Very rare solitary primary peripheral nerve onset cytotoxic molecule-positive peripheral T-cell lymphoma (PTCL)

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Running Head: Peripheral nerve onset CM-positive PTCL

Abbreviations used: CM, cytotoxic molecule; CSF, cerebrospinal fluid; ^{18}F-PET/CT, ^{18}F-positron emission tomography/computed tomography; M, months; ML, malignant lymphoma; MTX, methotrexate; NCS, nerve conduction study; NF-κB, nuclear factor-kappaB; PTCL, peripheral T-cell lymphoma; RA, rheumatoid arthritis; TNF, tumor necrosis factor; WBC, white blood cell; Y, years.

Abstract

Here we present the first report of solitary primary peripheral nerve onset cytotoxic molecule (CM)-positive peripheral T-cell lymphoma (PTCL) diagnosed after nerve biopsy. An 84-year-old female with rheumatoid arthritis (RA) complained of asymmetric severe tenderness in her upper limbs. The biopsy pathology revealed a direct invasion of CM-positive PTCL. When RA patients complain of numbness, tenderness or weakness, lymphomatic peripheral nerve invasion should be considered.

Key words

Neuro-Oncology, Peripheral Neuropathy/Peripheral Nerve, Neurolymphomatosis, T-cell lymphoma, rheumatoid arthritis

Introduction

Although the primary lesion of malignant lymphoma (ML) are usually restricted to the lymph node, the onset of some ML are extranodal[1)]. Very few cases of the onset of ML are linked to the peripheral nerve, and most are of the B-cell type[2)]. Thus, solitary primary peripheral nerve onset T-cell lymphoma is extremely rare. The subject in the present case developed a chronic progressive sensorimotor disturbance in the left upper limb during treatment of rheumatoid arthritis (RA). Left median nerve biopsy pathology proved that the patient was suffering from solitary peripheral nerve onset cytotoxic molecule (CM)-positive peripheral T-cell lymphoma (PTCL).

Case report

The patient is a female diagnosed as seronegative rheumatoid arthritis (RA) on the basis of tenderness and morning stiffness in her finger joints at the age of 77 and treated with MTX for 5 years. When she reached 82 year-old, she complained of numbness in her left thumb, index and middle fingers. Iguratimod (25 mg/day, NF-κB inhibitor) was added because the exacerbation of RA was suspected.

In spite of the treatment, the numbness in her fingers persisted for 6 M, and subcutaneous injection of golimumab (50 mg/M, anti-tumor necrosis factor (TNF-α) monoclonal antibody) replaced MTX. However, her numbness in her fingers gradually spread over her left forearm over the next 7 M. Although the dose of golimumab was

increased to 100 mg/M, her left arm showed progressive tenderness and weakness for an additional 2 M. She was thus admitted to our hospital at the age of 84, 6 years and 2 months after the diagnosis of RA (Fig. 1A).

Upon neurological examination, her left arm showed distal dominant moderate weakness with superficial muscle atrophy. Her soft touch sense and pain sense were decreased in left median nerve area distal dominantly with severe tenderness. Both Phalen test and Tinel sign were negative. On the other hand, her lower limbs showed no obvious weakness nor sensory disturbance. However, her vibration sense was also impaired in not only her left wrist joint (10 seconds in right, 0 second in left), but also in her bilateral distal lower limbs (2 seconds in both medial malleolus). Laboratory data revealed a normal WBC count, erythrocyte sedimentation rate and C-reaction protein and a slightly elevated level of soluble interleukin-2 receptor (502 IU/mL; normal 122-496 IU/mL). Anti-N-acetylglucosamine (GalNAc)-GD1a IgG antibody assessed by enzyme-linked immunosorbent assay (ELISA) was positive, while rheumatoid factor, anti-cyclic citrullinated peptid antibody (CCP) antibody, onconeural antibodies (targeting AMPH, CV2, PNMA2, Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65 and Tr) and antinuclear antibody were negative. Serum Epstein-Barr virus DNA assessed by polymerase chain reaction (PCR) was negative. Cerebrospinal fluid (CSF) examination revealed normal cell number (mono 1/mm^3), cytology and glucose with a slightly high protein level (49 mg/dl). A nerve conduction study (NCS) revealed a demyelinating

change in the left median and radial motor nerves, i.e., prolonged distal latency, temporal dispersion, conduction block and reduced velocity. The frequency of the F-wave action potential decreased. The left median nerve showed no evoked sensory nerve action potential (SNAP), and the left ulnar nerve had a low amplitude (Table 1).

As the whole body computed tomography (CT), magnetic resonance imaging of whole spine, gastroscopy and colonoscopy did not reveal any finding of malignancy, spinal canal stenosis nor inflammation, ^{18}F-Positron emission tomography (^{18}F-PET) /CT was conducted for further investigation. It showed abnormal uptake in left cervical roots and in the brachial nerve plexus (Fig. 1B and Fig. 1C, filled arrows), which indicated solitary primary peripheral nerve malignant neoplasm such as lymphoma. In case of malignant neoplasm, it would be fatal without appropriate treatment, So, we decided to conduct the median nerve biopsy. The biopsy specimen of the left median nerve (Fig. 1D) showed extensive infiltration of atypical lymphoid cells (Fig. 1E triangles, Fig. 1F and Fig. 1G), and peripheral nerve bundles disappearance. The number of large myelinated fibers was extremely low (3,600/mm^3) with frequent degenerated fibers (Fig. 1E, arrows). The lymphoid cells were positive for CD3 (Fig. 1H), CD8 (Fig. 1I) and T-cell intracytoplasmic antigen-1 (Fig. 1J), but negative for CD4, 20, 30 or 56 (Fig. 1K). The Ki67 index was high in these lymphoid cells (Fig. 1L).

Based on the above data, the patient was diagnosed as having solitary primary CM-positive PTCL. After treatment with methotrexate and then forodesine hydrochloride, her weakness and sensations gradually improved as ^{18}F-PET/CT uptake vanished (Fig. 1M and 1N, open arrows). Six month after hospital transfer for rehabilitation, she deceased because of recurrence of her original PTCL.

Discussion

ML usually involves the lymph node, but onset in around 30% of cases is extranodal[1)]. Only 0.7% of such extranodal ML are onset by the peripheral nerve, and most of them are of the B-cell type[2)]. Only three cases of peripheral nerve onset T-cell lymphoma have been reported thus far: NK/T-cell lymphoma[3)], an unclassifiable T cell lymphoma, and an adult T cell leukaemia/lymphoma[4)]. The present case is the first report of primary peripheral nerve onset CM-positive PTCL.

Peripheral neuropathies in ML are caused by direct invasion (neurolymphomatosis), paraneoplastic neuropathy, drug or radiation-induced neuropathy and infection[5)]. Although there are several anti-glycolipid antibodies found in lymphoma associated neuropathy patients, the pathogenesis remains improbable[6)]. Furthermore, the present case with sensory dominant neuropathy is positive for IgG anti-GalNAc-GD1a antibody, which is exclusively found in patients with pure motor variant Guillain-Barre Syndrome[7)]. So, the pathogenesis of the antibody in this patient is

unclear. Even though the present case showed distal dominant sensory disturbance which could not be explained with the lesion in spinal cord nor nerve root and a demyelinating pattern in NCS, as is frequently observed in paraneoplastic neuropathy[4], her asymmetric severe tenderness also suggested direct invasion[2], which was proven by biopsy pathology (Fig. 1D, Fig. 1E, Fig. 1F, Fig. 1G, Fig. 1H, Fig. 1I, Fig. 1J, Fig. 1K and Fig. 1L).

MTX is sometimes associated with lymphoproliferative diseases[8]. However, the present case emerged 7 M after MTX (6mg/week, oral administration) withdrawal and exacerbated after golimumab induction. Furthermore, her symptoms improved temporarily after treatment for her lymphoma with MTX (1,300mg, intravenous administration). Thus, MTX discontinuation or golimumab induction seemed more involved in the pathogenesis of the present case[9][10][11].

To the best of our knowledge, this is the first report of primary peripheral nerve onset CM-positive PTCL. When RA patients treated with not only MTX but also iguratimod and golimumab complain of numbness, tenderness or weakness, lymphomatic peripheral nerve invasion should be considered.

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Figure legends

(A) The patient's clinical course from the diagnosis of her rheumatoid arthritis to the admission to our hospital. M, months; Y, years. (B and C) The patient's ^{18}F-PET/CT on admission, showing abnormal uptake (filled arrows) in left cervical roots and brachial nerve plexus. (D) Site of the left median nerve biopsy (an arrow). (E) Toluidine blue staining of the biopsy specimen showing extensive infiltration of atypical lymphoid cells (filled arrows), and (F) magnification showing frequent degenerated fibers and disappearance of peripheral nerve bundles. (G) Hematoxylin-eosin staining showing extensive infiltration of atypical lymphoid cells and disappearance of peripheral nerve bundles. Immunostaining of the biopsy specimen was positive for (H) CD3, (I) CD8 and (J) T-cell intracytoplasmic antigen-1 (TIA-1), but negative for (K) CD56 with (L) an elevated Ki67 index in these lymphoid cells. (M and N) After treatment, ^{18}F-PET/CT showed the disappearance of abnormal uptake in left cervical roots and the brachial nerve plexus (open arrows).