CASE REPORT

An incidental finding of a nodal recurrence of cutaneous malignant melanoma after a 45-year disease-free period

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SUMMARY

We report the case of an 84-year-old woman who had a nodal recurrence of melanoma 45 years after the primary diagnosis of an extremity cutaneous melanoma. It is believed to be the longest disease-free latency period reported between primary melanoma diagnosis and recurrence to date. Late recurrences of melanoma are rare and recurrence after four decades extremely rare. This article suggests melanoma is a disease with a potentially lifelong risk of recurrence and thus clinicians and patients must be vigilant and aware of this risk, particularly if late recurrences are to be recognised early and management optimised.

BACKGROUND

Malignant melanoma has shown a rapid increase in the past decades, furthermore the disease has an unpredictable and varied course potentially undergoing a phase of dormancy that is poorly understood. Primary disease can either present confined to the skin (stage I and II American Joint Committee on Cancer (AJCC) melanoma), or with metastatic spread (stages III and IV).¹ Investigations such as the use of sentinel lymph node biopsy, can unmask occult disease, and upstage a primary. Where possible, primary disease (primary skin site and lymph node disease) is surgically excised with curative intent. After surgery, many patients remain disease free for the remainder of their life, whereas others can have disease recurrence (or progression) in the form of locoregional and/or distant metastases, which may be fatal.

A recurrence of malignant melanoma can be defined as recrudescence of disease following initial treatment aimed to eliminate the known primary disease. Recurrence rates are influenced by the stage at which the primary disease first presents, and by the treatment given. Most initial recurrences occur relatively early; 50% first present within 2 years and 82% within 5 years.² Initial recurrences 10 years following initial treatment are termed late recurrences, the incidence of which is 0.5–6.7%.^{3–6} Even rarer, are those occurring after a 15-year disease-free interval; the incidence of such ultralate recurrences is around 2%.⁷

CASE PRESENTATION

An 84-year-old woman presented to her local hospital with non-specific left thigh pain. D-dimer levels were elevated, Doppler ultrasound demonstrated no evidence of deep-vein thrombosis (DVT), however incidental note of an enlarged

lymph node (4.4×2.8 cm) in the left groin was made. CT confirmed the presence of a pathologically enlarged left inguinal lymph node; there was no definitive systemic (stage IV) disease, however there were borderline changes suggestive of mediastinal lymphadenopathy and pleural thickening of the right haemithorax. Incisional biopsy of the node was positive for metastatic melanoma, following which she was referred to our regional specialist unit for further management. The thigh pain was self-limiting and not thought to be attributed to the groin lymphadenopathy. She gave a history of having had a cutaneous malignant melanoma on her left pretibial area excised 45 years previously. A discharge summary documented 'radical excision of skin, fat, deep fascia and split thickness skin graft reconstruction which confirmed malignancy with no evidence of further spread'. She recalled no adjuvant therapy, or disease recurrence in the 45-year intervening period. There had been no recognisable deterioration in her general health prior to the metastasis discovery.

Clinical examination revealed a soft tissue defect with a split skin graft reconstruction over the middle third of the left anterior tibial area, consistent with the given history. There were no signs of local disease recurrence. A 4×5 cm mass was palpable in her left groin.

TREATMENT

The patient was obese with poor mobility and numerous comorbidities (aortic stenosis, ischaemic heart disease, chronic renal failure, hypertension, hypothyroidism and cerebrovascular accident). As her general health precluded a long general anaesthesia (and therefore a lengthy radical groin dissection), we performed a limited left groin dissection.

Histology confirmed a 7 cm lymph node almost completely replaced by metastatic melanoma with extracapsular spread. There were two tumour-free lymph nodes. No adjuvant treatment was given.

OUTCOME AND FOLLOW-UP

Wound healing was delayed due to a discharging seroma sinus, taking 6 weeks to fully heal. No clinical signs of recurrence were noted on her post-operative outpatient visits. Five months following surgery, she was investigated for breathlessness; subsequently she was diagnosed with multiple lung metastases, and she died from metastatic disease the same month.

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DISCUSSION

Our patient had no evidence of a second cutaneous primary melanoma. Anogenital examination and CT examination showed no evidence of a non-cutaneous melanoma. The nodal metastasis was in the draining basin appropriate for the original primary to be the cause and hence this supports the fact this was a recurrence. It is therefore assumed the metastasis was an ultralate recurrence, 45 years following the original melanoma. However, as with all such cases, we cannot altogether exclude the possibility of her disease recurrence being a metastasis from a second melanoma with an unknown primary location, particularly a regressed second primary melanoma.

Ultralate recurrence of cutaneous melanoma with several decades of quiescence is extremely rare; we found the current longest latency period of disease-free survival from diagnosis to recurrence to be 41 years, this being only one of two documented cases with a 40+ year latency period.^{3 4}

At 45 years, we believe this to be the longest disease-free latency period reported between primary melanoma diagnosis and recurrence to date.

In our case, the patient was asymptomatic and her melanoma recurrence was incidentally discovered. Had she not been investigated for a possible DVT, it is likely the first note of her melanoma recurrence would have been in the terminal stages with subsequent lung metastases. It is speculated that a number of patients may present or die with widespread metastasis, never being brought to the attention of the services that originally treated them; therefore the true incidence of late recurrences may be underestimated.

Melanoma has an unpredictable course in that recurrence can occur in any patient with invasive melanoma regardless of tumour thickness or other histological features. There are however well-recognised prognostic factors influencing overall and disease-free survival following treatment with curative intent for a primary melanoma. The strongest indicator of prognosis is Breslow thickness (depth of vertical invasion) which unfortunately is not known for our case. Nodal and regional metastatic spread are also strong negative-prognostic factors. Other factors adversely affecting prognosis are ulceration status, mitotic rate (for thin melanomas), age greater than 65 years, male gender and an axial location of primary tumour.^{1 2} However, these negative-prognostic features appear to be largely confined to patients having recurrences within 10 years of having their primary diagnosis.

Relapses of disease following a period of dormancy appear unique to melanoma, when compared with other malignant neoplasia. These late and in particular, ultralate recurrences of melanoma are a rare and poorly understood phenomenon, with often conflicting evidence in the literature. Briele *et al*,⁵ found higher rates of late recurrence in women, especially those who were premenopausal at primary diagnosis, and an association with extremity lesions. Further studies similarly observed that patients with late recurrence (compared with early recurrence) are more likely to be female, younger, have extremity melanomas or have thinner primary melanomas of intermediate thickness.^{8–10} This contrasts with several other studies which did not observe any link between tumour location/clinical characteristics and late recurrence.^{6 9 11–14} Moreover, Tsao *et al*⁷ concluded that ultralate recurrences can occur in any patient without identifiable risk factors.

Evidence linking immunological suppression with late melanoma recurrence also exists; immunosuppressed transplant recipients have been known to develop metastatic melanoma after

receiving organs from donors with a history of melanoma; likewise, patients with a history of melanoma, have been known to develop late recurrence when immunosuppressed through other illness.³ No such immunological cause for recurrence can be demonstrated in our patient.

The incidence of melanoma is rising in the developed world and life expectancy is increasing. This leads to speculation that late and ultralate recurrences of melanoma will be seen more frequently in the future. It is therefore imperative that all clinicians are aware of the potential for recurrence decades after the primary diagnosis. They should be aware of the different types of recurrence (local, regional and systemic), and may need to enquire specifically about a history of melanoma, as many patients may not spontaneously recall/volunteer this information. It is also important that clinicians routinely examine regional draining lymph node basins to elicit clinically detectable disease, when examining any patient with a history of melanoma, however distant it is.

Over the past few years there have been advances in systemic oncological therapies for advanced melanoma disease. Treatment agents such as ipilimumab and vemurafenib have shown significant survival benefits in the trial setting.^{15 16} Evidence has suggested they work better with low-volume asymptomatic disease.¹⁷ It thus translates that earlier identification of recurrent advanced disease would be anticipated to maximise favourable outcomes for survival benefits in the future of melanoma management.

Since late/ultralate recurrence is rare, we feel routine follow-up for patients with melanoma in secondary care beyond 10 years disease-free survival is not justifiable or feasible. There is no defined patient group who are at risk of late or ultralate recurrence. Strategies should be aimed towards patient and clinician education, promoting vigilance through lifelong self-examination with supplementary patient information leaflets. Our current practice is to advise patients they have a lifelong risk of melanoma recurrence, and they are followed up under the care of a hospital specialist for a period of time as advised by UK guidelines for management of cutaneous melanoma.¹⁸ As systemic oncological therapies improve the future guidelines are predicted to include more comprehensive investigations to detect early occult metastatic recurrences in patients in the early follow-up period. However, this is unlikely to benefit the patient group destined for late/ultralate recurrence.

Learning points

- ▶ Melanoma is a disease with a potentially lifelong risk of recurrence.
- ▶ However the majority of recurrences occur within 5 years of initial diagnosis/treatment.
- ▶ Breslow thickness is the strongest indicator of prognosis.
- ▶ Clinicians should routinely examine regional lymph nodes when examining any patient with a history of melanoma, particularly those with any new symptoms, irrespective of how long ago the melanoma was discovered.
- ▶ Clinicians should encourage patient vigilance through lifelong self-examination and early reporting of new symptoms/concerns.

Contributors SHL conducted the content review.

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