Case report: Bilateral spinal neurofibromatosis

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Spinal neurofibromatosis (SNF) is a rare form of Neurofibromatosis in which neurofibromas exist bilaterally throughout all spinal roots. Despite previous attempts made to characterize and classify the disease as a separate clinical form of the disease, the low incidence rate of the disease and scarcity of previous reports calls for further studies and reports to elaborate this clinical entity. The patient in this report was a 36-year-old man presenting with lower limb weakness, unsteady gait, and paresthesia. The patient also presented with multiple cutaneous café-au-lait spots, cutaneous neurofibromas, and a large neurocutaneous neurofibroma of right facial nerve. Magnetic resonance imaging (MRI) of spine revealed bilateral spinal neurofibromas across all spinal cord roots. MRI study of head revealed no abnormalities in the brain and optic tract. The patient fulfilled both NIH criteria as well as revised criteria for NF1. Despite total spinal cord involvement, surgical intervention was withheld from the patient due to high propensity of recurrence as seen with previous attempts in removing peripheral neurofibromas, slow progression of symptoms, and lack of significant pain and impairment. SNF is often described as a form of disease with infrequent presentation of classical NF1 symptoms other than spinal tumors. The case presented here however, presented with several cutaneous neurofibromas and café-au-lait spots. Considering the positive outcome of surgical intervention in a few other reports, the decision to surgically intervene should be left to the clinical judgement of the participating surgeon, patient preference and socioeconomic background in a case-by-case manner.

KEYWORDS
spinal neurofibromatosis, nerve sheath tumor, Von Recklinghausen’s disease, spinal tumor, neurosurgical oncology, case report

Introduction

The Neurofibromatoses are a group of genetic neurocutaneous disorders with an autosomal dominant inheritance pattern and significant morbidity and mortality. These conditions are characterized by dysregulated cell growth in tissues that lead to tumor growth in nerves throughout the body in any age (1, 2). Despite the significant heterogeneity in clinical presentation of the affected individuals and several reports of variants and alternate forms of the disease (2, 3), the neurofibromatoses have been generally classified into three clinical entities, Neurofibromatosis type 1 (NF1, 96% of
Neurology. As such, genetic sequence NF1 cases are represented by the primary source of gene mutation, about half of the inheritance in both NF types suggests vertical transmission to chromosome 17 comparable to NF2 excluding bilateral vestibular schwannomas in SMARCB1 or LZTR1 genes, but a clinical presentation of all NF cases) called Schwannomatosis with distinct mutations 1/2,558–1/3,333, is caused by mutations in NF1 that acts as a negative regulator of RAS/MAPK pathway (12).

Mutations in NF1 gene result in diminished tumor suppressive properties, RAS hyperactivation, and subsequent upregulation of mTOR and ERK pathways (6), which have also been linked to increased predisposition toward certain tumors and/or malignancies including pheochromocytoma, optic pathway glioma, astrocytomas and malignant gliomas, breast cancer, gastrointestinal stromal tumors, rhabdomyosarcomas, and peripheral nerve sheath neoplasms (13, 14). As such, genetic counseling should be offered to families with NF1 and tailored imaging guidelines have been developed for surveillance based on clinical symptoms (14, 15).

The disease phenotype is characterized by multiple skin pigmentation defects in the relevant genes, tumor type and location, and clinical determinants of each type, and a rare third type (<1% of all NF cases) called Schwannomatosis with distinct mutations in SMARCB1 or LZTR1 genes, but a clinical presentation comparable to NF2 excluding bilateral vestibular schwannomas and an older age of onset (4–8).

NF1, historically known as Von Recklinghausen's disease, affects all races and ethnicities with a reported incidence of 1 in 3,000–1 in 6,000 and an estimated birth incidence of 1/2,558–1/3,333, is caused by mutations in NF1 gene localized to chromosome 17 (6, 9). Although autosomal dominant pattern of inheritance in both NF types suggests vertical transmission as the primary source of gene mutation, about half of the NF1 cases are represented by de novo mutations in the NF1 sequence (10). The considerable proportion of cases without family history of NF1 reflects the high rate of mutation of NF1 locus, with the majority of the deletions and mutations being of maternal and paternal origin, respectively (11). The gene product of NF1, neurofibromin, is a GTPase-activating protein that acts as a negative regulator of RAS/MAPK pathway (12). The gene product of NF1, neurofibromin, is a GTPase-activating protein that acts as a negative regulator of RAS/MAPK pathway (12). Mutations in NF1 gene result in diminished tumor suppressive properties, RAS hyperactivation, and subsequent upregulation of mTOR and ERK pathways (6), which have also been linked to increased predisposition toward certain tumors and/or malignancies including pheochromocytoma, optic pathway glioma, astrocytomas and malignant gliomas, breast cancer, gastrointestinal stromal tumors, rhabdomyosarcomas, and peripheral nerve sheath neoplasms (13, 14). As such, genetic counseling should be offered to families with NF1 and tailored imaging guidelines have been developed for surveillance based on clinical symptoms (14, 15).

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SNF could be described as a distinct clinical entity in which bilateral neurofibromas in all spinal nerves and/or spinal roots are the main clinical presentation of the patients with a less frequent pattern of other NF1 manifestations such as
Lisch nodules, changes in muscle tone, or skeletal dysplasia. As a corollary, only a minority of SNF cases could completely satisfy the NF1 diagnostic criteria (18). Dermal neurofibromas are less common in SNF than in NF1 despite extensive peripheral nerve enlargement extending from each spinal nerve. As most reports described this phenotype in segregated families, SNF was initially referred to as hereditary/familial spinal neurofibromatosis. However, missense mutations in NF1 have been observed to be significantly higher in SNF. As such, individuals harboring de novo NF1 missense mutations
may develop SNF in a family without a history of the disease. Nevertheless, obtaining baseline MRI of the entire CNS to screen for asymptomatic tumors in newly diagnosed and asymptomatic individuals with NF1 is not currently recommended (14). Accordingly, imaging studies should be reserved for individuals demonstrating abnormal neurological examination, progressive symptoms of cord compression and polyneuropathy, or unexplained neurological deficits using localized imaging with multiple MR sequences (14).

At present, the treatment strategies revolve around symptomatic relief of disease manifestations and improving quality of life. Despite extensive research, recent clinical trials have demonstrated that pharmacological interventions have diminished ability to reduce tumor size in plexiform neurofibromas. Furthermore, spontaneous regression of neurofibromas is rarely seen in clinical settings (14).

The mainstay therapeutic approach for symptomatic neurofibromas are surgical excision of certain tumors which cause significant morbidity. Spinal cord compression symptoms and spinal deformity have been valid indications for anterior and/or posterior decompression with or without fusion/arthrodesis, and complete or partial resection of neurofibromas in classical NF1 (19, 20). However, bilateral involvement of all vertebrae in SNF restricts less invasive surgical approaches such as hemilaminectomy or tumor resection without instrumentation. Multilevel bilateral laminectomies are also prone to significant destabilization of spinal column, which may result in several postoperative complications (20). The authors therefore believe that surgical intervention should be reserved for cases of severe disability and to be limited to symptomatic lesions. A previous report found that the majority of preoperative symptoms improved in patients with non-NF2 spinal neuromas compared to their NF2 counterparts, with a low 5-year recurrence rate of 10.7%. However, the scarcity of NF1 cases in the study precludes definitive conclusions on the prognosis and recurrence of neurofibromas in SNF (21).

While classical NF1 symptoms is less frequently seen in SNF, this case presented with several cutaneous neurofibromas, café-au-lait spots, and movement disorder. It is of note to say that symptomatic SNF reportedly consists only 1.6% of all NF1 cases (9, 18). Although there was total spinal cord involvement with intradural extension of the tumors in several spinal levels in this case, surgical intervention was withheld from the patient due to high propensity of recurrence as seen with previous attempts in removing peripheral neurofibromas, slow progression of symptoms, financial burden on the patient in the context of economic inequality caused by NF1 (22), lack of significant pain or impairment in daily activities, and risk of complications. Considering the positive outcome of surgical intervention in a few other reports in improving patient quality of life and symptomatic relief without evidence of short term recurrence, the decision to surgically intervene should be left to the clinical judgement of the participating surgeon, patient preference and background in a case-by-case manner. At the time of writing this work, the conservative approach to the spinal tumors in this case was approved and well-tolerated by the patient.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patient provided their written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

AB designed and supervised the study and was the primary physician of the patient. SA and AT acquired data from the patient, investigated the patient history, and clinical data. SA and AB analyzed the data. SA and MC-N contributed with visualization and drafting the manuscript. SA and SSA edited the manuscript for clarity and scientific accuracy. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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