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CASE SERIES

Outcome of Surgical Intervention in Giant Neurofibromas in Two Sisters with Neurofibromatosis Type 1: A Case Series and Literature Review

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Abstract: Neurofibromatosis type I (NF1) is an autosomal dominant disorder involving the skin and nervous system. We present the surgical resection experience of two siblings with neurofibromatosis type I (NF1) and giant neurofibromas. The sisters had multiple skin discolorations and swollen areas that gradually increased in size with age. The gradually growing tumors have an impact on their lives and their quality of life. In one case, staged resection was performed following preoperative arterial embolization of the tumor. Through surgery, a tumor weighing 16 kg was removed from one sister and another weighing 11 kg from the other sister. Following surgery, both sisters demonstrated significant improvement in appearance and resumed normal daily activities. Regular follow-up visits were scheduled to monitor for recurrence or new growth.

Plain Language Summary: Two sisters with a genetic condition called neurofibromatosis type 1 (NF1) had surgery to remove very large, non-cancerous tumors (called neurofibromas). These tumors had caused noticeable skin changes and swelling that got worse as they got older. While most of their tumors grew slowly, some specific ones grew much faster. The younger sister had rapid growth on her right side from her waist down her leg. The older sister had rapid growth on her left neck, shoulder, chest, back, and arm. Their family has a history of NF1, which was also found in their father and in the older sister's children and grandchild. Doctors performed surgery to remove these massive tumors. One sister had a tumor weighing 16 kg (about 35 pounds) removed, and the other had an 11 kg (about 24 pounds) tumor removed. After the surgeries, both women looked significantly better and were able to return to their normal daily lives. They will continue to have regular check-ups to watch for any return of the tumors or new growths.

Keywords: neurofibromatosis type I, giant neurofibroma, resection

Introduction

Neurofibromatosis (NF) was first described by the German pathologist Friedrich Daniel von Recklinghausen in 1882.[1] This group of autosomal dominant genetic diseases with malignant potential includes NF1, NF2, and multiple schwannomas.[2] Among them, NF1 is the most common, with a birth incidence of 1/2500 and a prevalence of 1/3000. Compared with the general population, the life expectancy of patients is shortened by 8–15 years.[3] Approximately 42% of cases are caused by gene mutations. NF can affect individuals of any age and sex, with no racial differences.[4,5] NF1 is caused by a germline mutation of the *NF1* gene on chromosome 17q11.2.[6] Tumor-suppressor gene *NF1* mutations lead to the inactivation or down-regulation of neurofibromin expression, resulting in the abnormal activation of signaling pathways such as RAS/RAF/MEK/ERK.[7,8] The emergence of Next-Generation Sequencing (NGS) as significantly

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increased the diagnostic yield of NF1 and shortened the time required for molecular diagnosis. Pathogenic variants in the *NF1* gene can be identified in over 95% of NF1 cases.[9]

Patients with NF1 have a lifetime risk of 8–13% of developing malignant peripheral nerve sheath tumors (MPNST). Once malignancy occurs, treatment options are limited, and the 5-year survival rate is <50%.[10,11] Moreover, other secondary diseases such as gliomas, leukemia, pheochromocytomas, and gastrointestinal stromal tumors may occur.[12]

NF1 has diverse clinical manifestations and may encompass café-au-lait macules, axillary or inguinal freckles, Lisch nodules, cutaneous or subcutaneous neurofibromas, plexiform neurofibromas, MPNSTs, gliomas of the optic nerve and other parts of the central nervous system, cognitive and behavioral alterations, skeletal changes, and hypertension.[13]

NF1 has three subtypes: nodular, fascicular, and diffuse. The clinical diagnostic criteria for NF1 include (1) the presence of ≥6 café-au-lait macules with a diameter >5 mm (before puberty) or 15 mm (after puberty); (2) ≥2 neurofibromas; (3) melanin pigmentation resembling freckles in the axillary or inguinal regions; (4) optic nerve glioma; (5) ≥2 iris nodules (Lisch nodules); (6) bone abnormalities, such as cortical bone thinning and of pseudo fracture formation; and (7) at least one first-degree relative meeting the above criteria. The diagnosis of NF1 requires meeting at least two of the above criteria.[13,14]

Although rarely accompanied by giant neurofibromas, they may require surgical intervention. The tumor is highly vascular, and the risk of postoperative recurrence must be carefully assessed preoperatively. Here, we present two rare and challenging cases of two sisters with NF1. Giant neurofibromas located in the right lumbar hip, right lower extremity of the younger sister and left neck, shoulder, chest, back, and left upper extremity of the elder sister. Two siblings presented with massive neurofibromas, and multiple family members exhibited similar manifestations. Given the substantial risk of intraoperative hemorrhage and postoperative recurrence, preoperative arterial embolization was performed in the younger sister, followed by staged resection. Close postoperative follow-up was conducted. No significant growth was observed during follow-up: 7 years for the elder sister and 1 year for the younger sister.

Case Reports

The 56-year-old younger sister was hospitalized because of the gradual enlargement of various skin areas and discoloration that had been evident since birth. The swellings mostly grew slowly, with faster growth noted on the right waist, hip, and lower limb. In recent years, the swelling in the right waist and hip and lower limb had been growing rapidly, resulting in walking difficulties. Most of the tumors were peanut-sized, raised, and nontender, with a large tumor extending from the right waist and hip to the right ankle. The tumor was tan-colored and had two irregular granulation areas measuring approximately 8 cm in diameter at the distal end, which were covered with a small amount of secretion and did not emit any odor (Figure 1).

The older sister, aged 61, had a similar medical history. She exhibited scattered tan discoloration across her body, along with multiple skin swellings, nipple-like raised swellings of varying sizes, and numerous walnut-sized, tipped swellings that had been present since birth. She had a large tumor on her left neck, shoulder, chest, back, and left upper extremity, appearing dark brown on its surface and with various sizes of dispersed dark-brown discoloration. The anterior tumor involved the lower side of the breast, and the posterior tumor was close to the waist, which affected body balance and left upper limb movements (Figure 2).

The sisters had a family history of the disease, which affected their father and two daughters and one granddaughter of the elder sister (Figure 3). Preoperative routine blood, liver function, kidney function, electrolytes, and coagulation function tests of both sisters did not show any abnormalities. An ultrasound revealed huge masses within which point and strip blood flow signals were visible. Chest X-ray imaging did not show any abnormalities. Preoperative pathology of the skin ulcer and part of the tumor revealed neurofibroma, without any evidence of cancer.

In summary, the sisters' clinical presentation and family history strongly suggested NF1 combined with giant neurofibromas. The preoperative tests and examinations, including ultrasound and chest X-ray imaging, provided additional valuable information to guide surgical planning and management.

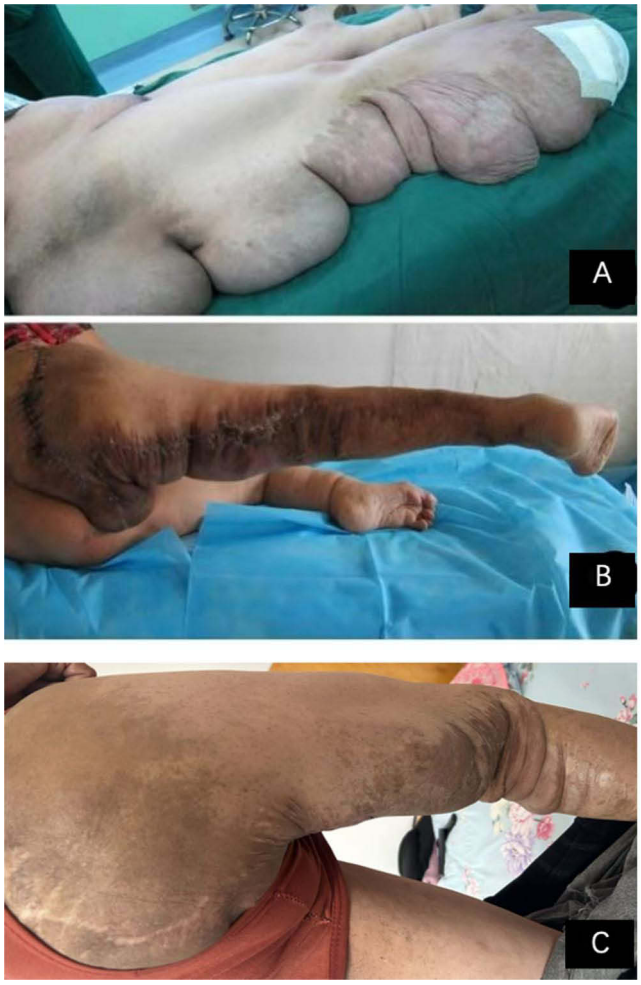

Figure 1 Pre-operative and post-operative conditions of the younger sister. (**A**) Pre-operative tumor appearance; (**B** and **C**) Appearance of the right lower extremity after two operations.

Surgical Procedures

The younger sister's tumor had a wide base; therefore, a staged resection plan was used. During the first surgery under general anesthesia, a distal major excision was performed with an electric tourniquet. The tumor was excised near the base to preserve the skin on both sides, and the wound was sutured, while bleeding was stopped by electrocoagulation and ligatures for larger vessels and their sinus cavities. Bleeding control was challenging because the tumor had numerous inelastic, large, and irregular vascular sinus cavities; thus, preoperatively, an interventional embolization procedure was performed on the arteries supplying the tumor. The puncture point was selected approximately 1cm below the left inguinal ligament at the site of the most pronounced femoral artery pulsation. A catheter was introduced and advanced to the right common iliac artery and then to the external iliac artery. Following contrast agent injection, tumor staining was observed in the right thigh region. A microcatheter was subsequently advanced into the tumor-feeding artery, through which gelatin sponge particles (350–560 μm) and PVA-500 particles were slowly injected. Approximately 26 hours after embolization, tumor resection surgery was performed, which lasted 4 hours and 50 minutes. The tumor, with a total weight of 16 kg, was resected in two stages, and the excised mass was sent for pathological examination. After surgery, a drainage tube was placed. Dressing changes were performed every one to two days, and the drainage tube was removed on postoperative day 6. The patient's postoperative recovery was uneventful. Although the base of the younger sister's tumor was wider and the excised tumor weighed approximately 5 kg more than that of the elder sister, the intraoperative blood loss was only about 400 mL. During and after the surgery, 3 units of red blood cells were transfused. This may be attributed to the preoperative arterial embolization.

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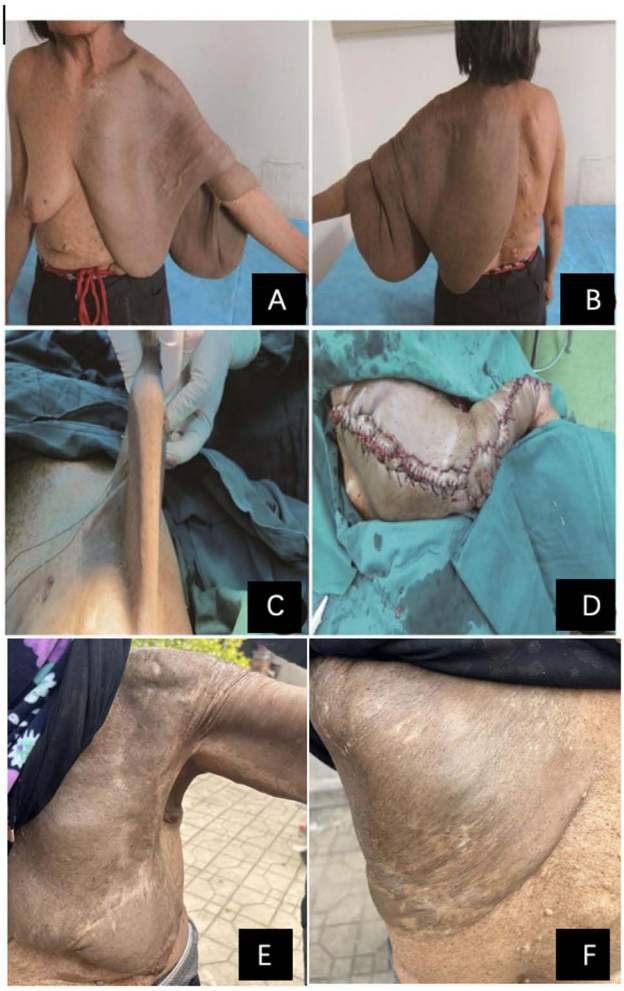

Figure 2 Pre-operative and post-operative situation of the elder sister. (**A**) Pre-operative swelling Tumor appearance (front); (**B**) preoperative tumor appearance (back); (**C** and **D**) intraoperative condition; (**E** and **F**): postoperative appearance.

In contrast, the older sister's tumor had a narrower base, so a different surgical approach was employed. Under general anesthesia, the tumor was elevated and tugged to control bleeding, and a straight, long cone needle was used to ligate it through its base. When the tumor was excised outside the ligature line, care was taken to preserve the breast glandular tissue, particularly on the anterior side of the breast. The wound edges were sutured; because no significant intraoperative bleeding occurred, the surgery was completed promptly, leading to a smooth recovery. The excised tumor weighed 11 kg and was sent for pathological examination. The older sister had undergone surgery in 2015. At that time, the interventional department of the local hospital was not yet fully operational. Moreover, preoperative arterial embolization of the tumor was not performed because of financial constraints. Although the intraoperative bleeding was not excessive, the large size of the tumor led to a significant blood loss, necessitating the transfusion of 7 units of red blood cells during and after the surgery.

Outcomes

Pathological examination confirmed both tumors to be neurofibromas, consistent with the clinical manifestations of NF1. The lesion tissue is located beneath the squamous epithelium. The neurofibroma cells are arranged diffusely. The cell nuclei are round, oval, short spindle-shaped, with mild atypia. Some cells infiltrate the fat, and some areas have interstitial edema. There is scattered lymphocyte infiltration. Immunohistochemistry: CD34: dim+; Desmin: −; Ki-67: <2%+; NSE: −; S-100: +; SMA: −; SOX-10: +; Vimentin: + (Figure 4). Follow-up after 1 and 7 years revealed that both

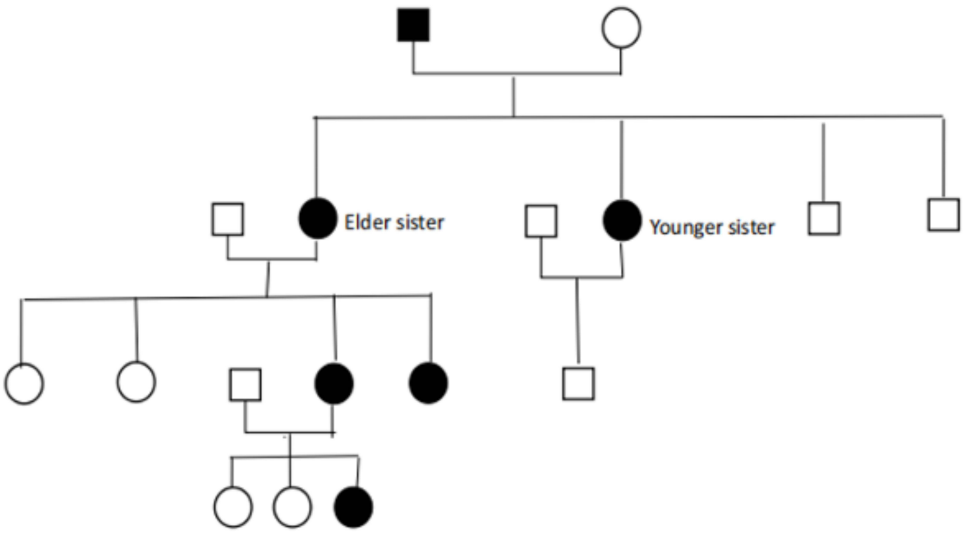

Figure 3 Pedigree of the family. Unaffected males are represented by unfilled squares, and affected males by filled (black) squares. Unaffected females are represented by unfilled circles, and affected females by filled (black) circles.

sisters had a normal life and were extremely satisfied with the surgical results. Despite some degree of hyperplasia in the hip of one of the sisters and the chest and left upper limb of the other, it did not significantly affect their quality of life.

Informed Consent

Written informed consent was obtained from the patients for the use of personal identification information and medical records for publication.

Discussion

Although surgery remains the primary treatment of NF and early surgical intervention is of significant value as the mass continuously enlarges, complete resection of NF is often unfeasible because of its extensive growth and invasion into surrounding tissues and nerves. Postoperatively, surgery may also lead to serious complications, and tumor recurrence is common.[6] In recent years, targeted therapy has gained increasing recognition as an alternative or adjuvant treatment for NF. Recent studies have indicated that the oral highly selective MEK1 and MEK2 inhibitor selumetinib achieved composite improvement of tumor control.[15] Targeted therapy may offer new avenues for the management of these complex tumors, particularly in cases where surgical resection is not feasible or in the presence of residual disease after surgery.

However, although massive neurofibromas are not life-threatening, they typically represent the most urgent concern for patients with NF1 because of its substantial psychological and physical burden. Surgical resection remains the primary treatment modality for such patients.[16] Malignant transformation should be suspected if pain persists for >1 month, new neurological deficits appear, the consistency of the neurofibroma changes from soft to firm, or the size increased rapidly. In some previous cases of rapidly growing neurofibromatosis that required surgical intervention, the tumors continued to grow with a fatal end.[17] Previous studies have indicated that surgical resection does not increase the risk of developing new neurofibromas or malignant transformation in residual lesions.[18] The presence of numerous, variably sized, and diffusely distributed lesions in individual patients makes complete surgical resection and eradication of the disease challenging. Therefore, the goal of surgical treatment is to debulk the tumors or remove those that are large enough to cause compression, pain, or organ dysfunction. This approach aims to improve appearance, alleviate discomfort, and restore organ function. Effective hemostasis during tumor resection is critical to procedural success.[19] Achieving hemostasis is particularly challenging owing to the fragile tumor tissue, abundant vascular supply, and the thin, non-elastic walls of sinusoidal vessels. As a result, patients often require blood transfusions during surgery. In these cases, autologous blood transfusion, with its high safety profile, is the preferred transfusion method, and preoperative

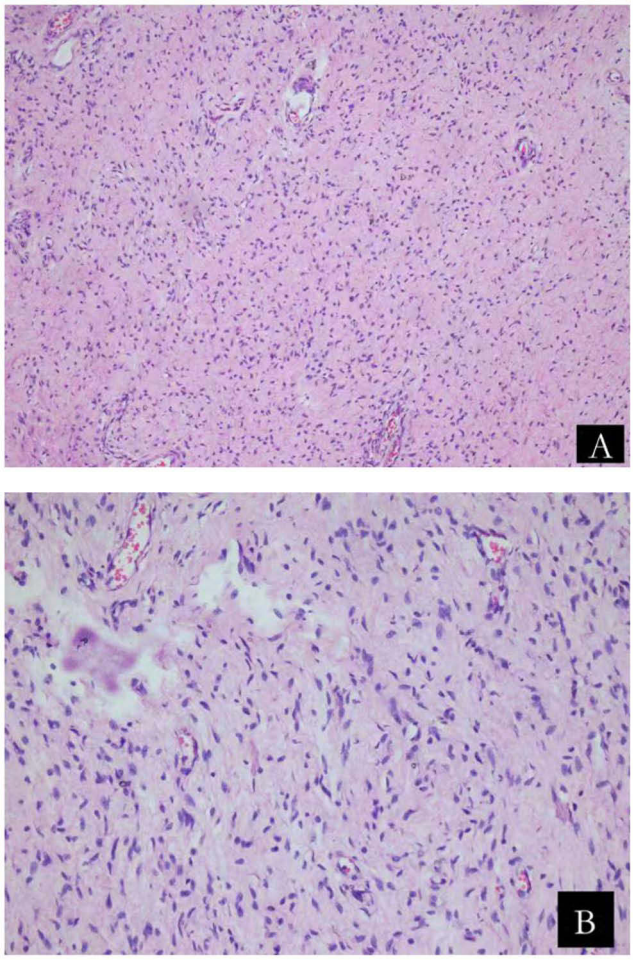

Figure 4 (**A**) The specimen demonstrates tissue is located beneath squamous epithelium and is arranged diffusely (Hematoxylin and Eosin, ×40). (**B**) Higher magnification demonstrates The Neurofibroma cells nuclei are round, oval, or short spindle-shaped, with mild atypia. Some are infiltrating fat, and some areas have interstitial edema (Hematoxylin and Eosin, ×200).

autologous blood donation is recommended. As patients with NF typically do not require emergency surgery, they are well-suited to meet the criteria for autologous blood transfusion. Preoperative interventional embolization can effectively reduce the intraoperative blood loss. When removing a neurofibroma weighing approximately 9 kg, which accounts for 15% of the patient's total weight (60 kg), the intraoperative blood loss is only about 300 mL. This may contribute to preoperative interventional embolization.[20,21]

In the presented case series, both surgical procedures were successfully performed, achieving complete resection of the tumor mass. The younger sister's surgery procedure required a staged resection because of the broad-based nature of the tumor and the presence of numerous vascular sinusoids, performed following preoperative interventional embolization. These cases appear to support meticulous planning and execution of surgical interventions for the optimal management of massive neurofibromas in patients with NF1. Follow-up outcomes further substantiate the efficacy of surgical resection in treating NF1-associated massive neurofibromas.

Meticulous planning and execution are critical for the surgical resection of NF1-associated massive neurofibromas, particularly those with large dimensions and complex anatomical locations. For tumors with a broad base, a staged resection approach may be necessary. A tourniquet can aid in hemostasis; however, if its application is not feasible, surgical techniques should be carefully employed to minimize bleeding. To control hemorrhage, large vascular sinus cavities should be meticulously dissected and ligated, whereas minor bleeding points can be managed with

electrocautery. When addressing pedunculated tumors following traction, continuous suture at the base is preferred, as it reduces operative time, limits blood loss, and ultimately enhances patient tolerance and accelerates recovery.

Surgical resection remains one of the primary treatment modalities for neurofibromas. Its success largely depends on the surgeon's skill and experience in managing associated complexities. Meticulous preoperative planning, refined surgical technique, and diligent attention to hemostasis are crucial for optimizing patient outcomes. These factors should be emphasized in any academic discussion on the surgical management of neurofibromas.

Conclusion

Meticulous planning and precise technique are critical for resecting massive NF1-associated neurofibromas, especially those with large size or complex anatomy. Staged resection may be required for broad-based tumors. Hemostasis is key: use a tourniquet if possible; otherwise, ligate large vascular sinuses and employ electrocautery for minor bleeding Preoperative embolization of the tumor's blood vessels may be of considerable assistance. For pedunculated tumors, continuous suture at the base reduces operative time, blood loss, and enhances recovery. Surgical resection remains a primary treatment for neurofibromas, with success dependent on the surgeon's skill. Careful preoperative planning, refined technique, and strict hemostasis are essential for optimal outcomes.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

Two patients of this report provided informed consent for publication of their clinical data and photographs, and no potentially identify individual information will be disclose. Weifang Yidu Central Hospital has given its approval for the cases details to be disclosed after obtaining approval from its own Ethics Committee.

Consent for Publication

Both patients provided written informed consent for their case details and images to be published.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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