should be utilised in ambiguous cases to distinguish clear cell sarcoma from melanoma that usually displays a complex karyotype.^{4,10} Early studies suggested that *BRAF* mutations are exclusively seen in melanoma. However, rare tumours with morphological features of clear cell sarcoma have been recently shown to harbour concurrent *EWSR1* fusions and *BRAFV600E* mutations, providing an avenue for targeted treatments in these cases.^{11,12} Whether these tumours represent melanoma rather than clear cell sarcoma is perhaps debatable and probably academic in the context of a poor prognosis tumour harbouring a targeted therapeutic mutation (*BRAF*).

The case reported here clearly highlights the diagnostic difficulty in distinguishing clear cell sarcoma from melanoma, made more challenging by the cutaneous location, extensive ulceration and intraepidermal growth with Pagetoid spread, not previously described in this disease. This unique presentation broadens the morphological spectrum described in clear cell sarcoma and highlights that intraepidermal growth, previously thought to exclude clear cell sarcoma from diagnostic consideration, can occur.⁶ An awareness of cutaneous presentations of clear cell sarcoma, its salient morphological features, as well as the importance of utilising specific molecular testing when appropriate, should allow for navigation through this diagnostic pitfall.

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Dedifferentiated melanoma with *MDM2* gene amplification mimicking dedifferentiated liposarcoma

Sir,

We present a 73-year-old female with melanoma that mimicked dedifferentiated liposarcoma (DD-LPS) both morphologically and molecularly in a subclone

demonstrating *MDM2* gene amplification. Patient consent was obtained for the purpose of this publication.

The patient presented with a rapidly growing tumour in the left breast at the 2 o'clock position suspicious for primary breast carcinoma. A core biopsy demonstrated morphological features of metastatic melanoma characterised by an epithelioid morphology and supported by immunohistochemistry (IHC) (SOX10+/HMB45+/PanCK–). A somatic *BRAF* V600E mutation was detected by a targeted next generation sequencing (NGS) panel (FIND IT Melanoma Panel; Contextual Genomics, Canada). A wide local excision was performed. On the cut surface, the specimen showed what appeared to be two relatively circumscribed tumours, 60×56×49 mm and 40×30×25 mm. The two lesions abutted each other but showed distinct appearances. On microscopic assessment, the smaller tumour showed epithelioid morphology (Fig. 1A,B) with an immunophenotype consistent with melanoma and similar to that seen in the preoperative core biopsy. Mutation specific IHC with the VE1 clone for the *BRAF* V600E mutation was positive in keeping with underlying V600E somatic mutation.

The larger mass was composed of hyperchromatic cells with spindled to oval nuclei on an extensively myxoid background containing chicken-wire blood vessels in a patchy distribution and resembling myxoid liposarcoma (ML) (Fig. 1C,D). Other more cellular areas with a primitive appearance were additionally present with features more suggestive of DD-LPS with ML-like areas. The cells were negative for a comprehensive panel of IHC (SOX10, S100, HMB45, MiTF, MelanA, PanCK, SMA, CD34, CK5/6, MUC4, Desmin, STAT6 and CD117) and *BRAF* VE1 was equivocal (Fig. 1E). IHC for PRAME demonstrated strong heterogeneous expression in at least 60% of the cells (Fig. 1F). Although the overall appearances were thought to be compatible with a dedifferentiated melanoma, the possibility of a collision DD-LPS or high-grade ML was considered and fluorescence *in situ* hybridisation (FISH) was performed to elucidate the diagnosis. FISH for *MDM2* [*MDM2* (12q15) Red + Copy Control 12 Green FISH Probe; Biocare Medical, USA] detected gene amplification in 30% of the tumour cells including high level of amplification (>20 copies) with the remaining nuclei showing diploid and polysomic signals (Fig. 2A,B). FISH for *DDIT3* (12q13;

Fig. 1 (A,B) H&E images of melanoma with epithelioid morphology. (C,D) H&E stained sections of myxoid liposarcoma (ML)-like areas. (E) *BRAF* VE1 immunohistochemical (IHC) stain showing strong cytoplasmic expression in melanoma with epithelioid appearance (left panel) and equivocal granular cytoplasmic expression in ML-like areas (right panel). (F) PRAME IHC showing strong and diffuse expression in ML-like areas (red chromogenic stain).

Fig. 2 (A,B) Fluorescence *in situ* hybridisation (FISH) for *MDM2* (12q15)/CC12, showing a cell (arrow head) with high level of amplification (>20 copies) in a background of cells with diploid signals (arrow). (C) FISH for *DDIT3* (12q13) and (D) *EWSR1* (22q12) break-apart probes demonstrated an average 3 extra non-rearranged copies and increased isolated red and/or green signals for both probes.

Vysis *DDIT3* Break Apart Probe Kit; Abbott, USA) and *EWSR1* (22q12; Vysis LSI *EWSR1* Dual Color Break Apart Probe Kit; Abbott) were negative for rearrangement but demonstrated extra non-rearranged copies (3–4 copies per cell) (Fig. 2C,D). In view of the FISH *MDM2* amplification reported as positive and to completely rule out the possibility of *MDM2* amplified DD-LPS, *BRAF* V600E mutation testing was repeated on the same block submitted for FISH analysis. *BRAF* V600E mutation was also present in the same block tested for *MDM2* FISH analysis (in spite of the equivocal VE1 immunostain). Given the presence of shared *BRAF* V600E mutation indicative of clonal relationship between the two components with one of these representing unequivocal melanoma together with the focal (rather than diffuse) nature of *MDM2* amplification, the final diagnosis rendered was dedifferentiated melanoma.

Well differentiated liposarcoma/atypical lipomatous tumour (WDL/ALT) and DD-LPS are associated with high-level amplifications of chromosome 12q13-15, particularly of the *MDM2* and *CDK4* cell cycle oncogenes.^{1,2} *MDM2* gene amplification is one of the earliest event and main driver genes in WDL/ALT/DD-LPS and is routinely used as diagnostic tool to confirm the diagnosis.^{1,2} DD-LPS can arise *de novo* at any anatomical location and can mimic a wide range of sarcoma types. Identification of *MDM2* gene amplification is diagnostic for DD-LPS in the context of an undifferentiated sarcoma.^{1,2} Nonetheless, *MDM2* amplification is not a pathognomonic gene alteration of WDL-ALT/DD-LPS, as it is also found in other sarcomas, mainly low-grade central osteosarcoma and intimal sarcoma.^{3,4} Additionally, *MDM2* amplification has been documented to be present in the ‘triple wild-type’ (*BRAF* V600E/K, *NRAS* and *NF1*) melanoma subtype, enriched in acral and mucosal melanoma^{5,6} but also in a small proportion of cutaneous melanomas of the other

molecular subtypes co-occurring with *BRAF*, *NRAS* and/or *KIT* mutations.^{3,4} The site of primary melanoma in our patient is unknown but it represents an example of *BRAF* V600E mutated melanoma co-occurring with *MDM2* focal amplification. Importantly, *MDM2* amplification has been linked to hyperprogression in melanoma patients treated with immune check-point inhibitors.⁷ In such cases, *MDM2* co-amplifies with *CDK4* as occurs in WD-LPS/DD-LPS.⁷

Our case demonstrated strong PRAME immunostaining with completely negative expression for S100 and SOX10. Although PRAME can be used to confirm the diagnosis of dedifferentiated or undifferentiated melanoma in the appropriate clinical setting,⁸ the expression of this marker is non-specific for melanocytic origin and can be seen in a range of sarcomas.⁹ Hemminger *et al.*¹⁰ and others¹¹ demonstrated that 100% of MLs (including high-grade ML) showed strong and homogenous immunoreactivity for PRAME. A further study by Albertsmeier *et al.*⁹ demonstrated that sarcomas other than ML express PRAME: angiosarcoma (44%), malignant peripheral nerve sheath tumour (MPNST; 38%), synovial sarcoma (11%), undifferentiated pleomorphic sarcoma (UPS; 7%), leiomyosarcoma (6%) and DD-LPS (4%).⁹ Therefore, we can conclude that although in this particular case PRAME could have been useful (not available in our laboratory before FISH was performed) to prove dedifferentiated melanoma, in the context of a sarcomatoid tumour, it cannot be reliably used in the differential diagnosis.

In summary, our case highlights the importance of recognising that molecular findings should be carefully interpreted in the appropriate morphological and clinical context. In this case, the focal nature of *MDM2* amplification alerted us to the possibility that this represented a secondary genomic alteration associated with an underlying complex karyotype rather than representing the driving gene alteration as expected in

DD-LPS. The additional non-rearranged copies of *EWSR1* and *DDIT3* could also be expected in a tumour with complex karyotype and are of not diagnostic value. The identification of a melanoma-compatible genotype or the demonstration of a shared mutation between metastatic and primary melanoma is a more robust criterion for the diagnosis of undifferentiated and dedifferentiated melanoma¹² and we were able to demonstrate the co-occurrence of *MDM2* gene amplification and *BRAF* V600E mutation in the same tissue block. Interestingly, if the initial tissue core biopsy had targeted the myxoid DD-LPS-like areas, it is likely that this patient could have been initially misdiagnosed and potentially mismanaged. Increasing awareness of potentially conflicting molecular findings can help pathologists avoid pitfalls in interpretation. In particular, there is increasing demand to perform comprehensive diagnostic work-up and molecular testing on smaller biopsy material, and sampling factors in heterogeneous tumours may thus become more significant in terms of diagnosis and management.

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Agminated Spitz naevus with an activating *HRAS* Q61R mutation

Sir,

Spitz naevi (SN) are benign melanocytic tumours arising preferentially after childhood.¹ Under microscopic examination, SN appear as a well demarcated compound proliferation arranged in nests of epithelioid and spindled, often mildly pigmented melanocytes. Frequent epidermal hyperplasia is associated. Related oncogenes include mutually exclusive translocations involving *ALK*, *ROS1*, *RET*, *MET*, *MERTK*, *BRAF*, *LCK*, *NTRK*, *MAP3K3* and *MAP3K8* genes.^{2–6} In addition, *HRAS* exon 3 mutation is detected in a subset of SN harbouring desmoplastic morphology.⁷

Although most SN appear as solitary tumours, rare cases of multiple SN either disseminated or clustered have been reported under the terminology agminated SN (ASN).⁸ Few genetic studies have been performed in this setting. Herein, we report a case of ASN with a previously undescribed Q61R *HRAS* mutation.

The study was conducted according to the Declaration of Helsinki and was approved by the research ethics committee of the Center Léon Bérard, Lyon, France (Ref: L20-72).

A 2-year-old boy presented with multiple pigmented papules restricted to the right side of the face (Fig. 1). The tumours arose after birth, increased rapidly in number (more than 40 at time of diagnosis) and size (ranging from 0.3 to 3.0 cm diameter). Physical examination of the skin revealed no additional skin, neurological or skeletal disorders. Surgical excision of the largest tumour was performed.

Microscopic examination revealed a wedged-shaped melanocytic proliferation (Fig. 2A). A few packed junctional nests of bland or spindled melanocytes were present associated with epidermal hyperplasia (Fig. 2B). No pagetoid spreading or ulceration were observed. In the underlying dermis, fascicles of medium-sized spindled melanocytes entrapped in a desmoplastic stroma were arranged in a plexiform growth pattern. Neither cytological atypia nor mitotic activity were seen (Fig. 2C).

Immunohistochemical study confirmed diffuse expression of the melanocytic marker MelanA, while no significant positivity was observed with antibodies against *ALK*, *ROS1* and *NTRK1/2/3* proteins.

Whole exome RNA-sequencing identified a *HRAS* Q61R mutation. No anomaly was present in other Spitz-related genes including *ALK*, *ROS1*, *NTRK1*, *NTRK3*, *RET*, *MET*, *MERTK*, *LCK*, *BRAF*, *MAP3K3*, and *MAP3K8*. Immunohistochemistry