Atypical late presentation of muscular metastasis of melanoma in the contralateral limb

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SUMMARY

A man in his 50s presented to plastic surgery again with a lesion on his left upper arm. He had previously been treated for a malignant melanoma (MM) on his right arm over 5 years earlier. Sentinel lymph node biopsy (SLNB) had been negative, and he had completed the recommended 5 years follow-up period. Imaging was suspicious for an intramuscular soft tissue malignancy within the triceps muscle. After discussion with the regional sarcoma service, a core biopsy was performed. Histopathology suggested a diagnosis of metastatic MM, which was confirmed after surgical excision. This case highlights a rare example of an isolated muscular metastasis of MM, which presented at a distant site, over 5 years from the original treatment. This case highlights the unpredictable nature of MM, reminding clinicians of the need for a low threshold for investigation of soft tissue masses in patients with a history of cutaneous malignancy.

BACKGROUND

Malignant melanoma (MM) is the fifth most common cancer in the UK, with over 16 000 cases per year.[1] It accounts for 4% of new cancer diagnoses, and is the 20th most common cause of death from a cancer, with over 2000 deaths per year.[1] The incidence of MM in the UK has doubled over the last 30 years, particularly in men over the age of 50, and is predicted to peak between 2030 and 2035.[2]

Patients with MM typically present with a pigmented lesion, which has undergone recent changes in appearance (eg, becoming larger or changing in colour) or become symptomatic (such as bleeding or itching). Excision biopsy confirms the diagnosis, and further wide local excision (WLE) is then performed, with margins dependent on Breslow thickness of the tumour.[3] Sentinel lymph node biopsy (SLNB) is offered depending on tumour stage (American Joint Committee on Cancer, AJCC, 8th Edition, Stage 1B–2C). Further treatment is then based on results of SLNB and the presence or development of distant metastases. This may include a combination of surgical treatments such as completion lymphadenectomy or excision of local or distant metastases. Patients with lymphatic or distant metastatic disease may also be offered oncological treatments, including immunotherapy, which has revolutionised melanoma care in the last 10 years.[4] Targets for immunotherapy include 'Checkpoint' inhibitors such as pembrolizumab and nivolumab, as well as 'Targeted' therapies against common mutagens including BRAFV600E (dabrafamenib, vemurafenib) or MEK (cobimetanib, trametinib).[5]

CASE PRESENTATION

A man in his early 50s presented to his general practitioner with a soft, asymptomatic mass on his left upper arm. He had noticed the lesion late the previous year, and it had gradually increased in size, which prompted attendance to his GP approximately 8 months later.

He was known to the regional skin cancer multidisciplinary team (MDT) following treatment and follow-up of a cutaneous MM diagnosed and treated approximately 68 months earlier. He had initially presented with a 7 mm pigmented lesion on his right upper arm. Excision biopsy had confirmed a 4.5 mm Breslow thickness nodular melanoma with a mitotic index of 14 per mm^2 and no perineural/lymphovascular invasion. 'Incipient' ulceration was present, which according to AJCC criteria, is considered as 'non-ulcerated'.[6] Final staging was that of a pT4a melanoma. He had undergone a 2 cm WLE and SLNB after MDT discussion. The WLE confirmed no residual melanoma, and the single (hot but not blue) node was negative.

The patient remained under routine surveillance through the MDT skin cancer service. In the time since his MM treatment he underwent excisions of numerous other benign cutaneous lesions including several compound and intradermal naevi. Most recently he underwent excision of basal cell carcinomas from his scalp and nose. He also received Efudix treatment for widespread actinic keratosis over his scalp in the same year as his re-referral.

He was otherwise relatively fit and well, suffering only with a previous cataract and benign prostatic hypertrophy, for which he took finasteride and tamsulosin.

INVESTIGATIONS

Urgent ultrasound arranged by his GP demonstrated a 26 × 19 × 14 mm heterogenous mass within the lateral head of the left triceps muscle. Vascular features suggested that this was unlikely to be a simple lipoma. A MRI scan was recommended and performed later that month (figure 1). This demonstrated a mass with increased signal on short τ inversion recovery imaging and intermediate signal on T2. T1 imaging showed increased signal relative to muscle, with postcontrast enhancement suggesting the presence of fatty or protein-rich material. Although non-diagnostic, findings were in keeping with a malignant soft tissue tumour or sarcoma. Staging CT demonstrated no other masses of concern.

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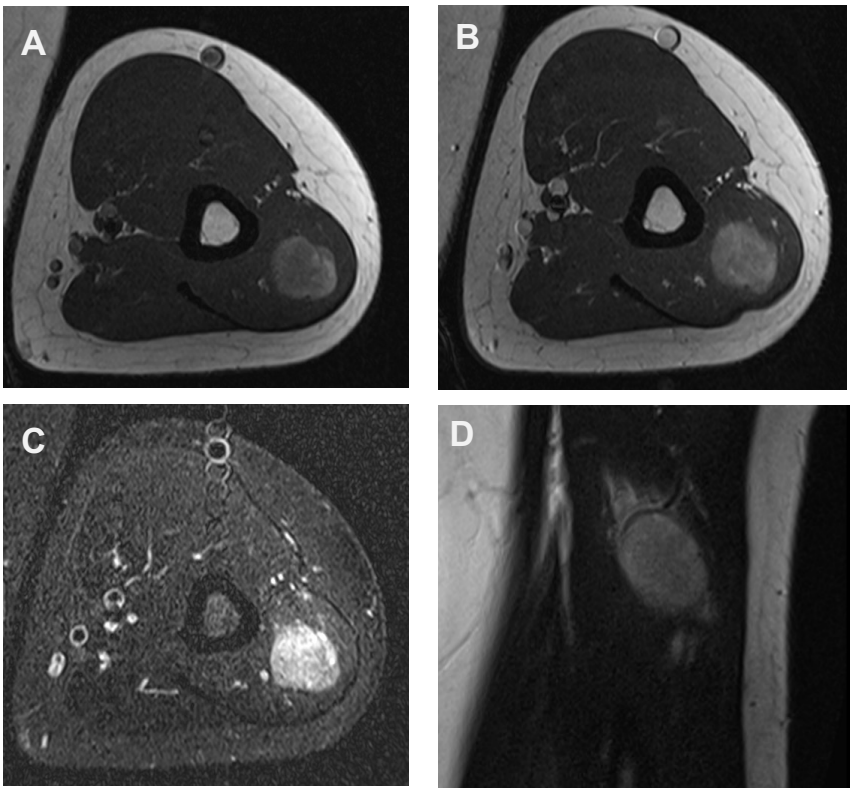

Figure 1 MRI of left upper arm demonstrating enhanced signal in T1 precontrast (A) and postcontrast (B) T1 STIR sequence (C) demonstrating increased signal, T2 image (D) showing intermediate signal. STIR, short τ inversion recovery.

DIFFERENTIAL DIAGNOSIS

Soft tissue masses of the upper limb are not unusual presentations to primary and secondary care services. The vast majority of soft tissues masses are benign, among which simple lipomas and cysts are most common. Malignant soft tissue masses include primary soft tissue cancers such as sarcomas, and secondary metastatic lesions.[7] Solitary musculoskeletal metastasis is uncommon, with a prevalence of <5%.[8]

TREATMENT

The patient was referred to the regional sarcoma MDT as per local guidelines. Core biopsy, 1 month after his initial ultrasound scan, suggested a diagnosis of metastatic MM. Excision was performed within 3 weeks of his core biopsy (figure 2). The lesion was completely excised, although with narrow margins (0.1 mm).

OUTCOME AND FOLLOW-UP

Formal pathology confirmed the diagnosis of metastatic MM. Genetic analysis demonstrated an NRAS variant, however no mutations were identified in either BRAF or KIT. As per National Institute for Health and Care Excellence guidance for stage IV MM,[3] he has started taking and completed seven cycles of nivolumab (anti-PD-1 antibody) immunotherapy under the care of the oncology service with most recent CT imaging demonstrating no evidence of further metastases or recurrent disease.

DISCUSSION

MM typically metastasises locally to other cutaneous areas, subcutaneous tissue or lymph nodes, and to distant sites including the liver, brain and bone. In a retrospective study spanning 14 years and 67 cases of cutaneous MM which had developed metastases, Tejera-Vaquerizo *et al*[9] found that 55% developed lymph node metastasis in the first instance, with 14.9% developing distant metastasis. Similarly, Meier *et al*[10] reviewed 466 cases of metastatic cutaneous MM and found 50.2% presented in lymph nodes and 28.1% presented with distant metastasis. Distant metastasis was the least common form of metastases overall in both of these studies. Interestingly, in both studies, development of distant metastases occurred on average 25 months following initial MM treatment, regardless of whether the primary cutaneous MM had lymph node involvement at the time of primary treatment. The authors of these studies suggest development of distant metastases that was not dependent on initial lymphatic spread, and highlighted the lack of role for SLNB in improving the prognosis of this group of patients.

Muscular metastasis of any tumour is uncommon. Reasons for this are unclear, but are thought to relate to factors including variable blood flow, higher tissue pressures and an acidic environment.[11] The most common primary carcinomas which metastasise to muscle are lung, kidney and colon.[11]

Melanoma metastasis to muscle is rare and when it occurs, most commonly affects the lower limb muscles, followed by the trunk. In a retrospective review of 305 patients with MM over a 7-year period, Gómez-León *et al* reported an incidence of 1.3% for solitary distant muscular MM metastasis.[12] Two series of patients with muscular metastases demonstrated MM primaries in 0.13%[13] and 3.4%[8] of cases, respectively. Thigh muscles were the most frequent site of metastasis.

This case is unusual compared with previous case report publications in the literature. First, it reports a muscular metastasis in a patient with a negative SLNB, in the era of routine lymph node investigation. For stages 1B and 2 melanoma, SLNB is

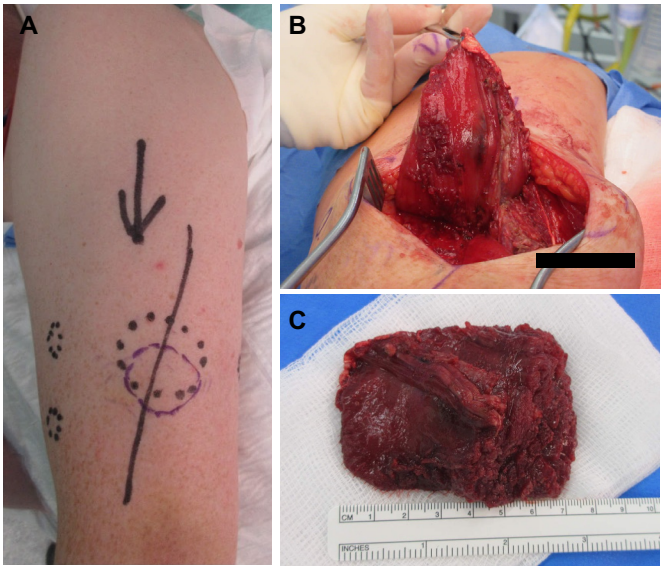

Figure 2 Clinical photography demonstrating location of palpable mass in left upper arm. (A) Preoperative marking and identification of lesion (central dotted area). Note adjacent dotted circles identify incidental lipomas also located in left upper arm. These may have led to delay in patient presentation to primary care. (B) Intraoperative image of lesion within left triceps muscle. (C) Specimen of left triceps muscle and metastasis after excision.

recommended due to the likelihood of early lymphatic metastasis, which may not be identified on imaging.[3] A negative SLNB however, does not exclude risk of occult or future metastasis, with up to 20% false-negative rates for SLNB reported in the literature.[14] Furthermore, as discussed previously, SLNB status may be a poor predictor of distant, non-lymphatic, metastasis in MM.[9 10] For this reason, patients are often followed-up for a 5-year period, in which the majority recurrences will occur.[15] In this case, the metastasis presented late—more than 5 years after initial MM diagnosis, beyond the standard follow-up period. Previous case series report muscular metastases of primary MM within significantly shorter timeframes postinitial excision, usually with presence of nodal disease at the time of presentation.[11 12] Third, recurrence was on the contralateral upper limb—an unusual site for muscular metastasis, without other identifiable metastases elsewhere. Lastly, this recurrence has occurred in an era with availability of more effective oncological therapies for metastatic disease. One would expect survival to now exceed that in the previously reported case series of muscular metastases, however data remain outstanding on the effectiveness of immunotherapy on muscular metastases in MM.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

Patient's perspective

Having being diagnosed with melanoma 6 years ago, I have always been careful with moles, blemishes, etc on my skin and always have had them checked out. Having had my '5 year all clear', I was delighted and felt that while I knew I still had to check my skin regularly, I felt that melanoma was something that was behind me. Six years after my initial diagnosis, I happened to feel a small lump just above my elbow on the back of my arm under the skin. It was small and painless and I thought nothing of it as in the same area I already had two other small lumps under the skin which had been looked at and were diagnosed as lipomas.

I was aware of the lump, but it caused me no concern. So much so, when I got in touch with my skin cancer nurse to look at a wart-like lesion on my nose which had appeared (which was later removed and found to be a basal cell carcinoma), I did not even mention it. However, I felt the lump increase in size quite a bit in 4–6 weeks a few months after first noticing it, and on the advice on the skin cancer nurse, made an appointment with the GP to have it looked at. I visited the GP, fully expecting them to confirm it was indeed another lipoma and was quite shocked when on examination the GP said that it "didn't feel fatty and was quite hard" and as a result would like to refer me for an urgent ultrasound.

I had the ultrasound the following week and even then, expected them to say it was actually a lipoma despite the GP's concern. However, I was told they could not say for sure what it was, and I was referred for an MRI. This MRI confirmed a 'malignant mass' which then led to the biopsy to determine whether this was a sarcoma or melanoma. At the time I felt confused as I did not know whether I 'wanted' it to be a sarcoma or melanoma again, which I knew would be a spread from the original site. The biopsy confirmed melanoma which then left me with many questions mainly: How did it get there? I thought melanoma was on the skin only so why is this a lump? Throughout the last 5 years, the only 'lumps' I had looked out for were when checking my lymph nodes in my armpit—nobody had ever said to keep an eye out for other lumps as they may be connected.

In the 6 weeks before my operation to remove the lump, it still remained painless to touch but there were times that my arm would ache a little, similar to a muscular ache. The operation to remove the lump went as planned and I was discharged the next day and recovered well at home. I have not lost any movement from my arm but it is definitely marginally weaker than my other arm. Five months on, the tenderness has gone and everything has healed well. I am undergoing immunotherapy with nivolumab for the next 12 months with regular CT scans every 6 months and I can only hope that these remain clear.

On the whole, I have always had a very positive outlook and I feel that this has helped me get through the whole situation. If anything, it has been worse for my family. I do not feel unwell and do not consider myself as having an illness in any way. It certainly has not stopped me doing anything. The support from my skin cancer nurse throughout has been excellent and the plastics team at the hospital have always given me reassurance. In hindsight, had I known that melanoma could return in this way I may have got checked sooner, but that is all in hindsight and I feel lucky to have been treated as quickly as I have been.

Learning points

- This report highlights a rare case of skeletal muscle metastasis of MM.
- It is a pertinent reminder that though rare, a painless soft tissue mass in patients with a history of MM—even with a negative SLNB and many years post the initial diagnosis—should raise clinician suspicions and be thoroughly and appropriately investigated.
- Patients with a diagnosis of MM should be reminded of the importance of self-surveillance and early presentation if new masses or lesions develop, regardless of the time since their original diagnosis.
- With increasing availability of oncological therapies for metastatic and recurrent disease, survival is improving. Therefore, early identification and treatment of recurrence in patients may allow them to commence potentially curative therapy sooner, leading to improved outcomes.

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