

Frequent *CTNNB1* p.S45 Mutations and Aggressive Clinical Behavior in Neuromuscular Choristoma-Associated Fibromatosis

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BACKGROUND: Neuromuscular choristoma (NMC) is a peripheral nerve malformation frequently associated with a fibromatosis (NMC-DTF) that mimics sporadic desmoid-type fibromatosis (DTF). Sporadic DTF is often managed conservatively but its clinical behavior varies. *CTNNB1* mutational subtypes in sporadic DTF have prognostic value. We have previously identified *CTNNB1* mutations in NMC, and 3 paired NMC-DTF but the clinical behavior of NMC-DTF is poorly understood.

OBJECTIVE: To evaluate patients with NMC-DTF to determine (1) *CTNNB1* mutational subtypes in NMC-DTF, and (2) associated clinical behavior and response to treatment.

METHODS: Retrospective review of clinical, imaging, and pathologic features of patients with NMC and NMC-DTF, and molecular testing for *CTNNB1* mutations.

RESULTS: Among 7 patients with NMC of the sciatic nerve (median age: 18 yr), NMC-DTF (mean size 10.7 cm) developed shortly following NMC biopsy (N = 5) or spontaneously (N = 2): 6 NMC-DTF had *CTNNB1* p.S45X mutations and 1 NMC-DTF had a p.T41A mutation. All patients with *CTNNB1*-p.S45-mutated NMC-DTF developed local progression after wide local excision or active surveillance, including one distal metachronous NMC-DTF. No patient had spontaneous disease stabilization. Following adjuvant radiation or systemic therapy, disease stabilization was achieved in 4 (of 6) patients. One patient progressed on sorafenib treatment.

CONCLUSION: NMC-DTF frequently contain *CTNNB1* p.S45 mutations, behave aggressively, and require adjuvant therapies for disease stabilization. We now use imaging alone to diagnose NMC, and routinely surveil the NMC-affected nerve segment to identify early NMC-DTF. In contrast to sporadic DTF, earlier adoption of systemic therapeutic strategies may be required for optimal disease management of NMC-DTF.

KEY WORDS: *CTNNB1*, Neuromuscular choristoma, Fibromatosis, Beta-catenin

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Neuromuscular choristoma (NMC) is a rare developmental lesion characterized by the presence of mature skeletal muscle within peripheral nerve fascicles.^{1–9} NMCs typically involve major nerves or plexuses, and patients typically present with neuro-pathic symptoms or chronic undergrowth in the affected nerve's territory.^{4,10} In our experience, approximately 80% of patients with NMC develop a soft tissue fibromatosis within the

innervation territory of the NMC-affected nerve segment.^{11–14} This NMC-associated desmoid-type fibromatosis (NMC-DTF) is an infiltrative myofibroblastic proliferation, histologically identical to sporadic DTF, which lacks metastatic potential, but can recur.

Sporadic DTF frequently harbors somatic activating mutations in genes involved in beta-catenin/Wnt signaling, most often in exon 3 of *CTNNB1* (beta-catenin), and *CTNNB1* mutational subtypes have been associated with clinical behavior of DTF and recurrence risk.^{15–18} Three cases of NMC and paired NMC-DTF with identical activating *CTNNB1* exon 3 mutations have been published.¹⁹ However, the *CTNNB1* mutational status, associated

ABBREVIATIONS: DTF, desmoid-type fibromatosis; FFPE, formalin-fixed paraffin-embedded; LN, lipomatosis of nerve; MRI, magnetic resonance imaging; NMC, neuromuscular choristoma

clinical behavior, and response to contemporary adjuvant treatments have not been well characterized in NMC-DTF. We expanded our series of patients with NMC and biopsy-confirmed NMC-DTF to assess (1) *CTNNB1* mutational status, and (2) the clinical behavior of NMC-DTF and response to therapeutic interventions.

METHODS

The study was approved by our Institutional Review Board. Patient consent was not needed due its retrospective nature. Our institutional and consultation archives were searched for cases of NMC and DTF. Clinical details were obtained from electronic medical record review. Magnetic resonance imaging (MRI) studies were reviewed by a musculoskeletal radiologist (BMH). Pathologic materials were reviewed by a soft tissue pathologist (JMC).

Immunohistochemistry

Immunohistochemical stains were performed on formalin-fixed paraffin-embedded (FFPE) tissue sections (DAKO Envision, automated system, DAKO, Carpinteria, California) using antibodies generated against the following antigens desmin (DER11, 1:100, Leica, Buffalo Grove, Illinois) and beta-catenin (14, prediluted, Ventana Medical Systems, Tucson, Arizona).

CTNNB1 Sequencing

Genomic DNA was obtained from FFPE lesional tissue using the QIAamp® DNA FFPE Tissue kit (QIAGEN, Valencia, California). Following polymerase chain reaction-based amplification of the target region of *CTNNB1* codons 41 and 45 (primers forward: GACAGAAAAGCGGCTGTTAGTCA; reverse: TTGGGAGGTATCCACATCCTCTT), PCR products were pyrosequenced (sequencing primer GATTGCCTTTACCACTC) and analyzed for *CTNNB1* T41A, S45P, and S45F mutations.

RESULTS

The clinicopathologic features of the 7 cases are summarized in the [Table](#). We have previously reported, in part, the clinical and radiologic features of the NMC and NMC-DTF in a subset of patients.^{4,13,20,21} NMC-DTF occurred in 7 patients (4 males and 3 females), all with NMC of the sciatic nerve. Five patients presented in childhood (median 18 yr, range 5–42 yr) with localized neuropathies or limb undergrowth within the affected nerve's territory. Among 6 cases with follow-up, 4 patients developed NMC-DTF, arising at or near the NMC biopsy site, at a postbiopsy interval ranging from <6 mo to 8 yr. Two patients presented initially with clinical and imaging features of presumed sporadic DTF (enlarging masses in the popliteal fossa or posterior thigh respectively) ([Table](#), cases 2 and 3). However, upon retrospective review, radiologic and/or pathologic features of an NMC and NMC-DTF were identified.

NMC and NMC-DTF Imaging

All 6 cases demonstrated characteristic imaging features of NMC involving segments of the sciatic nerve: fusiform enlargement of the affected nerve bundles with <50% of nerve enlargement from intrafascicular fat, T1W (weighted) signal isointense and T2W signal iso- to mildly hyperintense to skeletal muscle, and no to minimal enhancement with gadolinium administration ([Figure 1A](#) and [1B](#), [Table](#); case 1). In all cases, the NMC-DTF formed lobular, heterogeneous masses (range 6.5–16.2 cm), arising in proximity to the NMC and with one or more points of contact. NMC-DTF showed heterogeneous signal characteristics: T1W signal isointense to skeletal muscle with areas hypointense to skeletal muscle. They were hyperintense on T2W images with areas of low signal corresponding to the areas of decreased signal on the T1W signal ([Figure 1C](#) and [1D](#), case 1). All masses demonstrated intense heterogeneous postgadolinium enhancement.

Pathology and *CTNNB1* Status

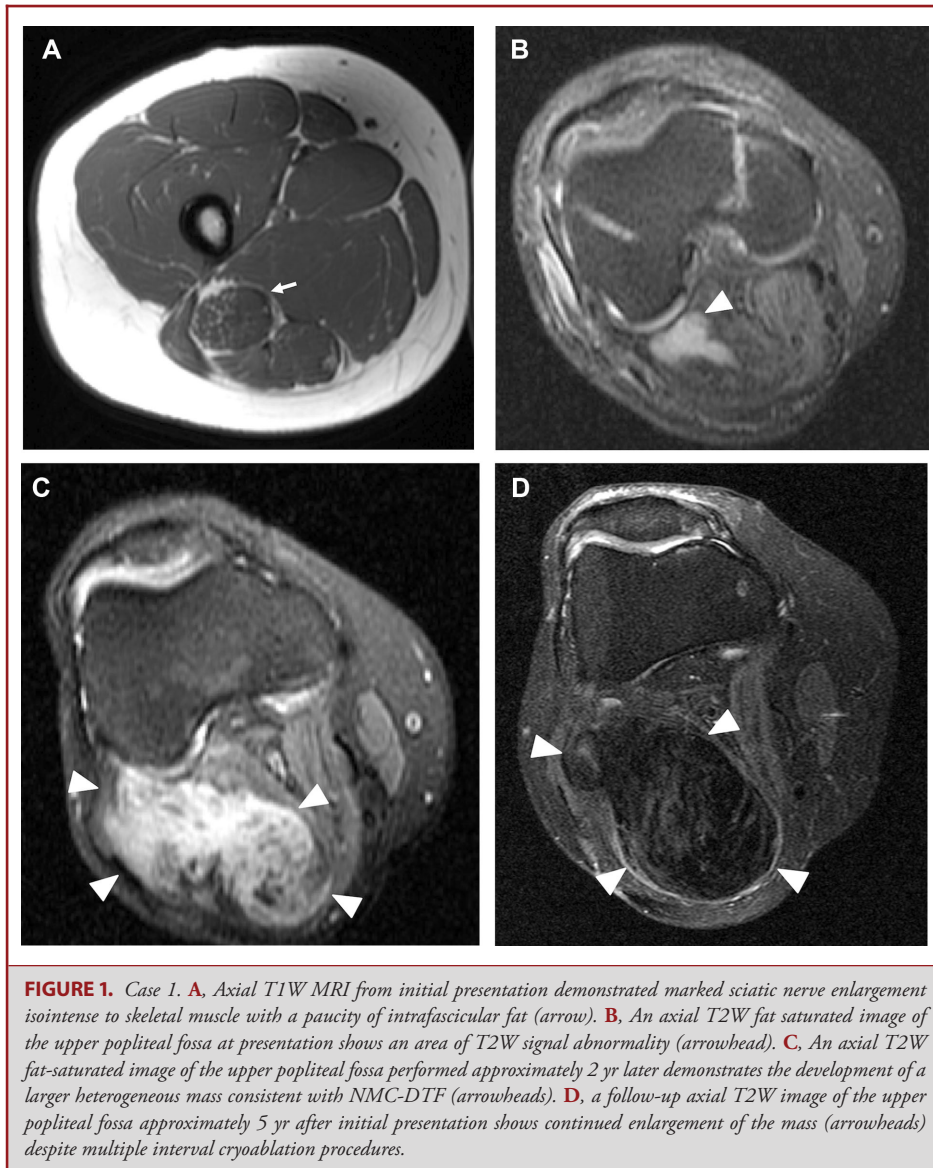
The NMC showed characteristic enlargement of the peripheral nerve fascicles with endoneurial intercalation of mature skeletal muscle fibers ([Figure 2A](#) and [2B](#)). NMC-DTF were identical to sporadic DTF, forming widely infiltrative masses composed of cytologically bland, spindled (myo)fibroblasts forming long fascicles ([Figure 2C](#)). No cytologic atypia was seen, and mitoses averaged <1 per 50 high powered fields. All 7 NMC-DTF had *CTNNB1* mutations: p.S45F (N = 5), p.S45P (N = 1), and p.T41A (N = 1). In prior testing of 3 NMCs, identical *CTNNB1* p.S45 mutations were observed in the NMC and NMC-DTF ([Table](#)).¹⁹ Beta-catenin staining showed aberrant nuclear localization in the lesional (myo)fibroblasts, compatible, with *CTNNB1* mutations ([Figure 2D](#)). In one patient with metachronous NMC-DTF ([Table](#)), both NMC-DTF were histologically identical and contained the same *CTNNB1* p.S45P mutation. This patient was initially diagnosed with sporadic DTF and a sciatic nerve NMC was identified only in retrospect.¹³

Treatment and Outcome

All 6 patients with follow-up information had *CTNNB1* p.S45X mutations, including 5 p.S45F and 1 metachronous NMC-DTF with p.S45P mutations in both sites ([Table](#)). All 6 patients had local progression of their NMC-DTF, irrespective of their initial treatment strategy: surgical resection (N = 3); cryoablation (N = 1), endocrine therapy (N = 1), or observation (N = 1). The 3 patients treated initially with complete surgical resection (with negative surgical margins) had recurrence of NMC-DTF at 6 to 9 mo postoperatively ([Table](#)); all had adjuvant radiation therapy. Among them, patient no. 3 had disease stabilization, whereas patient no. 2 developed a metachronous NMC-DTF distally (knee) 3 yr later and patient no. 5 had local disease progression. Patient no. 1 (NMC-DTF of the popliteal fossa) progressed following 3 rounds of cryoablation therapy. She progressed on vinblastine and methotrexate treatment, and again on sorafenib

TABLE. Clinicopathologic Features and CTNNB1 Status in Patients With NMC-DTF

Patient	Age/sex	Initial clinical presentation: (NMC or NMC-DTF-related)	Location of NMC and location and size of NMC-DTF (cm)	CTNNB1 status		Treatment chronology	Clinical outcome (follow-up duration, yr)
				NMC	NMC-DTF		
1	15/F	Leg length discrepancy, foot drop (NMC)	Right sciatic nerve/right popliteal fossa (6.5 × 5.4 × 6.5)	NA	c.134 C > T p.S45F	Treatment 1: cryotherapy (X 4) Treatment 2: vinblastine and methotrexate Treatment 3: sorafenib (with dose escalation) + cryotherapy	Local progression Local progression Local progression (3 yr)
2	34/F	Lower extremity pain, posterior thigh mass (NMC-DTF)	Right sciatic nerve/right posterior thigh (4.7 × 4.8 × 16.2) and calf (metachronous NMC-DTF, 7.0 × 3.6 × 18.0)	NA	c.133 T > C p.S45P	Treatment 1: surgical resection Treatment 2: tamoxifen (6 mo) Treatment 3: tamoxifen and NSAID Treatment 4: radiation therapy Treatment 5 (metachronous NMC-DTF) capecitabine × 10 mo Radiation therapy (tomotherapy)	Recurrence at 8 mo Disease stable Disease stable Primary disease stable. Second, distal NMC-DTF in the calf Disease stable (6 yr)
3	20/M	Enlarging popliteal mass (NMC-DTF)	Left sciatic nerve/left popliteal fossa (7.6 × 8.1 × 13)	NA	c.134 C > T p.S45F	Treatment 1: surgical resection Treatment 2: radiation therapy	Local progression at 9 mo Disease stable (1 yr)
4	51/M	During w/u for hip replacement (congenital dysplasia), old foot drop (NMC)	Left sciatic nerve/left sciatic notch (9.5 × 6.4 × 5.8)	c.134 C > T p.S45F	c.134 C > T p.S45F	Observation	Local progression (2 yr)
5	18/M	Ankle fracture, foot drop, pain (NMC)	Right sciatic nerve/right posterior mid-thigh (6.0 × 9.0 × 12.0)	c.134 C > T p.S45F	c.134 C > T p.S45F	Treatment 1: surgical resection Treatment 2: radiation therapy (28 fractions of 5600 cGy)	Recurrence at 6 mo Disease stable (8 yr)
6	14/M	Gait disturbance, leg length discrepancy, muscle atrophy (NMC)	Right sciatic nerve/right posterior mid-thigh (4.6 × 4.3 × 7.1)	c.134 C > T p.S45F	c.134 C > T p.S45F	Treatment 1: tamoxifen + sulindac × 3 mo Treatment 2: doxorubicin (8 cycles/8 mo)	Local progression Disease stable (6 yr)

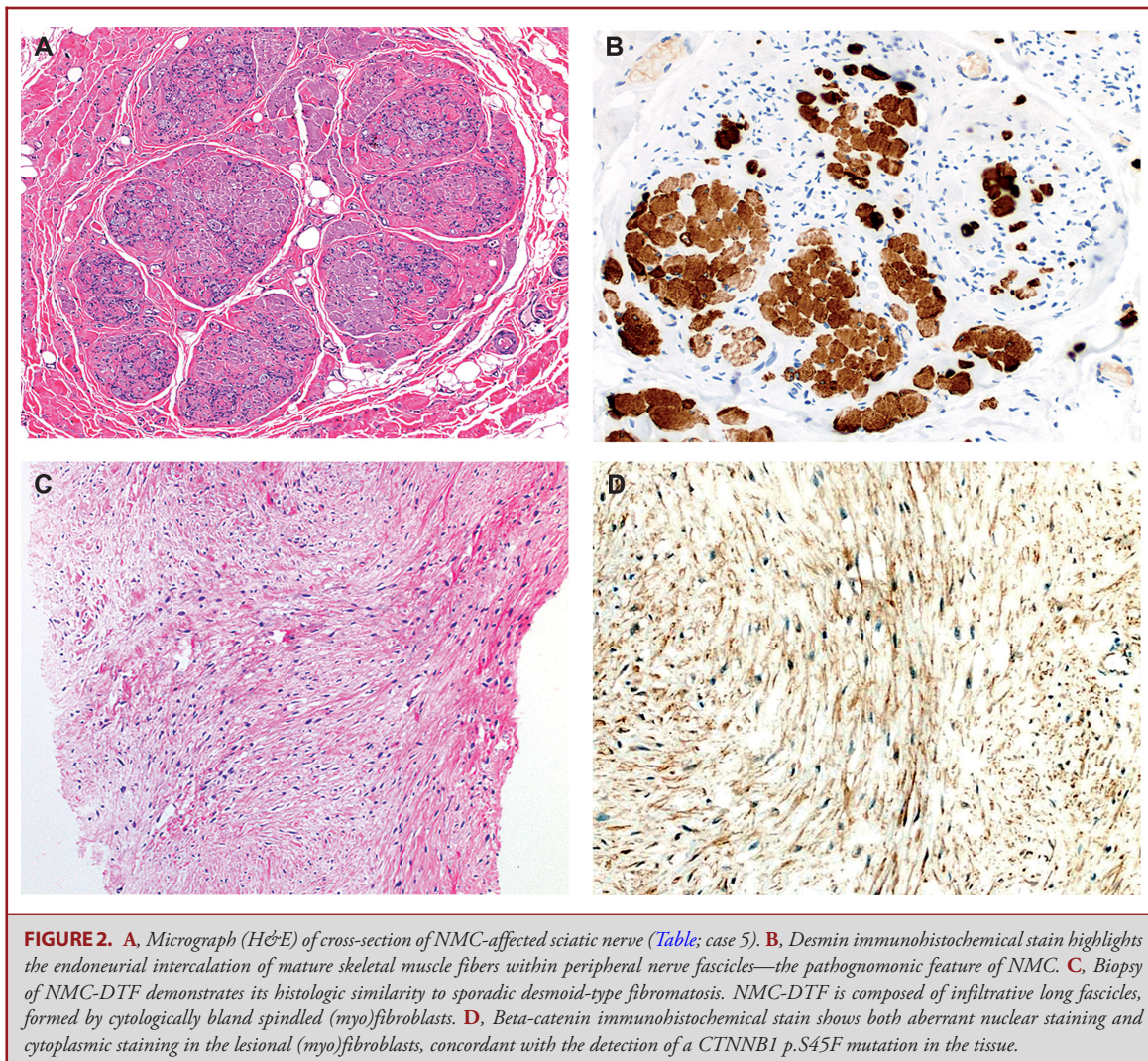


(200 mg BID escalated to 400 mg BID) with cryo-ablation therapy. Patient no. 6 had local disease progression with tamoxifen treatment, and disease stabilization following 8 cycles of doxorubicin (follow-up 5 yr) (Table). To date, radiologic evidence of disease stability is present in 4 (of 6) patients, including those that received adjuvant radiation (N = 2) or chemotherapy (N = 1). None of the patients developed DTF at any other anatomic sites.

Discussion

NMC is a developmental malformation of peripheral nerves, most often the sciatic nerve, causing undergrowth in the affected nerve's territory.¹⁻⁹ In our experience, NMC-DTF develops in approximately 80% of patients with NMC,²⁰ and invariably

arises within the NMC-affected nerve innervation territory.¹⁴ As biopsy of the NMC may trigger or accelerate development of the NMC-DTF, we now rely on clinicoradiological features for both diagnosis and surveillance of NMC.^{12,20,21} It is our view that MRI features of a fusiform enlarged nerve with signal characteristics similar to muscle, a paucity of intrafascicular fat, and minimal postgadolinium enhancement is pathognomonic of NMC in the appropriate clinical setting. The differential diagnosis for the MR findings of NMC includes lipomatosis of nerve (LN) and intraneural perineurioma, but imaging and clinical features can distinguish them. LN shows nerve enlargement, lack of enhancement, and an increase in intraneural fat (not seen with NMC) best appreciated on T1W



MR images. Unlike NMC, LN is associated with nerve-territory bone and soft tissue overgrowth.⁴ Patients with intraneural perineurioma present with weakness in the affected nerve distribution and may have evidence of undergrowth.²² Intraneural perineurioma has fusiform nerve enlargement on MRI, but classically demonstrates T2W hyperintensity and postgadolinium enhancement (not seen with NMC).

Based on these clinicoradiologic observations and the fact that NMC and NMC-DTF can have identical *CTNNB1* exon 3 mutations,¹⁹ we have argued that NMC-DTF most likely arises from a “primed” *CTNNB1*-mutated (myo)fibroblast population within or adjacent to the peripheral nerve sheath of the NMC-affected nerve segment, and is triggered by tissue trauma to proliferate and manifest as NMC-DTF.¹⁹ In support of this hypothesis, we have previously detected *CTNNB1*-mutated soft tissue adjacent to an NMC (with no histologic evidence of contemporaneous NMC-DTF).¹⁴ Herein, all 7 cases of biopsy-

proven NMC-DTF contained *CTNNB1* mutations, and arose in soft tissues surrounding the NMC-affected peripheral nerve segment. These data support our hypothesis that the beta-catenin/Wnt pathway is implicated in the pathogenesis of NMC-DTF. Similarly, sporadic DTF frequently contains the same somatic activating mutations in exon 3 of *CTNNB1* and the disease pathogenesis is attributed to aberrant activation of the beta-catenin/Wnt signaling.¹⁵ In addition to patient age, tumor size and anatomic site of DTF, *CTNNB1* mutational subtypes have been associated with prognosis and recurrence risk in sporadic DTF (specifically, *CTNNB1* p.S45 mutations and more clinically aggressive DTF^{16-18,23,24}). This is an important observation as the natural history of sporadic DTF is quite variable and up to 20% to 30% of cases may spontaneously regress.¹⁸

Due to the variable clinical behavior of sporadic DTF, treatment modalities range from active observation to surgery, radiation, systemic and chemotherapy.¹⁶⁻¹⁹ Consensus-based

guidelines for sporadic DTF recommend a front-line conservative “watch and wait” approach for 1 to 2 yr, with surgery or medical therapy only with imaging-based evidence of progression.²⁵ Among medical treatments, a clinical trial of sorafenib demonstrated higher progression arrest rates in patients with advanced or treatment-refractory DTF, including DTF with *CTNNB1* p.S45F mutations.^{20,21} However, studies with sporadic DTF-derived cell lines suggest that *CTNNB1* p.S45 mutations may confer higher resistance to sorafenib, as compared to *CTNNB1* p.T41A mutations.²⁶ *CTNNB1* mutational testing of sporadic DTF is now recommended to identify patients who are more likely to have local recurrence²⁵; but there are insufficient data to determine whether *CTNNB1* mutational status can determine the likelihood of spontaneous disease regression.

In this series, all 7 NMC-DTF harbored *CTNNB1* mutations, and 6 cases had p.S45 mutations with only one case with a *CTNNB1* p.T41A mutation. In contrast, in extra-abdominal sporadic DTF, *CTNNB1* p.T41A is the most frequent variant (50%) and p.S45F is the second most common (30%).^{15,27,28} Thus, although the case number is small in this series, the high number of cases with *CTNNB1* p.S45 mutations (6/7 cases) compared to *CTNNB1* p.T41A mutations (1/7) suggests that *CTNNB1* p.S45 mutations may be more common in NMC-DTF than sporadic DTF.

With regard to clinical outcomes, among the cases with follow-up, all had *CTNNB1* p.S45X mutations and showed aggressive clinical behavior. The one patient with NMC-DTF with a *CTNNB1* p.T41A was lost to follow-up. Five cases locally recurred following wide local excision of NMC-DTF, requiring either adjuvant radiation therapy or systemic therapy to achieve disease stabilization. With respect to novel treatments for DTF, one patient who progressed after vinblastine and methotrexate therapy initially showed evidence of disease stabilization with sorafenib, but local disease progression occurred at 2-yr follow-up. No case had spontaneous growth arrest, and one patient developed a second, anatomically distinct, metachronous NMC-DTF (Table; case 2) (both NMC-DTF contained the same *CTNNB1* p.S45P mutation). In contrast, in the one report of multifocal sporadic DTF with confirmed *CTNNB1* status, the 2 DTF had different *CTNNB1* mutations and were considered nonclonal.²⁹

As all cases of NMC-DTF with clinical follow-up had *CTNNB1* p.S45 mutations, but also occurred predominantly in younger patients and all involved the sciatic nerve-innervation territory, we cannot unequivocally ascribe the aggressive clinical behavior in NMC-DTF to the presence of *CTNNB1* p.S45 mutations. In sporadic DTF, younger patient age, tumor size and involvement of an extremity are independent adverse prognostic factors³⁰ and this may also be true for NMC-DTF. Moreover, most patients in this series did not undergo active observation, and thus, we cannot comment on any association between *CTNNB1* mutational status and the lack of spontaneous regression of NMC-DTF in this series. Nevertheless, these data indicate that NMC-DTF has a high frequency of *CTNNB1* p.S45

mutations and shows a proclivity for local recurrence requiring adjuvant radiation of chemotherapy for disease stabilization. Similarly, 3 published cases of NMC-DTF arising in association with NMC of the brachial plexus or sciatic nerve recurred multiple times after resection, ultimately resulting in forequarter or lower-limb amputation.^{1,3,9,31} These reports predated availability of molecular *CTNNB1* testing, and the patients did not receive contemporary treatment protocols. Based on these observations, we now use serial imaging to monitor all patients with NMC for early development of NMC-DTF. In addition to MRI, NMCs are [18F]fluorodeoxyglucose-avid on positron emission tomography-computed tomography and will show one or more direct points of contact with NMC-DTF.³²

Given the aggressive behavior of NMC-DTF, an additional important consideration is under-recognition of NMC-DTF in patients with subclinical NMC, who were misdiagnosed with “sporadic” DTF. In this series, 2 patients presented initially with manifestations of NMC-DTF rather than NMC. One patient was initially diagnosed with sporadic DTF and an NMC was identified only in retrospect. This case was among 3 NMC-DTF with imaging evidence of occult NMC in review of 22 “sporadic” DTF.¹³ While this observation requires confirmation in a larger retrospective series of DTF, these findings do suggest that NMC-DTF may be under-recognized or misdiagnosed as sporadic DTF in a subset of patients. In light of the aggressive behavior of NMC-DTF and the potential for multifocality along the NMC, clinical examination for features of NMC (eg, limb length discrepancy, foot drop) and MRI review for an underlying or occult NMC may be a consideration for young patients who present with “sporadic” DTF of the sciatic nerve territory. We now typically perform *CTNNB1* mutation testing in diagnostic biopsies or excisional specimens of DTF, albeit sporadic or NMC-DTF, both to confirm nonsyndromic, sporadic DTF (which almost universally has mutations in *CTNNB1*) and to identify the subset of patients who may have a more aggressive clinical course. As both sporadic DTF and NMC-DTF express estrogen receptor beta,¹⁹ and sporadic DTF can show accelerated disease progression in patients exposed to estrogen (eg, pregnancy), it will be of future clinical interest to determine whether the *CTNNB1* mutational status impacts progression of sporadic DTF or NMC-DTF in patients with estrogen exposure.

Limitations

While this series is limited by its modest size and relatively short clinical follow-up in a subset of cases (which may impact the clinical outcome data), it is the most comprehensive series available. We acknowledge the referral bias of symptomatic patients presenting with neuropathy of unknown etiology (NMC), most frequently involving the sciatic nerve. Due to the rarity of NMC and NMC-DTF, it is not well established how many patients develop NMC-DTF after biopsy vs those with radiologic diagnoses and conservative management. In the literature, development of NMC-DTF appears to be less than 50% of

patients with NMC; however, these individual case reports have short follow-up, and lack genetic testing or tissue review. It will be interesting to determine the prevalence of “spontaneous” NMC-DTF in patients diagnosed with NMC radiologically and treated conservatively at long-term follow-up.

CONCLUSION

Our data demonstrate that NMC-DTF of the sciatic nerve frequently contain *CTNNB1* p.S45 mutations, and behave aggressively with high local recurrence rates following excision, requiring adjuvant radiation or systemic therapies for disease stabilization. Together, these findings underscore the importance of an imaging-based approach for the diagnosis of NMC to prevent biopsy-triggering or possible growth acceleration of NMC-DTF, and the utility of imaging surveillance to monitor for clinically occult or early NMC-DTF.

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COMMENT

This paper is a logical extension of the authors' prior work on neuromuscular choristomas (NMC) and their likelihood (80%) of triggering adjacent desmoid fibromatosis (DF). In the seven patients reported here, all with NMC in the sciatic nerve, five developed DF after biopsy and two without prior biopsy; all had CTNNB1 gene mutation. I tend to agree with the authors' suggestion that avoiding biopsy may reduce the risk of NMC-associated DF. However, the presence in the series of 2 patients in whom DF developed without any surgical disturbance of the NMC makes one wonder to what degree biopsy is the true driver of DF formation vs such other possible factors as patient gender, NMC size, anatomical location, or mutational profile. No direct comparison as yet has been done of the risk of developing DF after biopsy vs. developing it after observation alone. Since the radiological appearance of NMC has been described as essentially pathognomic of that tumor type, it seems logical to avoid biopsy given the likelihood it will trigger DF and impose additional difficulty in lesion removal and

freedom from recurrence.^{1,2} Although interesting (and mirroring data already published for sporadic DF), the authors' association of p.S45X mutations in the CTNNB1 gene with exuberant growth of DF near an NMC does not prove that such mutations are a necessary precondition for DF linked to NMC. That would require knowing whether the 20% of patients who do not form DF after biopsy also carry similar mutations.

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