

A Cross-sectional Prospective Study of Pleural Effusion Among Cases of Chronic Kidney Disease

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ABSTRACT

Background. Pleural effusions of diverse aetiologies are encountered in patients with chronic kidney disease (CKD). The objectives of the present study were to examine the frequency of occurrence, causes, clinical features and management strategies of pleural effusion in patients with CKD including renal transplant recipients.

Methods. A prospective cross-sectional observational analysis of pleural effusion in adult patients with CKD (stages 3 to 5) attending the Departments of Nephrology and Respiratory Medicine of a tertiary care institution in Eastern India was performed over a period of one year (February 2010 to January 2011).

Results. Pleural effusion was found in 29 out of 430 patients with CKD (6.7%) and in two out of 34 post-renal transplant recipients (5.9%) evaluated during the study period. The mean age was 37.35±1.8 (mean±SEM [standard error of mean]) with a male to female ratio of 2:1. Exudates and transudates were found in equal frequencies. Heart failure was the single most common cause (41.9%, 13 of 31). Tuberculosis (TB) (n=8, 25.8%) and uraemic effusions (n=6, 19.4%) were responsible for the majority of exudates. Unilateral effusion with a normal heart size had a positive predictive value of 83.3% for non-heart failure aetiology.

Conclusions. Symptomatic pleural effusion was present in a small proportion of 6.7%; (n=29) patients with CKD including post-renal transplant recipients. Heart failure, TB and uraemic effusions accounted for most of the cases. Differentiating TB from uraemic effusion requires a combined clinico-pathological approach and this differentiation is absolutely necessary for proper management. [Indian J Chest Dis Allied Sci 2013;55:209-213]

Key words: Pleural effusion, Chronic kidney disease, Heart failure, Tuberculosis, Uraemic pleuritis.

INTRODUCTION

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal renal function, and a progressive decline in glomerular filtration rate (GFR). Pleural effusion in such patients is a common diagnostic dilemma as it may arise from CKD itself (fluid overload, nephrotic syndrome, uraemic pleurisy), concomitant infections (especially, tuberculosis (TB) in our country), pulmonary embolisms or diseases causing pleuro-renal syndromes, like systemic lupus erythematosus.¹ Uraemic pleurisy is a diagnosis of exclusion, that persists or recurs despite aggressive haemodialysis.² Management of TB raises issues of drug dosing and interactions, especially in renal transplant recipients.

Most studies looking into the incidence of pleural effusion in patients with CKD are retrospective studies of hospitalised patients on long-term dialysis.³⁻⁵ In the present study, we prospectively studied the occurrence, causes, clinical features and management issues of pleural effusion in patients with CKD (stages 3 to 5) including renal transplant recipients in the Indian perspective.

MATERIAL AND METHODS

Study Design

The study was a prospective cross-sectional observational analysis of adult patients having pleural effusion with CKD (stages 3 to 5) or post-renal transplant, who attended the Department of

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Nephrology or Respiratory Medicine of a tertiary care teaching hospital in Eastern India over a period of 12 months (February 2010 to January 2011). As chronic renal failure typically corresponds to CKD (stages 3 to 5) (GFR < 60 mL/min per 1.73 m²),⁶ stages 1 and 2 CKD patients were excluded.

Patient Selection

Adult patients with CKD (stages 3 to 5) and post-renal transplant recipients showing clinico-radiological evidence of pleural effusion were included in the study. Written informed consent was taken from all the patients and the study was cleared by the Institutional Ethics Committee.

Patients with age less than 18 years, acute renal failure, CKD (stages 1 and 2) and patients not willing to participate in the study were excluded.

A detailed history was taken and examination was done. The presence of comorbidities including hypertension (systolic blood pressure (BP) > 140 mmHg or diastolic BP > 90 mmHg), diabetes mellitus, ischaemic heart disease, human immunodeficiency virus (HIV) infection, history/treatment of TB and malignancy was documented. Blood for complete haemogram, fasting blood glucose, renal function tests, liver function tests including serum protein and lactate dehydrogenase (LDH), electrocardiography, HIV serology, hepatitis B surface antigen (HBsAg), anti-hepatitis C antibody (Anti HCV), sputum for Ziehl-Neelsen (Z-N) stain, urine for routine and microscopic examination and 24-hour urinary protein were done in all patients. Echocardiographic evidence of decreased ejection fraction (< 40%), increased left ventricular (LV) end diastolic size (diameter \geq 60 mm) and regional wall motion abnormality were looked for in clinically suspected cases of heart failure. Serum N-terminal-pro-brain natriuretic peptide levels were examined only in selected patients (cut-off level = 300 pg/mL). Immunological markers like anti-nuclear antibody, dsDNA, C3, ANCA were measured in required cases. Further evaluation and staging of CKD was done by ultrasound study of kidney and calculation of glomerular filtration rate (GFR) by Cockcroft-Gault equation. Ultrasound guided renal biopsy was done in selected cases.

Chest radiograph (postero-anterior and lateral views) was assessed for the presence of pleural (unilateral or bilateral) cardiomegaly, pulmonary oedema (peribronchial cuffing, perihilar haze, Kerly B lines), and associated parenchymal lesions. Pleural fluid was studied for biochemical parameters (protein, LDH), cytology and categorised as transudate or exudate as per Light's criteria.⁷ Exudative pleural effusion was studied additionally by Z-N stain, Gram stain and culture for pyogenic cytology. Adenosine deaminase (ADA) estimation,

pleural fluid culture for *Mycobacterium tuberculosis* (BACTEC MGIT-960 fluorescent technology) and pleural biopsy using Abram's needle were performed in all cases of lymphocyte predominant exudative pleural effusion. A non-contrast computerised tomography (CT) of thorax was performed in some cases. Sputum was sent for *M. tuberculosis* (BACTEC MGIT-960) culture in suspected cases of tuberculous pleural effusion.

Tuberculous pleural effusions were treated with self-administered standardised chemotherapy consisting of isoniazid (INH) 200 mg and rifampicin 10 mg/kg daily, and ethambutol 15 mg/kg, pyrazinamide 25-30 mg/kg and vitamin B₆ (50 mg) thrice weekly. Re-treatment TB cases were additionally treated with ofloxacin instead of streptomycin in the intensive phase. Uraemic effusion was initially treated with intensified haemodialysis and if not responsive by intercostal tube drainage.

STATISTICAL ANALYSIS

Statistical analyses were done using Statistical Package for Social Sciences (SPSS; version 10). A 'P' value was calculated using Fisher's exact test of significance for categorical variables and one-tailed student 't' test was used for continuous variables. For comparison between multiple groups, analysis of variance (ANOVA) was used. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) were also calculated where relevant.

RESULTS

A total of 31 cases of pleural effusion were observed during the study period. The mean age (mean \pm SEM) was 37.2 \pm 1.8 years with a male to female ratio of 2:1. Hypertension was present in approximately 70% (n=22) and diabetes mellitus in 25.8% (n=8) patients. Of the 29 patients with CKD and pleural effusion, 18 were on haemodialysis and the mean interval between the start of haemodialysis and onset of pleural effusion was 6.5 \pm 0.8 months. Shortness of breath was the commonest symptom (n=29, 93.5%) followed by cough (n=22, 70.9%) and these did not differ among the major causes. Fever and pleuritic chest pain were common in exudative pleural effusions (81.35% and 62.5% respectively, Table 1). On the other hand, engorged neck veins, S₃ gallop and bilateral fine basal crepitations were present in 84.6%, 38.5%, and 53.8% of cases, respectively, in pleural effusions due to heart failure, but were absent in all others.

No significant difference was noted among heart failure, tuberculous effusion and uraemic effusion regarding the onset of pleural effusion in relation to duration of haemodialysis (6.4 \pm 1.1 versus 8 \pm 1 months

Table 1. Clinical characteristics of different aetiological groups of pleural effusions in chronic kidney disease

Characteristic	Heart Failure (n=13)	Tubercular (n=8)	Uraemic (n=6)	Empyema (n=2)	Nephrotic Syndrome	P value*
Age (mean± SEM)	42.8±2.76	36.5± 3.5	38.5±2.8	32.5±14.5	35.5±0.5	0.488
Fever	0	7	4	2	1	<0.001
Cough	7	6	6	2	2	0.076
Shortness of breath	11	8	6	2	2	0.312
Chest pain	1	6	4	2	0	<0.0001
Oedema	13	6	5	2	2	0.503
Bilateral effusion	10	0	2	0	0	<0.001
Cardiomegaly	8	1	2	0	0	0.102

* P values are between heart failure and non-heart failure aetiology

versus 6.7±2.4 months) but in cases of post-renal transplants, transudative effusion occurred within first month of transplant whereas tuberculous pleural effusion occurred four months after transplant.

Ten out of 13 (76.9%) pleural effusions due to heart failure were bilateral, whereas 14 out of 16 cases of exudative pleural effusion were unilateral. Unilateral pleural effusion was found to have an 87.5% positive predictive value (PPV) for non-heart failure cause. No significant difference was noted between the groups regarding presence of cardiomegaly on chest radiograph, but a normal heart size (C/T ratio <0.5) on chest radiograph was usually indicative of a non-heart failure aetiology with a PPV of 83.3%.

High pleural fluid ADA levels (ADA>60unit/L) were observed in six out of eight (75%) cases of tuberculous pleural effusion and a pleural fluid ADA >60unit/L had 75% sensitivity, 100% specificity and 100% PPV for tuberculous pleural effusion (Table 2).

Table 2. Pleural fluid characteristics in pleural effusions of different aetiologies

	Heart Failure	Tuberculous (n=13)	Uraemic (n=8)	Empyema (n=6)	Nephrotic (n=2)	P value Syndrome (n=2)
Total cell count (/mm ³)	835±313	2365±535	1345±475	15635±4075	746±312	*0.03342
Neutrophil %	6±3	8±6	14±6	84±14	8±3	*0.02747
ADA (IU/L)	7.3±2.1	72.63±8.69	30.95±3.06	45.5±5.5	6.7 ±4	**0.02747
Glucose (mg/dL)	42±14.07	68±33.12	56±28.35	15±4.24	74±6.45	*0.026
LDH(IU/L)	76±8.45	192±22.39	178±32.67	784±62.04	64±4.35	

Pleural biopsy in all eight suspected cases of tuberculous pleural effusion revealed epithelioid granulomas and giant cells in all and caseation in three cases. Pleural fluid for Gram stain and culture was positive in both cases of empyema, organisms grown being *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Uraemic effusions were diagnosed on the basis of exudative effusion with lymphocyte predominance and pleural biopsy showing fibrinous pleuritis without any epithelioid granuloma.² Pleural fluid culture was negative for *M. tuberculosis* and non-

contrast CT thorax negative for any other obvious aetiology.

The occurrence of pleural effusion in adults with CKD (stages 3 to 5) was found to be 6.7% (29 of 430 hospital admissions), and, among post-transplant patients 5.9% (2 of 34). Aetiologically heart failure was found to be the commonest cause of pleural effusion (41.9% cases, 13 of 31), while tuberculous pleural effusion was diagnosed in 25.8% cases (n=8), uraemic pleural effusion in 19.4% (n=6), empyema and nephrotic syndrome in 6.5% (n=2) cases each (Figure). Of the CKD patients with pleural effusion, 55.2% were in stage 5, 34.5% in stage 3 and 10.3% in stage 4.

Two of the seven CKD patients with tuberculous pleural effusion had a history of anti-tuberculosis treatment and were treated with rifampicin, isoniazid, ofloxacin (400mg) daily and with ethambutol (15mg/kg), pyrazinamide (25-30mg/kg) and vitamin B6 (50mg) thrice weekly, after

haemodialysis (HD) in the intensive phase (three months), followed by rifampicin, isoniazid and ethambutol for the next five months. The patient of renal transplant with tuberculous pleural effusion was treated with isoniazid, ethambutol, ofloxacin and pyrazinamide daily for two months followed by seven months of rifampicin, ethambutol and ofloxacin. In two cases of uraemic effusion which did not respond to aggressive haemodialysis, an intercostal chest drain had to be inserted and pleurodesis was performed.

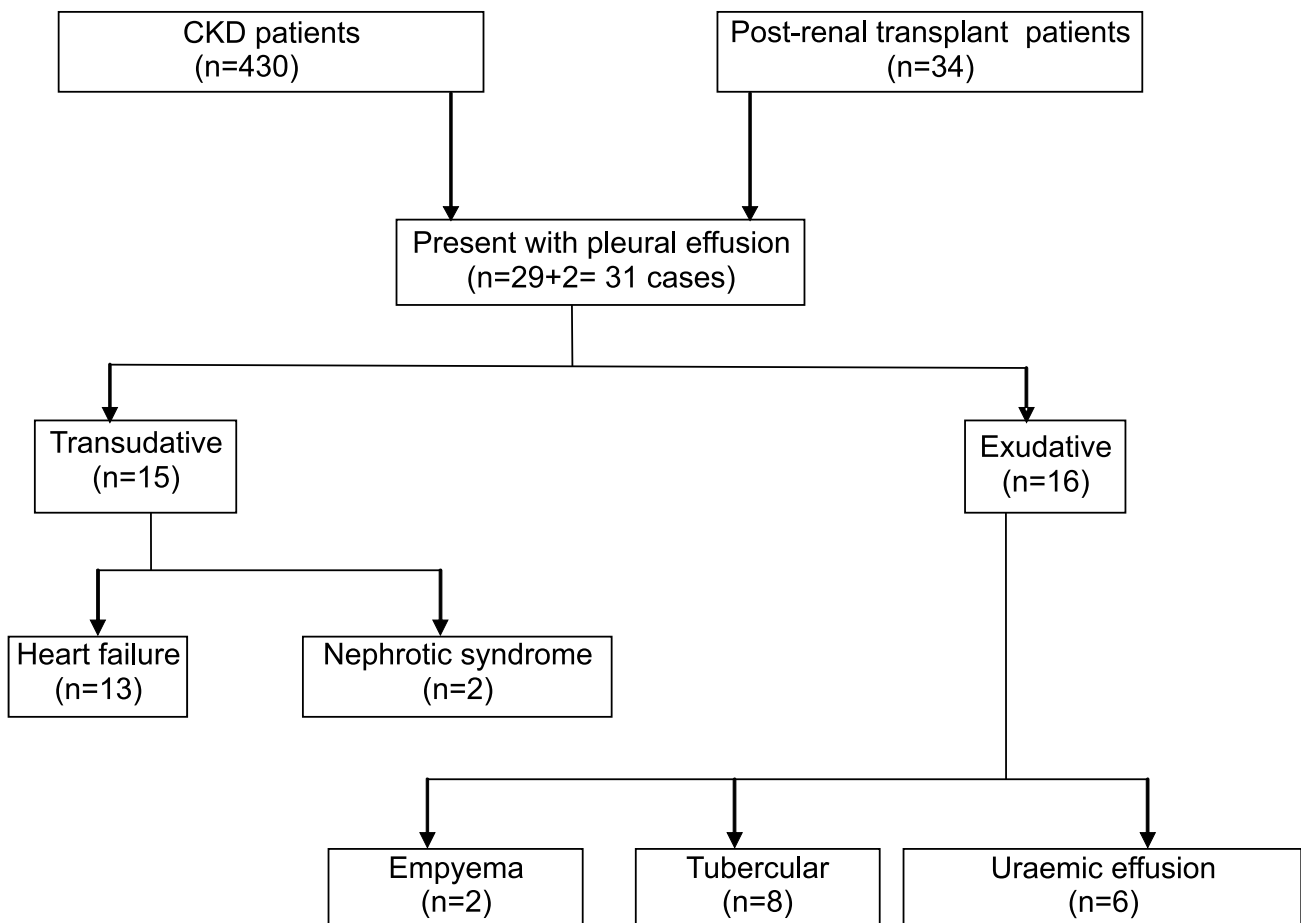


Figure. Aetiology of pleural effusions in chronic kidney disease/ post-renal transplant patients.

DISCUSSION

A pleural effusion may complicate CKD and may arise from renal or non-renal causes. In the present study, pleural effusion was observed in 6.7% of patients with CKD (stages 3 to 5) and 5.9% of post-renal transplant recipients. A higher incidence of approximately 20% had previously been reported from retrospective studies in patients on long-term haemodialysis.^{3,4} This may be due to the short time span of our study and a lower mean age of our patients (37 versus 55 years). In a more recent study,⁵ 82 of 1038 patients (7.9%) had to be investigated for pleural effusion while on peritoneal dialysis.

Although heart failure is the single most common cause of pleural effusion, overall exudative effusions and transudative effusions occurred with similar frequency (51% versus 48%, Table 1). Jarratt and Sahn³ also shared a similar observation, though hypervolaemia was seen in 61.5% of their patients with pleural effusion.

Unilateral pleural effusion on chest radiograph had an 89% NPV for heart failure as a cause of pleural effusion. Jarratt and Sahn³ also observed that

a normal cardiothoracic ratio and unilateral effusion had good PPV for a non-heart failure cause (89% and 81%, respectively).

Patients on dialysis are at a growing risk for tuberculosis (TB) worldwide with a recent summary article documenting a 6.9 to 52.5-fold increased risk.⁸ Besides defective-cell-mediated immune response and uraemia, comorbid conditions such as diabetes and prolonged cortico-steroid and immunosuppressive therapy also predispose patients to active TB. A high incidence of TB has been reported among patients with CKD in India, 8.7% in patients on maintenance dialysis and 12.3% in renal allograft recipients.⁹ Smear negative and extra-pulmonary forms are more frequent than in an immunocompetent individual. A high incidence of post-transplant TB has been reported in India, especially miliary TB. Taskapan *et al*¹¹ reported the incidence of TB in patients with CKD as 6.1% of which 77.8% were extra-pulmonary; pleural effusion was the commonest extra-pulmonary involvement. Management of TB in patients with CKD is an area of concern as most drugs except rifampicin require dose modification and directly observed treatment, short-course (DOTS) therapy is

not feasible in most cases. Post-transplant patients are further complicated by the interaction of rifampicin with cyclosporine, sirolimus and prednisolone. Ofloxacin is often used in place of rifampicin as the fourth drug in transplant patients with TB which prolong the treatment.¹² Adverse drug effects are common, and these require frequent monitoring. It further complicates management if there is hepatotoxicity.

Uraemic pleural effusion was first reported in 1955, when Hopps and Wissler demonstrated fibrinous pleuritis in 20% of uraemic patients at autopsy.¹³ Jarratt and Sahn³ reported an incidence of uraemic effusion of 16% while other studies have shown an incidence around 3%.² The pathogenesis of uraemic pleural effusion is not clear, but toxins like phosphates, uraemic acid and retained immune complexes have been implicated in the pathogenesis.¹⁴ Uraemic effusion has no relation to the degree of uraemia² and may occur at any time during the course of the disease. Pleural effusion may be bilateral in 20% cases.² In our study, the incidence of uraemic effusion was 19.4% (6 of 31) and in two cases (33.3%) effusion was bilateral. Uraemic effusion presents a real challenge because it must be differentiated from tuberculous effusion which it closely mimics. While the former is a reason for early transplant after proper drainage of fluid, active TB does not favour immediate transplant. A uraemic effusion is usually serosanguinous or haemorrhagic with lymphocytic predominance,⁸ and a pleural biopsy showing chronic fibrinous pleuritis is essential for the diagnosis.² Fibrinous pleuritis was demonstrated at pleural biopsy in all of our six patients. Uraemic effusions may progress or recur despite dialysis.² In two of our cases refractory pleural effusion necessitated intercostal tube placement and pleurodesis.

Due to reduced humoral- and cell-mediated immunity, parapneumonic effusion and empyema are common and mortality is 10 times higher in the setting of CKD than in the general population.¹⁵ Aerobic Gram-negative organisms¹⁶ or catheter-related aerobic Gram-positive organisms¹⁵ are the predominant pathogens. In our study, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were recovered on pleural fluid culture, both patients being on maintenance haemodialysis.

CONCLUSIONS

To summarise, exudative pleural effusions are found to be as common as transudative effusions among the

increasing number of patients on long-term haemodialysis and in renal transplant recipients. Though heart failure is the single most common cause of pleural effusion, other causes like tuberculosis, uraemic effusions, parapneumonic effusions, must be considered and investigated especially in the setting of a unilateral pleural effusion and a normal heart size. Tuberculous effusions must be differentiated from uraemic effusions in view of the implications for the management.

REFERENCES

1. Mark Cohen M, Sahn SA. Resolution of pleural effusions. *Chest* 2001;119:1547-62.
2. Berger HW, Rammohan G, Neff MS, Buhain WJ. Uremic pleural effusion: a study in 14 patients on chronic dialysis. *Ann Intern Med* 1975;82:2-4.
3. Jarratt MJ, Sahn SA. Pleural effusions in hospitalized patients receiving long-term haemodialysis. *Chest* 1995;108:470-4.
4. Bakirci T, Sasak G, Ozturk S, Aksay S, Sezer S, Haberal M. Pleural effusion in long-term hemodialysis patients. *Transplant Proc* 2007;39:889-91.
5. Kwan BCH, Chow KM, Pang WF, Leung CB, Li PKT, Szeto CC. Unexplained exudative pleural effusion in chronic peritoneal dialysis patients. *Perit Dial Int* 2010;30:534-40.
6. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002;39 (Suppl.1):S1-S266.
7. Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med* 1972;77:507-13.
8. Hussein MM, Mooji JM, Roujouleh H. Tuberculosis and chronic renal disease. *Semin Dial* 2003;16:38-44.
9. John GT. Infections after renal transplantation in India. *Indian J Nephrol* 2003;13:14.
10. Aggarwal DK, Ammann N, Marthy BVR, Neela P, Ratnakar KS. High incidence of post-transplant tuberculosis in India. *Indian J Nephrol* 1994;4:91.
11. Taskapan H, Utas C, Oymak FS, Gulmez I, Ozesmi M. The outcome of tuberculosis in patients on chronic hemodialysis. *Clin Nephrol* 2000;54:134-7.
12. Sundaram M, Adhikary SD, John GT, Kekre NS. Tuberculosis in renal transplant recipients. *Indian J Urol* 2008;24:396-400.
13. Hopps HC, Wissler RW. Uremic pneumonitis. *Am J Pathol* 1955;31:261-73.
14. Maher JF. Uremic pleuritis. *Am J Kidney Dis* 1987;10:19-22.
15. Sarnak MJ, Jaber BL. Pulmonary infectious mortality among patients with end-stage renal disease. *Chest* 2001;120:1883-7.
16. Chen CH, Hsu WA, Chen HJ, Chen W, Shih CM, Hsia TC, et al. Different bacteriology and prognosis of thoracic empyemas between patients with chronic end-stage renal disease. *Chest* 2007;132:532-9.