CASE REPORT

Primary pulmonary melanoma: the unexpected tumour

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SUMMARY

A 62-year-old woman was referred to our pulmonology team with exertional dyspnoea and chest tightness of 2 months duration. Her medical history included cervical cancer and thyroid nodules. Imaging studies showed collapse of left upper lobe. Fiberoptic bronchoscopy unveiled an endoluminal lesion and bronchial biopsy displayed features of melanoma. She denied a history of melanoma or excision of lesions of skin, mucous membranes or the eye. A thorough evaluation including combined positron emission tomography with CT scan excluded other possible sites of primary melanoma, but there was a metastasis in a thoracic vertebra. Palliative radiotherapy of the spine was performed. Chemotherapy initiation with dacarbazine was postponed by the appearance of a malignant pleural effusion, confirmed by pleural fluid cytology. After four cycles chemotherapy was discontinued due to disease progression. The patient is still alive with a follow-up of 12 months, currently on best supportive care.

BACKGROUND

Worldwide, approximately 160 000 new cases of melanoma are diagnosed each year.[1] It is known that malignant melanoma occurs most frequently on sunlight exposed areas, but it can also arise from other organs and tissues.[2] Among all, primary pulmonary melanoma (PPM) is the rarest type of visceral melanoma[3] accounting for only 0.01% of primary lung tumours.[2] On the other hand, pulmonary metastases are the most common presentation of advanced melanoma.[4] Therefore, to assure the diagnosis of PPM, an extrapulmonary origin must be ruled out by a thorough evaluation.[2] In confirmed cases, treatment of choice is surgical resection with an oncologically adequate margin and lymph node involvement at time of operation does not seems to impair long-term survival.[5]

This case recalls that, although rare, melanoma can be a primary lung tumour. An accurate diagnosis requires detailed investigation and fulfilment of specific criteria and we believe a PET-CT scan may assist this process.

CASE PRESENTATION

A 62-year-old Caucasian female was referred to our pulmonology team with progressive exertional dyspnoea and persistent chest tightness with 2 months of duration. Her medical history included a cervical cancer 15 years ago, which was treated with total hysterectomy and bilateral salpingo-oophorectomy. She also reported having newly diagnosed thyroid nodules still being evaluated by her family physician. She was a non-smoker. The physical examination was normal.

INVESTIGATIONS

A plain chest radiograph (PA view) showed a global mediastinal shift to the left and a soft tissue opacity in the left upper thorax with the shape of a semicircle, measuring about 35 mm of diameter. Its base was located in the mediastinum causing a loss of the normal radiographic contour of pulmonary trunk and left auricular appendix—silhouette sign (figure 1).

A thoracic CT scan was performed, confirming the mediastinal shift and revealing almost total collapse of left upper lobe. Presence of an endoluminal lesion on the left upper lobe bronchus was assumed. The remaining parenchyma was slightly hyperinflated and no other alterations were apparent (figure 2).

Fiberoptic bronchoscopy showed a polilobulated endoluminal lesion occluding the entrance in the left upper lobe bronchus, which was subjected to bronchial biopsy. The tumour displayed histological and immunohistochemical features compatible with malignant melanoma (figures 3–8). It caused ulceration of the bronchial epithelium. A dark pigment was observed in the cytoplasm of tumour cells, which showed positive staining for S-100 and negative staining for keratin.

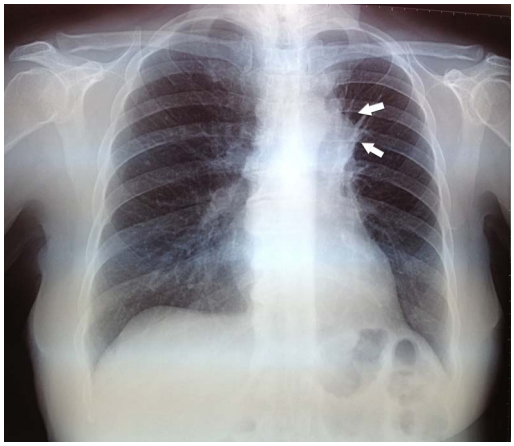

Figure 1 Chest radiograph (posteroanterior view) showing a semicircular opacity in the left upper thorax with the base located in the mediastinum (white arrows show the lateral edge).

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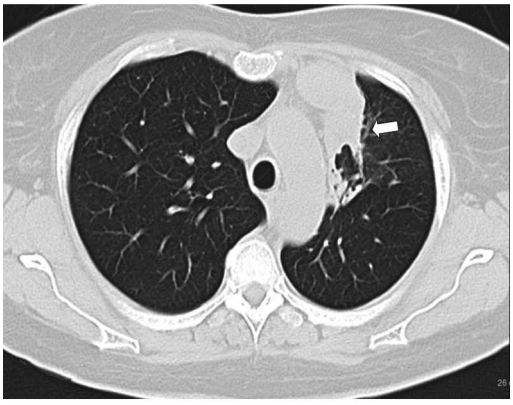

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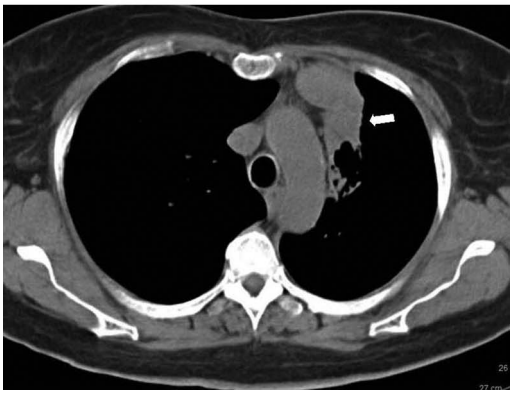

Figure 2 Thoracic CT scan showing mediastinal shift to the left and collapse of left upper lobe (white arrow) (A) lung window and (B) mediastinal window.

Whole body PET-CT scan showed a hypermetabolic lung lesion near the left hilum with 18 by 17 mm and 2 hypermetabolic lesions suggestive of secondary nodal involvement (one in the left hilum and another in the anterior mediastinum) and a suspected lesion in the second thoracic vertebra (figure 9). Spine CT scan and MRI confirmed the suspected bone metastasis (images not shown). A cranial CT scan showed no abnormalities (images not shown).

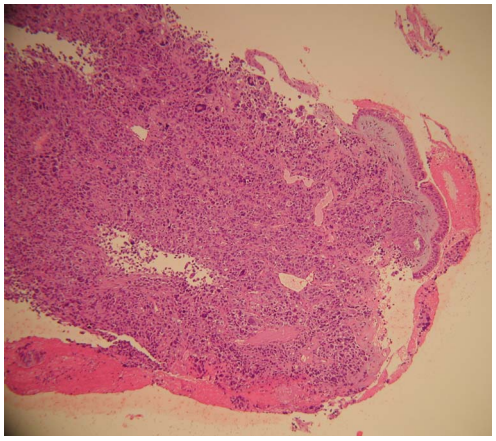

Figure 3 Bronchial biopsy: H&E, ×100 magnification. Malignancy with solid growth pattern underlying the mucosa.

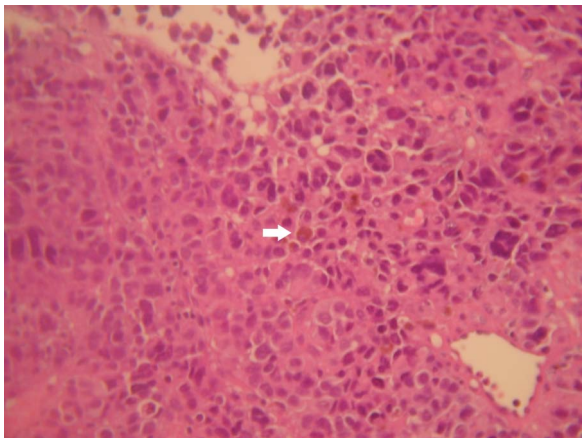

Figure 4 Bronchial biopsy: H&E, ×400 magnification. Presence of large cells with hyperchromatic and vesicular nuclei. Some cells have dark brown pigment in the cytoplasm (white arrow).

When questioned, the patient denied a history of melanoma or fulguration/excision of lesions of skin, mucous membranes or the eye. We performed a systematic and detailed search of possible sites of primary melanoma, including an inspection of the skin and mucous membranes, with assessment of scalp, palms and plants, eye, nasopharyngeal and oral mucosa, perineum and genitals.

DIFFERENTIAL DIAGNOSIS

The main differential diagnoses are PPM and pulmonary metastases of melanoma. Diagnostic criteria and required evaluation will be detailed during discussion.

TREATMENT

First, the patient underwent palliative radiotherapy of the spine. She did not present BRAFV600E mutation and therefore was proposed to chemotherapy with dacarbazine after discussion in multidisciplinary meeting.

At the time scheduled to begin chemotherapy, the patient presented with symptoms of dyspnoea, with no other symptoms. A left large pleural effusion was diagnosed. The patient was admitted and underwent a diagnostic thoracentesis, which revealed presence of malignant cells. The pleural cavity was evacuated, with symptom relief. Chemotherapy was then initiated.

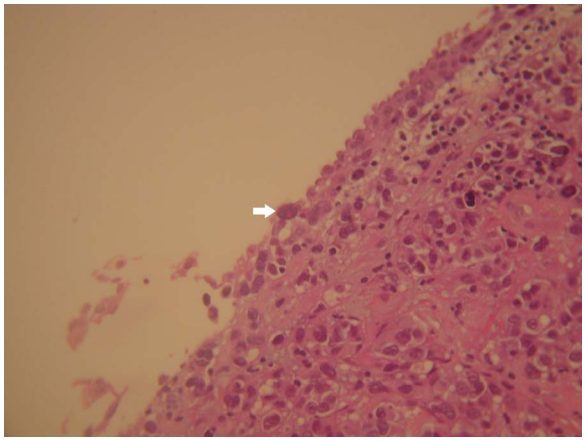

Figure 5 Detail of the tumour, where one can see the migration of malignant cells to the epithelium (white arrow). H&E, ×400 magnification.

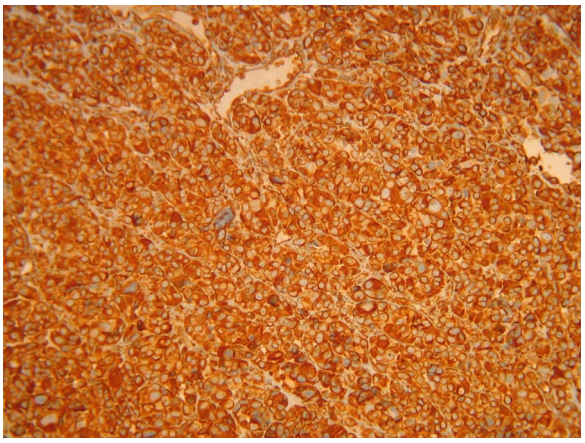

Figure 6 Bronchial biopsy: immunohistochemistry—vimentin antibody staining, ×200 magnification. Diffuse and intense immunoreactivity for neoplastic cells.

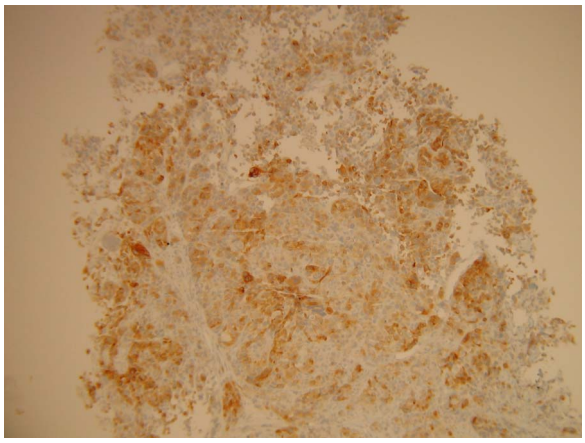

Figure 8 Bronchial biopsy: immunohistochemistry—melanin stain, ×200 magnification. Intense immunoreactivity for neoplastic cells.

OUTCOME AND FOLLOW-UP

We have now 12 months of follow-up. Chemotherapy was discontinued after four cycles due to disease progression with new vertebral metastases. Palliative radiotherapy was performed. The patient is currently on the best supportive care.

DISCUSSION

The occurrence of a primary melanoma of the lung remains a matter of controversy. Actually, the issue is 'how can melanoma develop as a primary lung neoplasm?'. For a melanoma to arise from the lung, melanin-containing cells, which serve as a precursor to the malignancy, must exist.[6] These cells do not seem to be present in normal tracheobronchial tree.[6] However, some investigators propose that pulmonary melanoma can arise from a small number of melanoblasts present in the respiratory tract due to the shared embryologic origin of trachea and oesophagus,[6] which is an organ with recognised existence of melanoblasts.[3] Despite this appealing assertion, during the investigation of a suspected PPM one must always bear in mind that a malignant melanoma of the skin might spontaneously regress despite having metastasised,[7] which poses a diagnostic challenge. Distinguishing primary melanoma of the lung from metastatic melanoma to the lung is not easy. In fact, lung metastasis may occur in 12% of melanomas, being solitary in about 25%.[8]

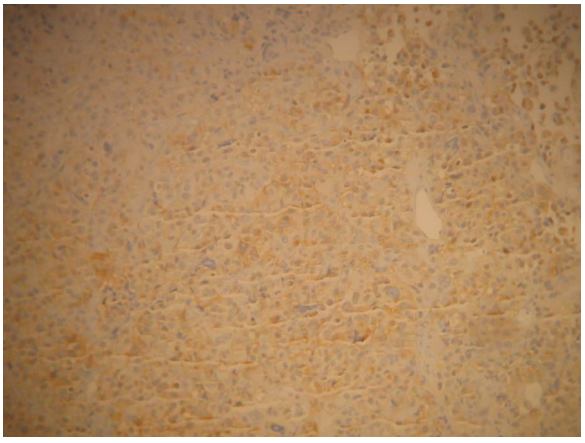

Figure 7 Bronchial biopsy: immunohistochemistry—S100 antibody staining, ×200 magnification. Focal and moderately intense immunoreactivity for neoplastic cells.

Because of the aforementioned, histological and clinical criteria for PPM were established.

Allen and Drash[9] proposed histological criteria. These included (1) junctional change with nesting of melanoma cells just beneath the bronchial epithelium; (2) invasion of bronchial epithelium by the malignant cells in an area without epithelial ulceration and (3) an obvious melanoma beneath the above described changes. However, the inability to demonstrate an intraepithelial component or nevus associated with the invasive component should not preclude the diagnosis of primary lung melanoma.[10] Another important aspect is the existence of ulceration of the bronchial epithelium. On one side, there are reports of metastatic melanomas to the lung which exhibit intraepithelial growth.[11] On the other hand, in some cases of PPM an overgrowth of the invasive component may occur, with ulceration of bronchial epithelium.[10] Therefore, some authors consider that the presence of an in situ component is not a reliable criterion of primary pulmonary origin[10] and that the presence of an intraepithelial component should not be included in the diagnostic criteria of PPM.[11]

Allen and Drash[9] also warned that melanomas can masquerade as poorly differenciated carcinomas, fibrosarcomas, liposarcomas and other histological types of tumour such that the pathologist must 'think melanoma' in order to diagnose melanoma.

The clinical criteria proposed by Jensen and Egedorf[12] are now broadly accepted. The diagnosis requires four clinical criteria: (1) a solitary lung mass or nodule; (2) typical histopathology confirmed by immunohistochemistry and/or electron microscopy; (3) no prior history of melanoma or excision/fulguration of a cutaneous, mucous membrane or ocular lesion unless the pathological examination explicitly ruled out a melanoma and (4) no demonstrable melanoma outside the chest at the time of diagnosis.

Histopathological and clinical criteria should be pursued to ensure the diagnosis of PPM. But although the diagnosis is still based in old criteria that refer to features present at surgery, the current widespread use of PET-CT warrants some comments and probably justifies a review of these criteria. PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has already demonstrated its utility in cancer, namely in lung carcinoma or lymphoma. Given

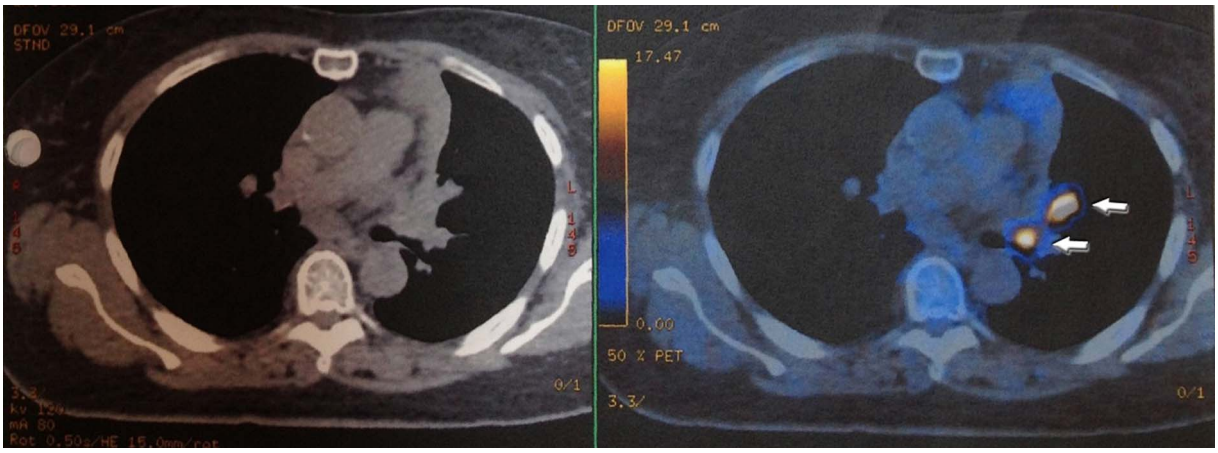

Figure 9 Positron emission tomography-CT scan showing a hypermetabolic lung lesion near the left hilum and an adjacent hypermetabolic lesion suggestive of secondary nodal involvement (white arrows).

the rarity of the disease, there are no large studies to define the exact role of a PET-CT in the investigation of PPM. However, some authors already described this exam as part of the diagnostic process. Praske *et al*[10] and Neri *et al*[13] reported cases of PPM in which a PET-CT scan was performed to confirm the hypothesis, showing the absence of a tumour outside the thorax. In their report of a case of PPM Ouarssani *et al*[14] stated that advent of PET scans will definitely change the diagnostic attitude since the probability of PPM increases if there is a single pulmonary uptake of 18F-FDG and histological diagnosis of melanoma. In fact, given its higher frequency, most studies about PET scan and melanoma are performed on cutaneous tumours. Nevertheless, some ideas can probably be extrapolated and applied to the PPM. Much like what happens with PPM, the main concern in cutaneous malignant melanoma is to exclude other sites of disease. But in this case the objective is deciding the most appropriate treatment. It is recognised that conventional imaging methods (radiography, ultrasonography, CT and MRI) may overlook secondary locations, because they are based solely on the existence of a morphological difference.[15] Therein arises PET scan, as it also provides a functional image. PET scan may be useful in distant staging[16] such as soft tissue, lymph nodes and viscera[15] with high specificity and intermediate-high sensitivity.[17] Fusion image of PET-CT scan allows a more precise diagnosis that isolated PET.[15] Concerning the role of PET-CT scan in the diagnosis of PPM we can probably assert the diagnosis with confidence in a patient without a history of extrapulmonary melanoma and with no suspected lesions outside the thorax in a PET-CT.

Our research, conducted in MEDLINE with the interface PubMed from 1947 to the present, in all languages, identified more than 40 published cases of PPM. Yet it is known that many do not meet the requested criteria, the main problem being the lack of trustworthy exclusion of an extrapulmonary origin. Reliable data about clinical behaviour, tumour markers, diagnostic modalities and prognostic factors are limited because of lack of large series.[5]

A review of English language literature published in 1999[6] found 19 cases which met the clinical criteria of Jensen and Egedorf. From 13 patients in whom fiberoptic bronchoscopy was performed, 8 had endobronchial disease. Among these, only four had a black or pigmented lesion. The frequent endobronchial location justifies the common symptoms: cough, haemoptyses, postobstructive pneumonia, lobar collapse and atelectasis.[5] The same review reported that 6 of 15 patients (40%) who underwent surgical resection of the tumour had lymph node involvement documented at the time of surgery. Two of these patients were free of disease at 3 and 11 years. The success of radical resection, with median survival of 30 months, suggested that an aggressive surgical approach with anatomic resection plus hilar and mediastinal lymphadenectomy must be the rule in PPM. Other authors also showed that prognosis for surgically resected patients is better than for non-surgically treated patients.[18] It is also proposed that adjuvant chemotherapy may prevent recurrences or distant metastases.[3] Treatment with dacarbazine and immunotherapy with interleukin-2 or interferon are described.[18]

A detailed medical history, a complete physical examination and ancillary studies make us believe that our patient had, at the time of diagnosis, a PPM with secondary nodal and bone involvement. She was excluded from surgical treatment because of the existence of bone metastasis and as she is still alive we do not have data on the autopsy. Between the end of palliative bone radiotherapy and chemotherapy start it was also diagnosed a malignant pleural effusion. In our case, PPM was successfully diagnosed based on bronchial biopsy, although there are known cases of misdiagnosis by such means that only come to be rectified after surgery.[3]

Learning points

- Although rare, primary melanoma of the lung should be considered in the differential diagnosis of a primary bronchial tumour.
- Histopathological and clinical criteria have been proposed and should be applied to ensure the diagnosis of primary melanoma of the lung. However, the widespread use of modern examinations, such as PET-CT scan, may assist the diagnosis process and probably justifies a review of these criteria.
- Melanomas can masquerade as other histologic types of tumour such that the pathologist must 'think melanoma' in order to diagnose melanoma.
- The success of radical resection suggests that an aggressive surgical approach with anatomic resection plus hilar and mediastinal lymphadenectomy must be the rule in PPM.
- Lymph node involvement at time of operation does not seems to impair long-term survival.

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Competing interests None.

Patient consent Obtained.

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