Original Research Article

A study of uric acid levels in serum and pleural fluid as to differentiate between transudate and exudate in pleural effusion

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A B S T R A C T

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

Aims: To assess the usefulness of uric acid levels in both serum and pleural fluid in differentiation between transudates and exudates in pleural effusion.

Settings and Design: Hospital based cross sectional study.

Materials and Methods: A total of 250 patients with pleural effusion were selected for the study. Uric acid level, total protein, albumin and LDH levels of Serum and pleural fluid were measured from the participants.

Statistical analysis used: Data analysis was done by using SPSS ver.23 and presented in proportions and student unpaired't' test was used to compare means.

Results: The mean uric acid level in serum and pleural fluid was 7.626±0.06 mg /dL and 10.27±0.07 mg /dL respectively in transudates, whereas in exudates it was 4.89±0.04 mg /dL and 2.49±0.06 mg /dL and the differences were found to be statistically significant.

Conclusion: Measurement of uric acid in association with Total proteins, LDH, Albumin will aid in differentiating the transudates and exudates in pleural effusion.

Key Message: Uric acid levels can be a better biomarker and cost-effective method to differentiate transudate and exudative pleural effusion easily, to diagnose and for better management of the patient.

1. Introduction

Pleural Effusion is an excessive accumulation of fluid in pleural space and it is the common complication of many disease processes either local or systemic. Normally pleural space contains 0.1 to 0.2 mL/kg body weight of fluid.[1] Effusion is of two types; one is exudative and other one is transudative. In cases of transudative effusions there is no need for further investigations but in cases of an exudative effusions further investigations needed to make a proper diagnosis, to plan management and assess prognosis.[1]

Tuberculosis is the major public health problem in developing countries like India, and Pleura serves as the initial presentation in about 25% of adults as pleural effusion.[2] Tuberculous pleurisy is the second most common form of extra pulmonary tuberculosis and a common cause of pleural effusions in endemic areas of tuberculosis like India.[3] An estimated prevalence of pleural effusion in industrialized countries is 320 per 1,00,00 people with a distribution of aetiologies related to the prevalence of underlying disease.[4] Various causes of pleural effusion are tuberculosis (30%), malignancy (27%), heart failure (20%), pneumonia (18%), and cirrhosis (3%), and other connective tissue disorders. Nearly 2/3rd of malignant pleural effusions occur in women associated with breast and gynaecological malignancies. Pleural effusion associated

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with systemic lupus erythematous is common in women and pleural effusion with chronic pancreatitis is common in men, with majority of cases were due to alcohol abuse. Rheumatoid effusions also occur commonly in adults whereas in children, pleural effusion is due to an underlying pneumonitis.[5] Fetal pleural effusion was also been reported and under certain circumstances may be treated prior to the delivery.[6]

Distinguishing an exudate from transudate and diagnosing the aetiology of pleural effusion clinically with certainty is a challenging task for physicians. Various pleural fluid parameters have been used to identify the cause. This differentiation is commonly achieved using the Light's criteria.[7] According to "Light's criteria", an exudate may contain one or more of the following, that is pleural fluid total proteins and serum total proteins ratio greater than 0.5, pleural fluid and serum Lactate Dehydrogenase (LDH) ratio greater than 0.6 or an absolute serum LDH more than 200IU/L. However, the Light's criteria bear a very high sensitivity (98%) but a lower specificity (77%). Recently many new parameters like pleural effusion cholesterol, Pleural effusion to serum bilirubin ratio, Uric acid and pleural effusion malondialdehyde (MDA) have been reported, but none shows better sensitivity and specificity than light's criteria.[8–11]

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 $C_3H_4N_4O_3$ is a product of metabolic breakdown of purine nucleotides.[12] Levels of uric acid present more in transudative pleural fluid as compared to exudates.[13] The difference between protein levels in the serum and the pleural fluid is greater than 3.1 gm/dL and serum-effusion albumin gradient greater than 1.2 gm/dL also can indicate that the pleural effusion is most likely a transudative effusion.[14] LDH is an enzyme found in nearly all living cells and catalyses the conversion of lactate to pyruvic acid and Pyruvic acid to lactate, as it converts NAD+ to NADH and it is a reversible step. As it is released during tissue damage, it is a marker of common injuries and diseases such as heart failure.

As there is no reliable biomarker that allows a complete differentiation between transudates and exudates in pleural effusion, Uric acid with other parameters like Total proteins, LDH, Albumin with Light's criteria will aid in the differentiation of pleural effusion with diverse aetiology. With this background, this study was undertaken to differentiate exudates and transudates in pleura by measuring uric acid level in serum and pleural fluid.

2. Materials and Methods

2.1. Study design

Hospital based cross sectional study.

2.2. Study setting

Government Chest hospital, Yerragadda, Hyderabad.

2.3. Study population

Patients admitted in Government Chest hospital, Yerragadda, Hyderabad.

2.4. Sample size

125 patients with exudative type of pleural effusion and 125 patients with transudative type of pleural effusion. Hence sample size is 250.

2.5. Inclusion criteria

Subjects of both sex with age group 20 years and above.

1. Subjects with pleural effusion.
2. Haemodynamically stable patients.

2.6. Exclusion criteria

Immunocompromised subjects

1. Pregnant women.
2. Patients with Trauma to chest wall.
3. Post-operative subjects.

2.7. Consent

An informed consent was taken from all the subjects. After fulfilling the inclusion and exclusion criteria and after prior consent from the subjects, clinical details were recorded and examination was done according to the proforma of the case sheet. A postero-anterior and lateral chest radiographs were done in all cases.

2.8. Sample collection

5ml of the venous blood was collected from all the study participants under aseptic conditions in a sterile plain bottle/vacutainer by using sterile disposable syringe. Sample is centrifuged at 3000rpm for 10 mins and serum was separated within two hours of collection of blood. Care was taken to prevent hemolysis of the sample. Lipaemic and icteric samples were discarded.5ml of pleural fluid sample was collected in a clean, sterile glass bottle.

2.9. Parameters analysed

Serum and Pleural fluid Uric acid by uricase / peroxidase method using semi-autoanalyzer.

Serum and Pleural fluid Total proteins using Colorimetric Biuret method-

Serum and Pleural fluid Albumin by Bromo-cresol-Green (BCG) method using Colorimetrically.

Serum and Pleural fluid LDH by an enzymatic End point method using Semi autoanalyzer.

2.10. Statistical analysis

Data was entered in Microsoft excel and analysis was done using SPSS statistical package version 23. Categorical data and continuous data was presented as proportion, mean with standard deviation. Student unpaired 't' test was used to assess statistical significance between two means and $p<0.05$ was considered as significant.

3. Results

Majority (35.2%) of the participants were of age group 30 – 40 years and male (64%) (Table 1).

Mean age of participants with exudate type of pleural fluid is 34.77 years and transudate type of pleural fluid is 35.21 years (Table 2).

Mean serum uric acid level and pleural fluid uric acid level was higher in subjects with transudate type when compared to exudate type and the difference was found to be statistically significant (p=0.009, p=0.033) (Table 3).

Mean serum total protein level, serum albumin and pleural albumin level was higher in subjects with transudate type when compared to exudate type and the difference was found to be statistically significant (p=0.001). Mean pleural fluid total protein level, serum LDH and pleural fluid LDH level was higher in subjects with exudate type when compared to transudate type and the difference was found to be statistically significant (p=0.001) (Table 4).

Mean serum uric acid level and pleural fluid uric acid level was higher in subjects with transudate type when compared to exudate type and the difference was found to be statistically significant in both genders (Table 5).

4. Discussion

Majority (35.2%) of the participants were of age group 30 – 40 years and male (64%). The study participants were divided into two groups based upon Light's criteria. Group-1(Exudates) and Group-2(Transudates). Mean age of participants with exudate type of pleural fluid is 34.77 years and transudate type of pleural fluid is 35.21 years.

The current study found that mean serum uric acid level and pleural fluid uric acid level was higher in subjects with transudate type when compared to subjects with exudate type and the difference was found to be statistically significant (p=0.009, p=0.033) which reflects the usefulness of estimating uric acid levels in differentiating transudates from exudates. Low uric acid levels are demonstrated in exudative pleural effusion which is secondary to the local factors that play role on capillary permeability increased or lymphatic flow obstruction or decreased. But in transudates, there is imbalances in hydrostatic and oncotic forces without change in the capillary permeability.[15] Increased

Uric acid in pleural fluid can be due to tissue hypoxia in which synthesis of uric acid synthesis is upregulated in tissue hypoxia and oxidative stress. Similar findings were observed in Jain A et al. study where uric acid level in pleural fluid of transudative pleural effusion is higher (9.25 ± 1.83mg/dl) than in exudative pleural effusion(4.81 ± 0.64 mg/dl).[12] Hazarika B et al. found an increased uric acid level in pleural fluid of transudative than exudative effusion and the optimum cut off level for pleural fluid uric acid was 5.35mg/dl.[16]

In the present study, it was observed that mean total serum protein level in participants with exudate type of pleural effusion was 6.266 ± 0.04 gm/dL and in participants with transudate type of pleural effusion was 8.788 ± 0.07 gm/dL and the difference was found to be statistically significant (p=0.001). It was also observed that mean total protein level in pleural fluid of participants with exudate type of pleural effusion was 4.983 ± 0.06 gm/dL and in participants with transudate type of pleural effusion was 3.739 ± 0.04 gm/dL and the difference was found to be statistically significant (p=0.001). The pleural fluid to serum total protein ratio was >0.5 in exudative condition, whereas it was <0.5 in transudative condition. Das AK et al. observed that, the pleural fluid to serum protein is 0.5 and in this study 23 cases were exudates and 17 cases were transudative type of effusion which is similar to our study.[17] Pergulwar A et al. explained that, the total proteins levels are increased in tubercular pleural effusion due to increased permeability of capillaries by delayed hyper sensitivity reaction. This causes Inflammation of the pleura, and leakage of proteins from the pleural capillaries into the pleural space, thus total protein level increases.[15]

Measurement of LDH activity and it's isoenzymes in serum and in pleural fluid specially in Broncho Alveolar Lavage fluid will aid as indicators of lung damage or inflammation.[18] In the present study, it was observed that mean serum LDH level in participants with exudate type of pleural effusion was 795.5 ± 5.844 IU/L and in participants with transudate type of pleural effusion was 349.7 ± 9.584 IU/L and the difference was found to be statistically significant (p=0.001). It was also observed that mean LDH level in pleural fluid of participants with exudate type of pleural effusion was 640.9 ± 8.33 IU/L and in participants with transudate type of pleural effusion was 180.5 ± 4.18 IU/L and the difference was found to be statistically significant (p=0.001).Das AK et al in their study concluded that LDH is useful in differentiating transudates and exudates in pleural effusion.[17]

In the current study, it was observed that mean serum albumin level in participants with exudate type of pleural effusion was 3.494 ± 0.06 gm/dL and in participants with transudate type of pleural effusion was 4.604 ± 0.08 gm/dL and the difference was found to be statistically significant (p=0.001). It was also observed that mean albumin level

Table 1: Age and Sex distribution of study subjects (n=250)

Age group	Frequency	Percentage (%)
20 – 30 years	82	32.8
30 – 40 years	88	35.2
40 – 50 years	80	32
Sex	**Frequency**	**Percentage (%)**
Male	160	64
Female	90	36

Table 2: Distribution of study subjects and mean age based on type of pleural fluid (n=250)

Pleural fluid	Frequency (%)	Mean age in years
Exudate	125 (50)	34.77
Transudate	125 (50)	35.21

Table 3: Uric acid levels of serum and pleural fluid of study subjects

Uric acid levels	Mean value in subjects with Exudate (n=125)	Mean value in subjects with Transudate(n=125)	p value
Serum	4.898 ± 0.04 mg/dL	7.626 ± 0.06 mg/dL	0.009
Pleural fluid	2.494 ± 0.06 mg/dL	10.27 ± 0.07 mg/dL	0.033

Table 4: Biochemical parameters of serum and pleural fluid of study subjects(n=250)

Biochemical parameters	Mean value in subjects with Exudate (n=125)	Mean value in subjects with Transudate (n=125)	p value
Serum Total proteins	6.266 ± 0.04 gm/dL	8.788 ± 0.07 gm/dL	0.001
Pleural fluid Total proteins	4.983 ± 0.06 gm/dL	3.739 ± 0.04 gm/dL	0.001
Serum LDH	795.5 ± 5.844 IU/L	349.7 ± 9.584 IU/L	0.001
Pleural fluid LDH	640.9 ± 8.33 IU/L	180.5 ± 4.18 IU/L	0.001
Serum albumin	3.494 ± 0.06 gm/dL	4.604 ± 0.08 gm/dL	0.001
Pleural fluid albumin	2.714 ± 0.05 gm/dL	2.99 ± 0.08 gm/dL	0.001

Table 5: Comparision of uric acid levels based on gender (n=250)

Gender	Uric acid levels	Pleural fluid Type	Number of subjects	Mean ± SD (mg/dl)	p value
Male	Serum	Exudate	82	4.870 ± 0.55 mg/dl	0.001
		Transudate	78	5.941 ± 0.95 mg/dl	
	Pleural	Exudate	82	2.545 ± 0.66 mg/dl	0.003
		Transudate	78	3.703 ± 3.30 mg/dl	
Female	Serum	Exudate	43	4.953 ± 0.51 mg/dl	0.001
		Transudate	47	6.315 ± 1.06 mg/dl	
	Pleural	Exudate	43	2.398 ± 0.85 mg/dl	0.009
		Transudate	47	3.605 ± 2.90 mg/dl	

in pleural fluid of participants with exudate type of pleural effusion was 2.714 ± 0.05 gm/dL and in participants with transudate type of pleural effusion was 2.99 ± 0.08 gm/dL and the difference was found to be statistically significant (p=0.001). According to Palange P et al. study, in Serum to pleural fluid albumin gradient, Serum Albumin-Pleural fluid Albumin level of 1.2gm/dl or less indicates Exudates and greater than 1.2gm/dl indicates Transudates. In Serum to pleural fluid protein gradient serum Protein levels of 3.1gm/dl or less indicates Exudates and greater than 3.1gm/dl indicates Transudate.[19]

The present study also observed that mean serum uric acid level and pleural fluid uric acid level was higher in subjects with transudate type when compared to exudate type and the difference was found to be statistically significant in both genders. These findings highlight the importance of assessing uric acid levels in differentiating transudate and exudate type of pleural fluid.

5. Conclusion

There is multifactorial aetiology in the development of pleural effusion, it is important to differentiate transudates

and exudates in pleural effusion to establish clear diagnosis. Uric acid is relatively better predictive, simple and cost ineffective to the patient and can do easily by using blood and pleural fluid samples from the subjects with pleural effusion with diverse aetiology. Total proteins, LDH, Albumin play a role in association with Uric acid and are supportive to Light's criteria in the differentiation of transudates and exudates in pleural effusion. Hence, Uric acid levels can be a better biomarker to differentiate transudate and exudative pleural effusion easily, to diagnose and for better management of the patient.

6. Acknowledgement

7. Source of Funding

8. Conflict of Interest

None Declared.

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