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Case Report

# Three cases of *BRAF*-mutant melanoma with divergent differentiation masquerading as sarcoma

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**Summary**

Melanoma is an important cause of skin cancer related death throughout the world, particularly in Europe, the United States, and Australia. Rarely melanoma undergoes divergent differentiation to simulate the full morphologic and immunohistochemical features of other malignancies, notably sarcoma. However, such cases retain the molecular signatures of melanoma, including *BRAF* gene mutations. Gene mutation analysis of tumour DNA, now standard practice for all melanomas of stage III or above, may establish the diagnosis of melanoma in some advanced malignancies of unknown lineage. A prior history of melanoma or risk factors for melanoma may be the first clue that an advanced malignancy represents metastatic melanoma. Recognition of this presentation of melanoma can allow a patient to access well-tolerated life-prolonging therapies such as targeted therapy, inhibiting the *BRAF*/*MEK* pathway, and immune checkpoint inhibitor therapy.

**Key words:** melanoma, proto-oncogene proteins B-raf, cell dedifferentiation, oncology, immunotherapy

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## Introduction

The frequency of melanoma in many parts of the world continues to increase. Melanoma, particularly in advanced stages, is an important cause of skin cancer related death in Europe, the United States and Australia [1]. Significant advances have been made in the treatment of melanoma, specifically in targeting *BRAF* molecular alterations and also through inhibition of immune checkpoints [2].

Rarely, melanoma can undergo divergent differentiation to simulate the full morphologic and immunohistochemical features of other malignancies, notably sarcoma. However, such cases retain the molecular signatures of melanoma, including *BRAF* mutations, permitting recognition and specific life-prolonging therapies.

In this article we present three illustrative cases from Australia who were diagnosed with sarcomas. After clinicopathologic review, supported by the presence of *BRAF* mutations, the diagnoses were revised to dedifferentiated melanoma, or melanoma with divergent differentiation. This rare but important presentation of melanoma higlights the utility of BRAF molecular testing not only in melanoma therapy, but also melanoma diagnosis.

## Case presentations

Case 1: a 57-year-old woman presented with abdominal pain. Eighteen months prior to this presentation she had *BRAF* V600E mutant metastases of cutaneous melanoma, involving soft tissues, vertebrae and the brain. She had obtained a complete radiological response with induction checkpoint inhibitor therapy, using ipilimumab and nivolumab. CT abdomen now showed a 9 cm mass. Following non-diagnostic cytology, she commenced targeted *BRAF*/*MEK* inhibitor therapy with dabrafenib and trametinib. The mass grew to 17 cm in 2 months, as shown by whole-body FDG-PET/CT (Fig. 1). Core biopsy showed a pleomorphic malignancy with rhabdomyosarcomatous differentiation, the tumour expressing myoid markers but lacking expression of a range of melanocytic markers (Figs. 2A, 2B). Resection of the symptomatic mass confirmed a predominance of rhabdomyosarcomatous areas, but focal zones demonstrated a spindled malignancy, expressing melanoma markers. BRAF mutation analysis confirmed a *BRAF* V600E mutation, leading to a revised diagnosis of melanoma with divergent rhabdomyosarcomatous differentiation. The planned neoadjuvant sarcoma chemotherapy was abandoned.

Case 2: a 55-year-old woman presented with a *BRAF* V600E mutation positive melanoma, metastatic to lung, liver, bone and left breast. The liver metastasis had shown areas of osteosarcomatoid differentiation (Figs. 2C, 2D). She had a partial response to first-line treatment with dabrafenib and trametinib. At 12 months, following radiological progression, anti-PD1 monotherapy, pembrolizumab, was used. During treatment, she developed a complex pelvic mass, suggestive of a gynaecological malignancy (Fig. 3). Hysterectomy, bilateral salpingo-oophorectomy and omental biopsy showed morphologic and immunohistochemical features of leiomyosarcoma. Molecular analysis demonstrated the same *BRAF* V600E variant as her original melanoma. Her final diagnosis was metastatic melanoma with divergent myogenic differentiation.

Case 3: an 84-year-old man presented with a cutaneous scalp lesion, morphologically and immunohistochemically consistent with leiomyosarcoma (Fig. 2E, 2F). In view of a previous history of melanoma, BRAF mutation testing was undertaken. Both the prior melanoma, and the new scalp lesion bore the less common *BRAF* G469K variant. This genomic link supported divergent differentiation in a melanoma recurrence. Surgical excision and 12 months of adjuvant immunotherapy followed.

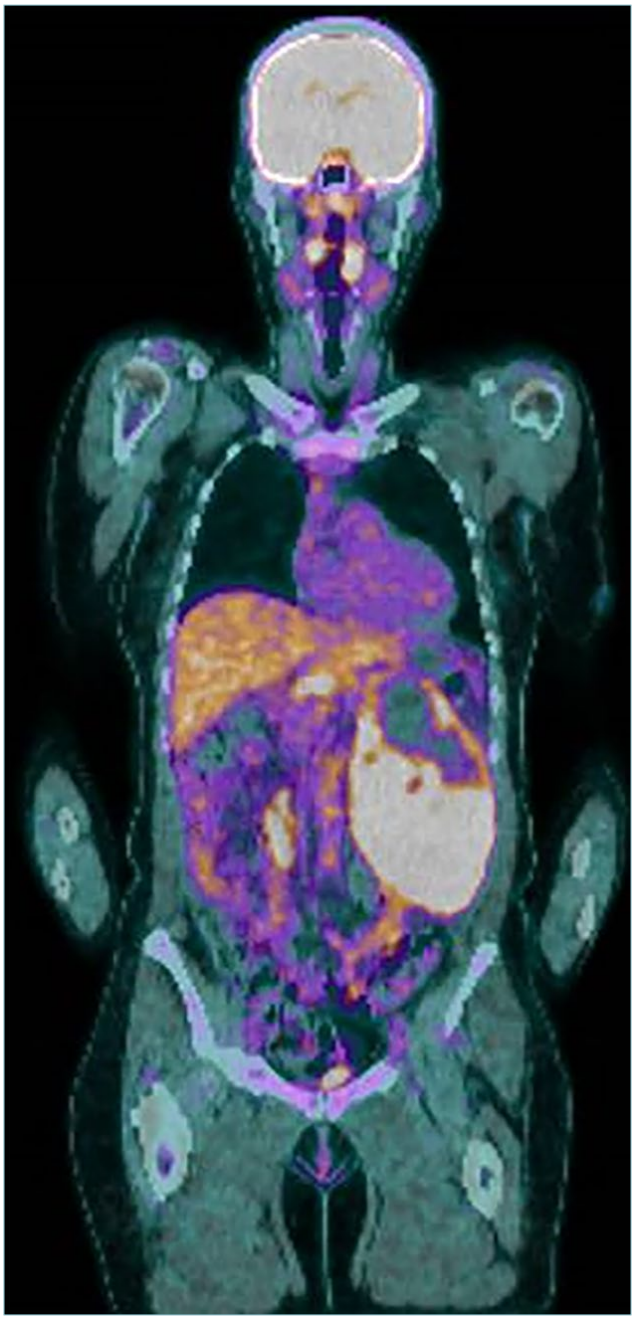

**Figure 1.** Whole body FDG-PET CT in case 1 showed an FDG avid 17 cm left upper quadrant abdominal mass, with a central area of photopaenia, consistent with necrosis.

## Discussion

The incidence of melanoma in Australia is high compared to other parts of the world [3]. Pathologists recognise melanoma as the universal mimic, and routinely include melanoma in the differential diagnosis

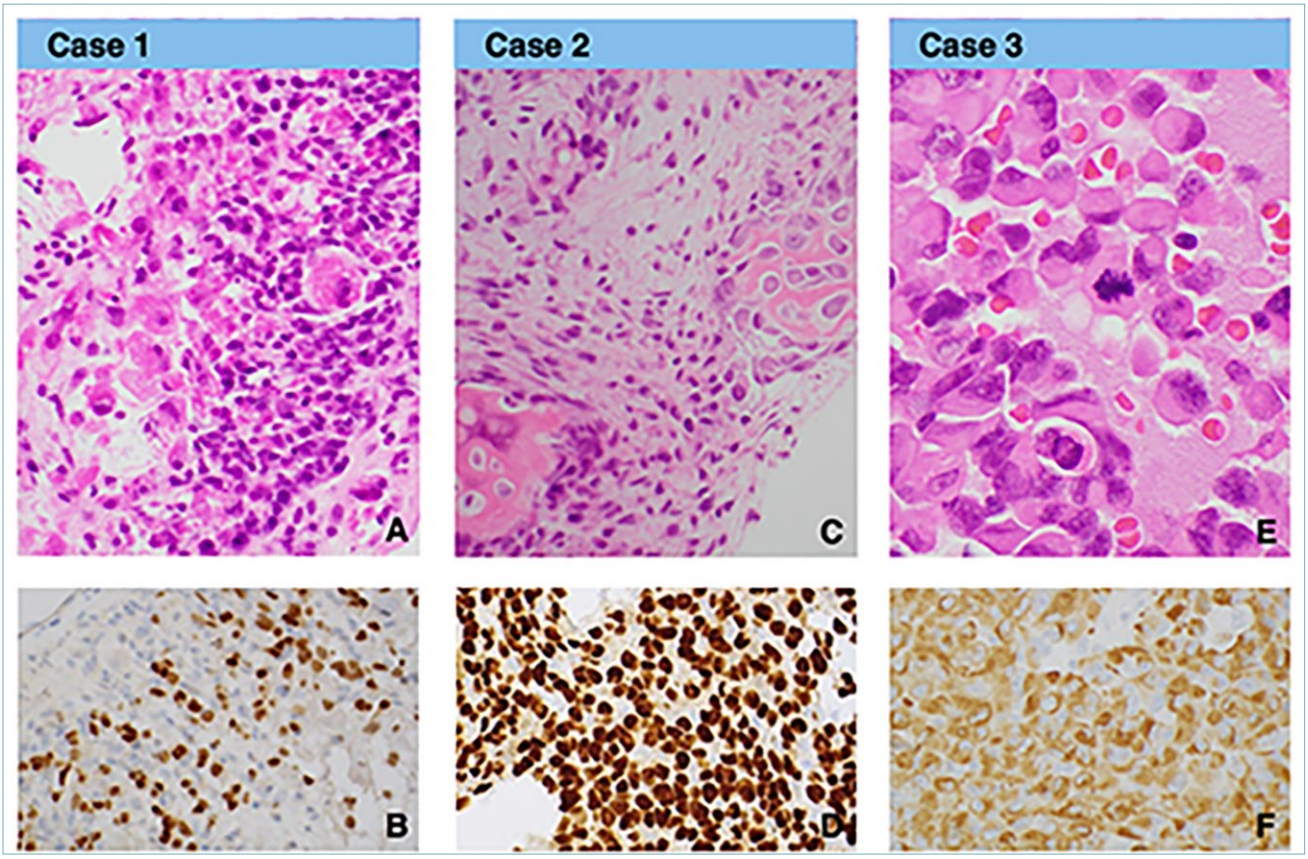


**Figure 2.** Photomicrographs showing divergent differentiation in 3 cases of melanoma. (2A): core biopsy of the abdominal mass in case 1 depicts two cell different cell populations; an undifferentiated small, round, blue cell malignancy, accompanied by distinctly different larger cells, with voluminous, eosinophilic cytoplasm, consistent with myoid differentiation and confirmed by strong staining with myogenin (2B). (2C): liver core biopsy in case 2 showed a heterogenous neoplasm, including areas of malignant osteoid deposition. Other areas displayed an undifferentiated tumour with strong SOX-10 reactivity (2D), supportive of metastatic melanoma with divergent osteosarcomatous differentiation. This patient later developed a pelvic mass with features of leiomyosarcoma but with the typical V600E BRAF mutation of melanoma. This case demonstrates that multiple lines of divergent differentiation may be exhibited in advanced melanoma. (2E): scalp tumour in case 3, showing pleomorphic cells with rhabdoid features. All melanocytic markers were negative, but the cells displayed strong desmin reactivity (2F), consistent with myogenic differentiation. The tumour shared the same G469K BRAF mutation, also found in the patient's original cutaneous melanoma.

of poorly differentiated tumours. The differing morphology and immunohistochemical profiles of various neoplasms permit their reliable classification in most cases, altbough the rare phenomenon of divergent differentiation of melanomas defies their identification by such means, requiring molecular analysis for diagnosis.

Divergent differentiation of melanoma is a rare phenomenon, recently described and still under-recognised [4]. This discovery of the capacity of melanoma to assume not only the morphology but the immunoprofile of other, well characterised neoplasms, mostly sarcomas, has come about through molecular profiling of tumours, both for diagnosis and targeted therapy selection.

When evaluating an apparent sarcoma at an unusual site, such as in a nodal basin, clinical history and physical examination are essential components of the diagnostic work-up. A history of previous melanoma and risk factors for melanoma may be crucially important and should be communicated accurately to the pathologist. Physical examination of the skin and lymph node basins in the neck, axillae and groin may also help, since nodal deposits are common in melanoma, whereas most sarcomas disseminate through the haematogenous route.

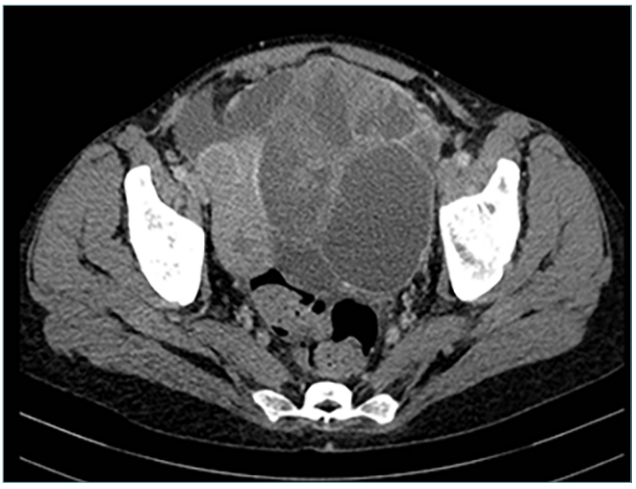

**Figure 3.** CT abdomen showing extensive solid cystic pelvic and adnexal masses, which displace small and large bowel loops.

Molecular alterations in the *BRAF* gene are an early event in melanoma pathogenesis [5]. These alterations are highly conserved throughout the progression of each tumour, being retained even when the morphology and immunoprofile diverge along the lines of a different, non-melanocytic neoplasm or dedifferentiate into an undifferentiated malignancy. As such they are invaluable for establishing a diagnosis of melanoma, which has two major clinical benefits. First, since these patients do not have sarcomas, they can avoid toxic chemotherapy. Second, should a *BRAF* variant be detected, immunotherapy or targeted therapy may be offered in case of a sensitising *BRAF* V600 mutation, or immunotherapy for a non-V600 BRAF variant.

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### Conflict of interest

The authors declare no conflict of interest.

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### Ethical consideration

This report and preparation of manuscript was performed in accordance with the ethical standards as laid down in the 1964 declaration of Helsinki and its later amendments, and conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). The study was approved by the Central Adelaide Local Health Network Inc. Human Research Ethics Committee (CALHN Reference Number: 14910).

### Author contributions

all listed authors contributed to the production of this manuscript and are listed in the appropriate order.

### Availability of data and material

All relevant material has been presented in the manuscript.

### Consent

Written informed consent was obtained from participants where able, a waiver of consent was provided for inclusion of a deceased patient by the local ethics committee (CALHN Reference Number: 14910).

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