Reversal of neurological deficit after chemotherapy in BCL-6–positive neurolymphomatosis

Case report

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Neurolymphomatosis, the infiltration of the peripheral nervous system (PNS) by malignant lymphatic cells, is a rare condition whose prognosis and treatment are not fully characterized. The authors report the case of a 69-year-old, previously healthy man who had a 1-month history of progressive pain in his right arm and associated weakness of several muscles of the right upper extremity when they first examined him. Initial MR imaging of the right brachial plexus showed no abnormalities, but over 3 months, symptoms gradually progressed to almost complete plegia of his right upper extremity. Subsequent MR imaging of his right brachial plexus showed an enhancing mass of the posterior cord of the plexus that encroached on the other cords. Positron emission tomography confirmed the presence of a hypermetabolic lesion in the right axillary region and also detected an asymptomatic hot spot in the gastric wall. Biopsy of the gastric lesion demonstrated a CD20+, diffuse large B-cell lymphoma that was immunohistochemically positive for BCL-6 and negative for p16. The patient underwent 6 cycles of dose-adjusted etoposide-vincristine-doxorubicin-cyclophosphamide-prednisone (EPOCH) and rituximab, intermixed with 3 cycles of high-dose intravenous and intrathecal methotrexate, and followed by 6 monthly doses of rituximab for consolidation. Follow-up MR imaging and PET of the plexus showed complete radiological response after 3 months of treatment, as demonstrated by normalization of brachial plexus caliber, contrast enhancement, and metabolic activity.

Twenty-eight months after symptom onset and 20 months after beginning therapy, the patient was disease-free, had recovered most upper extremity neurological function, and had only minimal remaining weakness of the right wrist and finger extension. (DOI: 10.3171/2008.11.JNS08291)

KEY WORDS • neurolymphomatosis • BCL-6 • chemotherapy

F irst described by Lhermitte and Trele in 1934,17 neurolymphomatosis (NL) consists of infiltration of the PNS by malignant lymphomatous cells; it is categorized as an extranodal lymphoma.10 Up to 35% of patients with NHL show signs of PNS involvement on electromyography.19 However, clinically relevant neuropathies as a consequence of the disease affect only 0.1–2% of patients31 and result more commonly from direct compression, vasculitis, paraneoplastic effects, and chemotherapy drug toxicity rather than from nerve infiltration by neoplastic cells.15

Unlike primary lymphomas of the CNS, which are well characterized and represent about 1% of all brain neoplasms24 and 1–2% of NHLs,9 lymphomas that infiltrate the PNS are unusual. Resulting neurological deficits manifest as weakness, decreased sensation, or, more commonly, both, and their treatment is uncertain: although radiation may enable remission of tumor from the segment of involved nerve, it is also likely to retard or eliminate nerve regeneration/remyelination and thus has limited utility. Surgical excision is rarely curative, because of the diffuse infiltration into the nerve by lymphoma cells, and it never allows neurological recovery. Chemotherapy has helped relieve disease outside the nervous system, but its use is not well characterized for these tumors, and the capacity of patients with these tumors to successfully recover nerve function following such treatment is not known.

Abbreviations used in this paper: CHOP = cyclophosphamide-doxorubicin-vincristine-prednisolone; EPOCH = etoposide-vincristine-doxorubicin-cyclophosphamide-prednisone; NHL = non-Hodgkin lymphoma; NL = neurolymphomatosis; PNS = peripheral nervous system.
We describe the case of a 69-year-old man with an 8-month history of unexplained progressive right-arm neuropathy progressing to right shoulder, arm, forearm, and hand plegia. Eventually a diffuse large B-cell lymphoma was diagnosed; the lesion had infiltrated the posterior cord of the patient’s right brachial plexus, encroached on other cords of the brachial plexus, and asymptptomatically involved the gastric wall. Complete disease remission after chemotherapy was confirmed by MR imaging and PET. At most recent follow-up examination, 28 months after symptom onset, the patient was disease-free with almost complete recovery of function in his shoulder, arm, forearm, and hand. We discuss this case and review the related literature.

Case Report

Presentation and History. This 69-year-old right-handed man presented with a 1-month history of progressive, dull aching pain of his right shoulder, which he first noticed after pitching in a softball game and which eventually was associated with increasing weakness of right upper extremity function. An element of his medical history that was thought to be significant consisted of a recent vaccination against influenza.

Examination. At physical examination, thinning of the intrinsic muscles of his right hand was evident. The patient also exhibited significant weakness in the right deltoid (3/5, motor scale), supraspinatus (2/5), and triceps (2/5) muscles. The right biceps (4/5) and right wrist/finger extension (4/5) musculature was also affected. The deep tendon reflexes in his right upper extremity were generally decreased, and both Hoffman and Babinski signs were absent.

Initial Diagnosis and Treatment. An initial diagnosis of Parsonage-Turner syndrome was made based on the history of pitching and on the neurological findings. The patient was treated conservatively with acetaminophen, hydrocodone, and amitriptyline to address his pain, while waiting for functional recovery. An electromyelographic examination with nerve conduction velocity testing also provided a diagnostic impression of a generalized brachial plexopathy with a superimposed C-6 and C-7 radiculopathy. One month later, because the neurological functions of the patient’s upper extremity continued to progressively deteriorate, an MR imaging study of the right brachial plexus was performed; no enhancement or anomalies on T2–weighted or FLAIR images or changes on STIR images were seen. Computed tomography and MR imaging of the neck revealed a large osteophyte on the right side of C5–6 that impinged on the C-6 nerve root and some foraminal narrowing at C6–7 and C4–5. A short course of steroid treatment did not result in improvement.

Operation and Postoperative Course. Three months after the initial visit, the patient underwent a 2-level C5–6 and C6–7 discectomy/osteophysectomy with allograft arthrodesis and anterior cervical fixation. The rationale for this procedure was that there was an underlying nerve root compression syndrome that was exacerbating the Parsonage-Turner syndrome and causing the progressive deficit. Although the patient recovered from the surgery well, his neurological deficit did not improve and, in fact, his symptoms continued to progress.

Six months after the initial visit, the patient’s right deltoid and supraspinatus had become significantly weaker (2/5), with visible and severe atrophy and gravity-induced dislocation of the head of the humerus from the glenoid. There was severe biceps (2/5) and grip weakness (1/5) with triceps, finger, and wrist extension at 1/5 motor strength. Repeated electrodiagnostic studies continued to show evidence of profound upper extremity muscle denervation without reinnervation potentials.

Additional Imaging and Biopsy. Seven months after the initial visit, repeated MR imaging of the right brachial plexus revealed a new 2.5 × 1.5-cm enhancing fusiform mass in the posterior cord of the brachial plexus encroaching on other cords of the brachial plexus with no evidence of local enlarged lymph nodes (Fig. 1A and B). A PET scan revealed that this was a hypermetabolic mass and that there was also a second solitary “hot spot” in the posterior wall of the gastric body, which was asymptomatic (Fig. 1C).

The gastric lesion was biopsied endoscopically, and cytological examination of the biopsy specimen confirmed the presence of a CD20+ diffuse large B-cell lymphoma. The results of additional immunohistochemical staining were negative for the presence of the p16 tumor suppressor protein and positive for the BCL-6 antiapoptotic peptide (Fig. 2). For disease staging, abdominal and thoracic CT images were obtained to exclude any other neoplastic foci. Central nervous system involvement was excluded by negative findings on MR images of the head and spine and analysis of the CSF. Moreover, bone marrow biopsy and blood studies excluded hematopoietic involvement. The patient’s serum lactate dehydrogenase (LDH) level was within the normal range at 158 U/L.

Chemotherapy and Follow-Up. The patient was treated with dose-adjusted EPOCH and rituximab, intermixed with high-dose methotrexate administered intravenously at 3.5 g/m², because of the described tendency of this rare form of lymphoma to spread to the CNS. To further minimize the possibility of CNS relapse, he was also treated with 3 intrathecal infusions of methotrexate. Shortly after treatment initiation, symptoms and objective findings related to the patient’s right brachial plexus lesion improved. Three months after initiation of therapy, MR imaging showed near normalization of the involved brachial plexus (Fig. 3A and B). A PET scan (Fig. 3C) demonstrated disappearance of all hypermetabolic areas seen on the previous scan, and repeated gastric biopsies confirmed complete clearance of the gastric lesion. Twenty months after the start of therapy and more than 28 months after symptom onset, the patient was disease-free by radiological and hematological criteria. Neuropathologically, function of his supraspinatus, deltoid, triceps, and biceps as well as his grip, had recovered to a level of 4+ to 5/5 with much less visible shoulder muscle atrophy. Although weakness in his wrist extension and finger extension had also been reversing (3/5), significant weak-
ness was still noticeable. Overall, his right upper extremity was functional enough to allow him to write, drive, and swing a golf club.

Discussion

This case report illustrates that a chemotherapy regimen for brachial plexus NL can reverse profound and significant upper extremity neurological deficits, in addition to successfully treating (as defined by radiological and hematological parameters) the disease itself.

Neurolymphomatosis is an aggressive disease, but survival is variable; patients have succumbed in weeks of symptom onset, with very few long survivals reported. In the few reported cases in which patients lived more than a year after symptom onset, most of the patients had evidence of relapsed disease and had to be treated with repeated cycles of chemotherapy or other salvage therapies, like bone marrow or autologous stem cell transplant. Patients affected with NL invariably present with neuropathic pain, and in the vast majority of patients the pain is associated with neurological deficits that manifest as decreased sensation, muscle weakness, or both. This common loss of neurological function is generally irreversible. Although treatment with steroids, chemotherapy, or even radiotherapy usually controls pain well and often at least temporarily stops the progressive loss of nerve function, we found only a few cases in which nerve function, after being severely compromised, recovered somewhat after treatment. Of the patients in these cases, only 2 returned to their premorbid functional status, and that was possible only after traditional chemotherapeutic approaches had failed and high-dose salvage chemotherapy with autologous bone marrow transplantation was implemented. Our case is unusual for the almost complete return of both sensory and motor function to normal baseline after treatment with intravenous chemotherapy without the need for bone marrow transplantation and without any relapse of the disease.

In an analysis of 4 cases of NL, patient survival was compared with the expression of the p16 tumor suppressor protein: the 2 patients whose lymphoma cells were positive for p16 survived longer than the other 2. There was no mention of neurological deficits in this report. The authors suggested a role for p16 in predicting NL behavior. This is in contrast to our case, in which p16 expression was not detected. Recent literature also shows that retention of the antiapoptotic protein BCL-6 confers a better prognosis not only to nodal diffuse large B-cell lymphomas but also to primary CNS lymphomas. Because we were able to detect strong immunopositivity for BCL-6 expression (Fig. 2), we speculate that the expression of BCL-6 may be more relevant than the absence of p16 in predicting chemotherapy response. In fact, although a larger study would be required to confirm this hypothesis, our finding is the first evidence suggesting that expression of BCL-6 in NL may confer a milder prognosis to the disease and a better response to chemotherapy.

Most cases of NL are classified as NHL, with only 1 having been described as Hodgkin disease. Diffuse large B-cell lymphomas account for approximately 30% of the cases of NHL in adults, tend to involve extranodal sites in 40% of cases, and are considered of intermediate to high grade. Although the number of reported cases of NL reported is limited, its incidence is estimated to be at least 1000 per year in the US. Diagnostic criteria for NL that specify radiological evidence of nerve involvement in the presence of histological proof of extraneural lymphoma are considered sufficient for diagnosis. In this case, MR imaging provided evidence of brachial plexus...
involvement with gastric endoscopic biopsy as the source of the diagnostic specimen. This approach not only spared the brachial plexus from possibly deleterious surgery, it also limited the risk of false negative results, which have been previously reported after nerve biopsy.

Clinically, our patient’s presentation and disease course resembled that of the vast majority previously described, that is, a history of subacute and progressive sensorimotor neuropathy, which was confirmed by results of electromyography/nerve conduction velocity testing that were positive for denervation and decreased conduction velocity. Although nonspecific, these findings are consistent with the usually described histopathological evidence of axonal degeneration and demyelination resulting from patchy atypical lymphocytic infiltrate localized around the vessels of the epineurium and in the endoneurium.

Our patient’s relatively normal laboratory test results were consistent with published findings: the blood cell count is usually in the normal range (in fact, most authors believe that the presence of leukemic transformation should be considered an exclusion criterion), and the serum LDH level may be elevated, as it frequently is in patients with lymphomas. Cerebrospinal fluid findings may vary, and their usefulness as NL inclusion criteria has been the object of vigorous debate.

One reason for the huge variability in outcomes reported in NL cases throughout the literature is that there has been no clear standardized approach to the treatment of the disease. Generally, it responds to therapy temporarily but almost invariably relapses. Corticosteroids usually have shown only transient efficacy; the CHOP regimen has been the most widely used chemotherapy. Lately, after its promising results in treating nodal lymphomas, the anti-CD20 antibody, rituximab, has been used in a few CD20+ NL cases for consolidation and maintenance of response. The reported results, though, are of dubious interpretation, and more cases will be needed to effectively evaluate the role of this treatment. In recent years, the addition of methotrexate, administered either intrathecally or systemically, has been proposed because of its ability to easily permeate the blood-brain barrier and its proven role in CNS lymphomas. Its use could be important for preventing CNS involvement and CNS diffusion. We administered a high dose of the drug to our patient both intrathecally and systemically between cycles of the EPOCH regimen. However, Descamps and associates recently described a case of primary NL involving the sciatic nerve that was treated with the CHOP regimen and rituximab but without methotrexate, and their patient was reportedly disease free at 48 months, with no evidence of CNS involvement.

The role of radiotherapy is uncertain as well for a disease proven to be extremely chemosensitive. Radiation has been used particularly in cases of single nerve involvement, with no patients described as completely recovering neurological function. Therefore, we avoided irradiation of the brachial plexus because of this probability of limited functional recovery in the setting of an evident and rapid response to chemotherapy. Radiation therapy should, however, be considered in case of relapse or incomplete response to pharmacological treatment.

Conclusions

Brachial plexus NL with loss of upper extremity neurological function was treated with a chemotherapy regimen consisting of the EPOCH regimen, rituximab, and methotrexate. Over a period of 20 months this resulted in almost complete reversal of the upper extremity neurological deficit and radiographic/hematological disappearance of the disease.

Importantly, the tumor expressed CD20+ and, more interestingly, BCL-6, a previously described marker of positive outcome in other lymphomas, suggesting that molecular analysis could prove useful in predicting the prognosis of NL and its response to chemotherapy, and formulating a patient-specific treatment for this disease.

Disclaimer

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

References

3. Baehring JM, Hochberg FH: Neurolymphomatosis, in Batch-
Chemotherapy in BCL-6–positive neurolymphomatosis


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