

## Everolimus Efficacy in the Treatment of Neurofibromatosis Type 1

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Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder induced by a mutation in the NF1 tumor suppressor gene resulting in devastating physical and emotional repercussions, potentially life threatening. The recognized therapeutic options for neurofibromas are surgery or radiotherapy; however, when these options have been exhausted, pharmacologic agents interfering specifically with the mTOR pathway can be utilized. Everolimus is an oral inhibitor of mTOR complex 1 (mTORC1) with an intrinsic anti-tumor effect recognized in various cancer subtypes. The FDA and Health Canada have approved everolimus for the treatment of advanced renal cell carcinoma, neuroendocrine pancreatic tumors and subependymal giant cell tumors (SEGA) associated with tuberous sclerosis. However, there is limited clinical data reporting the efficacy of everolimus in the treatment of neurofibromas. The manuscript presents the case of a 60-year-old male diagnosed with progressive cervical spine neurofibroma refractory to standard surgical and radiation treatment. Everolimus was administered due to the imminent risk of tetraplegia. This decision acted in the patient's favor. We faced the dilemma of observing the patient, progressing through his natural evolution, currently considered has the good practice and the standard of care, despite the risk of a potentially irreversible unfortunate condition. This manuscript discusses the situation we will face in a near future, when several therapeutic molecules will emerge from clinical trials and we will only rely on our judgment to determine the best clinical practice.

**Keywords:** Neurofibromatosis Type1; Quadriplegia; Mtor Pathway; Everolimus; Neurofibroma; Spinal Stenosis; Peripheral Nerve Sheath Tumor

**Case Report**

A 60-year-old male was referred to Princess Margaret Cancer Centre for the management of his Neurofibromatosis type 1 (NF1). This patient presented with pain, numbness and weakness in bilateral distal upper limbs, not following nerve territories. He mentioned also paroxysmal shooting pain radiating down his left arm. Significant muscle wasting in thenar and hypothenar muscles was noted. Imaging revealed neurofibromas in the cervical and upper thoracic spine, causing a mass effect on the brachial plexus. Specifically, masses at C1-C2 indenting the left side of the cervical cord,

and interval growth in the medial extent of the bilateral neurofibromas at C5-C6, with increased bilateral mass effect on the spinal cord, was observed. Schwannomas extending to L3 on the right and L4 on the left, with compression and posterior displacement of the cauda equina nerve were also visualized. A chest MRI revealed neurofibromas bilaterally in the soft tissues of the supraclavicular and axillary areas, impacting the course of the peripheral nerves involved in the brachial plexus. Pathology confirmed the benign nature of the cervical lesions consistent with grade 1 neurofibromas.

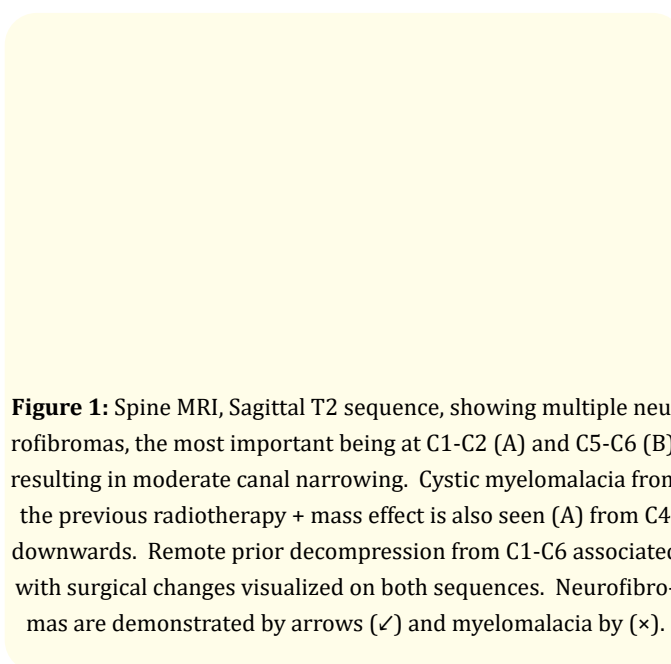
This patient was first diagnosed with NF1 35 years prior. Since then, he underwent three surgical procedures. Two of them aimed to decompress C4-C7 and the last one to relieve C6. The patient has also received “mantle” radiotherapy targeting lesions involving the cervical spine and the brachial plexus. At this point, the etiology of this patient’s pain, sensory and motor deficits was likely multifactorial. The surgical and radiotherapy treatment options had been exhausted, considering the risk of repeating any procedure in this anatomical area. What is a reasonable approach to management moving forward? What therapy would be best to employ given this patient’s symptoms and treatment history?

The diagnosis in this case was clear since the diagnosis of NF1 was made in 1982. However, the patient recently developed progressive sensory and motor loss in his upper extremities, impacting his daily activities. Compared to MRI imaging completed 8 months prior, there were no notable changes in the size of the neurofibromas invading neural foramina, although there was some extension into the epidural space and intrathecal lesions along the cauda equina. Bilateral neurofibromas at C4-C6 presented a similar appearance, as well as the extent of myelomalacia. The left-sided anterior neurofibroma at L4 resulting in compression of the thecal sac was stable. On the other hand, the L4/L5 indolently progressive compression of the cauda equina worsened slightly. We noted an absence of dural ectasia or scoliosis. While surgery and radiotherapy are typically employed to manage NF1-related tumors, this case was particular. The localization and size of the patient’s neurofibromas and the crucial role of the anatomical areas previously treated made him ineligible for any further invasive treatment. The risk of extended myelomalacia prevented any further radiation treatments. Furthermore, imaging revealed that the C-spine lesion was growing over the past year, confirming disease progression, implying an increasing risk of tetraplegia [1,2]. Thus, the only hope for a positive outcome was the employment of a novel systemic therapy [3]. What systemic therapies could be employed to help treat this patient? What therapies have proven effective in diseases with a similar pathogenesis?

In past case reports of patients with cervical spinal cord compression due to NF1, a variety of surgical treatments have been employed to decompress the cervical spine and alleviate symptoms [4,5]. The use of cervical suspensory traction, followed by posterior instrumentation and fusion to alleviate cervical compression was described in a 18-year-old NF1 patient [4]. Garg, *et al.* reported effective decompression in a 10-year-old patient with an extensive laminectomy followed by occipital-cervical fusion from to stabilize the spine and prevent further kyphosis [4]. Radiation therapy alone was not used to address significant com-

pression of the cervical spine due to NF1. Sarica, *et al.* reported improvements following physical rehabilitation and myorelaxant medication. On the other side, these therapies were only appropriate following post-surgical decompression. To our knowledge, there are no reports of such effective therapies without prior surgical interventions [6].

In the research of a novel systemic therapy to manage the patient’s NF1, the best options available in Canada was everolimus, an mTOR inhibitor and rapamycin analog [7]. The selection was based on the role of mTOR in tumor pathogenesis. The patient was administered a dose of 10 mg OD. Everolimus functions predominantly by inhibiting mTORC1, preventing cell division and proliferation, thereby reducing tumor growth [8]. Everolimus is well-renowned for its role in the treatment of several other pathologies such as renal cell carcinoma and advanced pancreatic neuroendocrine tumors [9,10]. This molecule is also efficient for the management of primary brain tumors such as subependymal giant cell astrocytoma, and meningiomas associated with NF2 and Bourneville tuberous sclerosis [11-14]. In each case, the everolimus-mediated inhibition of mTOR pathway has been able to reduce, even to interrupt, tumor growth. Twenty months after the initiation of everolimus, the two lesions compressing the cervical spine significantly decreased in size (Figure 1). While further evidence is needed to better characterize the therapeutic effect of everolimus in the management of NF1-associated tumors, if gold-standard surgery and radiation are not an option, systemic therapies, could be considered the neuro-oncologist, weighing risks and benefits.



**Figure 1:** Spine MRI, Sagittal T2 sequence, showing multiple neurofibromas, the most important being at C1-C2 (A) and C5-C6 (B), resulting in moderate canal narrowing. Cystic myelomalacia from the previous radiotherapy + mass effect is also seen (A) from C4 downwards. Remote prior decompression from C1-C6 associated with surgical changes visualized on both sequences. Neurofibromas are demonstrated by arrows (↙) and myelomalacia by (x).

## Disclosures

The authors have no disclosure.

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