Peripheral nerve fibromyxoid sarcoma

Case report

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Low-grade fibromyxoid sarcoma (LGFMS) is a rare soft-tissue neoplasm with metastatic potential and needs to be recognized as such, because it can be mistaken for other types of sarcoma due to its unremarkable appearance. This 49-year-old man presented with an approximately 5-cm mass on the anteromedial aspect of his left thigh that slowly increased over 10 years. Clinical symptoms were limited to local discomfort and intermittent distal numbness. Due to the location, imaging findings, and lack of serious symptoms, the initial differential diagnosis favored a schwannoma. An initial biopsy revealed histopathological findings consistent with a perineurioma, although with atypical features. The patient elected to have the mass excised, and the tumor, which arose from a branch of the saphenous nerve, could be separated well from the surrounding soft tissue. Histopathological investigation of the mass displayed characteristic features of a fibromyxoid sarcoma, which was confirmed by subsequent fluorescence in situ hybridization analysis. Due to concerns about infiltration beyond the margins, radical reexcision was advocated and performed, resulting in definite clear surgical margins. At follow-up, the patient had regained full strength with no residual neurological symptoms or any new deficits. He has since been healthy and disease free for a total of 4 years in follow-up. This case documents, to the authors’ knowledge, the first observation of an LGFMS associated with a peripheral nerve. It also supports the use of fluorescence in situ hybridization analysis as an essential diagnostic method in establishing the diagnosis of LGFMS.

Key Words • peripheral nerve tumor • oncology • prognosis • fibromyxoid sarcoma • fluorescence in situ hybridization

Abbreviations used in this paper: EMA = epithelial membrane antigen; FISH = fluorescence in situ hybridization; LGFMS = low-grade fibromyxoid sarcoma.

Soft-tissue sarcomas embody approximately 0.7% of all systemic cancers, and LGFMS represents only a small fraction of those, making it an exceedingly rare disease.8 Local recurrence and distant metastases have been found in as high as 75% and 58% of reported cases. However, advances in systemic medical treatment have reduced these to 9% and 6%, respectively.6,7 Because of its strikingly innocuous appearance, LGFMS probably remains an underdiagnosed entity because it can be mistaken for other types of benign sarcoma, although there are several distinct immunohistopathological staining patterns and characteristic microscopic morphological features. With the advancement of in vitro diagnostic procedures, recent cytogenetic immunofluorescence methods are now considered the gold standard for LGFMS diagnosis: a bal-
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anced translocation t(7;16)(q32–34;p11) creating a fusion gene FUS/CREB3L2 can be detected with fluorescence in situ hybridization (FISH) with high diagnostic specificity and a sensitivity ranging from 70% to 88%, in the appropriate histological context.3,9,11

We describe a unique clinical scenario of an LGFMS presenting as an indolent mass arising from a peripheral nerve, initially mimicking a benign peripheral nerve tumor. Probably because of tissue heterogeneity, its underlying pathology was initially not correctly diagnosed despite a biopsy procedure. Only its resection and the diligent workup of the specimen after complete excision revealed the underlying pathology of LGFMS associated with a peripheral nerve. It is, to our knowledge, the first such case to be reported in the literature. The likelihood that there is a higher than reported incidence of LGFMS motivated us to report this entity, because LGFMS should be included in the differential diagnosis of patients presenting with an indolent soft-tissue mass associated with peripheral nerves.

Case Report

History. This 49-year-old man initially presented with a large, approximately 5-cm mass on the anteromedial aspect of his left thigh. He reported that it had been slowly enlarging for approximately 10 years. The patient had not noted recent significant changes to the mass, and the only associated clinical symptoms were local discomfort when pressure was exerted on the lesion and some intermittent distal numbness in the saphenous nerve distribution. The patient’s medical history was only notable for hypercholesterolemia, knee arthroscopy, and tonsillectomy.

Examination. A full neurological examination was performed and the results were found to be unremarkable throughout. The painless mass itself was solid, noncompressible, and seemed firmly attached to the surrounding tissue. There was no visible discoloration or skin abnormalities. The Tinel sign was absent.

Neuroradiological Features. An MRI study (Fig. 1) showed a heterogeneous, partially contrast-enhancing 5-cm lesion with decreased intrinsic T1 signal intensity and areas of increased T2 signal intensity. There was heterogeneous contrast enhancement within the lesion and a sharp demarcation from the surrounding tissue. The lesion appeared to be arising off the descending saphenous nerve, whereas the adjacent femoral artery and veins appeared intact.

Due to the location of the mass, characteristics of the MR images, and the patient’s lack of significant clinical symptoms, the initial differential diagnosis favored a probable schwannoma as the underlying neoplasm. An ultrasound-guided needle biopsy was performed at another hospital to confirm the presumed diagnosis of a primary benign peripheral nerve lesion. The initial histopathological interpretation of the biopsy sample was based on standard immunostains, which were reported as positive for epithelial membrane antigen (EMA) and negative for S100 protein. This pattern was considered to be consistent with a perineurioma with some atypical features, and the lesion was consequently signed out as such. The patient continued to be bothered by the mass; he felt a profound “local discomfort” while sitting with pressure being exerted on the lesion, so he elected to have it surgically excised.

Operation. Surgery was performed as a standard peripheral nerve exploration, including direct peripher-

![Fig. 1. Preoperative MRI studies showing the tumor. A: Coronal T1-weighted image. B: Postcontrast coronal T1-weighted image. C: Sagittal T1-weighted image. D: Postcontrast sagittal T1-weighted image. E: Sagittal STIR image. F: Postcontrast axial T1-weighted image with fat suppression technique. G: Postcontrast axial T1-weighted image. H: Axial T2-weighted image.](image-url)
al nerve stimulation and triggered electromyography/spontaneous electromyography monitoring, and was performed after induction of general anesthesia (remifentanil-propofol) without any complications. At the time of surgery, the tumor was grossly found to be well demarcated and clearly came off a small branch originating from the saphenous nerve. It could be separated well from the surrounding soft-tissue layers and was dissected off the muscle, and the mass was sent in toto to the pathology laboratory to confirm the tissue diagnosis.

Pathological Findings

**Gross Pathology.** The specimen was an irregularly shaped, well-circumscribed, multilobulated, pink soft-tissue mass that measured 5.5 × 5.0 × 3.8 cm, with a thin capsule surrounding the mass. When sectioned, the specimen revealed a white, firm, fleshy cut surface. There was a central “cyst” filled with mucoid material as well as several small, blood-filled spaces.

**Microscopic Pathology.** Microscopically, the tumor was composed of a mix of collagenous and well-defined fibromyxoid areas (Fig. 2). The spindle cells were cytoologically innocuous with visible cytoplasmic processes, and the myxoid zones contained increased capillary density. Immunostains were positive for EMA and negative for S100, keratin, actin, and desmin. These results were recognized as features indicative of an LGFMS.

**FISH Analysis.** A FISH analysis was ordered to confirm the microscopy findings and revealed the pathognomonic FUS/CREB3L2 fusion gene caused by an 11:16 translocation. The FISH analysis was performed on interphase nuclei isolated from formalin-fixed paraffin-embedded tissue. The sections were deparaffinized and digestion was performed by collagenase XI (Sigma), followed by trypsin/EDTA (Life Technologies). The cells were spread on positively charged slides, baked, and treated with sodium bisulfite, followed by digestion in proteinase K (pretreatment solution and proteinase K both from Oncor). To detect FUS rearrangement, we used the LSI FUS (16p11) Dual Color, Break Apart Rearrangement Probe (Abbott Molecular/Vysis), which consists of a mixture of 2 FISH DNA probes. The first, an approximately 500-kb probe labeled in SpectrumGreen, lies distal (telomeric) to the FUS gene; the second, an approximately 270-kb probe labeled in SpectrumOrange, extends proximally (centromeric) from the FUS gene. There is a 120-kb gap between the 2 probes. The probes and nuclei were denatured simultaneously on a slide warmer (HYBrite, Abbott Molecular/Vysis), followed by hybridization and washing in formamide/standard saline citrate. At least 50 cells with strong, discrete FISH signals were analyzed. A signal pattern indicative of an FUS gene rearrangement appears as a separation of the red-orange and green signals from the normal fusion signal (yellow) (Fig. 3).

**Diagnosis and Postoperative Course.** The final pathological review revealed an LGFMS, and FISH-cytogenetic analysis confirmed this as the definite and correct diagnosis. Because the tumor extended to the periphery of the mass and had shown only a very thin capsule, there was concern about potential infiltration beyond its margins, which could lead to recurrence and possible metastasis. A radical reexcision was thus suggested by the interdisciplinary tumor board and was performed in a second-stage surgery, resulting in definite clear surgical margins. Adjuvant systemic therapy as well as postoperative radiation or chemotherapy were contemplated, but were put on hold until follow-up images were obtained. Gross-total wide excision was successful, and the margins were negative for any residual tumor. At the 3-month follow-up after radical reexcision the patient had regained full strength in his left lower extremity, with neither residual neurological symptoms nor any new deficits. Because no complications or recurrence have been observed thus far, surgery has remained the only treatment modality for this case. The patient is currently disease free after a total of 4 years of follow-up.

**Fig. 2.** Photomicrograph of tumor specimen showing a hypocellular lesion with areas of dense collagenization that are interspersed with well-circumscribed myxoid zones. The tumor cells are cytoplogically innocuous with long, tapered nuclei. Immunostaining, original magnification ×20.

**Fig. 3.** A FISH analysis image. The interphase nuclei on the left side of the panel show 2 normal fusion signals (yellow), indicative of 2 normal copies of the FUS gene. The interphase nuclei on the right side of the panel show the fusion; 1 orange and 1 green signal the hybridization pattern indicative of a rearrangement of 1 copy of the FUS gene.
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Discussion

A rare, indolent, but distinctive soft-tissue neoplasm with a high potential to form a metastasis, LGFMS is also sometimes referred to as the Evans tumor, which stems from its first description by Evans in 1987. There was initial skepticism whether LGFMS should be considered a distinct entity, but subsequent studies confirmed that its separate recognition was warranted. An LGFMS usually presents as a painless mass and tends to occur in young to middle-aged adults, with a male/female ratio of approximately 3:1; other sources suggest an equal chance of both sexes being affected. Histologically, LGFMS neoplasms characteristically show alternating fibrous and myxoid areas of varying size with deceptively benign-appearing fibroblastic spindle cells; low to moderate cellularity; and a partial to complete swirling, whorled growth pattern. The differential diagnosis includes peripheral nerve sheath tumors, such as neurofibroma and perineurioma, and various myxoid soft-tissue neoplasms, including myxofibrosarcoma and intramuscular myxoma. Although immunohistochemical investigation is very useful in excluding many of these lesions, the pathological diagnosis of this lesion remains difficult due to overlapping histological features; thus, FISH analysis can be a useful diagnostic tool for confirming the diagnosis of LGFMS.

The tumor has been found to metastasize in as many as 5%–10% of cases, and local recurrences are not uncommon but occur usually in less than 10%. Because of these features, long-term survival rates are good, with only an approximately 2% death rate. As for treatment for LGFMS, practitioners advocate radical resection of the tumor with clear margins, and a recent study showed that adjuvant radiation therapy can be used to achieve local control in up to 94% of cases.

To our knowledge, this particular case seems to be the first reported of an LGFMS associated with a peripheral nerve. In our patient, the tumor appeared radiographically to be growing off of the saphenous nerve; this led to the initial diagnosis of a benign peripheral nerve tumor, such as a schwannoma, perineurioma, or neurofibrosarcoma, which are major categories of nerve sheath tumors. A biopsy was performed, but the S100-negative and EMA-positive immunostaining pattern was more consistent with a perineurioma. This was most likely due to the heterogeneous nature of the lesion, yielding a nonrepresentative specimen from the ultrasound-guided biopsy. The final decision to seek complete resection was made by the patient, who was bothered by the lesion. Based on the completely excised specimen, the final pathological investigation revealed the unexpected fibromyxoid regions that led to the correct diagnosis of an LGFMS. When this was confirmed by FISH analysis, a radical compartmental reexcision was performed, which now has substantially improved the patient’s prognosis. Long-term clinical follow-up seems warranted because the tumor does have a potential to recur, and we have advocated sequential studies with dedicated MRI.

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Disclosure

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