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Prevalence of Benign Diseases Mimicking Lung Cancer: Experience from a University Hospital of Southern Brazil

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Background: Lung cancer is the most lethal type of cancer in the world. Several benign lung diseases may mimic lung carcinoma in its clinical and radiological presentation, which makes the differential diagnosis for granulomatous diseases more relevant in endemic regions like Brazil. This study was designed to describe the prevalence and the diagnostic work-up of benign diseases that mimic primary lung cancer in patients hospitalized at a university hospital from south of Brazil.

Methods: This was a transversal study, which evaluated the medical records of 1,056 patients hospitalized for lung cancer treatment from September 2003 to September 2013 at University Hospital of Santa Maria.

Results: Eight hundred and four patients underwent invasive procedures for suspected primary lung carcinoma. Primary lung cancer was confirmed in 77.4% of the patients. Benign disease was confirmed in 8% of all patients. Tuberculosis (n=14) and paracoccidioidomycosis (n=9) were the most frequent infectious diseases. The diagnosis of benign diseases was obtained by flexible bronchoscopy in 55.6% of the cases and by thoracotomy in 33.4%.

Conclusion: Infectious diseases are the most frequent benign diseases mimicking lung cancer at their initial presentation. Many of these cases could be diagnosed by minimally invasive procedures such as flexible bronchoscopy. Benign diseases should be included in the differential diagnosis during the investigation for primary lung cancer in order to avoid higher cost procedures and mortality.

Keywords: Lung Neoplasms; Mimicking; Respiratory Tract Infections

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Introduction

Lung cancer is a major cause of death among cancer patients[1]. In Brazil, it is the cancer with the second highest incidence in men after skin neoplasias, excluding non-melanoma skin cancer[2]. Some benign diseases can have an unusual presentation, mimicking lung neoplasia in its clinical and radiological manifestations[3,4]. Thus, separately diagnosing malignant and benign conditions is a frequent challenge in clinical practice[5,6].

There should be a balance in the approach to identifying lung lesions and resecting malignant lesions at their initial presentation, and avoiding resecting benign lesion[7]. Differential diagnosis is essential for the adoption of adequate practices[6];

in particular, the distinction between benign and malignant lesions is important because the treatment and prognosis of these two disease groups are distinct[8]. However, lung cancer high incidence and lethality can influence medical decisions and sometimes erroneously direct the diagnostic process to the search for malignant lesions[5,9], without including routine tests to diagnose other diseases. Thus, the diagnosis of a potential benign disease is delayed, which negatively affects its progression, increases hospital costs, and exposes patients to unnecessary risks[7].

There are few Brazilian studies on the prevalence of diseases that mimic lung cancer. These publications mostly consist of case reports and there is no national studies addressing this topic. Moreover, data from the international literature cannot be extrapolated to our reality because many of these diseases have a variable geographical distribution[7], especially infectious diseases endemic to Brazil. Knowledge regarding the prevalence of these diseases within the national epidemiological context is useful for the study of suspected cases of primary lung neoplasm.

Materials and Methods

This study was approved by the Research Ethics Committee of the Federal University of Santa Maria, under number 33554. This is a descriptive cross-sectional study. The data were obtained from medical records of patients hospitalized in the Department of Pneumology at the University Hospital of Santa Maria (HUSM) between September 2003 and September 2013. The HUSM is a tertiary hospital with approximately 300 beds that covers more than 1 million inhabitants in the Central-West region of the state of Rio Grande do Sul, Brazil.

The patients included in this study were ≥30 years old and were hospitalized at the HUSM with suspected primary lung cancer, which was suspected if there was a new lung nodular opacity or mass with one of the following findings: hemoptysis, digital clubbing, or weight loss. They underwent invasive diagnostic procedures, including the collection of material for anatomopathological and/or cytopathologic analysis.

These patients were selected from the electronic database of the Information System for Education (SIE) and the search was restricted to the cytopathologic results of specimens collected by fibrobronchoscopy, digital radiography and ultrasound-guided transcutaneous puncture as well as anatomopathological results of lung biopsies obtained via open surgery, fibrobronchoscopy, ultrasound-guided transcutaneous biopsy, and computerized tomography.

A subpopulation of patients for whom cancer diagnosis was excluded via invasive tests was formed and the diagnosis of benign disease was confirmed through pathology or other complementary tests. Carcinoid tumors were considered as malignant lesions when classified as atypical carcinoid tumors due to their aggressive behavior, high metastatic potential, and low mean disease-related survival. Typical carcinoid tumors were considered as benign lesions because they present a good prognosis after surgical treatment, with a reported survival of up to 100% 5 years after resection[10].

Patients who were less than 30 years old, those with previous malignant neoplastic disease and without filling lung cancer suspected criteria were excluded from the study.

The medical records of the patients included in the study were reviewed and epidemiological data, diagnosis, radiological characteristics of the lesion, and its location as well as the diagnostic method used were recorded. Subsequently, the collected information were tabulated and analyzed through descriptive statistics using the Statistica StatSoft, Inc. (2009) version 9.1 and the BioEstat 5.0 software (Instituto Bioestatístico de Ciência e Tecnologial, 2007).

Results

We identified 1,056 patients who underwent invasive diagnostic procedures and had anatomopathological and cytopathologic test results available in the SIE between September 2003 and September 2013. Of these patients, 252 patients who met the exclusion criteria were excluded and the medical records of 804 patients with suspected primary lung cancer were analyzed.

Definitive diagnosis was obtained in 676 cases (84.1%) and 128 patients (16%) had an inconclusive diagnosis. The group of patients without diagnosis included those who were still undergoing investigative tests, who refused to continue the investigation, or who died without a diagnosis for the suspected lesion. Among patients with established diagnosis, lung neoplasm was confirmed in 622 patients (92.1%) and benign disease was confirmed in 54 patients (8%).

The mean age of the patients with a benign disease diagnosis was 57 years (range, 36–79 years), there was a predominance of males (78%) over females (22%) and 83% of patients had a history of smoking. In most cases, benign diseases had radiological presentation of pulmonary nodule (31.5%), followed by single mass (24.1%), and were found in the lung right superior lobe (20,4%), left superior lobe (11.1%), and right inferior lobe (11.1%).

The most frequent diseases were tuberculosis in 14 cases (25.9%), paracoccidioidomycosis in nine cases (16.7%), hamartoma in four cases, and typical carcinoid tumor in four cases (7.4%) (Table 1).

The most frequent subgroup of benign lesions was infectious diseases (55.6%) followed by benign neoplastic diseases (16.7%) and inflammatory diseases (14.9%).

The most frequent infectious disease was tuberculosis in 14 patients, accounting for 46.7% of infectious causes, followed by paracoccidioidomycosis in nine patients (30%) and cryp-

Table 1. Benign diseases diagnosed

Disease	No. (%)
Tuberculosis	14 (25.9)
Paracoccidioidomycosis	9 (16.7)
Hamartoma	4 (7.4)
Typical carcinoid tumor	4 (7.4)
Foreign body	3 (5.6)
Amyloidosis	3 (5.6)
Organizing pneumonia	3 (5.6)
Inflammatory pseudo tumor	2 (3.7)
Cryptococcosis	2 (3.7)
Vasculitis	1 (1.9)
Histoplasmosis	1 (1.9)
Actinomycosis	1 (1.9)
Hydatidosis	1 (1.9)
Fungal ball	1 (1.9)
Middle lobe syndrome	1 (1.9)
Pulmonary infarction	1 (1.9)
Aspiration pneumonia	1 (1.9)
Rheumatoid nodule	1 (1.9)
Solitary fibrous tumor	1 (1.9)
Total	54 (100)

Table 2. Benign diseases diagnosed by fibrobronchoscopy

Disease	No. (%)
Tuberculosis	10 (33)
Paracoccidioidomycosis	7 (23)
Typical carcinoid tumor	4 (13)
Foreign body	2 (7)
Amyloidosis	2 (7)
Cryptococcosis	2 (7)
Other	3 (10)
Total	30 (100)

tococosis in two patients (3.4%). Fungal diseases, examined together, accounted for 43.4% of the infections and were only less prevalent than tuberculosis.

The diseases that mimicked cancer were mostly diagnosed via fibrobronchoscopy (55.6%), of which 15 cases were diagnosed by bronchoalveolar lavage and 15 by endobronchial biopsy, followed by surgical procedures (33.3%). Computerized tomography-guided biopsies accounted for only 5.6% of these diagnoses (Table 2, Figures 1–3).

Discussion

Lung cancer is a frequent condition observed in pneumologist and thoracic surgeon clinical practices. Its prevalence and lethality are a matter of intense concern. Several diseases mimic this condition. These are mostly of infectious etiology and vary according to the epidemiological characteristics of a given region[11,12].

In a study conducted in North America, Smith et al.[7] found that 9% of benign diseases mimic primary lung cancer. Rolston et al.[8] observed a 6.7% prevalence of benign diseases mimicking primary lung cancer. These findings are very similar to ours, which showed an 8% prevalence. However, we observed an important difference in the etiology of these benign lesions when compared to the North American data. Tuberculosis was the most frequent cause of benign diseases observed in our study, which suggests that geographical factors, in particular those associated with infectious diseases, have an essential role in this context.

Factors associated with national epidemiology such as high incidence of granulomatous infectious diseases that present with findings indicative of neoplasm such as tuberculosis, paracoccidioidomycosis, histoplasmosis, actinomycosis, and cryptococcosis tend to increase even further the importance of differential diagnosis in cases of suspected lung cancer.

The tuberculosis incidence rate in Brazil was 35.8/100.000 habitants in 2012[13], already the incidence of paracoccidioidomycosis is not well established, being estimated at 1–3/100.000 habitants[14]. These two diseases were the most common infectious etiologies observed in our study, which is in contrast with the study by Smith et al.[7] where no cases of these diseases were described. Rolston et al.[8] reported that tuberculosis accounted for only 27% of infectious causes and was surpassed by fungal diseases. However, no case of paracoccidioidomycosis was observed.

Taken together, non-infectious benign conditions form an important subgroup, accounting for 44.5% of benign causes. However, it is difficult to compare the prevalence of each disease with that reported in the literature because of the lack of detailed data[7,8].

With regard to diagnostic methods, we highlighted the importance of fibrobronchoscopy in the assessment of suspected lung cancer lesions. This minimally invasive method was used for the diagnosis of more than half of the patients studied (55.6%), and there was no record of procedure-related complications. The need for surgical samples was relatively high in our study (33.4%). However, studies published prior to the use of computerized tomography, have described up to 64% of samples from surgical material[3,15]. In addition, a significant reduction in the use of invasive procedures to establish a diagnosis of lung lesions has been observed in recent decades. Currently, the need for surgery is approximately 9%[7]. This re-

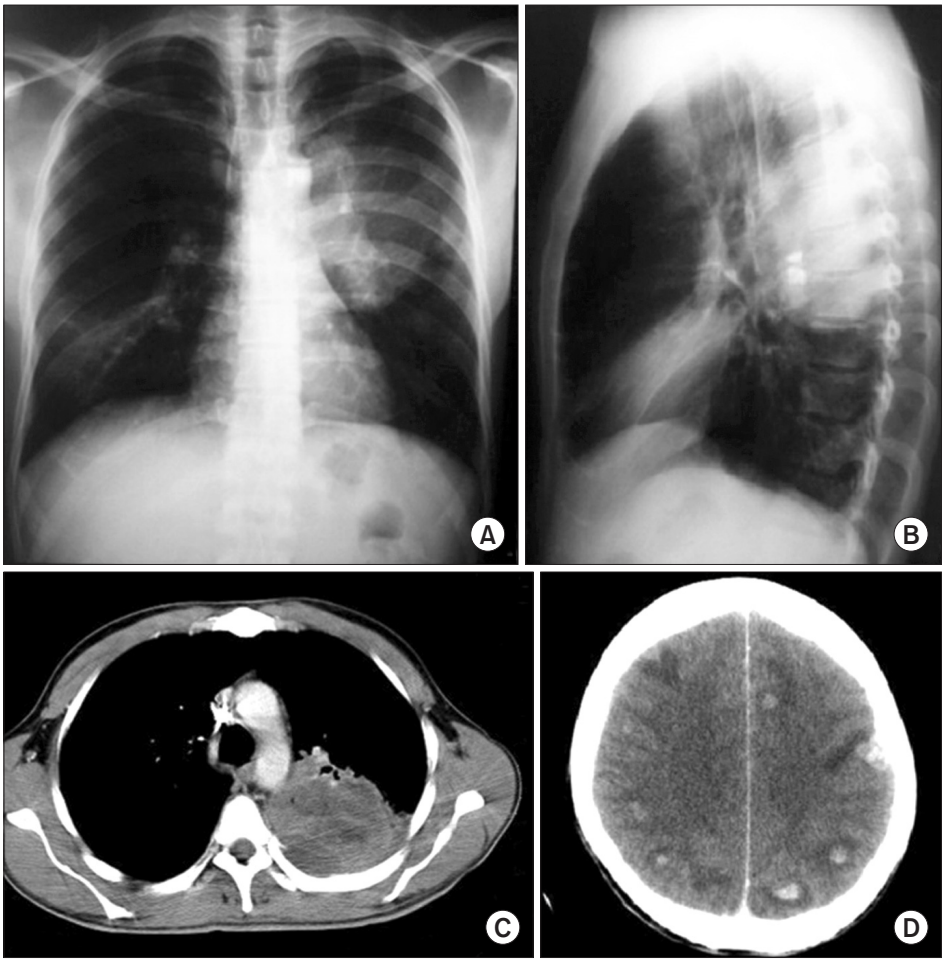

Figure 1. Chest radiographs and chest and skull computed tomography (CT) scans of a 36-year-old male, smoker, with progressive dyspnea, weight loss, and productive cough. (A, B) Chest radiograph with opacity in the inferior lobe and in the left superior lobe. (C) Chest CT scan with voluminous lesion in the left lung. (D) Skull CT scan with nodular lesions in the brain hemispheres. Fibrobronchoscopy with biopsy of polypoid lesion in the bronchus of the left inferior lobe identified *Cryptococcus* sp. cultured with *C. gatti* growth.

duction is probably a result of the improvement and dissemination of less invasive methods with excellent diagnostic yield such as computerized tomography or ultrasound-guided core lung biopsy[16].

In all cases of suspected cancer, it is important to obtain the patient's epidemiological and occupational information to estimate the risk of cancer and to perform an accurate analysis of the clinical and radiological presentation of the disease[7,17]. This information includes factors related to malignancy such as smoking history (in packets/yr), familial and personal history of cancer, advanced age, consumptive symptoms, and hemoptysis[17-19]. Moreover, it should be investigated whether the patient was in endemic regions for systemic mycoses, especially for men living in rural areas[20]. Similarly, history of exposure to endemic regions for tuberculosis and, particularly, of contact with patients known to have the bacillus can suggest tuberculosis infection. Alcoholism, poor oral hygiene, and history of orofacial trauma are indicative of actinomycosis[11].

In this study, the patients with benign lung disease exhibited a high prevalence of smokers (83%). The fact that the majority of patients were men (78%) and farmers (73%), and that the South region of Brazil is an endemic area for paracoccidioidomycosis[14,20] explains the high incidence of this disease, as opposed to the series of cases previously reported in the literature[7,8].

The high number of inconclusive results in pathological analyses could be considered as one limitation of this study. Many of these could indicate benign diseases mimicking cancer due to the absence of malignant cells in the analyzed samples, which would increase the prevalence of these diseases in the study. However, these results were not included owing to the absence of an accurate diagnosis. Despite this limitation, the persistent search for differential diagnoses through a diagnostic routine provided a significant number of alternative diagnoses, and the rate of benign conditions was similar to North American studies. This demonstrated that the search for differential diagnoses should not be limited by the lack of complementary tests and that other methods that may be more invasive, but that detect the cause of the disease, should be used to offer an appropriate treatment to the patients.

In conclusion, this study reinforces that the diagnosis of diseases that mimic lung cancer depends on their geographical

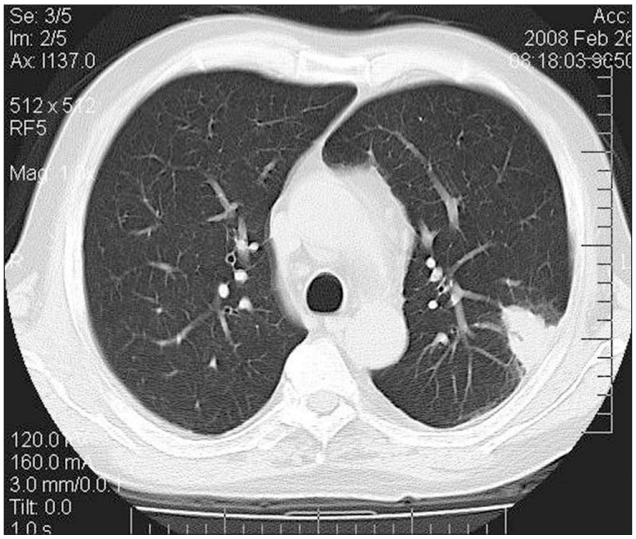

Figure 2. Chest computed tomography (CT) scan of a 59-year-old patient, ex-smoker, retired farmer with evening fever for 2 weeks, weight loss, and pleuritic pain. Chest radiograph with nodular lesion in the left inferior lobe. Chest CT with juxta-pleural lesion in the left inferior lobe. A thoracotomy biopsy was performed. The histopathologic analysis showed granulomatous processes with areas of necrosis and fungus consistent with *Paracoccidioides brasiliensis*, confirmed by fungus growth in Sabouraud agar.

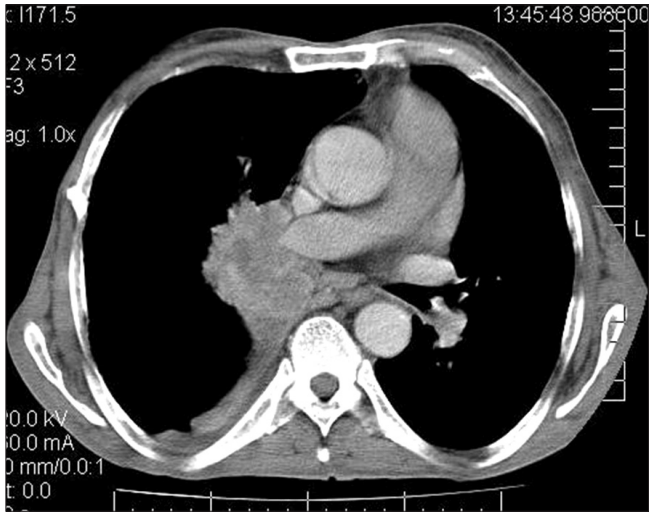

Figure 3. Chest computed tomography (CT) scan of a 70-year-old patient, retired farmer, smoker, alcoholic exhibits symptoms compatible with chronic obstructive pulmonary disease, progressing with loss of weight, cough, hemoptysis, and increased dyspnea. Chest radiograph with right perihilar opacity. Chest CT confirmed the finding. Fibrobronchoscopy with endobronchial biopsy of the lesion was performed and showed the presence of acid-fast bacilli, with confirmation of *Mycobacterium tuberculosis* in culture media.

distribution and that infectious diseases, in particular tuberculosis and paracoccidioidomycosis, should always be taken into consideration in the differential diagnosis of patients with suspected pulmonary neoplasm. In addition, a diagnostic routine for these diseases, with the adequate collection and storage of clinical specimens and laboratory evaluation using adequate staining and culture media, can lead to a diagnosis without the need for high-cost procedures.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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