Original Article

A stepwise approach to the etiologic diagnosis of pleural effusion in respiratory intensive care unit and short-term evaluation of treatment

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ABSTRACT

Background: Pleural effusions in respiratory intensive care unit (RICU) are associated with diseases of varied etiologies and often carry a grave prognosis. This prospective study was conducted to establish an etiologic diagnosis in a series of such patients before starting treatment. **Materials and Methods:** Fifty consecutive patients, diagnosed with pleural effusion on admission or during their stay in RICU, were further investigated by a two-step approach. (1) Etiologic diagnosis was established by sequential clinical history and findings on physical examination, laboratory tests, chest radiograph, CECT/HRCT/PET-CT and pleural fluid analysis. (2) Patients who remained undiagnosed were subjected to fiber-optic bronchoscopy, video-assisted thoracoscopic pleural biopsy, and histopathology. **Results:** Etiologic diagnosis of pleural effusion was established in 44 (88%) Metastases (24%); para-pneumonia (22%); congestive cardiac failure (18%); tuberculosis (14%); hemothorax (4%); trapped lung, renal failure, and liver cirrhosis (2% each). Six patients (12%) remained undiagnosed, as the final diagnostic thoracoscopic biopsy could not be performed in five and tissue histopathology findings were inconclusive in one. Out of the 50 patients, 10 died in the hospital; 2 left against medical advice; and 2 were referred to oncology center for further treatment. The remaining 36 patients were clinically stabilized and discharged. During a 3-month follow-up, eight of them were re-hospitalized, of which four died. **Conclusions:** Pleural effusion in RICU carries a high risk of mortality. Etiologic diagnosis can be established in most cases.

KEY WORDS: Cardiac failure, lung malignancy, pleural effusion, pneumonia, thoracoscopy, tuberculosis

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INTRODUCTION

Pleural effusion is common in the respiratory intensive care unit (RICU) patients, suggests a serious local or systemic disease and calls for urgent investigations to determine its cause. The pathophysiologic mechanisms underlying the accumulation of fluid in the normally dry pleural space include an increased pulmonary capillary pressure, decreased plasma oncotic pressure, increased permeability of pleural membrane, mediastinal involvement with reduced pleural lymphatic drainage, bronchial obstruction with high negative intrapleural pressure, and imbalance between formation and absorption of fluid.[1] The effusion occurring through pressure filtration without capillary injury is termed a transudate. Common examples are congestive cardiac failure (CCF), renal failure, superior vena cava obstruction, constrictive pericarditis, liver cirrhosis, fluid overload, and hypoalbuminemia. On the other hand, "inflammatory" fluid leaking between cells due to local factors is termed an exudate, as in bacterial pneumonia, viral infections, tuberculosis, malignancy, sub-phrenic pathology, and Dressler's syndrome. It may be noted that a malignant disease and pulmonary embolism may produce either a transudative or an exudative effusion. Exudates and transudates are best differentiated by Light's three criteria: [2] (i) Ratio of pleural fluid protein to serum

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protein >0.5; (ii) ratio of pleural fluid to the serum lactate dehydrogenase (LDH) >0.6; (iii) absolute value of pleural fluid LDH >two-thirds of the upper normal limit for serum. While exudates meet one or more of the three criteria, transudates meet none.

Ninety percent cases of pleural effusion in the western countries are reported to result from only five diseases: CCF, pneumonia, malignancy, pulmonary embolism, and viral infections.[3] Twenty to forty percent of hospitalized patients with bacterial pneumonia develop pleural effusion.[4,5] In India, unlike the western countries, tuberculous pleural effusion is common. The pleural cavity is involved in approximately 5% of all patients with tuberculosis,[6] which is next only to lymph node tuberculosis.[7]

In a medical intensive care unit at the medical university of South Carolina 62% patients were diagnosed with pleural effusion; 41% were detected on admission and 21% developed it post admission.[8] Pleural effusions in the RICU are often more complex and difficult to diagnose, due to frequently associated co-morbidities such as COPD, diabetes, CCF, liver cirrhosis, renal failure, superior vena cava obstruction, hypoalbuminemia, fluid overload, and thromboembolism.

Based on class I and IIa evidence, following a comprehensive search of world literature from 2003 to 2009, McGarth and Anderson[9] recommended a stepwise systematic approach to making the etiologic diagnosis of pleural effusion. Although clinical assessment, chest radiograph, and pleural fluid analysis including cytology and a marker for tuberculosis, such as adenosine deaminase (ADA), were often adequate in most cases, they failed to provide a diagnosis in 25% cases.[10] Options in such patients were contrast-enhanced computed tomography (CECT), positron emission tomography (PET) CT, fiber-optic bronchoscopy (FOB), video-assisted thoracoscopic biopsy, and thoracotomy.[11] According to the British Thoracic Society guidelines no diagnosis may ever be made in 10-15% cases.[1]

The present study was undertaken in a series of RICU patients diagnosed with pleural effusion: To determine its etiology by following a two-step investigational approach, provide appropriate treatment and evaluate its short-term outcome.

MATERIALS AND METHODS

Patient selection

This is a prospective study carried out in the RICU of the Metro Centre for Respiratory Diseases over a period of eight months (July 2011 to February 2012). Based on a diagnostic ultrasonography, 50 consecutive patients with pleural effusion were enrolled in the study from a total of 340 patients admitted during that period. Of the 50 patients 44 showed evidence of effusion on the day of admission, while 6 developed effusion post admission. As per the guidelines of the Indian Council of Medical Research and after obtaining approval from the local ethics committee, a written informed consent was obtained from each patient.

Detailed clinical evaluation of patients included history of cough, dyspnea, fever, pleuritic pain, hemoptysis, smoking, diabetes, leg swelling or deep vein thrombosis, chest wall trauma, and upper abdominal surgery. They were also assessed for co-morbidities like chronic obstructive pulmonary disease (COPD), diabetes, malignancy, and renal, hepatic, and cardiovascular disease. Terminally ill patients and those in whom effusion could not be tapped were excluded from the study. A two-step investigational approach was adopted to determine the etiologic diagnosis of pleural effusion [Figure 1]. All patients were assessed for associated co-morbidities.

Step-1 investigations

1. Routine blood tests, serum LDH, proteins and NT-pro-BNP assay; sputum examinations by smear and culture for acid fast bacillus (AFB), Gram stain, culture and sensitivity for pyogenic organisms, and chest radiograph were done in all cases
2. Special investigations included contrast enhanced computed tomography (CECT)/HRCT thorax, 12-lead ECG, and Doppler echocardiography in each case; ultrasonography or CT abdomen, and PET-CT in selected cases
3. Ultrasound-guided thoracentesis was done in all cases for pleural fluid analysis as well as for relief of symptoms in large effusions. The fluid was examined for AFB by smear/culture and for pyogenic organisms by culture and sensitivity tests, ADA, total and differential leukocyte counts, protein, LDH, malignant cells, cancer markers, etc. Simultaneously, blood samples were examined for comparisons, if required
4. Ultrasound-guided diagnostic tap of ascites fluid was done in two patients.

Step-2 investigations

The patients, in whom the etiologic diagnosis could not be established after step-1 investigations, were subjected to the following step-2 investigations.

1. Fiberoptic bronchoscopy and broncho-alveolar lavage (BAL) fluid examination were performed in 18 cases with recurrent effusion, mass lesion, non-resolving pneumonia, or mechanically ventilated patients
2. The procedure of video-assisted thoracoscopy, pleural biopsy, and histopathology was planned in sixteen patients. It was successfully carried out in 11, refused by four and was considered unsafe in one patient.

All patients were appropriately treated on the basis of clinical assessment and etiologic diagnosis. Thirty-six of the fifty patients were discharged from the hospital and followed up as outpatients.

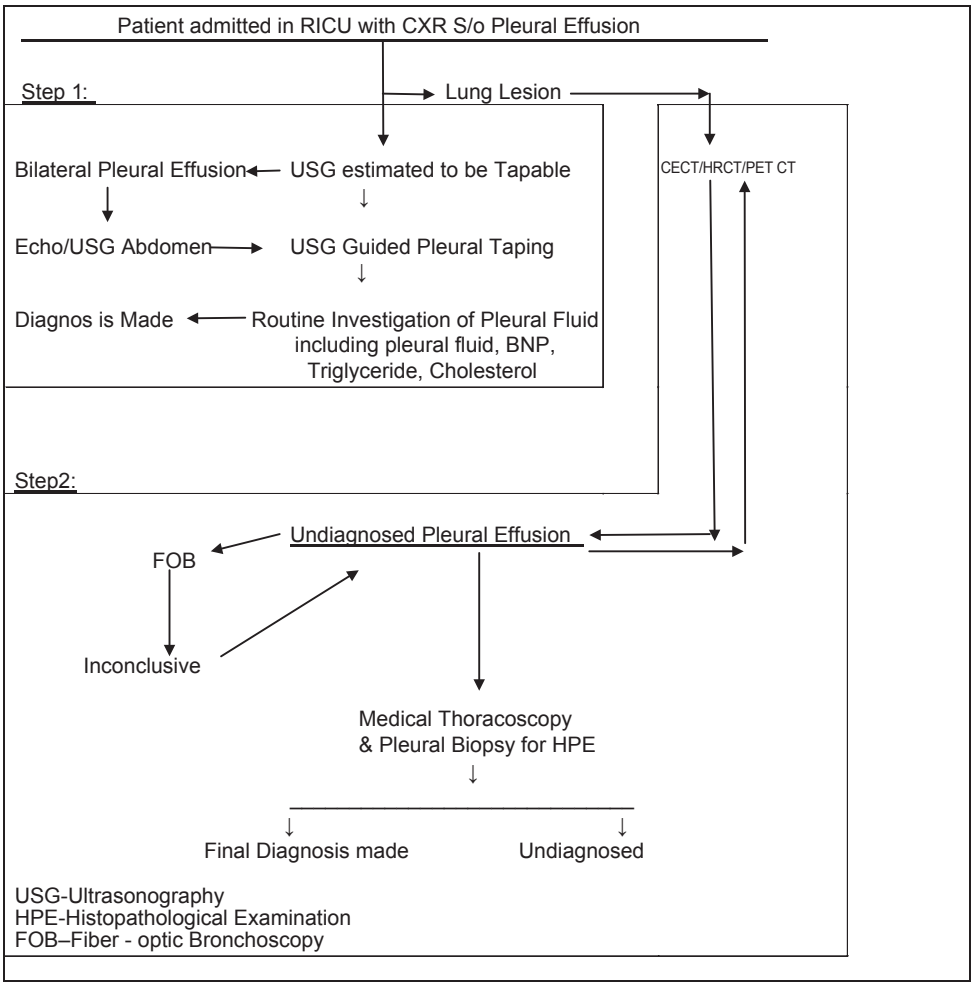

Figure 1: Two-step investigational approach to diagnosing pleural effusion in RCU

Statistical analysis of data

The parametric variables were defined as mean ± standard deviation (SD). The non-parametric variables, such as dyspnea on MMRC grading, presenting symptoms, and the amount of pleural fluid on ultrasonography, were defined as the modal occurrence of the event in terms of percentage of total sample size.

The mean age and duration of illness for the different etiologic characteristics of the pleural effusion were compared using Mann–Whitney test, to compare the significance of age and duration of illness in the development of pleural effusion.

The results of pleural fluid examination were analyzed, using Mann–Whitney test to compare the outcome of the pleural fluid examination of different etiologic characteristics.

RESULTS

Fifty consecutive patients diagnosed with pleural effusion constituted 14.7% of a total of 340 patients admitted in the RICU. Forty-four (88%) patients were assessed to have effusion on the day of admission, while 6 (12%) patients (finally diagnosed as para-pneumonic - 3; CCF - 1; undetermined etiology - 2) had developed it post admission.

Etiologic diagnosis

The two-step investigational approach in the 50 patients led to the following etiologic diagnoses of pleural effusion: Malignancy - 12 (24%); para-pneumonic - 11 (22%); CCF - 9 (18%); tuberculosis - 7 (14%); hemothorax - 2 (4%); trapped lung - 1 (2%); renal failure (on dialysis) - 1 (2%), and liver cirrhosis - 1 (2%). No etiologic diagnosis could be established in 6 (12%) patients and their etiology was categorized as "undetermined." It may be noted that four of these six patients had refused to undergo the final diagnostic procedure of thoracoscopic biopsy; one patient was too ill to undergo the procedure, while in the sixth patient the histopathology of biopsy material only revealed a non-specific inflammation. The study group patients were diagnosed with several co-morbidities: hypertension 19 (38%), COPD 18 (36%), diabetes mellitus 9 (18%), and tuberculosis 5 (10%). However, these co-morbidities did not show any distinct pattern of distribution related to the etiologic categories.

All 12 cases of malignant pleural effusion were confirmed to be due to metastases from adenocarcinoma (primary site not detected) - 3; adenocarcinoma lung - 2; small cell carcinoma - 2; and squamous cell carcinoma of tonsil, anaplastic carcinoma of thyroid, breast, ovary, and squamous cell carcinoma of left vocal cord - 1 each.

Clinical and investigational data

The clinical, laboratory, and other investigational data in different etiologic categories of pleural effusion are presented in Tables 1–4.

Table 1 shows the physical characteristics and clinical symptoms and signs in patients of each etiologic category of pleural effusion.

It can be seen that CCF patients were significantly older and tuberculosis patients younger, compared with other etiologic categories. The mean duration of illness in patients at the time of hospitalization was comparatively longer in tuberculous, followed by malignant and undetermined etiology categories. The distribution of BMI, symptoms of cough, fever, pleuritic pain, and modified medical research council (MMRC) grade of dyspnea did not follow any distinct pattern in the different etiologic categories.

Blood test data and estimated quantity of pleural fluid are presented in Table 2. It can be seen that loculated pleural effusions were seen in some cases of tuberculosis, hemothorax, and undetermined categories. All categories except hemothorax showed evidence of anemia – the lowest mean Hb values being in patients of undetermined etiology. Mean total leukocyte counts were comparatively higher in the para-pneumonic and undetermined etiology categories than others. Leukopenia of 1800 cells/mm^3 was found in the only case of liver cirrhosis.

Bilateral pleural effusion was most common in CCF followed by undetermined etiology category and in the only case of liver cirrhosis.

Pleural fluid analysis data

The pleural fluid analysis data are presented in Table 3a and b. Mean pH values in different etiologic categories ranged from 7.35 ± 0.09 in para-pneumonic to 7.48 ± 0.03 in the CCF category. Total leukocyte counts showed a wide range of variations in different etiologic categories with the highest value (2176 ± 2677) in para-pneumonic category. The hemothorax and para-pneumonic effusions were neutrophil predominant while all other categories were predominantly lymphocytic.

Serum protein and LDH values were increased in malignant, para-pneumonic, tuberculous, and hemothorax

Table 1: Physical characteristics, clinical signs, and symptoms in patients of each etiologic category of pleural effusion

Etiologic category (*n*)	Age (years)		Number of patients (%) BMI (kg/m^2)			Days of illness		Number of patients (%)						
	Mean	SD	<18.5	>18.5<25	>2 5	Mean	SD	Dyspnea (MMRC Gr)				Pleuritic		
								I	II	III	IV	Cough	Fever	Pain
Malignancy (12)	64.3	13.9	60	40	0	20.3	17.1	0	33	42	25	75	17	33
Para-pneumonic (11)	55.09	12.5	30	61	9	6.8	4.7	9	27	37	27	82	91	36
CCF (08)	75.0	11.4*	44	12	44	5.0	3.0	0	22	56	22	78	44	0
Tuberculous (07)	47.6	11.3*	43	57	0	26.4	15.7	14	57	14	14	100	100	29
Hemothorax (02)	47.0	11.3	100	0	0	6.0	5.7	0	100	0	0	100	50	100
Trapped lung (1)	75.0		100	0	0	03		0	0	100	0	100	0	100
Renal failure (01)	55.0		100	0	0	15.0		0	100	0	0	100	0	0
Liver cirrhosis (01)	68.0		100	0	0	8.0		0	100	0	0	0	0	0
Undetermined (06)	74.2	11.2	80	20	0	13.0	25.2	0	33	17	50	100	83	0
All categories (50)	62.4	16.4	52	40	8	13.3	13.0	4	36	36	24	84	53	26

*Statistically significant difference from other etiologic categories, CCF: Cardiac failure, MMRC Gr: Modified medical research society grade, SD: Standard deviation, BMI: Body mass index

Table 2: Results of routine blood tests and ultrasonography in each etiologic category of pleural effusion

Etiologic category (*n*)	Hb (g/dl)		TLC/cu mm		Number of patients (%) Pleural fluid on ultrasonography (ml)			
	Mean	SD	Mean	SD	≤500	≥500≤1000	≥1000	Loculated
Malignancy (12)	12.6	1.9	10675	4953	50	25	25	0
Para-pneumonic (11)	11.3	2.1	16945	7348	91	0	09	27
CCF (09)	10.8	1.1	10900	4069	89	11	0	0
Tuberculous (07)	10.7	2.0	9314	4309	57	29	14	14
Hemothorax (02)	14.6	1.8	9200	2969	50	0	50	50
Trapped lung (01)	11.6		4100		0	100	0	0
*Renal failure (01)	8.1		4700		0	0	100	0
Liver cirrhosis (01)	7.5		1800		0	100	0	0
Undetermined (06)	8.6	2.1	16050	9541	100	0	0	17
All categories (50)	11.1	2.3	12063	6706	70	16	14	12

*Patient on dialysis, CCF: Congestive cardiac failure, TLC: Total leukocyte count, SD: Standard deviation

Table 3a: Results of pleural fluid examination in each etiologic category of pleural effusion

Etiologic category (*n*)	PH		TLC/cu mm		Poly %		Lympho (%)		Protein (g/dl)		Glucose (mg/dl)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Malignancy (12)	7.55	0.03	692	490	17	24	73	23	4.22	1.46	104	62.32
Para-pneumonic (11)	7.35	0.09	2176	2677	62	32	30	32	3.24	1.13	119.5	68.7
CCF (9)	7.48	0.03	428	251	5.7	3.9	85.7	4.64	2.02	0.95	176.6	46.4
Tuberculous (7)	7.47	0.04	1439	823	6.7	6.2	84.3	6.24	5.34	1.23	112.1	43.3
Hemothorax (2)	7.42	0.03	990	297	52	23	45. 0	21.2	6.6	1.55	134	8.5
Trapped lung (1)	7.50		350		06		90.0		2.0		98.0	
Renal failure (1)	7.50		1400		02		90.0		1.9		100.0	
Liver cirrhosis (1)	7.48		122		28		62.0		1.7		77.0	
Undetermined (6)	7.47	0.04	462	356	5.3	2.6	85.3	5.3	2.67	1.27	163.5	56.4
All categories (50)	7.47	0.17	1056	1425	23.1	30	82.5	97.7	3.54	1.72	129.2	60.1

CCF: Congestive cardiac failure, TLC: Total leukocyte count, Poly: Polymorphonulear leukocytes, Lympho: Lymphocytes, SD: Standard deviation

Table 3b: Results of pleural fluid examination in each etiologic category of pleural effusion

Etiologic category (no. of patients)	LDH (u/L)		Creatinine (mg/dl)		Bilirubin (mg/dl)		Amylase (u/L)		NT-pro-BNP (pg/ml)		ADA (U/L)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Malignancy (12)	543	338	0.8	0.22	0.58	0.26	40.3	39.0	277.4	99.8	22.3	12.3
Para-pneumonic (11)	680	604.9	1.1	0.31	0.97	1.04	35.0	17.5	502.5	554.5	34.2	18.5
CCF (9)	80.8	22.5	1.48	1.1	0.59	0.39	46.8	66.2	20947	11332	31.7	41.6
Tuberculous (7)	371	265	1.21	0.8	0.52	0.26	86.3	105	448.1	393.4	138.0	66.1
Hemothorax (2)	9600	13385	0.8	0.35	0.70	0.14	82.6	62.9	295	7.10	34.0	11.3
Trapped lung (1)	70.0		0.8		0.50		10.0		180.0		18.90	
Renal failure (1)	63.1		6.70		0.60		29.0		200.0		21.5	
Liver cirrhosis (1)	87.0		0.80		1.60		35.0		105.0		21.0	
Undetermined (6)	89.0	5.0	1.06	0.61	0.47	0.21	28.2	14.7	625.0	692.6	16.7	8.1
All categories (50)	745	2675	1.21	1.01	0.67	0.57	46.04	54.5	4164	9153	42.5	49.9

LDH: Lactate dehydrogenase, ADA: Adenosine deaminase, CCF: Congestive cardiac failure, SD: Standard deviation. *On dialysis

Table 4: Findings on CT-scan, echocardiography, and pleural fluid examination for malignant cells and cancer markers in different etiologic categories of pleural effusion

Test parameters	Etiologic category (number of patients)								
	Malignancy (12)	Para-pneumonic (11)	CCF (08)	Tuberculous (07)	Hemotho-rax (02)	Trapped lung (1)	Renal failure (1)	Liver cirrhosis (1)	Undetermined (6)
CT-thorax									
Consolidation	17%	64%	0.00	0.00	0.00	0.00	0.00	0.00	33%
Mass lesion	17%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Cardiomegaly	0.00	0.00	22%	0.00	0.00	0.00	0.00	0.00	0.00
Lymph nodes	25%	9%	0.00	14%	0.00	0.00	0.00	0.00	17%
Abscess/cysts	0.00	9%	0.00	0.00	50%	0.00	0.00	0.00	0.00
Echocardio graphy									
LVEF %									
Mean (SD)	57.1 (11.7)	52.7 (11.7)	39.4 (11.8)	49.3 (14.0)	52.5 (3.5)	55.0	55.0	50.0	56.7
Wall motion									
Abnormality	0.00	9%	22%	0.00	0.00	0.00	0.00	0.00	0.00
Systolic									
Dysfunction	0.00	0.00	11%	0.00	0.00	0.00	0.00	0.00	0.00
Diastolic dysfunction	42%	55%	56%	43%	50%	100%	0.00	0.00	0.00
PAH	8%	9%	22%	0.00	0.00	0.00	0.00	0.00	0.00
LVH	0.00	0.00	11%	0.00	0.00	0.00	0.00	0.00	0.00
Valvular heart									
Disease	0.00	0.00	0.00	14%	0.00	0.00	0.00	0.00	0.00
Pleural fluid cytology									
Malignant cells detected	50%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Cancer mark-ER test +									
CEA	9%	-	-	-	-	-	-	-	-
CA 125	9%	-	-	-	-	-	-	-	-

LVEF: Left ventricle ejection fraction, PAH: Pulmonary artery hypertension, LVH: Left ventricle hypertrophy, CA 125: Cancer antigen, CEA: Cacinoembryonic antigen, SD: Standard deviation

effusions—the latter group had >6 gm% protein and >15,000 units LDH. Serum creatinine level was markedly raised in the only patient with renal failure who was on regular maintenance hemodialysis. Mean ADA

values were more than 125 units per liter in tuberculous effusion compared with <60 units per liter in all other categories. LDH discordant exudative effusion was found in different etiologic categories (malignant - 2/12; para-pneumonic - 3/11; and CCF - 2/9). Protein discordant effusions were found in 2/6 patients with effusions of undetermined etiology. It is noteworthy that mean NT-pro-BNP levels in pleural fluid were unequivocally and significantly elevated in all cases of CCF.

Microbiologic examination of pleural fluid by Gram-smear, culture, and sensitivity test for aerobes and anaerobes, and AFB smear and culture test for AFB yielded negative results. PCR test for tuberculosis DNA was positive in 6/7 cases of tuberculous effusion, whereas it was negative for each of the patient in other etiologic categories.

Other biochemical tests (data not tabulated)

Serum levels of creatinine, bilirubin, and amylase were raised in different etiologic categories, apparently due to sepsis. None of the tuberculosis patients showed evidence of renal toxicity related to anti-tuberculosis therapy. Serum amylase level was raised in one of the two cases of hemothorax - finally diagnosed as a congenital cystic adenomatoid malformation. Mean serum NT-pro-BNP levels were markedly raised (18480 ± 9397 pg/ml) in CCF patients compared with other patients (normal = <1500 pg/ml). Very significantly, the pleural fluid and blood BNP ratio was unequivocally >1.0 in all cases of CCF. A similar ratio was seen in 2 of 11 cases of para-pneumonic effusion and in the only case of liver cirrhosis, but with the important difference that blood levels in them were within the normal range.

Imaging, echocardiography, and cancer markers

The results of CECT thorax, echocardiography, pleural fluid cytology, and cancer marker studies are given in Table 4. It can be seen that lung consolidation was most commonly seen in pneumonia followed by malignancy and lymphadenopathy in tuberculosis and malignancy. Some cases of effusion of undetermined etiology were characterized by both consolidation and lymphadenopathy.

Left ventricular ejection fraction (normal >50%) was impaired in CCF (20–40%- 6/9 cases) and tuberculosis (25–35% - 2/7 cases) - suggestive of cardiac etiology of pleural effusion. Thus, two cases of tuberculous effusion were also complicated with CCF—an example of combined tuberculosis and CCF.

Pleural fluid cytology was positive for malignant cells in six (50%) cases of malignant effusion. Levels of cancer markers were elevated in two patients: Cancer antigen (CA 125) - 1 and carcino-embryonic antigen (CEA) marker - 1.

Fiber-optic bronchoscopy (FOB)

Diagnostic FOB in 16 patients revealed evidence of malignancy - 2; inflammation - 7; and was normal in 7 patients. In the last group of patients, however, thoracoscopic pleural biopsy led to a diagnosis of malignancy in 3 patients.

Video-assisted thoracoscopic pleural biopsy

Sixteen patients, who remained without an etiologic diagnosis after the step-1 investigations described above, were advised to undergo a video-assisted thoracoscopic pleural biopsy and histopathology examination. Four of them refused the procedure and one patient was too ill to undergo it. In the remaining 11 patients, including the three patients found normal on FOB, histopathology of the biopsy material showed unequivocal evidence of adenocarcinoma (5), squamous cell carcinoma (1), tuberculosis (3), trapped lung (1), and nonspecific changes (1).

Undetermined etiology category

No etiologic diagnosis was established in 6 (12%) of the 50 patients. Clinically, five of them were in sepsis. They were put in the category of undetermined etiology for want of a better term.

Treatment and short-term follow-up

Treatment with appropriate antibiotics, chemotherapy, diuretics and anti-cancer drugs were often supplemented with interventional procedures as detailed below.

Malignant effusion (n = 12)

Therapeutic aspiration was done in five patients. Tube thoracostomy drainage and pleurodesis were done in seven and five cases respectively. One patient died, one left against medical advice, two were referred to cancer hospital for further treatment, and the remaining eight patients were discharged and followed up. Two patients were lost to follow-up, two were re-hospitalized of whom one died; the remaining three patients remained clinically stable.

Para-pneumonic effusion (n = 11)

Intrapleural fibrinolysis with therapeutic aspiration was done in two patients and tube thoracostomy drainage was done in six patients (Portex ICD in five and pigtail catheter insertion in one patient with loculated effusion). Four patients died and one patient left against medical advice. Drainage of fluid in para-pneumonic effusion seemed to improve clinical outcome and prevent spread of infection and adhesions. The remaining six patients remained clinically stable.

CCF (n = 9)

Therapeutic aspiration was done in two patients, conservative treatment with diuretics etc. was given in four patients while three patients died. Post discharge, two patients had to be re-hospitalized of whom one died.

Tuberculous effusion (n = 7)

Chest tube was inserted after thoracoscopy in 3/7 patients; a pig-tail catheter was inserted in one patient with intrapleural adhesions. During the 3-month follow-up,

1 of the 6 patients had to be re-hospitalized and that patient died.

Effusion of undetermined etiology (n = 6)
Two patients died in the hospital; therapeutic aspiration was done in one patient; one patient was treated with tube thoracostomy. During the 3-month follow-up, one of the four patients was re-hospitalized and died.

Hemothorax effusion (n = 2)
Tube thoracostomy was done in one patient. Pneumonectomy was done in the other because of persistent bleeding which was later found to be due to congenital cystic adenomatoid malformation.

Trapped lung (n = 1)
The patient was discharged after the tube thoracostomy.

Renal failure (n = 1)
The patient was treated with therapeutic aspirations.

Liver cirrhosis (n = 1)
The patient was treated conservatively.

Treatment outcome and 3-month follow-up
Ten (20%) of the fifty patients died in the hospital, two left against medical advice, while two patients were referred to an oncology center for further treatment. Thirty-six patients were clinically stabilized and were followed up as out-patients for 3 months. Eight of them had to be re-hospitalized, four of them died. Thus, the overall mortality rate in the present series was 28%. The fate of two patients who were lost to follow-up and two other patients who were referred to cancer hospital were not known.

DISCUSSION

To the best of our knowledge, this is the first study on the etiology of pleural effusions in an RICU from India. It clearly demonstrates that they are associated with diseases of varied etiologies and carry a serious prognosis with a high risk of death. Malignancy, pneumonia, cardiac failure, and tuberculosis—in that order of frequency —were the most common conditions producing pleural effusion. Liver cirrhosis, hemothorax, renal failure, and trapped lung were the other rare causes. The incidence of pleural effusion in the RICU was 14.7%. This is by no means the national average, as this is largely determined by the patient intake policy of the intensive care unit of a hospital. Furthermore, the role of the associated co-morbidities in the onset and clinical course of pleural effusion remains unclear.[12] In contrast with the studies reported from western countries, there is a larger proportion of tuberculous pleural effusions than other etiologies in India.[3]

In making an etiologic diagnosis of transudates, pleura and lung can generally be ignored as the seat of pathology, as these often relate to cardiac failure, liver cirrhosis, renal failure, hypoalbuminemia, and fluid overload; and rarely neoplasm, pulmonary embolism, and rheumatoid arthritis. In case of exudates, on the other hand, a series of cytologic, biochemical, microbiologic, and cancer marker detection tests on pleural fluid are necessary to identify the nature of pathology in the pleura and lungs. Light's criteria are believed to be 100% sensitive for exudates, except that in 20% cases of heart failure on diuretics the fluid may be erroneously classified as exudates.[13] In such instances, if the difference between serum and pleural levels of protein is >3.1 g/dl, the effusion should be classified as transudate.

It is warranted that for best results, a definitive diagnosis of the cause of pleural effusion and associated co-morbidities is made before starting treatment. In the present series there was some overlap of the clinical manifestations as well as the results of complimentary investigations between different etiologic categories of pleural effusion. Therefore, the final diagnoses were always based on clinching evidences obtained on the characteristic features of the disease; and only in exceptional cases the diagnosis was based on circumstantial evidences alone.

The two-step investigational approach in the present study was highly successful in that, a comprehensive diagnosis of pleural effusion could be made in 88% patients. The first step comprising careful analyses of sequential medical history, physical examination, chest radiograph, and routine blood test data often provided useful leads to the likely diagnosis in a given patient. This facilitated in ordering and interpretation of the results of complementary investigations. Thus, an etiologic diagnosis could be established in 68% cases after chest radiograph, CECT/HRCT lungs, ECG, echocardiography and pleural fluid analysis. In cases of persistent exudative effusions in which pleural fluid analysis did not lead to an immediate diagnosis, step-2 investigations were carried out. The latter comprised of FOB, BAL fluid analysis, followed by thoracoscopic pleural biopsy and histopathology.

CT-thorax proved vastly superior to detect pleural fluid than chest radiograph alone, with the additional advantage of showing more clearly the state of underlying lung parenchyma, fluid loculations, and associated diseases of chest and cardiovascular system. For instance, consolidation was detected in 73% patients of para-pneumonic effusions. It is recommended that if the effusion shows signs of resolution, further investigations with CT-chest etc. may be withheld as these may not be warranted.[14] It is noteworthy that in the present series, even after step-2 investigations, the etiologic diagnosis of pleural effusion remained elusive in six (12%) cases–a finding which seems in consonance with the British Thoracic Society Guidelines on pleural effusion.[1]

Bilateral transudative pleural effusions result most commonly from CCF, liver cirrhosis, renal failure, and hypoalbuminemia; rarely from malignant neoplasm, pulmonary embolism, or rheumatoid arthritis.[3] In the

presence of clinical, radiologic and or echocardiographic evidence of cardiac failure, no further investigations need to be done.[9] In the present series, CCF was the most common cause of bilateral transudative pleural effusion. The diagnosis was based on clinical evaluation, echocardiography, and clinical improvement after diuretic therapy. Additionally, this was supported by significantly and unequivocally raised NT-pro-BNP levels both in pleural fluid and blood with a pleural fluid to blood ratio of > 1.0. The latter is considered as a specific test for CCF being the cause of pleural effusion. The diagnoses of renal failure and liver cirrhosis as causes of pleural effusion were based on organ-specific disease, and trapped lung was diagnosed on video-assisted thoracoscopy.

Diagnostic thoracentesis is required if bilateral effusions are unequal in size, do not respond to therapy, show loculations, patient has toxemia or non-radiating pleuritic chest pain.[12] The presence of neutrophils in pleural fluid indicates an acute process against mononuclear cells which indicate a chronic process.[15] For example, the presence of >50% lymphocytes was usually associated with pleural tuberculosis, malignancy, or post-CABG effusions.[2] It is noteworthy that in the present study most para-pneumonic effusions were neutrophil predominant, whereas 18% of such effusions were also lymphocyte predominant. The diagnosis of pneumonia was actually based on acute onset with febrile illness, chest imaging findings, results of blood test, and pleural fluid analysis. Bacterial cultures of blood, sputum, and pleural fluid did not contribute to identifying the infecting organisms. Effusion accompanying pneumonia compared with pneumonia alone increases the mortality risk by 3.4 times in unilateral and 7 times in bilateral effusions.[16] In the present series, in-hospital mortality in para-pneumonic effusion was 37% against an overall mortality of 20%. Polymorph predominant effusion may also occur in pulmonary embolism, acute tuberculosis, and asbestos exposure-related benign effusions.[15]

Malignancy as a cause of pleural effusion cannot be ruled out just because the effusion is polymorph predominant. In our study, 8% of malignant effusions had polymorph predominance. At least 60% patients with malignancy can be accurately diagnosed by pleural fluid cytology.[1,2] Repeat sample examination markedly increases the diagnostic yield.[17] Diagnosis of malignancy in the present study was made on the basis of pleural fluid cytology for malignant cells, cancer markers, and video-assisted thoracoscopic biopsies in those who did not provide a definitive diagnosis with pleural fluid cytology. Thoracoscopy successfully diagnoses approximately 90% cases.[18]

In the present series, pleural fluid ADA levels of >60 U/L, a lymphocyte-predominant effusion and a positive PCR test for tuberculosis DNA provided the best diagnostic evidence for tuberculous pleural effusion. ADA >60 U/L has a sensitivity of more than 90% and a specificity of about 85% for the presence of tuberculosis.[19,20] In the presence of lymphocyte-predominant effusion, the specificity of ADA for tuberculosis increases to >95%. Thoracoscopy further confirmed the diagnosis of pleural tuberculosis in three cases. In one recent series, thoracoscopy established the diagnosis of tuberculosis pleuritis in 42/42 cases.[21] Increased ADA levels also occur with malignant neoplasm, empyema, and rheumatoid arthritis.[22] It may be noted that ADA levels may be normal in patients with tuberculosis who are HIV positive.[23]

Video-assisted thoracoscopic pleural biopsy and histopathology established the diagnosis in eleven patients: Adenocarcinoma - 5; squamous cell carcinoma - 1; tuberculosis - 3; trapped lung - 1; and non-specific inflammatory changes - 1. It is noteworthy that three patients in whom FOB did not reveal any abnormality, thoracoscopic biopsy confirmed the diagnosis of malignancy. Recently, use of medical pleuroscopic pleural biopsy in the diagnosis of pleural effusion has been reported by several workers in India.[24-27]

CONCLUSION

A systematic two-step investigational approach successfully provides the etiologic diagnosis in a vast majority of cases of pleural effusion. Pleural effusion in RICU carries a high risk of death. It is imperative to establish the diagnosis before starting the treatment.

Video-assisted thoracoscopic pleural biopsy is a major advancement in the diagnosis of pleural effusion, when other procedures fail.

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