Solitary sciatic nerve lymphoma as an initial manifestation of diffuse neurolymphomatosis

Case report and review of the literature

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Solitary peripheral nerve lymphomas are exceedingly rare primary manifestations of diffuse peripheral nervous system or central nervous system (CNS) lymphomatosis. A 52-year-old man presented with progressive weakness in gastrocnemius and anterior tibial muscle function, which was associated with radiating pain in the right leg. Magnetic resonance imaging studies revealed a solitary fusiform tumor, extending from the sciatic nerve, at the level of the lesser trochanter of the femur, into the posterior tibial nerve below the popliteal fossa. Intraoperative gross examination found that the tumor diffusely expanded the nerve, but did not extend from or into surrounding muscle or tendons. The final pathological diagnosis was a solitary extranodal lymphoma (Burkittlike high-grade B-cell lymphoma). Postoperative staging did not reveal evidence of lymphomatous involvement of other organs, but additional chemotherapeutic agents were administered. Four months after the surgical biopsy, the patient presented with a right facial nerve palsy. The results of cytological examination of cerebrospinal fluid were positive for the presence of atypical lymphocytes, which was consistent with apparently progressive neurolymphomatosis; however, the results of radiological studies were negative for systemic progression. The patient underwent intrathecal chemotherapy followed by systemic myelosuppressive chemotherapy with bone marrow rescue, but died of respiratory failure while still receiving treatment. Postmortem examination revealed extensive lymphomatosis in the peripheral nerves and spinal nerve roots without evidence of cranial nerve, CNS, or other organ system involvement. The aggressive biological characteristics of these tumors, their management, and pertinent literature are reviewed.

KEY WORDS • Burkittlike lymphoma • extranodal lymphoma • neurolymphomatosis • non-Hodgkin’s lymphoma • sciatic nerve

LYMPHOMAS that occur in the CNS are relatively uncommon but well documented. In a large autopsy series, primary lymphomas of the CNS accounted for fewer than 1% of the lymphomas found at all sites. Subsequent reports from Zimmerman indicated that lymphomas accounted for approximately 1% of all types of neoplasms found in the brain. Recently, there has been an increase in primary CNS lymphomas, both in patients with acquired immunodeficiency syndrome and in immunocompetent individuals. Primary lymphomas of the PNS are even more of a rarity. Involvement of peripheral nerves by lymphomas, when it occurs, is typically secondary, either by direct extension of the neoplasm from an adjacent involved site (such as a lymph node) or in the context of systemic dissemination. The occurrence of a solitary lymphoma within a peripheral nerve is extremely rare. In fact, only five such cases could be found in a review of recently published literature. The natural history of a solitary lymphoma in a nerve and patient prognosis, management, and outcome are unknown.

Recently, we were confronted with the case of a 52-year-old man who presented with a solitary Burkittlike high-grade lymphoma of the right sciatic and posterior tibial nerves, which then progressed to diffuse neurolymphomatosis over a period of months despite chemotherapy. In this report, we discuss this case and review the available literature to formulate potential management guidelines.

Case Report

History. This 52-year-old man presented with progressive weakness and sensory disturbance of the right leg. One year before presentation, he had noticed intermittent right leg pain, which progressed to more severe and constant pain. This intensified pain became associated with weakness of right ankle movements. Finally, right leg edema was noticed by the patient immediately before referral to a neurosurgical specialist. There was no family history.
of cancer or neurogenetic tumor disorders. There was no history of immunosuppressive disorders, use of immunosuppressive medications, or unusual infections. There was no history of recent travel. The patient’s white blood cell count was within normal limits.

**Examination.** On neurological examination, the patient was found to have numbness along the posterior aspect of the right knee and calf and the bottom of the right foot. Proprioception and knee reflexes were normal, but the patient’s right ankle reflex was markedly decreased. Weakness of the right gastrocnemius muscle (Grade 2/5) and the right anterior tibial muscle and the long extensor muscle of the great toe (Grade 4/5) was evident. Edema of the right leg was visually noticeable. General physical examination did not reveal signs of cardiopulmonary, hepatorenal, or splenic abnormalities, and there was no evidence of systemic lymphadenopathy. Cutaneous examination did not show the stigmata of neurofibromatosis.

An electromyogram obtained with nerve conduction studies indicated a neuropathic process involving the right posterior tibial nerve more than the common peroneal nerve with ongoing axonal loss. The lesion was thought to be distal to the nerve root and was attributed to a right-sided sciatic nerve lesion. Magnetic resonance imaging revealed a fusiform tumor that involved the sciatic nerve, beginning 10 cm below the lesser trochanter of the femur and extending 6 cm below the popliteal fossa into the posterior tibial nerve (Figs. 1 and 2). The tumor displayed an intermediate signal on proton-density MR images and a hyperintense signal on T2-weighted images. It enhanced slightly and heterogeneously after administration of contrast materials, with a small amount of peripheral enhancement. There was no evidence of direct extension into the surrounding muscles, tendons, or fat. A preoperative radiological diagnosis of schwannoma was made.

**Operation.** The patient’s posterior right leg was prepared in a sterile fashion, and an incision was made from the midline of the thigh into the crease of the popliteal fossa. A neoplastic growth was found encasing the sciatic and posterior tibial nerves circumferentially, with relative sparing of the common peroneal nerve. A frozen section obtained intraoperatively contained an atypical lymphocytic infiltrate, which was consistent with the findings of a malignant lymphoma. Resection of the sheaths of tumor encasing the nerves revealed, by gross examination, that tumor tissue had likely infiltrated the entire nerve substance.

**Pathological Findings.** The neoplasm was composed of mitotically active, intermediate-sized lymphocytes with a prominent nuclear membrane, coarsely clumped chromatin, generally prominent nucleoli, and a scant-to-moderate cytoplasm (Fig. 3). Cytoplasmic vacuolation was not prominent. In areas, occasional macrophages were intermixed with neoplastic cells, yielding a starry sky-like appearance on low magnification. The majority of neoplastic cells were immunopositive for CD20, immunoglobulin M heavy chain, and κ light chain, whereas the intermixed, reactive, small lymphocytes were positive for...
the T-cell marker CD3. The final diagnosis was high-
grade Burkittlike B-cell lymphoma.9

**Postoperative Course.** Staging studies, instituted imme-
diately after surgery, did not reveal evidence for lympho-
matus involvement of other organs or the CNS. These
studies included computerized tomography scanning of
the chest, abdomen, and pelvis, with and without addition
of a contrast agent; bone marrow biopsy; lumbar punc-
ture; and MR imaging of the spinal cord. The results of
tests for human immunodeficiency virus were negative.
Nevertheless, to purge potential lymphoma cells, the pa-
tient underwent systemic chemotherapy, including four
cycles of cyclophosphamide, doxorubicin, vincristine, and
prednisone, over the following 4 months. At the conclu-
sion of this chemotherapy regimen, radiotherapy to the
sciatic and posterior tibial nerves was planned; however,
the patient developed a palsy of the right facial nerve. At
this juncture, repeated analysis of cerebrospinal fluid re-
vealed 503 white blood cells/ml, 97% of which were atyp-
ical lymphocytes consistent with lymphoma. Magnetic
resonance imaging of the brain and spinal cord (with and
without administration of gadolinium) did not reveal evi-
dence of parenchymal involvement of the CNS by tu-
mor. Repeated staging studies, including a biopsy of the
patient’s bone marrow, again proved negative for systemic
lymphomatous involvement. Intrathecal chemotherapy,
consisting of cytosine arabinoside and oral dexametha-
sone, as well as craniospinal radiation led to the elimi-
nation of white blood cells in the patient’s spinal fluid;
this treatment was associated with improvement in the
patient’s Bell’s palsy. Although additional staging studies
continued to demonstrate no systemic involvement, the
apparently rapid progression of tumor from the PNS in-
to the CNS prompted plans for further treatment that in-
cluded myelosuppressive doses of cyclophosphamide, fol-
lowed by an allogenic bone marrow transplant protocol.
On Day 2 of this chemotherapy regimen, the patient ex-
perienced the sudden onset of respiratory failure and could
not be revived, despite application of cardiopulmonary re-
suscitation.

**Postmortem Examination.** Malignant lymphoma was
identified in association with peripheral nerves, including
the right sciatic, common peroneal, and posterior tibial
nerves; the right and left proximal femoral nerves; and
multiple cervical, thoracic, and lumbar spinal nerve roots
and associated nerve root ganglia. Based on immuno-
cytochemical and histological studies, this neoplasm was
identical to that identified at the surgical biopsy. Diffuse
invasion of lymphoma cells was observed microscopically in
the epineurium between nerve fascicles (Fig. 4). Interest-
ingly, the intracranial portions of the facial and acoustic
nerves were not involved by the lymphoma. In addition,
there was no microscopic evidence of lymphomatous involvement of the subarachnoid space, arachnoid, or dura of the spinal cord or brain, although rare atypical lymphocytes were present, admixed with small benign-appearing lymphocytes in connective tissue adjacent to the sella turcica. There was no microscopic evidence of involvement of bone marrow, lymph nodes, or systemic organs by lymphoma cells.

**Discussion**

**Description of the Disease**

Malignant NHLs are defined as malignant proliferations of either B or T lymphocytes. The provisional diagnostic entity “high-grade B-cell lymphoma, Burkittlike,” was proposed by the international lymphoma study group as part of the revised European–American classification of lymphoid neoplasms (known as the REAL classification). This category was proposed to accommodate a group of lymphomas with histological features, including cell size and nuclear structures, that are intermediate between large-cell lymphoma (centroblastic or immunoblastic) and Burkitt’s lymphoma, have a high proliferation rate, and appear with or without a starry-sky pattern. Based on immunophenotypical studies, the neoplastic cells demonstrate positivity for B-cell antigens and negativity for CD5, CD10, and T-cell antigens. These aggressive and often fatal neoplasms are most common in adults with or without a history of immunosuppression. Usually they present within lymph nodes rather than in extranodal sites. A recent publication of the results of two studies in which the authors sought to validate the REAL classification found that high-grade Burkittlike B-cell lymphoma was the 10th most common diagnosis, reported in 30% of 1779 cases of NHL. Burkittlike lymphoma was recently shown to comprise 18.4% of cases in a series of 103 lymphomas in patients with acquired immunodeficiency syndrome.

When lymphomatous infiltration of spinal nerve roots, dorsal root ganglia, and peripheral nerves occurs, it is usually a consequence of hematogenous spread from systemic NHL or the result of invasion from adjacent structures. Diaz-Arrastia, et al., reviewed the manifestation of neurolymphomatosis in 39 patients and defined it as a clinical disorder with signs of peripheral neuropathy that is confirmed by histopathological evidence of lymphomatous infiltration of the nerves. Typically, patients present with a history of a subacute course lasting for weeks and less commonly with an acute or rapid onset. Pain is a very common symptom in patients with lymphomatous infiltration of the peripheral nerves. Two of the 39 cases reviewed by Diaz-Arrastia, et al., initially were thought to have presented with malignant lymphoma of the sciatic nerve, however, no autopsies were performed and histopathological evidence of infiltration of nerves by malignant cells to confirm this clinical diagnosis was not obtained. Purohit and associates described a patient who initially presented with clinical evidence of sciatic nerve lymphoma, which was followed by development of enlarged axillary lymph nodes 3 years later. Subsequent biopsy and histological analysis demonstrated the presence of systemic NHL, but no evidence of peripheral nerve tumor. In a case reported by Eusebi and colleagues, neoplastic involvement in the subarachnoid space and the retroperitoneum was found at autopsy, but there was no report of infiltration of peripheral nerves. A patient described by Roncaroli, et al., died 50 months after diagnosis, presumably due to spreading from the initial sciatic nerve lymphoma to the CNS; however, a postmortem examination was not performed to confirm this. Therefore, the hypothesis that a solitary lymphoma in a peripheral nerve can represent the initial presentation of a more severe and diffuse lymphomatous involvement of the CNS, PNS, or other organ systems has yet to be supported by pathological data in currently published literature.

The patient in the present case exhibited clinical characteristics that were similar to those of patients described in previous reports of primary lymphoma of the sciatic nerve. In all instances, the initial presentation consisted of progressive and painful paresis of muscles innervated by the sciatic nerve, without evidence of systemic or CNS involvement by tumor cells. A variety of treatments were instituted, but none seems to have affected the final, unfortunately fatal, outcome. The grade of the lymphoma also did not affect the outcome. For instance, the life expectancy of the patient presented in the current report and those presented by Purohit and associates, Eusebi and colleagues, and Roncaroli, et al., ranged from 16 to 50 months after detection of the sciatic nerve lesion. Although Pillay, et al., and Kanamori and coworkers did find regression of tumor in two patients treated with a combination of local radiotherapy and chemotherapy, the reported duration of follow up was for a period of only 12 or 30 months. The case reported by Kanamori and coworkers consisted of a diffuse, T-cell lymphoblastic tumor, whose natural history and biological behavior is likely to be very different from the B-cell lymphomas that constitute the subject matter of the present study.

**Speculation on Pathogenesis**

Failure to control lymphomatous involvement of the nervous system provides an impetus for speculating on its pathogenesis and on different approaches toward treatment. The pathogenesis of tumor infiltration in a solitary lymphoma of a peripheral nerve remains a mystery. Although a hematogenous route may be responsible for lymphomatous infiltration of the peripheral nerves, in the present case there seemed to be complete absence of tumor at sites outside the PNS, at least at initial presentation. Lymphoma cells were found within the CNS 4 months after surgical treatment; however, these were rapidly purged through intrathecal chemotherapy. Postmortem studies revealed extensive infiltration of multiple nerves within the PNS, but a remarkable absence of tumor in other organs and tissues, including the CNS. Several hypotheses concerning the pathogenesis of this particular tumor can be made.

**Original Spread of Lymphoma Cells to Multiple Nerves and to the CNS Through a Hematogenous Route.** Initial presentation through sciatic nerve disease would be fortuitous and, with time, other nerves would become infiltrated by tumor. Systemic and intrathecal chemotherapeutic interventions lead to purging of the tumor from all sites except the PNS. The presence of a blood–nerve barrier

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that limits the diffusion of chemotherapy agents could explain the failure of systemic chemotherapy regimens in eliminating tumor cells from the peripheral nerves of our patient and in other reported patients.

Specific Targeting of Peripheral Nerves by Lymphoma Cells Generated Elsewhere in the Body. The ability of immunoglobulin-producing B cells to course within nerves and react against nerve components is known to occur in polyneuropathies, and one might speculate that a similar phenomenon occurred in the present case. This would explain the predilection for the extensive lymphomatous involvement of nerves, which was observed at postmortem analysis.

Extranodal Generation of Lymphoma Within the Sciatic Nerve With Secondary Spread to Other Sites Within the PNS and CNS. We tend to favor this last mechanism of pathogenesis for the currently reported case because extensive imaging studies and postmortem analyses failed to demonstrate involvement of systemic organs. Involvement of the CNS occurred late in the course of the disease, suggesting that the CNS represented a secondary site. We postulate that the original lymphoma could have arisen from B cells that normally course through or reside in the sciatic nerve. This site provided the reservoir for dissemination of tumor cells along peripheral nerve tracts into the CNS. It is possible that additional spread into systemic organs may have occurred, but that the instituted chemotherapy regimens resulted in successful purging of tumor from all sites except the PNS.

The diffuse involvement of spinal cord nerve roots raises the possibility of a neurogenic basis for the respiratory failure that led to our patient’s fatal outcome. Therefore, the high mortality rate that is associated with the diagnosis of a B-cell lymphoma of a sciatic nerve suggests that aggressive and prophylactic treatment of the CNS may be required, even in the absence of initial lymphomatous involvement. Furthermore, aggressive and early radiotherapeutic and/or surgical management of the involved limb, including amputation, should be considered to eliminate a site that can provide neoplastic cells to the remainder of the body. Finally, initial administration of aggressive myelosuppressive chemotherapies may also have to be considered.

Conclusions

A solitary primary malignant peripheral nerve lymphoma can progress to a lymphomatosis involving the subarachnoidal spaces (potentially treatable by intrathecal chemotherapy) and to diffuse neurolymphomatosis of multiple peripheral nerves, whose treatment remains elusive, as illustrated in the reported case. As previously discussed, aggressive myelosuppressive chemotherapeutic regimens and extensive surgical or radiotherapeutic measures should be considered when a patient presents with a solitary high-grade B-cell lymphoma of a peripheral nerve because it may be the harbinger of a more disseminated tumor within the PNS and CNS.

References


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