Original article :

Role of Pleural Fluid Uric Acid Estimation In Differentiation Between Transudative And Exudative Pleurl Effusion

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ABSTRACT

Background : The very evaluation of pleural effusion begins with the understanding of the nature of the fluid being exudative or transudative as it points towards the different etiologies based on the pathogenesis.

Aims and objectives : To investigate the Role of pleural fluid uric acid estimation in differentiating between transudative and exudative pleural effusion.

Materials and methods : A total of 130 patients having pleural effusion from diverse etiologies were selected for the study.

Results : Increase uric acid level was observed in pleural fluid of transudative pleural effusion than exudative pleural effusion. The optimum cut-off level for pleural fluid uric acid was 5.35 mg/dl with sensitivity of 89.32% and specificity of 92.60%.

Conclusion : Routine measurement of pleural fluid uric acid value will aid in differentiating exudative from transudative pleural effusion.

Key words : Pleural effusion, transudate, exudates, uric acid

INTRODUCTION :

Pleural effusion is an excessive accumulation of fluid in the pleural space. It reflects an abnormal pathophysiological state resulting from the disequilibrium between pleural fluid formation and removal. The mean amount of fluid in right pleural space in the normal individuals is 8.4 ± 4.3 ml [1] and normally the volume of fluid in left pleural spaces is quite similar.

Based on the pathogenesis, there are two types of pleural effusions: either transudative or exudative. A transudative pleural effusion develops when the systemic factors influencing the formation or absorption of pleural fluid are altered so that pleural fluid accumulates. In contrast, an exudative pleural effusion develops with local cause at the pleural surfaces leading the capillaries in the location to exude fluid.

The diagnostic evaluation of pleural effusion begins with the understanding of the effusion been a transudate or an exudates. This differentiation is commonly achieved using the Light's criteria. [2] However, it (the Light's criteria) bears a very high sensitivity (98%) but a lower specificity (77%). [3] Several attempts have been recorded to improve the differentiation accuracy. They include the analysis of pleural fluid cholesterol level, [4], serum-pleural fluid albumin gradient [5] or bilirubin ratios [6], pleural fluid-to-serum cholinesterase ratio [7] and pleural fluid uric acid level [8]for the distinction of transudative from exudative pleural effusion.

Here, we have attempted to see the role of pleural fluid uric acid to differentiate between the transudative and exudative pleural effusions.

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MATERIALS AND METHODS :

The present work was a hospital based observational study conducted in the Department of Pulmonary Medicine. Both the indoor and outdoor patients from the department of pulmonary medicine and different other units of Internal Medicine and allied specialities (Nephrology, Cardiology and Gastroenterology) of Gauhati Medical College & Hospital, were included.

The study was conducted between August 2014 to July 2015 following the proper ethical clearance from the Ethics Committee of the Institution prior to the onset of study. Written informed consent was obtained from all the participants before inclusion. Patients having pleural effusions of undetectable or obscure origin or having hemothorax secondary to trauma were excluded from study.

A diagnostic algorithm was applied to all that included diagnostic thoracocentesis, blood sampling and other evaluations that appeared necessary to reach the etiological diagnosis of the effusion. This included serum and pleural fluid biochemistry, ultrasonography and / or computerized tomography of thorax and abdomen, biopsy of pleura or lungs, and bronchoscopic evaluations in selected and indicated patients. All the biochemical estimation was performed in the department of Biochemistry, Gauhati Medical College & Hospital, Guwahati. The biochemical analysis for Uric acid estimation was done by using standard uricase / peroxidase method. The nature of the pleural fluid and the etiology were determined.

The patients were therefore divided into two groups as a) having transudative effusion and b) transudative effusions based on the standard methods of diagnosis using the clinical, radiological, microbiological, biochemical, cytological, and histological evaluations. All the patients were uniformly investigated for differentiation between exudative or transudative effusion but the investigations for determination of etiology were chosen according to the decision of the clinicians as per the probability and feasibility in their real world practice. The evaluations were extended as per the demand of particular scenario; American College of Rheumatology Revised Classification Criteria for Systemic Lupus Erythematosus[9] was applied for a suspected case of systemic lupus erythematosus and the criteria of pleural fluid triglyceride level exceeding 110 mg/dL [10] was applied to one patient with suspicion of having chylothorax. Some special investigations as evaluation of ascetic fluid or measurement of NT-proBNP and liver biopsy were done in certain patients on specific clinical demand to determine the cause of pleural effusion.

Exudates were separated from transudates by Light's Criteria [2]. This included a) pleural fluid to serum LDH greater than 0.9, &/or Pleural fluid LDH more than 280 IU/L or pleural fluid LDH more than two-third normal upper limit for serum, b) pleural fluid / serum protein ratio greater than 0.5.

STATISTICAL ANALYSIS :

The usefulness of each of the biochemical parameters for identifying transudative and exudative effusion was evaluated in terms of sensitivity, specificity, positive predictive value, negative predictive value, and efficiency. Statistical analysis of data was done using SPSS 20. Appropriate statistical methods were applied as and when necessary. P values less than 0.05 were considered as statistically significant. Receiver operating characteristic (ROC) curves and areas under the ROC curves (AUC) with 95% confidence intervals were calculated for pleural fluid uric acid evaluating the optimum cut-off points.

THE RESULTS :

Out of 130 patients included in the study we had 103(79.24%) patients having exudative effusion and 27(20.75%) having transudative effusion. The etiological factors are listed in Table 1. Out of the study population the age ranged from 14 to 85 years and mean age was 50.5 ± 15.06 years and larger number of cases was observed in males 99 (76.15%) than in females 31 (23.84%). The pleural fluid biochemistry has been charted where apart from the parameters to meet the Light's criteria,

the pleural fluid uric acid levels are also noted (Table 2).

Table 1 – Etiological diagnosis of exudative and transudative pleural effusions (n = 130).

Causes	Patients
Exudative	**103**
Parapneumonic/Empyema	36
Tuberculosis	35
Malignancy	29
SLE	1
Chylothorax	1
Post CABG	1
Transudative	**27**
CKD	13
CCF	8
Cirrhosis	5
Hypoalbuminemia	1

Table 2 –the demographic profile of both the groups (exudative and transudative pleural effusions) with different biochemical estimations of pleural fluid as per the demand of the Light's criteria along with the uric acid levels. The significance of each in terms of the difference between transudate and exudates has also been noted (S – Significant, NS – Non significant).

We have done a Receiver operating characteristic (ROC) plots of pleural uric acid (Figures-1) to determine the demarcating cut-off value between exudates as compared to transudates. The optimum cut-off level was determined by selecting points of test values that provided the greatest sum of sensitivity and specificity. The optimum cut-off level for pleural uric acid was more than 5.35 mg/dl in transudate and less than 5.35 mg/dl in exudate with sensitivity and specificity of pleural uric acid in differentiating between transudative and exudative pleural effusion is 89.32% and 92.60% respectively (Table 3).

Figure 1 - ROC curve of pleural fluid uric acid:

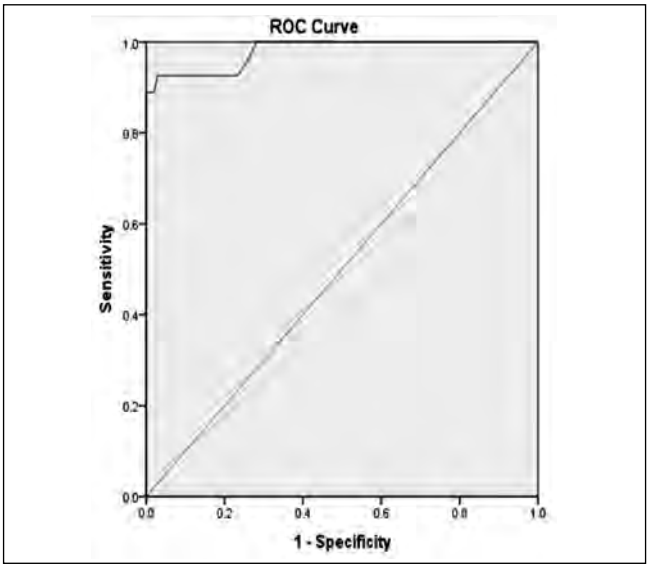

Fig:1: Receiver operating characteristic (ROC) curves of pleural fluid value of uric acid. The optimum cut off level for the differentiation between exudates and transudates was determined as the point that provides the greatest sum of sensitivity and specificity, in this case a level of > 5.35 mg/dl

Variables	Exudative (n =103)	Transudative (n =27)	P value
Age	49.36 ± 15.27	55.55 ± 13.39	
Gender			
Male	82	17	
Female	21	10	
Total pleural fluid protein	5.04 ± 1.1	3.05 ± 1.1	< 0.0001 (S)
Total serum protein	7.1 ± 1.3	6.9 ± 1.2	0.4713 (NS)
Pleural / serum protein ratio	0.58 ± 0.045	0.38 ± 0.071	< 0.0001 (S)
Total pleural fluid LDH	1026.90 ± 1639.36	377.74 ± 211.76	0.0427 (S)
Total serum LDH	561.70 ± 440.70	486.88 ± 157.93	< 0.0001 (S)
Pleural / serum LDH ratio	1.80 ± 1.18	0.70 ± 0.15	< 0.0001 (S)
Pleural fluid uric acid	4.08 ± 0.92 mg/dl	7.48 ± 1.11 mg/dl	< 0.0001 (S)

Table 3 - Showing cut off value of pleural fluid uric acid with sensitivity and specificity.

Test results variable	Positive if greater than or equal to	Sensitivity (%)	Specificity (%)
Pleural fluid uric acid	4.65	100	70.87
	4.75	100	71.84
	4.85	96.30	73.79
	4.95	95.59	76.70
	5.05	93.59	83.50
	5.15	92.59	87.38
	5.25	91.59	88.32
	5.35	**89.32**	**92.60**
	5.45	88.56	93.60
	5.55	87.45	95.18
	5.65	86.64	97.09
	5.80	85.67	98.06
	6.00	84.67	99.03
	6.35	82.49	100
	6.65	79.59	100

DISCUSSION :

Uric acid is the metabolic end product of purine nucleotides. This is one of the biochemical markers found in pleural effusion and is also easy to analysis in pleural fluid. Uric acid is sparingly soluble in aqueous media, and persistent exposure to high serum levels predisposes to urate crystal deposition within soft tissues and body fluid [11].

The present study reveals a good discriminating power of pleural fluid uric acid level between transudates and exudates with a sensitivity and specificity of 89.32% and 92.60% respectively when a cut off value of 5.35 mg/dl is considered.

It is interesting to appreciate the reasons for lower uric acid level in transudates than exudates. The low uric acid in exudative pleural effusion is likely secondary to the local factors that play role in such cases through their influence on capillary permeability (increased) and/or lymphatic flow (decreased) [13]. On the other hand transudates are the result of imbalances in hydrostatic and oncotic forces without change in the capillary permeability [14]. Increase in uric acid in pleural fluid can be regarded to be a manifestation of tissue hypoxia [12]. Uric acid synthesis is up-regulated in tissue hypoxia and oxidative stress. Patients with chronic renal failure have oxidative stress and those undergoing dialysis in particular, demonstrate hypoxemia to the tune of 10% to 20% from baseline [15]. The same applies to the patients of congestive cardiac failure who turn hypoxemic. Similarly, cirrhosis of the liver is often associated with oxidative stress [16]. In our series, most of the patients with reasons to produce transudative effusion had oxidative stress or hypoxemia to explain the increased uric acid synthesis. The respiratory tract, indeed, remains a major target of oxidative damage caused by both endogenous and exogenous processes [17, 18]. The reactive species produced by phagocytes are the major cause of tissue damage associated with chronic inflammatory lung disease.

Muzaffer Metintas et al [19]stated that the binding of uric acid is minimal to plasma protein and it is diffuse freely to different part of body

compartments. They suggested that the increase permeability, due to change in pleural-capillary pressure in formation of transudate, is the cause of the increase of uric acid levels in pleural fluid. So all these factors explains why uric acid level increases in transudative condition than exudative one.

The effort to differentiate pleural exudative from transudative pleural fluid with help of t measurement of pleural fluid uric acid has been tried earlier too. Uzan et al [12] had shown that the mean pleural fluid uric acid vary significantly between transudates (487.7±165 micromol/l) and exudates (279.9±142.1 micromol/l) with the specificity and sensitivity of pleural uric acid for diagnosis of transudative effusions being 73% and 80.6%, respectively. Another study elaborated anoptimum cut-off level of 5.5 mg/dl for pleural fluid uric acid has a sensitivity of 94.0% and specificity of 83.0% to diagnose transudative effusion. The power improves with sensitivity of 96.0% and specificity of 92.16% if the ratio of pleural fluid uric acid to serum uric acid is taken with optimum cut-off levels of 1.0. (20

CONCLUSION :

Although it appears that uric acid level in pleural fluid is a good marker for differentiating exudative from transudative effusions, it needs further validations and it will be interesting to see whether the addition of estimating the pleural fluid uric acid to the existing Light's criteria can actually improves the differentiating accuracy. We conclude that a routine measurement of pleural fluid uric acid may be worthwhile even at this state of information.

REFERENCES :

1) Noppen M, De Waele M, Li R, et al. Volume and cellular content of normal pleural fluid in humans examined by pleural lavage. Am J Respir Crit Care Med 2000; 162:1023-1026.

2) Light RW, Macgregor MI, Luchsinger PC, Ball WC. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972; 77:507–13.

3) Romero S, Candela A, Martin C, Hernandez L, Trigo C, Gill J. Evaluation of different criteria for the separation of pleural transudates from exudates. Chest 1993; 104:399–404.

4) Hamm H, Brohan U, Bohmer R, et al. Cholesterol in pleural effusions: a diagnostic aid. Chest 1987; 92: 296-302.

5) Roth BJ, O'Meara TF, Cragun WH. The serum-effusion albumin gradient in the evaluation of pleural effusions. Chest 1990; 98:546-549.

6) Meisel S, Shamiss A, Thaler M, et al. Pleural fluid to serum bilirubin concentration ratio for the separation of transudates from exudates. Chest 1990; 98:141-144.

7) Garcia-Pachon E, Padilla-Navas I, Sanchez JF, et al. Pleural fluid to serum cholinesterase ratio for the separation of transudates and exudates. Chest 1996; 110:97-10.

8) Kursat UK, Vural H, Ozer F, et al. Diagnostic value of uric acid to differentiate transudates and exudates. Clin Chem Lab Med 2000; 38:661-665.

9) American College of Rheumatology Revised Classification Criteria for Systemic Lupus Erythematosus, 1997.

10) Staats BA, Ellefson RD, Budahn LL, et al. The lipoprotein profile of chylous and nonchylous pleural effusions. Mayo Clin Proc 1980; 55:700-704.

11) Emmerson BT. The management of gout. N Engl J Med 1996; 334:445–51

12) Uzun K, Vural H, Ozer F, Imecik 0. Diagnostic value of uric acid to differentiate transudates and exudates. Clin Chem Lab Med. 2000; 38:661-65.

13) Porcel NK, Vives M. Classic, abbreviated, and modified Light's criteria: the end of the story? Chest 1999; 116:1833-34.

14) Light RW and Hamm H. Diagnostic principles in pleural disease. Eur Respir J 1997; 10: 476-81.

15) C. Brad Burns, MD; David J. Scheinhorn, MD. Hypoxemia during Hemodialysis. Arch Intern Med. 1982; 142:1350-53.

16) Fallon MB, "Mechanisms of pulmonary vascular complications of liver disease: hepatopulmonary syndrome," Journal of Clinical Gastroenterology, 2005 vol. 39, Supplement 2, no. 4, pp. 138–142.

17) Rajendrasozhan S,Yang SR, Edirisinghe I, Yao H, Adenuga D, and Rahman I, "Deacetylases and NF-κB in redox regulation of cigarette smoke-induced lung inflammation: epigenetics in pathogenesis of COPD," Antioxidants and Redox Signaling, 2008 vol. 10, no. 4, pp. 799–811.

18) Park TJ, Kim JY, Oh SP et al., "TIS21 negatively regulates hepatocarcinogenesis by disruption of cyclin B1-forkhead box M1 regulation loop," Hepatology, 2008 vol. 47, no. 5, pp. 1533– 1543.

19) Muzaffer M, Ozkan A et al, Comparative analysis of biochemical parameters for differentiation of pleural exudates from transudates Light's criteria, cholesterol, bilirubin, albumin gradient, alkaline phosphatase, creatine kinase, and uric acid.Clinica Chimica Acta 264 (1997) 149–162.

20) Jain A, Jain R, Petkar SB, Gupta SK, Khare N, Dutta J. A study of uric acid - a new biochemical marker for the differentiation between exudates and transudates in a pleural effusion cases. National Journal of Community Medicine 2014;5:2, 204-208.