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Case report

Synchronous mucinous and non-mucinous lung adenocarcinomas with different epidermal growth mutational status

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ABSTRACT

In recent years, the spread of more-sensitive diagnostic methods has resulted in an increase of synchronous multiple primary lung cancer diagnosis. Nevertheless, its occurrence is still rare. Distinction between synchronous lesions from second independent primary tumors is a problem when dealing with multiple lung tumors, particularly if the histological type is the same. We present a case report of a 78-year-old female patient referred to our institution due to pneumonia. A subsequent thoracic computed tomography (CT) was performed showing two suspicious lesions, one in the right upper lobe and the other in the right inferior lobe. The CT-guided transthoracic needle biopsy of both pulmonary lesions revealed two adenocarcinomas, but with a rare combination of distinct morphologic variants, as well as different immunophenotypes and epidermal growth factor receptor (EGFR) gene status. The patient refused surgery and was submitted to stereotactic body radiation therapy (SBRT). She maintained tight follow-up and until now, she has not shown any signs of relapse or metastasis. A multidisciplinary approach with clinical, morphologic and molecular evaluation in multiple lung cancer is important to diagnosis and treatment guidance.

1. Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide [1]. Lung adenocarcinoma is the most common form of lung cancer and comprises a group of diseases with heterogeneous clinical and pathological characteristics [2]. Specific histogenetic types of adenocarcinoma, genomic profiles and cancer signaling pathways have been clarified [3–5]. Thus adenocarcinoma has been subject to constant updates in classification and characterization, encompassing different morphological patterns, subtypes and variants, corresponding to different profiles, prognosis and also therapeutic options [6,7].

In recent years, the spread of more-sensitive diagnostic methods has resulted in an increase in the diagnosis of synchronous multiple lung cancer (SMPLC) [8]. The assessment of multifocal lung tumors and the distinction of synchronous primary tumors from intrapulmonary metastasis represent an important problem as this decision significantly influences tumor staging and subsequent treatment strategies [9].

A thorough morphologic assessment remains crucial [10,11] and the detection of *p53* and *EGFR* mutations can be useful in the evaluation of multiple primary lung cancers, as the mutational status could help in the differentiation between synchronous tumors and metastasis [12].

This case illustrates a rare occurrence of synchronous lung mucinous and non-mucinous adenocarcinomas with different morphological, immunophenotypical and EGFR mutational status.

2. Case presentation

A 78-year-old female retired nurse, never-smoker (but with passive exposure to the smoke of her sons and husband) with history of arterial hypertension, dyslipidemia and osteo-articular pathology was referred to our institution. The patient had a pneumonia diagnosed 2 months before and she has been treated with amoxicillin/clavulanate 875mg/125mg for 7 days. After 6 weeks, the patient had no symptoms but maintained a

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hypotransparency in x-ray.

A thoracic CT was made to clarify the x-ray image and it revealed a lung nodule with a discreet irregular margin that measured 10 mm in the right inferior lobe (RIL) (Fig. 1A) and a 23mm ground-glass opacity lesion located in the right upper lobe (RUL) (Fig. 1B).

An 8-fluorodeoxyglucose positron emission tomography-CT (PET-CT) scan showed no uptake of the lesions and the brain MRI showed no lesions. An abdominal CT was also performed without identification of additional suspicious lesions. The levels of serum tumor markers such as NSE, Cyfra21.1 and CEA were within normal ranges. The CT-guided transthoracic needle biopsy from the RIL nodule showed a non-mucinous adenocarcinoma with predominant lepidic pattern, type II pneumocyte morphology and phenotype (TTF1 positive). The biopsy from the RUL lesion contained an invasive mucinous adenocarcinoma with predominant lepidic pattern, tall columnar mucinous/goblet cell morphology and mucinous phenotype (TTF1 negative; Napsin A negative; Keratin 7 positive). The mucinous adenocarcinoma from RUL showed negativity for keratin 20 and CDX2 antibodies, favoring a lung origin (Fig. 2). The mutational EGFR status (exons 18, 19, 20 and 21) was evaluated in both tumors. An EGFR exon 19 microdeletion (mutation c.2240_2254del15) was identified in the adenocarcinoma of the RIL lesion, with no EGFR mutation found in the RUL lesion. A RAS mutational analysis was not possible due to insufficient tissue.

A colonoscopy was made and excluded colonic lesions. The different type of cells characterizing each lesion, the distinct immunophenotypes further attested by different EGFR status and the clinical and radiologic data, suggested synchronous adenocarcinoma of the lung. A definitive diagnosis of two synchronous primary lung adenocarcinomas cT1aN0M0 in RIL lesion (stage IA) and cT1bN0M0 in RUL lesion (stage IB) was made. Therapeutic options were discussed with the patient, who refused thoracic surgery. Given the patient's decision, the multidisciplinary team decided to initiate SBRT. Each lesion was treated using 48 Gy in 4 fractions of 12 Gy, during 8 days in alternate days.

One month after treatment ended CT scan showed discreet dimensional reduction of the RIL lesion, more evident in the 3rd month CT scan. The six months CT scan revealed an enlargement of two lesions what was interpreted as inflammatory lesions induced by radiotherapy. The patient maintained tight follow-up with stable lesions and until now, she has not shown any signs of relapse or adverse effects. Twelve months after the treatment, there are no signs of relapse or metastasis (chest CT, bone scintigraphy, brain magnetic resonance imaging).

3. Discussion

The increasing incidence of multiple primary lung cancers results from the development of higher-resolution chest imaging techniques and closer follow-up of patients with routine chest scans after initial surgical resection. The estimated frequency ranges from 0.2% to 8% as referenced by Gazdar et al. [13]. In another study, among 139 patients with a second malignancy after diagnosis of lung cancer, 78 patients developed a second primary lung cancer, 19 of which were diagnosed synchronously [14]. Among the rare cases of SMPLC, those of the bilateral type comprise 60–70%, while the unilateral type has been comparatively rare [15,16]. With regard to the combination of histological types in SPMLC, the occurrence of squamous cell carcinoma and squamous cell carcinoma has been the most common, followed by squamous cell carcinoma and small cell carcinoma, and squamous cell carcinoma and adenocarcinoma [17]. The combination of two synchronous adenocarcinomas is infrequent and the combination of a mucinous adenocarcinoma and conventional (non-mucinous) adenocarcinoma of the lung is extremely rare.

Before the diagnosis of SPMLC is entertained, the possibility of a metastatic adenocarcinoma to the lung should be excluded. In the case of a lung mucinous adenocarcinoma this discrimination can be troubling because of the morphologic and immunohistochemical similarities its colic and pancreatic counterparts can have. In this instance, endoscopic and radiological data are very important. The assessment of CDX2, keratin 7 and 20 beside TTF1/Napsin A immunomarkers is necessary and molecular evaluation can be a valuable adjunct to this diagnosis [6,7,10,11].

The distinction between multiple synchronous primary lung cancers and intrapulmonary metastasis is often a challenge, being decisive for the therapeutic management and prognosis of these patients. The approach for this distinction has been continuously refined, integrating new criteria and the ever-growing armamentarium of immunohistochemical and molecular resources. The definition of SPMLC came to light in 1924 [18] and Warren and Gates [19] first proposed criteria to the diagnosis in 1938. Martini and Melamed [20] based this distinction on tumors histologic characteristics, besides other features. The emergence of immunohistochemistry and latter molecular biology resulted in a more integrative approach [21,22]. Recently recommendations for resected specimens were published stressing the need for a multidisciplinary approach [23]. In cases of small biopsies the importance of discussing and reviewing all available data is paramount.

The prognosis of SMPLC remains unclear. Whereas the overall

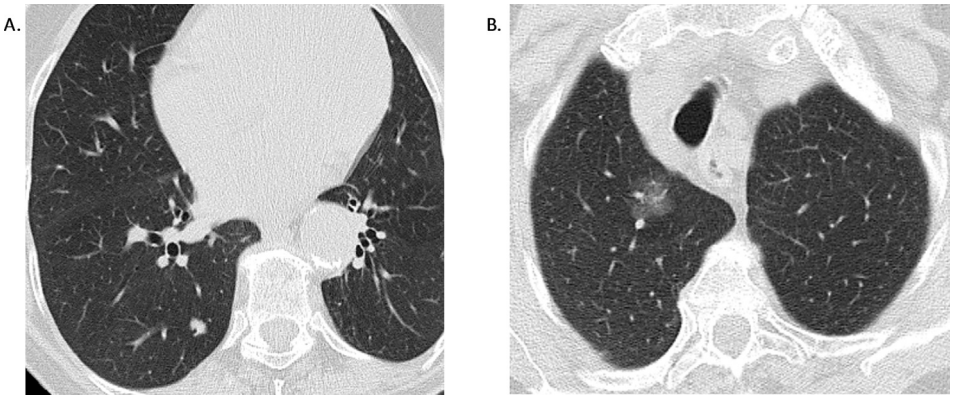

Fig. 1. A – Chest CT showed a nodule with an irregular margin that measured 10 mm (larger diameter) in the RIL; B – Chest CT showed a nodule with a ground-glass opacity lesion that measured 23 mm (larger diameter) in the RUL.