Peripheral neurolymphomatosis (NL) is an often-misdiagnosed condition characterized by lymphomatous infiltration within the peripheral nerves. Its rarity and complexity frequently result in delayed diagnosis and suboptimal patient outcomes. This study aims to elucidate the role of the paraneurium (circumneurium) in NL, emphasizing its diagnostic and therapeutic significance.

**OBSERVATIONS** A 72-year-old man presented with lesions on his right lower eyelid. Initial diagnostics were inconclusive until an excisional biopsy confirmed extranodal marginal zone lymphoma. Following a complete metabolic response to rituximab treatment, the patient relapsed 14 months later with progressive lymphoma and bilateral sciatic nerve involvement, as confirmed by positron emission tomography–computed tomography and magnetic resonance imaging.

**LESSONS** This paper underscores the critical role of the paraneurium in NL, enhancing understanding of its pathophysiology. Integrating advanced imaging techniques have proved essential in accurately identifying neurolymphomatous involvement within the paraneurium. This study paves the way for more effective management strategies in NL and similar conditions, focusing on improving patient care and outcomes.

**ILLUSTRATIVE CASE** A 72-year-old male initially presented with two lesions on his right lower eyelid, which had persisted for 1 month. Computed
Tomography demonstrated multiple periorbital soft tissue nodules, but subsequent percutaneous biopsy was nondiagnostic. Subsequent excisional biopsy confirmed extranodal marginal zone lymphoma (MZL). Further investigations, including bone marrow biopsy and positron emission tomography–computed tomography (PET-CT), revealed involvement of the bone marrow, spleen, and lymph nodes above and below the diaphragm. There was also a nodular $^{18}$F-fluorodeoxyglucose (FDG)-avid lesion along the left sciatic nerve, which was thought to be a peripheral nerve sheath tumor at the time. Treatment with rituximab resulted in a complete metabolic response.

Fourteen months later, the patient experienced a relapse, evidenced by progressive right periorbital lymphoma and new FDG-avid superficial soft tissue lesions throughout the trunk on PET-CT. Bilateral sciatic nerve involvement at the bifurcation was noted; therefore, FDG PET-MRI was performed for further evaluation. PET-MRI (Figs. 1 and 2) revealed moderate FDG uptake within both sciatic nerves, with a maximum standardized uptake value of 4.9 on the right and 6.6 on the left. Interestingly, MRI showed thickening of the sciatic nerves with decreased T1 and T2 signal within the subparaneurial space, atypical signal characteristics for NL. Given the lack of calcification on PET-CT, a component of hemorrhage (likely related to treatment) was suspected within the sciatic nerves. Despite these developments, the patient remained asymptomatic with no neurological symptoms.
To clarify the diagnosis of the lower-extremity lesions, which potentially included peripheral nerve sheath tumors, peripheral nerve involvement by MZL, or transformed large cell lymphoma, a targeted fascicular biopsy of the right sciatic lesion was performed. This procedure was crucial due to the significant treatment implications of an NL diagnosis.

Intraoperative findings revealed the distinct paraneurium and associated subparaneurial space, within which tumor involvement affecting the sciatic nerve was evident. The tumor exhibited a blackened appearance, possibly due to intratumoral hemorrhage, and exhibited avid fluorescence (Fig. 2). The sural branch was mobilized (with retrograde internal neurolysis into the sciatic nerve), excised, and examined intraoperatively, displaying fluorescent lymphoma nodules (Fig. 3). Pathological analysis of the excised specimen revealed tumor infiltration across all nerve layers and the presence of a nodule (Fig. 4 and Video 1). The histological evaluation confirmed the patient’s prior diagnosis of MZL (Fig. 5).

**VIDEO 1.** Clip showing dissection of the paraneurium from the sciatic nerve. Click here to view.

**Patient Informed Consent**

The necessary patient informed consent was obtained in this study.

**Discussion**

The intraoperative findings from our case study provide crucial evidence regarding the tumefactive appearance of peripheral NL and its association with the subparaneurial space. The tumefactive appearance, denoted by nerve bundles encased in a tumor within the subparaneurial space, reflects the novel imaging characteristics we previously reported. The distinct presence of the paraneurium as an anatomical space was clearly observed during surgery. These intraoperative images, which we believe are novel, significantly enhance the existing body of knowledge regarding NL and its spread.

**Observations**

Our intraoperative observations and histological confirmations offer pivotal insights into the surgical management of NL cases. The tumefactive appearance, especially at branching sites such as the ones reported here, should raise a high index of suspicion for NL and be surgically targeted for diagnostic confirmation. Biopsy specimens can be strategically obtained from the paraneurial space or minor branches, minimizing procedural morbidity. Additionally, fluorescein visualization of tumor-affected nerve bundles can further guide biopsies, enhancing intraoperative decision making and precision. These
findings align with the surgical management perspectives previously discussed, highlighting the need for targeted approaches in treating NL. These findings emphasize the need to advance imaging techniques, both preoperatively and intraoperatively, to improve diagnostic accuracy and surgical precision in NL cases. Further research is essential to deepen our understanding of NL’s pathophysiology, particularly its manifestation in the peripheral nerves. Investigating the molecular and cellular mechanisms driving the tumefactive appearance could lead to innovative diagnostic tools and targeted therapies, thereby enhancing patient outcomes in NL and similar hematological malignancies with peripheral nerve involvement.

Lessons
This study sheds light on the critical role of the paraneurium in peripheral NL, offering a new perspective on the diagnosis and management of this complex condition. Our findings underscore the importance of recognizing the paraneurium as a distinct anatomical and pathological entity in NL. The integration of advanced imaging techniques, including preoperative PET-MRI, alongside innovative intraoperative fluorescein imaging, has been instrumental in identifying the unique involvement of the paraneurium in NL. These methods enhance our ability to accurately detect and characterize the extent of neurolymphomatous involvement within this specific nerve compartment. The intraoperative revelation of the involvement of NL in the subparaneurial compartment not only advances our understanding but also informs the surgical approach, emphasizing the necessity of targeted biopsies for effective diagnosis and management. Future research should focus on further exploring the role of the paraneurium in NL and related conditions, enhancing imaging techniques, deepening our understanding of the pathophysiology, and ultimately improving patient care and outcomes. This study’s insights into paraneurial involvement in NL pave the way for more precise and effective management strategies in similar cases.

References


**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: Spinner, Barone. Acquisition of data: Spinner, Barone, Schembri Wismayer. Analysis and interpretation of data: Spinner, Barone, Broski, Schembri Wismayer. Drafting the article: Spinner, Barone, Kendziora. Critically revising the article: Spinner, Barone, Broski. Reviewed the submitted version of manuscript: Spinner, Barone, Broski. Approved the final version of the manuscript on behalf of all authors: Spinner. Administrative/technical/material support: Spinner. Pathology: Kendziora. Figures: Kendziora.

**Supplemental Information**

**Videos**


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