Chapter

Peripheral Nerve Tumors in Neurofibromatosis 1, Neurofibromatosis 2, and Schwannomatosis

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Abstract

Neurofibromatosis was first described in the nineteenth century. At the time, Friederich Daniel Von Recklinghausen detailed two cases of multiple neurofibromas. Although reports of similar cases had been published before his, Von Recklinghausen is credited with the initial description in 1882, postulating that the tumors originated from nerve sheath and plexal connective tissue. Similarly, in 1822 John Henry Wishart described what is believed to be neurofibromatosis type 2; however, it was Harvey Cushing's description of a case of bilateral vestibular schwannomas in 1916 that highlighted and increased awareness of the disease (albeit the original presentation was thought to be in the context of neurofibromatosis type 1). Since their original description, understanding of these neurocutaneous diseases has greatly expanded. Knowledge of the genotypic mutations and molecular mechanisms underlying the disease pathophysiology has resulted in natural history enlightenment and optimal treatment refinement. However, many aspects of neurofibromatosis have yet to be explained and remain active areas of investigation. In this chapter, clinical, radiological, and surgical considerations for peripheral nerve tumor management in the context of neurocutaneous disorders are reviewed. More specifically, clinical presentations, pathological and imaging findings, as well as management for neurofibromatosis type 1, type 2, and schwannomatosis are comprehensively discussed.

Keywords: nerve sheath tumor, tumor, surgery, neurofibromatosis, schwannomatosis

1. Introduction

Neurocutaneous disorders are a group of diseases characterized by systemic structural abnormalities of tissues derived from the embryonic ectoderm. Among other manifestations, this results in the growth of peripheral nerve sheath tumors (PNSTs). More specifically, of the many diseases that fall under this category, neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis (SWNTS) are the three that predominate when considering those associated

with PNSTs. Furthermore, each of these three diseases has a specific gene that upon mutation results in different, albeit overlapping, clinical manifestations [1, 2].

Many different mutations have been linked to these diseases, which may then be inherited (familial forms) or occur sporadically. However, it is the specific genotypic mutation pattern of a patient that will then dictate and drive the molecular pathogenesis leading to their phenotypic disease expression [3, 4]. Because of this, each of the three diseases is generally associated with a particular type of peripheral nerve pathology, including benign PNST (BPNST, whether neurofibroma or schwannoma and the subcategories of each) and/or malignant PNST (MPNST). Moreover, each disease has unique epidemiological characteristics separating one from another. In this chapter, these characteristics, as well as each disease's distinct clinical, radiological, and treatment-related challenges are discussed.

2. Neurofibromatosis type 1

2.1 Background

NF1 is the most common of the three neurocutaneous diseases with a reported incidence of 1:2500–3500 [5, 6]. It is characterized by a somatic or germ line mutation on the long arm of chromosome 17 (ch17q11.2) and is inherited in an autosomal dominant (AD) fashion. This genetic locus codes for the protein neurofibromin and is a tumor suppressor gene expressed in multiple tissues. In short, neurofibromin is a GTPase-activating protein that catalyzes the inactivation of Ras protein (acting as a negative regulator in the Ras/MAPK signal transduction pathway) [6–8]. Its genetic alteration (via point mutations, deletions, insertions, microdeletions, and splicing mutations) results in a loss of inhibition of Ras that leads to hyperactivation of downstream effectors MEK, ERK, and/or mTOR [8]. The latter then results in Schwann cell proliferation and tumor growth. Although NF1 may be inherited in an AD fashion, approximately half of NF1 cases arise from de novo mutations. With more than 500 mutations identified to date, there are also many different types of mutations that can lead to NF1. Although the disease's penetrance approaches 100%, the expressivity of NF1 can be quite variable and may be dictated by the underlying genetic alterations [9]. For example, large complete gene deletions have been associated with intellectual disability, tumor burden, and their malignant transformation [10, 11]. More specifically, the predominant tumor burden that occurs in NF1 patients consists of neurofibromas. Neurofibromas are BPNSTs made up Schwann cells and/or perineurial cells, fibroblasts, hematopoietic cells, among others. After schwannomas, they are the most common type of PNST in the general population with a reported prevalence of 10–24% [12]. Unlike schwannomas, however, neurofibromas tend to be more widespread and occur in a slightly younger population (typically 20- to 30-year-olds) without a clear sex predilection [12–14]. Furthermore, they may occur sporadically or in the context of NF. Those occurring with NF tend to be numerous and, as will be discussed in the next section, of a different histopathological category with a higher proclivity for malignancy.

2.2 Neurofibroma histopathology and subtypes

Neurofibromas are heterogeneous tumors believed to originate from Schwann cells [6, 15]. Grayish-tan in color, they are typically more fibrous and tenacious than schwannomas without necrosis or hemorrhage [16]. Microscopically, poorly organized spindle cells are seen within a myxoid tumor background of coarse collagen

bundles. Although somewhat variable, neurofibromas have low-to-moderate cellularity with minimal mitoses compared to their malignant counterpart described below [7, 16].

Dermal (or cutaneous) neurofibromas are a type of neurofibromas with several subcategories. They are believed to arise from a single nerve and may be further subcategorized into localized or diffuse (90% and 10% of dermal neurofibromas, respectively) [10, 17]. Moreover, 90% of cutaneous neurofibromas occur sporadically, while the other 10% are syndromic [18, 19]. Although both are typically unencapsulated, localized neurofibromas are well circumscribed, whereas diffuse are an en-plaque-like growth and less delimited from surrounding tissue. Dermal neurofibromas do not usually require treatment (unless they are painful, bleeding, or interfere with an individual's day-to-day function) [20], nor do they usually undergo malignant transformation [21].

Intraneural neurofibromas are localized, well-circumscribed BPNSTs arising as a fusiform enlargement of a single nerve. Localized intraneural neurofibromas may be seen as occurring cranially, spinally, peripherally, or from autonomic nerves; nerve is intermixed throughout the tumor [22]. Theses tumors are typically encapsulated and present as painful masses that can cause a sensorimotor neurologic deficit. Furthermore, they have an intermediate potential for malignant transformation [10].

Plexiform neurofibromas are complex lesions involving multiple nerve fascicles growing and coming together to make up an entangled neurofibromatous mass ("bag-of-worms"). These occur almost exclusively in the context of NF1 (many considering them pathognomonic) and grow most rapidly during the first decade of life. The most common locations for this type of neurofibroma are paraspinal and plexal areas; however, they may also be seen peripherally (e.g., from the sciatic or femoral nerve) [23]. Overlying these tumors, cutaneous changes may be seen such as hyperpigmentation and thinning of hair. They are also associated with an increased risk of malignancy (MPNST) [17]. An increase in the size, progressive pain, and neurological deficit have all been found to be clinical indicators of malignant transformation and should prompt immediate diagnostic and/or therapeutic management.

Elephantiasis neurofibromatosa is a rare, massive, soft tissue tumor with an intermediate malignancy potential that is exclusive to NF1 (pathognomonic). It is the least frequent type of neurofibroma and consists of diffuse soft tissue enlargement (often in the extremities) with an underlying plexiform neurofibroma or enlarged nerve within the mass [10].

Atypical neurofibromas are simply neurofibromas (of any histological subtype, although certain types display a higher proclivity for atypical transformation) that display histopathological and molecular features involved in malignant transformation. However, they do not fit into a single grading system and more recently they have been termed "atypical neurofibromatous neoplasms of uncertain biological potential" (ANNUBP). These lesions may be destructive locally but are less likely to metastasize [21]. Even though atypia may be present, it is the loss of neurofibroma architecture, high cellularity, and presence of mitotic activity that are more associated with malignant transformation. ANNUBP has its own specific histological criteria for diagnosis; however, the inclusion of "uncertain" within its name argues the need for more research. For example, some tumors exhibit benign, atypical, and malignant features within the same lesion [17]. Furthermore, these lesions can be positive on fluorodeoxyglucose positron emission tomography (FDG-PET) and include areas of hypercellularity and atypical nuclei without increased mitotic activity or malignant change [24]. However, as in the case of MPNST suspicion, diagnosis of such a lesion should prompt more diagnostic and/or therapeutic intervention.

Finally, hybrid neurofibromas are a histological class displaying characteristics of both schwannomas and neurofibromas. Approximately 60% of patients with these tumors carry a neurocutaneous diagnosis such as NF1, NF2, or SWNTS.

2.3 Malignant peripheral nerve sheath tumors

MPNSTs are aggressive sarcomas with a dismal prognosis arising from the peripheral nervous system (PNS) or peripheral nerve sheath cells. Grossly, they are typically fusiform or globoid in shape with a firm exterior and adherent to adjacent structures. Their center is often necrotic, with pseudocysts and evidence of hemorrhage. Microscopically, invasion into surrounding structures, vascular invasion, nuclear pleomorphism, increased cellularity, necrosis, and mitoses can be seen [9, 15, 16, 21].

They are graded according to the Enneking scheme and exist on a histological spectrum (low-grade, benign-like tumors on one end and high-grade, aggressive tumors with invasive and metastatic potential on the other) [15, 21]. Malignant transformation of BPNSTs in the context of NF1 patients is an area of active investigation. Akin to a two-hit hypothesis, mutation of the second neurofibromin encoding allele (or a second, intricately related gene) may be necessary for this transformation to occur [8, 10, 21, 25]. Approximately half of MPNSTs occur in the context of NF1 (one of the most important prognostic factors), and NF1 patients have approximately a 10% lifetime risk of acquiring this malignancy [26–28]. Of the subtypes, plexiform neurofibromas harbor the highest risk of malignant transformation with more than 80% of MPNSTs arising from them. These tend to occur between second and fifth decades of life (peak in third decade) [8, 11, 21] and typically occur at an earlier age in NF patients (second to third decade vs. third to sixth decade in the general population) [9]. Moreover, they are the most common type of malignancy in NF1 patients, as well as the most common cause of death [8]. In keeping with plexiform tumor characteristics, MPNSTs usually arise from large nerves or trunks (brachial and lumbosacral plexus or the sciatic nerve). They also often occur in a deep-to-fascial location (deep soft tissue and visceral tumors frequently being associated with NF1); however, they may occur more superficially as well [29]. As discussed in subsequent sections, MPNSTs are staged and treated as soft tissue sarcomas [8] with previous studies demonstrating a poor 5-year overall survival (OAS).

2.4 Clinical presentation

Neurofibromas are often an asymptomatic, incidental finding. However, when symptomatic, patients may experience pain, patchy anesthesia or paresthesia, and weakness [7]. The incidence of neurological deficit at presentation is higher for neurofibromas than schwannomas; furthermore, unlike sporadic cases, patients with NF1 can present with signs and symptoms from a multitude of different organ systems. Due to the ubiquitous and intricate nature of the Ras signal transduction pathway, the effects of NF1 can be widespread (segmental neurofibromatosis being an exception) [30, 31]. Diagnosis of NF1 is based on the National Institutes of Health clinical consensus criteria (with optional genetic confirmation), and the diagnosis of a neurofibroma (whether sporadic or syndromic, benign or malignant) is a histopathological one. However, the improvement in diagnostic accuracy of imaging investigations such as magnetic resonance imaging (MRI) and PET has resulted in the necessity of biopsies being an antiquated notion. If required, the benefit of a biopsy should be weighed against risks such as neurological deficit and insufficient/non-diagnostic sampling error [9, 15, 17, 21].

NF1 can present with cutaneous changes (café-au-lait spots and intertriginous freckling being reported in >99% and 85% of patients, respectively) [17], Lisch nodules (ocular hamartoma hyperpigmentations), skeletal abnormalities (long bone dysplasia and scoliosis), central nervous system (CNS) lesions such as optic nerve gliomas (15% of patients typically before 10 years of age), brainstem, and hemispheric gliomas may also occur [6, 32, 33]. Moreover, unlike the other neurocutaneous syndromes, cognitive impairment (60% of patients) is also much more prevalent, as is non-nervous system involvement (leukemia, pheochromocytoma and glomus tumors, gastrointestinal tract tumors, and breast cancer) [6, 17, 32, 34, 35]. Patients with NF1 can also suffer from neurofibromatous neuropathy (a tumor independent, symmetrical sensory-motor neuropathy). This results in sensory predominant symptoms including pain and pruritus [4]. This neuropathy stems from a non-progressive and diffuse neurofibromatous nerve infiltration and hypertrophy. Although only affecting 2% of NF1 patients, it is associated with increased tumor burden and MPNST [4, 21].

2.5 Imaging

MRI is the preferred imaging modality for PNSTs [6, 15]. MR neurography can further determine whether a mass is intrinsic or extrinsic to the peripheral nerve and can aid in presurgical planning. In addition, whole body MRI can be used both for screening patients (quantifying initial tumor burden), as well as for tumor surveillance (to monitor for growth and/or malignant transformation) [36]. Signal intensity of neurofibromas is usually low on T1-weighted imaging and high on T2-weighted imaging (although large tumors can display peripheral, central or heterogeneous hyperintensity on T2 imaging). Enhancement can also be variable ranging from none to homogeneous. The classic pattern of enhancement with solitary neurofibromas is central enhancement surrounded by non-enhancing tissue. Isolated, non-plexiform neurofibromas appear as round or fusiform masses with tapering cranial and caudal ends due to continuity with the nerve. A surrounding rim of intramuscular fat capping the edges of the lesion might give rise to the split-fat sign [23]. A target-sign (hyperintense ring of myxoid material with a hypointense center of collagen and fibrillary tissue) might also be present and is more commonly seen with neurofibromas than schwannomas [15, 23].

MPNSTs may arise from solitary or plexiform neurofibromas. MRI features suggestive of MPNSTs include larger size (≥5 cm), peripheral enhancement, adjacent tissue invasion and peritumoral edema, vascular encasement, and metastases. MPNSTs are often irregularly shaped with heterogeneous enhancement, ill-defined margins, intra-tumoral lobulations, central necrosis and hemorrhage, absence of the target-sign, and an apparent diffusion coefficient (ADC) value of $<1 \times 10^{-3}$ mm^2/s [8, 23, 37].

Functional imaging including PET may be helpful for the determination of malignancy, especially in atypical neurofibromas. A semi-quantitative assessment for the determination of malignancy can be done using a standard uptake value (SUV) cutoff [17]. While F-18-FDG PET activity is invariably present in both BPNSTs and MPSNTs, high SUVs favor the presence of malignancy. A SUV ≥4 is indicative of malignancy and can help direct the ideal site of biopsy [6, 8, 38].

Ultrasound (US) examination has also been shown to be helpful in the workup for neurofibromas. US findings may include hypoechoic lesions that are serpentine, oval-shaped, and well-circumscribed with a fascicular pattern. Plexiform lesions can be multiloculated and nodular, whereas subcutaneous neurofibromas often have heterogeneous echogenicity with multifascicular involvement and a target-sign [35].

2.6 Management and outcome

Management of PNSTs is either surgical or expectant in nature (with the role of radiation and chemotherapy being reserved for select cases). Due to the diverse nature of neurofibromas with respect to subtypes and locations, a concise yet comprehensive description of surgical approaches is difficult. However, like other PNSTs, indications for surgical resection of a neurofibroma may include neurological signs and symptoms referable to the lesion (pain, numbness, paresthesias, and weakness), growth demonstrated on serial imaging, questionable diagnosis or malignancy, and cosmesis.

Solitary, localized, and benign lesions can be completely resected for cure with recurrence being rare (excluding syndromic neurofibromas that may be as high as 15%) [7, 9, 39]. However, surgical resection of diffuse, plexiform, and soft tissue-type neurofibromas should rarely be undertaken and only in select cases with clear surgical goals due to the high associated morbidity [9, 39]. Compared to schwannomas and depending on the specific subtype, neurofibroma resection is often more challenging (greater nerve fascicle integration) and is associated with a higher risk of postoperative nerve injury [40]. To help mitigate this, intraoperative monitoring has been shown to be a useful adjunct to discern functional and non-functional tissue [15]. Postoperative motor deficits after neurofibroma resection have been reported in approximately 6% of cases with the incidence of new postoperative deficit being previously shown to be comparable to that of schwannomas. However, neurofibroma resection involved more extensive nerve dissection with a higher incidence of subtotal resection. Furthermore, in their study, Levi et al. showed that 85% of patients had stable or improved function after resection [15]. In keeping with this, in a separate study, all patients with a preoperative motor deficit remained stable or improved after neurofibroma resection [39].

For suspected or established cases of MPNSTs, systemic staging investigations should be done to help establish management goals. Cases should be referred to a tertiary care center experienced in MPNST patient management with an established multidisciplinary tumor board. In the setting of metastases, a palliative surgical resection with chemotherapy and/or radiotherapy is usually undertaken. In contrast, en-bloc surgical resection (with or without pre- and/or postoperative chemo-/radiotherapy) is the mainstay of treatment for localized tumors without evidence of metastases. Negative tissue margins are the resection goal when feasible and represent an important prognostic factor in the setting of high-grade MPNST [41]. However, in the case of low-grade MPNSTs and atypical neurofibromas, the effect of a negative surgical margin is still unclear and must be weighed against the associated morbidity in achieving this [42]. In general, functional reconstruction of surrounding structures is a secondary consideration and, when possible, should not impede surgical resection [9, 21].

In the setting of large tumors for resection, adjunctive preoperative radiation therapy may be used when en-bloc resection is difficult due to size and surrounding structures. This too, however, must be weighed against the increased difficulty associated with operating in an irradiated field. Furthermore, a survival benefit for its use has not been established [8]. In contrast, postoperative radiotherapy for MPNSTs is often required, especially for high-grade tumors or subtotal tumor resection. Again however, although it may limit local recurrence [21, 43], its effect on OAS is more ambiguous. Proton therapy has also been suggested as a potential adjunct [9]. More recent studies have suggested increased local control rates, though an effect on OAS remains to be seen [39]. More controversial than radiotherapy is

the role of chemotherapy for MPNSTs. MPNSTs typically only partially respond in a small subset of patients with no significant OAS benefit. More specifically, ifosfamide and doxorubicin have been previously used in metastatic disease or to reduce tumor size prior to surgery [9, 44]. Regardless of postoperative regimen, long-term, close postoperative clinical and radiological follow-up of patients with MPNSTs is essential due to the high rate of recurrence of these tumors [9, 39].

MPNSTs have a dismal overall prognosis [45]. Incidence of local recurrence can be as high as 65%. Previous studies have reported 5-year disease-free survival rates varying between 30 and 60%, and a 5-year OAS rate of approximately 30% [9, 10, 28, 39]. Poor prognostic factors have been previously shown to include tumor size ≥5 cm, truncal/midline location, subtotal resection (for high-grade tumors especially and its role in low-grade lesions being less certain), high-grade and advanced stage tumors, previous radiation, and NF1-associated tumors [28, 39, 41, 42].

2.7 Case presentation

A 42-year-old man with a history of NF1 presented with right buttock and lower extremity pain, accompanied by paresthesias. MR neurogram revealed a right sciatic nerve PNST (neurofibroma) at the sciatic notch and a left hemi-pelvis PNST arising from the inferior aspect of the left L5 nerve root (**Figure 1**). A posterior, transgluteal approach was used to successfully remove the right-sided sciatic neurofibroma with intraoperative neurophysiological monitoring. Clinical and radiological follow-up were planned for the left-sided lesion after treatment of his symptomatic lesion. The patient's pain and paresthesias resolved postoperatively, and he recovered without complication.

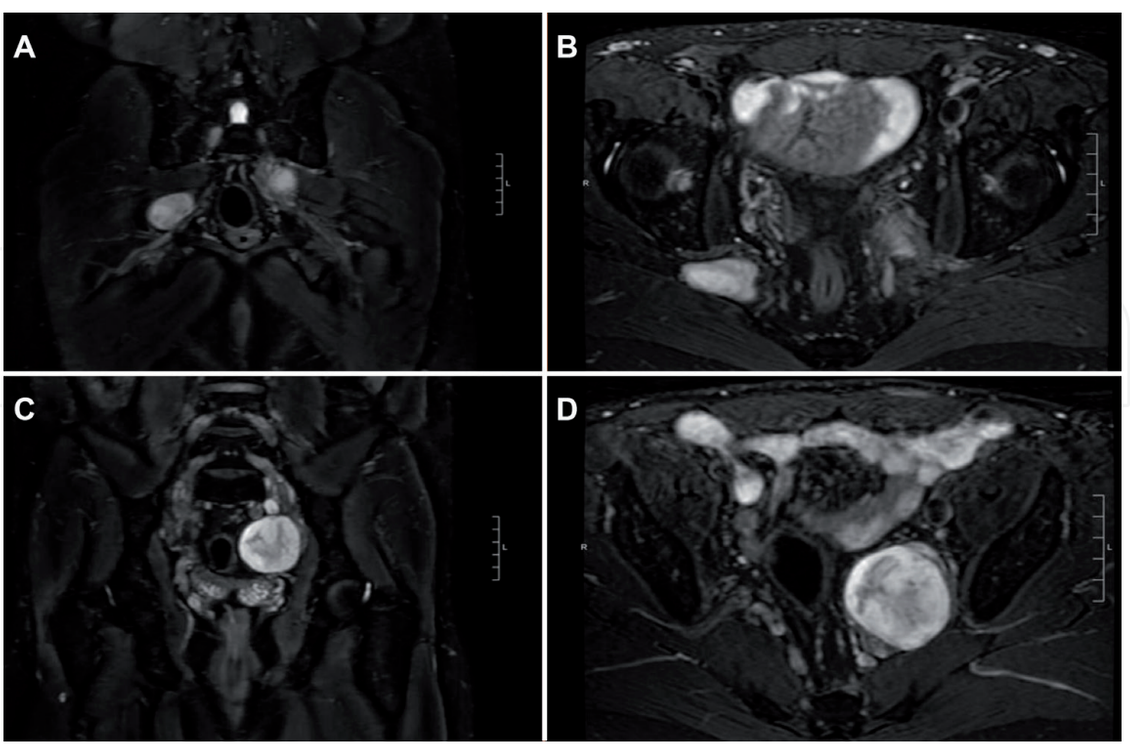

Figure 1.
(A) T2 weighted MRI, coronal section; (B) T2 weighted MRI, axial section; (C) T2 weighted MRI, coronal section; and (D) T2 weighted MRI, axial section. Large round nerve sheath tumor of the sciatic nerve at the sciatic notch (panels A and B), and large left nerve sheath tumor in the left hemi-pelvis, arising from the inferior aspect of the left L5 nerve root (panels C and D).

3. Neurofibromatosis type 2

3.1 Background

In keeping with NF1, NF2 is an AD neurocutaneous disease characterized by a propensity to form craniospinal lesions, most commonly vestibular schwannomas [30, 31]. Its incidence has been reported to range from 1:30,000 to 40,000 individuals. Also in keeping with NF1, NF2 results from a loss of function mutation of a tumor suppressor gene located on chromosome 22q12.2. This gene encodes a protein called merlin (or schwannomin). Merlin is a member of the ezrin, radixin, meosin (ERM) protein family whose function includes anchoring the cytoskeleton to the plasma membrane, interacting with cytosolic elements, and contact-dependent inhibition of proliferation [30, 31, 46, 47]. Through Ras modulation, merlin also acts as a negative regulator of several other transduction pathways [47].

Epidemiologically, NF2 shows no gender, nor racial predilection, and approximately half of NF2 patients acquire a de novo mutation resulting in its expression. Furthermore, 59% of the latter acquire mutation in a somatic mosaic pattern (as opposed to germ line mutation), which portends a better prognosis [47, 48]. Penetrance for the disease approaches 100% in familial patients; however, it may vary in the offspring of mosaic patients [48, 49]. Similar to NF1, specific phenotypic expression and its severity can be dictated by different genotypes; several phenotypes have been described. More specifically, Wishart, Gardner, and congenital types have been described. The Wishart phenotype has the highest incidence and typically displays more rapid disease progression with earlier onset. In contrast, the Gardner subtype is a less severe form of NF2 with onset later into adulthood [50, 51]. A third type, congenital NF2, is associated with dermal plaques in atypical locations, such as the face and hands [51]. The latter phenotype of NF2 tends to be more severe and heterogeneous [46].

3.2 Schwannoma histopathology and subtypes

As their name implies, schwannomas are BPNSTs that develop from Schwann cells and present as well-circumscribed, encapsulated lesions. They are the most common BPNSTs of adulthood and tend to displace rather than infiltrate nerves (fascicles being grossly visible to the exterior of the tumor). Lobular in shape with a rubbery external consistency, these tumors may include cystic cavities, foamy nests, fibrotic and mineralized components, in addition to a hemorrhagic core [4, 52]. Microscopically, two distinct architectures exist: Antoni A and B. Antoni A areas consist of higher cellularity with spindle-like cells and elongated nuclei arranged in palisades (Verocay bodies). Antoni B tumor areas have a lower cellularity with loose reticular fibers in a myxoid background.

Similar to plexiform neurofibromas, plexiform schwannomas are Schwann cell tumors that encompass multiple nerve fascicles coming together into a multi-nodular, loculated growth around the nerves. This subtype will frequently affect the cervical region, brachial plexus, and lumbosacral plexus [48]. They can be grossly distinguished from plexiform neurofibromas, however, by a less diffuse distribution and their typically affecting a single nerve or nerve trunk [35]. Though not pathognomonic for NF2, they occur more frequently in this population.

Dermal or cutaneous schwannomas are masses specific to NF2 patients. They do not occur sporadically or in association with SWNTS and present as a distinct

en-plaque-like mass. These lesions originate from neoplastic Schwann cells that expand the parent nerve and infiltrate adjacent structures including the dermis, hair follicles, and sebaceous glands [50].

Nodular are the most common type of schwannoma. They can occur in a myriad of locations and from a plethora of nerves—cranial, spinal, and peripheral [50]. These tumors tend to grow on flexor surfaces more than the extensor surface of extremities, as well as the head, neck, and upper extremities more than the lower. As mentioned, they will typically grow and displace nerve fascicles to the outside of their capsule. The growth rate of these sporadic growing schwannomas can vary substantially; however, it has been reported to be approximately 1–2 mm/year and 3 mm/year in those tumors demonstrating early growth at follow-up (although rates as high as 17 mm/year have been reported) [53].

3.3 Clinical presentation

NF2 patients usually present in the second to third decade of life (mean age 27-year-old with a mean time to diagnosis from symptom onset of 7 years) [47]. Diagnosis of NF2 is dependent on fulfilling the Manchester clinical criteria (although this may not be the most appropriate diagnostic scheme in, for example, congenital and childhood NF2) [46, 48, 54]. NF2 is characterized by the presence of several different CNS tumors, most notably the growth of bilateral vestibular schwannomas (affecting 90–95% of patients and typically presenting with sensorineural hearing loss, tinnitus, and balance difficulties). Other commonly occurring lesions include spinal tumors (60–90% of patients), meningiomas (50% of patients), gliomas, ependymomas, astrocytomas, posterior subcapsular cataracts, retinal hamartomas, and cerebral calcifications [30, 31, 46, 54, 55]. Congenital and childhood NF2 usually present differently than the typical adult onset presentation of vestibular schwannomas (least likely to occur); these patients are more likely to present with a spinal cord tumor, peripheral nerve, or skin lesion [55]. Approximately 70% of NF2 patients will also present with cutaneous and peripheral manifestations of the disease including hyperpigmented plaques, subcutaneous nodules, and neurofibromas (although nodular schwannomas are still more common and tend to occur around peripheral nerves) [46]. Furthermore, although more common in NF1, up to 50% of NF2 patients may also develop café-au-lait spots (typically smaller, less numerous, and paler with more irregular margins) [46, 56].

When they do occur, neurofibromas tend to have a hybrid neurofibroma-schwannoma histopathology [50, 52]. Furthermore, compared to SWNTS patients, NF2 schwannomas are more likely to present in childhood/young adulthood and result in neurologic deficit rather than pain [50]. These tumors have a predilection for sensory nerves with an average rate of growth of approximately 1–2 mm/year (though different lesions within the same individual may grow at different rates) [47, 57]. Finally, non-vestibular cranial nerves (e.g., cranial nerves 5, 7, 9, 10) affect about 50% of NF2 patients [50], and malignant transformation of NF2 (vestibular) schwannomas has not been demonstrated to be higher than the general population in non-irradiated cases [58]. However, aggressive retroperitoneal tumors and spinal SMARCB1-deficient MPNSTs do occur at an increased rate, and malignant transformation has been suggested to be 10 times more likely after radiation treatment [47, 59].

NF2 can also present localized to a particular part of the body or nervous system as seen in mosaic, or segmental forms of the disease. Segmental NF2 presents as a less severe form of the disease [59] and occurs more frequently in sporadic NF2 cases

(20–30% of patients carrying a de novo somatic mosaic mutation) vs. syndromic [30, 31]. This form of NF2 may also clinically overlap with sporadic SWNTS [51].

Akin to NF1, NF2 patients may also experience peripheral neuropathy (66% of NF2 patients) [60]. This typically presents as a mixed sensory-motor axonal peripheral mononeuropathy (not due to mass lesion) in children causing foot drop or wasting of thenar and hypothenar eminences, and severe progressive polyneuropathy in adults [50, 52, 56]. The pathogenesis might involve nerve compression by Schwann cell tumorlets or aberrant non-neoplastic Schwann cells [48, 50].

3.4 Imaging

MRI represents the most precise means of diagnosis [59]. On T1-weighted imaging, NF2-associated schwannomas appear isointense to muscle with a possible split-fat sign. On T2-weighted imaging, target-sign, fascicular-sign, and/or intratumoral cysts may be present resulting in heterogeneous high signal intensity. Enhancement is variable [52]. Internal calcification, hemorrhage, and cyst formation are more commonly seen in schwannomas than neurofibromas. Whole-body MRI can be used to assess tumor burden and distribution of schwannomas for the purposes of diagnosis, surveillance, and optimal treatment timing [46, 52]. MRI adjunct sequences such as diffusion tensor imaging (DTI) may help in distinguishing schwannomas by demonstrating the eccentric location of the lesion relative to nerve fibers. Tractography can also be useful in preoperative planning by demonstrating the nerve fiber displacement pattern around the lesion. The ADC value can be quite variable in NF2 lesions with a minimum ADC range of 0.8–2.7 × 10^{-3} mm^2/s (values <0.9 are concerning for malignancy).

Unlike in NF1 patients, FDG-PET imaging holds little value in the management of NF2 patients and schwannomas.

On US, solitary schwannomas appear as hypoechoic, homogeneous lesions with distinct borders, an oval shape, and the absence of vascularization. Normal fascicular displacement may be seen, as can focal nerve enlargements, hypoechoic cysts and fascicles, and hyperechoic calcifications [35, 60].

3.5 Management and outcome

In a similar fashion to neurofibromas, schwannomas (whether sporadic or syndromic) are typically slow growing and may not lead to neurological dysfunction for many years [57]. Surgical resection of a schwannoma may be indicated in cases of neurological deficit referable to the lesion (pain, numbness, paresthesias, and weakness), growth demonstrated on serial imaging, questionable diagnosis or malignancy, and cosmesis. Surgical treatment in the way of gross total resection is often curative and successful at alleviating presenting symptoms. Rarely does it lead to neurologic deficit, need for parent nerve resection, or tumor recurrence (depending on the location and size, notably vestibular schwannomas) [15, 51]. However, not all lesions are suitable for complete surgical resection (again depending on location, accessibility, and neural involvement, among others) in which case the goal should be maximal safe resection and functional preservation [61]. Schwannomas in the context of NF2 are more likely to result in subtotal resection than sporadic lesions (former tends to include more nerve fascicles and be more adherent to adjacent structures) [50].

Moreover, dermal tumors are not usually resected, unless they are disfiguring or are functionally burdensome.

Careful consideration should be given to the use of radiotherapy in NF2 patients due to the risk of inducing or accelerating the progression of tumors, especially in pediatric patients [57]. However, stereotactic radiosurgery has been successfully used in treating vestibular schwannomas of NF2 patients and resulted in a higher rate of facial nerve preservation [62]. Currently, little guidance in the literature exists for the use of chemotherapy or radiation in the treatment of NF2-associated PNSTs.

In the context of NF2, age of onset is one of the most important determinants of disease severity [46]. The clinical course of the disease is highly variable, but NF2 patients suffer from a shortened life-expectancy by about 10 years [61]. The twenty-year OAS rate has been reported to be as low as 38% [51]. Tumor burden, perioperative complications, and malignancy have been cited as the most common causes of mortality in this group of patients [47, 50, 51].

3.6 Case presentation

A 45-year-old woman with NF2 presented with a palpable mass in her popliteal fossa and pain in the area radiating down her calf into the sole of her foot. MR neurogram showed a PNST arising from the left tibial nerve, ADC values consistent with a benign tumor, and tractography showing splaying of nerve fascicles eccentric to the tumor (as shown in **Figure 2**). Operative resection of the tumor was completed with neurophysiological monitoring being used to identify silent tumor areas and viable nerve fascicles.

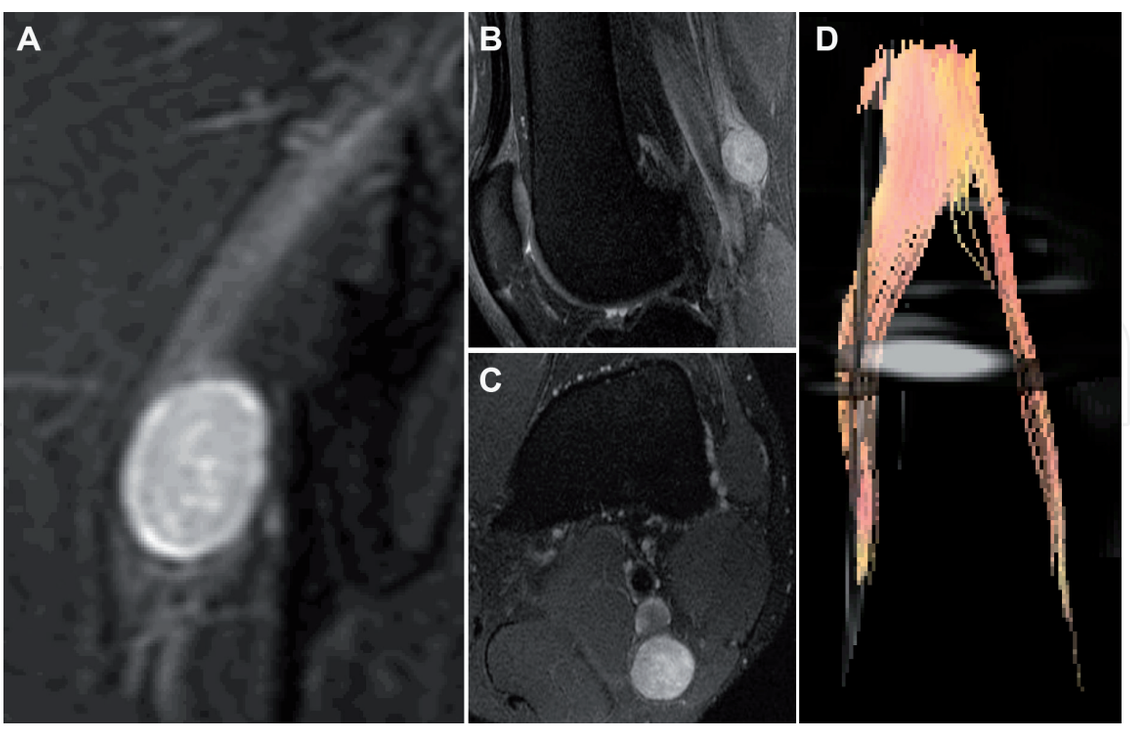

Figure 2.
(A) and (B) T2 weighted MRI, sagittal view. (C) T2 weighted MRI, axial view. (D) Diffusion tensor imaging with tractography reconstruction. Large, round, and well-circumscribed peripheral nerve sheath tumor (schwannoma) arising from the left tibial nerve in the popliteal fossa. Tractography demonstrated intact nerve fascicles being splayed eccentrically posterior and medial to the tumor.

4. Schwannomatosis

4.1 Background

Schwannomatosis is another neurocutaneous disease characterized by the development of multiple BPNSTs, namely schwannomas (in the absence of NF1/2 history). The disease typically has a later onset (second to fourth decade), and some reports suggest a female preponderance [63, 64]. The reported incidence for SWNTS is quite variable; however, many approximate it to be 1:40,000–1:70,000 with a prevalence of 1:70,000–1:160,000 [57]. In contrast to NF1 and NF2, it almost exclusively affects the PNS [31] and can be inherited in a sporadic or AD fashion due to germ line mutation. However, sporadic SWNTS is significantly more common (under 20% of patients having an affected parent), [64] and familial cases generally present at a slightly younger age [63].

As the most common adult PNST, most schwannomas present in the third to sixth decade of life [3]. Many are found incidentally, and due to their slow growing nature, many are quite sizeable before the onset of symptoms (typically presenting with pain and not neurological deficit). The occurrence of multiple schwannomas in one patient should raise suspicion for SWNTS. These tumors can occur in several different locations, including in the paraspinal and retroperitoneal areas, as well as brachial plexus [65]. SWNTS can also lead to the growth of other tumor types such as meningiomas. This, in addition to the presence of vestibular schwannomas in SWNTS, can result in considerable overlap and misdiagnosis of SWNTS as NF2 (especially as mosaic NF2) [57].

Two gene mutations related to chromosome 22q have been identified as resulting in SWNTS—LZTR1 and SMARCB1. Patients with the LZTR1-associated mutation are more likely be affected by a vestibular schwannoma and acquire the sporadic form of SWNTS. Malignant transformation in patients with SWNTS is rare, but does occur. However, mutations in the SMARCB1, LZTR1, and the CoQ6 genes have been implicated in the pathogenesis of SWNTS both in the familial and sporadic cases. Many, as of yet, unknown mutations may also be implicated considering that SMARCB1 and LZTR1 genes were found in only 10% of sporadic and 60% of familial SWNTS cases [66]. Furthermore, in sporadic cases, 55% of the patients did not have their pathogenic variant found, while this was the case in only 31% of the familial cases [40, 57].

4.2 Schwannomatosis histopathology and subtypes

Schwannomas are well-circumscribed, encapsulated, intraneural lesions that most frequently arise from a single fascicle and tend to grow extrinsic to their parent nerve. This results in surrounding fascicles being splayed to the tumor periphery (is in contrast to neurofibromas) [3, 39]. It is not uncommon for multiple schwannomas to occur along the same nerve [67]. Although the majority of lesions are solitary (96%), plexiform lesions do occur (4%) [68].

Morphologically, SWNTS-associated schwannomas are similar to lesions occurring in NF2 or sporadic cases. Namely, Verocay bodies, Antoni A/B architecture, encapsulation, and hyalinized vessels are present. In addition to the above anatomical description of schwannomas, there are also several different histological categories as well. These include conventional or ancient type (commonly displaying degenerative changes such as calcification, cystic change, necrosis and hemorrhage, though usually still follow an indolent course), cellular type (predominantly made up of Antoni A areas, hypercellular with occasional mitotic figures and nuclear atypia, and although may have a higher recurrence

rate, still considered benign), melanotic type (comprised of non-psammomatous and psammomatous types with melanin hyperpigmentation and associated with Carney's syndrome; may be or become malignant), and plexiform type (as previously described). Furthermore, mixed or hybrid neurofibroma-schwannoma histopathologic tumor appearance is more frequent in SWNTS than in the other tumor predisposition disorders [4]. Furthermore, although in the absence of radiation exposure schwannomas are not necessarily more prone to malignant degeneration in the setting of NF2, this may not be the case for SWNTS. In a previous study, MPNSTs were noted to occur in 3/181 cases of SWNTS associated with SMARCB1 mutations [69].

4.3 Clinical presentation

The clinical presentation of SWNTS is more non-specific than that of the other familial tumor syndromes discussed [57]. This is likely due to the fact that compared to NF1/2, SWNTS will present with more subtle findings related to slow tumor growth (as opposed to cutaneous manifestations). The most common presenting complaint is pain (focal or diffuse) without neurological deficit, and the presence of a large mass [3, 57, 63, 70]. One previous study found that approximately 60% of patients will have numbness and 30% will have paresthesias at presentation. However, motor deficits are rare [39]. Weakness and atrophy are typically late findings, [64] though they have been found in 12.8% of tumors in one study [39]. It should also be noted that due to mosaicism, SWNTS can also present as a localized, segmental process, which is the case in about 30% of patients [47, 68].

Compared to NF2 patients, SWNTS demonstrates a higher incidence of peripheral nerve and spinal lesions [57]. Schwannomas will affect peripheral nerves most commonly (95%), followed by spinal nerves (75%) with the lumbar spine most often affected [64]. Moreover, cranial nerves may be affected (trigeminal being the most common), though much less commonly [64]. Patients with SWNTS have a significantly lower incidence of meningiomas, ependymomas, trigeminal, and vestibular schwannomas (unilateral still being in keeping with an SWNTS diagnosis) than do patients diagnosed with NF2 [57]. Meningiomas in association with schwannomas do occur, as do isolated cutaneous neurofibromas; however, patients presenting with schwannomas tend to be older than those presenting with neurofibromas for NF1/2 [30, 31]. Diagnosis of SWNTS (and differentiating SWNTS from NF1/2) is predicated on clinical criteria or combined clinical-molecular criteria recently proposed by Kehrer-Sawatzki et al. [71]. However, biopsy to obtain a definitive diagnosis of schwannoma is no longer recommended given the associated risk of neurological injury and increased risk of postoperative neurological deficit after resection [15].

Similar to NF1 and NF2, SWNTS patients can also present with neuropathy (outside of that explained by obvious tumor compression). Patients may suffer from a tumor-independent, intrinsic nerve deficit presenting as a mononeuropathy or polyneuropathy [4]. After investigations are completed, the majority of SWNTS patients presenting with neuropathic pain do not end up having a causative tumor identified. Furthermore, although neurophysiological investigations are often normal in these patients, high-resolution MR neurography has previously demonstrated intrafascicular microlesions. As such, the notion of not finding a causative tumor may simply be an issue of commonly used investigations not being sensitive enough to detect them (tumorlets as seen in NF1/2 being the culprit). Alternatively, an abnormally and diffusely thickened nerve may be to blame [4, 68]. Whether or not these findings are the cause of the pain, and not merely correlative, is another issue. However, SMARCB1-deficient Schwann cells have also been shown to release

factors that stimulate nociceptive DRG neurons [4, 61, 68]. These are only a few of the ongoing research areas of SWNTS, as well as NF1/2, being actively pursued.

4.4 Imaging

Imaging characteristics for lesions in patients with SWNTS are similar to those found in solitary lesions previously described. On T1-weighted MRI, lesions appear homogeneously hypo- to isointense to muscle. Postcontrast T1 imaging typically demonstrates heterogeneous enhancement, while fluid-sensitive sequences demonstrate heterogeneous hyperintensity [68]. High-signal intensity on T2 is also usually seen. The use of whole-body MRI is an efficient way in SWNTS patients to evaluate and screen the overall tumor burden, as well as survey for tumor growth or change. With respect to other hallmark features, a target-sign (20%), split-fat sign (96%), tail-sign (36%), and tumor-nerve eccentricity (33%) may all be seen [68].

Although metabolic imaging is useful for malignancy surveillance in neurofibromas, its utility in schwannomas is limited due to the high FDG-avidity of schwannomas, which can consequently mimic malignancy [68, 70].

4.5 Management and outcome

Management for these tumors is similar in nature to that of schwannomas found in other neurocutaneous syndromes. Surgical indications have been outlined above in the NF1/2 sections. Previous studies have demonstrated good outcomes with surgical resection with very low risk of recurrence in the setting of gross total resection. Tumor resection with functional nerve/nerve fascicle preservation is the surgical goal when possible [39, 63]. Surgical removal is typically associated with little to no injury of the parent nerve, in contrast to neurofibromas in which there is a higher associated risk [3, 39]. Resection is carefully performed with removal of tumor capsule unless it is firmly adherent to the surrounding nerve. In the case of the latter, it is left in place. Gross total resection has been previously reported as being achievable in close to 80% of cases peripherally located (versus plexus) [39]. Recurrence of schwannomas after surgical removal is rare; however, it is greatest in cases of subtotal resection and in patients diagnosed with SWNTS (recurrence rate of 14.3% with an odds ratio of 4.29) [3, 39]. A revised diagnosis of NF2 is also associated with a worse overall prognosis. In comparison, SWNTS patients have a higher OAS than NF2 patients (mean age of 76.9 vs. 66.2 years, respectively) [18, 57, 67]. The most frequent postoperative complication is paresthesia; however, motor (5.2%) and sensory (7.5%) deficits can also occur, in addition to neuropathic pain despite appropriate surgical and nonsurgical management (often unrelated to tumor size) [3, 39, 47, 72].

No medical treatments are currently available for patients with SWNTS [3]. However, as for all PNST patients presenting with significant neuropathic pain, neuromodulatory medication such as amitriptyline, pregabalin, and gabapentin should be considered [4]. The use of radiation therapy for treatment of SWNTS-related lesions has not been rigorously assessed and considered only in cases of malignancy or clinically debilitating/unresectable lesions due to the risk of malignant transformation [47].

4.6 Case presentation

A 42-year-old man with a personal and family history of multiple, recurrent schwannomas presented with a palpable tumor arising from the dorsal aspect of the

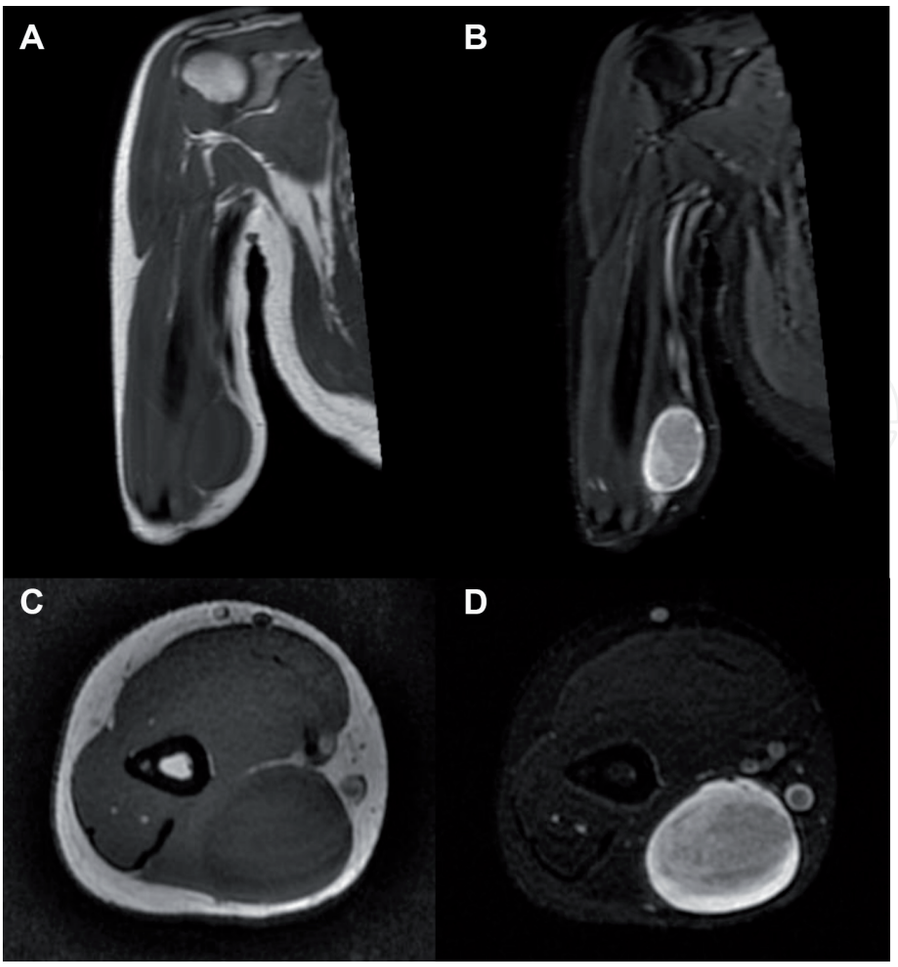

Figure 3.
(A) T1 weighted MRI, coronal section. (B) T2 weighted MRI, coronal section. (C) T1 weighted MRI, axial section. (D) T2 weighted MRI, axial section. Oval, homogeneously enhancing, mass in the dorsal right forearm medial to the triceps arising from the right ulnar nerve.

right ulnar nerve (progressively enlarging since childhood). The mass was located near the right medial epicondyle (as shown on his MRI depicted in **Figure 3**), and associated with painful paresthesias upon palpation in an ulnar distribution. On exam, he had weakness and atrophy of his dorsal and palmar interossei. Operative resection was completed using neurophysiological monitoring to identify silent tumor areas for its safe removal along with the fascicle of origin while preserving the parent ulnar nerve. At last follow-up, the patient's sensory symptoms had resolved, and he had regained some strength; however, his atrophy persisted.

5. Conclusion

Since the initial description of neurofibromatosis (and subsequently schwannomatosis), our understanding of the molecular pathogenesis underlying these neurocutaneous disorders, their clinical manifestations, and respective natural histories has greatly evolved. Technological advancements in areas such as genomic sequencing and radiological imaging have improved both the diagnostic and therapeutic aspects of these patients' care. Despite these advancements, however, substantial work remains in order to fully comprehend the depth of these diseases. It is only through the continued collaboration of research groups and consortiums that these obscure areas will come to light and translate into improved patient care.

Conflict of interest

The authors have nothing to disclose, nor conflicts of interest related to this article, and the contents of this manuscript have not been previously published.

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