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Treatment of Plexiform Neurofibromas : Current Perspectives on Surgery and Medical Treatment

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Plexiform neurofibromas (PNFs), a critical clinical feature of neurofibromatosis type 1, mainly involve several peripheral nerve branches and extend widely, including the skin and bones and the internal organs. Determining the appropriate treatment is difficult. Additionally, they possess the potential to develop into malignant peripheral nerve sheath tumors (MPNSTs), which are linked to an extremely poor prognosis. Active treatment is critical in patients with symptoms or progressive tumor growth, especially in pediatric cases. Surgery remains the standard treatment for managing PNFs and MPNSTs; however, it has often demonstrated insufficient results because of its wide distribution and the frequent involvement of major organs. Selumetinib, a recently approved mitogen-activated protein kinase kinase inhibitor, is gaining traction in treating inoperable PNFs in children.

Key Words : Neurofibromatosis 1 · Plexiform neurofibroma · Malignant peripheral nerve sheath tumors · Treatment.

INTRODUCTION

Neurofibromatosis is a group of autosomal-dominant tumor predisposition syndromes. It mainly affects the nerve tissue but can also demonstrate widespread impact on the cutaneous tissue, bones, and internal organs. "Neurofibromatosis type 1 (NF1)" was historically known as "von Recklinghausen disease" until 1988; it has been documented for centuries[51].

Its incidence rate is approximately 1 in 3000–3500, irrespective of sex and race[19,40,47]. The NF1 gene, situated on chromosome 17q11.2 and encoding neurofibromin, was identified in 1990[42,68].

NF1's hallmark features include several café-au-lait macules, multiple cutaneous neurofibromas, intertriginous freckling, Lisch nodules, and optic pathway gliomas[30]. Among these clinical manifestations, plexiform neurofibromas (PNFs) are NF1's distinct clinical feature, occurring in up to 50% of patients[34]. Evaluation and treatment remain challenging given that they can occur anywhere in the body and continue to grow throughout life. Moreover, PNFs have a transformation risk; that is, they can transform into atypical neurofibromas (ANFs) and eventually malignant peripheral nerve sheath tumors (MPNSTs). The

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meta-analysis demonstrated that patients with NF1 developed MPNSTs at a significantly younger median age compared to those without NF1 (28 vs. 41 years, $p<0.0001$)[65]. Moreover, NF1-associated MPNSTs are associated with a significantly lower 5-year survival rate compared to sporadic (non-NF1) MPNSTs (16–32% vs. 33–51%)[16,32,58]. Therefore, accurate prediction and timely management of malignant transformation in PNFs are critical for improving patient outcomes.

Surgical intervention has historically been, and remains, the standard treatment of choice; however, with selumetinib's recent and first approval, substantial changes have occurred in the treatment strategy. As an orally administered mitogen-activated protein kinase kinase inhibitor (MEKi), selumetinib has led a significant reduction in PNF size in children[13,23].

PNFs, ANFs, AND MPNSTs

A neurofibroma is a benign tumor that develops in peripheral nerves and is a mixed tumor composed of the nerve's various components, including nerve fibers, Schwann cells, and fibroblasts[29]. Additionally, macrophages and mast cells are commonly observed in the neurofibroma[37,49,61,72-74]. PNFs refer to a neurofibroma type that forms numerous bundles along several branches of the peripheral nerves. PNFs can be divided into nodular or diffuse types by imaging; the nodular type is confined to the nerve, whereas the diffuse type encroaches on the surrounding soft tissue[20].

PNFs grow more rapidly during early childhood; however, the mechanisms or the natural history of their growth remain elusive, with the growth rate being variable. PNF growth rates are of three patterns based on magnetic resonance imaging (MRI) assessment. Phase 1 constitute noninvasive tumors that slowly grow and are restricted to the cutis and subcutis. Phase 2 PNFs are relatively invasive and extensive but do not infiltrate the muscles or deeper tissues. Phase 3 is the most invasive PNF type, characterized by the absence of clear margins[43].

Clinically detectable PNFs are noted in 30–50% of patients in whom the mass compresses adjacent structures; besides the mass grows and causes considerable morbidity, such as severe pain or critical functional defects[31,63]. Symptomatic PNFs are most commonly found in the head and neck region in children (>60%), whereas those of the thorax and abdomen tend to remain asymptomatic[3,54].

PNFs are benign tumors; however, they can undergo premalignant transformation, ultimately progressing to malignant tumors. ANFs, considered a form of premalignant transformation, demonstrate at least two of the following features : cytological atypia, hypercellularity, altered neurofibroma structure, or an increased mitotic index[41,46]. Molecularly, ANFs are characterized by loss of CDKN2A/2B[9]. Detecting or suspecting ANFs within PNFs' extensive distribution poses a considerable challenge.

The final stage of malignant transformation from PNFs or ANFs culminates in MPNST development. Unlike PNFs and ANFs, MPNSTs exhibit a more complex mutational landscape, often involving loss-of-function alterations in components of the polycomb repressive complex 2, accompanied by global loss of histone H3 lysine 27 trimethylation and extensive chromosomal instability, including widespread copy number alterations[38,56,59]. These are highly aggressive sarcomas linked to peripheral nerves and are characterized by a high tendency for recurrence and resistance to treatment[16]. During their lifetimes, approximately 10% of patients with NF1 are diagnosed with MPNSTs, which are linked to poor 5-year survival rates of 35–50%[2,5,18,66]. The current approach is limited to surgical removal with adjuvant anthracycline-based chemotherapy and/or focal radiotherapy[11]. To date, no treatment has shown substantial therapeutic outcomes. Moreover, no phase II trials involving targeted therapies for MPNSTs have exhibited clinical benefits[71]. PNFs, ANFs, and MPNSTs represent a spectrum of peripheral nerve sheath tumors with distinct histopathological and molecular characteristics (Figs. 1 and 2).

MANAGEMENT

In NF1, the primary therapeutic concern is neurologic involvement caused by the mass effect of PNFs. Although classified as benign, these tumors possess the potential for malignant transformation. Further, they can cause pain or result in functional impairment due to their extensive lesion size. In addition to symptomatic area resection, systemic treatment targeting the extensive lesions should be considered. Additionally, precisely detecting and preventing premalignant and malignant lesions should be prioritized.

From a different perspective, evaluating the growth rate and the potential for impending clinical symptoms is essential for

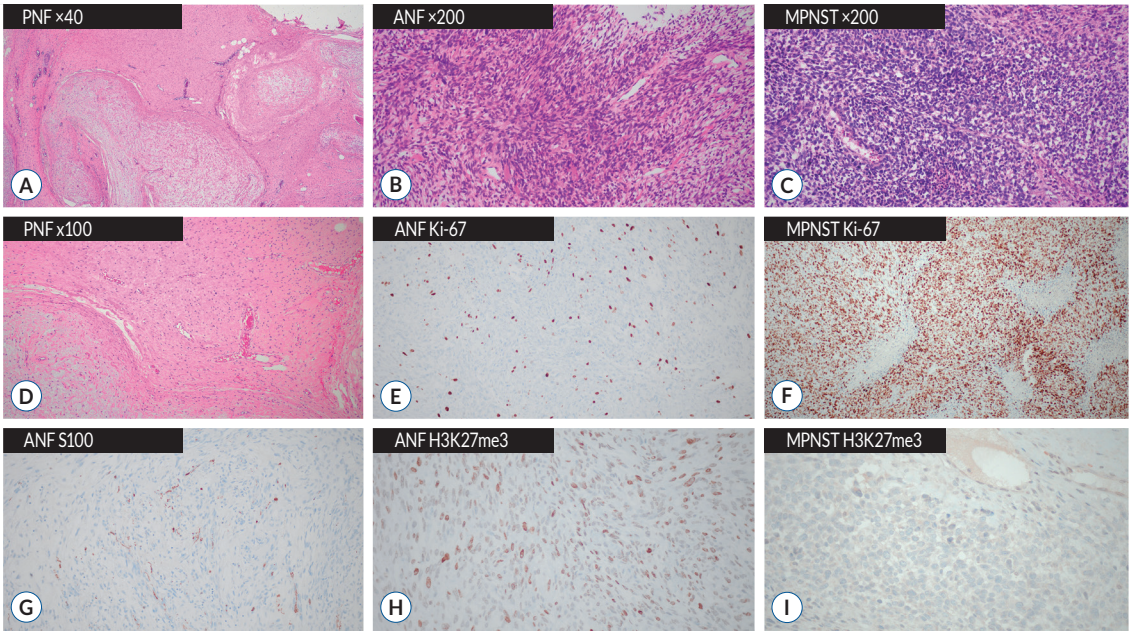

Fig. 1. A and D : PNF shows multiple enlarged, plexiform nerve fascicles embedded in a loose myxoid stroma. B, E, G, and H : ANF demonstrates a cellular short spindle cell tumor with increased cellularity. Immunohistochemically, it shows weak, focal S100 positivity with retained H3K27me3 expression. The Ki-67 labeling index is mildly elevated (5–10%). C, F, and I : MPNST displays a hypercellular short spindle cell tumor with multifocal necrosis. A high Ki-67 labeling index (>80–90%) and complete loss of H3K27me3 expression are observed. PNF : plexiform neurofibroma, ANF : atypical neurofibroma, MPNST : malignant peripheral nerve sheath tumor, H3K27me3 : H3 lysine 27 trimethylation.

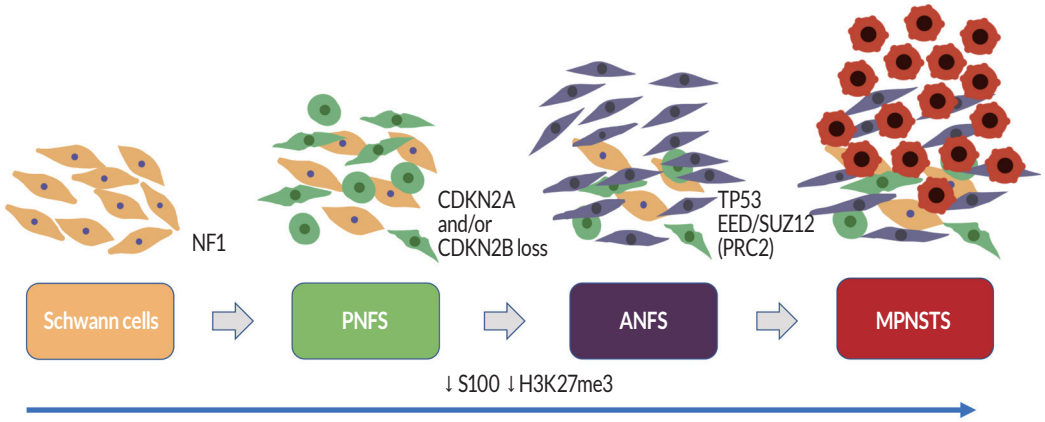

Fig. 2. Malignant transformation from schwann cells to MPNSTs is driven by stepwise molecular alterations. Biallelic inactivation of NF1 initiates the development of PNFs from Schwann cells. Subsequent mutations in CDKN2A/B are associated with progression to ANFs. Further alterations, including inactivation of PRC2 (such as EED and SUZ12) and TP53 mutations, contribute to the development of MPNSTs. This progression is accompanied by a gradual loss of S100 protein and H3K27me3 expression. NF1 : neurofibromatosis type 1, PNF : plexiform neurofibroma, ANF : atypical neurofibroma, MPNST : malignant peripheral nerve sheath tumor, H3K27me3 : H3 lysine 27 trimethylation.

managing PNFs. However, their extensive and heterogeneous nature poses major challenges to accurate examination before treatment.

According to the ERN GENTURIS tumour surveillance guidelines, a whole-body MRI should be performed at least once during the transition from childhood to adulthood. If internal PNFs are present, follow-up imaging with MRI every 1 to 3 years should be considered, guided by a multidisciplinary team discussion. If the PNF becomes symptomatic, the imaging interval may be shortened to every 6 to 12 months. In cases where malig-

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nant transformation is suspected, immediate MRI combined with fluorodeoxyglucose positron emission tomography should be performed, followed by surveillance every 6 months, and a biopsy should be considered[10].

Younger age is linked to faster tumor growth, making it a crucial factor that may influence decision-making[1,15,53,67]. In pediatric patients, the growth rate of PNFs surpasses the rate of body weight increase over time, implying that PNFs are not solely attributable to normal development[1,15,67]. Therefore, children with NF1 may need treatment more frequently compared to adults.

Thus, active efforts should be directed toward preventing PNF growth and mitigating the risk of impending morbidity. Contrarily, stable PNFs that do not cause neurologic symptoms could be monitored.

While the role of surgery remains crucial, the function of selumetinib, an oral selective MEKi, is becoming increasingly evident. Although other agents, and radiation and alternative therapies, have been studied, they have not demonstrated considerable impact to date.

SURGICAL TREATMENT

Surgery remains the standard treatment for patients with NF1 as it helps effectively manage conditions ranging from PNFs to MPNSTs. However, given the tumors' location and infiltration potential, complete removal may not always be possible; further, inaccessible location of some tumors could make surgical resection a nonviable option[36]. Moreover, PNFs infiltrate adjacent normal tissue and cannot be completely removed. Surgically resecting PNFs can result in relatively major complications since they pathologically involve several nerve branches and vessels and have poor margins.

In a previous study, 40–50% of PNFs demonstrated regrowth despite surgical resection being achieved[23]. Resection targeting the symptomatic location may provide localized relief; however, it is fundamentally insufficient to prevent disease progression or achieve comprehensive therapeutic results.

Surgical decisions (indications and scope) must be tailored to factors such as location, size, growth rate, presence of malignant potential, and marginal resectability. Moreover, the overall health of the patient should be considered before as surgery is a major undertaking.

From the perspective of reducing the malignant transformation rate, ANF identification and removal is crucial. Microdissection by an experienced surgeon, combined with intraoperative nerve stimulation, is necessary to achieve fascicle-sparing and gross-total extracapsular resection of ANFs[52].

Surgical treatment plays a more crucial role for paraspinal PNFs than PNFs in other locations. PNF growth can compress the adjacent nerve roots, resulting in the worsening of symptoms. Direct spinal cord compression may result in clinical manifestations such as radiculopathy or myelopathy; lesions at the cervical or thoracic level tend to present with additional critical symptoms.

Two small studies examined the favorable outcomes of surgical resection for paraspinal PNFs involving several levels. In one study, 10 patients with progressive myelopathy or cauda equina dysfunction were involved; nine of the patients underwent gross total resection of the intraspinal component and completely recovered neurological function, whereas one demonstrated considerable improvement[57]. In another study involving 13 patients with cervical cord compression, subtotal resection of the intraspinal part of PNFs was conducted. The cervical lesions involved several levels in 85% of the cases, making subtotal resection inevitable. Nevertheless, 45% demonstrated improvement in weakness, and 18% revealed no further progression of neurological abnormalities[39].

To date, an expert panel committee has not recommended surgical treatment for orbital-periorbital plexiform neurofibromas (OPPNs); however, this should also be considered[4]. In the study by Avery et al.[4], surgical intervention for OPPN is considered under a multidisciplinary approach, particularly in the presence of tumor growth accompanied by progressive visual decline, the potential for invasion into critical structures such as the cavernous sinus, or progressive disfigurement. Among patients with OPPNs, 10–22% demonstrate vision loss due to strabismic amblyopia[21]. The orbit is anatomically characterized by a confined space densely packed with critical nerves, muscles, and the nasolacrimal duct. Even minor alterations can lead to severe functional symptoms due to its proximity to the brain and facial structures. Presently, no studies have proven surgical intervention to be effective for strabismus or OPPNs. However, surgery has the potential to prevent critical functional challenges or disfigurement owing to progressive OPPNs[21].

Surgical intervention in the form of a biopsy for identifying malignant transformation remains a crucial aspect of manag-

ing a lesion when it is not resectable. Before initiating therapy for PNFs, determining whether malignant transformation has occurred is important. An increase in the tumor growth rate, the highest SUV, or diffusion restriction on imaging and acute pain onset may indicate possible malignancy. These factors are more applicable as a guide for targeting biopsy than as tools for diagnostic purposes. Additionally, performing several biopsies and targeting rapidly growing lesions are recommended[21].

From other perspectives, prophylactic or cosmetic surgery may be considered; however, their effectiveness in treating PNFs remains uncertain.

MEDICAL TREATMENT

MEK1/2 inhibitor (selumetinib)

Selumetinib, as the first Food and Drug Administration (FDA)-approved medication, is presently the most prominent therapeutic option to treat PNFs. As an oral medication, it can be used for children with NF1 (>2 years old) who have inoperable, symptomatic PNFs[25]. Selumetinib is a selective MEK1/2 inhibitor targeting the RAS pathway.

Selumetinib showed partial responses (PRs) (≥20% reduction) in 71% and 68% of participants in two separate studies involving children with NF1[14,27].

In a phase 1 trial (AZD6244 or ARRY-142886), among 24 pediatric patients with inoperable NF1-related PNFs, 17 (71%) experienced a median 31% volume reduction (range, 6–47%)[14]. In a phase II trial, the selumetinib dosage was further specified; 25 mg/m^2 was administered every 12 hours in 28-day cycles. This demonstrated PR in 74% of patients after a median of eight cycles. Furthermore, it showed benefits in decreasing disfigurement and PNF-related pain, resulting in improvements in quality of life[27,35]. No complete reductions were noted. Nevertheless, achieving a considerable reduction in tumor volume and preventing subsequent progression in extensive PNFs are critical for improving symptoms. Although a case report has demonstrated the efficacy of selumetinib in a patient with MPNST harboring specific molecular alterations, its clinical effectiveness in MPNST has not yet been clearly established[50].

The majority of complications that selumetinib caused were relatively mild and reversible, including concerns of the digestive symptoms, a mild creatine phosphokinase increase, mucositis, fatigue, paronychia, and rash[25]. The adverse event (AE) frequency was the highest in cycle 1, with decreasing frequencies as the cycles progressed. Supportive therapy alleviated all AEs irrespective of severity, and drug discontinuation was not necessary[35].

Although extremely uncommon, it may cause substantial cardiac adverse effects and ocular complications[6,45]. Among the 74 patients in phase 1 and 2 studies, only one patient experienced bilateral and mild central serous retinopathy (CSR), exclusively identified through optical coherence tomography during post-cycle 94 assessment, without any visual symptoms. The medication cycle was continued with a repeated evaluation and the CSR disappeared 3 weeks later[14,25].

In the same cohort, 16 participants demonstrated a decrease in left ventricular ejection fraction (LVEF) without symptoms[64]. Fifteen cases revealed grade 2 toxicity (a 10–19% drop from baseline) and one case showed grade 3 toxicity (a >20% drop from baseline). The LVEF decrease was first detected at a median of 20 cycles (range, 4 to 95)[25]. Fourteen patients (88%) demonstrated recovery or cardiac function stabilization without progression or the requirement for further intervention, and no drug hold was necessary[25].

Nevertheless, two limitations exist regarding selumetinib's efficacy in treating PNFs. First, in the phase 1 study, slow PNF regrowth was observed in some patients who underwent dose reduction due to adverse effects[14]. This suggests that extended use is necessary to maintain the inhibitory effect on PNFs. Intermittent administration proved effective in an animal study, although complete withdrawal of the drug was not possible[7]. Secondly, neither the phase 1 nor the phase 2 studies were randomized controlled trials and most studies have focused on childrens with PNFs, in whom tumor growth tends to be more rapid compared to adults. Selumetinib has shown a considerable effect in reducing PNFs over several years in most children with NF1. Recently, Gross et al.[26] reported meaningful efficacy of selumetinib in adults with inoperable PNFs; however, additional studies are needed to further validate these findings.

Other agents

Most completed trials have failed to show a clinically meaningful improvement in progression-free survival (PFS) or achieve a PR for PNFs.

To treat symptomatic or progressive PNFs, some agents targeting downstream effectors of the RAS-MAPK pathway, such as oral and selective MEKi, are under investigation in trials.

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Trametinib showed PR in 46% (12/26) of patients from a phase 1/2a trial in children (NCT02124772)[44]. Mirdametinib demonstrated a 42% response rate (8/19) in adolescents and adult patients[69]. Binimetinib has revealed PR in 70% (14/20) of pediatric and 65% (13/20) of adult participants in an ongoing phase 2 study (NCT03231306)[21,48].

Imatinib, a tyrosine kinase inhibitor, showed PR specifically in PNFs with small volumes (<25 mL)[58]. Cabozantinib, another tyrosine kinase inhibitor, showed PRs in 42% of patients by regulating the PNF microenvironment[22].

Tipifarnib, a farnesyltransferase inhibitor, substantially prolonged the median PFS to 29.4 months, compared to the 10.6 months in the placebo arm, in a double-blind, randomized trial. Peginterferon-α-2b, a cytokine that activates the immune system, advanced to a phase II study; however, it showed only rare PRs[33,70].

Additionally, multiple anti-inflammatory, antifibrotic, and antiangiogenic therapies were tested in early trials. However, they did not exhibit therapeutic efficacy in managing PNFs[28,60,70].

Radiation therapy (RT)

The evidence supporting RT use to treat PNFs is confined to retrospective studies, considering that they are pathologically benign lesions. The biological rationale for using RT is based on its application in treating similar benign tumors, such as schwannomas and meningiomas. Studies on stereotactic radiosurgery for schwannomas and meningiomas mostly involve adult patients, which varies from the younger NF1 patient population. Although a few patients with NF1 may be included in those studies, the findings specific to PNFs could not be separately assessed[12,24,62].

NFs demonstrate the potential for malignant transformation into ANFs or MPNSTs as part of their natural course. Furthermore, the risk of RT-induced neoplasms may contribute to a compounded risk[8,18,55,64]. Considering the malignant potential of PNFs and the relatively young age of patients with NF1, RT is generally not recommended. If deemed unavoidable, low-dose or stereotactic RT should be preferred.

Alternative therapies

Overall, vitamin D, fish oil, turmeric/curcumin, bee propolis, cannabis derivatives, and the Mediterranean diet have been commonly discussed and used as nutraceuticals to manage pain, potentially reducing PNF size. Evidence supporting the efficacy of these therapies in treating PNFs remains limited, although they are widely accessible and frequently used as alternative treatments[17,54].

CONCLUSION

Managing NF1-related PNFs remains challenging; however, selumetinib, the MEK inhibitor, as the first FDA-approved medication for children with symptomatic and inoperable PNFs, represents a crucial advancement. Further research is required to investigate the long-term use, adjustable dosage, and effects in adults, as well as other related factors.

Although not extensive, surgical treatment continues to play a major role, especially given the lack of effective alternatives for ANFs or MPNSTs.

Regrettably, prophylactic agents or treatments that ensure a complete response for NF1 are currently considered premature. Extensive and active research is being conducted on other treatments as well.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : DSK; Data curation : JHK, SHK; Formal analysis : JHK, SHK; Funding acquisition : DSK; Methodology : JHK, SHK, DSK; Project administration : DSK; Visualization : JHK, SHK, DSK; Writing - original draft : JHK, SHK, DSK; Writing - review & editing : JHK, SHK, DSK

Data sharing

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