Sub-acute Demyelinating Polyradiculoneuropathy as an Initial Symptom of Peripheral T Cell Lymphoma, Not Otherwise Specified (PTCL-NOS)

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Abstract

Here we report the first case of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), who initially presented with peripheral neuropathy. Nerve conduction, cerebral spinal fluid studies and his clinical course were compatible with sub-acute demyelinating polyradiculoneuropathy. In addition, left cervical lymph node swelling was observed on admission. Diagnosis of PTCL-NOS was made by the histological, immunohistochemical, and Southern blot analyses on the biopsy specimen from the enlarged lymph node. Combination chemotherapy composed of cyclophosphamide, vincristine, doxorubicin and prednisolone (CHOP) was effective for polyneuropathy as well as for lymphoma. Several antibodies relating to paraneoplastic syndrome such as Ma1, Ma2, Amphiphysin, CV2, Ri, Yo and Hu were all negative. Because sural nerve biopsy performed prior to CHOP therapy revealed no infiltration of lymphoma cells, immune dysfunction mediated by some cytokine or unidentified autoantibody related to PTCL-NOS was thought to be involved in the polyradiculoneuropathy.

Key words: peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), demyelinating polyradiculoneuropathy, paraneoplastic peripheral neuropathy (PPN), CHOP chemotherapy

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Introduction

Peripheral T-cell lymphoma (PTCL) includes several types of lymphoma and comprises 5-20% of all non-Hodgkin lymphoma (NHL). PTCL, not otherwise specified (PTCL-NOS) accounts for about 25% of all PTCL (1). Peripheral neuropathy occurs in patients with malignant lymphoma with a frequency of 5-8% at various clinical phases of lymphoma because of several distinct reasons (2). Here, we report the first case of PTCL-NOS presenting with peripheral neuropathy as an initial symptom; it was thought to be caused by immunologic reactions.

Case Report

A 60-year-old man visited our hospital because of pain in the lower limbs and high fever in late September 2009. On the first examination, he had the symptom of sciatica, which was relieved by a caudal block temporally. In early October, he complained of paresthesias of both hands and walking difficulties and was admitted to our hospital. Neurological examination revealed sensorimotor neuropathy with mild weakness of both arms (greater distally) and mainly proximal weakness in the legs. Deep tendon reflexes decreased in the lower limbs, while the cranial nerves seemed to be intact. In addition, elastic hard, relatively immovable lymph

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Figure 1. FDG-PET scans before (A) and after three cycles of CHOP chemotherapy (B).

node swelling about 10 to 20 mm in diameter was observed at cervical and axillary lymph nodes on admission. Liver and spleen were not palpable, and skin eruption was not observed.

The laboratory findings were as follows: hemoglobin 15.4 g/dL (normal 13.9-17.0), platelets 336,000/mm³ (normal 167,000-362,000), white blood cells 5,400/mm³ (normal 3,900-9,300) with 46.7% neutrophils (normal 38-77%), 10.7% monocytes (normal 2.7-9.3%), 5.0% eosinophils (normal 0.2-4.1%), 19.0% lymphocytes (normal 20.2-53.2%) and 18.7% atypical lymphocytes. Similar atypical lymphocytes account for 11.6% of total bone marrow cells. Although these atypical lymphocytes were like malignant lymphoma cells, we could not prove their clonality in the bone marrow cells by flow cytometric analysis and Southern blot analyses for the rearrangement of immunoglobulin H chain (Ig JH) and T-cell receptor (TCR) J β -1 and J- γ genes. Serum glucose was 95 mg/dL (normal 65-110), lactate dehydrogenase (LDH) 262 IU/L (normal 100-225), C-reactive protein (CRP) 1.2 mg/dL (normal <0.3). Serum protein was 9.1 g/dL (normal 6.5-8.2)[43.8% albumin (normal 61.6-71.2%), 3.0% α 1-globulin (normal 1.9-3.0%), 7.7% α 2-globulin (normal 5.3-8.9%), 8.2% β -globulin (normal 6.9-10.9%), and 37.3% γ -globulin (normal 10.8-19.6%)]. Serum IgG was 3,635 mg/dL (normal 870-1,700), IgA 360 mg/dL (normal 110-410), IgM 106 mg/dL (normal 33-190), and IgE 579 mg/dL (normal <295). Neither M-protein nor Bence-Jones protein was detected by immunoelectrophoresis in serum or urine. Serum β 2-microglobulin was 1.8 μ g/mL (normal 0.8-1.9), soluble interleukin-2 receptor (sIL-2R) 6,983 U/mL (normal 150-505), vascular endothelial growth factor (VEGF) 761 pg/mL, interleukin-6 (IL-6) 4.6 pg/mL (normal <4.0). Serological tests for cryoglobulin, anti-nuclear antibody (Ab), anti-DNA Ab, anti-SS-A/SS-B Abs, anti-neutrophil cytoplasmic Abs (P-ANCA and C-ANCA), angiotensin-converting enzyme (ACE), and several Abs relating to paraneoplastic syndrome (PNS) such as Ma1, Ma2,

Amphiphysin, CV2, Ri, Yo and Hu were all negative. Also, Abs against human T lymphotropic virus type I (HTLV-I) and human immunodeficiency virus (HIV) were negative by ELISA. Abs against Epstein-Barr virus showed the latent infection pattern; VCA (viral capsid antigen)-IgG 80-fold (normal <10-fold), VCA-IgM less than 10-fold (normal <10-fold), and EBNA (EB nuclear antigen) 40-fold (normal <10-fold). At lumbar puncture, the initial pressure was 15 cm of water. Cerebrospinal fluid (CSF) was clear and contained 32 lymphoid cells and 1 neutrophil per cubic millimeter; the glucose concentration was 60 mg/dL (normal 50-75), the protein 72 mg/dL (normal 15-45), and IL-6 3.4 pg/mL (normal <4.0). A bacterial culture was negative. Although lymphocytes in CSF were slightly abnormal in morphology, their morphologic features alone were not enough to judge these cells as lymphoma cells. Thus, we subjected these cells to flow cytometric analysis and PCR analysis to detect gene rearrangement of TCR J β -1 and J- γ genes. However, we could not obtain any result because the number of lymphocytes was not sufficient for these analyses. Magnetic resonance imaging (MRI) with contrast for the lumbosacral spine revealed a mild enhancement in the cauda equine. Nerve conduction studies showed a decrease in the conduction velocity and F wave in the median, ulnar, and sural nerves. These results were compatible with demyelinating polyradiculoneuropathy. In addition, chest and abdominal computed tomograms showed enlarged cervical, mediastinal, pulmonary hilum, axillary and paraaortic lymph nodes. Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) examination indicated the uptake at the enlarged lymph nodes with moderately enhanced intensity [maximum value of standardized uptaking velocity (SUVmax) 2.66-4.87] (Fig. 1A).

In early October, his muscle weakness of lower limbs severely worsened and he became wheelchair bound. Because of the pain in the lower limbs which was uncontrollable with non-steroidal anti-inflammatory drugs, he was treated with intravenous methylprednisolone (125 mg/day on day 1) under the probable diagnosis of demyelinating polyradiculoneuropathy, followed by oral prednisolone (20 mg per day for 2 weeks). By two weeks later, his neurologic abnormalities had not been improved. So, he was treated with intrathecal dexamethasone (4 mg/day for one day), which somewhat relieved neurologic symptoms. During this period, we administered steroid at a low dose in order not to interfere with the subsequent diagnostic lymph node biopsy. Then, we administered intravenous immune globulin (IVIG), which has been shown to be effective for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). However, his muscle weakness of lower limbs still continued.

Left cervical lymph node biopsy was performed at the end of October. The expansion of the interfollicular area was noted in the largest node, which was composed of pleomorphic, medium- to large-sized lymphocytes with single or multiple nucleoli and an abundant amount of weakly eosinophilic cytoplasm. Numerous high endothelial venules were

Figure 2. Histological and immunohistochemical findings of the lymph node. (A) (B) Hematoxylin and Eosin staining, (A)×10, (B)×40 (objective) (C)-(H) immunohistochemical stain for cCD3 (C), CD4 (D), and CD25 (E), CD20 (F), CD8 (G) and CD10 (H) ×40.

present, but an arborizing pattern was not apparent. Plasma cells, histiocytes, and eosinophils were sparsely seen in the background (Fig. 2A, B). Immunohistochemical examination showed that proliferating cells were positive for CD2, cytoplasmic CD3 (cCD3), CD4, CD5, and CD25, and negative for CD8 and CD10. CD20-positive large cells were less dense in the interfollicular area (Fig. 2C-H). EBV-encoded small nonpolyadenylated RNA (EBER)-positive cells were not detected in any area of the lymph nodes by the *in situ* hybridization analysis. The rearrangement of the TCR β -1 and J- γ genes but not Ig JH was detected by Southern blot analysis (Fig. 3A, B, C). Also, monoclonal integration of HTLV-1 proviral DNA was not detected (data not shown). The results of the flow cytometric analysis using floating cells from the biopsy specimen were as follows: positive cells for CD3 92.9%, CD4 80.8%, CD8 14.2%, CD5 94.3%, CD19 6.8%, and CD20 11.4%, CD25 26.6%. In addition, we did not detect chromosomal abnormality in the biopsy specimen with the G-band technique. Based on these findings, we made a diagnosis of PTCL-NOS in the WHO classification. The clinical stage of this patient was considered to be stage III, because we could not prove the clonality of the atypical lymphocytes in the bone marrow or CSF as described above. Neuromuscular biopsy was performed from the left sural nerve in mid-November. Onion-bulb formations, which are histological features of repeated demyelina-

tion and remyelination, were the most prominent findings (Fig. 4). These changes were indicative of sub-acute demyelinating polyradiculoneuropathy caused by axonal degeneration. Large lymphoid cells with CD3 antigen were not apparent.

From early December, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was started for PTCL-NOS. However, severe bone marrow suppression caused pneumonia after 1 cycle of CHOP. Thus, we conducted CHOP therapy with a 4-week interval from after the 2nd cycle. After one cycle of CHOP, his muscle weakness in the lower limbs was gradually improved, and he became to be capable of walking on his foot. After two cycles of CHOP, he was almost free of the symptoms of peripheral neuropathy. FDG-PET/CT examination after three cycles of CHOP demonstrated no abnormal uptake in the cervical, mediastinal, pulmonary hilum, axillary or paraaortic nodes, indicating the achievement of complete remission (CR) (Fig. 1B). Also, sIL-2R was normalized to 294 U/mL at this point. Because clinical outcomes of PTCL-NOS are poor due to the high rate of relapse, we performed high-dose chemotherapy with autologous stem cell transplantation after six cycles of CHOP at the upfront setting. He has remained CR and has been free from neurological symptoms for 2 years.

Figure 3. Results of the Southern blot analysis on the biopsy specimen from the lymph node. (A) After digestion with EcoR I (lane 1), BamH I (lane 2), and Hind III (lane 3), the rearrangement bands of TCR J β 1 were detected in lane 1 of the present case (b) compared with the negative control (a). (B) After digestion with EcoR I (lane 1), BamH I (lane 2), Hind III (lane 3), the rearrangement bands of TCR J γ were detected in lane 1 and lane 3 of the present case (b) compared with the negative control (a). (C) After digestion with EcoR I (lane 1), BamH I + Hind III (lane 2), Hind III (lane 3), the rearrangement bands of IG(H) JH were not detected in any lane of the present case (b) compared with the negative control (a). Arrows on both figures indicate rearrangement of respective genes.

Figure 4. Histological findings of the sural nerve. Toluidine blue, $\times 400$.

Discussion

PTCL includes several types of lymphoma and the present case revealed several clinical features similar to those observed in angioimmunoblastic T-cell lymphoma (AITL). However, the present case lacked many of the typical histological characteristics of AITL such as proliferation of pale cells with arborizing blood vessels, proliferation of CD10-positive T cells with CD21-positive fibroblastic reticular/follicular dendritic cells in the background, and the association of EBV-positive B-cells. Also, some clinicolaboratory findings were different from those of AITL (lack of fever and obvious CRP elevation). Thus, we diagnosed this case as

PTCL-NOS but not AITL.

Previous reports showed that neuropathies associated with T-cell lymphoma were primarily caused by the direct invasion of lymphoma cells (3-5). However, Vallat et al. reported 13 cases of B-cell lymphoma and otherwise associated with the peripheral neuropathy (6, 7), which occurred independent of the direct invasion of lymphoma cells. In these reports, several other additional explanations have been made: (a) infection (especially by Herpes Zoster), (b) side effects of chemotherapeutic drugs (especially by vinca alkaloids) or radiation (c) vascular impairment, (d) metabolic disorders, and (e) immune-mediated mechanisms including PNS. The present patient had no history of chemotherapy or metabolic disorders. In addition, the biopsy specimen from the sural nerve showed no apparent features of direct invasion of lymphoma cells or obstruction of epineurial vessels. Thus, we speculated that the immune-mediated mechanism including PNS is involved in the polyradiculoneuropathy in our patient.

PNS is defined as a remote effect of malignant cells on the peripheral nervous system. Most of the PNS cases in adults are associated with lung cancer, especially small-cell lung cancer, and gynecological tumors. Detection of highly specific autoantibodies directed against onconeural antigens led to the current hypothesis of an autoimmune pathophysiology. Several findings indicate that a tumor would be responsible for neuropathy as follows. First, the neuropathy occurs within a short time after the tumor development in most of the reported cases. Second, latent malignancies are detected in about 10% patients with CIDP (5), and the treat-

ment of the tumor can result in an improvement of CIDP (8, 9). Furthermore, cross-immunological reactions between the tumor and the peripheral nervous system have been shown in some cases of CIDP associated with melanoma (10). The guidelines for the diagnosis of PNS was proposed by the task force organized by Federation of European neuroscience societies (FENS) and PNS Euronetwork in 2004 (11). Because chemotherapeutic therapy was effective for the neurological symptoms and no autoantibody related to PNS was detected, the present case was considered to be categorized as non-classical syndrome in PNS according to this guideline. A small but significant proportion of patients with malignant lymphoma, especially those with T-cell lymphoma, has been reported to be associated with PNS. However, to date, less than ten cases have been reported. In addition, as far as we searched, this case is the first case of PTCL-NOS, who presented with polyradiculoneuropathy as an initial symptom.

We diagnosed the neuropathy observed in the present patient as sub-acute demyelinating polyradiculoneuropathy because his clinical course was relatively rapid and not recurrent compared with typical CIDP. However, the histological findings of onion-bulb formations in the sural nerve were indicative of repeated demyelination and remyelination, which were compatible with CIDP. So, we assume that polyradiculoneuropathy in the present patient might pursue the clinical course of CIDP if chemotherapies for PTCL-NOS was not effective. Also, we speculate that a similar mechanism that would cause CIDP might be involved in our patient. In fact, a Guillain-Barre' Syndrome (GBS) or CIDP was reported to be complicated with lymphoma cases (12, 13). As for the roles of T cells in the development of CIDP in the non-lymphoma setting, the infiltration of T cells into the nerve has been observed in the biopsy specimen (14). Because such infiltration of T cells including normal and lymphoma cells into the sural nerve was not observed in our patient, we speculate that some inflammatory cytokine(s) released from PTCL-NOS cells or associated cells might cause demyelination of the peripheral neurons. In addition, although we could not detect any autoantibody related to PNS in our patient, an unidentified autoantibody might cause peripheral neuropathy with a similar mechanism observed in PNS. In agreement with our speculation, his neurological symptoms and signs were slightly improved by steroid therapy and IVIG, both of which are established treatments for CIDP and other immune-mediated neuropathies (15-17). Together, these results suggest the involvement of an immune-mediated process in his neuropathy. Furthermore, because his neurological symptoms almost completely disappeared after repeated CHOP chemotherapy, lymphoma cells were assumed to be indirectly involved in his peripheral neuropathy. However, the present case is unusual in this point, because the treatment of underlying lymphoma can only rarely improve the associated neuropathy in the reported cases (18).

In conclusion, we here report the first case of PTCL-

NOS, who presented with peripheral neuropathy as an initial symptom. Further analyses on the immunologic dysfunction in similar cases would be expected to clarify the mechanism of lymphoma-associated peripheral neuropathy.

The authors state that they have no Conflict of Interest (COI).

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