocedural pain that was relieved by simple analgesics and there was minimal surgical emphysema in 4 (16.7%) cases. **Table 5**

Table 5: Complications of pleural cryobiopsy:

Complications	Bleeding	9 (37.5%)
	Pain	19 (79.2%)
	Surgical emphysema	4 (16.7%)

Discussion

Medical thoracoscopy or pleuroscopy," is a minimally invasive endoscopic technique using rigid semi-flexible thoracoscopes that directly visualize the pleural surfaces. In cryobiopsy the pleural tissue is frozen and removed with the probe and the thoracoscope together. This enables us to take a larger and better preserved tissues.

This prospective study was done on 30 patients with undiagnosed exudative pleural effusion that underwent thoracoscopic pleural cryobiopsy, 6 of them were excluded as they were proved to be of inflammatory origin as revealed by histopathological results, While the remaining 24 patients with malignant pleural pathology were included in the study.

The mean age in this study was 57.50 y (± 8.1 SD) and this consistent with other Egyptian studies; In Muhammad et al. [7] the mean age was 51.03 y (±7.518 SD), In Baess et al. [8] the mean age was 53.6 y (± 15.1 SD) . In our study, 13 (54.2%) cases were males and 11 (45.8%) cases were females, and this was in agreement with M.D and Tealeb [9] where males (60%) and females (40%), so according to these studies malignant pleural effusion is more common in elderly (above 50y) and more common in males.

As regard smoking status, most of our patients (66.6%) were smokers (current 33.3%, ex-smokers 33.3%) and this agrees with West [10] and Magkouta et al.[11] who admitted that smoking is a risk factor for mesothelioma, but Klepe et al.[12] mentioned that smoking is not a risk factor for mesothelioma.

As regard the histopathological diagnoses, the diagnostic yield of pleuroscopic cryobiopsy was (100%) and this was in agreement with Baess et al. [8] study in which the two groups (cryobiopsy and rigid forceps biopsy groups) had 100% diagnostic yield and in Giri et al.[13] the diagnostic yield in cryobiopsy group was (94.1%) compared to (91.3%) in rigid forceps group. These studies indicate no significant differences between both methods of diagnosis.

The most common diagnosis in our study was mesothelioma 17/24 (70.8%), followed by metastatic adenocarcinoma in 6/24 (25%) and 1/24 (4.2%) case of Non-Hodgkin's lymphoma. In this Egyptian study M.D and Tealeb [9] they assessed the cryobiopsy efficacy in undiagnosed exudative pleural effusion versus rigid forceps biopsy and the most common diagnosis was mesothelioma (64%) followed by tuberculous pleurisy (16%), this agrees with Muhammad et al. [7] where mesothelioma was the most frequent diagnosis (43.3%). In another Egyptian study El Sayed et al. [14] they compared thoracoscopic cryobiopsy with flexible forceps in undiagnosed pleural effusion; (65.4%) of cases were metastatic adenocarcinoma. So, these studies showed that mesothelioma and metastatic adenocarcinoma are among the most common causes of exudative pleural effusion in Egypt.

As regard CT chest findings, (54.2%) of cases presented with moderate pleural effusion, (41.7%) with massive pleural effusion, (37.5%) with pleural thickening and (16.7%) had mediastinal lymphadenopathy. Thoracoscopic pleural findings were: pleural nodules in (66.7%), pleural thickening in (25%) and pleural mass in (8.3%). Pleural nodules were the most common finding also in Xu et al. [15] , Ahmed et al.[16] and Baess et al.[8]

In this study, managed to obtain deep biopsies that contained fatty tissues in (83.3%), they are very important for the histopathological diagnosis of mesothelioma because the pleura is very tough and thick. In contrast to, Wurps et al. [3] who obtained deep tissue by rigid forceps in (63%), (49.5%) by cryoprobe and (39.5%) by flexible forceps. Thomas et al.[6] reported obtaining deep tissues in (63.3%) by the cryoprobe and (22.7%) by flexible forceps and Muhammad et al.[7] obtained deep tissues in (70%) by cryoprobe and (40%) by rigid forceps, which means that cryobiopsy is more deep than flexible and rigid forceps biopsy.

As regard tissue viability, there was no crushed cells detected in tissue biopsies (100%) and this agrees with Dhooria et al. [17] study that reported no crushed cells in (97.8%) by cryoprobe but (93.9%) in flexiple forceps and Muhammad et al. [7] who repoted (100%) no crushed cells by cryoprobe but (30%) by rigid forceps. So, according to these studies cryobiopsy is better than rigid and flexible forceps in preserving tissue viability which is important for histopathological and immunohistochemical diagnosis.

The mean surface area of the tissue biopsy was 3.377 mm² (±2.471 mm² SD) ranged from 0.6 mm² to 9 mm². In Dhooria et al. [17] study the cryoprobe specimen size ranged from 6 to 10 mm² while the specimen size of flexiple forceps biopsy was smaller and ranged from 3 to 5 mm², this may be explained by the small cups of the flexible forceps. Moreover, Wurps et al. [3] reported that the cryoprobe biopsy was larger than flexible forceps biopsy but was smaller than the biopsies taken by rigid forceps.

As regard the complications of the procedure, minor bleeding was recorded in (37.5%), post procedural pain in (79.2%) and surgical emphysema in (16.7%) of cases. Dhooria et al.[17] reported minimal bleeding from cryobiopsy in (100%), Baess et al. [8] reported postoperative mild local pain in (79.2%) of cases and minimal bleeding in (29.2%).

In conclusion, thoaracoscopic cryobiopsy has been proven to be of high diagnostic value in the diagnosis of undiagnosed pleural effusion. It is safe with controllable mild complications in most cases.

We recommend more studies on a larger number of patients. More studies

evaluate the difference between biopsiestaken by cryoprobes and rigid forceps regarding preserved architecture of cells and its role in improving the diagnostic yield.

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Conflict of Interest: Nil

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