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Synchronous multiple primary pulmonary neoplasms. hamartoma as the main tumor and pulmonary adenocarcinoma

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Abstract: The presence of the multiple primary lung neoplasms is a rare event, with few series described in the literature. These can manifest synchronously, or metachronous, the latter being is the most common. The prognosis in the patients with synchronous tumors appears to be more unfavorable than in the patients with a single lung neoplasm. Method: Because it involved bioethical aspects, the research complied with the ethical-bioethical principles, was carried out attentive to ethical-moral objections, and also under the focus of the current regulations (requirements of the Good Clinical Practices-GCP-, and adherence to ethical-bioethical principles originating in the Helsinki Declaration and the habeas data law). The Informed consent was obtained from the patient through which all information about the risks and the benefits was provided, as well as full autonomy to accept or reject the research as well as anonymity. Likewise, the case was approved by the bioethics committee. Clinical case: Patient with a preoperative histopathological diagnosis of hamartoma-type lung neoplasia. The surgery was carried out through the right lower lobectomy through posterolateral thoracotomy (Sweet). The postoperative evolution was satisfactory and the pathological and the immunohistochemical diagnosis reported primary multiple pulmonary neoplasia hamartoma and adenocarcinoma as the synchronous one, the two lesions being of different origin. Conclusion. The multiple primary lung neoplasia is a rare form of presentation, such as at the hamartoma with focal acinar-type lung adenocarcinoma, which is difficult to diagnose on certain occasions and has a reserved prognosis.

Key words: multiple primary neoplasia; lung; hamartoma; synchronous

1 Introduction

Multiple primary lung neoplasms are a rare condition, with an incidence ranging from 0.5% to 3.5% of all lung neoplasms according to sources consulted, primarily surgical series and/or autopsy reports; therefore, they can be considered a rarity, with few cases described in the literature. They may present synchronously (simultaneous onset) or metachronously (with an interval of more than two years between onset), the latter being the most common. Their highest incidence is observed in heavy smokers [1].

In turn, a distinction can be made between synchronous neoplasms, in which these tumors occur simultaneously, and metachronous neoplasms, in which there is an interval of more than approximately two years between the detection of the first and the second tumor. It is precisely the latter that are most common, accounting for between 55% and 70% of cases,

according to different series [1,2].

The diagnostic criteria for multiple primary lung neoplasms were established by Martini and Relamed (1975), although they clearly defined and established the differences between synchronous and metachronous neoplasms. Subsequently, other authors have made some modifications to this classification, such as Antaki et al., which were accepted by most authors; however, today there is no unified model for diagnosis, which, combined with the variability of the studied series, could explain the differences observed regarding their prevalence. However, a distinction can be made between synchronous neoplasms, if they occur simultaneously, or metachronous neoplasms, if the interval between their onset is greater than two years; the latter is the most common presentation, generally diagnosed in patients who have undergone surgery and in whom a new lung infiltrate appears on follow-up radiological examinations [3,4].

The most common location for multiple primary lung neoplasms is in the upper lobes, and when they tend to present synchronously, they usually do so in the same lung. This is because, in most cases, there is a clustering or association of more than one oncogenic factor over an extended period of time, with tobacco use being, in essence, the primary one. Smith Abbey established an average tobacco consumption of forty cigarettes per day in patients with multiple primary lung neoplasms, finding no cases of nonsmoking patients.

Thus, there is a clear gender predominance, with a higher incidence in males: the ratio is 3:1. Multiple primary lung neoplasms have a particularly high incidence in the sixth decade of life, and, furthermore, patients share a significant smoking habit, which is due to the presence of multiple known carcinogens in cigarette smoke. In our case, the patient was a 70-year-old former smoker of fifty (50) packs per year, with no other oncogenic stimuli from continuous exposure clearly identifiable [4,5].

The association of these two neoplasms—hamartoma and adenocarcinoma—as occurred in our case may be coincidental or due to the existence of a common risk factor for the development of both. The likelihood that this is a coincidence is higher if these two entities are located in anatomically distant sites, whether in different lungs or in different lobes of the same lung, whereas if they are adjacent or in the same lobe, one may speculate that they are related [6,7].

From a pathological perspective, there have been variations and changes regarding the most common histology. However, decades ago, squamous cell carcinoma was considered the most common histological type among the two neoplasms (primary and secondary); nevertheless, more recent studies show a higher incidence of adenocarcinoma. Between 50% and 70% of patients show similarities in their pathological anatomy; in both neoplasms, there is a clear predilection for the upper lobes. However, cases with different histological origins may be found between the two, which would not raise doubts regarding the diagnosis. Therefore, it must be noted that bronchoalveolar carcinoma is excluded here due to its tendency to present bilaterally [8].

The objective is to present a clinical case of interest due to this type of presentation in a patient with multiple primary lung neoplasms, with hamartoma as the primary tumor associated with focal acinar-type lung adenocarcinoma (non-small cell), and we reviewed the literature on this topic.

2 Case report

A 70-year-old female patient with the following history: former smoker (50 pack-years), moderate COPD, controlled hypertension, and type 2 diabetes mellitus. She presented with a persistent dry cough, and her physical examination was unremarkable. She denied hemoptysis, thoracic pain or constitutional syndrome. She consulted a physician who ordered a posteroanterior chest X-ray film, revealing an oval, radiopaque, mass-like parenchymal lesion with smooth margins, located in the basal lateral segment of the right lung (Figure 1).

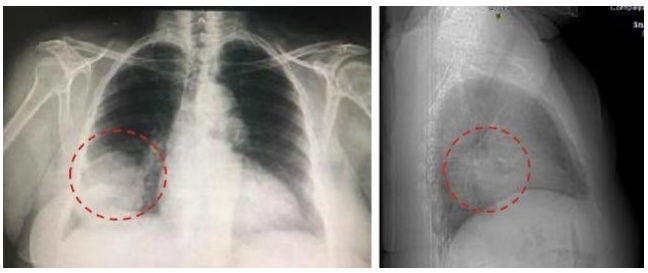

Figure l. Chest X-ray, posteroanterior view; oval mass-type parenchymal lesion, radiopaque, with smooth borders, located in the lateral basal segment of the right lung.

Study performed using a GE multidetector CT scanner, model LIGHT SPEED VCT 64, chest CT scan® . An image is observed that is isodense to soft tissue, irregular, poorly defined, and heterogeneous, with areas of lower density that could correspond to cystic degeneration and/or necrosis, as well as internal calcifications. The lesion is related to the pleura and fissure, measuring 9.3 cm x 6.7 cm x 6.3 cm, for an approximate volume of 204 cm^3 . This raises the diagnostic possibility of a primary infiltrative process; pulmonary hamartoma is less likely. A histopathological examination is recommended for better characterization (Figure 2).

The first diagnostic possibility suggested by the radiologist on the CT scan was hamartoma, and he recommended a core needle biopsy (CNB) to confirm the diagnosis. She was referred to the thoracic surgery department, where this option was presented to the patient, who agreed to undergo a CT-guided transthoracic fine-needle biopsy (14 G); the results were reported as consistent with hamartoma versus pulmonary lipoma, and malignancy was not ruled out (Figure 3).

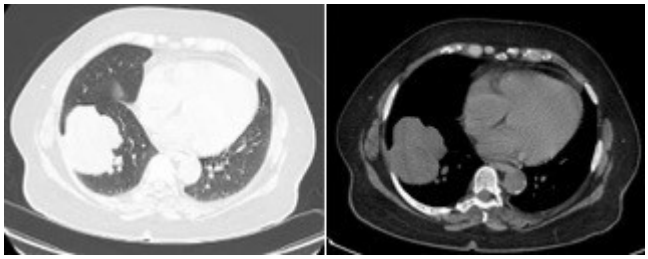

Figure 2. Computed tomography: (A) axial section, showing a mass-like lesion with heterogeneous density and irregular, popcorn- like margins, measuring 26 mm × 21 mm

Figure 3. Automatic disposable biopsy device (BARD-MONOPTY®). 14 gauge. Micrograph: histological section shows a neoplasm consistent with hamartoma versus pulmonary lipoma; malignancy was not ruled out.

For this reason, surgical treatment was proposed, which the patient accepted, and a right posterolateral thoracotomy (Sweet incision) with inferior lobectomy was performed; the resected specimen was fixed in formalin.

The surgical specimen was sent for anatomopathological and immunohistochemical examination: MRFF consisting of the right upper pulmonary lobe, measuring 12 cm x 6 cm x 3 cm; the external surface is smooth and grayish-brown; on sectioning, a well-defined, tumor-like lesion measuring 8 cm x 5 cm x 3 cm is observed, with a heterogeneous appearance

and areas of mucoid and cartilaginous appearance (Figure 4).

Biopsy sections of lung tissue reveal a benign, well-circumscribed mesenchymal lesion composed of hyaline cartilage, fibro-adipose tissue, and bland spindle cells in a myxoid stroma. The mesenchymal elements appear to entrap the respiratory epithelium, which is largely benign and composed of cuboidal cells. Focally, the epithelium is replaced by anaplastic cylindrical cells with pleomorphic and hyperchromatic nuclei— some vesicular with irregular chromatin, mostly with prominent nucleoli — with few atypical mitoses, arranged at different heights, and with amphophilic cytoplasm. There is evidence of thickening of the surrounding fibrous septa and abundant histiocytes laden with anthracotic pigment, as well as accumulations of lymphoplasmacytic infiltrate.

From an immunohistochemical perspective, the tumor cells were positive for broad-spectrum cytokeratin AE1/AE3 (3+), CEA (3+), and TTF1 (2+). Calretinin was negative. The cells corresponding to the mesenchymal lesion showed focal positivity for ER (2+), PR (2+), and AR (2+). Diagnosis: consistent with synchronous pulmonary hamartoma with focal acinar-type pulmonary adenocarcinoma (non-small cells) (Figure 5).

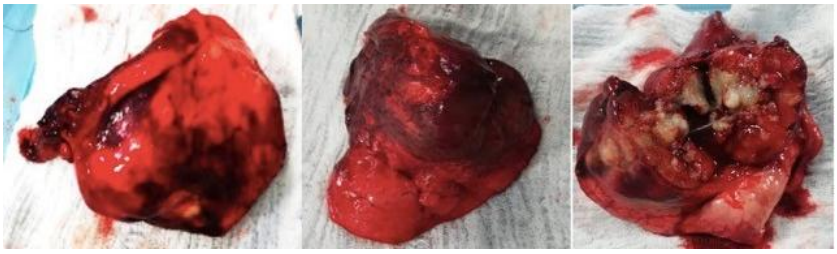

Figure 4. Surgical specimen. Right upper pulmonary lobe, 12 cm x 6 cm x 3 cm. The outer surface is smooth and grayish-brown. On sectioning, a well-defined, tumor-like lesion measuring 8 cm x 5 cm x 3 cm is observed, with a heterogeneous appearance and areas of mucoid and cartilaginous appearance.

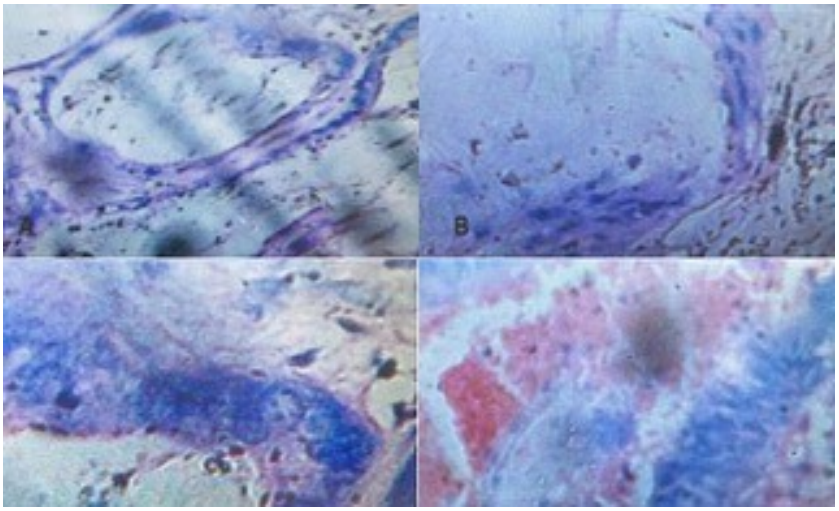

Figure 5. Microphotograph: histological section stained with hematoxylin-eosin (10x). Neoplasia is evident: (A) Hamartoma as the primary neoplasm (B). Focal acinar-type pulmonary adenocarcinoma as a synchronous neoplasm (10x).

Course of the disease. The patient described in this article had a satisfactory postoperative course, with no dyspnea and minimal pain. Forty-eight hours after admission, following radiological control, the chest tube was removed, and the patient was discharged from the hospital. She has remained asymptomatic to date. The clinical and morphological characteristics of this case suggest that it involves a pulmonary hamartoma as the primary neoplasm with focal acinar-type lung adenocarcinoma as a synchronous neoplasm.

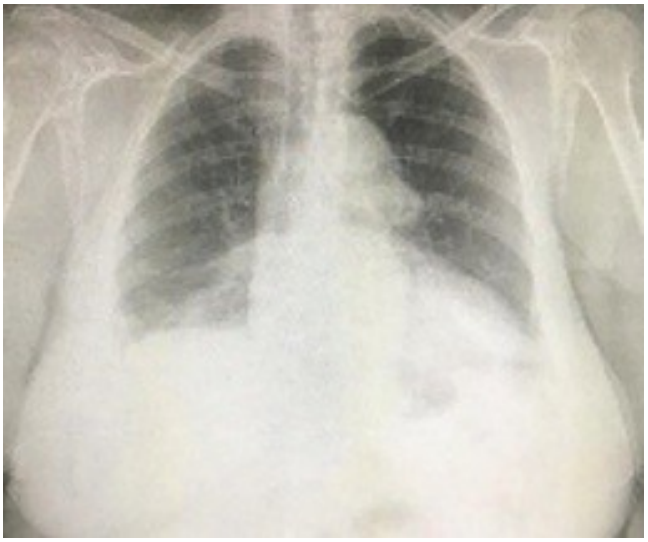

Figure 6. Postoperative follow-up anteroposterior chest X-ray six months later

3 Discussion

Multiple primary neoplasms as a phenomenon in a single individual were originally described by Billroth in the late 19th century, but it was Warren who first outlined the diagnostic criteria for defining them in 1932. The estimated incidence of multiple primary neoplasms varies. The literature reports that this clinical entity may occur in 2%–12% of cancer patients. Various theories have been proposed to explain the origin of multiple neoplasms, but none have been proven, although the main risk factors appear to be smoking and family history.

The incidence of multiple primary tumors, as well as secondary primary neoplasms, has increased in recent decades and is the focus of our review. The detection of multiple lung tumors is a rare occurrence. The first case of multiple primary lung cancer was reported by Beyrenther in 1924. Synchronous multiple primary lung neoplasms account for 0.26%–1.33% of all lung tumors, and bilateral involvement accounts for 60%–70%. The unilateral form is rare, and its most common location is in the upper lung lobes [8] .

Multiple primary tumors can be defined as the coexistence of more than one primary neoplasm in different organs, or the coexistence of two or more primary neoplasms of different cell types in the same organ. However, all multifocal neoplasms in the same organ (bladder tumors), simultaneous neoplasms in the same organ or in paired organs (breast cancer), asynchronous neoplasms in the same organ or in paired organs (colon polyps), and progressive neoplastic disease (cervical carcinoma in situ and, subsequently, cervical carcinoma) [9].

It is relatively rare for more than one primary tumor to be present at the time of diagnosis, i.e., a synchronous tumor; its incidence ranges from 1% to 2% in the case of synchronous neoplasms. This is why the most commonly used diagnostic criteria in the literature to classify two or more tumors as synchronous have been defined by Wu: 1. Each tumor must be malignant. 2. The tumors must be anatomically distinct and separate. 3. The tumors must be histologically different. 4. If the histology is the same in synchronous tumors, each tumor must have its own site of origin, without invading lymph nodes. 5. Each tumor must have its own metastases. 6. No evidence of extrapulmonary metastases. However, these criteria may vary slightly from one study to another [9,10].

The most common histological type in synchronous tumors is squamous cell carcinoma; approximately half of patients have tumors of the same histological type. When tumors have different histological types, the most common combination is squamous cell carcinoma with another histological type. regard to location, the lesions most frequently

appear in the same lung in nearly 50% of cases; generally, the left upper lobe is the most commonly affected. In most cases, the diagnosis is made based on chest X-rays and CT scans, although in many cases the diagnosis is reached intraoperatively or through pathological examination of the resected specimen [11].

Multiple mechanisms have been described in the pathogenesis of the increased incidence of multiple tumors, including hereditary, immune, environmental, tobacco, viral, chemotherapy, and ionizing radiation factors. This increased risk applies to second primary tumors related to smoking. However, the duration of smoking and the number of cigarettes smoked per day (cpd) influence the development of lung cancer. The more a person has smoked prior to the development of an initial primary neoplasm or tumor, the higher the likelihood or probability of developing a second primary neoplasm, and a longer follow-up period increases the probability of detection [12,13].

Another factor that could contribute to the development of specific types of second primary tumors is strongly linked to the patient's age at the time of diagnosis of various tumors over the years, particularly in recent decades, and includes the accumulation of free radicals, which may lead to errors in DNA replication. Another cause of tumors in older age may be lipid-laden macrophages, which are more prevalent in the elderly and impair the host's immune system function, such as a specific hormonal environment, immune status, and genetic inheritance [14] .

The treatment of choice is surgery, whether through formal resections (pneumonectomy, lobectomy, bilobectomy, segmentectomy), more economical resections, or a combination of both. No significant differences have been found in the survival curves of patients treated with formal resections and those who underwent a more economical resection, provided that the tumor could be completely resected. Although the diagnosis of the disease is usually made on a specimen sent to the pathology department [16].

We describe the case of a 70-year-old female patient with a history of smoking. During an evaluation with preoperative imaging studies—including plain radiography and chest computed tomography—a solid, oval pulmonary mass with irregular, "popcorn-like" margins was observed; it was hypodense, heterogeneous, and had a possible diagnosis of pulmonary hamartoma. Therefore, a CT-guided core-needle biopsy was performed, which reported a pulmonary hamartoma-type neoplasm in the right lower lobe. Consequently, the treatment of choice was surgery, specifically resection via lobectomy of the right lower lobe. The results of the postoperative pathological studies, including immunohistochemical findings, reported a diagnosis of pulmonary hamartoma as the primary neoplasm, with focal acinar-type lung adenocarcinoma (non-small cell) as a synchronous neoplasm.

Multiple primary lung neoplasms are a rare clinical presentation, such as a hamartoma with focal acinar-type lung adenocarcinoma; which is sometimes difficult to diagnose and carries a guarded prognosis. For these reasons, they require the specialized expertise of a pulmonologist. Thus, a detailed medical history and the development of relatively straightforward diagnostic algorithms would allow for differentiation between metastatic, synchronous, or metachronous tumors.

Multiple primary lung neoplasms can be classified as synchronous or metachronous, and the management of these patients remains a challenge. However, the use of high-resolution computed tomography has improved diagnostic capabilities.

The patient in this case had a good postoperative course and has remained asymptomatic to date. The clinical and morphological characteristics of this case indicate that it is a benign pulmonary tumor of mesenchymal origin, specifically a pulmonary hamartoma with a focal acinar-type lung adenocarcinoma. Hamartomas are rare benign tumors compared to malignant lung tumors; due to their central location, they are difficult to diagnose with transthoracic biopsy and may be misinterpreted, so resection is recommended.

The thoracic surgeon plays an essential role in the management of patients with multiple primary tumors and secondary primary tumors and must be aware of this responsibility. Oncological follow-up is currently conducted almost exclusively with regard to recurrence or metastasis of the primary cancer, and subsequent malignant diseases occurring during follow-up have not been considered relevant.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Additional information

Declaration on ethical aspects: As it involves bioethical issues, the research complied with ethical and bioethical principles, was conducted in accordance with ethical and moral considerations, and likewise under current regulations (requirements of Good Clinical Practice – GCP – and adherence to ethical-bioethical principles originating from the Declaration of Helsinki and habeas data legislation). The implications and purpose of the research were explained to the patient. For its implementation, informed consent was completed by the patient, through which all information regarding risks and benefits, as well as anonymity, was provided. The patient had full autonomy to accept or reject the research. The case was approved by the bioethics committee.

Ethical responsibilities, protection of human subjects and animals: The authors declare that no experiments on humans or animals were performed for this research.

Data confidentiality: The authors declare that they have followed the protocols of their workplace concerning the publication of patient data.

Right to privacy: The authors declare that no patient data appear in this article.

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