# CASE REPORT

## ADENOSQUAMOUS LUNG CARCINOMA COMPLICATED WITH MARANTIC ENDOCARDITIS AND CHRONIC DISSEMINATED INTRAVASCULAR COAGULATION

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**ABSTRACT**

***Background***: *Adenosquamous lung carcinoma is a relatively rare subtype of non-small-cell lung cancer that contains both adenocarcinoma (ADC) and squamous cell carcinoma (SCC) components. It is difficult to reach a proper diagnosis before surgery, with the histopathological examination of the resected specimen being the method of choice. A supplementary immunohistochemistry examination of the sample is needed. In order to initiate targeted treatment, molecular testing is mandatory.*

***Case presentation***: *A 47-year-old female, smoker (15 packs-year), without pathological personal history, presented for fatigue and moderate bilateral leg edema for about 3 months. The blood tests showed severe microcytic, hypochromic anemia and chronic disseminated intravascular coagulation. Computed tomography (CT) scan revealed a tumor in the right basal pleura with secondary pleural effusion, multiple lymphadenopathies, disseminated in the mediastinum, abdominal and pelvic cavity. Two other tumors were noticed, one in the right breast (7 mm) and the other in the vesicouterine pouch (7/10 mm). Prior to lung biopsy, a transthoracic and then transesophageal echocardiography were performed, highlighting the presence of a band on the aortic valve, suggesting marantic endocarditis. Tumor markers were also elevated. In evolution, the patient became bradypsychic, with head CT showing a brain metastasis in the left high-parietal region. Immunohistochemistry examination of the biopsy sample suggested a adenosquamous lung carcinoma.*

***Conclusion***: *We reported the diagnostic path of a rare subtype of lung cancer in a young female without known comorbidities, with an atypical presentation - multiple extrapulmonary non-metastatic manifestations: metabolic etiology - weight loss, fatigue; vascular and hematological etiology – marantic endocarditis (a very rare complication), severe microcytic, hypochromic anemia and chronic disseminated intravascular coagulation; neurological etiology – peripheral sensorimotor neuropathy of the right arm. A tissue biopsy was performed from the most accessible region – 1/3 inferior right thorax, posterior axillary line. The particularity of the adenosquamous lung carcinoma in this case lies in multiple metastases in less common sites (breast, vesicouterine pouch and probably kidney).*

**Keywords:** lung carcinoma, disseminated intravascular coagulation, endocarditis.

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## INTRODUCTION

According to the International Agency for Research on Cancer - Global Cancer Observatory (IARC – GCO), lung cancer ranks second in incidence (after breast cancer) and first in mortality in both sexes. In addition, lung cancer has overtaken prostate cancer, ranking first in incidence among men in 2020. In women, lung cancer ranks third in incidence after breast and colorectal cancer, and second in mortality after breast cancer [1].

Men are twice as likely to be diagnosed with lung cancer, given tobacco use, although women may be more susceptible due to the higher amount of epidermal growth factor receptor mutations and the effects of estrogen. Lung cancer is divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) –the latter having a higher incidence (85%) and being further divided into: adenocarcinoma (ADC), squamous cell carcinoma (SCC) and neuroendocrine cancers [2].

## CASE PRESENTATION

We report the case of a 47-year-old female, smoker (15 pack-year), without known comorbidities who came to the emergency room for progressively worsened fatigue that started 3 months before presentation, bilious vomiting that occurred three days before presentation, moderate bilateral leg edema and inappetence. The patient also reports unintentional weight loss of approximately 10 kg in about a year.

At presentation, the patient had an altered general state and pale skin. She had hypertension (blood pressure = 169/75 mmHg) and peripheral edema in both legs. Respiratory auscultation revealed the presence of sibilant rales in the left basal lung without the need for oxygen support (saturation level of 97% while breathing room air). The patient had reported pain in the right lumbar area with a positive Giordano's sign.

She was admitted to the internal medicine clinic presenting mild leukocytosis with neutrophilia, inflammatory syndrome (C-reactive protein (CRP) 73.55 mg/L), severe microcytic, hypochromic anemia – hemoglobin 2.9 g/dL – for which she received 2 IU of RBC transfusion isogroup, isoRh, iron deficiency (1.81 umol/L), ferritin – untested, hypoalbuminemia (2.8 g/dL), mild hyperglycemia (146 mg/dL) and chronic disseminated intravascular coagulation (high D-dimer 9759 ng/mL, low fibrinogen 103 mg/dL, prolonged prothrombin time 18.6 sec, but normal platelet count). The electrocardiogram was normal. Moderate biliary residue, 3 mm cholesterol polyp, alithiasis and 50 mm liquid in the right costophrenic sinus were seen at abdominal ultrasonography. Given the symptomatology, a chest X-ray (Figure 1) was performed and revealed infra hilar alveolar opacities on the right side and pleural effusion in moderate quantity in the same region.

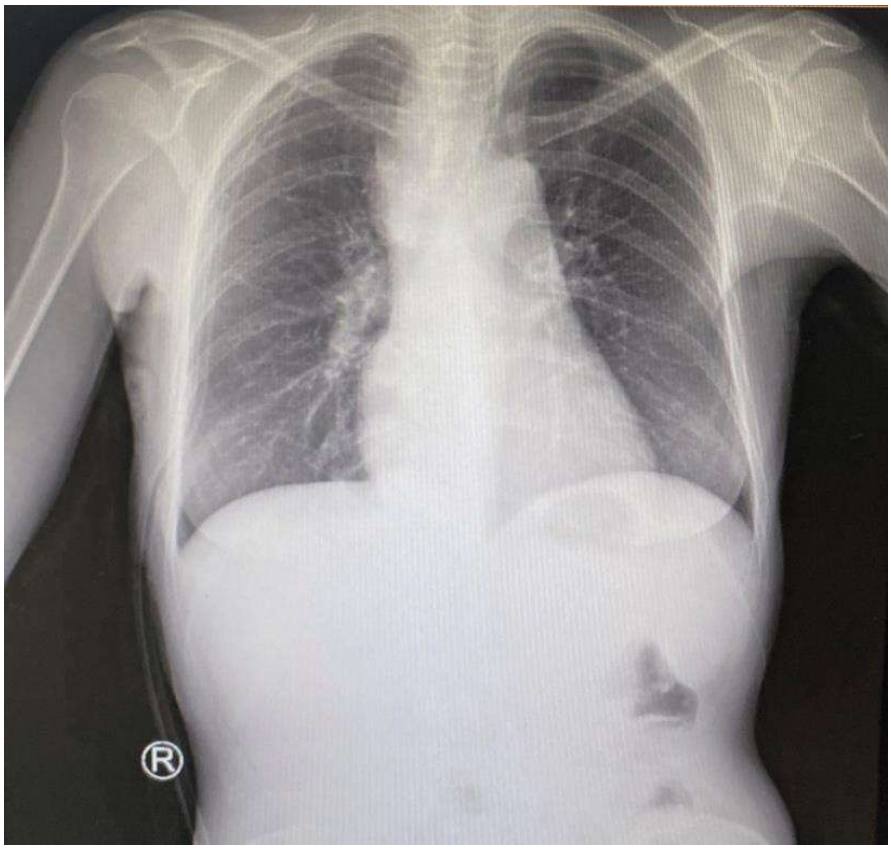

**Figure 1.** Chest X-ray showing infrahilar alveolar opacities and pleural effusion in moderate quantity on the right side

Taking into consideration the presentation particularities of the patient and the paraclinical findings, an aggressive disease was suspected, and the computed tomography (CT) +scan was decided. It showed a tumor in the right basal pleura with secondary pleural effusion of 40 mm (Figure 2), multiple mediastinal adenopathies bilateral and confluent, present in all lymph node groups, most of them necrotic, mediastinal and hilar adenopathies bilateral, gastric pericardial, lumboaortic, and possibly pelvic peritoneal adenopathies. Areas of ground glass opacities located in the lateral middle lobe and inferior right lobe at the Fowler level were also seen. In the left costodiaphragmatic recess, ground glass opacities were identified similar to those on the right side. In addition, pulmonary parenchymal changes were seen, more extensive on the right side with an uncertain substrate, and bilateral renal changes, more extensive on the right side with a post-pyelonephritic residual/secular type appearance (Figure 3). Moreover, a tumor of the right breast in the upper outer quadrant of approximately 7 mm and a tumor in the utero-vesical recess of a maximum of 7/10 mm were revealed (Figure 4).

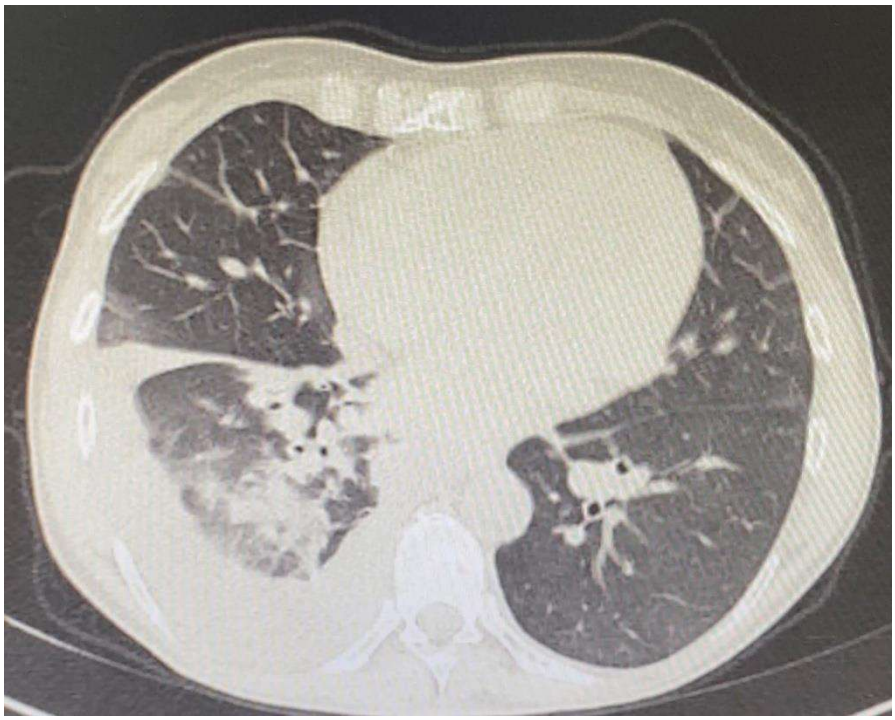

**Figure 2.** Chest CT scan showing a tumor in the right basal pleura with secondary pleural effusion of 40 mm

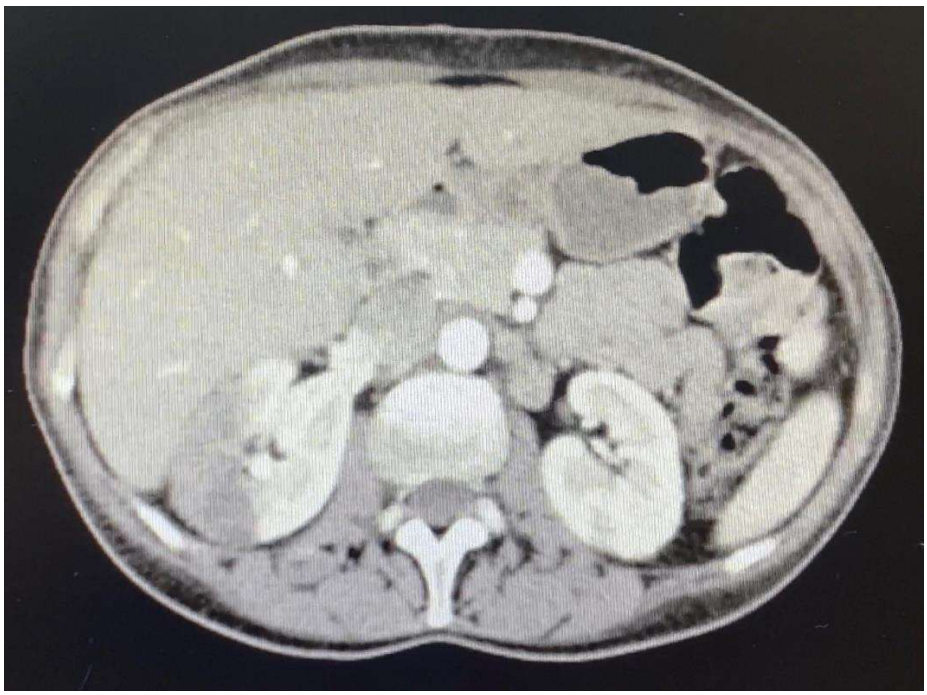

**Figure 3.** Abdominal CT scan showing bilateral renal changes, more extensive on the right side with a post pyelonephritic residual/secular type appearance

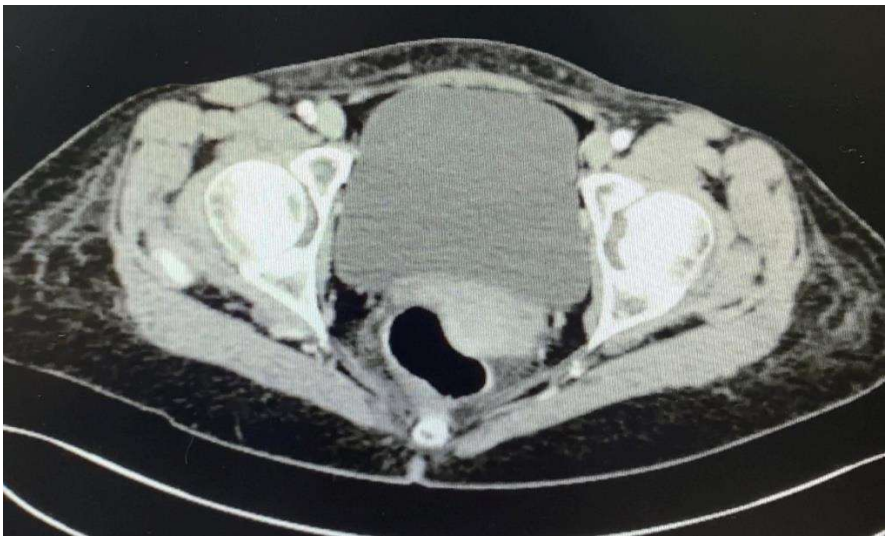

**Figure 4.** Pelvic CT scan showing a tumor in the utero-vesical recess of maximum 7/10 mm

The patient was seen by the gastroenterologist, general surgeon, otorhinolaryngologist and gynecologist. No signs of active bleeding were evident at the clinical examinations. Given the right lumbar pain and the post-pyelonephritic appearance of the right kidney, a urine culture was performed, showing no sign of a bacteria or yeast infection (negative). The upper gastrointestinal endoscopy did not detect any pathological processes in alignment with the current symptomatology. A Schatzki ring and a small trans-hiatal gastric hernia were identified. A colonoscopy cannot be performed entirely due to insufficient preparation. Sigmoidoscopy was performed, revealing uncomplicated hemorrhoidal disease.

Together with the thoracic surgeon, it was decided that the most accessible biopsy site remains the lung lesion. Before surgery, a transthoracic echocardiogram was performed, showing the left ventricle at the upper limit of normal, non-hypertrophic, with preserved systolic function, severe aortic insufficiency due to the presence of a mobile, hyperechoic mass attached to the aortic valve (tumor? vegetation?). Mild mitral insufficiency, mild pulmonary hypertension, pericardial fluid in a minimal amount (4 mm), dilated cavities, normal kinetics, left ventricle ejection fraction of 55% and diastolic function with delayed relaxation were also seen.

The transesophageal echocardiography confirmed the presence of a band (thrombus) on the aortic valve supposing that it was most likely a non-infectious endocarditis (marantic endocarditis). Mild to moderate aortic regurgitation was also seen.

Tumoral markers such as CA 125 >1000 U/mL, CA 15-3 154 U/mL, CA 19-9 149 U/mL and CEA 4.28 ng/ml were performed, noticing the highest increase among CA 125.

Multiple diagnoses were considered. Considering the location of the lesions identified on CT, it could have been a solid tumor - non-microcellular lung cancer, breast cancer, synchronous tumors, renal cell cancer, or uterine cancer - or a hematological malignant disease such as large B-cell malignant non-Hodgkin's lymphoma or peripheral T-cell lymphoma. The patient underwent pre-anesthetic and thoracic surgery consultations prior to the lung tumor biopsy. Thoracoscopy with mass biopsy of the right pleural tumor was conducted for histopathology and immunohistochemistry. Locally, a pleural drainage catheter was inserted.

Upon returning to the internal medicine department, the patient was bradylalic and bradypsychic, without motor deficits, nystagmus, or metabolic changes. An expansive intracranial process was suspected, and brain CT was performed, revealing a left-high parietal metastasis (5 mm) with small perilesional edema (Figure 5), that reduced in size (Figure 6) after intravenous corticosteroid treatment.

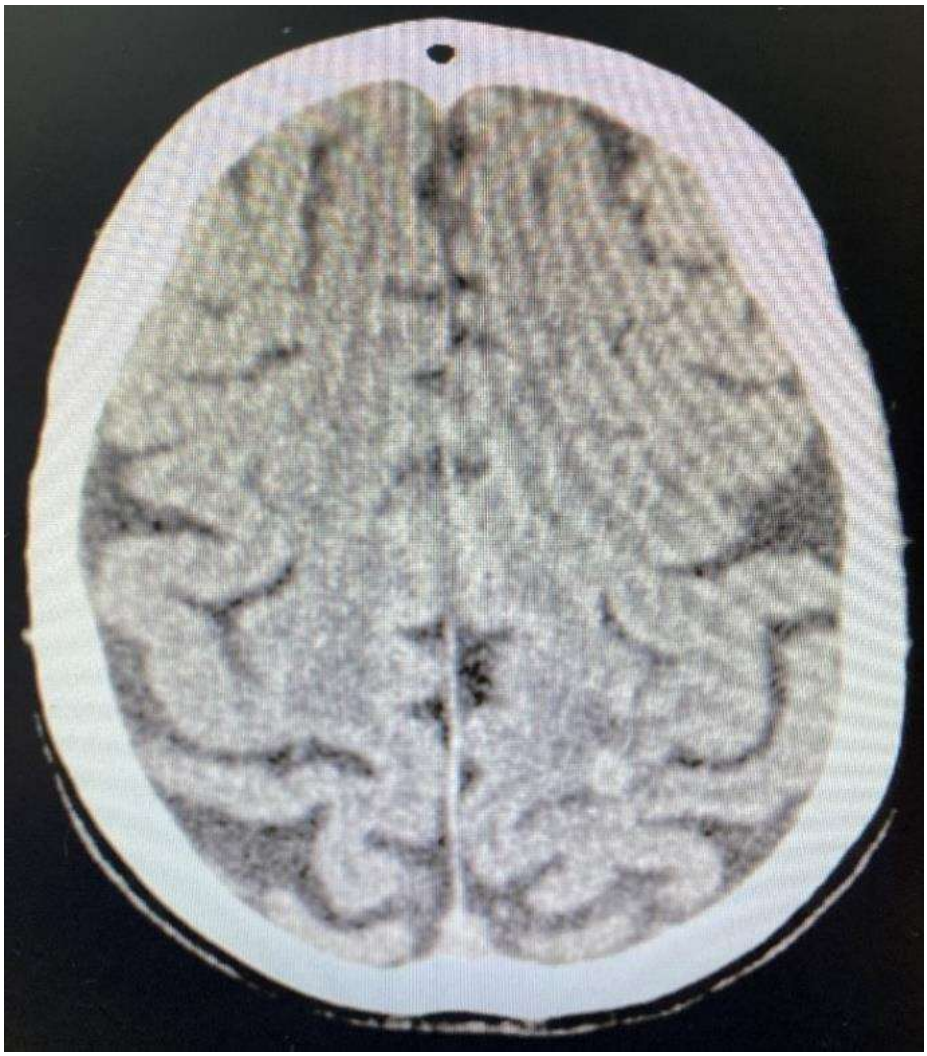

**Figure 5.** Brain CT revealing left-high parietal metastasis (5 mm) with small perilesional edema

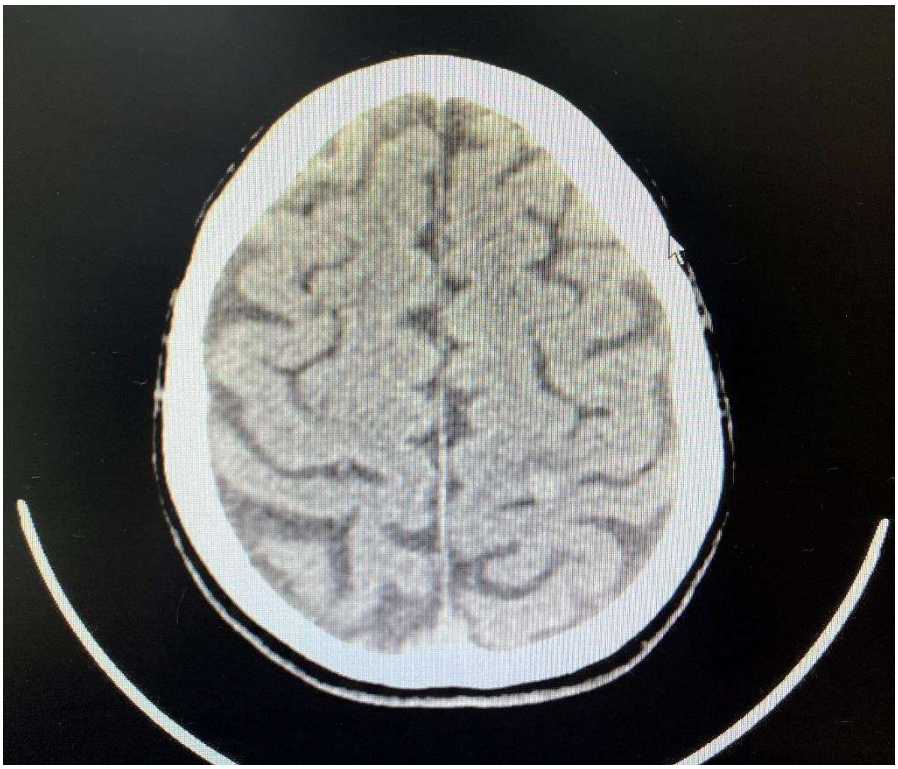

**Figure 6.** Brain CT revealing reduction in the size of the perilesional edema after intravenous corticosteroid treatment

During hospitalization the patient received loop diuretic (Furosemide 1 dose x3 daily), anticoagulant - prophylactic dose (Enoxaparin 0.4 ml daily), antihypertensive (ACE inhibitor - Enalapril 10 mg when systolic blood pressure exceeded 140 mmHg), nonsteroidal anti-inflammatory drugs if needed (Diclofenac), antiemetics if needed (Metoclopramide) and later she received corticosteroid treatment to reduce the perilesional edema of the left-high parietal metastasis (Dexamethasone once daily). Leukocytosis with neutrophilia, inflammatory syndrome (CRP 73.55 mg/L) and the multiple necrotic adenopathies identified on the CT scan examination made us initiate antibiotic treatment with piperacillin/tazobactam 1 dose every 8 hours (5 days), replaced after the transthoracic echocardiogram result with ceftriaxone 2g daily (8 days) to cover any bacterial pathogen involved in endocarditis, given the ambiguity of the etiopathogenity of the aortic valve mass (vegetation, tumor, thrombus).

The patient was discharged with moderate anemia (hemoglobin 10g/dL) and clinical sensory-motor peripheral neuropathy in the right arm. She was advised to stop smoking, to get an outpatient mammography and colonoscopy re-evaluation and to get a cardiology re-examination and a cardiac MRI to differentiate infective endocarditis from marantic endocarditis or aortic valve metastasis.

She was referred to an oncology clinic even though the tumor histopathological characterization and immunohistochemistry were not ready. In addition, she was advised to take iron tablets 2 capsules daily, before lunch and folic acid 5 mg daily for 3 months. Oral corticosteroids (32 mg daily) and pantoprazole (40 mg daily) were given for another 7 days to ameliorate the perilesional edema of the left-high parietal metastasis. Famotidine 40 mg daily was prescribed to prevent acid reflux given the Schatzki ring fragment and trans-hiatal gastric hernia. There were also prescribed metoclopramide if

nausea occurs, diclofenac 25 mg daily if needed (pain) and enalapril 10 mg at systolic blood pressure over 140 mmHg.

Histopathological examination from the pleural tumor biopsy had shown the appearance of a carcinoma with large epithelioid cells and clear and eosinophilic cytoplasm. Tumor cells were arranged in solid structures. An increased mitotic rate and necrosis were present. The histopathological specimen revealed a pleural metastasis of poorly differentiated large-cell carcinoma. The aspects pointed towards an adenocarcinoma of bronchopulmonary origin.

Immunohistochemistry was needed to differentiate a large B-cell malignant non-Hodgkin's lymphoma or a peripheral T-cell lymphoma from an adenocarcinoma given the fact that they are histologically similar. It was revealed by immunohistochemistry: CK-7 + and CK-20 - in tumor cells – pattern characterized of metastatic lung adenocarcinomas,[3] Napsin A + with moderate intensity in lung cells – expressed in over 80% of lung adenocarcinomas,[4] Nuclear PTR1 + with moderate intensity in tumor cells, CK34BE12 + membranous and focal cytoplasmic in tumor cells, GATA3 - in tumor cells, Ki67 nuclear index and in tumor cells = 10%. Immunohistochemistry revealed adenosquamous carcinoma of primitive pulmonary origin.

## DISCUSSION

It was discussed the case of a young patient, without known pathology, who presented herself to the emergency room with severe symptomatic anemia, diagnosed with lung cancer, with probably multiple metastases in less common sites such as the breast, vesicouterine pouch and maybe the kidney, for which a biopsy was performed from the most accessible tumor process.

The non-metastatic extrapulmonary manifestations present in this case were metabolic (weight loss, fatigue), vascular, hematological (non-bacterial thrombotic endocarditis/marantic endocarditis, which occurs very rarely, severe microcytic hypochromic anemia, chronic disseminated intravascular coagulation) and neurological (sensory-motor peripheral neuropathy at right arm level).

While non-bacterial thrombotic endocarditis is a rare paraneoplastic finding, it is common in lung adenocarcinomas [5]. Marantic endocarditis is usually silent, as it is also seen in our patient presentation.

Disseminated intravascular coagulation (DIC) as a paraneoplastic phenomenon is common in non-small cell lung cancer patients, especially in advanced stages (III or IV). Usually, DIC appears in any solid tumor [6]. No active bleeding was identified in our patient, as it is less common in chronic DIC that develops over a longer period (weeks or months), but a hypercoagulability status (heavy smoker, malignancy, female gender) conducted to non-bacterial endocarditis [7].

A differential diagnosis was made between a solid tumor – adenocarcinoma (non-microcellular lung cancer, breast cancer, synchronous tumors, renal cell cancer, uterine cancer) and a hematological malignant disease – large B-cell malignant non-Hodgkin's lymphoma or peripheral T-cell lymphoma, given the location of the lesions identified on CT TAP and because from a histological point of view, they are similar to each other.

Having seen the histopathological and immunohistochemistry results, but also the aspect of the CT scan, we concluded that the patient had adenosquamous carcinoma in the right lung, with extensive lymph nodes involvement and with multiple metastases, placing the disease in cT2aN3M1c, stage IV B [8].

Molecular testing should be performed if adenocarcinoma is present in the biopsy specimen of an otherwise squamous tumor. Biomarkers such as EGFR mutations can be present in adenosquamous carcinoma [9,10].

Adenosquamous carcinoma is a rare type of non-small cell lung cancer that occurs in 0.4 - 4% of patients diagnosed with malignant

lung cancer. It is a mixed type, having components of both adenocarcinoma and squamous cell carcinoma. To be identified as adenosquamous, the tumor needs to have at least 10% of each cellular subtype. This type of lung cancer has a low incidence, increased aggressiveness, and poor prognosis rates. The overall survival rates in all stages are 53.5% at 3 years and 25.6% at 5 years [11].

There is no specific treatment for this type of cancer. Current treatment is based on guidelines for non-small cell lung cancer. Surgical excision (lobectomy with lymphadenectomy) is recommended in curative cases. For patients with EGFR+, tyrosine kinase inhibitors (erlotinib, gefitinib) represent the first-line treatment. The platinum doublet (4 cycles) is considered the first line in the case of EGFR-positive patients or if the molecular profile is not known [10,11].

At discharge, the patient presented a relatively good performance status (ECOG grade 2). She was referred to an oncologist to perform molecular testing (EGFR, ALK, KRAS, ROS1, PD-L1) before starting a targeted treatment.

## CONCLUSIONS

We reported the diagnostic path of a rare subtype of lung cancer that is usually diagnosed after the surgical removal of the tumor, presented in a young female without known comorbidities. The patient had an atypical presentation with multiple extrapulmonary non-metastatic manifestations, of which the most important were marantic endocarditis (a very rare complication), severe microcytic hypochromic anemia, and chronic disseminated intravascular coagulation. A tissue biopsy was performed from the most accessible region: 1/3 inferior right thorax, posterior axillary line. Immunohistochemistry revealed adenosquamous carcinoma of primitive pulmonary origin, a cT2aN3M1c, stage IV B.

In this case, the tumor's particularity lies in the multiple metastases presented in less common sites (breast, vesicouterine pouch, and probably kidney).

**Author Contributions:**

*A.D.S and R.M.V conceived the original draft preparation. A.D.S, C.C.D. and R.M.V were responsible for conception and design of the case report. A.D.S, C.C.D. and R.M.V was responsible for the data acquisition and for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.*

**Compliance with Ethics**

**Requirements:** *"The authors declare no conflict of interest regarding this article".*

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