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Localized mosaic neurofibromatosis type 1

Lokalizovaná neurofibromatóza typu 1 v mozaice

Dear editors,

Localized mosaic neurofibromatosis (LMN) is one of the least common genodermatoses of the neurofibromatosis family. LMN arises due to post-zygotic somatic mosaicism in the *NF1* gene [1] and is a member of the mosaic neurofibromatosis 1 (NF1; MIM: 162200) group. The classic definition of LMN describes the condition as café au lait macules (CALM) and/or neurofibromas present in only one unilateral segment of the body, usually superficially.

Hundreds of adult LMN cases [2] and dozens of pediatric LMN cases [3] have been clinically described in the literature. However, only a few individuals have undergone genetic testing, e.g., only 15 adult patients mentioned by García-Romero et al [2] underwent molecular genetic testing for the presence of NF1 mosaicism, eight patients were tested by Marwaha et al [4], two by Messiaen et al [1], and another five cases were reported individually [5–9].

A 65-year-old female was referred to our center with multiple neurofibromas on her right shoulder (Fig. 1). No CALM or other NF1 related signs were detected at this stage. Lisch nodules were not detected on the ophthalmological evaluation. Subsequently, skin excision of one of the nodules was performed, and a 15 × 10 × 5 mm tissue sample, including a 5 × 5 mm suspect neurofibroma, was indicated for histological evaluation, which confirmed the neurofibroma diagnosis (Fig. 2).

DNA for molecular genetic diagnostics was isolated from formalin-fixed paraffin-embedded (FFPE) tissue biopsy samples from two locations, i.e., the neurofibroma itself and some of the healthy skin adjacent to the neurofibroma. We also isolated DNA from the patient's peripheral blood lymphocytes and buccal smear cells.

Fig. 1. Multiple shoulder neurofibromas.
Obr. 1. Mnohočetné neurofibromy ramene.

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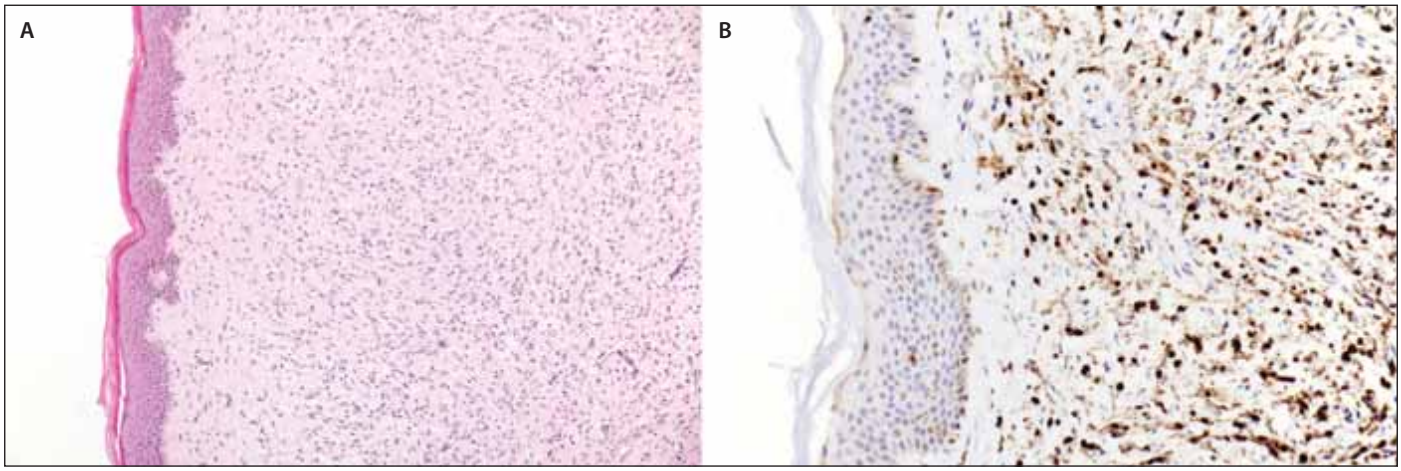

Fig. 2. Neurofibroma histology.
(A) Hematoxylin & eosin, 100× – elongated Schwann cells with darkly stained, pointy ended wavy nuclei. Collagenous stroma in the background; scattered mast cells. Findings typical of a neurofibroma.
(B) Immunohistochemistry S100, 200× – Schwann cells are strongly positive for S100 protein.

Obr. 2. Histologie neurofibromu.
(A) Hematoxylin & eosin, 100× – prodloužené Schwannovy buňky s tmavě obarvenými, vlnitými a špičatě zakončenými jádry. V pozadí kolagenní stroma, roztroušené žírné buňky. Typický obraz neurofibromu.
(B) Imunohistochemie S100, 200× – Schwannovy buňky jsou silně pozitivní na protein S-100.

Initially, we analyzed DNA from peripheral blood lymphocytes to evaluate germline pathogenic variations. Targeted MPS of the neurofibromin gene *NF1* (MIM: 613113) was performed on a MiSeq platform, and data were analyzed using SOPHiA DDM software (SOPHiA GENETICS, Boston, MA, USA). Peripheral blood lymphocyte DNA revealed no single nucleotide variants (SNV) or copy number variants (CNV) in the *NF1* gene (Classes IV–V). Next, we analyzed the DNA extracted from the excised neurofibroma using the same analytical approach. Sequencing data were analyzed using FinalistDX (GeneTiCA, Prague, Czech Republic) bioinformatics software. The neurofibroma sample was also analyzed using MLPA (kits P081-NF1 and P082-NF1).

A heterozygous *NF1* gene pathogenic variant of interest was found in 13% of the NF1 reads, i.e., NM_001042492.2: c.7549C>T, p.(Arg2517*). The variant was annotated as class 5 (pathogenic) according to ACMG criteria. The variant's reference SNP cluster ID is rs866445127. Furthermore, using MLPA, we detected a decrease in peak heights corresponding to exons 3, 5, 6, 7, 9, 11, 15, 16, 21, 23, 24, 25, and 56 of the *NF1* gene. This could represent mosaic somatic heterozygous deletions in a subset of sample cells. This finding is consistent with Knudson's "two-hit" hypothesis. Deletion-based loss of heterozygosity is a common finding in NF1-related neoplasias. The SNV and CNVs not found in DNA were extracted from blood lymphocytes and buccal smears, which were analyzed using Sanger DNA sequencing and MLPA. We tried to analyze the DNA from the adjacent non-neoplastic tissue resected from the neurofibroma sample. Unfortunately, DNA extraction from the FFPE block did not yield adequate amounts of DNA of sufficient quality, and the analysis could not be completed successfully. We concluded that our findings were causative for the observed LMN in our case.

Since mosaic forms of NF1 can afflict the gonads, this represents a risk of NF1 to the offspring of patients, making it crucial to pursue molecular genetic diagnostics so that proper genetic counseling can be provided. When the mosaic form of NF1 is suspected, localized or not, investigations of peripheral blood lymphocytes will often fail to identify the causative variant since the post-zygotic variants are only harbored by a specific subset of the patient's cells. In this regard, molecular genetic examination of other tissues should follow.

Reports identifying the pathogenic variants in LMN via MPS are still lacking. Ko et al [6] reported a patient diagnosed using a procedure similar to ours. García-Romero et al [2] described four mosaic NF1 patients who underwent testing of the affected tissue and blood lymphocytes; in one case, the variant was only found in the affected tissue, and in three cases, it was found in both tissues. Whether it was the localized form of the disease was not specified. Furthermore, Maertens et al [10] described another patient with mosaic NF1 (though not localized) in whom different tissues were examined, including hair, urine, and a buccal smear, and the causative variant was found to varying degrees in different tissues. In patients described by Marwaha et al and Freret et al [4,5], both first- and second-hit variants were identified in diseased tissue but not in peripheral blood lymphocytes. In another patient described by Marwaha et al [4], unpigmented skin above a plexiform neurofibroma was examined, but no pathogenic variant was detected. The major limitation of most of these studies, including ours, was that healthy tissue around the affected area was not tested; this assumes that the identified variant in the diseased tissue was present throughout the entire segment of the patient's body, i.e., in both healthy and affected cells alike. Moreover, if only one variant is determined, this could lead to erroneous genetic counseling in risk assessment, i.e., when the variant found in neoplasia is used in preimplantation/prenatal diagnostics to rule out the risk of NF1 due to gonadal mosaicism in the offspring.

Another critical point to consider is related to oncological prevention in neurofibroma-

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tosis. In this regard, the risk of neoplasms in LMN is similar to that in NF1 patients with the typical form of the disease. Female carriers of germline NF1 pathogenic variants have a higher lifelong risk of breast cancer and thus should receive preventive care, e. g., regular mammographic screening. Since LMN skin lesions are often present on the thorax and abdomen, we suggest oncological screening of female patients with LMN, similar to that for carriers of the germline NF1 pathogenic variant, i.e., using the newest NCCN guidelines, taking into account relevant family history.

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