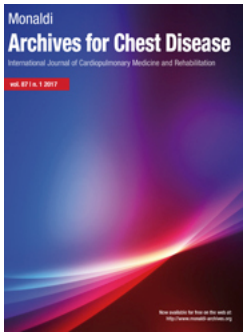

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Synchronous lung cancer presenting with small cell carcinoma and squamous cell lung carcinoma: a case report

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Abstract

Synchronous multiple primary lung cancers are separate tumors presenting at the same time with different histology. We present a rare case of a 64-year-old patient with a combination of small-cell lung carcinoma (SCLC) and squamous carcinoma in two different sites with metastasis of SCLC in the mediastinal lymph node. The SCLC diagnosis was performed via bronchoscopy, and the other diagnosis via CT-guided transthoracic biopsy. It is often difficult to distinguish a synchronous tumor from intrapulmonary metastases. To date, there are no guidelines for the treatment of these cases. The management of synchronous multiple primary lung cancer (SMPLC), mainly surgical with chemotherapy or radiotherapy, must be studied according to the histological type, staging and molecular testing of the tumors. These rare cases of SMPLC require individual treatment and a multidisciplinary approach.

Key words: small cell lung carcinoma, squamous cell lung carcinoma, synchronous multiple primary lung cancer

Case Report

A 64-years old man, current smoker (40 P/Y) with a medical history of arterial hypertension and echinococcus cyst of the seventh hepatic segment (no need for treatment), was referred to our department because of the finding of two pulmonary nodulations first detected by chest X-ray and then confirmed by CT scan of the chest. The thorax-CT scan showed non-calcific polylobular solid nodulation (18×9 mm) of the anterior segment of the left upper lobe (Figure 1A), and two lesions with similar characteristics and a sub-pleural base (29×24 mm and 10x8 mm) in the posterior segments of the upper segment of the lower right lobe (Figure 1B). The positron emission tomography (PET-CT) showed hyperaccumulation of the radionuclide, of probably lymph node significance (12R), localized in the right pulmonary hilar region (SUVmax 6.5). The right lower paratracheal region showed a sub-centimetric lymph node (4R) with a very slight uptake (Figure 1C). The patient was in good general condition on his arrival at the ambulatory, normal vital signs (SpO_2 97%, HR 72/min, blood pressure 125/68 mmHg). He underwent bronchoscopy with transbronchial needle aspiration of lymph node 12R, which showed atypical small epithelial elements with granular chromatin, nuclear moulding aspects, immunohistochemically positive for CD56, TTF-1, CkCAM5.2, compatible with small cell carcinoma of the lung (Figure 2A). The patient's case was then brought to a multidisciplinary thoracic oncology meeting, from which it emerged that the left upper lobe lesion also needed to be characterized. For this reason, the patient underwent a CT-guided transthoracic pulmonary biopsy, and it revealed moderately differentiated squamous cell carcinoma (G2) (Figure 2B), immunophenotype: p40: +; TTF1: -; negative PD-L1 expression (TPS < 1%), negative EGFR and BRAF mutations, negative for ROS1 rearrangement, immunohistochemical evaluation of Alk. According to the TNM 8th edition lung cancer classification, the staging of the two tumors was therefore as follows: SCLC limited disease St IIA (T3N1M0); squamous carcinoma St IA2 (T1bN0M0).

Therefore, the oncologic multidisciplinary team decided to perform stereotactic radiotherapy for the left upper lobe lesion and, subsequently, concomitant radio-chemotherapy (carboplatin and etoposide) for the small cell carcinoma. CT images obtained after therapy, showed a dramatic shrinkage of the lung lesions and lymphadenopathies. Full-body CT scans showed no brain lesions and numerous new liver metastases.

Discussion

Lung cancer is a leading cause of death in both men and women worldwide and many diagnoses are performed at an advanced stage. During or after the staging or treatment of the disease, the patient may develop another lung tumor. Distinguishing between intrapulmonary metastases and a new

primary cancer may be difficult (especially when the histologies are similar) [1]. Lung tumors with more localizations beyond the primary lesion in the lung at the same time are defined as synchronous multiple primary lung cancer (SMPLC). The incidence of SMPLC has continuously increased because of the improved radiological techniques, but the diagnosis and management are still not clear [2].

The most recognized diagnostic criteria for SMPLC were summarized by *Martini and Melamed*. According to these criteria, synchronous cancers are distinct neoplastic processes, histologically identical or different, but appearing in different segments, lobes, or lungs. If they originate from carcinomas in situ, they do not metastasize to the lymph nodes; furthermore, extrapulmonary metastases are not present at diagnosis time [3]. In 2016, the International Association for the Study of Lung Cancer (IASLC) provided well-defined criteria classifying lung cancers with multiple localizations into four patterns: SMPLC, multifocal ground-glass/lepidic lung cancers, primary lung cancer with separate tumor nodules (intrapulmonary metastasis), and pneumonic-type lung cancer by considering clinical, imaging, histologic, and genetic assessment together [4]. According to the TNM 8th edition lung cancer classification, if the neoplastic lesions are found in the same lobe as the main tumor, it is categorized as T3; if the tumor is in a different lobe but on the same side - T4; and if it is positioned on a contralateral side - M1a [5]. If there is more than one primary lung tumor, it is very difficult to distinguish a multi-center lung cancer from a primary tumor in a different organ [6]. Presently, based on histopathology, several succeeding lung tumors are misdiagnosed, especially if the patient develops a multiple pulmonary neoplasia histologically not recognizable [7]. However, such distinction is possible via genetic and immunohistochemical procedures and an appropriate diagnosis is required for the choice of appropriate treatment. Many searches report variations in certain tumor gene mutations, chromosomal aberrations, and microsatellite alterations involving different SMPLCs [1]. Commonly, most of the multiple primary lung neoplasms described are generally multifocal adenocarcinoma. As diagnosing SMPLC, it is essential to differentiate it from combined small cell lung carcinoma (C-SCLC), such as the one described here. C-SCLC is defined by the World Health Organization (WHO) as SCLC combined with other components consisting of any of the histological types of NSCLC: adenocarcinoma (ADC), squamous cell carcinoma (SCC), large cell carcinoma (LCC), large cell neuroendocrine carcinoma (LCC), large cell neuroendocrine carcinoma (LCNEC) or, less frequently, giant cell carcinoma or carcinoma. C-SCLC usually appears in the same lobe, while multiple primary lung cancers are more likely to occur in different lobes or lungs [8]. In our case, the two tumors were in two different lungs and the NSCLC was in the right lower lobe. The combination of SCLC and SCC is a relatively rare case. Based on the analysis of 125 patients with SMPLC, Trousse *et al.* showed that the combination with ADC accounted for 52% and that with SCC accounted for 28.8% [9]. SMPLC, including SCLC, are significantly rare. The

described incidences are 0.03% and 0.04% for SCC and ADC, and SCLC and SCC, respectively [10]. In series of SMPLC, Ghattas *et al.* reported that squamous cell carcinoma and small cell carcinoma were only 8.3% of these cases [11].

High-resolution chest-CT and PET-CT augmented the amount of diagnosis of synchronous multiple lung nodules, which of these nodules could be SMPLC or pulmonary metastasis from the lung or other tumor [12]. CT screening augmented the incidence of early-stage lung cancer and significantly reduced cancer mortality and cancer-related deaths in the screened population. In their meta-analysis *Nye et al*, described that stage I SMPLC patients were 64% and that they had more favorable outcomes, with a 5-year overall survival of 62%. The results were worse in comparison with stage I solitary lung cancer, but they were better in comparison with intrapulmonary metastatic diseases. This result highlights the necessity for early diagnosis of SMPLC, which not only decreases the frequency of lymphatic or haematogenic metastases, to remove treatment difficulties, but also to control the disease development at an early stage to increase the therapeutic effect of surgical treatment. If considered together, most patients with SMPLC are diagnosed at an early stage and they can get favorable long-term survival only with surgical treatment [2]. The approach for multiple malignant lung tumors treatment is critical because they are different for prognosis and whether they are SMPLC or lung metastases. For SMPLC, each tumor should be staged and treated distinctly and a TNM stage should be performed based on a combination of all tumors [13]. For primary lung cancer, intralobar lung metastases are indicated for surgery, but extralobar are not. In patients with history of other malignancies, metastatic lung cancers should be contemplated as a differential diagnosis. In such cases, surgical indications are evaluated on the situation. Currently, there are various treatments for SMPLC, including medical therapy, surgery, stereotactic ablative radiation (SABR), immunotherapy and ablation. An interesting insight comes from a recent small study by Monjazeb *et al*. They studied the addition of six cycles of Atezolizumab to SABR in a cohort of 20 high-risk, medically inoperable, early-stage NSCLC patients. They observed a median progression-free survival of 26 months in patients not suitable for systemic chemotherapy [14]. Various methods of management of SMPLC are possible, principally surgery with combination of chemotherapy or radiotherapy should be performed in agreement with the histologic types, staging and molecular testing of the cancers. If possible, complete lesion resection and lung parenchymal preservation in functionally limited patients, should be performed and the lymphadenectomy in both [15]. Only about 15% of lung cancer patients are eligible for surgery and post-operative clinical outcomes are different. Surgery, combined or not with chemotherapy, is the best treatment option in patients with early-stage lung cancer. Depending on the extent, lung resections lead to different levels of loss of lung function. Thoracic surgery along with COPD results in a greater decline in lung function, so a pre-operative clinical evaluation is necessary to select the correct surgical technique, with FEV1 as a predictor of post-operative

complications [16]. If multiple lung cancers are diagnosed as intrapulmonary metastasis (IPM), the therapeutic strategy should follow the standard of treating T3/T4. Despite these tumors are treated with SABR and ablation, there are limited studies on the topic and the levels of evidence are low. On the other hand, surgical approach remains the mainstream treatment, although there is still a lack of prospective randomized controlled trials based on large samples. For these patients, surgery is not a curative treatment. However, there are many patients at high risk due to advanced age or with underlying cardiopulmonary comorbidities, for whom thoracic surgery could lead to severe intraoperative and/or postoperative complications. Some patients have pulmonary nodules scattered in more than one lobe. The removal of all nodules seems impossible for these people or would lead to a severe loss of lung function, as the removal of the tumor to its full extent is essential to ensure the patients' quality of life after treatment [17]. Furthermore, it was shown that post-operative adjuvant therapy did not benefit patients further because most SMPLCs were early stage, rather than with intrapulmonary metastases (T3, T1a). That makes surgery necessary for most SMPLC patients [2]. In our case, therapy was targeted to SCLC. According to the European Society for Medical Oncology Clinical Practice Guidelines for SCLC treatment all patients with T1-4, N0-3 M0 tumors who are in good performance status should be treated with concurrent chemotherapy and thoracic radiotherapy [18].

Conclusions

The diagnosis of SMPLC has become increasingly common and more precise in recent years, due to advances in both radiological and molecular diagnostics. The concurrent presence of NSCLC and SCC is one of the rarest occurrences in SMPLC. The careful assessment of the patient's clinical features and staging are decisive for the therapeutic approach. Currently, there are no guidelines for the treatment protocol of these cases. These cases therefore require individual treatment and a multidisciplinary approach.

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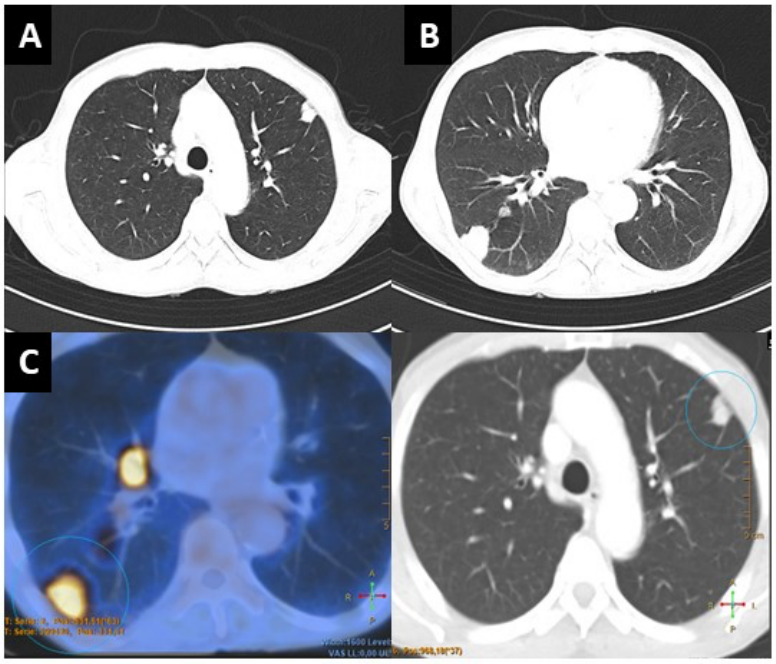

Figure 1: A) Upper left lobe lesion; B) lower right lobe lesion; C) PET-TC

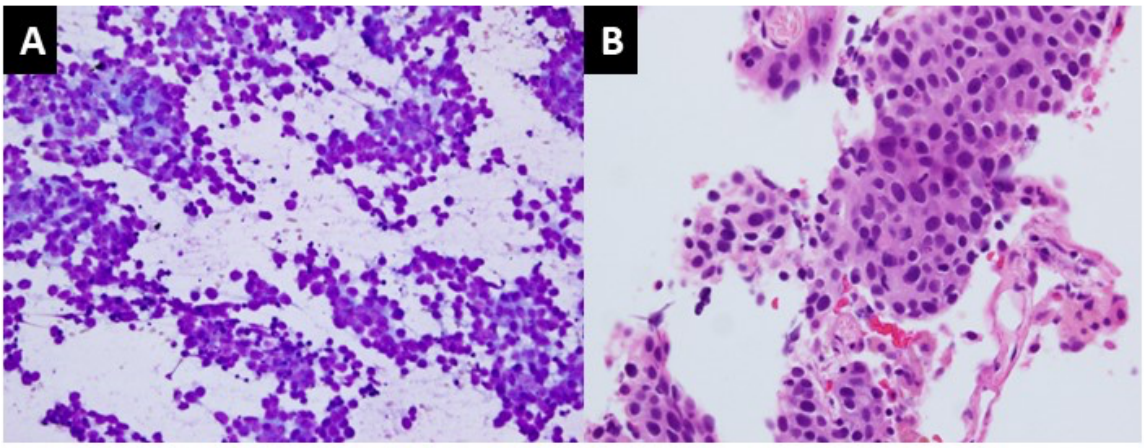

Figure 2: A) small cell lung carcinoma; squamous cell carcinoma