Original Article

A STUDY OF URIC ACID - A NEW BIOCHEMICAL MARKER FOR THE DIFFERENTIATION BETWEEN EXUDATES AND TRANSUDATES IN A PLEURAL EFFUSION CASES

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ABSTRACT

Background: Pleural effusion is an excessive accumulation of fluid in the space lies between the lung and chest wall i.e. pleural space. In normal condition, pleural space contains 0.1–0.3 ml/kg body weight of fluid (near about of 10 ml of fluid on each side) between the parietal and visceral pleura.

Objectives: To investigate whether uric acid measurement in fluid is more sensitive and specific marker for differentiating between exudates and transudates, as confirmed clinically.

Materials and Methods: A total of 60 consecutive patients with diverse etiologies having pleural effusion were selected for the study.

Results: Increase Uric acid level was observed in pleural fluid of transudative pleural effusion than exudative pleural effusion. It was also observed that the level of uric acid was more in pleural fluid than serum and ratio (pleural fluid / serum) of uric acid was ≥ 1 in transudative conditions but in case of exudative condition the this ratio was < 1. The optimum cut-off level for P uric acid was 5.5 mg/dl with sensitivity of 94.00% and specificity of 83.00%. The optimum cut-off levels for P/S uric acid ratio was 1.0 with sensitivity of 96.00% and specificity of 92.16%.

Conclusion: Routine measurement of pleural fluid uric acid value and the calculation of fluid to serum total protein and lactate dehydrogenase (LDH) ratios will aid in differentiating exudates from transudates.

Keywords: Pleural effusion; exudates; transudates; uric acid

INTRODUCTION

Pleural effusion is an excessive accumulation of fluid in the space lies between the lung and chest wall i.e. pleural space.[1] In normal condition, pleural space contains 0.1–0.3 ml/kg body weight of fluid (near about of 10 ml of fluid on each side) between the parietal and visceral pleura.[2-4] Fluid filtered from systemic capillaries down a small pressure gradient. Fluid drains into the systemic circulation via a delicate network of lymphatics and eventually enters the mediastinal lymph nodes. This pleural fluid acts as a lubricant and allows the visceral pleura to slide along the parietal pleura during respiratory movements.[5]

Uric acid or 2, 6, 8-Trioxypurine [IUPAC name 7, 9-Dihydro-1H-purine-2, 6, 8(3H)-trione] is a heterocyclic compound of carbon, nitrogen, oxygen, and hydrogen with the formula $C_5H_4N_4O_3$. Uric acid is a product of the metabolic breakdown of Purine nucleotides. One of the biochemical markers found in pleural effusion. Only two studies have used uric acid to differentiate between exudates and transudates. This study was thus undertaken to confirm the usefulness of uric acid in differentiating exudative from transudative pleural effusion.

MATERIALS AND METHODS

Present study was carried out at the People's College of Medical Sciences and research center Bhopal. All samples collected (June 2013 to Dec 2013) during this

period were taken as a sample. 94 patients were reported d We have got a total of 60 (male and female of all age groups) samples during study period, patients with pleural effusions of diverse etiologies, attending various departments (pulmonary, cardiology and surgery) of People's College of Medical Sciences and research center Bhopal. The protocol for this study was approved by the Institutional ethical Committee, and informed consent was obtained by all participants before percutaneous thoracocentesis and blood sampling. All estimation was performed in the Department of Biochemistry in People's college of Medical Sciences and research center Bhopal.

In all cases, a standard clinical protocol was followed and routine laboratory tests of pleural fluid and serum were carried out. Pleural fluid culture and pleural biopsy (Transthoracic needle biopsy as well as tru cut biopsy) were also done to obtain a definitive diagnosis.

The patients were divided in two groups: Group I - exudates, and Group II - transudates on the basis of extensive clinical, radiological and biochemical evaluation, achieved by standard methods.

Group – I (exudates) – This group comprised of 30 patients –1) twelve Patients of tubercular pleural effusion in which diagnosis was confirmed by clinical and radiological evaluation; 2) nine patients with parapneumonic pleural effusion or empyema in which diagnosis was confirmed by clinical presentation, positive microbial culture and a radiographic pulmonary infiltrate that disappeared after antibiotic treatment; 3) seven patients with malignant pleural effusion in which diagnosis were confirmed by medical history (about family members and sibling and addiction) and histopathology and cytology examination of the pleural fluid, sputum and fiber optic brochoscopy guided transthoracic biopsy tissue for malignant cells; and 4) Two patients of rheumatoid arthritis diagnosed clinically and as having rheumatoid nodule and increased serum rheumatoid factor; one patient of systemic lupus erythematosus diagnosed clinically and having LE cell phenomenon and antinuclear factor.

Group – II (transudates) – This group comprise of 30 patients, out of which six were of nephrotic syndrome diagnosed if the patient had proteinuria, edema and hypoalbuminemia; four patients of cirrhosis of liver diagnosed by liver biopsy in the presence of ascitis; twelve patients of congestive cardiac failure diagnosed due to cardiomegaly, radiological evidence of congested lungs, peripheral edema and response to treatment of congestive cardiac failure and remaining eight patients of chronic renal failure who were receiving hemodialysis showing increase urea, creatinine level in blood.

Patients, who met the diagnostic criteria of more than one of the previous categories or had pleural effusions of undetectable or obscure origin or had obvious hemothorax secondary to trauma, were excluded from study.

Exudates were separated from transudates by Light's Criteria.[6]

1. 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.
2. Pleural fluid / serum protein ratio greater than 0.5.

The following studies were performed on the pleural fluid and serum of all patients: Pleural fluid uric acid concentration (P uric acid), serum uric acid concentration (S uric acid), and pleural fluid/serum uric acid ratio (P/S uric acid ratio). Biochemical analysis of Uric acid was done on Biosystem A25 fully automatic analyzer using Biosystem Kits and by uricase / peroxidase method.

Statistical Analysis: The collected data was analyzed using SPSS windows (version 20). Results were expressed as mean ± SD. Student's t-test was employed to determine statistical significance. P value less than 0.05 were considered statistically significant. Receiver operating characteristic (ROC) curves and areas under the ROC curves (AUC) with 95% confidence intervals were calculated for each of the criteria for evaluating the optimum cut-off points

RESULTS

Out of 60 cases studied, 38 (63%) were men and 22 (37%) women. According to the clinical diagnosis, there were 30 (50%) cases of exudate pleural effusion of which 16 (53%) were men and 14 (47%) women with a mean age of 31.7 years (range 17-60). There were 30 (50%) cases of transudative pleural effusion of which 22 (73%) were men and 08 (27%) women with a mean age of 39.3 years (range 23-72) (Table – 1).

Table 1 – Pleural fluid estimation*

Variables	Exudate (n=30)	Transudate (n=30)
Age	31.7 ± 10.8	39.3 ± 9.5
Gender,		
Male	16(53%)	22(73%)
Female	14 (47%)	08(27%)
Pleural fluid cells	2700 ± 842	470 ± 122
Total protein pleural fluid	3.89 ± 0.37	2.39 ± 0.38
Total protein serum	6.31 ± 0.77	7.08 ± 0.56
Total protein pleural fluid/serum ratio	0.62 ± 0.087	0.34 ± 0.059
Pleural fluid LDH IU/L	507.7±195.9	134.6 ± 35.0
Serum LDH IU/L	739.0±259.6	372.3±110.1
LDH pleural fluid/serum ratio	0.68 ± 0.03	0.27 ± 0.09
Pleural Fluid uric acid	4.81 ± 0.64	9.25 ± 1.83
Serum uric acid	5.04 ± 0.52	7.88 ± 1.07
Uric acid pleural fluid/serum ratio	0.95 ± 0.08	1.18 ± 0.20

*Values are given as the mean ± SD, unless otherwise indicated

Table 2 – Etiology of Pleural Effusions (n = 60)

Cause	Patients (%)
Exudates	30 (50%)
Tuberculosis	12 (20%)
Empyema	09 (15%)
Malignancy	07 (11.7%)
Rheumatic	02 (3.33%)
Transudates	30 (50%)
Congestive cardiac failure	12 (20%)
Nephrotic syndrome	06 (10%)
Chronic Renal Failure	08 (13.3%)
Cirrhosis	04 (6.7%)

In this study mean serum and pleural uric acid levels are decreased in exudates as compared to transudates. Taking 5.5 mg% as cut-off value of pleural uric acid for differentiating exudates from transudes, 5(17%) of the 30 patients with exudate were having pleural uric acid above 5.5 mg% and none of 30 patients with transudates were having pleural uric acid below 5.5mg% and these values correlated with Muzaffer Metintas et al (1997) and Uzan K et al (2000).[7&8]

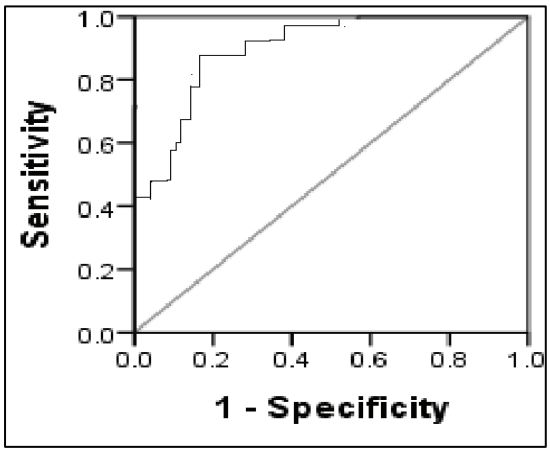

Figure -1

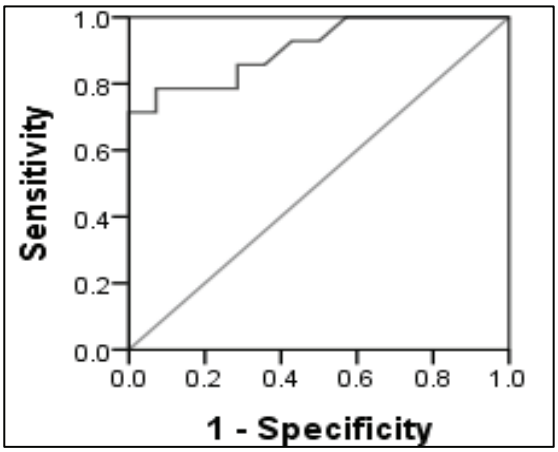

Figure - 2

Fig 1 & 2: 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 > 5.5 mg/dl

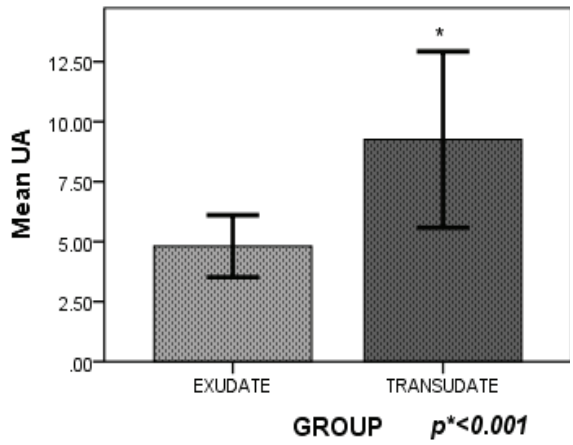

Figure – 3

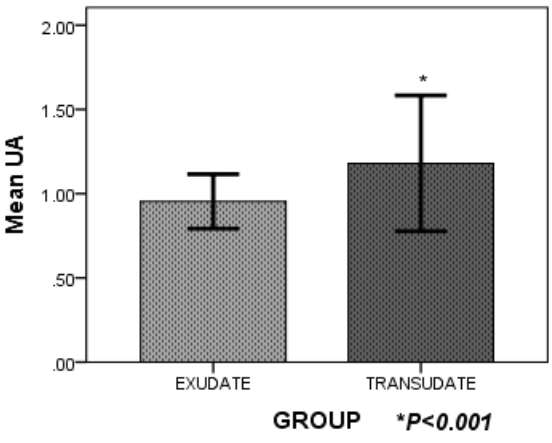

Figure – 4

Figure 3: The graphic representation (Bar Diagram) of Mean ± SD values of uric acid. Figure 3 shows mean pleural fluid uric acid level in exudates and transudate.

Figure 4 shows mean pleural fluid / serum uric acid ratio in exudates and transudate. The observation shows statistically significant differences (p) in both groups.

P/S UA ratio greater than one was observed in 5 (17%) out of 30 cases of exudative pleural effusion and 26 (87%) out of 30 cases of transudative pleural effusion. ROC plots of P uric acid and P/S uric acid ratio are shown in [Figures 1 and 2] respectively. 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 5.5 mg/dl in transudate and less than 5.5 mg/dl in exudate with sensitivity of

94.00% (95% CI 0.78-0.97) and specificity of 83.00% (95% CI 0.68-0.93) [figure 1]. The area under the ROC curve was 0.926. The optimum cut-off levels for P/S uric acid ratio was 1.0 with sensitivity of 96.00% (95% CI 0.78-0.99) and specificity of 92.16% (95% CI 0.69-0.96). The area under the ROC curve was 0.972 [fig 2].

DISCUSSION

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.[9]

In present study, the mean serum uric acid level in exudates and transudates are 5.04 ± 0.52 mg/dl and 7.88 ± 1.07gm / dl respectively and they are statistically significant. The mean pleural fluid uric acid level in exudates and transudates are 4.81 ± 0.64 mg / dl and 9.25 ± 1.83mg / dl respectively and they are statistically significant [figure 3]. The mean pleural fluid / serum uric acid ratio in exudates and transudates are 0.95 ± 0.08 and 1.18 ± 0.20 respectively and they are statistically significant [Table 1] [figure 4].

In this study the level of uric acid is increase more in transudative pleural fluid (group comprise CCF, peritoneal dialysis, cirrhosis and nephrotic syndrome patients) as comparatively to exudative condition. The reason behind that, in exudative condition the local factors influencing the accumulation of pleural fluid are altered. Exudates involve increased capillary permeability and lymphatic obstruction. [10] Whereas transudates are the result of changes in hydrostatic forces [imbalances in hydrostatic and oncotic forces], with capillary permeability remaining normal. [11] In this study all the condition which produces transudative pleural effusion exerts much oxidative stress and hypoxia in the tissue. Uzan et al (2000) stated that increases in uric acid may be found in clinical conditions associated with tissue hypoxia .[8] In case of hemodialysis uric acid level increases by dual pathology.

Patients with chronic renal failure receiving hemodialysis experience hypoxemia during routine dialysis. The fall in Pao_2 is typically 10% to 20% of baseline.[12]

Oxidant stress contributes to morbidity in hemodialysis patients. Three possible causes of oxidant stress have been suggested: the uremic state, the dialyzer membrane, and bacterial contaminants from the dialasis.[13]

In case of cirrhosis uric acid level increases by following pathology –

An association between liver disease and pulmonary disorders is common in patients with chronic liver disease.[14] The development of cirrhosis is often associated with oxidative stress.[15] The respiratory tract is a major target of oxidative damage caused by both endogenous and exogenous processe.[16-17] The reactive species produced by phagocytes are the major cause of tissue damage associated with chronic inflammatory lung disease. The involvement of oxidative stress in lung injury leads to increased levels of markers of lung injury and pro-inflammatory cytokines (i.e., IL-1β, IL-6, and TNF-α).[18]

Beside of above all mention mechanism increase level of uric acid can exert local effect on capillaries of pleura by following mechanism: Uric acid can stimulate granulocyte adherence to the endothelium and peroxide and superoxide free radical liberation.[19] Therefore uric acid may have a deleterious effect on the endothelium through leukocyte activation and interestingly a consistent relationship has been noted between elevated serum uric acid concentration and circulating inflammatory markers. [20-23] Uric acid traverses dysfunctional endothelial cells and accumulates as crystals, these crystals may contribute to local inflammation and plaque progression, and we speculate that crystal accumulation may be greater in patients with elevated serum uric acid concentration.[24]

Muzaffer Metintas et al (1997) [7] 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. In our study, the mean pleural fluid and serum uric acid level as well as pleural fluid and serum ratio are significantly raised in transudative pleural effusion than exudative effusion group. Hence serum and pleural uric acid level as well as pleural to serum uric acid ratio may be helpful for differentiating exudates from transudate.

The result of present study confirms that Uric Acid level is a useful parameter for differentiating exudative from transudative pleural effusion. The value of P Uric Acid and P/S Uric Acid ratio were higher in patients with transudative pleural effusion as well as we found that the sensitivity and specificity of P Uric Acid concentration to be 94.00% % and 83.00% % and for P/S Uric Acid ratio 96.00% and 92.16% respectively for diagnosing transudative pleural effusion which was provided by ROC curve analysis. Further, while differentiating exudates from transudates,

CONCLUSION

To conclude, if uric acid in pleural fluid is more than 5.5 mg/dl in transudate and less than 5.5 in exudate is helpful in separating exudate from transudate in pleural effusion. However, further studies, involving larger number of patients, to evaluate the parameter covered in our study are needed in order to draw any conclusion or to achieve higher sensitivity.

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