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

Fig. 1 (A–C) Clinical and (D) dermoscopic features of the case. (A) Clinical features at the age of 14, (B) 23 and (C) 33 months: 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). (D) Dermoscopic examination of the largest tumour revealed an inhomogeneous tumour harbouring two highly pigmented areas and devoid of clearly distinguishable pattern (Fig. 1).

confirmed diffuse cytoplasmic positivity in tumoural melanocytes with the anti-(*N, H, K*)*RAS* Q61R antibody (clone SP174, dilution 1/50; Abcam, UK) (Fig. 2D).

We report a case of ASN harbouring a previously undescribed Q61R *HRAS* mutation. Pathogenic *RAS* mutations promote cell growth through the permanent activation of the MAP-kinase pathway and therefore constitute an oncogenic driver in many cell lineages including melanocytes. *HRAS* mutations involving both exons 2 and 3 are commonly found in isolated SN.⁷ However, in ASN and especially those arising in the setting of naevus spilus, exon 2 G13R *HRAS* mutations have so far been described.^{9,10} Sarin *et al.* demonstrated that a post-zygotic G13R mutation of *HRAS* in a melanocytic progenitor resulted in naevus spilus formation.¹¹ Furthermore, their study demonstrated that the proliferating Spitz melanocytes arising within the naevus spilus also presented an amplification of the mutated *HRAS* gene, suggesting this supplementary anomaly was needed for SN tumour development.⁹ Although RNAseq did not allow us to assess the presence of a *HRAS* amplification, the level of *HRAS* expression observed in our case was extremely high compared to other melanocytic tumours present in our cluster (rank 2/568), with the 20 first ranked cases all being *HRAS* mutants (data not shown). This suggests that an *HRAS* amplification could be present in this tumour.

The papular naevus spilus syndrome is categorised among RASopathies, a heterogeneous group of diseases

characterised by mosaicism of *RAS* mutations occurring in various somatic cells (either keratinocytes, melanocytes or both) during embryonic development,¹¹ resulting in various other conditions such as Schimmelpenning syndrome, epidermal and sebaceous naevi, and phakomatosis pigmentokeratolica.

Interestingly, since exon 3 *HRAS* mutations combined with *HRAS* amplification are also detected in a subset of isolated SN,⁷ it is conceivable that similar post-zygotic Q61R *HRAS* mutations occurring in the melanocytic lineage during the embryonic life, represent a preliminary step to isolated *HRAS* mutated SN development.

ASN have also been associated with other genetic anomalies. Goto *et al.* detected a complex rearrangement of *TRPM1-PUM1-LCK* in an ASN case arising in a giant congenital hyperpigmented macule.⁵ More recently the same authors identified a *GOPC-ROS1* mosaicism in two ASN cases.¹² Clinically, a patchy pigmented macule was present in two of these three described cases. Both these anomalies involve a 5'-fused intact oncogenic tyrosine kinase domain. Fluorescence *in situ* hybridisation techniques confirmed the anomaly was also present in normal-appearing melanocytes in the basal layers of the epidermis surrounding the Spitz proliferations. This association mimics the features of ASN arising in naevus spilus, suggesting supplementary anomalies are needed for further tumoural development.

Fig. 2 (A–C) Microscopic and (D) immunohistochemical features of the Spitz naevus. (A–C) Microscopic examination revealed a dermal plexiform proliferation of spindle non-atypical melanocytes entrapped in a desmoplastic stroma. (D) Immunohistochemistry demonstrated the RAS Q61R mutant in tumour cells.

To conclude, our observation reports that in addition to *G13R* *HRAS* mutations, *ROS1* and *LCK* fusions, a post-zygotic activating Q61R *HRAS* mutation in a melanocytic progenitor might constitute a preliminary step to ASN development.

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SMARCA4-deficient anaplastic carcinoma arising in a primary retroperitoneal mucinous adenocarcinoma

Sir,

Primary mucinous tumours arising in the retroperitoneum are uncommon and approximately half are histologically malignant, the remainder showing benign or borderline appearances according to ovarian-type criteria.¹ As with primary ovarian neoplasms, retroperitoneal mucinous