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Running Title: Intravenous melanoma metastasis

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Abstract

Tumour thrombus is a complication that occurs when a malignancy invades into the vasculature, occluding its lumen. Here, we present a rare case of melanoma tumour thrombus of the great saphenous vein of the left thigh, which was diagnosed on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) and ultrasound guided biopsy, and responded well to immunotherapy with pembrolizumab.

Five key words

F-18 FDG PET/CT; melanoma; metastasis, tumour thrombus, immunotherapy.

Main Text

Case Report

A 64-year-old man was referred to a tertiary specialist service for management of a palpable left thigh mass which developed over 2 weeks. The patient had a history of a left calf 2.3mm non-ulcerated superficial spreading primary melanoma with a negative sentinel node biopsy 2 years prior. On examination, a firm 1x1cm nodule was evident on the mid left thigh. There were no associated skin changes, tenderness, swelling or lymphoedema, no signs of melanoma recurrence at the left calf excision site, and no palpable lymphadenopathy.

Given the presenting lesion was proximal to the primary cutaneous melanoma, metastasis was suspected. F-18 FDG PET/CT scanning revealed a tract of multifocal metabolically active tissue in the left lower limb which tracked along the course of the great saphenous vein (Figure 1). Ultrasound examination demonstrated an occlusive mass (Figure 2a) filling the length of the vein to the level of the knee. Ultrasound-guided core biopsies of the intraluminal mass (Figure 2b) confirmed the diagnosis of melanoma (Figure 2c).

The extensive intravenous disease was deemed surgically unresectable. Molecular testing revealed a NRAS Q61R mutation and the patient was commenced on pembrolizumab (200 mg every three weeks). A follow-up F-18 FDG PET/CT scan after four months of pembrolizumab revealed substantial reduction in the burden of disease (Figure 3).

Discussion

Intravascular metastases are commonly reported in solid cancers such as renal cell carcinoma, Wilms tumour, adrenal cortical carcinoma and hepatocellular carcinoma[1]. Presence of tumour thrombus has been associated with worse prognosis and may impact on the patient's overall management[1]. Although

melanoma is an aggressive form of skin cancer with the propensity for lymphatic spread to lymph nodes and haematogenous spread to distant organs, tumour thrombi are rarely reported. Sites of reported venous involvement by metastatic melanoma include the superior vena cava, the inferior vena cava, and the pulmonary, portal, renal, femoral and great saphenous veins[2-11]. Similarly to our case, most cases presented a number of years after the initial primary cutaneous melanoma. One case presented as an extension into the inferior vena cava from a primary adrenal melanoma[8].

Diagnosis of tumour thrombus is often made incidentally during imaging[1]. The differential diagnoses in our patient included adjacent intra-lymphatic tumour or bland intravenous thrombus. Whilst intra-lymphatic tumour cannot be completely excluded, the dynamic features on ultrasound and histological findings from imaging-guided biopsy of the intravenous mass were consistent with intravenous location of tumour. The distinction between tumour thrombus and bland thrombus has a significant impact on management, and the uses of PET/CT, ultrasound, and ultrasound-guided biopsy in this case were critical.

Management options for intravascular metastasis includes surgical resection, systemic therapy such as immunotherapy or targeted therapy, and palliative radiotherapy[1,5,7]. In our case, the finding of extensive intravenous NRAS mutant melanoma directed the initial treatment recommendation to immunotherapy with pembrolizumab, which induced an excellent anti-tumour response. This extends the spectrum of disease contexts in which metastatic melanoma may respond to anti-PD1 therapy.

Acknowledgements

None

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Figure legends:

Figure 1. F-18 FDG PET/ CT findings: Tract of multifocal metabolically active soft tissue in the left lower limb extending from the upper calf to the upper thigh.

Figure 2. Ultrasound findings: mass occluding the lumen of the left great saphenous vein. **a)** Short axis, transverse view of the palpable portion of the mass in the left mid-thigh revealed a non-compressible hypoechoic lesion (arrow). Focal rounded portions of the mass were seen at venous valves, with linear portions in the remainder of the vein (not shown). Lack of colour in the green colour-boxed region demonstrated the lesion was not filled with flowing blood despite tracking within the vein. **b)** Ultrasound-guided core biopsy: biopsy needle (dotted arrow) shown passing through the palpable left thigh mass (arrow). **c)** Histopathological findings: haematoxylin and eosin stain of the biopsy of the mass-filled vein showing extensive infiltration by melanoma cells with pigment extravasation (scale bar 100 µm). A second imaging-guided intravenous biopsy taken from another site, inferior to the lesion, revealed identical histological features (not shown).

Figure 3. F-18 FDG PET/ CT findings following immunotherapy with pembrolizumab, showing significantly reduced disease in the left thigh. A site of

new avidity at the left rectus femoris origin had clinical and imaging features of an enthesopathy.

Figure 1

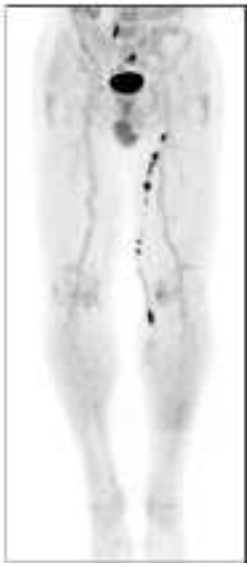

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Figure 2

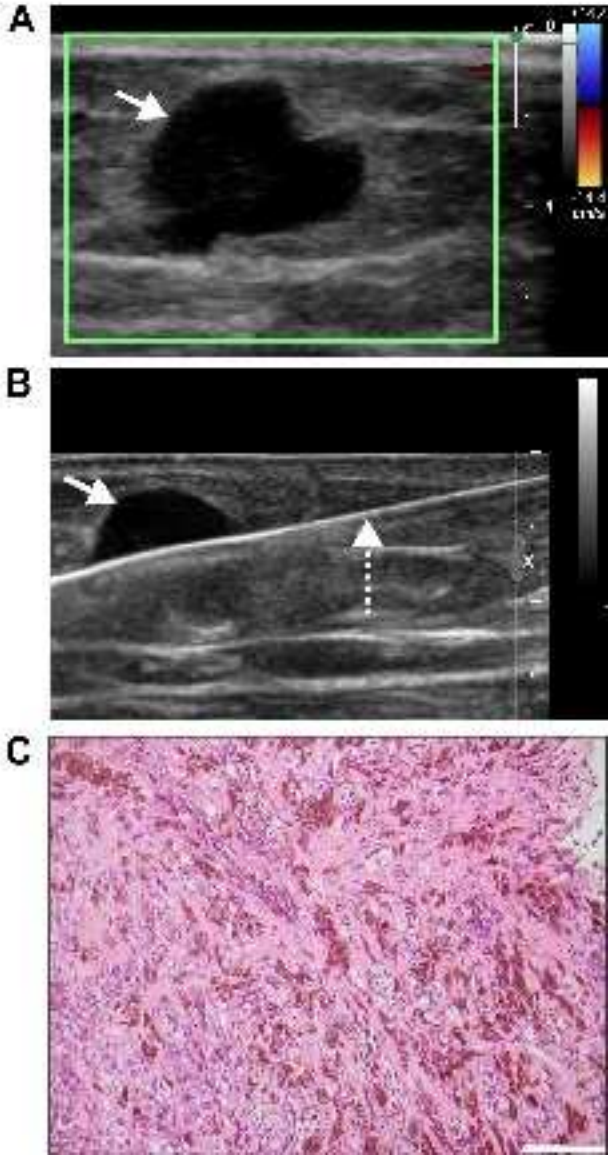

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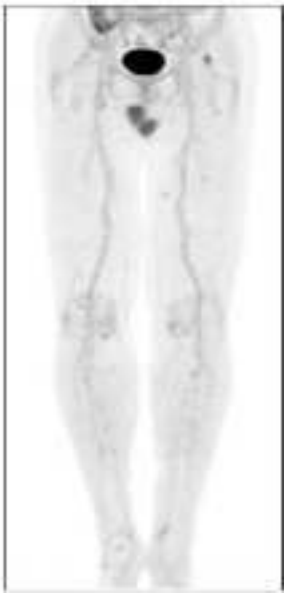
Figure 3



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