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IDEAS AND INNOVATIONS

Peripheral Nerve

Targeted Muscle Reinnervation and Regenerative Peripheral Nerve Interfaces for Prophylactic Pain Control in Neurofibromatosis Type 1 Amputees

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Summary: Neurofibromatosis type 1 (NF1) is an inherited multisystem disorder that affects one in 2500 to one in 5000 people. Neurofibromas are the second-most common benign peripheral nerve sheath tumors arising from Schwann cells and are associated with neurofibromatosis. Chronic pain and opioid use is elevated in patients with NF1 when neurofibromas are associated with sensory nerves. Surgical excision is the primary treatment of neurofibromas when they become large, malignant, or painful, but they are associated with high rates of recurrence. Targeted muscle reinnervation and regenerative peripheral nerve interfaces are two prophylactic surgical techniques that are used to prevent neuroma-associated residual limb and phantom pain in amputees. Both techniques stimulate physiologic regeneration of the nerve via trophic stimulus from denervated muscle. This case report describes two patients with NF1 who underwent targeted muscle reinnervation and/or regenerative peripheral nerve interfaces at the time of amputation. Despite the abnormality of the peripheral nerves involved, both patients had excellent postoperative outcomes with minimal pain. This experience advocates for the use of prophylactic nerve management techniques in neurofibromatosis patients despite baseline nerve pathology. *(Plast Reconstr Surg Glob Open 2023; 11:e5405; doi: 10.1097/GOX.0000000000005405; Published online 20 November 2023.)*

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disorder resulting from mutation of the *NF1* gene, which encodes for the neurofibromin tumor suppressor protein.[1–8] Patients with NF1 are characterized by café-au-lait macules, freckling in the axillary or inguinal region, Lisch nodules, bony dysplasia, and peripheral neurofibromas.[7] NF1 patients have a higher risk of malignant transformation of peripheral nerve tumors, including schwannomas and neurofibromas.[3,4] When peripheral nerve tumors become painful, or large enough to be at risk for malignant transformation, they require resection. Unlike schwannomas, neurofibromas are commonly unencapsulated and involve nerve fascicles, which make a complete excision more difficult.[3,4,6,8] Unfortunately, malignant neurofibromas are not highly sensitive to chemoradiation and therefore may require amputation of an involved extremity.[6,8]

Originally used to improve myoelectric prosthetics, targeted muscle reinnervation (TMR) and regenerative peripheral nerve interfaces (RPNI) are prophylactic surgical techniques designed to prevent neuroma formation and chronic pain after amputation. Both rely on trophic stimulus from denervated muscle to stimulate amputated nerves to reinnervate muscle.[9,10] TMR is a surgical technique that coapts the end of amputated mixed major or sensory peripheral nerves to motor nerves in the surrounding muscle.[9] RPNI is a surgical technique that implants the amputated nerve end on a section of denervated autologous muscle graft.[9] Both techniques have been found to prevent or reduce chronic residual limb and phantom limb pain in amputee cohorts. Chang et al recently demonstrated excellent results in amputees treated with TMR despite severe vasculopathy and associated nerve pathology.[11] To our knowledge, there have been no reports of using these techniques, specifically in the neurofibromatosis patient population. Herein, we report two cases of excellent postoperative pain control in NF1 amputees, despite presentation with known

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baseline neuropathy. In both cases, the patients were counseled preoperatively that the TMR and/or RPNI may have no effect. It was explicitly stated that although there was a low chance of making their pain worse, to date, no known data were available about TMR or RPNI in NF1 patients. The patients both agreed to participate electively.

Patient A is a 26-year-old NF1 patient, diagnosed at age 12, who presented with a large left foot plexiform neurofibroma after two previous limb salvage operations. However, by age 25, she was dependent on a wheelchair for long distances due to tumor recurrence, multiple large tumors, and left lower extremity hemihypertrophy (Fig. 1). She reported chronic sharp, stabbing pain from her knee to her foot, rating an 8 of 10. She did not take consistent pain medications. Physical examination revealed significant gait instability, deformity of the left femur and tibia, and extensive soft tissue involvement from the ankle to the knee. PET-CT showed several areas of increased uptake in the left foot and lower leg, suggesting malignant peripheral nerve sheath tumor with no evidence of distant metastasis. She agreed to a low transfemoral amputation. At the time of amputation, she underwent immediate TMR with five nerve transfers: (1) saphenous nerve to a motor branch to the gracilis, (2) one tibial nerve bundle to a motor nerve to the semimembranosus, (3) a second tibial nerve bundle to a second motor nerve to the semimembranosus, (4) superficial peroneal nerve to a motor nerve to the biceps femoris, and (5) deep peroneal nerve to a second motor nerve to the biceps femoris. The operating surgeon divided the tibial and peroneal nerves into two bundles due to mismatch in recipient and donor nerve caliber. The surgery was uneventful, and the patient was discharged on postoperative day 5. Postoperative PET-CT re-staging showed no residual disease or metastasis. At 10 months follow-up, she is residual-limb pain free with occasional 1 of 10 phantom pain as she falls asleep. The patient is ambulatory, experiencing no pain while donning her prosthetic, slowly increasing prosthetic use, and living independently.

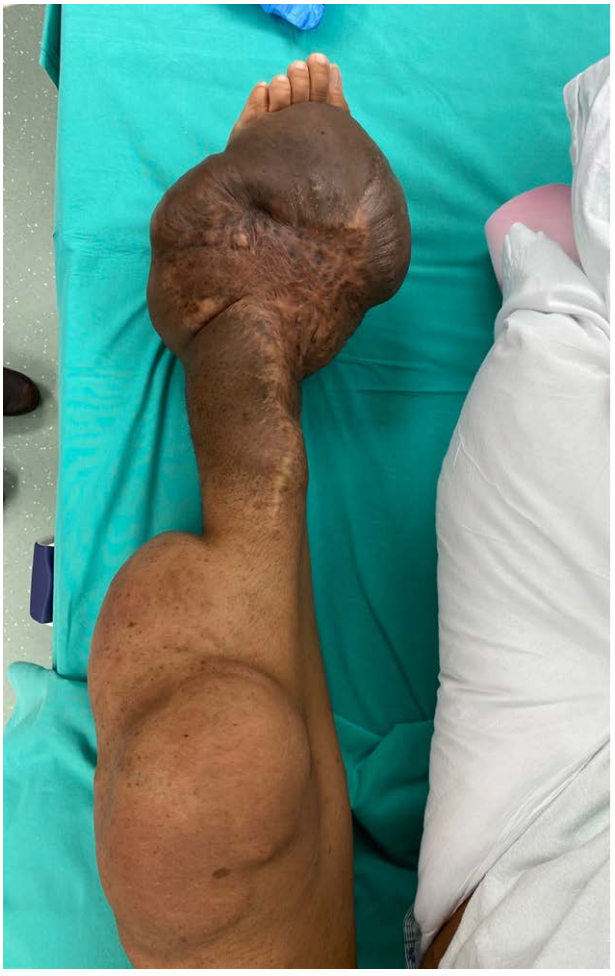

Fig. 1. Patient A's preoperative photograph of her left lower extremity depicting hemihypertrophy and large size of multiple tumors.

Takeaways

Question: How can post-amputation pain be improved in neurofibromatosis type 1 (NF-1) patients?

Findings: We report two successful cases of NF-1 patients who experienced decreased pain and increased prosthetic use after receiving TMR and RPNI with amputation, despite baseline nerve pathology. TMR and/or RPNI should be considered with amputation of malignant neurofibromas.

Meaning: TMR and RPNI should be considered in the treatment of amputated nerves in NF1 patients.

Patient B is a 40-year-old NF1 patient who presented with a history of transtibial amputation at age 19 after multiple limb salvage operations as a child. He presented with complex regional pain syndrome, hypertension, and adrenal insufficiency. He reported pain from his transtibial amputation site and his known inoperable abdominal neuroma, which were managed by three pain medications. He reported constant, shooting nerve and phantom pain in the lower extremity, rating 7–8 of 10, which would consistently become exacerbated and interfere with work and school. He had poor compliance with his prosthetic due to pain. Unfortunately, at age 38, he experienced hardware failure and bony erosion after a femoral condyle fracture. This left the patient unable to use a prothesis and dependent on wheelchair and crutches. The patient agreed to conversion to a transfemoral amputation with TMR and/or RPNI (Fig. 2). The patient underwent two TMR nerve transfers: (1) common peroneal nerve to a motor branch to the biceps femoris and (2) tibial nerve to a motor branch to the semitendinosus. The patient received RPNI of the saphenous nerve, which was chosen by the attending surgeon due to lack of available motor nerves. For the first 6–8 weeks post-transfemoral amputation with TMR and/or RPNI, he experienced 8 of 10 pain, which slowly regressed to a 0 of 10. He is not taking pain medications for his amputated limb but

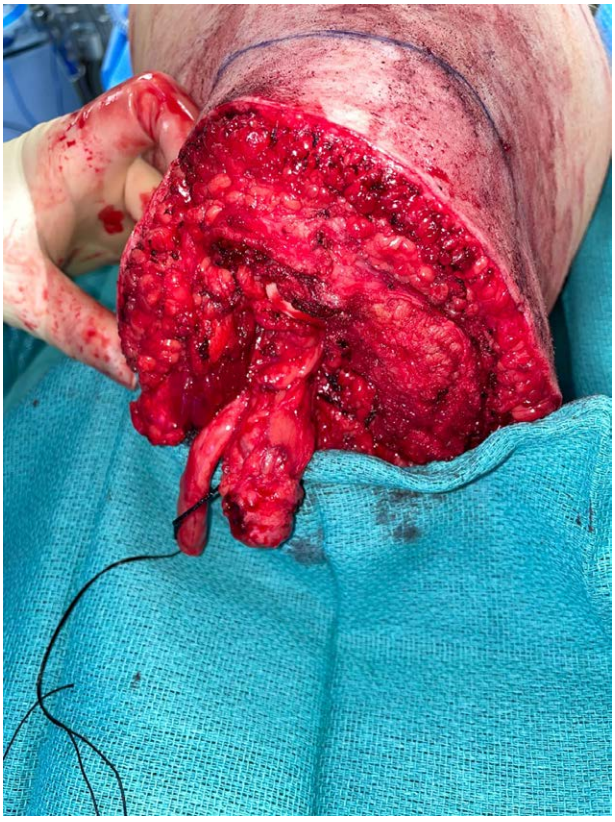

Fig. 2. Intraoperative image of patient B's amputated limb before TMR and RPNI. Tibial nerve on the right-hand side of the photograph is highly abnormal, whereas the common peroneal nerve on the left-hand side seems more normal. Nerve transfers were performed on the more proximal sciatic nerve where no palpable tumors were present.

continues to take two pain medications for his inoperable abdominal neuroma. Despite decades of chronic pain in the lower extremity, at 18 months follow-up, he now reports no pain, better gait, and standing on his prosthetic up to 18 hours a day (Fig. 3).

Even though both patients' nerves were found to be highly abnormal at the time of surgery, both have done exceptionally well postoperatively. Both report a pain score less than 1 of 10 in the extremity. Although it cannot be proven that the prophylactic nerve management is entirely responsible for this, both patients believe their pain is far less than after their previous operations and amputations. With the high rates of neurofibroma recurrence, and painful neuroma symptoms after traditional traction neurectomy or excision, this anecdotal evidence supports prophylactic nerve measures at the time of intervention.[2,12] Therefore, TMR and RPNI should be considered in future treatment for amputated nerve in NF1 patients.

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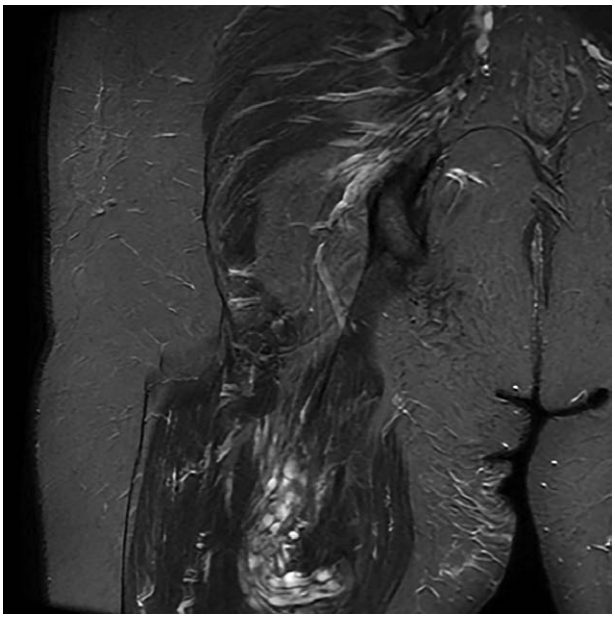

Fig. 3. Patient B's amputated limb 18 months after TMR and RPNI. The sciatic nerve is highly diseased, as evidenced on MRI, but doing well coapted to the nearby motor nerves. The patient reports no pain.

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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