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Case Report

Coexistent Lung Adenocarcinoma and Non-Hodgkin Lymphoma

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Abstract

Patients diagnosed with one lung cancer are at an increased risk of developing another lung neoplasm. Clinical situations in which patients present with two distinct lung lesions with a high pre-test probability of malignancy can pose a diagnostic and therapeutic challenge in terms of accurately determining clinical stage and the best management strategy. We present a case of a 64-year-old woman with a history of non-Hodgkin lymphoma (NHL) treated with resection and chemotherapy followed by radiation 26 years prior to the current presentation. This patient now presented with chest pain, persistent cough, and abnormal chest imaging. Computed tomography (CT) revealed a 2.4-cm left-upper-lobe (LUL) lung lesion and a distinct 2.3-cm right-middle-lobe (RML) lung lesion, both suspicious for malignancy. A positron emission tomogram (PET) CT showed significant avidity in both LUL and RML lesions (SUV = 6.8 and 7.5, respectively). CT-guided biopsy of the LUL mass revealed adenocarcinoma. Navigational bronchoscopy of the RML mass was positive for metastatic, recurrent NHL. Our patient was not a candidate for lung resection due to poor lung function and was treated with stereotactic radiation for the LUL adenocarcinoma and chemotherapy for the metastatic NHL (extranodal marginal zone B-cell lymphoma). In the presence of two lung masses, distinguishing between multiple primary lung cancers (MPLCs) is of great clinical and prognostic significance. The presence of two new lung nodules in opposite sides should raise suspicion for synchronous MPLCs (in the absence of bulky or fluorodeoxyglucose-avid hilar/mediastinal adenopathy). Obtaining tissue is of utmost importance, especially when the PET/CT pattern is not easily explained. Invasive tissue diagnosis is recommended in patients with an ipsilateral, different lobe nodule and in those with a contralateral lung nodule. Patients diagnosed with MPLCs should be approached with curative intent, with each tumor being evaluated and treated independently of the other. Our patient was ultimately diagnosed with a Stage I LUL adenocarcinoma that was treated with stereotactic body radiation therapy, and with metastatic extranodal marginal zone B-cell lymphoma that was treated with chemotherapy. A high index of suspicion should be maintained tumors of different histological subtypes, especially in patients presenting without mediastinal adenopathy.

Keywords: *Multiple Lung Nodules; Multiple Primary Lung Cancers; Lung Cancer Staging; Navigational Bronchoscopy; Endobronchial Ultrasound*

Abbreviations

CT: Computed Tomography; EBUS: Endobronchial Ultrasound; FEV1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; DLCO: Diffusion Capacity of Carbon Monoxide; LUL: Left Upper Lobe; MPLCs: Multiple Primary Lung Cancers; NHL: Non-Hodgkin Lymphoma; NSCLC: Non-Small Cell Lung Cancer; PET: Positron Emission Tomography; RML: Right Middle Lobe; rp-EBUS: Radial Probe Endobronchial Ultrasound; SBRT: Stereotactic Body Radiation Therapy

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. The National Lung Cancer Screening Trial and its implementation in clinical practice have led to increased detection of early-stage lung cancer, thereby decreasing mortality associated with lung cancer [1]. With increased lung cancer surveillance, there has been a significant rise in the detection of multiple lung nodules suspicious for lung cancer. Advanced diagnostic modalities such as navigational bronchoscopy [2] with radial probe endobronchial ultrasound (rp-EBUS) along with computed tomography (CT)-guided biopsy [3] have improved our ability to differentiate lung nodules histopathologically, which in turn helps us appropriately diagnose and stage patients with suspected lung cancer. Stereotactic body radiation therapy (SBRT) along with traditional surgical treatments have increased our armamentarium to treat early-stage lung cancer, especially multiple primary lung cancers (MPLCs) [4,5]. Here, we report a case of synchronous MPLCs in a patient with history of non-Hodgkin lymphoma (NHL) who presented with two lesions with significant avidity on positron emission tomography (PET) in contralateral lungs. These lesions were ultimately diagnosed as non-small cell lung cancer (NSCLC) and NHL (extranodal marginal zone B-cell lymphoma).

Case Report

A 64-year-old woman with a history of NHL presented with chest discomfort, shortness of breath, cough, and fatigue. She had been diagnosed with NHL (diffuse large B cell lymphoma) in her left hip 26 years earlier, and her treatment at that time included tumor resection and chemotherapy followed by radiation. 13 years later, she was diagnosed with recurrence of her NHL in the right parotid gland and was treated with chemotherapy followed by radiation, which resulted in sustained remission of her disease. The patient had a 30-pack-year smoking history but stopped smoking when she was originally diagnosed with NHL. She was also diagnosed with chronic hypersensitivity pneumonitis related to mold exposure 10 years prior to the current presentation, and was treated with oral corticosteroids. The patient has required 2 to 3 liters of supplemental oxygen per minute since then.

Two months prior to her presentation, she experienced pleurisy-like chest pain and shortness of breath that prompted diagnostic imaging. A chest CT revealed a 2.4-cm mass in the left upper lobe (LUL, Figure 1A) and a 2.3-cm mass in the right middle lobe (RML; Figure 1E), with left hilar and subcarinal lymph nodes sized at the upper limit of normal. A PET scan demonstrated notable uptake in the LUL lesion (SUV=6.8; Figure 1B) as well as a PET-avid RML mass (SUV = 7.5; Figure 1F) without any uptake in the mediastinal lymph nodes. Uptake in the anterior portion of the left parotid gland was also noted (SUV = 3.7).

A transthoracic needle aspiration of the LUL mass revealed poorly differentiated adenocarcinoma of the lung (Figure 1C and 1D). Further pathological analysis confirmed the lung origin of the tumor, with a thyroid transcription factor 1, p53, and napsin. The next clinical question was whether the RML PET-avid lung lesion was a metastatic focus or a new primary lung cancer that would significantly change the clinical stage. Staging endobronchial ultrasound (EBUS) was performed to determine the clinical stage, and navigational bronchoscopy with rp-EBUS was simultaneously carried out to diagnose the RML lesion. Because the possibility of two primaries or oligometastatic disease was high on the differential diagnosis, sampling of the RML lesion was done prior to staging EBUS. Pathology of the RML mass revealed atypical lymphoid infiltrate consistent with metastatic recurrent extranodal marginal zone B-cell lymphoma (Figure 1G and 1H). Cytopathology of the hilar and mediastinal lymph nodes revealed normal lymphoid sample without evidence of malignancy.

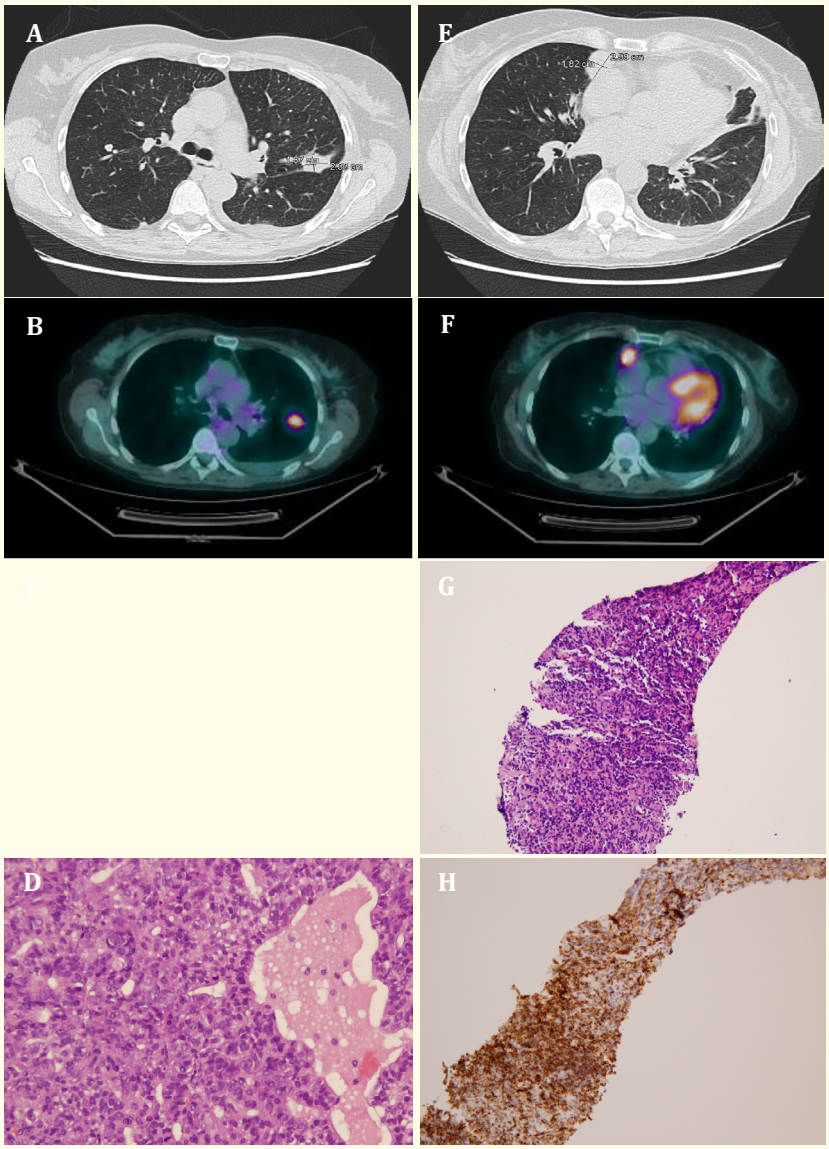

Figure 1: *Computed tomogram of the chest (A) and positron emission tomogram (B) showing a mass in the left upper lobe of the lung, ultimately diagnosed as pulmonary adenocarcinoma ([C]: Hematoxylin and eosin, 10X; [D]: Hematoxylin and eosin, 40X). Computed tomogram of the chest (E) and positron emission tomogram (F) showing a mass in the right middle lobe, ultimately diagnosed as non-Hodgkin lymphoma (G & H).*

The patient's pulmonary function tests showed a restrictive lung defect with a forced vital capacity (FVC) of 46% predicted, forced expiratory volume in one second (FEV1) of 45% predicted, and a diffusion capacity (DLCO) of 28% predicted. Given the metastatic recurrent diffuse large B cell lymphoma and her low lung function, she was deemed unsuitable for lung resection surgery for the Stage I adenocarcinoma. After multiple tumor board discussions and shared decision making with the patient, a multimodal treatment plan consisting of SBRT for the LUL adenocarcinoma and rituximab-based chemotherapy for the RML metastatic extranodal marginal zone B-cell lymphoma was initiated. Follow-up imaging was carried out 6 months after SBRT and chemotherapy conclusion, and revealed complete resolution of the PET-avid lung and parotid gland lesions.

Discussion

Lung cancer is by far the leading cause of cancer-related death in both men and women; each year, more people die from lung cancer than from cancers of the colon, breast, and prostate combined. Lung cancer accounts for 13% of all new cancer diagnoses, but for 26% of all cancer deaths [1]. First described in 1924, MPLCs have been an increasingly well-recognized entity [6]. MLPCs can either be synchronous (i.e. diagnosed at the same time as the other primary lung cancer) or metachronous (i.e. diagnosed at a later time) [7]. Diagnosis of MLPCs can be extremely challenging, and a firm understanding is critical to determine the clinical stage accurately.

The incidence of synchronous MPLCs is between 2% and 8% [7,8], and is on the rise due to early detection on CT. The survival of MPLCs is also increasing, thanks to advances in cancer therapy. Several reports proposing clinical–pathological diagnostic criteria are well known [9,10]. The American College of Chest Physician Guidelines from 2007 state that the diagnosis of synchronous lung cancer is suggestive when lesions have different histologic or molecular genetic patterns, or when lesions with the same histological pattern are found in different lobes of the lungs [11,12]. No N2 or N3 nodal involvement or distant metastasis should be noted [12].

The pathogenesis of MPLCs was first proposed by Slaughter., *et al*. in 1953 [13]. In that report, the authors describe the concept of field cancerization, in which various parts of the lung have different susceptibilities to environmental carcinogenic agents [13]. Continued exposure to cigarette smoke, for example, is a significant risk factor for development of metachronous lesions [14]. Pathological diagnosis of histologically similar synchronous lesions remains a clinical challenge. The presence of mediastinal lymphadenopathy can suggest a higher probability of the other nodule or lesion being a metastatic focus, but tissue diagnosis is still required due to staging implications. Even after a diagnosis of MPLC is confirmed, detailed examination to look for distant metastasis and mediastinal staging either with EBUS or mediastinoscopy should be performed, as synchronous MPLCs carry a high mortality rate, even if the lesions are histologically different [15]. In histologically similar lesions, genetic and molecular testing should be performed to differentiate between MPLCs and metastasis.

The management of synchronous MPLCs can be challenging. Current guidelines recommend surgical resection, but the type of procedure selected depends on tumor size, tumor location, and the patient's cardiopulmonary status. If the patient cannot tolerate complete resection, a limited resection can be considered as an acceptable alternative; however, this approach does involve the risk of local recurrence [11,12]. Synchronous lung cancers are more common in the same lung and can be treated by single or double lobectomy or even a pneumonectomy (if the lung function can tolerate it). For patients who cannot undergo surgery, SBRT is a reasonable option [4,5].

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type is a distinct subgroup of NHL. It is extremely rare; and only a few cases of synchronous lung cancer and pulmonary extranodal marginal zone B-cell lymphoma have been reported. It accounts for less than 0.5% of all lung malignancies and less than 1% of all lymphomas [16], and is characterized by reactive follicles with lymphoepithelial lesions in the bronchiolar and alveolar epithelium. Treatment options include observation, radiation, chemotherapy, surgical resection, or some combination thereof. It has a good overall prognosis, with a five-year survival around 90% [16]. Pursuing a tissue diagnosis of suspected MLPCs in our patient resulted in the diagnosis of metastatic NHL with relatively good prognosis, and we were able to accurately characterize the LUL lesion as a Stage I adenocarcinoma that we treated with SBRT.

Conclusion

With increased cancer surveillance and improved therapeutic options, we continue to see an increase in multiple PET-avid lung nodules. It is critical to differentiate the etiology of such nodules as metastatic lung cancer, synchronous MLPCs, or lesions of completely different etiologies (as was the case in our patient). The differentiation between MPLCs and intrapulmonary metastatic disease is extremely important in determining patient prognosis and cancer management. When the histopathology of two lesions is similar, molecular testing should be used to determine whether the tumors are of the same origin or are synchronous MLPCs. Advanced diagnostic bronchoscopy techniques, including navigational bronchoscopy and EBUS, aid in the diagnosis of such lesions with high diagnostic yield [2,3].

Conflict of Interest

None of the authors has a relevant conflict of interest to disclose.

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