

# Solitary Epicranial Neurofibroma with Neurofibromatosis Type 1-Related Germline Mutation: Case Report

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## Abstract

A 33-year-old male became aware of a painless soft mass in the left occipital region. His medical and family history were unremarkable for neurofibromatosis type 1 (NF1) or other genetic disorders. Physical examination showed no signs of NF1. Neurological and ophthalmological examinations found no abnormality. Cranial computed tomography showed an isodense mass located subcutaneously with irregular deformities in the adjacent occipital bone. Magnetic resonance (MR) imaging demonstrated that the lesion, 7.5 × 5.5 cm in diameter, was hypointense both on T<sub>1</sub>- and T<sub>2</sub>-weighted images and intensely enhanced after gadolinium infusion. The patient requested to remove the large mass. The subcutaneous tumor was well circumscribed, encapsulated, and less vascular, and resected en bloc. The histological diagnosis was neurofibroma without findings of cell atypia, whereas genomic exploration identified abnormal gains in NF1 gene, and resultant absence of neurofibromin, a protein coded on NF1 gene. Solitary neurofibromas in “clinically” non-NF1 patients may originate from the genomic changes in NF1 gene.

Key words: epicranial neurofibroma, neurofibromatosis, germline mutation

## Introduction

Neurofibromas are benign tumors arising from the peripheral nerve sheath and are characterized by proliferation of Schwann cells, perineural cells, and fibroblasts. Microscopically they are composed of elongated, spindle-shaped cells with round or fusiform nuclei and eosinophilic cytoplasm within a loose matrix of fine fibrillary collagen.<sup>1</sup> Historically, neurofibromas have been divided into subtypes according to different classifications on the basis of the mode of tumor extension,<sup>2</sup> histological characteristics,<sup>3</sup> or anatomical locations in the cutaneous and subcutaneous layer.<sup>4</sup> Neurofibroma in the head region is uncommon.<sup>5–11</sup> A fraction of these tumors develop massive intratumoral hemorrhage<sup>5,9</sup> and malignant transformation.<sup>12</sup> Most cases of epicranial neurofibromas and other neurofibromas originating in the head region were associated with neurofibromatosis type 1 (NF1), a genetic disorder at 17q11.2, an oncosuppressor gene coding neurofibromin and acting on the *ras*-related system.<sup>6,9–11</sup> In contrast, only 3 cases of neurofibromas that are not associated with NF1 have

been documented.<sup>7,8,10</sup> Those diagnoses were based on the conventional clinical criteria for NF1, and genetic exploration has not been performed so far. Here we present a unique case of solitary epicranial neurofibroma in an adult male with no clinical association with NF1, but with genetic indications of NF1-related germline mutation.

## Case Report

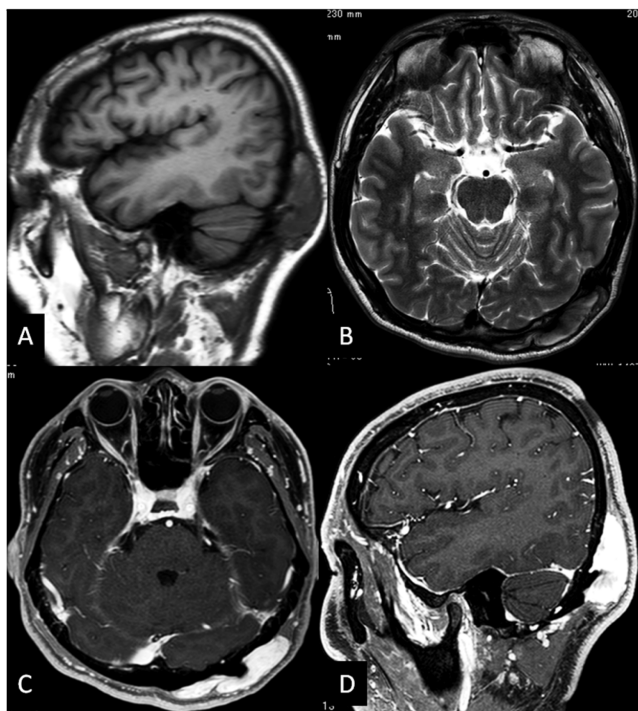
A 33-year-old male was aware of a painless soft mass in the left occipital region for 2 months. His medical history was unremarkable without mental retardation, family history of NF1, or other genetic disorders. The patient had not been aware of any subcutaneous mass in the occipital region or any preceding head trauma. At presentation, he had no macules, freckles, or tumors of the skin. The spinal alignment was normal without deformity. Neurological and ophthalmological examinations did not find any abnormalities. Cranial computed tomography showed an isodense mass located subcutaneously associated with irregular deformities in the outer surface of the adjacent occipital bone (Fig. 1). Magnetic resonance (MR) imaging demonstrated that the lesion

appeared hypointense on both T<sub>1</sub>- and T<sub>2</sub>-weighted images, was 7.5 × 5.5 cm in diameter, entirely located epicranially, and intensely enhanced after gadolinium infusion. No concurrent intracranial or orbital tumor was found (Fig. 2).

The patient requested to remove the large mass. He



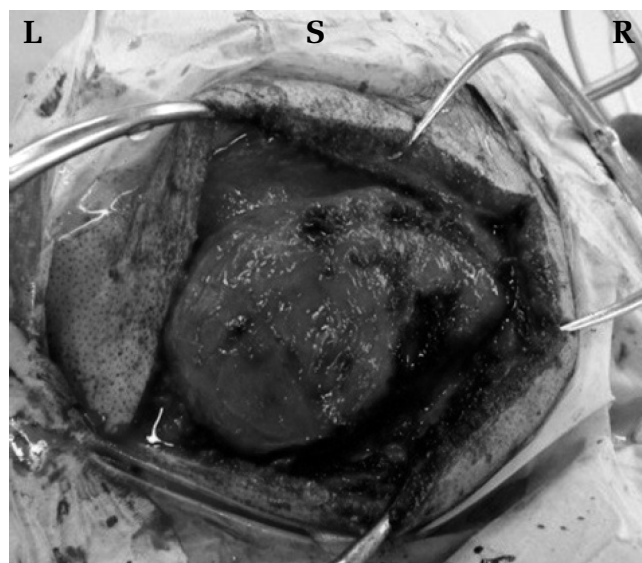
**Fig. 1** Axial computed tomography scan showing an isodense subcutaneous mass associated with irregular deformities in the outer surface of the adjacent occipital bone (arrow).



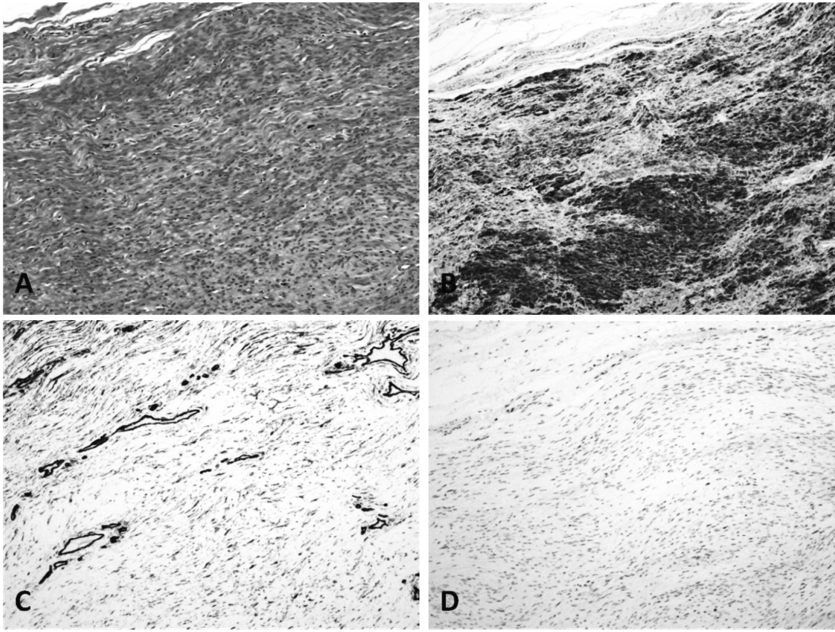
**Fig. 2** Sagittal T<sub>1</sub>-weighted (A) and axial T<sub>2</sub>-weighted (B) magnetic resonance (MR) images showing a hypointense epicranial tumor, 7.5 × 5.5 cm in diameter, and axial (C) and sagittal (D) T<sub>1</sub>-weighted MR images after gadolinium infusion showing intense tumor enhancement.

underwent tumor resection with the presurgical diagnosis as lipoma, fibroma, neurofibroma, and myogenic tumor. The subcutaneous tumor was elastic, soft, well circumscribed, entirely encapsulated, and less vascular, with firm adhesion to the periosteum, so was dissected circumferentially and resected en bloc (Fig. 3). The main trunk of the left occipital artery coursed above and supplied small tributaries to the tumor capsule. Macroscopically, the sections of the tumor were homogeneous and did not contain hematoma. Histological examination found spindle-shaped tumor cells with round or fusiform nuclei and eosinophilic cytoplasm within a matrix of fine fibrillary collagen consistent with neurofibroma. Immunohistochemical staining for tumor cells was positive for S-100 protein, but negative for CD34. The Ki-67 labeling index was less than 1%. No cell atypia, endothelial proliferation, or intratumoral hemorrhage was found (Fig. 4).

Genomic exploration was carried out by the single nucleotide polymorphism (SNP) method. The genomic deoxyribonucleic acid was extracted from paraffin-embedded tissue blocks using Puregene Core Kit A (QIAGEN, Hilden, Germany). Then SNP oligonucleotide microarray analysis was performed with the Affymetrix Gene Chip Human Mapping 6.0 SNP array (Affymetrix, Santa Clara, California, USA). Sample preparation, hybridization, and scanning were performed according to the manufacturer's specifications. Data were analyzed with Genotyping Console v2.0 (Affymetrix) and Ingenuity Pathway Analysis v7.5 (Ingenuity Systems, Redwood City, California, USA), which confirmed abnormal gains in NF1 gene (Fig. 5A). Immunohistochemical staining for neurofibromin, a protein coded on 17q11.2, was absent (Fig. 5B). No abnormalities in the neurofibromatosis type



**Fig. 3** Intraoperative photograph demonstrating the subcutaneous mass dissected circumferentially. L: left, R: right, S: superior.



**Fig. 4** Photomicrographs of the resected tumor showing spindle-shaped cells with round or fusiform nuclei and eosinophilic cytoplasm within a matrix of fine fibrillary collagen, without findings of cell atypia, endothelial proliferation, or intratumoral hemorrhage (A: hematoxylin and eosin [HE] stain). Immunohistochemical staining for tumor cells was positive for S-100 protein (B), but negative for CD34 (C). Ki-67 labeling index was less than 1% (D). Original magnification  $\times 50$  (A–D). A: HE,  $\times 50$ ; B: S-100,  $\times 50$ ; C: CD 34,  $\times 50$ ; D: MIB-1 < 1%.

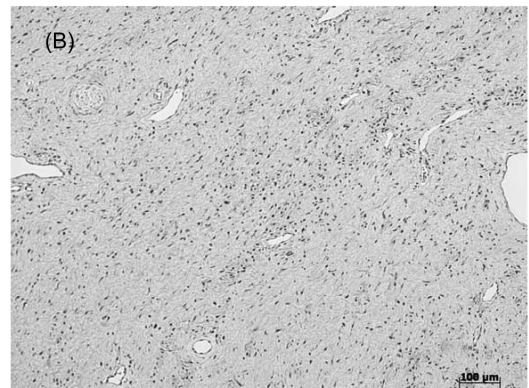
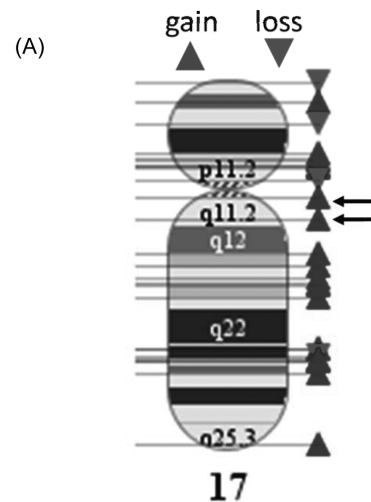
2 (NF2) gene, located on the 22q11.23, were found. These findings were indicative of neurofibroma originating from germline mutation in NF1 gene.

### Discussion

In the present case, solitary epicranial neurofibroma occurring in a young adult male appeared to be clinically non-NF1 based on the normal cutaneous, ocular, and skeletal findings without brain or orbital tumor, in addition to the unremarkable family history of NF1. Review of epicranial neurofibromas found extraordinarily slow progression and predisposition for the occipital region, with manifestation as skull defect or thinning, and hypervascularity.<sup>10</sup> Intraoperative findings revealed an encapsulated epicranial tumor with deformities in the adjacent skull. The histological appearance of the tumor was indicative of benign pathology with low mitotic activities, no cell atypia, and no intratumoral hemorrhage. These findings were consistent with typical neurofibroma manifesting after extraordinarily indolent growth. In contrast, genetic exploration was indicative of a tumor originating from NF1-related germline changes.

Neurofibromatoses are commonly diagnosed based only on the clinical manifestations and may miss “clinically silent” cases, which are genetically evident as neurofibromatoses. This possibility implies that the “clinical” definition of neurofibromatosis may not cover the entire spectrum of this disease and emphasizes the possibility of more diverse pathophysiology.

The exact genesis of neurofibromas is not well understood, but recent investigation has suggested that the hair follicle apparatus, including the nerve tributaries, may be



**Fig. 5** A: Genomic exploration by the single nucleotide polymorphism identification method showing abnormal gains in NF1 gene (17q11.2) (arrows). B: Immunohistochemical staining for neurofibromin demonstrating negative staining. Original magnification  $\times 10$ .

an origin of NF1-associated cutaneous neurofibromas.<sup>9)</sup> Recently Beert et al. described a pediatric case of sporadic neurofibroma arising in the lumbosacral region without signs of NF1. They concluded on the basis of genomic analysis that biallelic NF1 gene inactivation may be the underlying pathomechanism.<sup>13)</sup> Germline mutations in NF1 may include diverse spectrum with cases not presenting signs of NF1. Similarly, germline changes of the *SMARCB1* gene, also called *BAF47* or *hSNF5*, which is located at 22q11.23 and functions as a chromatin remodeling gene, may be a locus of familial and sporadic NF2 that originates from changes at 22q12.2.<sup>14–16)</sup> In the present patient, no germline mutations were identified at 22q12.2.

Solitary neurofibromas in “clinically” non-NF1 patients may originate from germline changes in NF1 gene. Further genetic investigation combined with more case experience can provide updated diagnostic criteria including the germline mutations of neurofibromatosis, which would be useful for better delineating the genesis, pathophysiology, and biological behavior of neurofibromas.

### Conflicts of Interest Disclosure

The authors have no personal, financial or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of the Japan Neurosurgical Society (JNS) have registered online self-reported conflict of interest disclosure statement forms through the website for JNS members.

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