Segmental Spinal Neurofibromatosis 1: A Novel Phenotype

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Abstract

Segmental neurofibromatosis (SNF) is a rare subtype of neurofibromatosis (NF). The disease is characterized by features circumscribed to one or more body cutaneous and/or subcutaneous segments. This is a classic example of somatic mosaicism which occurs by postzygotic mutation of the NF1 gene late in the course of embryonic development affecting localized neural crest lines in the fetus. Our case series reported three novel patients who had segmental spinal expression of the disease classified as true mosaic/segmental NF1, along with their management plan treated at one of the largest NF1 center.

Introduction

Neurofibromatosis Type I (NF1) is a relatively common phakomatosis estimated to occur in 1:3,000 live births. It is extremely variable in its clinical presentation from generalized expression of the disease (90% of the cases) [7] to localized neurofibromas or café-au-lait (CAL) spots [8]. Within this spectrum of phenotypic heterogeneity, several distinct syndromes have been described. SNF is a rare variant of NF1 with an estimated prevalence between 0.0014-0.002% [9]. This disease is generally thought to result from postzygotic NF1 gene mutation in a primitive neural crest cell [10]. Therefore, these lesions should be strictly unilateral and noninherited. The clinical manifestations as described by Riccardi et al [7] include CAL spots and/or neurofibromas in a single unilateral segment of the body, with no crossing of the median line, no family history, and no systematic involvement. Further, Roth et al [8] has subdivided SNFs into four subtypes that include true segmental, localized with deep involvement, hereditary, and bilateral. Spinal neurofibromatosis is another rare NF1 phenotype, characterized by histologically proven bilateral neurofibromas of all spinal roots and eventually of all peripheral nerve branches with or without manifestations of classical NF1 [6, 9].

We describe here a novel phenotype of NF1 that incorporates both the SNF and spinal NF component: three of our patients are presented with segmental spinal expression of the disease. This variant of NF1 is distinct from previously described segmental and spinal NF1 variants in the literature.

Case Presentation

Case 1

57-year-old female with a history of schwannomatosis presented with enlargement of left cervical mass. She had increased dysphagia and difficulty in swallowing because of her enlarged mass. The patient had a history of posterior neck ‘benign’ tumor removed at outside institution 20+ years prior. She underwent surgery for removal of vagus nerve and sympathetic chain tumor; pathology confirmed neurofibroma. There were no tumors in brain, cervical, thoracic or lumbar spine. On physical exam, neither CAL macules nor axillary freckling was noted. The patient had no skeletal manifestations of disease. Pertinent positive findings included several cutaneous neurofibromas identified on the ipsilateral (right) shoulder and a plexiform neurofibroma of the right suprascapular area. (Figure 1)

Case 2

71-year-old male patient presented with radiculopathy. MRI revealed foraminal tumors involving every level from L1-sacrum. He had a history of plexiform neurofibroma of right buttock s/p multiple resections. No tumors were seen on MRI of the thoracic and cervical spine. On physical exam no axillary freckling was noted. The patient had no skeletal manifestations of disease. Though there were no cutaneous tumors or CAL macules, the patient had history of removal of several small cutaneous tumors that by clinical history were compatible with neurofibromas. Genetic testing revealed a heterozygous splicing mutation at intron 22. (Figure 2)

Case 3

29-year-old male with history of craniotomy for foramen magnum tumor confirmed on pathology to be a neurofibroma. Other manifestations included intradermal plexiform neurofibroma of scalp, and another identifiable cutaneous lesion, most probably neurofibroma. MRI revealed non-enhancing bright T2 tumors from C1-T2. There were no tumors in the spine below T2. Multiple neck masses, including sympathetic chain, brachial plexus and carotid sheath were present bilaterally. (Figure 3)

Discussion

All of the three affected patients in the present case series exhibit a distinct clinical entity of SNF, consisting of extensively and apparently symmetrically distributed, histologically proven, neurofibromas involving one segment of the spine and/ or body (i.e. cervical spine and neck in two cases and lumbar spine and buttock in the other). Surgical intervention is indicated when myelopathy and motor losses develop, which are frequently localized to the cervical and lumbar regions.

In our case series, one patient presented in middle age, and one as a teenager. None of them have cognitive or skeletal involvement, and all have very limited cutaneous disease. The patient with lumbar disease has a large plexiform tumor of the buttock. One of the two cervical patients has an extensive tumor burden in the soft tissue of the neck including the sympathetic chain and/ or brachial plexus. In our opinion, bilateral neurofibromas in all roots of a given spinal segment should be regarded as segmental phenotype. Since 2 of the 3 patients presented later in their life, it is reasonable to refer to them as phenotypically segmental/mosaic NF1 which involves bilateral neurofibromas in all the spinal roots of a given segment later involved entire spinal roots bilaterally. Furthermore, the plexiform neurofibroma observed in one of our patients is part of spinal NF1 phenotype or part of a phenotype where spinal root neurofibromas are seen along with plexiform neurofibroma. The involvement of sympathetic chain and brachial plexus in the nearby area of the spinal involvement also fits with the spinal NF1 phenotype. However, this is in contrast with the previously described MNFSR and/or MNFSR/Spinal Neurofibromatosis phenotypes [5, 9].

We believe that the patients in our cohort belonged to true mosaic/segmental NF1 [3], since we found pathogenic mutation in the tumor with lack of pathogenic mutation in the blood. This is different from

the classical NF1 in which NF1 pathogenic mutation is found in both the blood and the tumor. It is possible that patients had mild to classical NF1 phenotype which was superimposed by more aggressive NF1 manifestations (i.e., bilateral spinal root tumors). Nevertheless, there is a high likelihood that the NF1 pathogenic mutation could not be detected either in the blood or in the tumor, hence more extensive genomic analysis like WES and/or WGS should be carried out.

True spinal NF1 has a relentless and progressive course, while mosaic/segmental phenotype has a more indolent and slower course [1]. Hence, if the patients present in their early ages they should be closely observed, in contrast if they present in the later stages there is more likelihood of a benign course. Genetic testing would certainly help to better characterize these individuals, or at least, to exclude or confirm NF1 pathogenic mutations [2]. Although Selumetinib [4] has proven effective in plexiform neurofibromas within the context of classical NF1, there are currently no reports on its use in spinal NF1 and/or mosaic phenotypes.

Abbreviations

CAL: Café-au-lait, SNF: Segmental Neurofibromatosis, NF1: neurofibromatosis 1, MR: Magnetic Resonance imaging

Declarations

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Availability of data and material: All data generated or analyzed during this study are included in this published article

Consent to Participate: Obtained from all patients

Consent to Publish: Obtained from all patients

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Figures

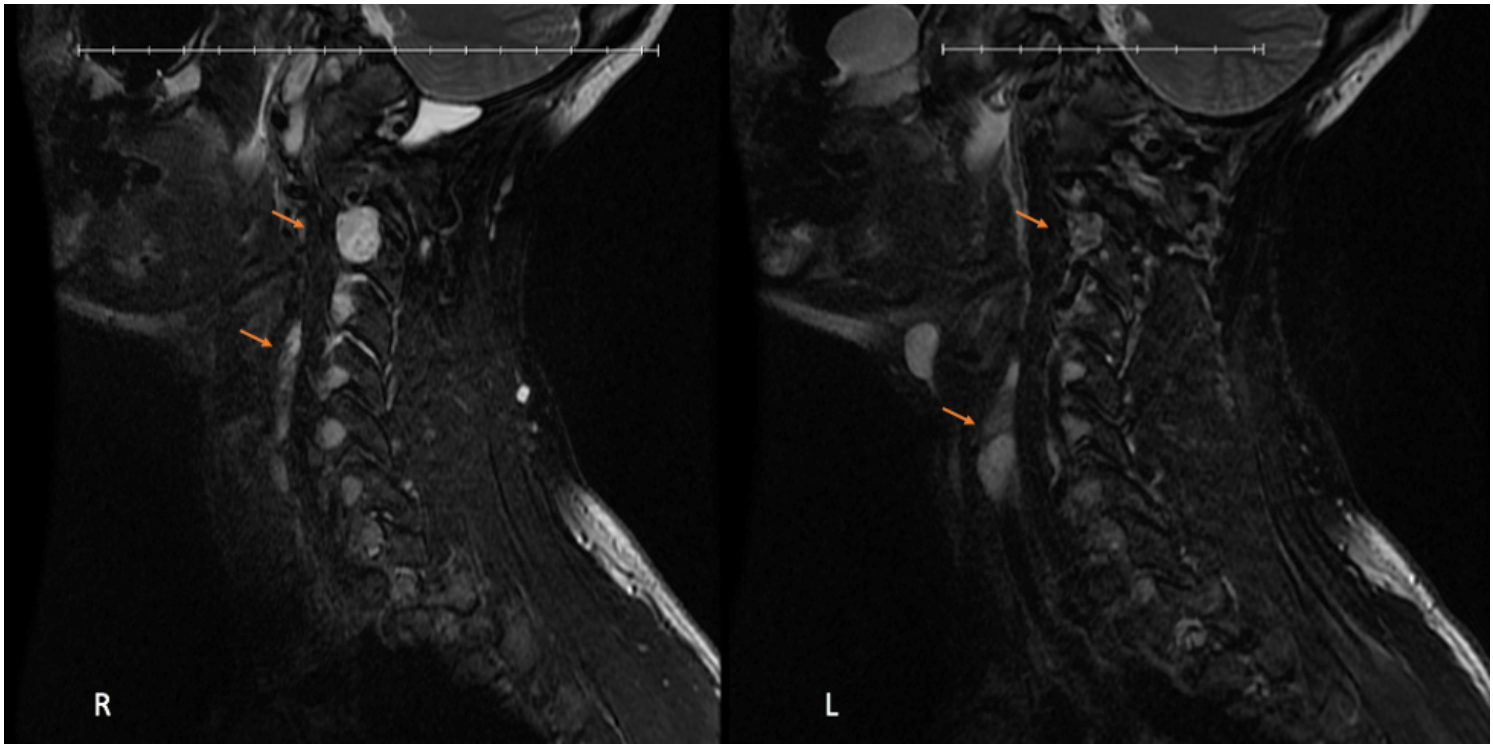

Figure 1

MRI sagittal view-57-year old female with multiple foraminal and neck tumors (pointed arrows).

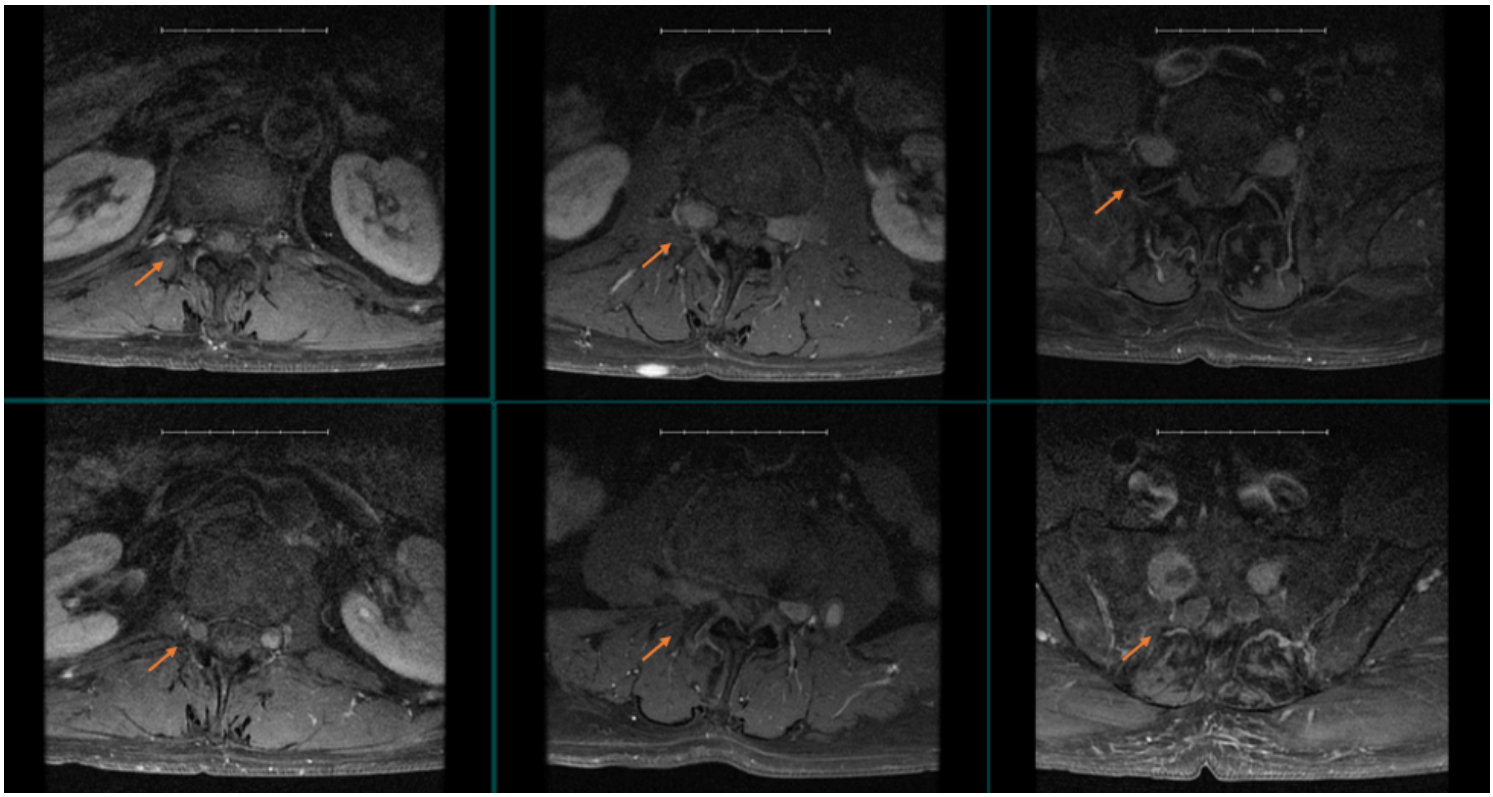

Figure 2

MRI axial view-71 year old male with lumbo-sacral spinal NF1 (pointed arrows).

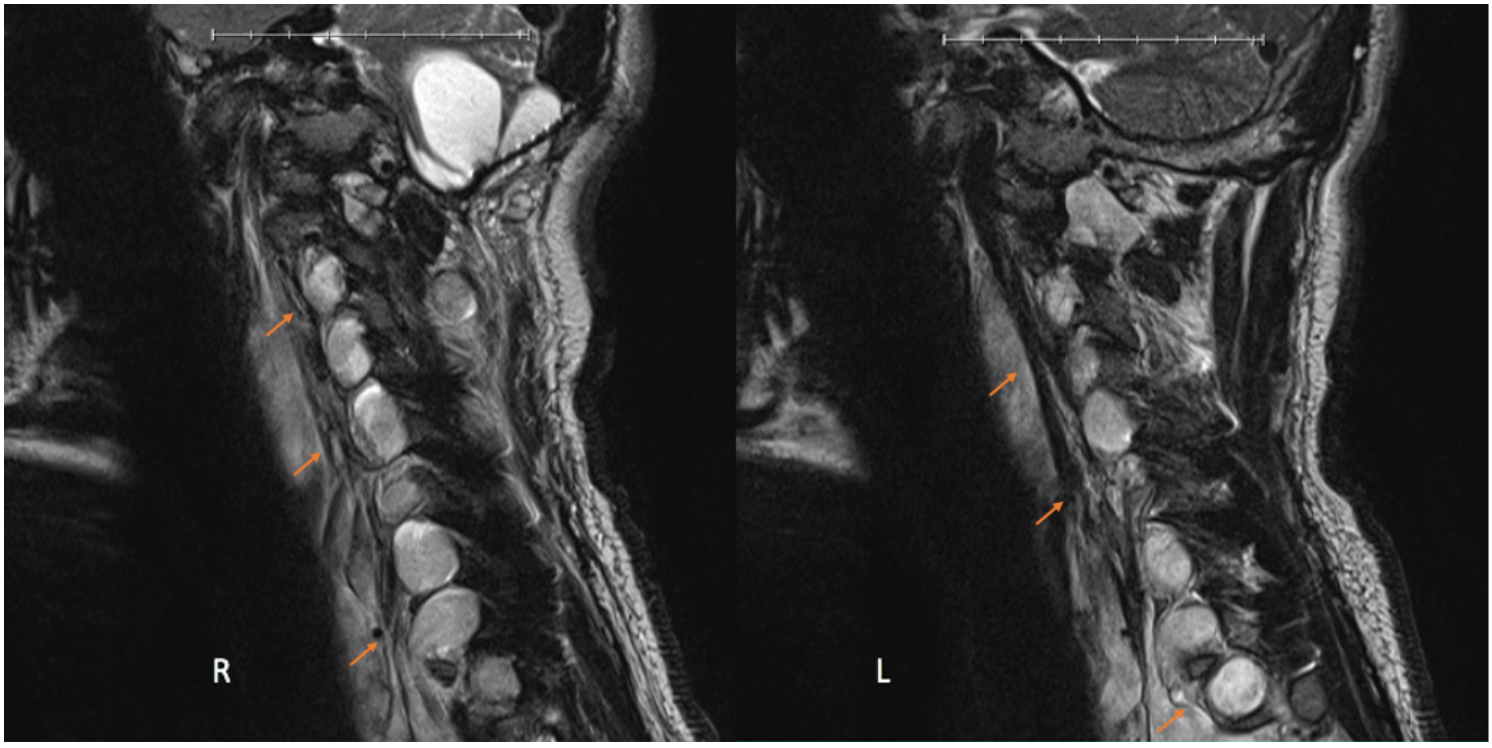

Figure 3

MRI sagittal view-29 year old male with multiple foraminal tumors C1-T2 (pointed arrows).