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# An Uncommon Lung Neoplasm in a Young Patient: Diagnostic Challenges

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**Patient:** Female, 29-year-old  
**Final Diagnosis:** Lung adenosquamous carcinoma  
**Symptoms:** Cough • Low back pain • night sweats • thoracic pain • weight loss  
**Medication:** —  
**Clinical Procedure:** Chemotherapy • CT-scan • fiberoptic bronchoscopy • radiotherapy • transbronchial biopsy  
**Specialty:** Oncology • Pulmonology

**Objective:** Rare disease

**Background:** Adenosquamous carcinoma of the lung (ASC) is a rare subtype of non-small-cell lung carcinoma (NSCLC), histologically defined by the presence of both squamous cell carcinoma and adenocarcinoma components. This aggressive malignancy has been rarely described in young female patients. Due to its low incidence and difficult-to-establish preoperative diagnosis, little is known about the complete clinical course for young patients with this specific NSCLC subtype. Moreover, a history of smoking is positively associated with ASC, but evidence for an association with exposure to secondhand smoke is sparse.

**Case Report:** We present the case of a previously healthy 29-year-old woman with a long-standing history of secondhand smoke exposure, who was ultimately diagnosed with advanced ASC via fiberoptic bronchoscopy with transbronchial biopsy after a number of different investigations and treatments performed outside our service. She had visited many clinicians in 4 months of symptoms, initially presented as thoracic pain and cough thought to be due to a complicated pneumonia. Symptoms progressed despite empiric treatment and eventually included low back pain, weight loss, and night sweats. The hypothesis of tuberculosis was then investigated and discarded, at which point, 3 months after the onset of symptoms, she had a CT scan of the chest, revealing a pulmonary mass. She was referred to our hospital to further investigate this finding via fiberoptic bronchoscopy with transbronchial biopsy. During the procedure, she experienced an acute exacerbation of the low back pain, which prompted her admission in the Emergency Department, and she was later admitted to our pneumology ward. An extensive treatment plan including chemotherapy and radiotherapy was initially started, but could not be completed due to rapid disease progression, defined by pulmonary and spine metastatic implants, which limited treatment to palliative care. The patient died 6 months after the initial onset of symptoms.

**Conclusions:** This case report shows the clinical course of a difficult and rare diagnosis, and demonstrates the high level of suspicion required for the early diagnosis of lung neoplasms in young patients.

**MeSH Keywords:** Carcinoma, Adenosquamous • Early Detection of Cancer • Rare Diseases

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## Background

Adenosquamous carcinoma (ASC) of the lung is a rare pathological subtype of non-small-cell lung carcinoma (NSCLC), accounting to 0.4–4% of all primary lung cancers [1]. It has been histologically defined by the presence of both adenocarcinoma and squamous cell carcinoma, with each component comprising at least 10% of the tumor cells [2].

Based on the predominant histological feature, ASC is categorized into 3 subtypes, adenocarcinoma-predominant ASC (AD-ASC, the proportion of ADC  $\geq$ 60% of tumor), squamous-predominant ASC (SCC-ASC, the proportion of SCC  $\geq$ 60% of tumor), or balanced structures of ASC (the proportion of ADC and SCC is between 40% and 60%). These subtypes of ASC have various clinical and radiological profiles and significantly different prognoses [3,4].

ACS is an aggressive malignancy and is associated with poor prognosis. It is significantly more common in men, with an average age of 60 years, which is older than the age of patients with other types of lung cancer. It was reported that 55.6% of ACS patients have been smokers [5]. ASC has been rarely described in young patients. Only 23% of ASC patients are 60 years old or younger [6], and the largest review to date found that only 1% of ASC patients were between 18 and 25 years old [7].

Here, we report the case of a previously healthy 29-year-old woman with a long-standing history of exposure to second-hand smoke, diagnosed with advanced ADC-predominant ASC. Unfortunately, the diagnosis was made at a late stage, which restricted our treatment to palliative care chemotherapy. The report was approved by the Clementino Fraga Filho University Hospital (HUCFF/UFRJ) Ethics Committee (#20419219.0.0000.5257).

## Case Report

A 29-year-old woman was admitted to the Clementino Fraga Filho University Hospital (HUCFF) Emergency Department after experiencing acute exacerbation of a pre-existing low back pain during a fiberoptic bronchoscopy (FBS) requested by an outside attending doctor, when she was medicated with symptomatic drugs and admitted to the Pulmonology Services for diagnostic investigation.

She complained of chest pain in the lower third of the right hemithorax during the past 4 months, which was continuous, non-ventilator dependent, and associated with dry cough and night sweats, without fever or chills. In addition, she developed low back pain shortly after the onset of the respiratory

symptoms, which was aggravated by walking and coughing and was associated with lower-limb paresis. She was a non-smoker but had a history of exposure to secondhand smoke from her father for 18 years.

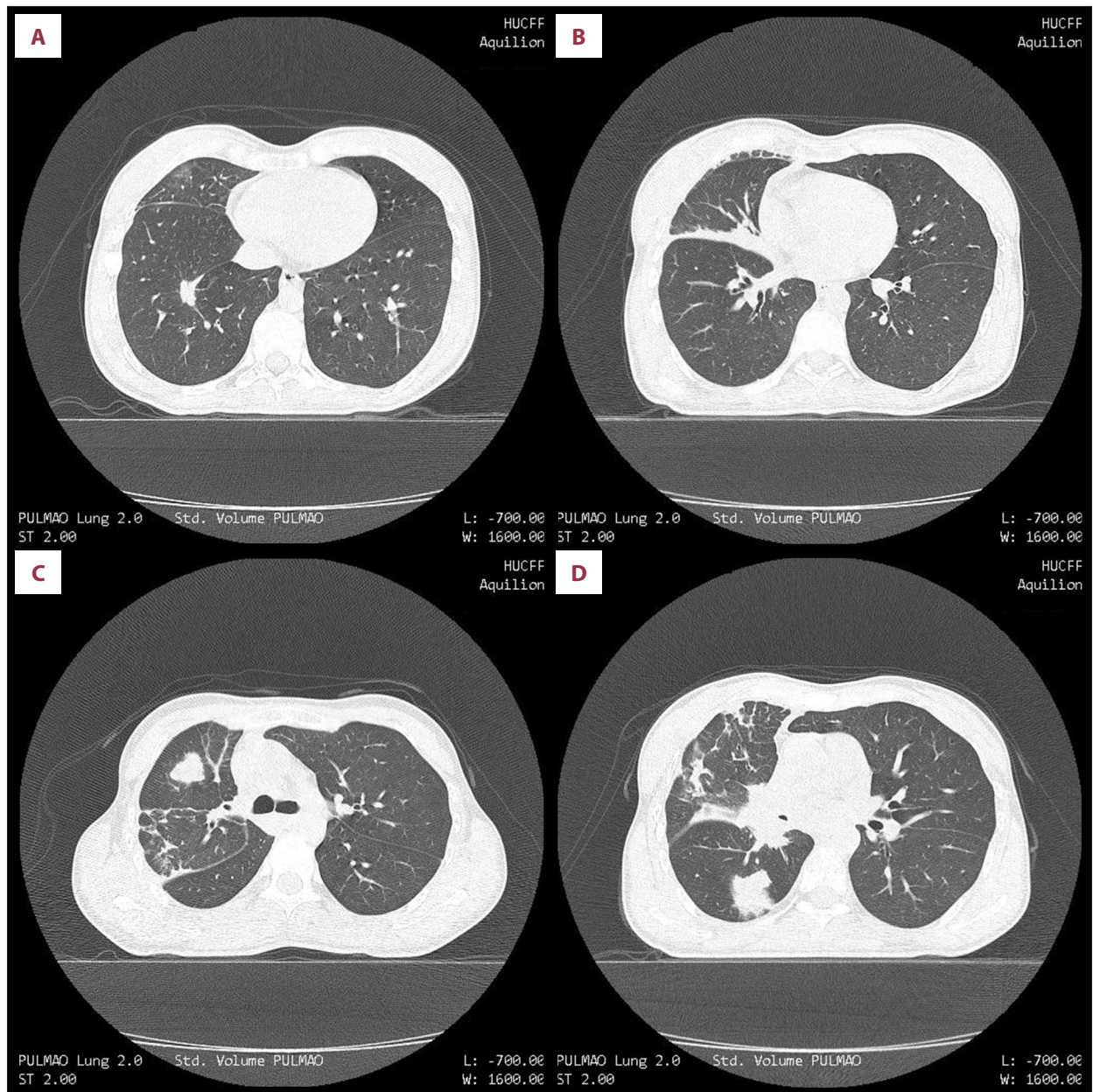
She initially sought medical attention in a primary health care unit, where she was prescribed anti-inflammatory drugs and oral antibiotics for suspected pneumonia, but without clinical improvement. She developed dyspnea on medium exertion and an episode of hemoptysis, followed by hemoptoic sputum, with worsening of the lung condition.

A clinical investigation of suspected pulmonary tuberculosis was performed using sputum acid-fast bacilli investigation and GeneXpert, both with negative results. A chest computed tomography (CT) scan performed 3 months after the onset of symptoms showed a soft-tissue density mass of lobulated contours involving the bronchovascular structures of the right pulmonary hilum, with obliteration of the middle bronchus, atelectatic consolidation, and infiltration in the middle lobe (frosted glass pattern), in addition to consolidation foci in the upper and lower right lobes, presence of a 15×11 mm spiculated nodule in the lower quadrant, and mediastinal lymph node enlargement with pleural effusion (Figure 1). She was referred for FBS based on these findings, the complication of which motivated her hospitalization.

Upon admission, the hypothesis of metastatic lung cancer was explored. A full-body bone scan was performed, which showed focal uptake in bilateral costal arches and L4 (Figure 2). Nuclear magnetic resonance imaging revealed a reduction in the height of the T4 vertebral body associated with a Schmörl node (Figure 3). Based on this, we staged the disease as stage IVA (T4N2M1b) lung cancer.

Cytopathological analysis of bronchoalveolar lavage was positive for malignancy and compatible with adenocarcinoma. Immunohistochemistry with TTF-1 labeling showed diffuse positivity in neoplastic cells, confirming the initial microscopic impression of adenocarcinoma, while the p63 labeling indicated an immunophenotype of double glandular and squamous differentiation, defined by a striking prevalence of the adenocarcinoma component, which comprised more than 60% of the tumor, with a final diagnosis of AD-ASC of the lung (Figure 4).

She was hospitalized for 17 days, developing a rapid progression of symptoms, defined by local and metastatic tumor growth, causing extrinsic compression of neighboring structures. These symptoms included pulmonary symptoms, mainly defined by debilitating cough and thoracic pain, weight loss complicated by the acute onset of esophageal dysphagia for solids and liquids, and progressive low back pain that restricted her movements. A gastrostomy was performed to establish a



**Figure 1.** CT scan of the chest with a lung window showing a spiculated 15×11 mm nodule in the lower lobe of the right lung (A), pleural thickening in the region of the interlobar fissure (B). Two soft-tissue density nodules in the right upper lobe (C) and in the right lower lobes (D), in addition to a lobed contour mass involving bronchovascular structures of the right pulmonary hilum and causing partial obstruction of the right middle bronchus and ground-glass infiltration in the middle lobe (D).

long-term route for enteral nutrition, which was well tolerated. We were able to control the pain symptoms using a combination of daily maximum-dosage acetaminophen, dipyrrone, and codeine, with morphine as needed. Codeine was also sufficient to mitigate coughing. She had good clinical recovery and was able to be discharged to start an outpatient chemotherapy program. First, we sought to investigate epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutation and the PD-L1 expression for therapeutic targeting on the

diagnostic biopsy, as this would greatly aid in selecting an appropriate chemotherapy scheme [1,2]. Unfortunately, we lacked the resources to perform testing in a timely manner. Given the rapid progression of disease, we decided on the prompt initiation of treatment while waiting on the tests results. Due to lack of solid evidence on the best treatment scheme specifically for patients with ASC, 10 cycles of Gemcitabine/Carboplatin were initially scheduled, based on one of the first-line schemes for advanced or metastatic non-small-cell lung cancer [7–11].



**Figure 2.** Magnetic resonance imaging of the lumbar spine showing reduced height of the L4 vertebral body with hypointense area in T1 (A) and with heterogeneous contrast enhancement (B) in the upper plateau of L4 with an associated Schmorl node, suggesting a metastatic implant, probably responsible for the patient's lumbar spine pain.

However, the patient could only tolerate 3 cycles due to toxicity. She was hospitalized again after 2 weeks due to an L4 fracture. We opted for a program of 10 radiation therapy sessions after chemotherapy. We also received, by that time, the results of EGFR, ALK, and PD-L1 expression, which were inconclusive. Unfortunately, there was no response to the treatment, and the patient died 177 days (6 months) after the first hospital admission.

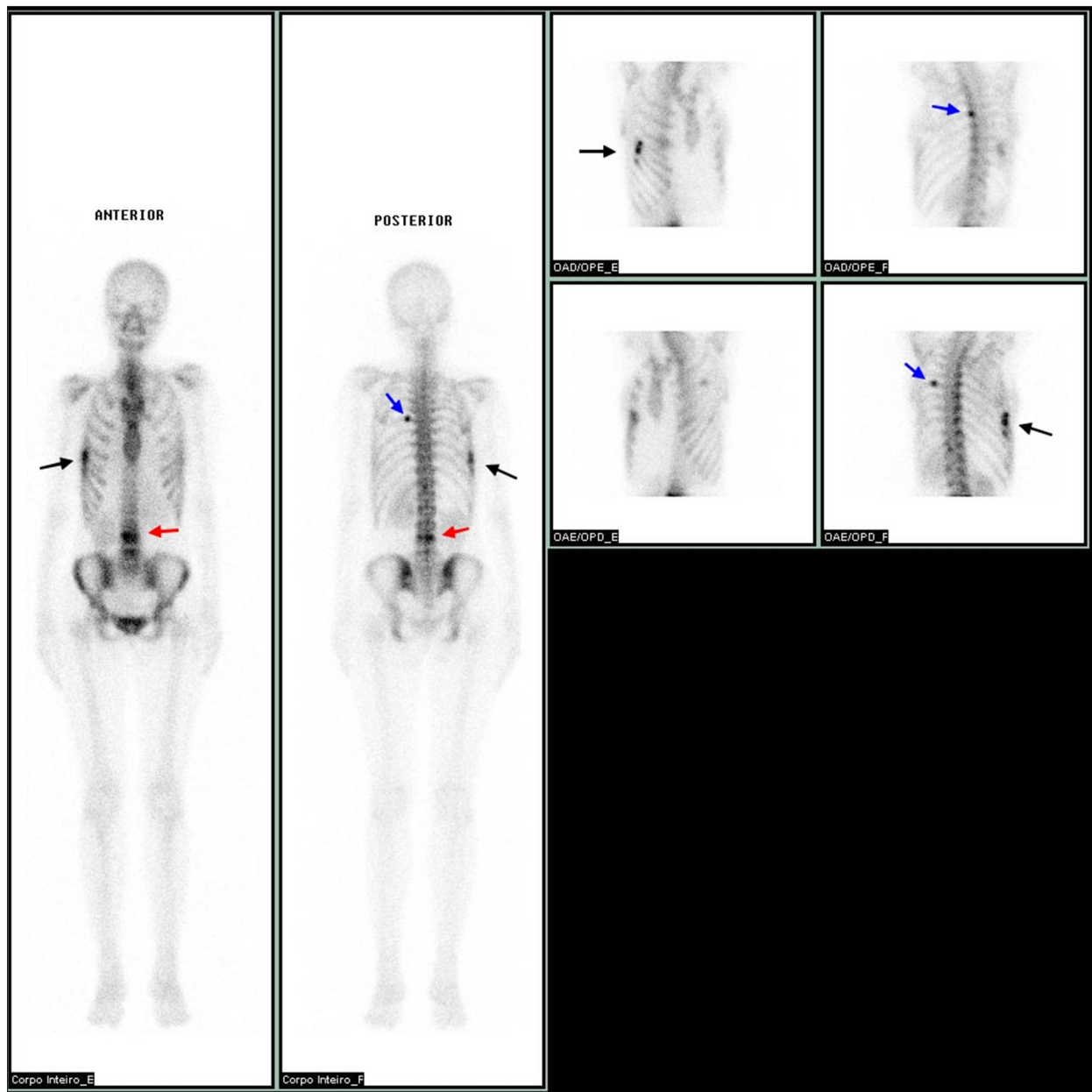
## Discussion

The timely diagnosis of pulmonary neoplasms in young non-smoking women is notoriously challenging, and most cases are detected as stage IV metastatic disease [12]. Specifically, the rarity of ASC cases described within this epidemiological profile not only hinders the deployment of diagnostic procedures, but also complicates clinical management decisions and prognostic prediction [12,13]. Therefore, it is crucial to conduct more studies to better inform the clinical, pathologic, and radiographic aspects of lung ASC in these patients.

To date, the largest review describing the clinical profile of young lung cancer patients (35 years old or younger) included a total of 120 patients, but only 2 of those patients had ASC [12]. Nevertheless, the results indicated that young lung cancer patients tend to show a different clinical course than their older counterparts, with more advanced disease staging at diagnosis and worse prognosis.

Specific radiological data for young ASC patients are scarce. In studies of patients with the more common older patient profile, it is usually described as a peripheral lung lesion, especially for the AD-ASC subtype [4,14]. Thus, it is important to highlight that our patient presented ASC as a central lung lesion.

Even in well-documented epidemiological groups, ASC has been shown to be extremely difficult to diagnose preoperatively, mainly because samples obtained preoperatively often do not contain both AC and SCC components [13]; therefore, the most effective method of adequate diagnosis of ASC is considered pathology examination of surgically-resected gross specimens [4]. However, this is not possible for most cases, as they are usually diagnosed in locally advanced or metastatic stages, in which patients are no longer candidates for surgery. Only 2% of 141 cases reviewed by Mordant et al. [13] could be diagnosed preoperatively through needle biopsy based on the WHO definition, which requires that each component comprises at least 10% of the tumor under light microscopy [2]. This classification is valid but still controversial [4]. Even in those patients undergoing biopsy, the histopathological diagnosis itself is quite difficult [4]. The correct histological and immunohistochemistry diagnosis is paramount to proper clinical management, influencing treatment decisions and prognosis. Therefore, immunohistochemistry can be an especially useful strategy to classify these types of uncommon lung neoplasm with mixed histology in the age of molecular medicine [15]. Therefore, we used p63 and TTF1 labeling, which are sensitive



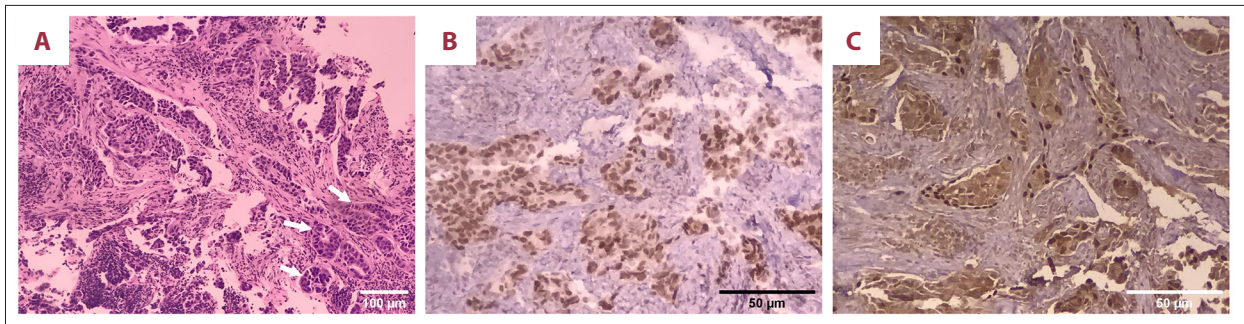
**Figure 3.** Bone scintigraphy showing high-grade focal uptake in the posterior segment of the 7<sup>th</sup> left costal arch (blue arrows), in the posterior segment of the 7<sup>th</sup>, 8<sup>th</sup>, and 9<sup>th</sup> right costal arches, (black arrows) and in the anterior segment of L4 (red arrow), indicating multiple metastatic implants of an advanced staging disease.

markers for squamous cell variant and adenocarcinoma variant, respectively [15].

The preferred treatment option for ASC is surgery, with lobectomy with lymphadenectomy being considered a standard treatment, while early-stage disease can be treated with sublobar resection. Gawrychowski et al. showed that the cumulative postoperative survival rates at 5 and 10 years are 25.4% and 19.2%, respectively. Platinum-based postoperative adjuvant chemotherapy is the standard treatment for stage II–IIIA

NSCLC and is an independent positive prognostic factor for stage IA–IIIB patients with ASC [16].

There are specific target chemotherapy treatments for oncogenes EGFR/ALK mutations and PD-L1 high-expressing tumors, which helps planning clinical management. The frequency of these specific markers is better described in adenocarcinomas, in which EGFR/ALK mutations can be identified in 36% of tumors, as PD-L1 high expression is usually seen in approximately 30% of tumors [17]. Recent data show that ASC



**Figure 4.** Histological aspect of the lesion biopsy showing infiltrating nests with a carcinomatous characteristic with poorly differentiated glandular structures in the lower right corner (A) Immunohistochemistry with TTF-1 labeling showing diffuse positivity in neoplastic cells (B) and p63 labeling with nuclear positivity in about 10% of neoplastic cells (C), indicating immunophenotype of double glandular and squamous differentiation, compatible with a diagnosis of ASC.

has similar rates of expression of these markers [18]. The EGFR mutation was found in 27–57% of lung ASC, depending on the study [19,20], while ALK rearrangement was seen in 5.3–6.25% of cases [21,22] and PD-L1 high expression was found in 39.22% of lung ASC [22].

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) can be used as first-line therapy for advanced EGFR-mutant NSCLC. ALK inhibitors are promising alternatives in NSCLC patients with confirmed ALK mutations, as shown by Wang et al., although further studies are needed. Ongoing studies show that immune checkpoint blockade therapies, such as programmed death 1 (PD-1) and its ligand PD-L1, may be a potential treatment choice for ASC patients with high PD-L1 expression [21].

The history of secondhand smoke (SHS) exposure related by our patient should have heightened the early clinical suspicion of lung cancer. SHS has been shown to increase the risk of all histological types of lung cancer, although it is especially associated with small-cell subtypes. This fact is particularly relevant in our case because it has been suggested in the literature that individuals whose first exposure occurred before age 25 have a higher lung cancer risk compared to individuals first exposed after age 25 years [23,24].

## Conclusions

The initial presentation of the unusual diagnosis of lung cancer in young patients can be mild and mimic many more common pulmonary conditions, which can delay the use of more advanced diagnostic tools, as shown in this case report. The history of long-standing secondhand smoke exposure could be important to heighten the suspicion of ASC and other lung cancers in young patients.

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## Conflict of interest

None.

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