

Original article:

Malignant pleural effusion in carcinoma ovary: Experience of a tertiary care teaching hospital in northern India

¹ Agrawal Anurag, ²Tandon Rajeev, ³Shashibala, MS, ⁴Prajapati Neeraj, ⁵ Agarwal Aastha

¹ Associate Professor, Department of Pulmonary Medicine, Sri Ram Murti Smarak Institute of Medical Sciences, Bareilly, UP, India

² Assistant Professor, Department of Pulmonary Medicine, Sri Ram Murti Smarak Institute of Medical Sciences, Bareilly, UP, India

³ Associate Professor, Department of Obstetrics and Gynaecology, Sri Ram Murti Smarak Institute of Medical Sciences, Bareilly, UP, India

⁴ Assistant Professor, Department of Radiology, Sri Ram Murti Smarak Institute of Medical Sciences, Bareilly, UP, India

⁵ Post Graduate Resident, Department of Obstetrics and Gynaecology, Sri Ram Murti Smarak Institute of Medical Sciences, Bareilly, UP, India

Corresponding author: Dr. Anurag Agrawal

Abstract:

Background: Approximately one fourth of all pleural effusions in a hospital are secondary to cancer^[1]. Worldwide, ovarian carcinoma is among the most common cancers and major causes of malignant pleural effusion in women^[2]. We intend to find out the incidence of pleural effusion in ovarian carcinoma and impact on treatment.

Observations: Out of 88 cases of ovarian cancer, 43 patients developed Ascitis and 23 patients developed clinically evident pleural effusion. The mean age of presentation was 47.89 years (range- 30- 70 Years). Pleural fluid cytology was positive in 16 (69.58%) patients. CT scan of thorax helped in diagnosis of pleural effusion in seven patients. Thoracoscopy/biopsy was performed in seven patients and macroscopic pleural infiltrations were found in all the patients. The level of CA 125 was elevated in all the patients and the mean value was 2716.62 IU/L. The level of CA 125 declined dramatically with treatment. We performed intercostals drainage and chemical pleurodesis in 15 patients and achieved complete responses. Only 38 patients could be followed for a minimum of six month, 29 of them never had ascitis or pleural effusion.

Conclusion: More than 1/3rd patients of ovarian carcinoma suffered from pleural effusion. We must actively search for pleural metastasis by using newer means of diagnostics like CT scan or thoracoscopy as presence of pleural metastasis affects the treatment and outcome adversely.

Key words: ovarian carcinoma, malignant pleural effusion

Introduction

Approximately one fourth of all pleural effusions in a hospital are secondary to cancer^[1]. Worldwide, ovarian carcinoma is among the most common cancers in women^[2], along with breast and cervical cancer and major causes of malignant pleural effusion. Epithelial Ovarian Carcinoma accounts for over 90% of all ovarian malignancies^[3]. Approximately 75% of patients with Ovarian Carcinoma are diagnosed at advanced stages (III-

IV), which include tumour spread into the pleural space^[3]. The most common extra-abdominal site of disease dissemination is the pleural surface. Pleural effusion is present in more than one-third of stage IV patients at presentation^[4]. Presence of malignant pleural effusion renders poor prognosis and adversely affects treatment options. The five- and 10- year survival rates for stage IV are approximately 20% and <5%, respectively^[5].

Materials and Methods

Aim of the study was to find out the incidence and impact of malignant pleural effusion in cases of ovarian carcinoma. The present study included admitted patients of pleural effusion in the department of Pulmonary Medicine and the referred patients of pleural effusion from the department of Obstetrics and Gynaecology over a period of 5 years (January 2009 to December 2013). Presence of Pleural effusion was confirmed with the help of chest radiograph, ultrasonography and CT scan. Pleural fluid was aspirated and cytological evaluation was done. A maximum of three samples were sent for cytological examination. Ultrasound or CT scan guided pleural biopsy was done in a 10 patients. Thoracoscopy was done in seven patients. All the patients of carcinoma ovary were further investigated for staging and metastasis. All the patients were intended to be followed up for at least six months.

Observations and Results

A total of 88 cases (including 28 post operative cases) of ovarian carcinoma were included in the study. Out of 88 patients, 43 patients developed Ascitis and 23 patients developed clinical evident pleural effusion too (table 1). (Another seven patients were diagnosed with pleural effusion on CT scan). The mean age of presentation was 47.89 years (range- 30- 70 Years). The mean age of the patients, those suffering from ascitis/ Pleural effusion, was 48.32 years. The mean duration of symptoms was 3.35 months (range- 1-8 months). The mean duration of symptoms in patients, suffering from ascitis, was 3.45 months while patients those developed pleural effusion had mean duration of 4.75 months (table 2).

Pleural fluid was hemorrhagic in 13 patients while other 10 patients had straw colour fluid. All the samples were lymphocytic (lymphocytes> 80%) exudates (fluid protein> 3 gm %). Pleural

fluid cytology was positive in 16 (69.56%) patients, while ascitic fluid cytology was positive for malignant cells in 34 (79.07%) patients. CT guided biopsy of pleura was done in 10 patients and found to be positive in seven patients. Thoracoscopy was performed in seven patients and macroscopic pleural infiltrations were found in all. Multiple biopsies were taken, found to be positive for metastatic malignancy in all the patients. Twenty nine patients presented with one or more distant metastasis (liver, spleen and brain).

The level of CA 125 was elevated in all the patients and the mean value was 2716.62 IU/L. The mean value of CA 125 was 3898.60 IU/L in patients with ascitis while this value was 5745.59 IU/L in those who developed pleural effusion too. Intercostals drainage was done in 15 patients and chemical pleurodesis was performed in all the patients using tetracycline (n=11) or bleomycin (n=4). Both agents gave complete response. All the patients were offered surgery and/ or chemotherapy depending on the staging and 36 patients received Surgery and chemotherapy, while 27 patients received chemotherapy alone. The level of CA 125 declined dramatically with surgery (n=15, 134.8 IU/L) or post-chemotherapy group (n=12, 778.5). During hospital stay period 12 patients (13.64%) died, all had massive ascitis with or without pleural effusion and other metastases. Only 38 patients (43.2%) were followed for a minimum of six month, of these 29 (64.4%) were out of those 45 patients who never had ascites or pleural effusion. Four such patients developed ascitis and pleural effusion. Five (33.3%) out of 15 patients who were treated with ICD and chemical pleurodesis were maintaining satisfactory performance status.

Discussion

Ovarian cancer is among the common causes of malignant pleural effusion. In a prospective study in Spain^[6], ovary cancer (50 patients, 7%) was

among the leading aetiologies of malignant pleural effusions along with lung (37%), breast (17%), haematologic (10%) and gastrointestinal malignancies (6.5%). However, if only the women of this series are considered, ovarian carcinoma represents the third most common cause, accounting for 14% of all malignant effusions, after breast (34%) and lung (14.5%) primaries.

In present study, a total of 88 cases of Carcinoma Ovary were diagnosed. A woman with a pelvic mass and ascitis must be diagnosed as Ovarian Carcinoma until proven otherwise^[7]. In a study of 125 women with pelvic masses, of which 45% were of malignant origin, the presence of ascitis on physical examination or imaging had a positive predictive value of 95% for ovarian carcinoma^[7]. One common ovarian carcinoma presentation is increasing abdominal girth and difficulty of breathing owing to development of ascitis and/or pleural effusion. In present study 43 patients developed Ascitis and 30 of them developed pleural effusion too (twenty three patients developed clinically evident pleural effusion; seven patients were diagnosed with CT scan). However, the combination of ascitis and pleural effusion can also be found in disseminated carcinomatosis from another primary source (e.g. stomach, colon, pancreas, and breast), cirrhosis, benign ovarian tumours, tuberculosis, heart failure, constrictive pericarditis, endometriosis and ovarian hyper-stimulation syndrome.

Ovarian Carcinoma may also present initially with a pleural effusion. In present study only seven patients presented initially with pleural effusion. In a retrospective analysis^[8] of 123 women with malignant pleurisy, the effusion was the presenting manifestation of cancer in 36 (29%). Malignant pleural effusions in ovarian carcinoma most probably result from the pleural invasion from contiguous structures, such as the diaphragm, or the

trans-diaphragmatic migration of malignant cells thorough pleura-peritoneal communications^[6]. Metastases to the parietal pleura via a haematogenous route might also be considered as a potential pathogenic mechanism. In present study, the mean age of presentation was 47.89 years (range- 30- 70 Years). The mean age of the patients, those suffering from ascitis/ Pleural effusion, was 48.32 years. The mean duration of symptoms was 3.35 months (range- 1-8 months). The mean duration of symptoms in patients, suffering from ascitis, was 3.45 months while patients those developed pleural effusion too had mean duration of 4.75 months. Longer duration of symptoms suggest dissemination of disease and development of pleural effusion.

In present study, pleural effusions were unilateral in 25 (83.34%) of the cases, of which 23 (92%) were on the right side. Bilateral effusion was found in five (16.67%) cases. In 17 (56.66%) patients, effusions occupied half or more of the hemithorax. All these patients presented with shortness of breath. In this study, pleural fluid was hemorrhagic in 13 patients while remaining 10 patients had straw colour fluid. All the samples were lymphocytic (lymphocytes > 80%) exudates (fluid protein > 3gm%). Pleural fluid cytology was positive in 16 (69.58%) patients, while ascitic fluid cytology was positive for malignant cells in 34 (79.07%) patients. Cytological tests were found more frequently positive in patients with ovarian carcinoma than in other tumour types in a study^[9] of 556 malignant effusions submitted to thoracoscopy. Pleural fluid cytology had 83% sensitivity in 27 patients with ovarian carcinoma, but only 57% in lung cancer, 41% in mesothelioma and 18% in lymphoma. CT guided biopsy of pleura was done in 10 patients and found to be positive in seven patients.

In present study, eight patients develop malignant pleural effusion after surgery for ovarian carcinoma. A study^[10] found that 27 (36%) of 75 patients with apparent stage IIIc ovarian carcinoma with diaphragmatic involvement and no preoperative pleural effusions on imaging were upgraded to stage IV after the demonstration of pleural metastases through a trans-diaphragmatic thoracoscopy. Some studies suggest that in patients with involvement of the diaphragmatic peritoneum, a surgical exploration of the chest cavity may be justified because the pleural space frequently harbours undiagnosed disease^[10, 11]. Treatment failure is often associated with the inability to eradicate cancer cells in effusions, which may need specific management. In present study we perform thoracoscopy in five patients of diagnosed ovarian cancer with cytology- negative pleural effusion and found macroscopic pleural infiltration. Multiple biopsy of thoracoscopic lesions were taken, which came out to be positive for metastatic malignancy. If initial cytological studies are normal but the diagnosis of pleural malignancy is strongly suspected on clinical grounds, a thoracoscopic examination of the pleural space for taking biopsies is indicated^[12]. In one study, four (36%) of 11 patients with ovarian carcinoma and a negative cytological examination of pleural fluid had macroscopic pleural malignancy on thoracoscopy^[13]. The rationale behind the use of invasive procedures as a last resort is that poor prognosis associated with malignant effusions may affect the management plan.

In present study seven patients with pleural involvement were diagnosed with the help of CT scan. All of them had minimal pleural effusion. Five of them had mediastinal lymph nodes enlargement of >1 cm and pleural nodules too. In a retrospective series^[14] of 38 patients with ovarian carcinoma and preoperative pleural

effusions, the radiological predictors of malignant pleuritis were an effusion of moderate-to-large size (81% vs 9%), supra-diaphragmatic lymph node enlargement of >1 cm (75% vs 9%) and pleural nodules of >3 mm (50% vs 0%). In present study, the level of CA 125 was elevated in all the patients and the mean value was 2716.62 IU/L. The mean value of CA125 was 3898.60 IU/L in patients with ascitis while this value was 5745.59 IU/L in those who developed pleural effusion too. The level of CA125 showed a dramatic drop in post operative (n=15, 134.8 IU/L) or post-chemotherapy group (n=12, 778.5) of patients, but it again became high on the development of pleural effusion (n=8, 4785.85). CA125 antigen is a glycoprotein expressed in the embryonic coelomic epithelium. The antigen can also appear in many adult tissues such as the epithelium of the fallopian tubes, endometrium, endocervix, and ovaries. In addition, it is found in mesothelial cells of the pleura, pericardium and peritoneum. This tumour marker is found elevated in ovarian malignancies and in some benign conditions such as endometriosis, peritonitis or cirrhosis, particularly with ascites.

A symptomatic pleural effusion should be drained to optimize pulmonary function before surgery. The best palliation is achieved by intercostals drainage and chemical pleurodesis to prevent fluid reaccumulation. We performed intercostals drainage followed by pleurodesis in 15 patients using tetracycline (n=11) or bleomycin (n=4). Both agents resulted in complete response in all the patients but tetracycline group experienced more pain, on the other hand it was inexpensive too. In seven patients, we performed repeated pleurocentesis as all of them had poor performance status. Remaining five patients had minimal pleural effusion, only diagnostic tapping was done. A few studies^[12, 15] have shown that the concomitant presence of ascites does not adversely affect the

response to pleurodesis in patients with gynaecologic malignancies.

The standard treatment of advanced epithelial Ovarian Carcinoma includes primary cytoreductive surgery followed by adjuvant systemic chemotherapy^[16]. However, administration of chemotherapy before surgery (neoadjuvant chemotherapy) is an accepted alternative. All the patients were offered surgery and/ or chemotherapy depending on the staging and 36 patients received Surgery (staging laparotomy) and chemotherapy, while 27 patients received chemotherapy. Malignant pleural effusions upstage the disease but are not a contraindication to initial cytoreductive abdominal surgery^[12]. Patients in advanced stage have an improved prognosis with optimal debulking. In order to achieve maximal cytoreduction, any visible tumours need to be surgically removed. Here comes the role of thoracoscopy as metastatic pleural nodules can be removed surgically by means of video assisted thoracic surgery (VATS). In a few cases, VATS may identify unresectable pleural disease and the potential benefits of an abdominal cytoreduction may be negated. In this scenario, patients should be considered for neoadjuvant chemotherapy.

In an study^[17], patients with optimally debulked stage IV disease (with malignant pleural effusions) had a shorter time to recurrence and decreased overall survival compared with optimally debulked patients who had stage III disease. This can be explained by a higher tumour burden in the former group due to pleural-based disease that was not surgically approached. The negative effect of

pleural effusions on survival has been by one study^[18], in which authors found that the presence of moderate-to-large-sized effusions as compared with no or small effusions, was independently associated with poorer overall survival.

During hospital stay period (range- 5-28 days) 12 (13.64%) patients died, all had massive ascitis with or without pleural effusion and other metastases. Only 38 (43.2%) patients were followed for a minimum of six month, of these 29 (64.4%) were out of those 45 patients who never had ascites or pleural effusion while four such patients developed ascitis and pleural effusion after surgery. Only five (33.34%) out of 15 patients who were treated with ICD and chemical pleurodesis were turned up and doing fine. Only 11 patients could be followed for 12 months, nine of them were treated surgically and doing fine. While remaining two were treated with ICD and pleurodesis along with surgery and chemotherapy. Presence of pleural effusion affected prognosis badly and mortality rate was higher in patients with pleural effusion.

Conclusion

More than one-third patients of ovarian carcinoma suffered from malignant pleural effusion. We must actively search for pleural metastasis by using CT scan or thoracoscopy as presence of pleural metastasis changes the treatment and outcome adversely. Mortality rate was higher in patients with malignant pleural effusion. Intercoastal drainage with chemical pleurodesis can be used judiciously to improve the quality of life of patients with malignant pleural effusion.

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Table no. 1- type of ovarian carcinoma and pleural effusion

S N	Type of ovarian carcinoma	Total Patients	Ascitis	Pleural Effusion
1	Adenocarcinoma NOS	21	11	11
2	Papillary ca	5	nil	nil
3	Endometroid ca	5	nil	nil
4	Serous Cystadenocaa	17	3	3
5	Cystadenocaa	5	6	3
6	Mucinous cystadenocaa	10	9	nil
7	Mucinous adenocaa	nil	nil	nil
8	Poorly differentiated	25	14	13
	TOTAL	88	43	30

Table no. 2- Relation of pleural effusion with age, duration and CA 125 level.

S N	Clinical scene	No.	Age (in Years)		Duration (Months)		Mean level of CA 125 (IU/L)
			Mean	Range	Mean	Range	
1	All Patients	88	47.89	30- 70	3.35	1-8	2716.62
2	Patients without Ascitis or PE	45	47.44		2.67	1-6	746.64
3	Ascitic patients	43	48.32		3.45	1-6	3898.60
4	Pleural Effusion	30	47.13		4.75	3-8	5745.59

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