Reminder of important clinical lesson

It is never too late: ultra-late recurrence of melanoma with distant metastases

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Correspondence to Dr Dina Mansour, dmansour299@yahoo.co.uk**Summary**

The authors present the case of a 73-year-old lady presenting with weight loss, personality changes, transient confusion and visual loss, 38 years after initial surgical excision of a melanoma of the neck. CT and MRI of the brain showed cerebral metastases and positron emission tomography (PET)-CT showed an additional fludeoxyglucose avid lesion in the lung, which was biopsied. Histology confirmed metastatic malignant melanoma. She declined whole brain radiotherapy in favour of best supportive care and died 4 months after diagnosis. Life-long vigilance among patients with previous melanoma and awareness among physicians are necessary if late recurrences are to be recognised early, and outcomes improved. New imaging techniques including PET-CT may be helpful in diagnosing and staging melanoma recurrence. Treatment options for patients presenting with distant metastases are limited and the prognosis remains poor.

BACKGROUND

Melanoma is a malignant tumour arising from melanocytes. The annual incidence has increased consistently in recent years, possibly reflecting increased exposure to UV radiation.¹ According to most recent WHO statistics, the cumulative lifetime risk of developing melanoma in the Western world is 0.9–1.0%, and although melanoma accounts for only 5% of all skin cancers, it causes 75% of skin cancer deaths. The overall prognosis depends on Breslow depth (tumour thickness in mm) and dermal mitotic rate (number of mitoses/mm²), as well as the presence of ulceration or invasion.² Standard treatment is surgical excision, with adjuvant chemotherapy, radiotherapy or immunotherapy considered in high-risk or metastatic tumours.³

Although recurrence is relatively common in melanoma, late recurrence (defined as greater than 10 years after initial diagnosis) is rare. In a large series of over 7000 patients with melanoma, late recurrence occurred in 2.4% of cases; 48.2% of these occurred between 10 and 12 years after initial diagnosis.⁴ The most common site of recurrence was loco-regional lymph nodes followed by the lung.⁴ Current recommendations for follow-up vary, but generally include

routine 3–12 monthly history and examination for up to 10 years, with or without laboratory tests and radiographic imaging.³

We present the case of a 73-year-old lady who presented with metastatic disease 38 years after initial diagnosis and surgical excision of a melanoma, one of the longest disease-free intervals reported to date. This acts as a reminder that melanoma can never be considered ‘cured’ and life-long vigilance is required.

CASE PRESENTATION

A 73-year-old lady presented to the rapid access medical assessment clinic. She described a 6-week history of weight loss, progressive lethargy, nausea and anorexia and changes in her personality. Two weeks before presentation she had transient blurring of her vision and 3 days ago she had had an episode of confusion lasting several hours.

She had a previous cutaneous melanoma of the neck surgically excised 38 years earlier. She had no other medical history but in view of her recent symptoms she had been started on dosulepin as treatment for depression by her general practitioner.

Figure 1 Contrast CT of the brain and T2 weighted images of MRI brain with gadolinium showing metastatic melanoma lesions.

Figure 2 Positron emission tomography-CT images showing brain metastasis and lung metastasis in apex of left lung.

Clinical examination was entirely normal with no skin lesions and no focal neurology. Her abbreviated mental test score was 9/10 with one point lost on recall.

INVESTIGATIONS

Routine laboratory investigations were all normal. Chest x-ray showed a 20 mm calcified lesion in the left upper lobe. She went on to have a CT head which showed a large left occipitoparietal mass, 33 mm in diameter and a second, 18 mm diameter right frontal lobe lesion with surrounding oedema. These lesions were confirmed on MRI with the tumours demonstrating eccentric cystic change and necrosis (figure 1). CT of the chest, abdomen and pelvis showed a 20 mm left apical mass with the appearance of a benign healed granuloma. There was no evidence of any malignancy in the abdomen or pelvis.

As no primary tumour had been identified a positron emission tomography (PET)-CT was performed which showed intense fludeoxyglucose (FDG) uptake by the left upper lobe lung lesion along with two intensely FDG avid lesions in the right frontal lobe and left parietal lobe (figure 2). Histology from a CT guided biopsy of the lung lesion revealed a vascular fragment displaying trabecular architecture, nuclear pleomorphism with some prominent nuclei and intracytoplasmic brown pigment. Cells showed strong, diffuse expression of S100 and Melan A on immunohistochemistry with no expression of CK5/6, consistent with malignant melanoma.

TREATMENT

She was treated with dexamethasone and her symptoms initially improved. She was offered whole brain radiotherapy but, following discussions with family and her oncologist, she opted for best supportive care.

OUTCOME AND FOLLOW-UP

Her disease continued to progress and she was admitted to a hospice for supportive care. She died on 4 months after initial presentation.

DISCUSSION

Malignant melanoma is the third most common cause of brain metastases behind lung and breast cancer.³ The incidence of brain metastasis in melanoma patients is 9.6%⁵ and autopsy series report a prevalence of 55%–75% in patients who die of melanoma.^{5–8} The median interval from diagnosis of primary disease to development of brain metastasis is 2.2 to 3.8 years^{9 10} but disease-free intervals of

up to 17 years following treatment of primary melanoma have been reported.¹¹ In this case the interval was considerably longer.

Recurrence occurs in 30% of patients with completely resected stage I to stage III primary cutaneous melanomas.^{5 12 13} The disease free interval (time from treatment of primary melanoma to development of recurrence) is significantly longer in patients with thinner, less advanced lesions with no lymph node metastasis.¹⁴ Patients who are young at initial diagnosis and patients presenting with distant metastases as first sign of relapse are also more likely to have prolonged disease free period.¹⁴

There are no randomised controlled trials formally evaluating follow-up after treatment of primary cutaneous melanoma. Although various follow-up regimes have been proposed, few are evidence based.^{15–17} The British Association of Dermatology guidelines suggest that the follow-up interval and duration should be tailored to the stage group of the primary melanoma, which reflects the risk of recurrence.³ Duration of follow-up advised therefore ranges from 12 months in patients with stage 1A disease (tumour <1 mm thick with no ulceration), to 10 years in patients with stage IIIB, IIIC and resected stage IV melanoma (lymph node involvement or distant metastases).³ Life-long follow-up is not advocated due to limits on resources, but, as this case illustrates, patients and doctors should be aware of the risk of late recurrence, as well as new primaries, and patients should be taught how to self-examine.^{2 3}

Laboratory and imaging studies are not offered as part of routine follow-up, due to a low positive predictive value, a high false positive rate, lack of cost effectiveness and their tendency to generate patient anxiety.^{12 13 18} PET-CT is useful in the detection of visceral metastases in melanoma and therefore can be useful in diagnosis and staging of melanoma recurrence, particularly if surgery is being considered.¹⁹ CT scans of the brain can detect most brain metastases >10 mm and most haemorrhagic lesions but MRI is far more sensitive, particularly for smaller lesions, lesions in the posterior fossa and leptomeningeal lesions.¹⁹

The prognosis for patients presenting with distant recurrences of melanoma is dismal with a 5-year survival of 6.5% to 11%.¹¹ Median survival in patients with brain metastases is less than 1 year despite treatment.¹⁹ Surgery or stereotactic radiosurgery is the standard of care for patients with single brain metastasis, but only complete resection improves survival.¹⁹ SRS can be used for patients with two to five metastases in patients with a good

functional status. Whole brain radiotherapy continues to be the treatment of choice for poorly functional patients as well as those with multiple metastases, despite having little survival benefit.¹⁹

Learning points

- ▶ Life-long vigilance in patients and a high index of suspicion in physicians is required to detect recurrences early in patients with previous curative treatment for melanoma. Patients must be educated at the time of initial diagnosis and treatment as to the possibility of recurrences even decades after initial presentation.
- ▶ More research is required to try to define subgroups of patients prone to late recurrence and the most effective way of conducting long-term surveillance.
- ▶ PET-CT may become increasingly useful in the detection, diagnosis and staging of melanoma recurrence.
- ▶ Recurrent melanoma, particularly presenting with distant metastases, remains difficult to treat with a very poor prognosis.

Competing interests None.

Patient consent Obtained.

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