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When biopsy goes wrong: a case series of misdiagnoses and complications from biopsies of masses of unknown origin potentially originating from a peripheral nerve

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OBJECTIVE Biopsies of peripheral nerve tumors (PNTs) are often used to plan an efficient treatment strategy. However, performing a biopsy is controversial when the mass is likely to be a benign PNT (BPNT). The aim of this study was to evaluate the side effects of biopsies in patients with potential PNTs.

METHODS A retrospective and cross-sectional study was conducted on 24 patients who underwent biopsy of a mass of unknown origin potentially originating from a peripheral nerve (MUOPON), performed in nonspecialty services, and who were later referred to the authors' service for resection of their lesion between January 2005 and December 2022. The patients were evaluated for pain score, presence of a motor or sensory deficit, biopsy diagnosis, and definitive histopathological postsurgical diagnosis.

RESULTS The location of the tumor was supraclavicular in 7 (29.2%) patients, in the axillary region in 3 (12.5%), in the upper limb in 7 (29.2%), and in the lower limb in 7 (29.2%). Twenty-one (87.5%) patients were evaluated by MRI before biopsy, and 3 (12.5%) underwent ultrasound. One patient did not have an examination before the procedure. Based on the biopsy findings, 12 (50%) analyses had an inconclusive histopathological result. The preexisting pain worsened, as measured 1 week after biopsy, in all patients and had remained unchanged at the first evaluation by the authors (median 3 months, range 2–4 months). In 1 case, the open biopsy had to be interrupted because the patient experienced excruciating pain. Four (16.7%) patients developed motor deficits. Subsequent surgery was hampered by scar formation and intratumoral hemorrhage in 5 (20.8%) patients. The initial diagnosis obtained by biopsy differed from the final histopathological diagnosis in all patients, of whom 21 (87.5%) had BPNTs, 2 (8.3%) malignant peripheral nerve sheath tumors, and 1 (4.2%) an ancient schwannoma.

CONCLUSIONS Biopsies of PNTs are controversial and may result in misdiagnosis, neuropathic pain, or neurological deficit due to axonal damage, and they may also hinder microsurgical resection when if performed when not indicated. Indications for biopsy of an MUOPON must be carefully considered, especially if BPNT is a possible diagnosis.

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KEYWORDS biopsy; malignant peripheral nerve sheath tumor; MPNST; benign peripheral nerve tumor; BPNT; soft-tissue neoplasms

ABBREVIATIONS BPNT = benign PNT; ENMG = electroneuromyography; FNA = fine needle aspiration; MPNST = malignant peripheral nerve sheath tumor; MUOPON = mass of unknown origin potentially originating from a peripheral nerve; PNT = peripheral nerve tumor; STM = soft-tissue mass; VAS = visual analog scale.

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Soft-tissue masses (STMs) may depict a manifestation of neoplasms such as a peripheral nerve tumor (PNT), a pathological entity that could be benign or malignant in nature, each of which poses distinct morphological characteristics and clinical signs. PNTs may manifest as a palpable lump with or without paresthesia, are generally painless, and sometimes present with a neurological deficit due to compression or tissue infiltration, which distinguishes them from masses that are located remotely from nerves.[1–3] The differential diagnosis of PNTs includes benign peripheral nerve sheath tumors such as schwannomas, neurofibromas, and perineuriomas, as well as malignant peripheral nerve sheath tumors (MPNSTs).[4,5]

Diagnostic information on whether an STM is benign or malignant is crucial when planning treatment.[6,7] For instance, internal debulking to preserve nerve function can be performed in the setting of a neurofibroma. In MPNSTs, however, tumor spillage should be avoided and total resection, including the nerve from which the lesion originated, should be performed, thereby deliberately sacrificing function. Noninvasive diagnostic examinations such as ultrasound, MRI, and MRI tractography can be used to differentiate an extrinsic mass (although in contact with the peripheral nerve trunk) from a mass intrinsic to the nerve.[8] However, even with modern imaging techniques, distinguishing between benign and malignant tumors is not always possible.[9–11]

The efficacy and necessity of biopsies prior to surgical excision, as an adjunct to imaging, is not always straightforward.[12] If the mass appears to be a clinically benign PNT (BPNT), biopsy is not always warranted.[6,8,9,13] In general, however, when an STM is symptomatic, presenting with worsening pain or motor deficit, > 3 cm, or growing rapidly, it is more likely to require a biopsy.[7] Both percutaneous (fine needle aspiration [FNA] or core needle biopsy) and open biopsy image-guided procedures may be used.[14] Even though the histopathological diagnosis of the mass has significant value for decision-making, the accuracy of these techniques is unclear.[12,15,16]

Here we introduce the term "mass of unknown origin potentially originating from a peripheral nerve" (MUOPON) to refer to all STMs that could have a neuronal origin. We evaluated a group of patients who underwent biopsy of their lesions elsewhere and performed a detailed study of the misdiagnoses and complications found. Additionally, we evaluated the negative impact of biopsy on the treatment of BPNTs.

Methods

We retrospectively reviewed the clinical records of 279 patients with MUOPON treated at our center between January 2005 and December 2022, of whom 24 (8.6%) patients had a biopsy prior to referral to our hospital for resection. We analyzed the clinical data of each patient, the biopsy result, and the definitive postsurgical histopathological result. The data collected for our patient cohort included age, sex, clinical presentation, mass location, and complementary examinations performed before the biopsy.

At admission, we performed a complete neurological examination in all patients. In addition, we performed complementary examinations such as MRI, ultrasound, and electroneuromyography (ENMG). Pain scores were documented before and 1 week after biopsy, and at the first evaluation with us, and then classified on a 10-point visual analog scale (VAS).[17] Muscular strength at referral was graded according to the British Medical Research Council classification regarding the specific muscles innervated by the affected nerve.[18] During surgery, loss of cleavage plane, scar formation, or intratumoral hemorrhage encountered in the track of the previous biopsy were documented. This study was approved by the Ethics and Research Committee of our institution.

Results

Data on clinical presentation, tumor location, demographic information, and imaging examinations prior to the biopsy are depicted in Table 1. The mean age of our patients was 41.04 years (median 40 years, range 16–61 years), and 14 (58.3%) patients were female. Fifteen (62.5%) lesions were located on the right side. The location of the mass was supraclavicular in 7 (29.2%) patients, in the axillary region in 3 (12.5%), in the upper limb in 7 (29.2%), and in the lower limb in 7 (29.2%). All patients presented with a palpable mass, and 17 (70.8%) reported pain prior to their first biopsy. Before the biopsy, 21 (87.5%) patients were evaluated by MRI, 9 (37.5%) patients underwent ENMG, and 3 (12.5%) patients had ultrasound. All patients underwent MRI after referral to our institution (Fig. 1).

The preoperative biopsy technique, its diagnosis, and the final histopathological diagnosis based on the tissue obtained during surgery at our institution are shown in Table 2. The preoperative biopsies were either open (70.8%) or done by FNA (33.3%). The biopsy-based diagnosis provided by the referring institution was considered conclusive in only 10 (41.7%) patients: 4 (16.7%) with schwannomas, 3 (12.5%) with neurofibromas, 1 (4.2%) with an MPNST, 1 (4.2%) with a lipoma, and 1 (4.2%) patient with neuritis. One (4.2%) patient had a presumptive diagnosis of lipoma. The remaining 13 (54.2%) patients lacked a conclusive report. The final diagnoses from surgical specimens were discordant in all 10 patients; a definitive histopathological diagnosis was obtained in the remaining 14 cases. In total, there were 12 (50%) schwannomas, 5 (20.8%) neurofibromas, 2 (8.3%) lipomas, 2 (8.3%) MPNSTs, 1 (4.2%) ancient schwannoma, 1 (4.2%) liposarcoma, and 1 (4.2%) desmoplastic small round cell tumor.

Pain scores prior to and 1 week after biopsy, as well as iatrogenic motor deficits, are summarized in Table 3. The median time between biopsy and pain evaluation was 3 months (range 2–4 months). After biopsy, all patients reported new-onset pain or a worsening of preexisting pain that had remained unchanged by the time of their first evaluation with us. The median VAS score before the procedure was 2.5 (range 0–6) and increased to 7.8 (range 5–9) after the procedure. Four (16.7%) patients developed motor deficits following the biopsy. Perineural and intratumoral hemorrhage (Figs. 2 and 3) and fibrosis, which hindered dissection of the planes, were identified during

TABLE 1. Patient demographics, clinical presentation, lesion location, and complementary examinations done before biopsy

Patient No.	Age, yrs	Sex	Clinical Presentation	Lesion Location	Complementary Exams
1	61	F	Mass & pain	Rt supraclavicular	MRI
2	48	F	Mass & pain	Lt supraclavicular	MRI
3	43	F	Mass	Rt supraclavicular	MRI
4	49	M	Mass & pain	Rt axillary	MRI
5	52	F	Mass & pain	Rt proximal arm	MRI/US/ENMG
6	40	F	Mass & pain	Rt lower limb	MRI/ENMG
7	41	M	Mass & pain	Rt supraclavicular	MRI/ENMG
8	52	F	Mass & pain	Rt thigh	MRI/ENMG
9	36	M	Mass	Rt axillary	MRI
10	38	F	Mass	Rt distal arm	MRI/ENMG
11	39	M	Mass & pain	Lt lower limb	MRI/ENMG
12	49	F	Mass & pain	Lt distal arm	US
13	32	M	Mass & pain	Rt supraclavicular	MRI
14	37	M	Mass & pain	Rt proximal arm	MRI
15	40	F	Mass & pain	Lt axillary	MRI
16	35	F	Mass	Lt proximal arm	*
17	16	F	Mass & pain	Rt lower limb	MRI
18	35	M	Mass & pain	Rt distal arm	Bad-quality US
19	43	F	Mass & pain	Rt supraclavicular	MRI
20	34	F	Mass	Lt lower limb	MRI/ENMG
21	39	F	Mass & pain	Lt supraclavicular	MRI
22	49	M	Mass & pain	Lt distal arm	MRI/ENMG
23	45	M	Mass	Rt thigh	MRI/ENMG
24	32	M	Mass	Lt thigh	MRI/ENMG

US = ultrasound.
* Patient 16 did not have any complementary examination performed before biopsy.

surgery in 5 (20.8%) patients, 2 of whom developed a new motor deficit.

Discussion

We studied the inaccurate diagnosis and clinical consequences of biopsies performed in patients with an MUOPON. All our patients had undergone a biopsy at nonspecialized centers and were subsequently referred to our hospital for further surgical treatment. Our overall findings in this series were that biopsy of an MUOPON had little to no benefit. Furthermore, biopsies were associated with several adverse consequences, including misdiagnosis that delayed the best approach to each specific pathology, new-onset or increased pain, motor deficits, and fibrosis and/or hemorrhage that hindered proper resection with preservation of neurological function. It has been our observation that these iatrogenic consequences are undervalued, but they should play a role in planning the best approach to an unknown lesion.

Physicians who treat patients with an STM should keep in mind that the differential diagnosis includes PNTs.[19,20] The clinical presentation and management may be different from those of STMs.[5,6,11] Patients with a PNT may be asymptomatic or have a variety of symptoms, ranging

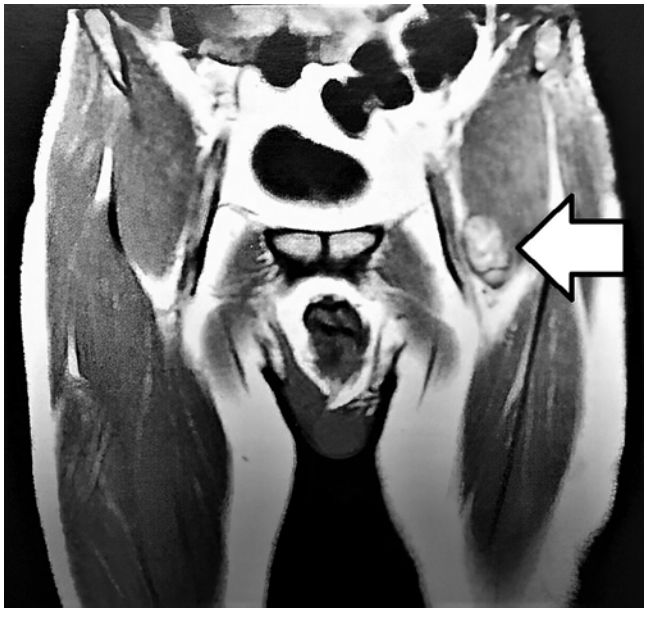

FIG. 1. Patient 24. T2-weighted MR image of the pelvis showing a hyperintense mass on the path of the left femoral nerve (*white arrow*).

TABLE 2. Type of biopsy, biopsy diagnosis, and postsurgical histopathological diagnosis

Patient No.	Type of Biopsy	Biopsy Diagnosis	Postop Histopathological Diagnosis
1	Open	Schwannoma	MPNST of rt brachial plexus
2	FNA	MPNST	Schwannoma of lt brachial plexus
3	Open	Inconclusive	Neurofibroma of rt brachial plexus
4	FNA	Inconclusive	Schwannoma of rt ulnar nerve
5	Open	Inconclusive	Lipoma adhered to rt radial nerve
6	Open	Inconclusive	Schwannoma of rt peroneal nerve
7	Open	Schwannoma	Neurofibroma of rt brachial plexus
8	Open	Lipoma	Liposarcoma adhered to rt femoral nerve
9	Open	Neurofibroma	Schwannoma of rt median nerve
10	FNA	Neuritis	Schwannoma of rt median nerve
11	Open	Schwannoma	Neurofibroma of lt peroneal nerve
12	Open	Inconclusive	Intraneural lipoma of lt median nerve
13	Open	Inconclusive	Schwannoma of rt brachial plexus
14	Open	Schwannoma	Neurofibroma of rt proximal arm
15	Open	Inconclusive	DSRCT of lt brachial plexus
16	Open	*	Neurofibroma of medial cutaneous nerve
17	FNA, then open	Inconclusive	MPNST of rt femoral nerve
18	Open	Probable lipoma	Schwannoma of rt radial nerve
19	FNA	Inconclusive	Schwannoma of rt accessory nerve
20	FNA	Inconclusive	Schwannoma of lt lumbosacral plexus
21	Open	Inconclusive	Schwannoma of lt brachial plexus
22	FNA	Neurofibroma	Schwannoma of lt radial nerve
23	Open	Inconclusive	Schwannoma of rt sciatic nerve
24	FNA	Neurofibroma	Ancient schwannoma of lt sciatic nerve

DSRCT = desmoplastic small round cell tumor.
* The biopsy was interrupted due to the patient experiencing excruciating pain.

from tingling sensations to pain of different grades and neurological deficits, which hamper the diagnosis.[1,2] In patients presenting with severe nocturnal or continuous excruciating pain, Tinel's sign, or a rapidly growing mass that is adherent to deeper tissues, there should be a high level of suspicion for malignancy, mostly in patients with neurofibromatosis type 1.[1,8,21] In our series, the majority of patients experienced pain, but it was mostly mild. Therefore, our clinical suspicion of malignancy, based only on the patient's pain, was generally quite low.

Noninvasive diagnostic procedures have shown high value in the diagnostic workup of PNTs.[10,22] MRI can be used to accurately diagnose schwannomas up to 91% of the time.[8] Ultrasound is becoming a valuable first low-cost screening technique.[23] Biopsy is a relatively complex procedure in the staging process that should be performed carefully, in specific situations, and with prior imaging.[24] When lesions identified on imaging suggest a differential diagnosis of PNT, we propose using the flowchart shown in Fig. 4 for determining whether a biopsy is indicated.

Masses > 5 cm in maximum diameter require histological evaluation, although some have argued that tumors as small as 3 cm also warrant histological evaluation. The currently available literature is inconclusive regarding a cutoff size for determining when to perform a biopsy, and further studies are needed.[7] Rapid growth, invasion of surrounding tissue, neurological deficits, and considerable pain should raise suspicion for malignancy, and hence are indications for a biopsy. Small masses that do not exhibit noticeable growth and are superficially located, painless, solitary, and not adherent to the deep fascia have a low probability of being malignant.[25] These can be managed with a wait-and-scan policy.[26] PET/CT can be used as an adjunct imaging procedure if the clinical and MRI findings are unclear.[27,28] In addition to these criteria, Martin et al. proposed that 40% of all biopsies may be avoided in the presence of a target sign and in the absence of ill-defined margins, perilesional edema, or signs of bleeding on MRI, all of which make the diagnosis of MPNST more likely.[29]

The precise identification of a PNT can be challenging when there is insufficient tissue, a lack of specific morphological criteria, the absence of an experienced neuropathologist, or any combination of these.[5,30,31] Our study is the first to discuss the misdiagnosis of MUOPON based on biopsies, because all our patients had either an inconclusive or erroneous diagnosis based on their examination. Misdiagnosis may lead to the need for a new biopsy procedure or to nononcological management for lesions that are actually malignant.

The literature is controversial regarding the diagnostic accuracy of biopsy. Pendleton et al.[32] reported that they were unable to attain precise results from biopsies for

TABLE 3. Pain scores before and after biopsy and motor deficits developed within 1 week after biopsy

Patient No.	VAS Score Before Biopsy	VAS Score After Biopsy	Difference in Score Btwn Before & After Biopsy	Motor Deficit After Biopsy*	Hemorrhage & Loss of Cleavage Planes
1	5	8	3	–	–
2	2	9	7	–	–
3	0	8	8	–	–
4	6	9	3	–	–
5	6	9	3	Radial nerve: M2	+
6	4	8	4	–	–
7	4	8	4	–	–
8	2	8	6	Leg extension: M4	–
9	0	8	8	–	+
10	0	8	8	–	–
11	2	8	6	Foot extension: M2 (at least)	–
12	1	9	8	–	–
13	2	8	6	–	–
14	5	9	4	–	–
15	4	9	5	Upper trunk: M3	+
16	0	8	8	–	–
17	4	6	2	–	–
18	5	6	1	–	–
19	1	7	6	–	+
20	0	7	7	–	–
21	3	8	5	–	–
22	4	9	5	–	–
23	0	6	6	–	–
24	0	5	5	–	+

– = absent; + = present.
* Graded according to the British Medical Research Council classification.

21.9% of the patients with MPNST in their series, which was the largest complication in their work, and Ogose et al.[33] observed that of 30 patients with PNTs, 7 (23.33%) received an incorrect diagnosis after biopsy, and the procedure most associated with misdiagnosis was FNA. On the other hand, Graham et al. found that malignancy was accurately identified in 94% of their samples after image-guided core needle biopsy was performed.[34] In the present study, all our patients had an incorrect or inaccurate diagnosis based on the material collected from the biopsy, preventing correct management or any treatment at all.

Incorrect diagnosis of an STM by biopsy may hinder optimal patient management. For example, an MPNST may be misclassified as a sarcoma.[19,35] The former classification of MPNSTs as sarcomas is currently being discussed, because these two entities have different cellular lineages and thus may require different treatment modalities.[5,35] The authors of a French study observed that 18.1% of their sample with an initial diagnosis of MPNST were reclassified as having other pathologies, including some type of BPNT, such as a neurofibroma and perineurioma.[36] In our study, one patient had an initial diagnosis of MPNST that was actually a schwannoma, another patient had an initial diagnosis of a lipoma that was actually a liposarcoma (Fig. 5), and a third patient had an initial diagnosis of neurofibroma that was later diagnosed as an ancient schwannoma. Meanwhile, 2 (8.3%) patients were given initial results of schwannoma and inconclusive, but after resection an MPNST was identified. These inaccuracies may increase the risk of worse outcomes, delay gross-total resection and radiotherapy in cases of malignancy, and increase the psychological burden of patients who have a benign lesion instead of a malignant one.

FNA has been associated with an overall accuracy of 16.6%–52.73% for MPNSTs, with particularly low rates for primary tumors (7.7%–30%), which makes its preoperative use controversial.[15,16] Combining biopsy methods with in-time imaging examinations is associated with better diagnostic accuracy but harbors risks, as observed in a CT-guided core needle biopsy series of 41 patients with PNTs that found that temporary pain exacerbation was induced in 12% of cases assessed 1 day later.[26] Worsening of neuropathic pain has been reported as a complication even after MRI-guided percutaneous biopsy of a PNT.[25] New targeted fascicle MRI-guided biopsy techniques are being developed with promising results, but experience with le-

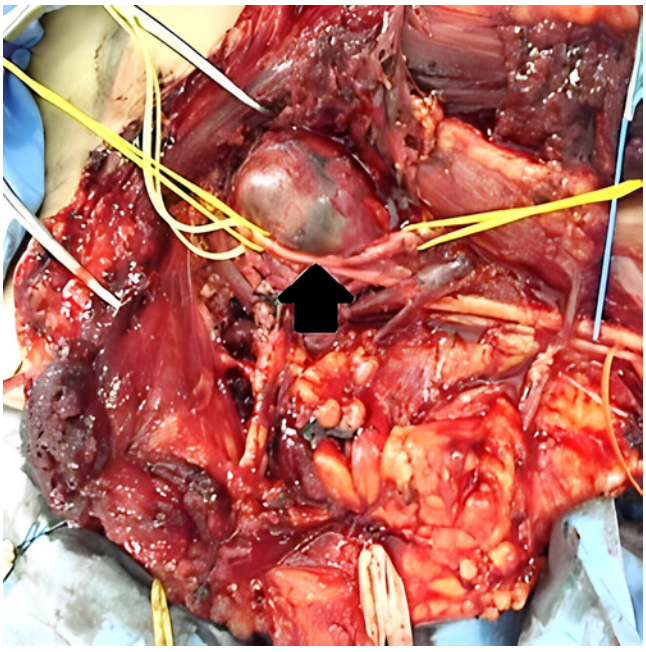

FIG. 2. Patient 9. Intraoperative photograph during axillary access to the lesion, showing an area of intratumoral hemorrhage at the biopsy site (*black arrow*). Figure is available in color online only.

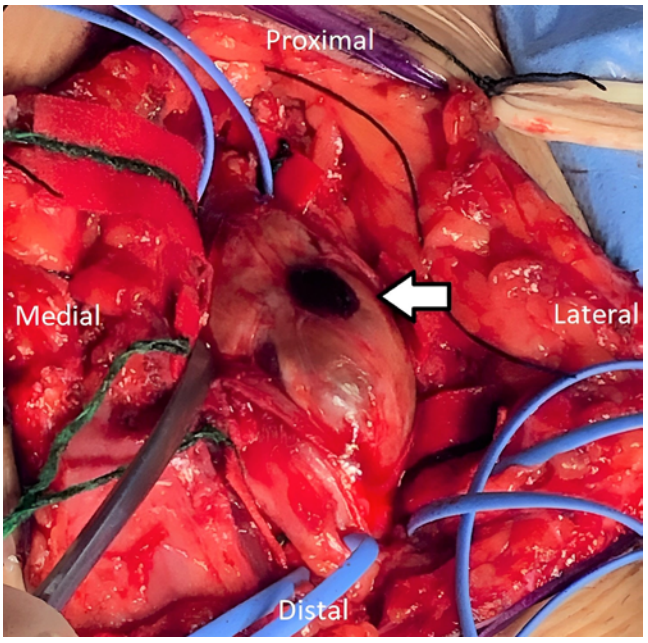

FIG. 3. Patient 24. Intraoperative photograph showing an area of intratumoral hemorrhage at the biopsy site, left of femoral nerve, limited by the blue vessel loops (*white arrow*). Figure is available in color online only.

sions affecting the peripheral nerve is still scarce.[37,38] The introduction of diffusion tensor imaging to detect the location of nerve fascicle bundles crossing the tumor might reduce iatrogenic nerve damage and improve the safety of biopsy procedures.[30]

From the scarce literature covering this topic, we conclude that our findings are in line with those of others regarding neurological deficit and pain after a biopsy without a precise indication and technique.[4,39] In our study, 4 (16.7%) patients had a new-onset motor neurological deficit after the procedure, none of whom had a malignant lesion, corroborating the questionable benefit of biopsies of suspected benign masses. Furthermore, we also observed that all our sample had new-onset or worsening pain, with a mean VAS score of 7.8 after the biopsy, that remained until complete resection of the tumor was achieved. Levi et al.[39] found that patients with a PNT who underwent a biopsy before surgery had a significantly higher risk of neurological deficits after subsequent tumor resection, and in the study by Perez-Roman et al., 42.9% of patients had a new or worse neurological deficit following a biopsy.[28] Meanwhile, Pendleton et al. observed that only 9.5% of their patients had a decline in neurological function, and that almost all of them presented with transient pain.[32] In another report, the incidence of lost function after surgery was considerably higher for both schwannomas and neurofibromas for which a biopsy was performed.[4] The odds of developing sensory loss or motor deficits in PNT patients who undergo a biopsy compared with those who do not has been estimated to be 2.7 ($p < 0.001$).[39] Occasionally, even graft repair has been required.[40]

The indications of biopsy are well documented, mostly when a malignancy is suspected, but the removal of tissue for analysis in cases of a probable benign masses is controversial. Our experience, as well as that of other authors, indicates that the risks of iatrogenic nerve damage and misdiagnosis are considerable and should be balanced with any potential benefits.[4,28,30,39] All our patients reported worse pain within 1 week after biopsy that remained until resection, a finding that goes against the literature that affirms this manifestation is transient in almost all cases.[32,33] Given this fast deterioration, it is probable that identification of nerve fascicles was not performed during biopsy and axonal damage occurred, leading to neuropathic pain.[41] All patients had some degree of fibrosis, but what was extremely unexpected was that dissection of the planes was hindered in only 20.83% of those patients, who needed delicate removal of the tumor and tissue, since the most frequently performed technique was open biopsy.

Our work has some limitations. First, our sample size was relatively small and heterogeneous. Furthermore, biopsy is a skill-dependent procedure. Thus, it would be inappropriate to generalize our results to all STMs that undergo biopsy. The use of invasive procedures for diagnosis and the documentation of unwanted side effects, such as those found in our patients, should be monitored in larger groups of patients with various types of MUOPONs. Second, our follow-up period was relatively short, and some of the iatrogenic complications (e.g., pain) may have subsided or resolved over time. Lastly, objectively quantifying pain is not currently feasible. However, the VAS for pain has been used repeatedly in prior studies and has been shown to correlate with other pain ratings.[17] Further studies comparing patients surgically treated for MUOPON who underwent biopsy, versus those who did not, may help to solidify and validate the indications for biopsy.

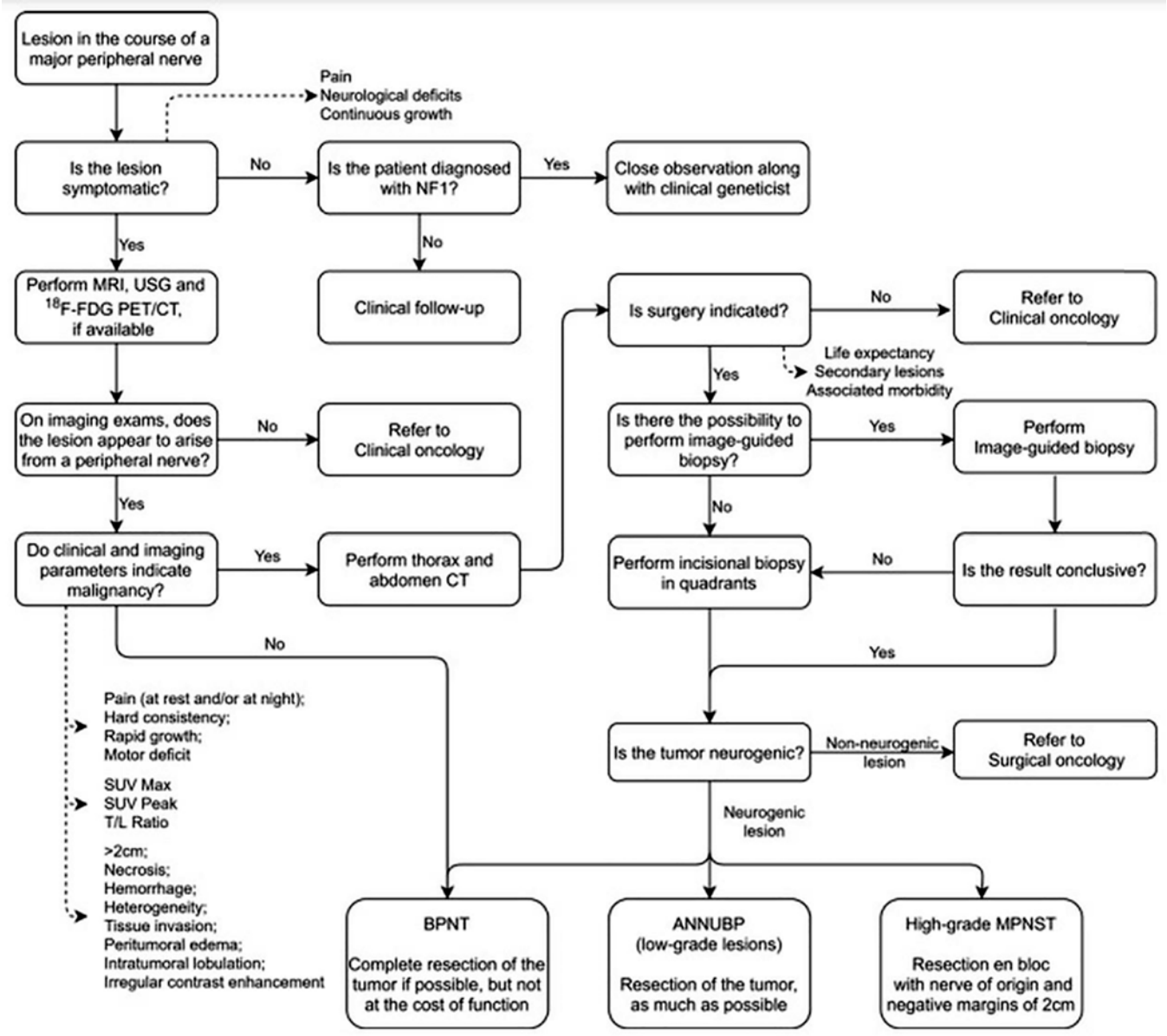

FIG. 4. Flowchart showing our recommendations for the management of MUOPON. ANNUBP = atypical neurofibromatous neoplasm with unknown biological potential; NF1 = neurofibromatosis type 1; SUV = standardized uptake value; T/L = tumor/liver ratio; USG = ultrasonography. Reprinted by permission from Springer Nature Customer Service Center GmbH: Springer Cham, *Diagnostic Assessment and Treatment of Peripheral Nerve Tumors* by F Guedes, EL Zager, D Garozzo, L Rasulic, M Socolovsky, eds. © Springer Nature Switzerland AG 2021 (https://link.springer.com/book/10.1007/978-3-030-77633-6).

Conclusions

The biopsy of any PNT is questionable and may increase the burden of a patient with a painful and palpable mass if performed when not indicated. Patients who undergo a biopsy for a PNT have an increased risk of misdiagnosis, neurological deficits, worsening of pain, and local hemorrhage or loss of cleavage planes, making the surgical intervention more technically demanding and troublesome and increasing the risk of clinical worsening and incomplete resection. To best evaluate and minimize the potential injuries of biopsies and increase the accuracy of the histopathological analysis, all patients should undergo imaging examinations such as MRI or ultrasound because excising a lesion fragment that could be part of or in proximity to a peripheral nerve is extremely dangerous. Physicians should be aware of these risks whenever determining that a biopsy should be performed for a presumed PNT, as well as remember that the presence of an experienced pathologist for cases of STM or PNT greatly increases a patient's chance of attaining an optimal outcome. Biopsies of MUOPONs should not be performed at nonspecialized centers or in the absence of both a prior imaging examination and a specialist consultation before the procedure.

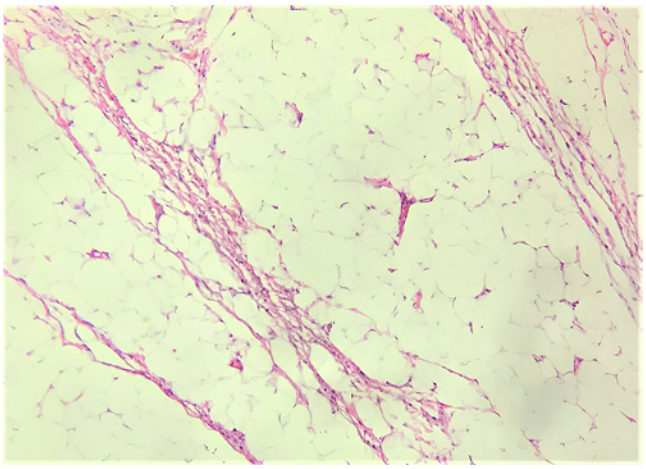

FIG. 5. Liposarcoma. Some atypical adipocytes show variation in size, in addition to bands of the fibrotic stroma. H&E, original magnification ×100. Figure is available in color online only.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Guedes, Henriques, Sanches, Barbosa, Malessy. Acquisition of data: Guedes, Henriques, Torrão, Haikal. Analysis and interpretation of data: Guedes, Henriques, Haikal, Sanches, Marsicano, Siquara, Malessy. Drafting the article: Guedes, Henriques, Sanches, Barbosa, Marsicano, Rosa, Malessy. Critically revising the article: Guedes, Henriques, Torrão, Sanches, Barbosa, Marsicano, Siquara, Malessy. Reviewed submitted version of manuscript: Guedes, Barbosa, Siquara. Approved the final version of the manuscript on behalf of all authors: Guedes. Statistical analysis: Guedes, Henriques. Administrative/technical/material support: Guedes, Torrão, Sanches. Study supervision: Guedes. Lead surgeon: Guedes.

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