Autoantibody-Mediated Sensory Polyneuropathy Associated with Indolent B-Cell Non-Hodgkin’s Lymphoma: A Report of Two Cases

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Background and Purpose
Abnormalities of the peripheral nervous system occur in 5% of patients with lymphoma. Polyneuropathy has not been described in patients with mantle-cell and marginal-zone B-cell lymphomas.

Case Report
Two elderly patients with indolent non-Hodgkin’s lymphoma developed a progressive sensory polyneuropathy that was associated with serum autoantibodies directed against asialosyl/sialosyl gangliosides and myelin-associated glycoprotein/sulfated glucuronyl paragloboside, respectively, which are peripheral-nerve antigens. The oligoclonal pattern of these antibodies hinted at a lymphoma-induced immune dysregulation. The neuropathy stabilized clinically during treatment with intravenous immunoglobulin G. B-cell lymphoma was managed with a “watchful waiting” approach.

Conclusions
The concept of antigen-specific, immune-mediated neuropathy associated with slow-growing lymphoma of mature B-cells may be underrecognized. The principle of treating the illness underlying neuropathy may not be always indicated or necessary if risk-benefit and cost-benefit analyses are taken into account.

Key Words
autoimmunity, neuropathy, non-Hodgkin’s lymphoma.

INTRODUCTION

Non-Hodgkin’s lymphomas (NHLs) are a group of more-or-less malignant diseases that are characterized by transformation and proliferation of B- or T-lymphocytes. Abnormalities of the peripheral nervous system occur in 5% of patients with lymphoma; the evident clinical heterogeneity has been ascribed to various pathogenic processes that have been linked to the different lymphoma subtypes.7 There have been isolated reports of patients with B-cell NHL subtypes with multifocal motor neuropathy or subacute sensory/sensorimotor demyelinating polyneuropathy associated with serum autoantibodies against peripheral-nerve glycolipid or glycoprotein antigens.

I report herein on two patients with low-grade B-cell NHL with progressive sensory polyneuropathy linked to serum autoantibodies directed against peripheral-nerve antigens. Maintenance intravenous immunoglobulin G (IgG; IVIG) infusions halted the neuropathy symptom progression, and a “watchful waiting” approach was chosen to manage the lymphoma.
CASE REPORTS

Patient 1
A 77-year-old woman presented with a history of slowly progressive, symmetrical numbness of the feet that had first appeared a few weeks previously. Examination findings were compatible with a mild sensorypolyneuropathy. The patient had been diagnosed with lymph-node mantle-cell lymphoma 6 months previously.

Immunophenotyping revealed the presence of CD19+ and CD20+ lymphocytes coexpressed with CD5/CD19 antigens; κ light-chain restriction of B-cells was also observed. These findings indicated a monoclonal B-cell population, consistent with B-cell lymphoma. Two whole-body 18F-fluorodeoxyglucose positron emission tomography computed tomography (18F-FDG PET CT) scans conducted 6 months apart revealed stable, mildly hypermetabolic lymphadenopathy. Blood tests produced the following findings: an elevated sedimentation rate (32 mm/hour); no M-protein on serum immunofixation electrophoresis, but elevated levels of κ free light chain and a normal κ:λ free light chain ratio; an elevated antinuclear antibody (ANA) titer (1:320) with a diffuse ANA staining pattern; and a serum antiganglioside panel with a “strong” (index value, >101) positive autoantibody reactivity to asialo-ganglio-N-tetraosylceramide (GM1) IgG/immunglobulin M (IgM; IV, 202), GM1 IgG/IgM (IV, 102), and ganglioside GD1a IgG/IgM (IV, 108; ARUP Laboratories). The findings of an electrodiagnostic study of the legs were compatible with an axonal sensory polyneuropathy: decreased superficial peroneal and sural sensory-nerve action potential amplitudes with normal sensory conduction velocities.

The patient was treated with monthly maintenance-dose IVIG (1 g/kg/day) infusions; her sensory symptoms did not progress during the 7-month follow-up period. A “watchful waiting” management approach was chosen for this lymphoma based on the predicted indolent nature of the disease.

Patient 2
A 70-year-old man presented with a 1-year history of slowly progressive, ascending numbness and tingling to the below-knee level. His examination findings were compatible with a sensory polyneuropathy. Blood tests produced the following findings: presence of monoclonal IgM-κ (0.2 g/dL) on serum immunofixation electrophoresis, with an elevated κ:λ free light chain ratio; and positive/elevated serum titers of autoantibodies against sulfate-3-glucuronyl paragloboside [SGPG; 1:204,800; enzyme-linked immunosorbent assay (ELISA)] and myelin-associated glycoprotein (MAG)-IgM (1:3,200; ELISA and positive Western blot; Athena Diagnostics).

The patient submitted to an electrodiagnostic study of the legs, the findings of which were compatible with a mixed (axonal-demyelinating) sensory peripheral polyneuropathy (motor nerve studies revealed no conduction blocks). A whole-body 18F-FDG PET CT scan yielded normal findings. Flow cytometry of samples of peripheral blood and bone marrow aspirate revealed B-cells with polytypic surface immunoglobulins. A bone-marrow biopsy sample and aspirate exhibited increased B-cells [without expression of cluster differentiation (CD5) and cyclin-D1/B cell lymphoma-1 antigens]. Immunoglobulin rearrangement studies demonstrated a monoclonal B-cell population.

A polymerase chain reaction (PCR) study was performed to assess for immunoglobulin heavy-chain gene rearrangements. A distinct and predominant band was identified in duplicate reactions, indicative of the presence of a monoclonal B-cell population. The sensitivity of clonality detection was increased by performing additional PCR studies to assess the common rearrangements of the immunoglobulin κ light-chain gene using BIOMED-2 assays. A distinct monoclonal B-cell population was identified by this method. A cytogenetic study of a bone-marrow sample revealed a normal karyotype of the analyzed metaphase cells. These findings were consistent with a marginal-zone B-cell lymphoma.

Treatment with monthly maintenance-dose IVIG (1 g/kg/day) infusions stabilized this patient’s sensory symptoms during an 8-month follow-up period. A “watchful waiting” management of the lymphoma was chosen based on the asymptomatic, predicted benign nature of the disease.

DISCUSSION

This report draws attention to the concept of presumed autoantibody-mediated sensory polyneuropathy associated with indolent lymphomas of mature B-cells. Sophisticated technological analyses were applied to accurately diagnose mantle-cell and marginal-zone lymphomas in our two patients. These two lymphomas constitute about 6% and 8% of B-cell NHLs, respectively; a progressive axonal sensory polyneuropathy has not previously been reported against a background of these typically indolent lymphoma subtypes.

Based on all available evidence, we presumed that the pathogenesis of neuropathy in our patients was autoimmune; therefore, nerve biopsy sampling was deemed unnecessary and was not performed. Clinical or serological evidence of autoimmunity in patients with NHL commonly (70%) precedes the diagnosis of lymphoma. However, based on the presumed slow-growing behavior of the NHL subtypes of our patients, we presumed that the lymphoma probably existed prior to the onset of the neuropathy symptoms. The mechanism underlying neuropathy in patients with lympho-
ma varies,2 which makes it important to identify the cause of this neuropathy in these patients in order to help determine the optimum therapeutic approach.

This is the first report on sensory neuropathies associated with elevated serum autoantibodies directed against peripheral-nerve antigens in patients specifically with mantle-cell and marginal-zone B-cell lymphomas. In patient 1, we hypothesized that anti-GD1a antibodies played a pathogenic role in the unusual presentation of sensory (rather than motor) axonal neuropathy,6,7 while in patient 2 the concept of an association between anti-MAG/SGPG antibodies and sensory-nerve damage was deemed better established.8 The development of clinical or biological signs of autoimmunity at initial diagnosis/during the disease course of lymphoma implicates an interrelationship between lymphoproliferative malignancies and autoimmune diseases.9

It appears that the frequency of biological and/or clinical autoimmunity is higher in patients with indolent (e.g., marginal-zone or follicular) lymphoma than in those with more aggressive lymphomas.10 In our patients, the detection of multiple serum autoantibodies directed against various distinct antigens suggested that these immunoglobulins were not secreted by a specific tumoral clone, but were probably the consequence of a lymphoma-induced generalized more-or-less disordered immune regulation. It is conceivable that the regulatory T-cells (T-reg cells; which are frequently over-represented in biopsy specimens of B-cell NHL11) that modulate the immune response against lymphoma cells may also be involved in the development of autoimmune manifestations.9 T-reg cells have been shown to prevent autoimmune diseases by suppressing self-reactive T-cells as well as the immune response against cancer. Other hypotheses on lymphoma-induced immune dysregulation include 1) autoantibody production after malignant transformation (e.g., due to continuous challenge by autoantigens) of autoreactive CD5+ B-cells12 (but also B-cells that lose CD5 expression during lymphomatous transformation13); 2) an alteration of the cell-surface receptor Fas-Fas-ligand pathway involved in cell-death signaling (acquired somatic mutations of Fas may be acquired during normal germinal center reaction, and are prevalent in NHL with autoimmune manifestations14); and/or 3) lymphocyte chronic antigenic (e.g., infectious agents) stimulation that leads to an emergence of autoreactive lymphoma cells.15

A bone marrow evaluation was deemed reasonable in patient #2 based on progression of polyneuropathy in this patient with a serum M-band with elevated anti-MAG/SGPG antibodies; other established independent clinical-laboratory predictors of a possible hematological malignancy did not apply (e.g., serum M-protein level >1 g/L or constitutional symptoms such as weight loss, unexplained fever, or night sweats).16 It is conceivable that adhering to a combination of these predictors too strictly may lead to underinvestigation of the marrow and underestimation of the true frequency, particularly of indolent malignancy.

We managed the immune-mediated neuropathy with monthly maintenance-dose IVIG infusions. Since the neuropathy symptoms stabilized during the observation period in both patients, this approach to care appears to have been appropriate. Based on a risk-benefit analysis, the oncologists elected for a “watchful waiting” approach to management of these indolent lymphomas in our elderly patients. Thus, the principle of treating the source of the illness underlying neuropathy does not always seem warranted or necessary—the diagnosis of low-grade B-cell lymphoma in our patients had no immediate treatment implications. It is generally believed that treatment of lymphoma rarely leads to recovery of the associated neuropathy.11 Moreover, it has not been established with certainty that the presence of neuropathy warrants a more aggressive treatment of quiescent hematologic malignancies.17 Since the pathogenesis of lymphoma-associated neuropathy varies, a case-by-case approach to patient care seems most appropriate and sensible.

Based on this case series, we cannot advocate routine bone-marrow examination in elderly patients with autoantibody-mediated neuropathies, in part because the diagnosis of low-grade B-cell lymphoma appears to have no immediate treatment implications. Conversely, it seems reasonable to test for the presence of serum autoantibodies in patients with established indolent B-cell NHL who develop neuropathy, since detection of antibodies directed against specific nerve antigens has therapeutic implications, in terms of providing an evidence-based decision to offer immune modulation therapy to patients.

Conflicts of Interest

The author has no financial conflicts of interest.

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