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Comparison of clinical utility of Cancer Ratio, CEA, Malignant Cytology in diagnosis of suspected malignant pleural effusion

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ABSTRACT

Introduction: Pleural effusion is one of the manifestation of a malignant disease which may be malignant pleural effusion with demonstrable malignant cells in the fluid or para-malignant pleural effusion which is reactive response or due obstruction of lymphatic drainage rather than invasion of pleural cavity. Various modalities are there to investigate this condition including routine microscopy, cytology, biopsy etc. **Objective:** To understand and compare the utility of cancer ratio, tumor markers, malignant cytology in cases of suspected malignant pleural effusion. **Material and Methods:** This Case Control Cross sectional study was conducted among patients attending respiratory OPD at Sir Sunder Lal Hospital, BHU, Varanasi, diagnosed with malignant pleural effusion and non-malignant pleural effusion. **Results:** Significant association was found between Cancer Ratio-Carcinoembryonic Antigen, CEA ($p = 0.0069$), CEA-Cytology ($p = <0.01801$)

Keywords: Malignant Pleural Effusion, Cancer Ratio, Cea, Tumor Marker, Pleural Effusion, Malignant Cytology.

Introduction

Malignant pleural effusion is a common manifestation in patient with advanced lung cancer and other cancers. Therapy primarily is directed to control symptoms and improve the quality of life rather than to cure the disease. Careful evaluation of the effusion to establish its etiology and patient treatment customization is required in order to decrease the volume of intrapleural fluid, to control the associated symptoms and to improve the quality of life and the survival. Among routinely performed pleural fluid analyses, neutrophilic predominance is indicative of a parapneumonic pleural effusion, and a raised ADA level is highly suggestive (specificity of 92%) for TB, but to date, no test is specific to "rule - in" MPE.[1, 2] Given the sinister nature of this pathology, low diagnostic yield of pleural fluid cytology (60%), and the invasive nature of closed or thoracoscopic pleural biopsy, this is a significant limitation for routinely performed biochemical tests.[3–5] Conventionally, the first step in pleural fluid analysis is determining if the effusion is a transudate or an exudate, according to the criteria of Light et al.

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The second step is to analyse the fluid using standard routine laboratory tests, including biochemistry, nucleated cells, microbiology, and non-routine markers (eg, adenosine deaminase, ADA), to identify the most likely aetiology. However, a diagnostic challenge that is often confronted is lymphocytic pleural exudates. Tuberculosis (TB) and malignancy are the two most frequent causes of exudative pleural effusions, with lymphocytes predominantly found in pleural fluid. The "cancer ratio" (CR) is a quotient of serum lactate dehydrogenase (LDH) and pleural fluid ADA. It has shown a high diagnostic accuracy for pleural malignancies. Cancer ratio showed high diagnostic value based on the observations that MPE is often associated with high serum LDH levels and comparatively low pleural fluid ADA levels and lymphocyte count. [6, 7] Higher Serum LDH: pleural fluid ADA ratio in patients presenting with exudative pleural effusion can distinguish between malignant and non‐malignant effusion on the first day of hospitalization.[8] Carcinoembryonic Antigen (CEA) is a glycoprotein produced during foetal development. Non‐smoking, healthy adults typically produce low to undetectable levels of CEA. Serum concentrations of CEA may be elevated in patients with certain malignancies that secrete CEA into circulation, including breast, lung, medullary thyroid carcinoma, gastrointestinal tract, colorectal, lung, ovarian, pancreatic, and prostate cancers.[9] Pleural fluid concentrations of CEA have been reported to be elevated in patients with certain malignancies.[9] This study demonstrates significant association between the tumor markers, cytology, cancer ratio and biopsy. Cancer Ratio, CEA, and in adjunct to cytology can aid in diagnosis of malignant pleural effusion with good sensitivity and specificity.

Material and Methods

This case-control cross-sectional study was conducted among patients attending respiratory OPD at Sir Sunder Lal Hospital, BHU, Varanasi, who were diagnosed with malignant pleural effusion on the basis of history, examination, Chest X-Ray, pleural fluid routine microscopy, ADA, tumor marker, Cancer Ratio, cytology and pleural biopsy from October 2020 – July 2022.

Adults more than 14 years without any sex specifications with suspected malignant pleural effusion or diagnosed were included in the study

Inclusion criteria:

- Patients with Pleural Effusion
- Age > 14 years
- Hemodynamically stable patients
- Hospitalised patient

Exclusion criteria

- Patients not giving Consent
- Patients with Tubercular Pleural effusion
- Patients with Parapneumonic Pleural effusion
- Pregnancy

Under aseptic conditions, 2 ml of blood was drawn from each patient's medial cubital vein into vacutainers and measured for Serum LDH. Under aseptic precaution, thoracentesis was performed and pleural fluid analysis done, along with cytology and pleural fluid tumor marker CEA.

Statistical Analysis: Data analysis was performed using SPSS (ver 22.0) software. Cut off value was determined for the parameters upon comparison with the benign pleural effusion patients and then Chi Square test and cross tabulation was performed for to find difference between proportion of observation; whether observed frequencies

significantly different from expected frequencies and o test discontinuous categorical variables for association, p value of <0.05 was taken as significant.

Observation and Results

Age and sex distribution: In the study 100 cases of suspected malignant pleural effusion were included. Mean age of the patient was 60 years. Out of the total 100 patients 44 (44%) of the participants were male and 57 (57%) of the participants were female. In the study, 85 (85%) of the participants had dyspnea as chief complaint followed by cough in 26 (25%) participants. 18% cases had mild pleural effusion, 65 (65%) had moderate effusion and 17 (17%) had massive effusion. 55% of malignant pleural effusion had hemorrhagic pleural fluid and 89 (89%) were exudative 34 (34%) patients had history of smoking.

In our study, the sensitivity and the specificity were calculated by using the best cut-off value and the observed sensitivity and the specificity of the Cancer Ratio, CEA, are as following in Table 1

Table- 1: Sensitivity and Specificity of Cancer Ratio & CEA

Test	Cut-off	Sensitivity	Specificity
Cancer Ratio	19.50	97	90.5
CEA	2.05	84	85.7

In a study by Akash Verma et al[8] the Sensitivity and specificty of Cancer Ratio were 97% and 94%, with sensitivity similar to our study. The same study showed CRP as significant biomarker as well, for inflammation in cancer, with a negative correlation. In another study by Samrad Mehrabi et al, [10] reported a specificity of 85% for CEA similar to our study. In study conducted by Romero et al[11] a higher specificity of 99% was reported for cases of lung malignancies. A study by Michela Paganuzzi et al[12] employing a higher cut-off of 9 ng/mL showed a sensitivity of 53% in carcinomatous effusion and when combined with CYFRA 21-1 the combined sensitivity for malignant pleural effusion in mesothelioma increased to 93%. In a study by Krishnan et al [13] demonstrated that pleural fluid CEA of >2.15 had asensitivity of 93.5% and a specificity of 73% in diagnosing malignant pleural effusion.

In our study Cancer Ratio was found to be significantly associated with CEA, and cytology. A significant association was also observed between CEA-cytology (Table 2).

Table-2: Association with cancer ratio and CEA

Association with Cancer Ratio		Cancer Ratio				p-value
		<19.5		>19.5		
		No.	%	No.	%	
CEA	<2.05	3	100	13	13.4	0.0069
	>2.05	0	0	84	86.6	
Cytology	Negative	3	100	39	40.2	0.03877
	Positive	0	0	58	59.8	
Association with CEA		CEA				p-value
		<2.05		>2.05		
		No.	%	No.	%	
Cytology	Negative	11	68.8	31	36.9	0.01801
	Positive	5	31.3	63.1	84	

Limitations

The present study is a case control cross-sectional study with a small sample size from a single centre and a tertiary hospital. The histo-pathological subtype, whether adenocarcinoma, small cell or non-small cell carcinoma was overlooked. As there have been no previous study assessing associations among cancer ratio, CEA, cytology, hence comparison with previous studies could not be made. Patients were not followed up or assessed before and after treatment for response and influence of response after treatment on the tumor markers.

Conclusion

In conclusion, when the cytologic analysis does not allow a final PE diagnosis, increased cancer ratio, CEA, Ca-125 concentrations may represent, for the clinician, a useful decisional criterion before embarking on a more aggressive approach to treatment. When patients are in good performance status, pleural biopsy and/or thoracoscopy are necessary in order to stage the cancer and plan a correct therapeutic approach. In patients with poor clinical conditions, because of age or low performance status, diagnosis should be made on the basis of tumor markers alone, avoiding more aggressive diagnostic techniques.

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