HRAS-mutated Spitz Nevus on the Cheek in a Middle-aged Man

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Spitz nevus (SN) was first described in 1948, and was referred to as melanoma of childhood (1). Although SNs are benign melanocytic neoplasms, these lesions share many histopathological findings with malignant melanomas (MMs) (2). Despite the diagnostic criteria, the similarities between SNs and MMs make their distinction very difficult even among expert dermatopathologists. Studies using molecular biological techniques, such as loss of heterozygosity analysis, comparative genomic hybridization (CGH), multiplex ligation-dependent probe amplification (MLPA), and DNA sequencing, have provided important clues to the genetic basis of SNs and MMs (3–11). These studies have shown that most MMs have multiple chromosomal aberrations and frequent mutations in oncogenes in the mitogen-activated protein kinase signal transduction pathways, such as BRAF, NRAS and KIT (4, 8, 12). Multiple genetic aberrations, including copy number loss of the CDKN2A gene on chromosome 9p21, are characteristic of MMs (13). However, most SNs have normal karyotypes, whereas increased copies of chromosome 11p associated with mutations in the HRAS gene are found in a minority of cases showing atypical histopathological features (5, 7). HRAS-mutated SNs have been reported to tend to be infiltrative, larger, intradermal and markedly desmoplastic (5, 7). Furthermore, some degree of atypicality could be seen (5, 7). Several histopathological features overlapped those of MMs. To our knowledge, however, there have only been a few reports describing this lesion.

CASE REPORT

A 47-year-old man presented with a black oval nodule measuring 9 × 8 mm on his right cheek (Fig. 1). Dermoscopic findings demonstrated a globular pattern with a negative pigment network and dotted vessels.

Histological examination demonstrated a well-demarcated, symmetrical, top-heavy nodule, accompanied by conspicuous regular elongation of rete ridges (Fig. 2). The nodule was composed of sheets of large spindle and epithelioid cells from the lower epidermis to the middle reticular dermis. These cells showed high nucleo-cytoplasmic ratios, a few large nucleoli and a few mitoses. There was no maturation. Pagetoid spread could not be seen. Focal lymphocytic infiltrates were arranged around the nodule.

There was no superficial lymphadenopathy. The results of routine laboratory examinations were within normal limits. There was no evidence of malignancies on computed tomography scan of the chest and abdomen, or in fluorodeoxyglucose positron emission tomography (FDG-PET) studies.

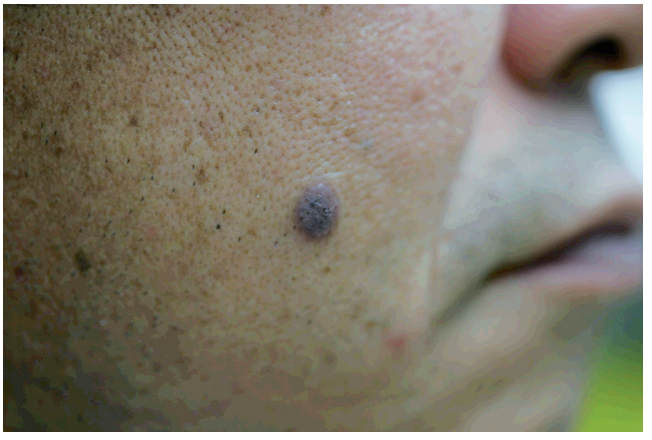

Fig. 1. A black oval nodule measuring 9 × 8 mm on the right cheek in a 47-year-old man.

First, an excisional biopsy was performed with a 1-mm margin. A wide local excision with a 1-cm margin and sentinel lymph node biopsy were performed 3 weeks later. On histopathological examination there was no sign of sentinel lymph node metastasis. Neither local recurrence nor metastasis has appeared during 4 years' follow-up after wide local excision.

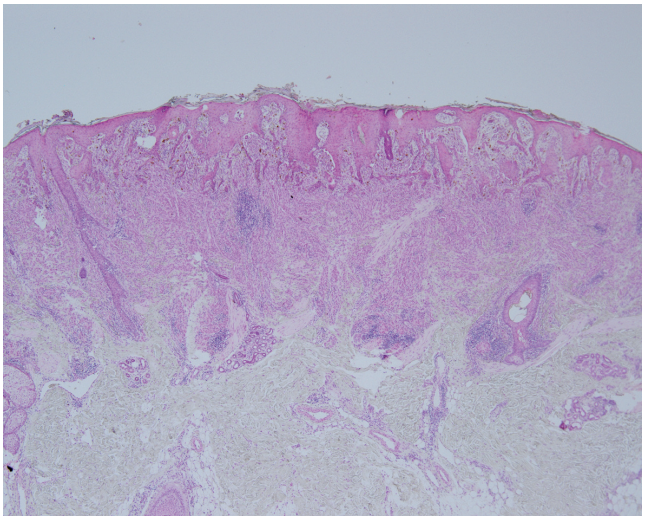

Fig. 2. A well-demarcated, symmetrical nodule with conspicuous, regular elongation of rete ridges (haematoxylin and eosin; low magnification).

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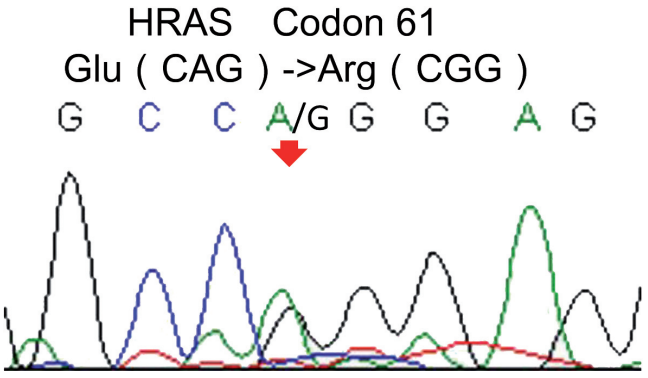

Fig. 3. Mutation in HRAS codon61 (Glu(CAG)->Arg(CGG)) (PCR direct sequencing).

For genetic analysis we extracted DNA from 10-μm paraffin-embedded tissue sections mounted on glass slides. Methylation-specific (MS-) MLPA analysis proved copy number increases of chromosome 11p only. There was no methylation of tumour suppressor genes (APC, RARB, and others). To detect the reported mutations, a PCR assay was performed to amplify BRAF exon 15, NRAS exon 3 and HRAS exon 3, as described previously (5). PCR direct sequencing detected mutation in HRAS codon61 (Glu(CAG)->Arg(CGG)) on chromosome 11p (Fig. 3). Both BRAF codon600 and NRAS codon61 were the wild type. Accordingly, the present case could be considered an HRAS-mutated SN.

DISCUSSION

MLPA analysis is a novel technique to measure the copy number of up to 45 nucleic acid sequences in one single reaction (14). This method is easy to perform, requiring only 50 ng of DNA extracted from routinely processed paraffin-embedded sections, and thus can be used as an adjunctive diagnostic tool more easily than CGH. MS-MLPA analysis is a modified method of MLPA.

MS-MLPA analysis demonstrated copy number increase only for chromosome 11p in the present case. The reported hotspot mutations are BRAF codon600 and NRAS codon61 in MMs (3, 4, 15) and HRAS codon61 in SNs (5). PCR direct sequencing detected mutation in HRAS codon61 in the present case.

SNs share numerous histopathological findings with MMs. Furthermore, pigmented lesions on a sun-exposed area in a middle-aged man would cause dermatologists to include MM in the differential diagnosis. Although the present case had typical histopathological findings of SNs rather than MMs, we could not definitively decide between the two, and performed wide local excision and sentinel lymph node biopsy. However, MS-MLPA analysis and PCR direct sequencing confirmed the diagnosis of SN. In conclusion, genetic analysis is useful for distinguishing between SN and MM.

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