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Is Biopsy Needed in a Patient with Multiple PET Positive Cavitating Nodules Following Laryngeal Carcinoma

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Abstract

Laryngeal cancers have a significantly high morbidity and mortality (one-third of all head and neck cancers) with the incidence mostly related to exogenous substances such as tobacco and alcohol overconsumption. In addition to chest CT, PET-CT plays an important role in the treatment of laryngeal carcinomas as the detection of increased FDG metabolic activity in the tumor cells allows for a better assessment of tumor size, location, spread and response to therapy. Early stages can often be resected minimally invasively. Close follow-up examinations are mandatory to detect possible recurrences early. The nodular lesions in Langerhans Cell histiocytosis (PLCH) can resemble lung metastases and exhibit FDG avidity and sometimes necrotizing melting. As with laryngeal carcinoma, LHCH is associated with an increased risk of recurrence due to chronic nicotine use as an aggravating factor. The primary treatment of LHCH is consistent nicotine withdrawal, which in most cases leads to restitution of the lesions. Additional administration of glucocorticosteroids or chemotherapy is rarely necessary.

Keywords: Pulmonary nodules; Metastatic cancer; Cryobiopsy; VATS; Langerhans cell histiocytosis

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Abbreviations

PET/CT: Positron Emission Tomography Computed Tomography; HRCT: High Resolution Computer Tomography; BAL: Bronchoalveolar Lavage; TBB: Transbronchial Biopsy; ANA: Antinuclear Antibiodies; ANCA: Anti-Neutrophil Cytoplasmatic Antibodies; VATS: Video Assisted Thoracoscopic Surgery; PLCH: Pulmonary Langerhans Cell Histiocytosis; LCH: Langerhans Cell Histiocytosis; MAPK-ERK: Microtubule-Associated Protein Kinase or Extracellular Regulated Kinase (MAPK/ERK); BRAF: Gene Encodes a Protein Belonging to the RAF family of serine/threonine protein kinases; FEV1: Forced Expiratory Volume in one second.

Introduction

Laryngopharyngeal cancer is predominantly diagnosed in men with exposure to precancerous risk factors (tobacco and alcohol abuse) with a 5- to 25-fold increased risk compared to non-smokers [1-3] but is also associated with human papillomavirus and Epstein-Barr virus infection. Minimally invasive larynx-preserving surgical techniques are the treatment of choice in early stages. Close follow-up, including chest CT scans, is indicated to detect future local recurrences or metastases, as local recurrences can occur in 80–90% of cases within the first 4 years. After 5 years, follow-up is continued primarily to assess for second primary malignancies, especially in patients with a significant smoking history. Furthermore, consistent smoking cessation is essential. When suspicious nodules occur, rapid and targeted examination is important to distinguish between a possibly uncontrolled stage of the underlying malignant disease and an independent cause. Langerhans cell histiocytosis is usually a rather benign histiocytic multisystemic disease with expression of CD1a, Langerin and S100 on the surface of Langerhans cells. In fact, there is also a connection between the manifestation of the disease and chronic nicotine consumption. Up to one-fifth of affected patients are asymptomatic, and the suspicion of LCH is based on incidentalomas in the sense of suggestive findings in CT scans.

Case Presentation

History of Present Illness

A 56-year-old woman with known laryngeal carcinoma (pT1a cN0 cM0 L0 V0 Pn0 R1), treated in July 2019 with microlaryngoscopic laser surgery and curative radiation (47.25 Gy), underwent routine High-Resolution CT (HRCT) two years later for tumor follow-up care. HRCT showed multiple partially cavitating pulmonary nodules, some ground-glass opacities, and an enlarged right hilar lymph node (Figure 1A), suspicious for multiple lung metastases. The patient described dysphagia and a weight loss of approximately 10 kg over the past three months. She was a smoker (20 pack-years) with a nonproductive cough but denied night sweats, fever, or shortness of breath.

Physical Examination and Laboratory Values

Clinical examination was unremarkable except for residual hoarseness. Laboratory values were normal, including C-reactive protein, ANCA, ANA, differential blood count, liver and kidney parameters.

Radiological Examinations

On PET/CT, all lung nodules were FDG-avid.

Interventions: Laryngostroboscopy revealed a swollen larynx with normal vocal fold movement but no mucosal wave movements, interpreted as scarring after radiotherapy. Pulmonary tumor recurrence was assumed, and Bronchoalveolar Lavage (BAL) and Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA) of the right hilar lymph node were performed, showing no malignancy or infection. Transbronchial biopsy (TBB) revealed only lung parenchyma with smoker's macrophages, with no correlate for the ground-glass opacities or cavitary lesions. A transbronchial cryobiopsy, despite adequate tissue, showed only parenchyma with emphysema. After multidisciplinary discussion, Video-Assisted Thoracic Surgical (VATS) lung biopsy and laryngoscopic laser biopsy were performed.

Histological work-up: VATS wedge resection showed bronchiolocentric aggregates of mononuclear cells with intermixed eosinophils (Figure 2A and 2B). Metastasis of subglottic laryngeal carcinoma was ruled out. The larynx biopsy was tumor-free with nonspecific inflammation. The pattern was suggestive of Pulmonary Langerhans Cell Histiocytosis (PLCH) with emphysema and smoker's macrophages. Immunohistochemistry for CD1a was diffusely positive in Langerhans cells, confirming PLCH (Figure 2C).

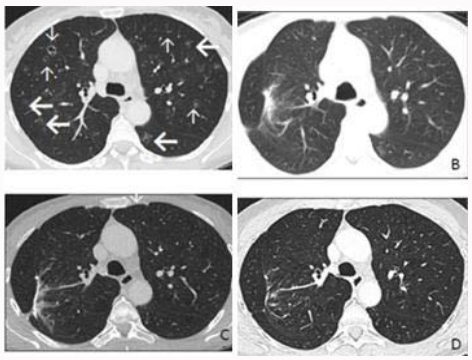

Figure 1: A: Initial HRCT scan with multiple noduli (cavitating ↓ and subsolid ↕), B: 3 months follow up PET/CT, C: 6 months follow up CT, D: 16 months follow up HRCT.

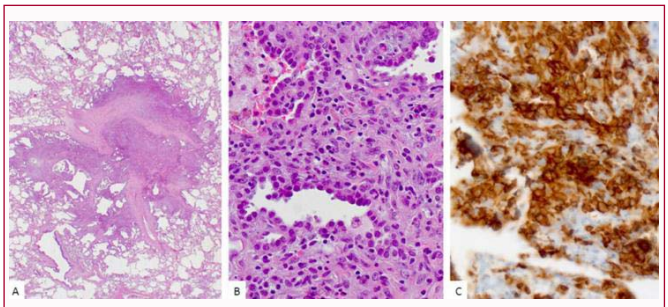

Figure 2: Wedge resection of a subsolid nodule in the right upper lung lobe with histologic diagnosis of Langerhans cell histiocytosis: A: Bronchiolocentric nodule with ill-defined margins (HE, original magnification 100x). B-C: The nodule consists of Langerhans cells, which stain for CD1a by immunohistochemistry, with some eosinophilic granulocytes and lymphocytes (B: HE, original magnification 200x; C: CD1a immunohistochemistry, original magnification 400x).

Discussion

In this case the chest HRCT with solid and partially cavitary lung nodules was highly suspicious for metastases of the laryngeal carcinoma despite the early stage of the tumor at diagnosis (pT1a cN0 cM0 L0 V0 Pn0 R1). Distant metastases of laryngeal carcinoma occur most commonly in the lungs, followed by the liver and bone [4]. HRCT scan identifies possible other malignant findings in high-risk patients with relevant smoking history and is suggestive in up to 20% of newly diagnosed head/neck cancers while failing in 5% of all cases [5]. The swollen larynx together with multiple PET positive nodules in the lung and a considerable weight loss led to the strong suspicion of multiple pulmonary metastases. In retrospect the local findings of the larynx, the weight loss and the dysphagia most likely represented side effects of the curative radiotherapy. Highly specific for PLCH are reticular and nodular centrilobular opacities (2 mm to 10 mm in size) typically seen in the middle to upper lung zones. In addition, thin-walled cysts can sometimes occur in a bizarre shape. Lymphadenopathy is rare. The costophrenic angle is usually spared [6]. According to one study pulmonary PLCH could be confirmed in 50% with TBB, in 45% with surgical lung biopsy and only in 5% with BAL alone [7]. In our case TBB and additional cryobiopsy did not lead to a definitive diagnosis.

LCH is a rare neoplastic histiocytic disease characterized by Langerhans cells with expression of CD1a, langerin and S100. Smoking associated PLCH is most common, representing 3-5% of all diffuse lung diseases in adults [8]. In PLCH the percentage of CD1a-positive Langerhans cells is >5% [9]. Multisystem disease mainly affects the skeleton/ skin, but also the lung (50%), liver, bone marrow, central nervous system, and spleen [10]. Up to 20% of affected patients are asymptomatic. Isolated lung manifestation is most often associated with smoking [11,12]. LCH is more common in males and in childhood. Symptoms and disease distribution and severity vary widely. The distinction of mono-organ manifestation and multisystemic involvement affects prognosis and management. LCH is a clonal disorder with activation of the MAPK-ERK signalling pathway. BRAF V600E mutations are present in more than 50% of all cases, offering the possibility of targeted therapy [13].

A large proportion of LCH patients improve their disease by consistent smoking cessation and avoiding further exposure to smoke. If the disease progresses, glucocorticoids (0.25 to 0.5 mg/kg daily) can be used for approximately 6 months with subsequent

tapering. If there is no response, cladribine or targeted therapy with BRAF inhibitors can be considered if a mutation in the MAPK signalling pathway has been detected. In very advanced cases, a lung transplant is the last option [13]. To detect treatment failure early, regular lung function tests are recommended.

Clinical Course

Due to the only minor impairment of FEV1 and diffusion capacity, we encouraged the patient to strictly stop smoking to avoid the need for immunosuppressive therapy. Three months after smoking cessation a follow-up PET/CT was showed a subtotal regression of almost all intrapulmonary lesions. After one and a half years there was complete regression of the nodules and no new lesions on chest HRCT (shown in Figure 1B,1C and 1D).

In summary, this patient with laryngeal cancer was diagnosed with histologically confirmed PLCH with spontaneous regression of the disease after smoking cessation. The lung nodules in HRCT were not metastases from laryngeal carcinoma. This case shows that even if there is a high clinical suspicion of recurrence in a patient with previously treated cancer, histology is necessary to decide on further treatment.

Unfortunately, the patient started smoking again and recently the nodules reappeared in a different distribution. However, since this was a minor finding, we decided not to escalate therapy and fortunately the patient was eventually able to stop smoking.

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