Clinical Case Report

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Endobronchial melanoma metastasis 40 years after the excision of the primary cutaneous tumor

A case report

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Abstract

Rationale: Endobronchial melanoma metastases are rare, comprising 4.5% of all endobronchial metastases. They are diagnosed at a median time of 48 months from primary tumor presentation, and survival of these patients is poorer when accompanied by other metastatic sites or malignant pleural effusion. We present a case of endobronchial melanoma metastasis happening 40 years after the initial diagnosis. The need of adjuvant techniques in the diagnosis of this tumor is highlighted and a short review on this rare phenomenon is provided.

Patients concerns: An 83-year old nonsmoking woman, presented with dyspnea.

Diagnoses: Left lung atelectasis was found.

Interventions: Endobronchial resection of a tumor of the left main stem bronchus was achieved by rigid bronchoscopy under general anesthesia with complete reventilation of the left lung.

Outcomes: Histopathological, immunohistochemical and molecular diagnostics of the resected tumor led to a diagnosis of an endobronchial melanoma metastasis.

Lessons: Melanoma is a type of tumor that cannot be regarded as cured even after long disease-free periods, and thus, any new symptomatology in these patients warrants stringent work up.

Abbreviations: AE1/AE3 = cytokeratin AE1/AE3, BRAF = v-raf murine sarcoma viral oncogene homolog B1, CD34 = cluster of differentiation 34, CT = computed tomography, CTLA-4 = cytotoxic T lymphocyte-associated antigen 4, DAB = 3,3′-diaminobenzidine, EMA = epithelial membrane antigen, GFAP = glial fibrillary acidic protein, HES = hematoxylin, eosin, saffran, HMB-45 = human melanoma black-45, KL1 = cytokeratin KL1, MDM2 = mouse double minute 2 homolog, MEK = mitogen-activated protein kinase, MiTF = microphthalmia-associated transcription factor, p40 = ΔNp63 isoform, PD-1 = programmed-death 1, PEC = perivascular epithelioid cell, PET = positron emission tomography, S100 = S100 protein, STAT6 = signal transducer and activator of transcription 6, TTF1 = thyroid transcription factor 1.

Keywords: *BRAF*, differential diagnosis, lung, recurrence

1. Introduction

Endobronchial melanoma metastases are rare, comprising 4.5% of all endobronchial metastases.[1] We recently showed that survival of patients presenting with endobronchial melanoma metastases is poor when accompanied by other metastatic sites or malignant pleural effusion.[2] Furthermore, we found that endobronchial metastases present from 0 to 120 months (median 48) after the diagnosis of the primary tumor.[2] We present here the case of an endobronchial melanoma metastasis developing 475 months (almost 40 years) after the initial diagnosis, which is of the most delayed recurrences of melanoma ever described.

2. Case presentation

An 83-year old nonsmoking woman, presenting with dyspnea, was referred to our center for endobronchial resection of a tumor of the left main stem bronchus causing left lung atelectasis. Successful tumor resection was achieved by rigid bronchoscopy under general anesthesia with complete reventilation of the left lung. The tumor stalk was on the posterior and distal part of the left main stem bronchus with invasion of the Nelson bronchus (B6) (Fig. 1).

The microscopic examination showed a tumor composed of fusiform or rarely epithelioid cells (Fig. 2). Atypia was moderate and mitotic activity was 14 mitoses/10 high power fields. An immunohistochemical study showed that tumor cells were focally positive for the S100 protein; they were negative for epithelial markers [AE1/AE3 (AE1/AE3: cytokeratin AE1/AE3), KL1 (cytokeratin KL1), EMA (epithelial membrane antigen), p40 (ΔNp63 isoform), TTF1 (thyroid transcription factor 1)], mesenchymal markers (desmin, myogenin, caldesmon), melanocytic markers [HMB-45 (human melanoma black-45), Melan A, MiTF (microphthalmia-associated transcription factor)], CD34 (cluster of differentiation 34), STAT6 (signal transducer and

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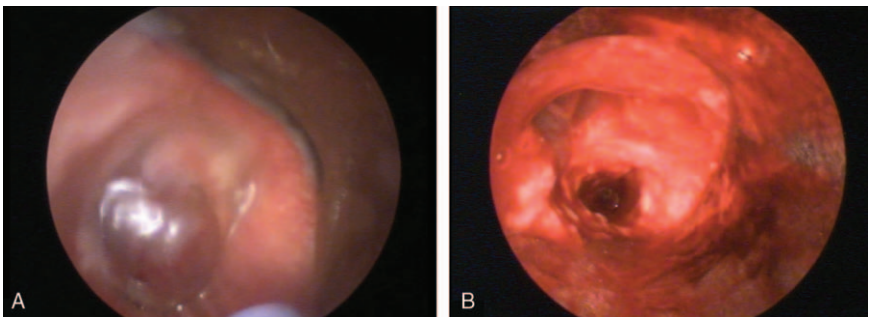

Figure 1. (A) Complete obstruction of the left main stem bronchus by a pinky and soft exophytic tumor, as seen by the rigid bronchoscope. (B) After bronchoscopic debulking, reopening of the left main stem bronchus. The lower lobe bronchus is open. The upper lobe bronchus is at this step of treatment partially obstructed by pus.

activator of transcription 6), and GFAP (glial fibrillary acidic protein). The main differential diagnoses of this S100+ poorly differentiated fusiform neoplasm were dedifferentiated liposarcoma and melanoma. Therefore, *MDM2* (mouse double minute 2 homolog) amplification and *BRAF* (v-raf murine sarcoma viral oncogene homolog B1) mutation were searched for. There was no *MDM2* amplification, but *BRAF* V600E mutation of exon 15 was present. As such, a diagnosis of melanoma was made. Clinical history revealed that the patient had a dorsal melanoma excision in 1977, whose slides were impossible to retrieve. Informed consent has been obtained. The patient died 3 months after endobronchial resection.

Regarding other entities entering the differential diagnosis of this tumor, sarcomatoid carcinoma should be suspected due to the localization and the fusiform morphology; it was excluded in the basis of epithelial markers negativity, a notion also reinforced by the nonsmoking status of the patient. S100 positivity and endobronchial localization should also set the suspicion of a myoepithelial carcinoma with overgrowth of the myoepithelial component; however, negativity for epithelial markers and GFAP made this diagnosis less possible. Sarcomas primary or metastatic were also excluded in the absence of relative markers expressed and clinical history. PEC (perivascular epithelioid cell)oma was also considered, due to the S100 positivity but morphology and negativity for other melanocytic markers excluded this possibility.[3]

3. Discussion

This case is unique in many aspects. First, to the best of our knowledge, such a late melanoma recurrence is hardly reported. In a recent retrospective analysis of 1372 stage I-II melanoma patients that survived more than 10 years, recurrence at least 10 years after the initial diagnosis was found in 5.6% of them; however, the time of the recurrence is not specified.[4] Age under 40 years, Breslow thickness >2 mm, and Clark Level IV/V were associated with late recurrence.[4] When all stages are included, the risk of recurrence at 15 and 25 years is 6.8% and 11.3% respectively, with thinner Breslow lesions, age<50 years, and negative lymph nodes being independent factors for late recurrence.[5] Recurrences can be locoregional with a reported frequency of 46%[5] to 67.5%[4] or distant with lung and brain being mostly affected.[4] In another series examining late melanoma recurrences, 48.2% are reported at 10 to 12 years after initial diagnosis, 23% at 13 to 15 years, 14% at 16 to 19 years, and the rest of them 20 years after the initial diagnosis.[6] The 2 most distant recurrences were at 45 and 47 years, but both in patients with ocular melanoma; the mean disease-free interval for cutaneous melanomas was 14.3 years.[6]

Second, this was an endobronchial metastasis of melanoma, which is a rare occurrence, as endobronchial metastases are mostly found with breast, kidney, colon, stomach, and prostate carcinomas.[1] Patients with endobronchial melanoma metastasis have 6 months overall median survival[2] confirming the poor survival in the case of our patient.

Third, histopathological diagnosis was a difficult one, as this was an undifferentiated tumor, not only morphologically but also immunohistochemically. A broad spectrum of immunohistochemical markers were employed to finally exclude a sarcomatoid carcinoma, an often proximal lung tumor typically presenting in smokers and showing epithelial markers expression, a myoepithelial carcinoma which is a proximal endobronchial salivary

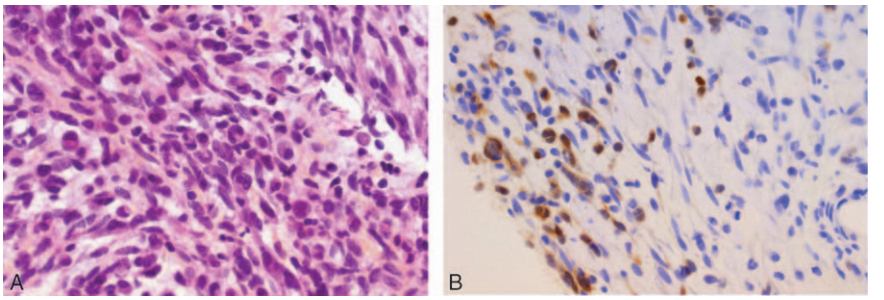

Figure 2. (A) The neoplasm is composed of fusiform or epithelioid cells into a loose fibrous background. No pigment is seen (HES × 400). (B) S100 protein expression from some of the tumor cells, mostly the epithelioid ones (DAB × 400). DAB = 3,3′-diaminobenzidine, HES = hematoxylin, eosin, saffran.

gland-type tumor, showing a dual morphology and epithelial markers, S100 and GFAP positivity, as well as various sarcomas or even PEComas in view of the S100 positivity. Finally, melanoma is always a consideration in undifferentiated cases, as it can mimic virtually any tumor. Amelanotic melanomas, as in this case, are characterized by the absence of melanin production, and as such can cause diagnostic difficulties. Of melanocytic markers, the S100 protein is the most sensitive one, but even this marker can be negative in rare occasions.[7] Molecular techniques were finally used as an adjunct to the correct diagnosis. *BRAF* mutation, however, like most mutations, is not diagnostic as it can be found in other tumors too, such as lung, colon and thyroid carcinomas and Langerhans cell histiocytosis.[8] Nevertheless, the combination of the data, that is, clinical history, morphology, immunohistochemistry, and molecular profile, points to a melanoma metastasis diagnosis.

No other melanoma sites or suspect skin lesions were found. This makes the possibility of being a metastasis of a second primary melanoma rather unlike; on the other hand, we cannot completely exclude the very rare case of a primary bronchial melanoma. Given, however, the clinical history, an endobronchial metastasis should be considered much more possible. In this direction, a morphological, immunohistochemical, and molecular comparison with the primary lesion could be of help; however, metastases can always have a different profile in comparison to the primary tumor, and thus a negative (different to that of the primary tumor) result would not exclude metastasis.

Melanoma patients follow-up includes advice for regular self-examinations of the skin and peripheral lymph nodes, as well as clinical examination the frequency of which varies between recommendations.[9] Similarly, there is no consensus on the use of imaging techniques; routine imaging techniques are not recommended for patients with a thin primary melanoma, whereas in high-risk patients (thick primary tumors or metastatic disease) lymph nodes ultrasound, CT (computed tomography) or whole-body PET (positron emission tomography)/PET–CT scans can be used.[9] Serum S-100 is the most accurate blood test in the follow-up of melanoma patients, but blood tests are not widely recommended.[9]

New treatments, especially for metastatic disease, include immunotherapy, such as CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) blocking agents and anti PD-1 (programmed-death 1) antibodies, and targeted therapy such as BRAF and MEK (mitogen-activated protein kinase) inhibitors. The recommendations for first-line treatment of metastatic disease vary, but for BRAF-mutated melanomas, combination of BRAF inhibitors with MEK inhibitors is reasonable, whereas anti CTLA-4 and anti PD-1 approaches are efficient in wild-type BRAF melanomas.[9] Thus, molecular analysis preferentially of the metastatic disease guides treatment, and our patient would also benefit from such an approach.

Our case, thus, shows one of the most late recurrences and provides further evidence for the theory of dormancy according to which tumor cells can exist but remain asymptomatic for long periods. As shown in a mouse model, tumor cells disseminate early during growth of the primary tumor, and not later as largely believed, and these disseminated cells stay dormant through immune control.[10] The development into overt macrometastases varies among organs and reflects the need for additional site-specific adaptation, such as the permissiveness of the immune environment.[10]

To conclude, melanoma is a type of tumor that cannot be regarded as cured even after long disease-free periods. It can show very delayed recurrences, even 40 years later, and at sites not traditionally expected, as inside the bronchus. Thus, any new symptomatology in these patients warrants stringent work up.

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