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THE MULTIPLE FACES OF LUNG ADENOCARCINOMA: CHALLENGES IN DIAGNOSIS

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Abstract

Lung cancer dominates the current picture of malignancies worldwide, remaining a tragic first place in mortality statistics. Despite the continuous improvements in lung cancer screening, the refinement of surgical techniques, and innovations in oncological treatments, lung cancer remains the main contributor to fatalities among all forms of neoplastic conditions[(1,2)].

Lung adenocarcinoma is not just one of the most common histological types of lung cancer but also one of the deadliest worldwide due to its late diagnosis and high heterogeneity. Smoking tobacco is one of the main risk factors for any lung cancer, including adenocarcinoma, but there are also other factors that can increase the risk, such as family history of lung cancer and professional exposure to noxious agents such as silica, asbestos, radon, heavy metals, and diesel fumes[(3)].

Therefore, through this case series report the authors attempt to present their experience with three cases with a broad range of differences such as past medical history, living and work conditions, and other vicious habits such as smoking. This paper strives to establish the potential faces that lung adenocarcinoma can adopt, disguising itself under the umbrella of many other lung parenchymal syndromes, mimicking non-malignant processes, often displaying features very similar to an infection, and misdiagnosed as pneumonia, thereby delaying the diagnosis. Additionally, we provide a brief synthesis of the best resources available in lung adenocarcinoma-specific literature, including the importance of distinguishing early signs and symptoms, medical imaging, differential diagnosis, and early treatment.

Keywords: *adenocarcinoma, lung cancer, diagnosis, treatment.*

Rezumat

Cancerul pulmonar domină tabloul actual al malignităților la nivel mondial, rămânând pe primul loc tragic în statisticile mortalității. În ciuda îmbunătățirilor continue în screening-ul cancerului pulmonar, a perfecționării tehnicilor chirurgicale și a inovațiilor în terapiile oncologice, cancerul pulmonar rămâne principala cauză de deces în rândul afecțiunilor neoplazice[(1,2)].

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Adenocarcinomul pulmonar nu este doar unul dintre cele mai frecvente tipuri histologice de cancer pulmonar, ci și unul dintre cele mai mortale din lume, ca urmare a diagnosticului tardiv și heterogenității ridicate. Fumatul este unul dintre principalii factori de risc pentru orice cancer pulmonar, inclusiv adenocarcinomul, dar există și alți factori care pot crește riscul, cum ar fi antecedentele familiale de cancer pulmonar și expunerea profesională la agenți nocivi precum siliciul, azbestul, radonul, metalele grele și vaporii de motorină[3].

Prin urmare, prin prezentarea acestei serii de cazuri autorii încearcă să-și prezinte experiența în trei cazuri cu particularități diferite, cum ar fi antecedentele medicale, condițiile de viață și de muncă și alte obiceiuri vicioase, cum ar fi fumatul. Lucrarea se străduiește să arate potențialele fețe pe care le poate adopta adenocarcinomul pulmonar, deghizându-se sub umbrela multor altor sindroame parenchimatoase pulmonare, mimând procese non-maligne, prezentând adesea caracteristici foarte asemănătoare infecțiilor și fiind diagnosticat greșit ca pneumonie, întârziind astfel diagnosticul. În plus, oferim o scurtă sinteză a celor mai bune resurse disponibile în literatura specifică adenocarcinomului pulmonar, inclusiv importanța distingerii semnelor și simptomelor precoce, imagistica medicală, diagnosticul diferențial și tratamentul precoce.

Cuvinte cheie: *adenocarcinom, cancer pulmonar, diagnostic, tratament.*

Introduction

Adenocarcinoma is the most common histological type of lung cancer with a wide spectrum of clinical, molecular, pathological, and imaging features. Recognition of the uncommon clinical and imaging manifestations of lung adenocarcinoma is mandatory, especially for establishing an early diagnosis and differentiating these tumors from infectious pulmonary processes, with which they are often confused. Within this category, a rare subtype known as primitive mucinous lung adenocarcinoma exists, formerly known as bronchioalveolar carcinoma, represents the rarest subtype of lung adenocarcinoma, accounting for approximately 2-6% of all non-small cell pulmonary carcinomas[4,5].

This particular subtype displays an unusual presentation, often giving rise to diagnostic uncertainties. The variability in imaging patterns arouses interest, encompassing a broad range of imaging characteristics that can make transition from subsolid to solid and manifesting as either single or multifocal

densities. Thus, the present cases summarize and subscribe to the same subtype of neoplastic disease, an established diagnosis, not without challenges.

Case 1

A 52-year-old woman, non-smoker, without occupational exposure to respiratory irritants, with no significant medical history, sought medical evaluation due to recurring episodes of dry cough for about 6 months. The physical examination was non-contributory while other pulmonary routine tests such as spirometry, plethysmography, and transfer factor of the lung for carbon monoxide (TLCO) were all normal.

Because the cough persisted, the patient underwent a chest CT examination in March 2020, revealing an alveolar condensation in the right lower lobe (RLL) and a small pulmonary nodule in the middle lobe (ML). These findings were primarily attributed to a probable infectious origin, leading to a recommendation for symptomatic treatment, and a 6 months follow-up of the patient was recommended.

Since the cough syndrome remained unresolved despite the prescribed treatment, the patient underwent a CT examination six months later, revealing subtle changes in the previously observed abnormalities (Figure 1b). Notably, a new feature observed was aeric bronchogram and tendency to excavate. While this typically suggests a benign nature and supports an infectious origin, however, its appearance in this context arouses interest in a particular way.

After performing a fibrobronchoscopic examination, no macroscopic changes were identified in the bronchial mucosa. Further, a broncho-alveolar lavage (BAL) in the RLL bronchus was attempted and did not reveal any evidence of tumor cells or germs or negative staining for acid-fast bacilli. Consequently, the next diagnostic step involved a surgical procedure to both remove the lesion and determine its underlying cause. Afterward, atypical lower right lobe resection was performed, and histopathological examination confirmed the presence of pulmonary adenocarcinoma as the nature of the lesion.

The scenario in this case is a classic one, where the diagnosis of pulmonary adenocarcinoma is made in a young, non-smoking female who had persistent right basal consolidation. Therefore, it highlights the challenge of distinguishing a rare form of pulmonary cancer, primary adenocarcinoma, where a definitive diagnosis and differentiation from other infectious or inflammatory lung conditions could solely be achieved through a surgical pulmonary biopsy.

Case 2

A 38-year-old patient, a formerly smoker with a 15-pack-year history, who quit smoking two years ago and currently switch to IQOS, with no professional exposure to respiratory irritants, and no significant family or personal medical history, requested a medical consultation due to a lung X-ray that was described as abnormal by the presence of an alveolar consolidation syndrome located in the right lower lobe.

Although the x-ray was modified, the patient does not recognize a definite symptomatology, but on a detailed evaluation, he mentioned episodes of coughing with a mixed character, placed in the context of the fact that he was a smoker until recently. He had been well till five weeks ago when he started reporting profuse night sweats.

Therefore, his x-ray revealed heterogeneous, irregular opacity with features resembling

alveolar consolidation, accompanied by the presence of an air bronchogram, localized in the lower half of the right lower lung field (Figure 2). Later he was admitted to the regional pneumology department to continue the investigations, including a chest CT scan (Figure 3) and bronchoscopy. Following the results of these the patient was diagnosed with right lower lobe pneumonia. It is important to mention a positive culture for Enterobacter spp in the bronchial aspirate, but after 17 days of antibiotic treatment carried out, according to the antibiogram, there were no favorable radiological signs.

In the absence of a clinical and radiological benefit, the patient was referred to our clinic for further investigations. Taking into account several factors, including the disjunction between the radiological findings, highly suggestive of an inflammatory-infectious process, and the lack of clinically suggestive symptoms (such as fever or chest pain), doubled by the absence of any inflammatory markers in the blood tests and the absence of improvement radiological with antibiotic therapy, it was considered that the most appropriate course of action was to refer the patient to a surgical lung biopsy and establish the etiology of the consolidation process located in the right lower lobe (RLL).

The histopathological examination of lung biopsy established a diagnosis of bronchopulmonary neoplasm-Lepidic-predominant adenocarcinoma (LPA) (Figure 4a) with a positive IHC ALK test, EGFR - negative. The patient was further referred to the oncology service for initiating specific therapy. After two and a half months of chemotherapy with oral receptor tyrosine kinase inhibitor including ALK (Crizotinib 250 mg per/day), the patient returns for a pulmonary reevaluation and this time is argued unfavorable evolution through progression of the underlying disease under the current treatment.

Next CT chest scan (Figure 5) revealed the appearance of areas with an infiltrative character and patchy ground glass appearance, both at the level of the right lung and at the lower lobe of the contralateral lung. Hence the patient is guided to seek an oncological re-evaluation with the reconsideration of the therapeutic scheme. After 9 months of treatment, returns once again to the hospital in severe condition. Not only that the cancer was at an advanced stage of progression, with possible bone metastases, but in the context of disease-related immunosuppression, there was also severe lung infection with Staphylococcus Aureus, Klebsiella pneumonia, and Morganella morganii.

Despite the efforts made by the multidisciplinary team that took care of the patient, the evolution was rapidly unfavorable, with deterioration of the

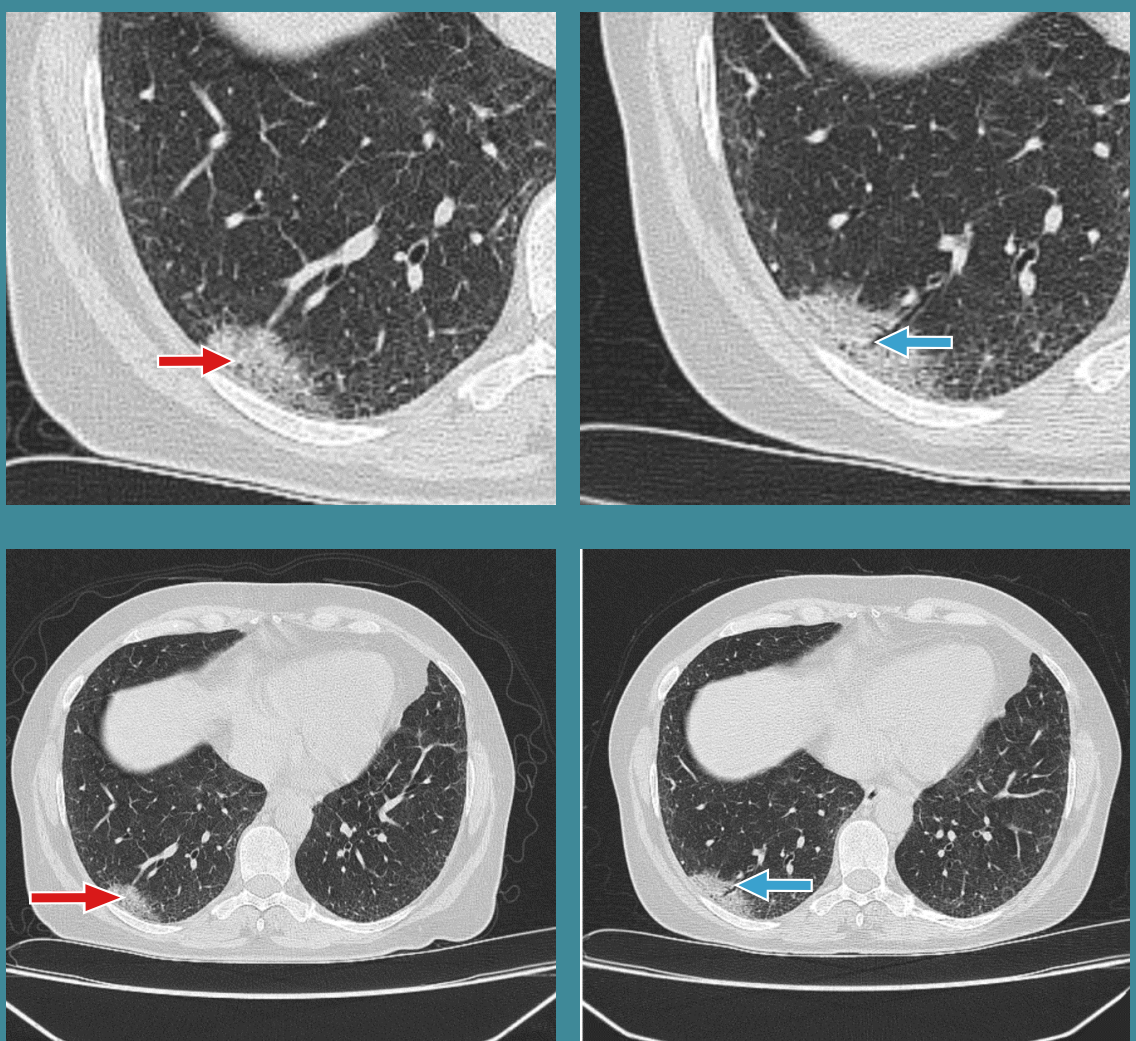

Figure 1. *The right CT scan (June 2020) shows a process of subpleural pulmonary condensation at the RLL level, with suspicious CT features (red arrow), dimensionally stable compared to the left CT scan (march 2020), but with progression through aeric bronchogram (blue arrow)*

respiratory status and the emergence of cardiac arrest.

Case 3

A 71-year-old woman, who has never smoked, but previously had occupational exposure to respiratory irritants as a hairdresser, is known to have a complex medical history due to multiple somatic comorbidities. These include a history of a medium-form SARS-CoV-2 infection in 2020, arterial hypertension, cholecystectomy in 1990, myomectomy in 1994, ovarian cyst surgery in 1983, and thrombophlebitis of the left lower limb in 1990. She was referred to our clinic for evaluation in the context of experiencing a dry cough and mild, nonspecific posterior chest discomfort. Upon physical examination, left basal subcrepitant rales were detected, along with pleural friction. Additionally, there were subtle signs of edema and symptoms of venous stasis of chronic venous insufficiency observed in both legs bilaterally.

The initial CT scan showed lesions that closely resembled those typically associated with a previous SARS-CoV-2 infection. However, during a follow-up CT scan approximately 9 months later, it was observed that some of these post-SARS-CoV-2 infection lesions had started to heal. Notably, there was an exception in the form of an alveolar consolidation process with visible air within the pulmonary bronchogram in the left Fowler segment. This process exhibited dimensional changes despite being treated with antibiotics and oral cortisone for more than a year (as shown in Figure 7).

Following bronchoscopy that did not reveal any cancerous cells and with no evidence of a bacterial infection, the patient was referred to the thoracic surgery clinic for a pulmonary biopsy. During the intraoperative assessment, extemporaneous examination of the biopsy fragment revealed the presence of a tumoral substrate. As a result, left lower lobectomy with mediastinal lymphadenectomy was recommended and performed. Subsequent histopathological examination of the tissue resected during the lobectomy confirmed the nature of the lesion as an adenocarcinoma.

Therefore, the diagnosis of lung adenocarcinoma was established in a female patient who had never smoked, aligning with information found in specialized medical literature, regarding incidence of lung adenocarcinoma.

The results of the immunohistochemical tests did not allow the patient to qualify for molecular targeted therapy, initiating classical chemotherapeutic treatment.

Therefore, 3 years later, the patient is still continuing the maintenance treatment, gaining disease control and a good performance status.

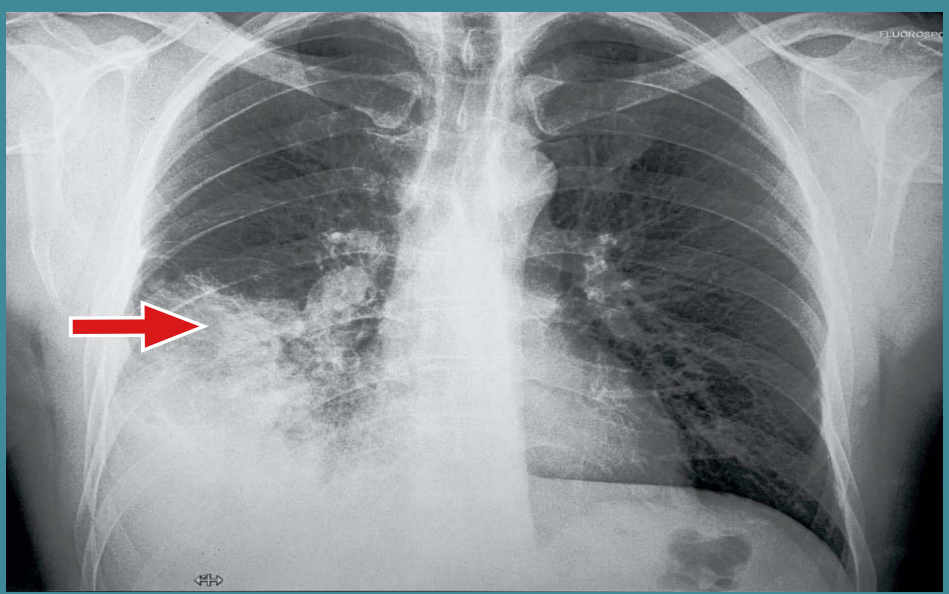

Figure 2. *Chest X-ray (August 2018) showing a non-uniform, unsystematized opacity, of medium intensity, located at the level of the right lung field in the lower half*

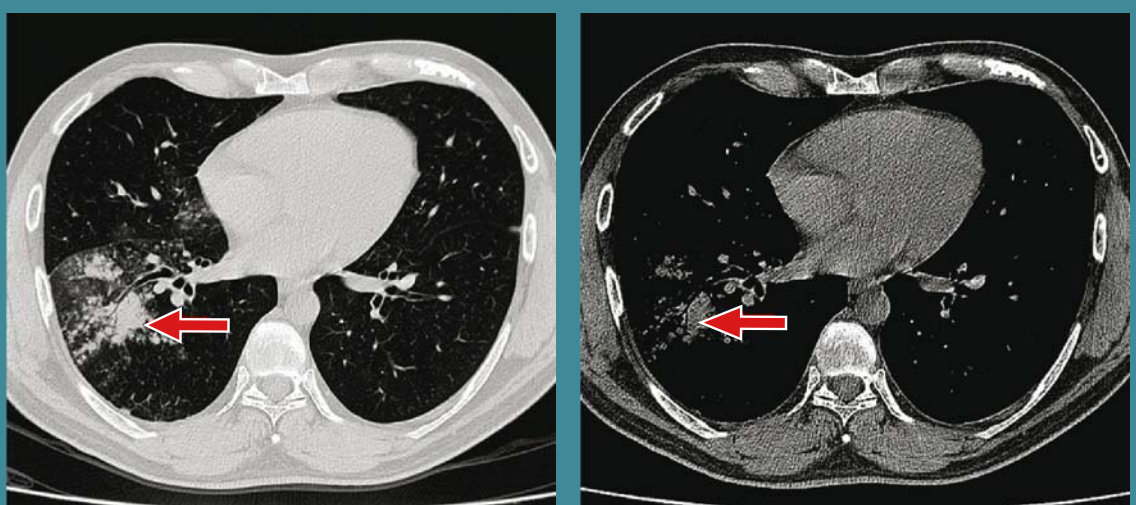

Figure 3. *Chest CT scan with contrast (August 2018) - consolidation process, at the RLL level, at the time believed to be most likely with an infectious or inflammatory substrate*

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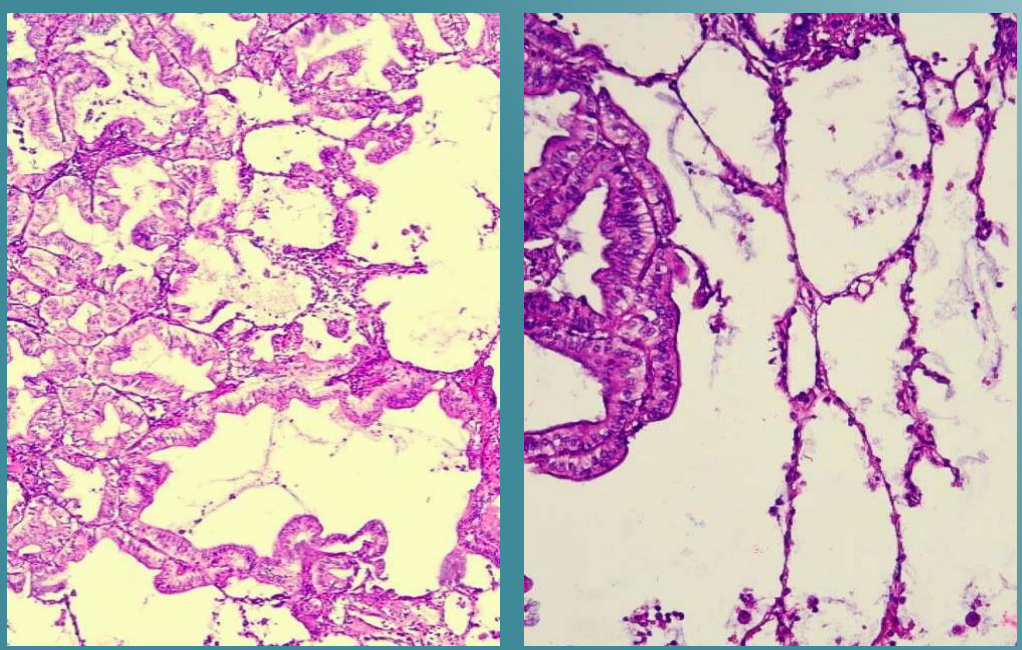

Figure 4. *HP Examination - tumor proliferation represented by a cylindrical carcinomatous cellularity, secreting zonal mucus with predominantly lepidic arrangement;*

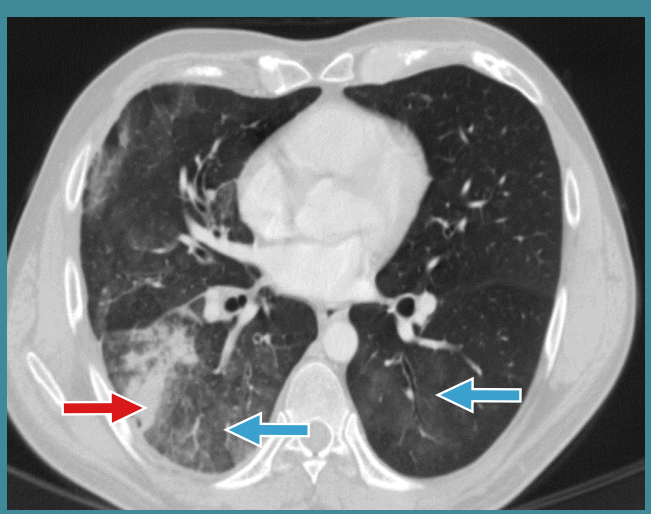

Figure 5. *Chest CT scan with contrast (December 2018) - Regression in intensity and size of the consolidation process in RLL (red arrow), respectively ground-glass opacity (GGO) in RLL and left lower lobe (LLL) (blue arrow)*

Discussion

Lung adenocarcinoma is a subtype of non-small cell lung carcinoma (NSCLC) and accounts for approximately 40% of all lung cancer cases[3]. Other types of NSCLC include adenosquamous carcinoma, squamous cell carcinoma (LUSC), and large cell carcinoma (LCC).

It typically develops in the outer regions of the lungs and exhibits a slower growth rate compared to other lung cancer types. Additionally, there is a higher likelihood of detecting it at an early stage compared to other NSCLCs. In all three cases described above, the initially identified lesions, primary categorized as having an inflammatory or infectious origin, were situated in the outer regions of the affected area, highlighting a clinical picture suggestive for pneumonia.

Therefore, the differential diagnosis of pneumonic processes must be done exhaustively, combining clinical and paraclinical elements, making sure that a possible neoplastic substrate has been excluded. In addition, the differential diagnosis of lung adenocarcinoma typically involves distinguishing it from benign lung lesions, granulomas, hamartomas, metastatic lesions, and pneumonia. A conclusive diagnosis relies on confirmation through histopathological and immunohistochemical methods, although it can be challenging to differentiate between primary pulmonary carcinoma and secondary determinations originating from a carcinoma outside the lungs.

This particular lung cancer is commonly associated with smokers and former smokers, but interestingly, it's also the most prevalent type in individuals who have never smoked. Moreover, it occurs more frequently in women than in men and tends to affect relatively younger individuals compared to other lung cancer types[1,3]. In the previously reported cases, the average age is 53.6 years, according to the statistical data from the literature, with patients also being former smokers or nonsmokers.

Despite the advent of many innovative therapies, the 5-year survival rate still remains relatively low, hovering at approximately 15%. In the last two decades, adenocarcinoma has surpassed squamous cell lung cancer to become the prevailing subtype of NSCLC[1,4].

According to WHO Classification of Lung Tumors, adenocarcinoma can be classified into 4 types, namely, adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma, and other variants of adenocarcinoma[7, 8]. AIS and MIA both exhibit a highly favorable prognosis, boasting nearly 100% 5-year survival rates, and it's worth to notice that both are believed to serve as precursor lesions for more advanced-grade adenocarcinomas[5].

Significant advancements in the recognition and comprehension of "driver mutations" in NSCLC adenocarcinoma have been achieved by researchers. This progress has led to the development of targeted therapies, which constitute a highly precise approach to treating cancer. These include mutations in KRAS (found in approximately 30% of cases), EGFR (in 15-30%), and BRAF (in 5-10%). Additionally, there are rearrangements involving ALK (in 5%) and ROS1 (in less than 2%), among other alterations[3,6]. Other studies have reported EGFR mutations in up to 75% of pulmonary adenocarcinoma, compared to 48.5% in patients with other forms of NSCLC. In order to be able to talk about the treatment of lung cancer, we first must discuss about a correct staging.

Limited disease stages refer to stages I/II/IIIA, and tumors falling into these stages are typically characterized as either limited

invasive tumors (NO) or featuring limited involvement of nearby lymph nodes. The primary goal in such cases is to assess resectability, with a focus on surgical resection and the accompanying sampling of lymph nodes. In cases where surgery is not a viable option, the alternative is to consider radiotherapy, potentially complemented with adjuvant chemotherapy when the patient has affected lymph nodes or is at elevated risk. In certain situations, opting for neoadjuvant chemoradiation may emerge as the most suitable course of action[3,9,10].

Stage III B and Stage IV denote advanced stages in the disease's progression, characterized by the presence of mediastinal, subcarinal, and/or contralateral lymph nodes, along with metastatic disease. Resectability is not a viable option in advanced stages, making chemoradiation the primary consideration. Simultaneously, discussions about palliative care may arise to enhance the patient's quality of life[11].

In a study of 119 patients with confirmed bronchoalveolar carcinoma, Okubo et al reported that patients without symptoms and findings of a mass lesion on chest X-ray had a better prognosis compared to those who were symptomatic and had infiltrative findings on x-ray. It is also mentioned that complete surgical resection in the absence of evidence of lymph node metastases conferred a good prognosis[12].

Conclusions

Even in our non-smoking/ex-smoking patients, disease progression was initially mistaken for pneumonia. As we mentioned previously, in all three cases, the disjunction between X-ray image, absence of an inflammatory-infectious clinical picture, absence of biological inflammatory syndrome, and persistence of the modified radiological image under antibiotic treatment, represented arguments to consider that the diagnosis of pneumonia is unlikely.

The diagnosis could only be confirmed by surgical lung biopsy, which remains the diagnostic gold standard. In addition, lung adenocarcinoma can be confused with a plethora of other diseases, therefore the differential diagnosis needs to be rigorous and definitive.

This disease is very “stubborn”, which is why the faster the diagnosis is made, the faster the treatment can be started. It is important to refrain from hastily categorizing an alveolar process as pneumonia. Instead, I suggest maintaining a vigilant focus on accurately documenting the infectious source.

Conflict of interest

There was no conflict of interest.

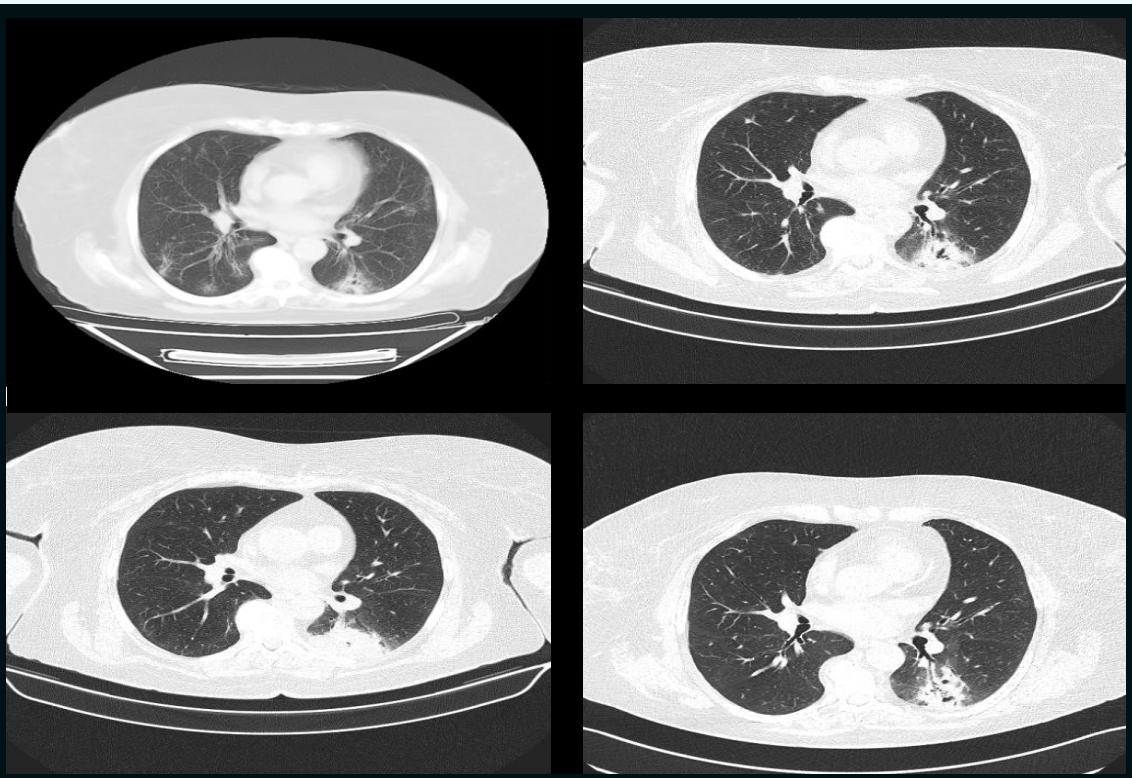

Figure 6. *Multiple CT scans done over the course of a year that initially show the specific post-infection SARS-CoV-2 aspect, but later highlight a pathological process in the left Folwer segment*

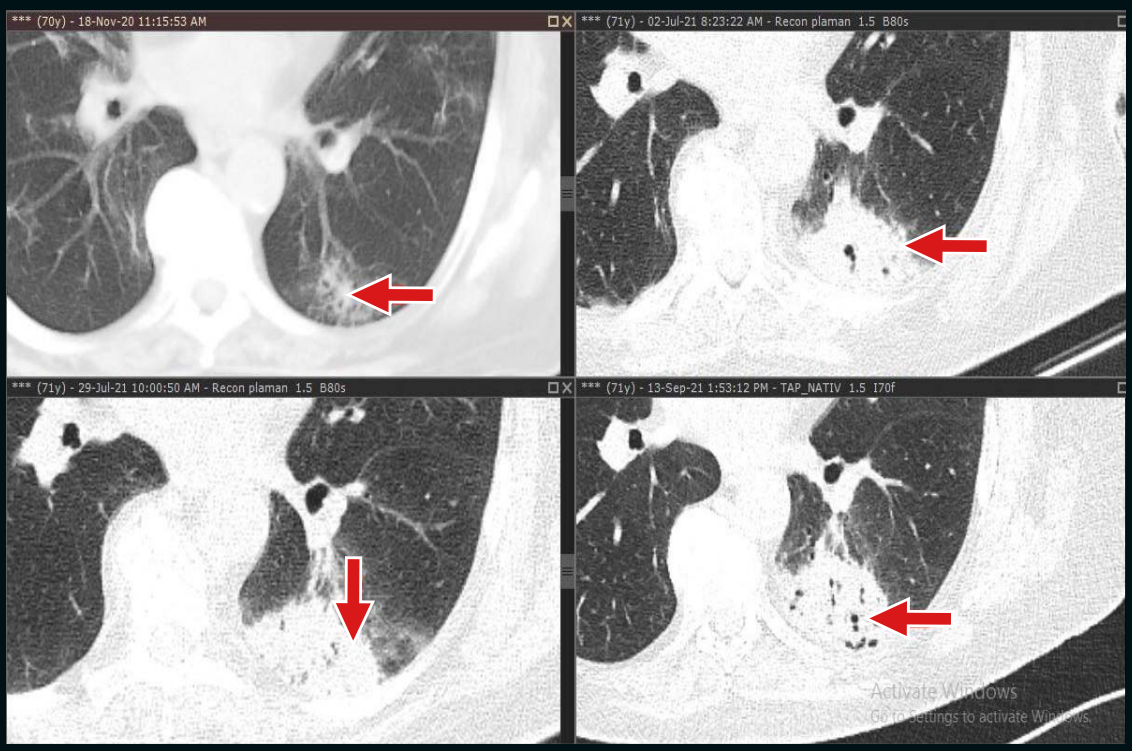

Figure 7. *CT scan evaluations (axial section) throughout the year have shown the progression of alveolar consolidation with air bronchogram in the left Fowler segment, with specific changes in its dimensions (red arrow)*

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