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Case Report

A rare case of endobronchial melanoma of unknown primary

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ABSTRACT

A 62-year-old man who presented with complaints of cough and hemoptysis was found to have an endobronchial tumor which obstructed the lingular bronchus. Histopathologic examination of a bronchoscopic biopsy of the tumor was consistent with malignant melanoma. Skin, mucosal, and eye examinations failed to detect the primary site of melanoma and the patient was diagnosed with endobronchial melanoma of unknown primary (MUP). Although the patient underwent a curative surgical resection, recurrence was detected in 4 months. Endobronchial MUP is a rare presentation of melanoma and better therapeutic strategies need to be established.

1. Introduction

Malignant melanoma is a potentially fatal neoplasm arising from the melanocytes in the deeper layers of the skin [1]. Although melanoma is mostly of cutaneous origin, it can occur at any location where melanocytes are present such as the oral cavity, larynx, esophagus, anogenital mucosa, and eyes [2]. Melanoma of unknown primary (MUP) is a histologically confirmed melanoma metastasis to the lymph nodes, subcutaneous tissue, or visceral organs, occurring without any known primary lesion [3]. MUP accounts for up to 3% of all melanomas [4,5], among which nodal metastasis is the most common (approximately 40–60% of all cases), followed by subcutaneous metastasis (approximately 30% of cases) [6]. Visceral organs are the least commonly diagnosed MUP sites and endobronchial MUPs are particularly rare [7]. Due to the rarity, guidelines on the treatment of MUP are not well-established. We report a case of an endobronchial MUP that recurred shortly after curative surgical resection.

2. Case description

A 62-year-old man presented to our hospital with cough and hemoptysis that started a week prior. The patient's vital signs were stable. The patient was under medication for hypertension and type 2 diabetes, and had been treated for pneumonia of the left upper lobe 2 months ago. Chest computed tomography (CT) scan revealed an endobronchial lesion in the lingular division (Fig. 1). The patient underwent bronchoscopy, which revealed an endobronchial mass obstructing the lingular bronchus (Fig. 2). The mass was ocher-colored, firm, and had prominent superficial vessels oozing with blood. Biopsy samples sent for pathologic evaluation showed

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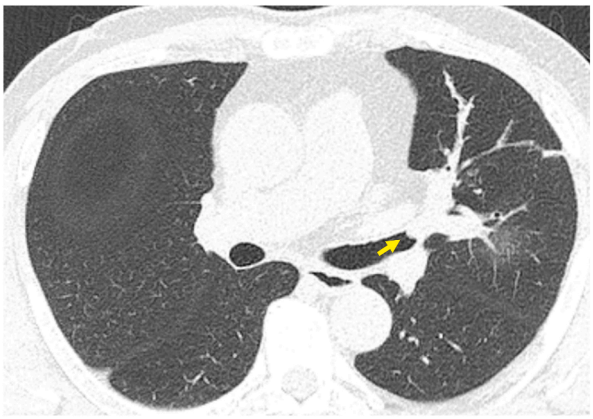

Fig. 1. Chest computed tomography scan of the patient
A suspicious endobronchial lesion in the lingular division is visible.

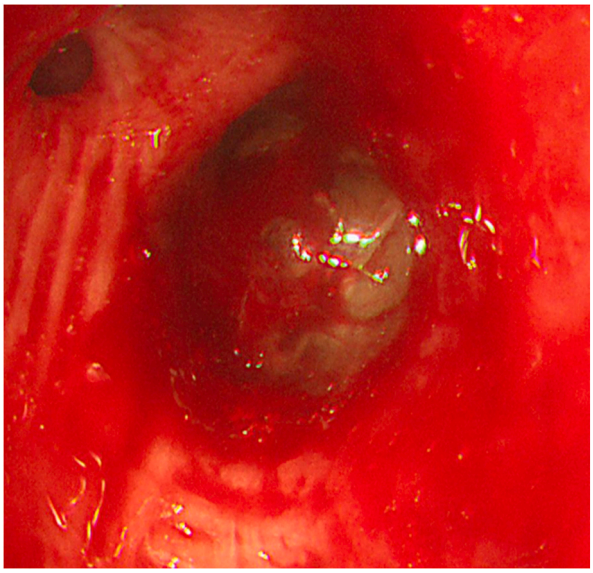

Fig. 2. Bronchoscopy image of the endobronchial melanoma of unknown primary at the initial diagnosis
It shows a round, firm, and ocher-colored mass, almost completely obstructing the lingular bronchus.

tumor cells with round to pleomorphic contours and plump cytoplasm. Additionally, dark brownish, coarse melanin granules were present in some of the tumor cells (Fig. 3A). On immunohistochemical staining, the tumor cells were found to be strongly positive for S-100 and HMB-45 (Fig. 3B), which supported the diagnosis of malignant melanoma.

F-18 fluorodeoxyglucose positron emission tomography/CT scan was performed and a hypermetabolic lesion in the lingular division was noted. However, any other lesion that suggested a primary site of melanoma was not detected. Thorough examinations of the skin and mucosa, endoscopy including nasopharyngoscopy, and ophthalmic magnetic resonance imaging (MRI), did not show evidence for cutaneous, ocular, or mucosal melanoma. Brain MRI showed no metastases in the brain. Based on this, the patient was diagnosed with endobronchial MUP.

The patient underwent left upper lobectomy and mediastinal lymph node dissection via video-assisted thoracic surgery. The pathologic findings of the surgical specimen were similar to the prior findings from the bronchoscopic biopsy specimen, showing a 1.7 $\times$ 1 cm sized tumor consistent with malignant melanoma; 17 dissected mediastinal lymph nodes were negative for malignancy. Immunohistochemical staining with BRAF(V600E) mutation specific antibody was positive. The patient developed hemoptysis 4 months after the surgery. Subsequent bronchoscopy revealed multiple, irregular-shaped endobronchial masses partially obstructing the left main bronchus (Fig. 4A) and numerous ocher- or brown-colored nodules scattered in the distal trachea, carina, and left main bronchus (Fig. 4B), suggesting the recurrence of malignant melanoma. The patient was referred to the oncology department for immunotherapy with pembrolizumab. Although pulmonary lesions initially showed partial reduction with pembrolizumab, progression was noted on the follow-up chest CT scan 7 months after the start of treatment. Additionally, MRI detected brain metastasis. Treatment was changed to dabrafenib plus trametinib and a partial response has been shown for 2 months so far.

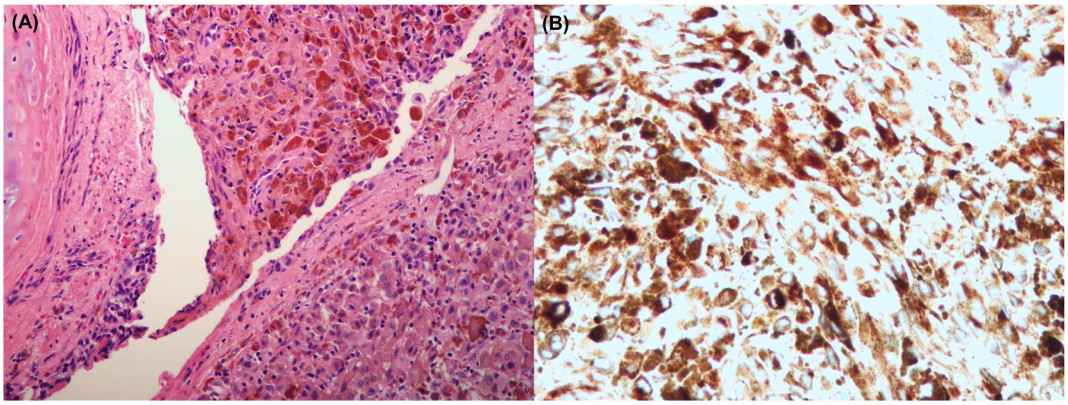

Fig. 3. Pathologic examination of the bronchoscopy biopsy specimen
(A) Tumor cells demonstrate round to pleomorphic contours with plump cytoplasm. Some of tumor cells show dark brownish and coarse melanin granules (× 200 H&E). (B) Tumor cells' cytoplasm shows strong staining with HMB45 immunohistochemistry (Common marker for melanoma, × 400).

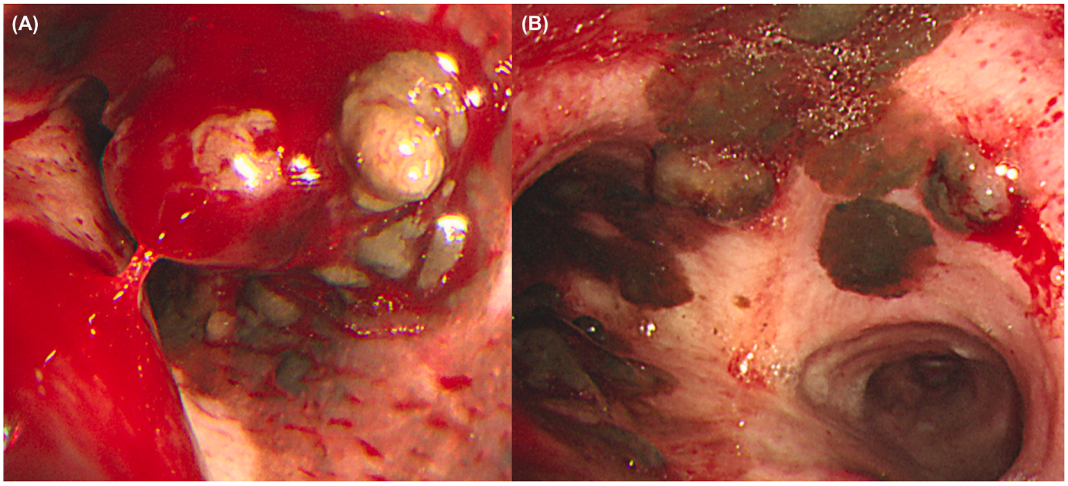

Fig. 4. Bronchoscopy images of the recurrent endobronchial melanoma of unknown primary
(A) Multiple irregular-shaped, brown-colored endobronchial tumors are partially obstructing the left main bronchus. Numerous ocher- or dark-colored nodules and patch-like lesions are also visible. (B) The recurrent melanoma extends up to the carina and distal trachea. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

The incidence of malignant melanoma has increased steadily over the last several decades [8]. However, the incidence is far lower in Asian populations than in Caucasians owing to predisposition of individuals with a fair skin tone [9]. Endobronchial MUP is a very rare presentation of melanoma and only a few cases have been reported to date in South Korea [7,10,11]. Herein, we have described a rare case of endobronchial MUP, which was accompanied with hemoptysis. The tumor was confined to a bronchus and treated with surgical resection; however, recurrence was detected after 4 months.

A thorough search for the primary site should be undertaken before making a diagnosis of MUP. In 1963, Dasgupta et al. described some exclusion criteria to help define MUP: 1) evidence of previous orbital exenteration or enucleation; 2) evidence of previous skin excision, electrodessication, cauterization, or other surgical manipulation of a mole, freckle, birthmark, paronychia, or skin blemish; 3) evidence of metastatic melanoma in a draining lymph node with a scar in the area of the skin supplying that lymph node basin; 4) lack of a non-thorough physical examination, including the absence of an ophthalmologic, anal, and genital examination [3]. Incomplete examination can result in neglected melanoma lesions and inappropriate treatment. Therefore, the diagnosis of MUP should be made with caution.

Another conceivable diagnosis when a melanoma lesion is found in the lung is primary pulmonary melanoma. Primary pulmonary melanoma, or primary melanoma of the lung, is a very rare manifestation of melanoma arising from bronchial epithelium. There were only 40 cases reported in the literature with the diagnosis of primary pulmonary melanoma from 1916 to 2017 [12]. For the diagnosis of primary pulmonary melanoma, strict histopathological criteria should be met: (1) presence of a solitary lung mass or nodule; (2) evidence of junctional change with a “dropping off” or “nesting” of melanoma cells just beneath the bronchial epithelium; (3) invasion of the intact bronchial epithelium by melanoma cells in an area without epithelial ulceration [13]. Our case patient did not fulfil

the histopathologic criteria of primary pulmonary melanoma, and therefore was diagnosed as endobronchial metastasis from unknown primary melanoma.

The exact pathogenesis of MUP is unknown; however, several hypotheses have been proposed. One hypothesis is that it occurs due to complete spontaneous regression of a primary melanoma [14,15]. Spontaneous tumor regression of melanoma is not uncommon and has been described in previous reports [16–18]. Immunological mechanisms to explain this phenomenon have also been suggested [19,20] Another hypothesis is that MUP originates from ectopic melanocytes that have undergone malignant transformation [14]. Ectopic benign melanocytes have occasionally been found in lymph nodes and other tissues.

Several studies have attempted to compare the prognosis of MUP to melanoma with a known primary. Interestingly, some studies reported better outcomes in patients with MUP than in matched patients with melanoma with a known primary. Lee et al. have shown a greater survival in patients with stage III and IV MUP than those with melanoma with a known primary [21,22]. A meta-analysis also found better survival outcomes in patients with MUP than in those with a known primary at the same corresponding stage [23]. It can be speculated that the absence of primary cutaneous melanoma translates into lesser tumor burden and better prognosis [4]. In addition, MUP may have a different biology that initially induced the regression of the primary lesion, favoring a better prognosis [24]. Nevertheless, the prognosis of endobronchial MUP has not been well described due to its rare occurrence. The prognosis may be different among various MUPs depending on the site of development. Previous studies have shown a significantly better prognosis for nodal MUP, compared to subcutaneous or visceral MUP [6]. In fact, recurrence occurred shortly after complete surgical resection in the present case, suggesting an aggressive nature of the tumor.

Patients with endobronchial melanoma metastasis are considered to have overall poor survival. A previous study including 19 patients with endobronchial metastasis from melanoma showed that the median overall survival was 6 months [25]. Different treatment modalities including surgery, radiotherapy, chemotherapy, and bronchoscopic procedures did not impact the survival rate. Although the patients included in that study had been treated before the era of novel therapeutics such as immune check point inhibitors, the dismal prognosis of endobronchial melanoma metastasis is notable. In general, early aggressive surgical treatment should be sought in eligible patients with MUP in a similar fashion as in patients with melanoma with a known primary [6]. In addition, the introduction of novel therapies has dramatically improved survival in advanced melanoma. The first-line therapeutic options include immunotherapy with PD-1 inhibitors (either as monotherapy or in combination with a CTLA-4 inhibitor) or targeted therapy with BRAF and MEK inhibitors. A population-based study conducted in Netherlands investigated the treatment outcomes of MUP in the era of novel therapies [24]. In patients with stage IV melanoma, the median survival has significantly increased after the introduction of novel therapies (11 months vs. 4 months). Our patient was referred to the oncology department for immunotherapy after the recurrence.

It is estimated that approximately 75–80% of patients who undergo metastasectomy develop recurrences [26]. The role of adjuvant immunotherapy as monotherapy or in combination in patients with resected or completely irradiated stage IV melanoma was not known. A couple of years ago, promising results of a randomized phase 2 trial were reported comparing the efficacy of adjuvant nivolumab plus ipilimumab versus nivolumab alone versus placebo in patients with metastatic melanoma that was completely treated by surgical resection or radiotherapy [27]. Nivolumab plus ipilimumab and nivolumab alone improved relapse-free survival compared to placebo (hazard ratio 0.23 and 0.56, respectively). Updated data on the study with a longer follow-up of 49.2 months were recently reported [28]. The updated recurrence-free survival results confirmed the benefit of nivolumab plus ipilimumab and nivolumab alone. The overall survival was also significantly improved with nivolumab plus ipilimumab. Given these results, more effective therapeutic strategies by combining immunotherapy or targeted therapy with surgical treatment are warranted in endobronchial MUP.

In conclusion, this was a rare case of endobronchial MUP. A thorough examination for the primary site is important for making a diagnosis of MUP. Better understanding of its pathogenesis, prognosis prediction, and treatment is warranted.

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Declaration of competing interest

The authors have no potential conflicts of interest to disclose.

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