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Case Report

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Hearing loss, why bronchial tree may be involved?

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Authors' contributions: MA, FR, LN and FDM conceived the idea and designed the research. MA, FR, LN, GC, CA, SB, CC and LM collected clinical records data. EC and AG performed and supervised all molecular and biological analyses. FDM and AG were the responsible for the research activity, management and coordination. MA, LN, CC and FDM wrote the initial draft. All the authors critically analyzed data and revised the draft. FR, LN and FDM prepared the final version of manuscript after revision and final approval by all the authors. All the authors have read and approved the final version of the manuscript and agreed to be held accountable for all aspects of the work.

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Abstract

A 62-years-old man former occasional smoker was hospitalized for progressive hearing loss and Magnetic Resonance Imaging (MRI) detected multiple round hyperdense lesions in each cerebral hemisphere. Total body Computed Tomography (CT) scan showed a lobulated consolidative lesion on the right lung lower lobe associated to conglomerate lymph nodes (11R) suspected for primary lung cancer. Endoscopy showed an endobronchial invasion and integrated endobronchial ultrasound did not demonstrate any accessible lymph node for sampling. Forceps biopsy report on the endobronchial specimen led to histopathological diagnosis of metastatic melanoma. Skin and ophthalmologic examinations were negative for suspicious pigmented lesions findings and patient had no history of familiarity for melanoma. Malignant melanoma is rarely observed to metastasize to endobronchial tissue and it is represented only in the 4.5% of cases. The vast majority of endobronchial metastases are metachronous, even after several years. Nevertheless, the anachronous manifestations are possible.

Case Report

A 62-years-old male, former occasional smoker working as bricklayer, experienced in early December 2021 a mild left hearing loss. He had no previous significant medical history except for gastro-gastroesophageal reflux disease. The hearing impairment got worse during December and therefore the patient underwent a clinical evaluation. The patient was asymptomatic for dyspnea or other systemic general symptoms. The physical examination showed normal vital signs, including arterial blood pressure and oxygenation, and a normal head-to-toe and cardio-pulmonary assessment. A brain MRI was performed and detected multiple hyperdense round-shaped lesions in each cerebral hemisphere. He was then admitted to Internal Medicine Unit for further investigations.

Thereafter a total body Computed Tomography (CT) scan was obtained and a lobulated inhomogeneous consolidative lesion (40x38x37 mm) was found between lateral and posterior segment of the right lung lower lobe (shown in Figure 1). The mass was associated to homolateral hilar adenopathy (11R). A total-body Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) was performed and detected multiple areas of pathological uptake at the level of the cerebral lesions, mediastinal and pulmonary masses, spine and a soft tissue focal uptake was found in the posterior compartment of left thigh.

The patient was referred to our Interventional Pulmonology Unit and a bronchoscopy was performed and showed an endobronchial invasion of the posterior segment of the right lower lobe with a mass of mucosa projecting into the lumen, where multiple forceps samples were taken (shown in Figure 2). This area presented a pale smooth superficial aspect with erosion borders and a friable texture

associated to abundant bleeding at simple instrument light touch. The exam was integrated with Endobronchial Ultrasound (EBUS) but, unfortunately, it did not demonstrate any accessible lesions or lymph node suitable for a transbronchial needle sampling.

Forceps biopsy report on the endobronchial specimen was characterized by diffuse infiltration of poorly differentiated cells with single elements with discrete cytoplasm and enlarged irregular nucleus with thickened chromatin. Immunohistochemical studies on the sample were performed with a negative immunophenotype for cytokeratin AE1/AE3, cytokeratin 7, TTF1, p40, CD20, CD3 and a positive immunophenotype for SOX10, MELAN-A, S-100.

The imaging findings were suggestive for a probable lung cancer with mediastinal adenopathy, brain and spine metastasis. However, immunohistochemical strains on endobronchial forceps specimens showed a negative immunophenotype typical for tumors of epithelial origin and of hematologic origin, while the positivity for SOX10, MELAN-A, S-100 strains was consistent with a histopathological diagnosis of metastatic Malignant Melanoma (MM). Moreover, there was no evidence of BRAF mutation and PD-L1 expression was <1% in the sample.

Thereafter, the patient underwent head-to-toe skin physical assessment and ophthalmologic complete examination, both negative for suspicious pigmented findings. Furthermore, the patient confirmed the absence of family history of MM. For those reasons, the final oncological diagnosis was anachronous endobronchial metastatic MM.

Discussion

The lung is one of the most common sites of cancer metastasis, as from 20% to 54% of solid extrapulmonary malignancies spread as a secondary site in lung parenchyma during their disease progression.[1,2] However, metastasis with endobronchial growth are quite unusual and rare and epidemiological and clinical pathology data on large homogeneous series are lacking. Indeed, only few articles are available in scientific literature about this issue and mainly represented by anecdotal case reports as single case descriptions or very limited case reports. Marchioni *et al.* in 2014,[3] in a time span of 18 years, collected the largest group in literature of endobronchial metastases from extrapulmonary malignancies, disclosed in routine practice (total of 174 cases, mean of 5.6 cases per year). The large population studied highlights the clinically relevant occurrence of this phenomenon, as among all bronchoscopic procedures performed in the suspicion of lung cancer, the overall incidence was about 4% per year. The authors observed that potentially all types of solid tumor could metastasize into the bronchial tree, but the extrapulmonary neoplasms most often resulting in endobronchial metastasis were breast carcinoma (30%), colorectal carcinoma (24%) and renal carcinoma (14%), while MM represented just the 4.5% of cases. Furthermore, the authors reported in their series a majority of detection of metachronous metastasis (89%), most of which derived from breast (48%) and colorectum (40%) primary tumors, and only the 6% of cases were characterized by a synchronous metastasis (principally stomach cancer) and about 5% of all cases by anachronous metastasis. It is interesting to note that in this last group, the 50% of anachronous metastatic cases was represented by kidney tumor, while no anachronous metastasis of MM was found in their report. Moreover, it must be remembered that in a retrospective review about metastatic MM, only in 2.6% of the described 2485 cases the primary lesion was not identifiable at the moment of diagnosis.[5]

Despite what is more frequently expected thinking about MM metastasis, in our patient, the prominent endobronchial lesion detected was unpigmented, making it harder to guess the possible melanocytic origin. As known by clinical practice, the appearance of MM subtypes may be characterized by amelanotic or hypomelanotic lesions and different studies have reported that hypomelanotic lesions represent 2% to 20% of all MM.[6]

The last questionable part of the diagnosis is the definition of the endobronchial lesion as a metastasis and not as a primary tumor. Mucosal melanoma is a rare and aggressive subtype of MM that is epidemiologically and biologically distinct from cutaneous melanoma.[7] Mucosal melanoma was represented only in 0.8-3.7% cases of MM and the genitourinary, gastrointestinal, and respiratory tract are the most reported sites of detection.[8] From literature, lung primary MM is extremely rare, accounting for only 0.4% of mucosal melanoma, representing the 0.01% of all primary lung tumors.[7,9] Primary pulmonary MM usually could be characterized by similar symptoms to other chest tumors, such as cough, dyspnea, hemoptysis, post-obstructive pneumonia, lobar atelectasis, weight loss, fatigue and signs and symptoms related to metastases.[8,10] Nevertheless, primary pulmonary MM can be totally asymptomatic in 9.2% of cases.[10] In 1968, Allen and Drash[11] proposed diagnostic criteria for the primary pulmonary MM, which are still used in scientific reports: i) no previous history of melanoma, ii) no evidence of suspicious pigmented lesions findings, iii) presence of a solitary tumor in the surgical specimen of the lung, iv) histological morphology compatible with a primary tumor, v) no evidence at autopsy of primary melanoma elsewhere, vi) cytology positive for melanoma cells confirmed by immunohistochemical staining for S-100 and HMB-45, vii) evidence of junctional change, viii) "nesting" of cells beneath the bronchial epithelium, ix) and invasion of the intact

bronchial epithelium by melanoma cells. Our patient didn't meet some of those criteria, so it was not possible to define the lesion found as a primary neoplasm following Allen and Drash's criteria.

Immunohistochemistry does not allow to distinguish pulmonary origin from other cutaneous form of malignant melanoma.[7] By analyzing recent reports, focusing on molecular features of MM, about 50% of skin MM present the BRAF mutation as their main oncogenic driver with NRAS,[12] whereas it is rarely detected in mucosal melanoma (<10%), as over half of genetic drivers in mucosal melanoma remain unknown.[7,12] Mucosal melanoma is probably less immunogenic than cutaneous melanoma, as PD-L1 expression in generally lower. Generally, it has been found that the mutational burden is 5-10-fold lower in mucosal melanoma in comparison to cutaneous melanoma.[7,12] Our case of mucosal melanoma actually reflects this mutational and immunohistological panorama (absence of BRAF mutations and a PD-L1 expression <1%). Given that, returning to our patient, the presence of multiple abnormal FDG uptake sites at total body FDG-PET scan, the multiple cerebral metastases together with the tumor molecular assessment of the sample and the absence of skin or eye findings, make the hypothesis of considering a mucosal MM with anachronous lung metastases reasonable.

Chaussende *et al.*[13] collected data from 19 patients with histologically proven endobronchial metastasis from MM between 1990 and 2014 and found a median overall survival of 6 months after the diagnosis, ranging from 1 to 46 months, depending on, as main factor, the number of metastatic organs involved, as a significant worse survival was observed when pleural metastatic effusion and soft tissue invasion were present. The study also displayed no influence in patient's survival given by

different treatment options, pointing up the importance to preserve the quality of life that sometimes require debulking invasive endobronchial treatment to provide rapid recanalization of the airway.

Conclusions

This case gives clue to an in-depth analysis of a rare entity of endobronchial metastasis of malignant melanoma. A great deal of light and shadow is present in the making of this diagnosis and a more literature evidence should be addressed. With new strategies and protocols for lung cancer screening and the ever-increasing endobronchial diagnostic accuracy, it cannot be excluded that incidental endobronchial lesions may be more frequently reported and the importance of a multidisciplinary Lung Cancer Unit team becomes fundamental for the correct management of the individual case.

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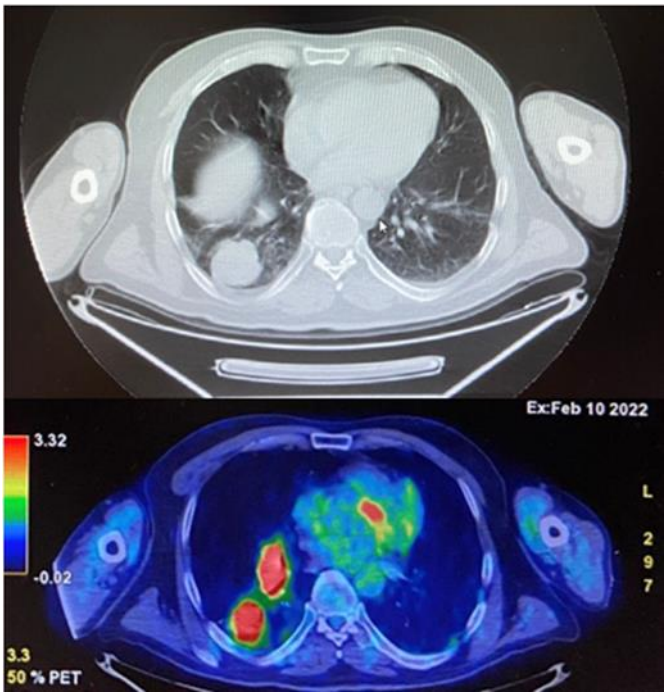

Figure 1. A) total body Computed Tomography (CT) -scan frame showing between the lateral and posterobasal segment of the right lower lobe the expansive lesion with inhomogeneous density (4x3.8x3.7 cm); **B)** PET-FDG-scan frame showing pathological uptake between the lateral and posterobasal segment of the right lower lobe.

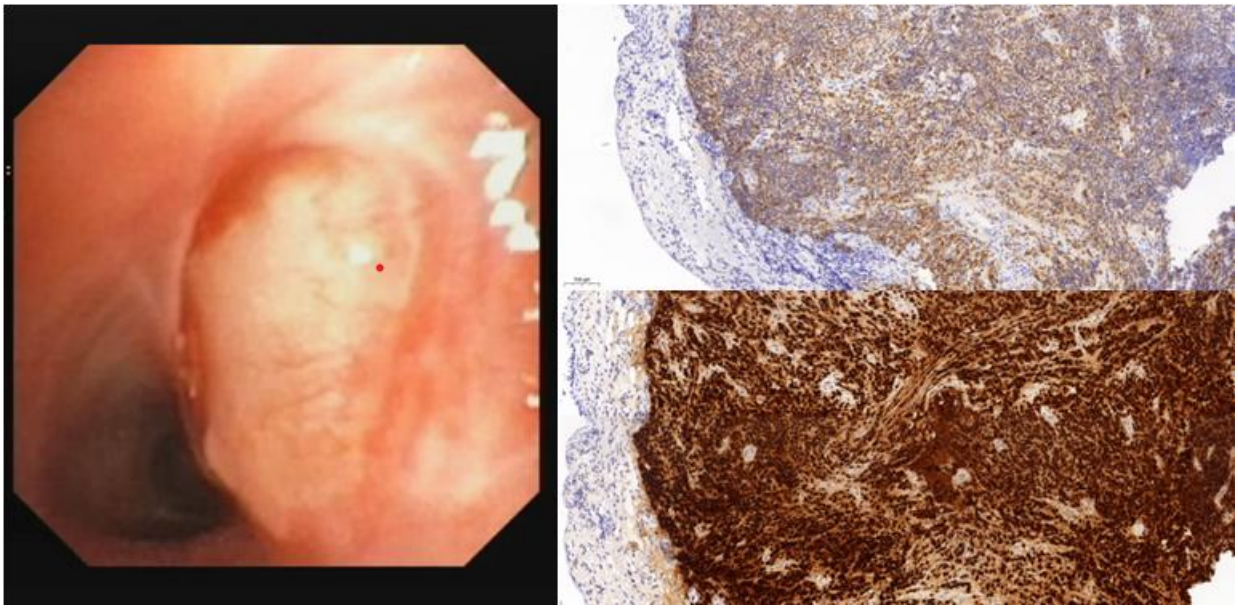

Figure 2. A) the endoscopic presentation of the endobronchial invasion of the posterior segment of the right lower lobe; **B, C)** immunophenotype positive for SOX10, MELAN-A, S-100 and negative for cytokeratin AE1/AE3, Cytokeratin 7, TTF1, p40, CD20, CD3.