

## CASE REPORT

# Difficulty in positive diagnosis of ascites and in differential diagnosis of a pulmonary tumor

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## Abstract

Ascites is the most frequent complication of cirrhosis and occurs only when the portal hypertension has already installed but ascites is caused by neoplasms, heart failure, tuberculosis, pancreatic illnesses, as well as other kind of affections. We describe the case of a 67-year-old patient, a retired person, without significant personal or familial history, nonsmoker, infrequent alcohol and coffee consumer with following chief complaints at onset: loss of appetite, weight loss, serious physical asthenia, delayed intestinal transit, diffuse abdominal pain and increase of abdominal circumference. Initially was misdiagnosed with liver cirrhosis. After discharged from our Clinic, suspicion of diagnosis was mesothelioma as well as after first thoracoscopy and pleural biopsy performed in a Clinic of Thoracic Surgery. Several pleural fragments collected by biopsy were sampled for the histopathological exam. The stainings used were Hematoxylin-Eosin (HE) and Periodic Acid-Schiff (PAS) for the mucopolysaccharides. For the immunohistochemistry was used the labeled Streptavidin-Biotin (LSAB)-Horseradish peroxidase (HRP) method, as well as the antibodies: cytokeratin (CK) cocktail (AE1/AE3), vimentin, calretinin, CK7, CK5/6, CK20, epithelial specific antigen/epithelial cell adhesion molecule (Ep-CAM) (BerEP4), thyroid transcription factor-1 (TTF-1), E-cadherin, CDX2, carcino-embryonic antigen (CEA) and the Hector Battifora mesothelial antigen-1 (HBME-1). The aspect at immunohistochemistry establishes a positive diagnostic of poorly differentiated mucinous pulmonary adenocarcinoma, with "signet ring" cells. The rapid and accurate determination of the diagnostics will allow not only for a decrease in the expenses for inefficient treatments, but also for the guidance of the patients towards clinics or centers able to provide and supervise these treatments.

**Keywords:** ascites, mesothelioma, signet ring cells, mucinous adenocarcinoma, thoracoscopy.

## Introduction

From the many complications of cirrhosis, ascites is the most frequent, as much as 60% of patients with compensated disease have a chance to develop the condition during the first 10 years [1]. Ascites occurs only when portal hypertension has already installed [2].

Around 75% of ascites patients from in Western Europe and the United States have as main cause hepatic cirrhosis. For the rest of the patients, neoplasms, heart failure, tuberculosis, pancreatic illnesses, and other diseases cause ascites [3].

Our aim is to present a case of ascites, initially misdiagnosed as liver cirrhosis but at which the final diagnosis was pulmonary mucinous signet ring cell adenocarcinoma (SRCA).

## Case presentation

We present here the case of a 67-year-old patient, retired, who lived in the urban environment, with appendectomy approximately 30 years ago, and no other significant personal or familial history, nonsmoker, infrequent alcohol and coffee consumer.

The general practitioner (GP) initially consulted him for the following complaints: loss of appetite, weight loss (approximately 10 kg in three months), serious physical asthenia, delayed intestinal transit, diffuse abdominal pain and increase of abdominal circumference. The decision of GP was to send the patient for more qualified medical consultation to a specialist doctor in general internal medicine. The next physical examination showed the following: weight 68 kg, height 173 cm, body mass

index (BMI) 22.7 kg/m<sup>2</sup>, normal teguments and mucous membranes, the absence of pitting or non-pitting edema, the absence of superficial nodes and a slight difficulty in the mobility of the big articulations, thin thorax, with no adventitious pulmonary sounds, rhythmic cardiac sounds, blood pressure (BP) 155/95 mmHg, atrio-ventricular (AV) rate 78 beats/min, abdominal distension, ever increased in volume, liver and spleen in normal limits, normal neurological examination.

The laboratory tests showed just the following changes: erythrocyte sedimentation rate (ESR) 26 mm/h, cholesterol 235 mg/dL,  $\alpha_2$ -globulins 13.6% and  $\beta_2$ -globulins 6.3%, the rest of the values of electrophoresis being normal. The complete blood count did not show any changes, the glycemia, the urine exam, the creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase ( $\gamma$ -GT), the total cholesterol and triglycerides have had a normal value. Hepatitis B surface antigen and the antibodies against hepatitis C virus were absent. The abdominal ultrasonography showed just ascites fluid in a big quantity and a prostate with increased dimensions and calcifications in parenchyma. The electrocardiogram registered no changes. Despite of these findings, the patient was suspected of hepatic cirrhosis and received diet and treatment for this disease.

The subsequent evolution of the patient was unsatisfactory. This is the reason why, two weeks later, he is coming to our Clinic and is hospitalized for ascites and reevaluated. The symptoms have persisted, being similar to the initial ones, whereas the objective examination has emphasized a thin thorax with decrease expansion on the basis, tactile fremitus and breath sounds absent in the 1/3 inferior side of the left thorax and at the basis of the right thorax. Abdomen increased in circumference, soft, painful, with sign of ascites in physical examination. The liver span between upper and lower borders about 13 cm, slightly increased consistency, regular surface. Spleen was not palpable. Blood pressure values registered normal values.

The laboratory tests emphasized the ESR 90 mm/h, cholesterol 235 mg/dL, a normal complete blood count, normal values of the blood glucose, creatinine, amylase, ALT, AST and  $\gamma$ -GT. The urinalysis examination was normal. We have also performed the paracentesis and the cytology of ascites showed smears with moderate cellularity, with active and reactive mesothelial cells, both isolated and grouped, neoplastic cells, characterized by a reduced quantity of cytoplasm, bi-lobate nuclei or binucleated, hyperchromatic and irregular outline. Rare lymphocytes and neutrophil cells. Squamous epithelial cells, some of this, pleating. The electrocardiogram registered a normal aspect.

The chest radiography showed opacity with a hardening on the left side of thorax, and opacity inside the right diaphragmatic sinus, reticular areolar, right basal and left para-cardiac opacities. The abdominal radiography showed a diffuse abdominal liquid opacity, excluding the presence of the air-fluid levels.

Taking into account the results obtained at the ascites cytology, radiological aspects and oncological exam, it was recommended the performance of the follow tumoral markers: carcinoembryonic antigen (CEA) 2.91 ng/mL,  $\alpha$ -fetoprotein (AFP) 0.87 IU/mL and prostate-specific

antigen (PSA) 2.2 ng/mL that registered normal limits and the exam concerned with iodinate contrast computerized tomography (CT) of the thorax, the abdomen and the pelvis, that showed: effusion fluid in large quantity at the level of both pleural cavities with the flattening of the subjacent parenchyma; basal bilateral lamellar atelectasis; nodes with 11 mm in size, situated at the right superior side of trachea, and in the aortic-pulmonary window, 13.8/12.4 mm, before of carina; nodes less than 1 cm in the rest of the mediastinum; degenerative modifications at the level of the thoracic spine; the left suprarenal gland, with a nodular hypertrophy of 11 mm; cortical cysts of 9 mm in size on left kidney; prostate increased in dimensions, inhomogeneous with calcifications and central and peripheral nodular formations of less than 1.8 cm; retroperitoneal and pelvic nodes less than 1 cm in size; big quantity of retroperitoneal fluid. The endoscopic evaluation of the gastrointestinal system was normal. Anyway, was excluded cardiovascular, hepatic, pancreatic, gastrointestinal and renal conditions.

We do not have possibility to perform another imaging exploration like bronchoscopy; transthoracic lung biopsy using fine-needle aspiration (FNA), positron emission tomography (PET), PET with fluoro-2-deoxy-D-glucose (PET-FDG) or positron emission tomography/computed tomography (PET/CT). Without these techniques, at this stage, it has not succeeded a diagnosis of certainty for lung tumor nor for staging of tumor.

Therefore, the patient is discharged from our Clinic with suspicion of mesothelioma. The patient was recommended the hospitalization in a Clinic of Thoracic Surgery for additional investigations and diagnostics, after getting in contact with a doctor working in this Clinic.

During first hospitalization in the clinic of thoracic surgery, 800 mL of serous citrine fluid were eliminated and it was performed a left thoracoscopy, noticing a thick parietal pleura and a visceral pleura with pseudo-follicular formations also present on the diaphragmatic side of the left inferior lobe. Several pleural fragments collected by biopsy were sampled for the histopathological exam and a pleural talc poudrage was performed.

During the second hospitalization, in the Clinic of Thoracic Surgery, two weeks later, 1200 mL of serous citrine fluid were eliminated by pleural puncture and 4000 mL of serous citrine fluid by paracentesis. A right thoracoscopy was performed and it was noticed a thick pleura in 1/3 inferior and on the diaphragm. Multiple pleural biopsies and pleural talc poudrage were performed. Aspects of pleura during thoracoscopy and harvesting of pleural samples by biopsy are illustrate in Figure 1, a–f. The fragments of the sampled parietal pleura were examined within the department of pathological anatomy.

The working material, represented by small fragments from the parietal pleura, was processed, examined, according to the standard technique of paraffin inclusion protocol, going through different stages: the fixation in tamponade 10% formalin, washing with water or alcohol 80%, dehydrating – by means of successive washes in alcohol, the cleaning – by benzene, toluene, xylene washes and the paraffin. The stainings used were Hematoxylin–Eosin (HE) and Periodic Acid–Schiff (PAS) for the mucopolysaccharides.

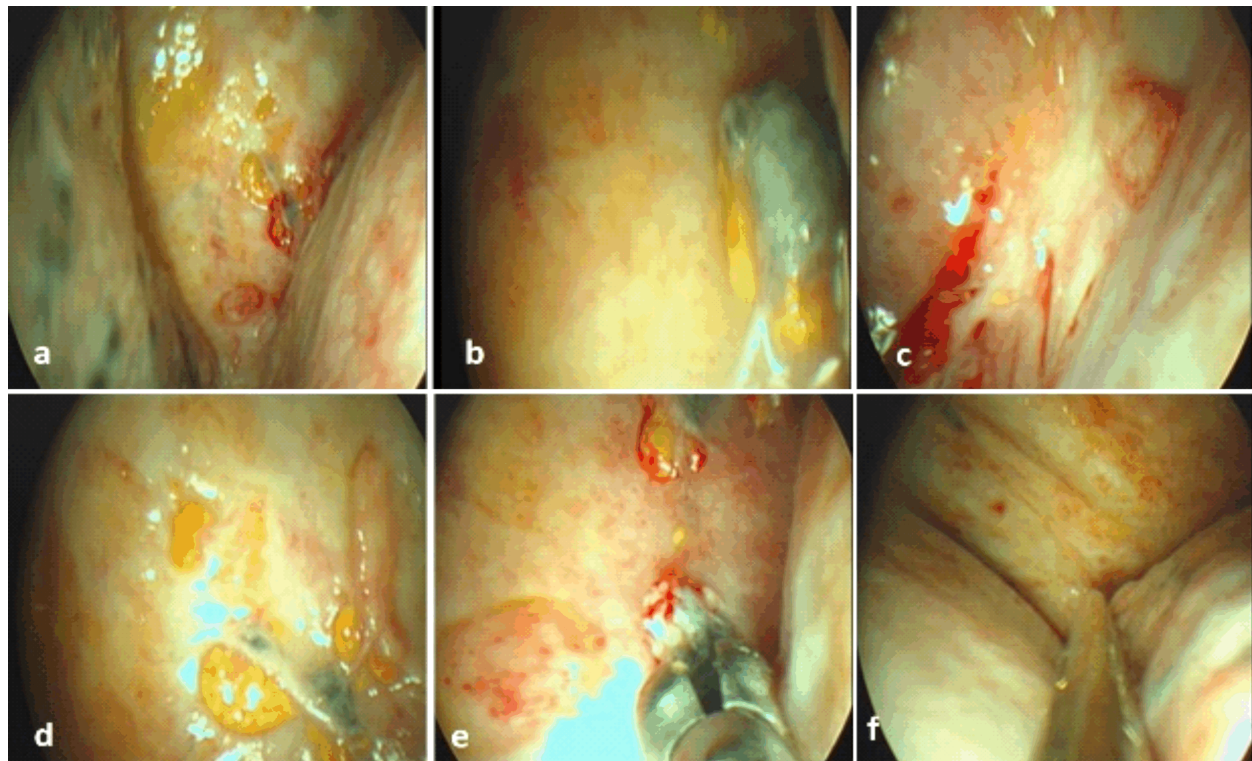
The microscopic examination revealed fragments with



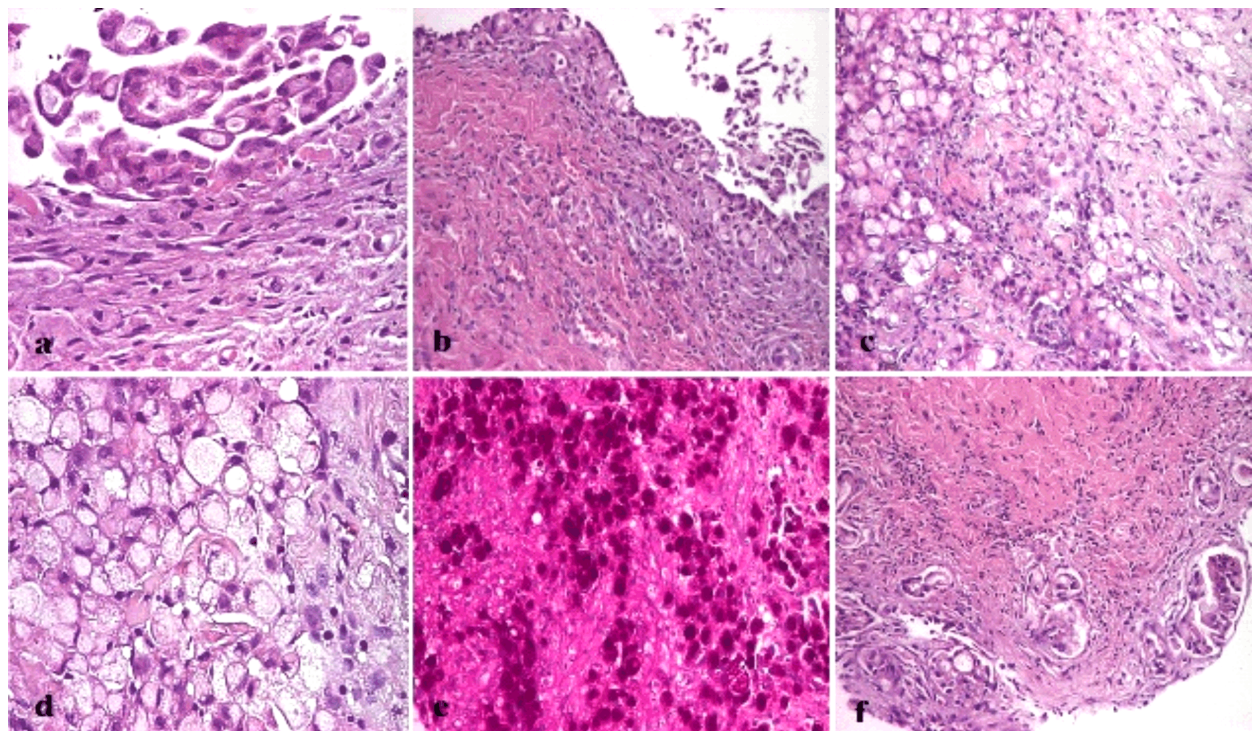
a microscopic structure of fibro-connective and adipose tissue, some of them characterized by a diffuse malign proliferation, with cells of medium size and numberless cells grouped in “signet (seal) ring” cells.

The carcinoma with “signet ring” cells presented as groups of tumoral cells, diffusely placed under the pleural

mesothelium. The tumoral cells had a round oval shape, were of various sizes, contained vacuolar cytoplasm and peripheral nuclei, giving the classical aspect of “signet ring” cells. PAS staining for the mucopolysaccharides pointed out the intracytoplasmic mucus of a lively red (Figure 2, a–f).



**Figure 1 – Thoracoscopy – aspects of pleura and biopsy of pleura: (a) Tumoral thickness of the parietal, visceral and diaphragmatic pleura; (b–d) Tumoral formation in the left costophrenic sinus; (e and f) Harvest of pleural samples by biopsy.**



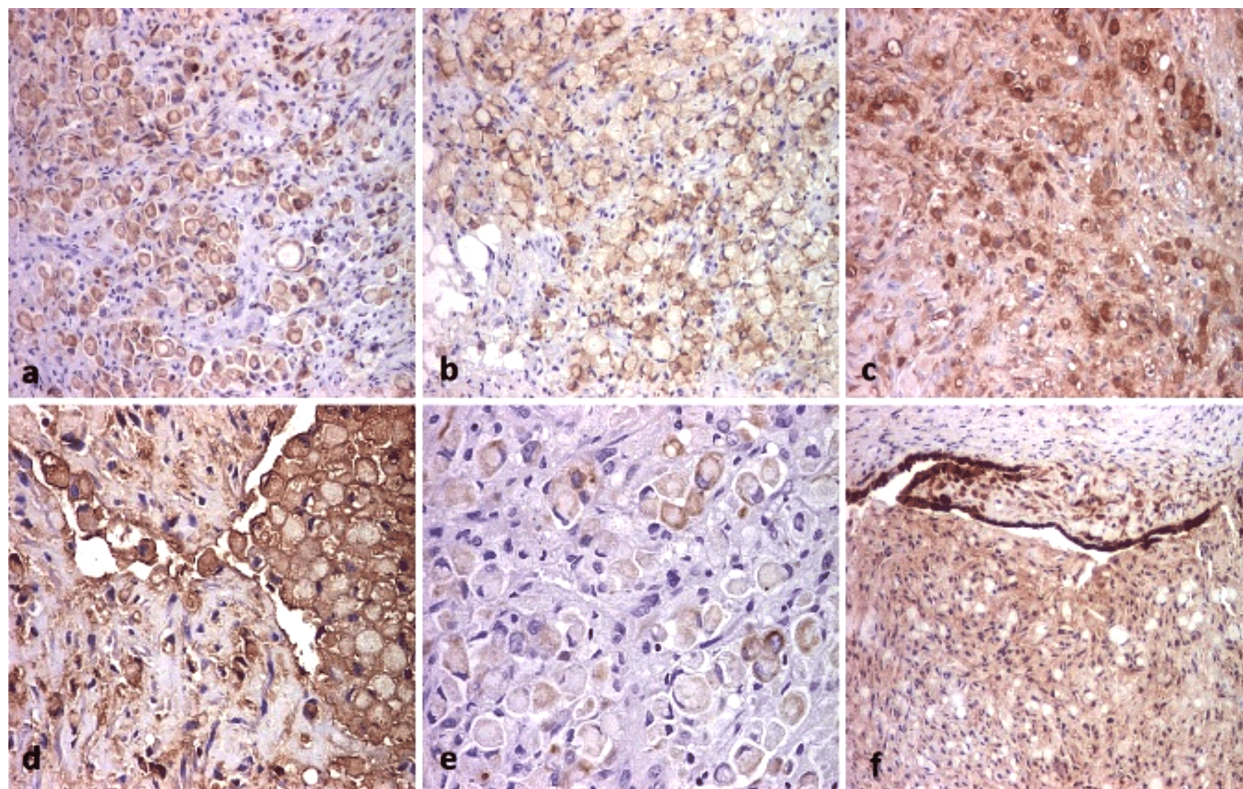
**Figure 2 – Signet ring cell carcinoma: (a) Signet ring cell; (b) Cell carcinoma islands located under the pleural mesothelium; (c) Round cells with the eccentric nuclei; (d) Round or oval cells with the vacuolar cytoplasm and peripheral nuclei; (e) Cells with intense color PAS-positive cytoplasm; (f) Vascular tumor invasion (tumor emboli). HE staining:  $\times 100$  (b, c and f);  $\times 200$  (a and d). PAS staining:  $\times 100$  (e).**



For immunohistochemistry (IHC), we used the labeled Streptavidin–Biotin (LSAB)–Horseradish peroxidase (HRP) method, as well as the antibodies: cytokeratin (CK) cocktail (AE1/AE3), vimentin, calretinin, CK7, CK5/6, CK20, epithelial specific antigen/epithelial cell adhesion molecule (Ep-CAM) (BerEP4), thyroid transcription factor-1 (TTF-1), E-cadherin, CDX2, CEA and the Hectofora mesothelial antigen-1 (HBME-1).

We highlighted by IHC positive tumoral cells for

AE1/AE3, BerEP4, calretinin positive in the reactive mesothelial cells and negative in the tumoral cells, CK7 positive in the isolated tumoral cells. TTF-1, E-cadherin, CK5/6, CDX2, CK20, vimentin, CEA were negative in the tumoral cells. The aspect at IHC correlated with the histopathological findings, advocated for a poorly differentiated adenocarcinoma with “signet ring” cells (Figure 3, a–f). The positive diagnostic in this case was that of mucinous pulmonary adenocarcinoma with “signet ring” cells.



**Figure 3 – Signet ring cell carcinoma:** (a) Diffuse and intense positive AE1/AE3 immunostaining in tumor cells; (b) BerEP4 positive diffuse and with variable intensity in tumor cells; (c and d) Diffuse and intense positive CEA immunostaining in tumor cells; (e) Weak positive CK7 immunostaining in isolated tumor cells; (f) Negative calretinin immunostaining into tumor cells and positive in reactive mesothelial cells. IHC:  $\times 100$  (a–c and f);  $\times 200$  (d and e).

## Discussion

The adenocarcinoma is a form of bronchopulmonary carcinoma most often met in the case of young men (<50 years old) and of women, whatever their age, in the case of smokers and former smokers [4].

In our case, the onset of the patient's symptoms, among which loss of appetite, weight loss (about 10 kg in three months), diffuse abdominal pains, severe physical weakness and delayed intestinal transit, make us suspect the presence of a neoplasia, but they do not guide us towards pulmonary affection, but rather towards a digestive one. The physical examination showed signs of a bilateral accumulation of liquid, in larger quantities at the level of the left thorax, which, associated with ascites, can also guide us towards a digestive affection, which, together with its evolution, determined a pleural accumulation of liquid.

Amongst the chief complaints of patients having lung cancer we can cite irregular cough, hoarseness or loss of voice, hemoptysis, dyspnea and sometimes chest pain. Often recurrent pneumonia may be the main feature in

some patients. Adenocarcinoma is more often asymptomatic, being more frequently identified in screening studies or as an incidental radiological finding [5, 6]. No sign or symptom is pathognomonic for the lung cancer, but they can be classified into manifestations caused by the local tumoral growth and by the intrathoracic dissemination; manifestations caused by metastases; non-specific general symptoms; paraneoplastic syndromes [7]. The clinical manifestations of the lung cancer are determined by the local tumoral growth and the intrathoracic dissemination [8].

The non-specific manifestations are common, in the case of both small-cell carcinoma (SCC) and non-small-cell carcinoma (NSCC), signifying an unfavorable prognosis [9, 10]. The paraneoplastic manifestations appear more often in the SCC and rarely in the case of the epidermoid carcinoma and adenocarcinoma. They include the following major categories: endocrine, neurological, cardiovascular, musculoskeletal and cutaneous [9, 11].

In our case, the suspicion of bronchopulmonary neoplasm could have been indicated by the weight loss,

but the irritating cough was absent and the phenomena associated with the respiratory failure manifested later. The paraneoplastic manifestations were absent in our case.

As far as the imagistic exploration is concerned, the abdominal ultrasonography emphasized the presence of a big quantity of fluid in the abdomen, excluding the presence of some suspicious hepatic, pancreatic, renal, splenic formations and of the suprarenal glands, whereas the pulmonary radiography represented the imagistic exploration that was not performed during the first consultation and which would have simplified the diagnostic orientation. This has been done during the second hospitalization and it emphasized a left basal liquid opacity and the thickness on the left lateral thoracic wall, opacity inside the right diaphragmatic sinus. Taking into account all these elements, the final diagnostic was difficult to establish.

It was only after the implementation of the paracentesis with an exploratory and therapeutic aim (evacuation with a view to improving the quality of life), as well as of the cytological examination of the ascites liquid that underlined the presence of the tumoral cells that the neoplasia was confirmed, whereas the subsequent explorations such as the CT and the tumoral markers were performed.

The native CT examination and with an iodine contrast has a fundamental role in the diagnostic of the bronchopulmonary cancer as well as in the pre-therapeutic examination summing-up. More precisely, it allows for the emphasis and proper delimitation of the tumor, of the mediastinal adenopathy and of the possible secondary tumoral determinations [12]. The investigations such as PET-FDG is very useful because the current clinical indications in the imaging of pulmonary neoplasms are: the differentiation of the benign pulmonary focal anomalies (the solitary pulmonary nodules, pulmonary masses and the weakly shaped opacities) from the malignant ones; staging, especially in the case of non-small-cell lung cancer (NSCLC); the diagnostic of the mediastinal adenopathy, of the extra-thoracic metastases; the post-therapeutic monitored of the patients diagnosed with bronchopulmonary cancer (BPC) [13, 14].

There is a series of reference points, ample in diversity, related to the endoscopic aspects of the bronchopulmonary neoplasm [15]. The fundamental elements of the endoscopic semiology in the bronchopulmonary neoplasm equally belong to the proliferative-vegetative modifications and to the infiltrative lesions [16].

The cytological examination of the sputum stands for an excellent method for the diagnostic and is based on the capacity of cellular exfoliation from the level of the bronchial tumor and on the identification of the malignant cells in the sputum or the liquid of bronchial lavage, after the fixation and coloration of the sample. The cytological evaluation has a great diagnostic value, but the positive or negative predictive value, as well as the diagnostic accuracy certainly depends on simple mistakes, on the preservation of the tissue, the quality of the process and the experience of the observer [17].

The establishment of a clear diagnostic in this case could not be obtained in the clinic due to the absence of the bronchoscope and of the qualified person, able to use it. PET/CT was not available, as it is not too much

used in our country, because of the precarious equipment of the hospitals.

In the absence of the diagnostic instruments described above, due to the presence of a massive accumulation of liquid and being suspected of the presence of a mesothelioma, we have resorted to a surgeon specialized in thoracic surgery for the performance of the surgical intervention, and the sampling of pleural fragments for the histopathological exam. In the Clinic of Thoracic Surgery was performed a left thoracoscopy with pleural biopsies and talc poudrage.

According to the medical literature, the technique preferred for surgical biopsy is by pleuroscopy that allows for the sampling of a proper biopsy samples and also the drainage of the pleural liquid and the evacuation of the flattened lung [18]. Furthermore, if the lung is not flattened, we can introduce talc at the end of the procedure to achieve the pleurodesis. The wrong diagnostics by pleuroscopy were rare, and they were caused by the adherences that have obstructed the access to the main tumor [19]. The intraoperative insufflation with talc has a rate of success bigger than 95% in the prevention of accumulation of pleural liquid [20] talc pleurodesis does not apparently influence the subsequent surgical procedures, but it can interfere with the intra-pleural therapy, modifying the aspect of the images obtained by PET in the sense that it increases the activity in those areas where it deposits for a long period of time from the pleurodesis and in these cases, PET/CT can be useful [21, 22].

In our case, the histopathological and immunohistochemical examinations were decisive for both the positive and the differential diagnosis. The tumoral cells emphasized CK AE1/AE3, BerEP4, CEA, and CK7 was weakly rendered in the isolated cells and they were negative, such as the CK5/6, CK20, CDX2, E-cadherin, vimentin, calretinin, TTF-1 and HBME-1.

The immunohistochemical profile of the tumoral cells guided us towards a carcinoma with "signet ring" cells, more exactly a mucinous adenocarcinoma, as the tumoral cells have rendered the markers both intensely and diffusely: CK AE1/AE3, BerEP4, CEA and they were negative for TTF-1, calretinin, CK5/6, CK20, CDX2, E-cadherin, vimentin and HBME-1. CK7 was weakly rendered in the isolated tumoral cells, which makes us think of a pulmonary metastasis from a gastric mucinous carcinoma. In this case, the tumoral cells are positive for CDX2 too, but in our case, the tumoral cells proved to be negative for this marker.

The carcinoma with "signet ring" cells, if it is primitively pulmonary, according to the *World Health Organization* (WHO) classification, is part of the pulmonary mucinous adenocarcinomas that represent about 15% of the non-microcellular cancer [23]. The dates from the medical specialty literature showed that the immunohistochemical profile of the pulmonary mucinous adenocarcinoma is the following: the tumoral cells are positive for the CK AE1/AE3, BerEP4 and CK7. They are also positive for CEA, TTF-1 and E-cadherin [24].

For the differential diagnostic, the following markers were added: CK5/6, CK20, CDX2, vimentin, calretinin and HBME-1. The differential diagnostic was performed with pleural mesothelioma, pulmonary metastasis of a

gastric mucinous carcinoma and pulmonary metastasis of a colorectal mucinous carcinoma.

In our case, the tumoral cells were positive for calretinin, CK5/6, HBME-1 and negative for CEA, BerEP4, E-cadherin, TTF-1, hence different from pleural mesothelioma. Ordóñez reported, in 2013, a series of 23 cases presenting with signet ring cell mesotheliomas which he investigated by IHC, 12 of which were also studied by electron microscopy [25].

Few signet ring cell mesotheliomas were reported so far in the literature, with only two reports of mesothelioma. They were initially considered to be signet ring cell carcinoma. In these cases, all signet ring cell mesotheliomas exhibited positive staining for mesothelin, CK5/6 and CK7, calretinin, with negative reactions for CEA, CD15, tumor-associated glycoprotein-72 (TAG-72), TTF-1, napsin A or MOC-31. The mesothelioma subtype can be confused with tumors that exhibit signet ring features [25].

Rajkumar *et al.* described the rare case of an Asian-American young patient, heavy smoker, who presented with primary signet ring cell carcinoma (SRCC) of the lung, in whom bronchial lavage, brushing and trans-bronchial fine-needle aspiration showed signet ring cells. Pathology confirmed through IHC of the biopsy fragment, with positive CK7 and CK20, p63, thyroglobulin, napsin A, prostatic specific acid phosphatase (PSAP), PSA, TTF-1 and CDX2. This is one of the few cases of pure SRCC of the lung, as opposed to the mixed type variant which is more common [26, 27]. Mucin-producing adenocarcinomas include invasive mucinous adenocarcinomas, enteric and colloid adenocarcinomas, SRCC being the lung type of disease [26, 28]. SRCA is the denomination for variants having above 50% signet ring cells [29]. Also, our case is different of pulmonary metastasis from a gastric carcinoma or of a colorectal mucinous carcinoma. Kish *et al.* first described in 1989 a primary SRCA of the lung [30] as a rare aggressive type of adenocarcinoma, usually having poor prognosis [31]. NSCLC was characterized in previous studies, showing positive staining for echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) [32, 33]. The EML4-ALK is a lung cancer induced fusion gene, which was discovered in 2007, demonstrating the presence of a SRC component was an important pathological element [34, 35].

Kish *et al.* [30] and Tsuta *et al.* [29] showed that primary SRCC of the lung is a very rare disease because in a largest series of 2640 cases surgically resected primary lung carcinomas just 39 showed SRCC components. Because of the rareness of the disease, it is important to distinguish the primary SRCC of the lung from metastatic SRCC's from other sites of the body like stomach, colon, breast, urinary tract, which are more common. Immunohistochemical studies and molecular diagnostics should help in making the differential diagnosis.

Merchant *et al.* [27] showed that with SRCC's from various organs (lungs, breast, stomach and colon) 82.4% were TTF-1 positive and 94.1% has the cytokeratin profile CK7(+)/CK20.

Villin was positive in 29.4% of cases [27]. Positivity for both TTF-1 and napsin A is a strong indicator for

pulmonary origin [36, 37]. Hayashi *et al.* reported that from five cases of primary lung SRCC, 80% of the cases were immunoreactive for lactoferrin, 100% showed K-Ras mutations, 100% were positive for MUC-1 and 100% were negative for MUC-2. MUC-1 is seen in SRCC and the solid adenocarcinoma of the lung than in SRCC of other organ sites [38]. TTF-1 can also be expressed in carcinomas originating from other primary sites [39]. Negativity for TTF-1 does not exclude pulmonary SRCC if the tumor is CK7 positive [40].

Castro *et al.* showed in a clinico-pathological study of 15 cases that immunoreactive CEA was positive for patients with primary signet ring cell adenocarcinoma of the lung [41]. In 2012, Terada showed that cancer antigen (CA) 19-9 and epithelial membrane antigen (EMA) were positive indicating that these molecules are present in the pulmonary SRCA [42].

## ✎ Conclusions

The ascites syndrome can offer large diagnostic surprises, because it can be determined by the existence of an affection whose cause is extra-abdominal. Most of the extra-abdominal affections that determine the intra-abdominal accumulation of liquid are usually serious affections, more precisely neoplasia, with an unforeseeable evolution, a prognostic with reduced responsiveness to treatment.

The superficial, incomplete investigation of the intra-abdominal accumulation of liquid can generate diagnostic errors, if we omit the fact that they can also be caused by extra-abdominal affections. The fact that ascites is generated by an extra-abdominal affection can be easily established by the anamnesis, clinical examination, biological and imaging investigations that are currently accessible in any clinic. However, the determination of the positive diagnostic needs sometimes a sophisticated medical equipment and personnel capable to use it correctly and efficiently. The simple determination of a neoplasia is not sufficient, as we need to specify its histopathological type, the local spread or the spread to the neighboring organs, the existence of metastases and of the organs affected by them, as well as the surveillance of the evolution under treatment. A correct diagnostic is equally provided by the access to an equipped laboratory of pathological anatomy that implies experienced pathologist.

The rapid and accurate determination of the diagnostics will allow not only for a decrease in the expenses for inefficient treatments, but also for the guidance of the patients towards clinics or centers able to provide and supervise these treatments.

## Conflict of interests

The authors declare that they have no conflict of interests.

## Author contribution

Mircea-Cătălin Forțoiu and Dragoș-Marian Popescu equally contributed to this article and share first authorship.

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