Pneumologia
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# The pleural effusion in ovarian tumors: often a diagnosis challenge

## *Revărsatele pleurale în tumorile ovariene: adesea o provocare diagnostică*

**Abstract**

*Pleural effusions associated with ovarian tumors are not always malignant. Neoplastic etiology of pleural efussion needs histopathological confirmation. We present three cases that illustrate various etiologies for pleural effusions in patients with ovarian tumors: thromboembolism, malignancy and Meigs syndrome. For these patients, it is essential to establish the correct etiology of the pleurisy, since it may change the therapeutic approach. All the cases must be carefully assessed and all the efforts must be done by a multidisciplinary team in order to offer the best solution for each case.*

***Keywords:*** *ovarian tumor, pleural effusion, cancer*

**Rezumat**

*Revărsatele pleurale asociate cu tumori ovariene nu sunt întotdeauna maligne. Etiologia neoplazică a unei colecții pleurale are nevoie de confirmarea histopatologică. Prezentăm trei cazuri care ilustrează diferite etiologii ale revărsatelor pleurale la pacientele cu tumori ovariene: tromboembolism, neoplazie și sindromul Meigs. La acești pacienți, este esențială stabilirea etiologiei corecte a revărsatului pleural, deoarece aceasta poate schimba abordul terapeutic. Toate cazurile trebuie să fie judecate cu atenție și toate eforturile depuse de o echipă multidisciplinară, în scopul oferirii celei mai bune soluții pentru fiecare caz în parte.*

***Cuvinte-cheie:*** *tumoră ovariană, revărsat pleural, cancer*

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## Introduction

Ovarian tumors are a heterogeneous group of neoplasms that affect the ovary ranging from benign to malignant. Ovarian cancer is the second most common gynaecological malignancy[(1)] with an increasing incidence and late stage detection - 75% in advanced stages[(2)]. It causes more deaths than any other cancer of the female reproductive system. Depending on the stage the 5-year survival rates vary from 80-90% in early stages to 25% in advanced stages of disease[(2)]. Pleural effusions can be found in association with ovarian tumors, but they do not always prove a metastatic dissemination. However, it is essential to establish the correct etiology of pleurisy in patients with ovarian cancer since it can modify the stage of the disease and also the therapeutic options.

In the following article we present three different cases of pleural effusion accompanying the ovarian tumors, supporting the idea that in such cases the pleurisy is not always malignant, therefore, it does not represent a contraindication to curative therapy.

## Case reports

### Case 1

We present the case of a 47-year-old woman, active smoker 23 PA, whose symptoms started with abdominal pain 3 months before seeking medical care. When the patient decided to attend a physician examination, the clinical exam revealed an increased abdominal volume and pain at palpation. The abdominal ultrasound and CT scan revealed the presence of an ovarian tumor and a small amount of pleural fluid above the right diaphragm. The serum level of CA-125 was elevated (1190 U/ml).

The patient was referred to the Surgical Department where she underwent an exploratory laparotomy with the detection of a peritoneal carcinomatosis, ascites and multiple regional metastatic disseminations. An epiploic biopsy was performed and the histopathological examination found a well differentiated serous ovarian adenocarcinoma. The tumor was staged IIIC FIGO.

The chest X-ray revealed a small amount of right sided pleural effusion (fig. 1, A, B). Reviewing the patient's medical history, 2 weeks before the patient experienced sudden thoracic pain associated with shortness of breath that spontaneously disappeared after a few days, with no treatment. No haemoptysis occurred. The oxygen saturation was 94%, blood pressure 125/70 mm Hg. There was no fever or cough associated with the thoracic pain episode, elements who could suggest a respiratory infection. The ECG showed a right bundle branch block (not present on previous ECG).

Due to the small amount of pleural liquid, a thoracentesis could not be performed at that time. A lower limb Doppler ultrasound was performed who showed the absence of compressibility of the right popliteal vein, despite the fact that there was no clinical sign of deep vein thrombosis.

Given the presence of the neoplastic status, the sudden onset of symptoms, the presence of pleural effusion and the deep vein thrombosis the most probable diagnosis was a ***pulmonary thromboembolism with secondary pleurisy.*** The anticoagulation treatment was started. The patient evolved favourably and after 1 month the pleural effusion disappeared on radiographic examination.

Reclamă PN 65(2)0105

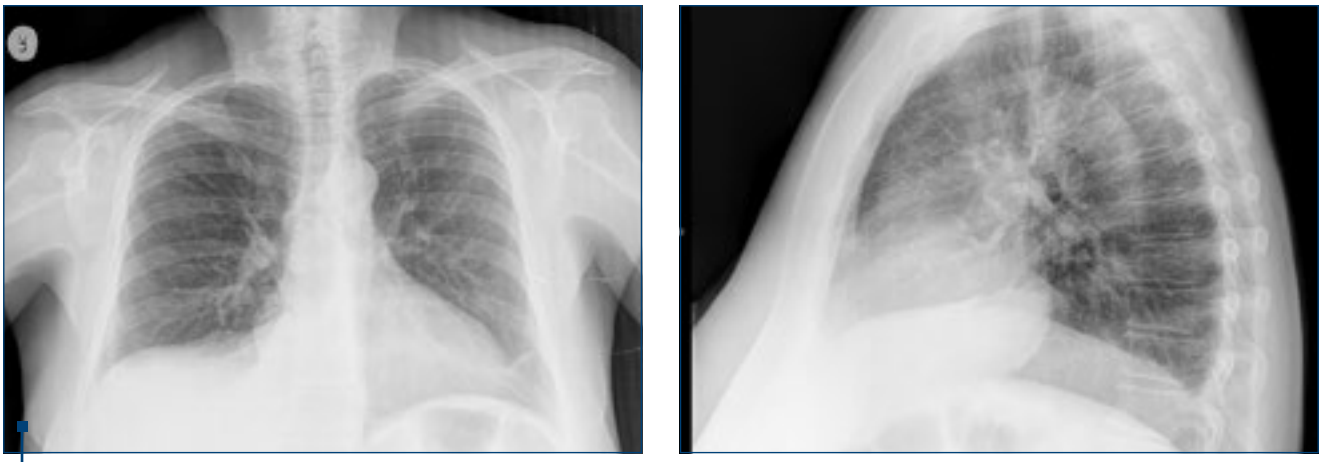

***Figure 1.*** *Chest X-ray.* ***A.*** *postero-anterior view.* ***B.*** *Lateral view*

In this case, the differential diagnosis could be made with neoplastic pleurisy, but the sudden onset of the symptoms, ECG changes, deep vein thrombosis and the small amount of pleural effusion with total resolution after anticoagulation treatment are in favour of thromboembolic aetiology.

The patient's further evolution was good. She received 10 cycles of chemotherapy. After 11 months she underwent cytoreductive abdominal surgery with a pelvic tumorectomy.

**Case 2**

A 62-year-old woman attended the Surgical Department complaining about abdominal pain and pressure, constipation and loss of weight (5 kilograms in 3 months). The symptoms started 3 months before. She was a non-smoker and the medical history included arterial hypertension and cardiac failure. The clinical examination revealed an increased abdominal volume with percussion dullness. The abdominal ultrasound detected an ovarian tumor with ascites.

An exploratory laparotomy was performed with biopsy of a peritoneal carcinomatosis nodule. Histologically, this nodule was found to be malignant, adenocarcinoma type, with ovarian origin. Intraoperative, tumor invasion reached the bladder and the rectum areas.

The thoracic CT scan performed revealed the presence of a right pleural effusion in moderate amount and a bilateral calcified nodule (fig. 2). At this time, the patient didn't complain of any respiratory symptoms, the oxygen saturation was normal (97%). She underwent thoracentesis with the extraction of a serocitrin pleural liquid. The pleural fluid analysis showed a 4.7 g/dl protein (exudate) and the cytology revealed adenocarcinoma cells. Due to local and distant invasion, the patient's ovarian tumor was staged IVA FIGO. Adjuvant chemotherapy was started.

After 6 months, MRI scan showed right pleural effusion in regression. 8 months following chemotherapy, cytoreductive surgery was performed, i.e. hysterectomy, bilateral salpingo-oophorectomy, omfalectomy, total omentectomy, anterior rectum resection, left terminal colostomy.

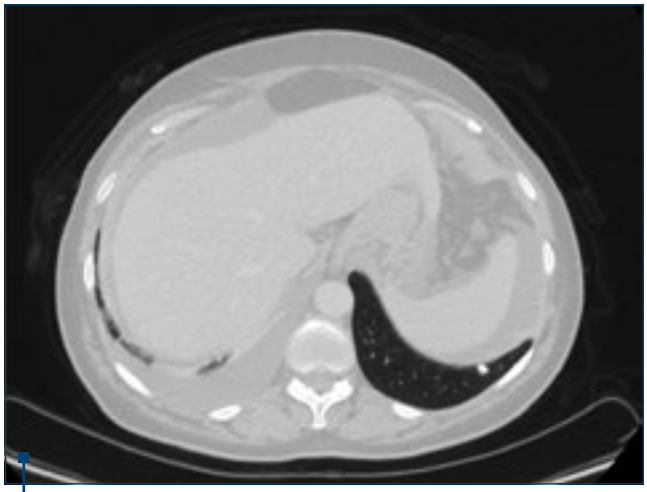

***Figure 2.*** *Thoracic CT scan showing right pleural effusion and calcified left pulmonary nodule*

In this case, ***the pleurisy etiology was confirmed as malignant***; the presence on the thoracic CT scan of a calcified nodule could lead to a differential diagnosis with tuberculous pleural effusion. Also, the cardiac failure history could be an alternative explanation for the right-sided pleural effusion.

**Case 3**

The third case is a 66-year-old female, with 25 Pack-year history of smoking. She addressed the physician for dyspnoea during exercise and at rest, right thoracic pain, asthenia, weight loss, symptoms started 6 months before. The anamnesis revealed that the patient was diagnosed 7 months before with an abdominal tumor, but she didn't undergo further supplementary investigations. The patient's medical history included: gastric ulcer, hyperthyroidism, and arterial hypertension.

Clinical assessment revealed an abdominal enlargement of liquid consistence, left abdominal wall oedema with prominent lymphatic vessels, inferior legs oedema, secondary uterine prolapse, and cachexia. The oxygen saturation was 93% in ambient air; there was a percussion dullness of the right thoracic side, with absent vesicular breath sound. The blood tests found anaemia

(haemoglobin level 7.7 g/dl), hypoalbuminemia (albumin=2.64 g/dl), elevated CA-125 level (1180 U/ml), increased ESR level (79 mm/1 h).

Chest X-ray revealed a significant amount of right pleural effusion. CT scan (fig. 3) confirmed the presence of a massive right pleural effusion, ascites, with the presence of a 13/15 cm tumour in the pelvi-abdominal space. The tumor was inhomogeneous, multilobular and exerted compression on the intestinal loops, abdominal vessels, and bladder.

A thoracentesis was performed, showing a non-haemorrhagic pleural fluid, whose analysis revealed an exudate, with 3.9 g protein level, normal glucose level. Differential cytology of the pleural liquid showed the predominance of lymphocytes (68%). There were no malignant cells found at three repeated pleural fluid analysis. An evacuatory thoracentesis was performed with an extraction with 1000 ml of pleural fluid.

After the investigations were completed, the surgical treatment of the abdominal tumor was proposed. During the surgery, a giant multilobular ovarian tumor was found, with the dimension of 40 / 20 cm in the right iliac fossa. After the extemporaneously pathological examination that found benign cells, the tumor was removed and the procedure was completed with total hysterectomy and bilateral adnexectomy. The final histopathological report revealed that the ovarian tumor was a fibroadenoma.

Ten days following the surgical removal of the ovarian tumor, there was a significant reduction of the patient's dyspnoea with regression of the pleural effusion on chest X-ray. The patient was evaluated at 1 month and 3 months postoperatively, when chest X ray showed a total resolution of right pleural efussion, with no sign of relapse.

In the case of this patient, the final diagnosis was ***Meigs syndrome***.

## Discussions

The three cases presented illustrated three possible causes of pleural effusion associated with ovarian tumors. Every association between ovarian tumors and pleural effusions must be carefully assessed, due to a low highlighting possibility for malignant pleural cells[3].

Pleural cavity is the most frequent site of distant metastasis in ovarian cancer and the presence of neoplastic cells in pleural liquid cytology classifies the tumor as stage IV. But not all the pleural effusions found during radiological investigations, associated with ovarian cancer, are malignant. According to Mironov study, for patients with advanced epithelial ovarian carcinoma who had pleural anomalies detected on CT scan, the pleural biopsies obtained by thoracoscopy were malignant in 59% cases[4].

The presence of malignant pleurisy signifies a median survival of 2 years. A study performed in 203 patients with stage III and IV epithelial ovarian carcinoma who underwent computer scan CT before cytoreductive surgery found that the presence of a moderate-to-large

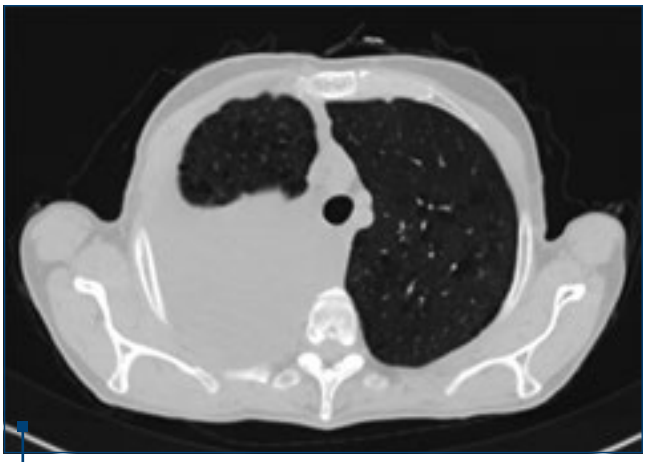

***Figure 3.*** *Thoracic CT scan showing massive right pleural efussion*

pleural effusion on preoperative CT images was independently associated with poorer overall survival[5].

The easiest way to obtain pleural liquid sample is a thoracentesis, but in 30% of cases the pleural cytology obtained gives false negative results. The exploration of pleural space can benefit from modern thoracoscopic procedures, as video-assisted thoracoscopic surgery (VATS) which can increase the rate of positive results and an accurate diagnosis[6].

A study that used thoracoscopy as a diagnostic tool on 24 patients with stage IV ovarian cancer found that for 13 patients with intrathoracic lesions the abdominal cytoreduction was influenced[7]. It can subsequently change the therapeutic decisions in FIGO stage III and IV ovarian cancer[8,9]. In his study, Klar described a series of 17 patients with ovarian cancer in which VATS was performed and changed the therapeutic decision in 6 cases out of 17 (3 up staging, 3 down staging)[8].

In some cases the patients present first to the respiratory physician with dyspnea due to the malignant pleural effusion and subsequently the investigations lead to the ovarian tumor diagnosis[8]. In these cases, the thoracoscopy can be successful used for obtaining histological results from pleural samples[10].

There are case reports of ovarian adenocarcinoma that were first diagnosed by this procedure. In these cases, the tumor cells obtained by thoracoscopy lead to a tumor origin finding[11].

The main recommendation of a surgical approach in a neoplastic pleural effusion is the palliative treatment, and the failure in pleurisy eradication is one of the main causes of ovarian cancer treatment failure[12]. Herrinton shows that although the pleural effusion was present in 12% of patients with final stage ovarian cancer, in almost 50% of the patients this complication was left untreated[13].

The malignant pleurisy does not exclude abdominal surgical debulking, but the excision of pleural nodules with VATS may be necessary for achieving an optimal cytoreduction. These patients can benefit from Taxane-platinum neoadjuvant chemotherapy[6].

The thromboembolic disease can be another cause for pleural effusion associated with ovarian tumors. In ovarian cancer there is a higher rate of the venous thromboembolism than in other malignancies. In a series of 344 patients with ovarian cancer, venous thromboembolism was identified in 33 cases, 16 being with pulmonary embolism[14].

The differential diagnosis may also include the association cancer- pleural tuberculosis by the presence of two causes of immunodepresion (chemotherapy and neoplasia itself).

Another cause of pleural effusion associated with ovarian tumor is Meigs syndrome. It is an association of benign ovarian tumor, pleural effusion and ascites, first described by Meigs and Cass in 1937[15]. It may mimic the metastatic ovarian cancer, but the histology shows a benign ovarian tumor, in the majority of cases a fibroma[15,16]. Elevated CA-125 levels can also be found. Pleural effusion resolves after removal of the pelvic mass.

As for our patient's case, the pleurisy is most frequent in the right side and the amount is independent to the amount of ascites. There are some theories regarding the pleural effusion etiology in Meigs syndrome. Efskind and Terada advanced the hypothesis that the ascitic liquid reaches the pleural space through transdiaphragmatic lymphatic channels, which are larger in diameter on the right side. They injected ink, respectively labeled albumin in the abdomen of the patient with Meigs syndrome and found the substances in the pleural space

The pleural liquid in our patient was found to be exudative. Altough classically the pleurisy from Meigs syndrome is considered transudative, though the literature review of Krenke, in of 541 cases reported with Meigs syndrome, revealed that exudative pleural effusion was more frequent than the transudative one[17].

In conclusion, a pleural effusion in the presence of an ovarian tumor does not always indicate a metastatic dissemination, and malignancy diagnosis can be sustained only by histopathologic examination. Every case must be carefully assessed and all the efforts must be done in order to obtain an accurate diagnosis. A multidisciplinary team (surgeon, oncologist, pathologist, etc) is required to manage these cases. ■

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