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CASE REPORT

Unique association of Waldenström macroglobulinemia with optic neuritis and monoclonal T cell expansion

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Abstract Waldenström macroglobulinemia is a lymphoplasmacytic lymphoma characterized by production of the immunoglobulin M (IgM) monoclonal protein. Commonly involved sites are the bone marrow, lymph nodes, and spleen. Lymphoplasmacytic infiltration of the central nervous system (CNS), in contrast, is referred to as Bing–Neel syndrome, and is an extremely rare phenomenon. Here, we present a unique case of Waldenström macroglobulinemia with optic neuritis accompanied by monoclonal expansion of T cells, which recovered after administration of CNS-targeting chemotherapy. Although the underlying causal relationships in this case remain obscure, aberrantly expanded T cells may have contributed to the development of optic neuritis, and we should be reminded that some types of cranial neuropathy in Waldenström macroglobulinemia may be reversible.

Keywords Waldenström macroglobulinemia · T cell · Monoclonal · Optic neuritis · Bing–Neel syndrome

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Case report

A 63-year-old Japanese male was referred to our hospital for moderate anemia. His past medical history was otherwise unremarkable except for the left optic neuritis, which was treated with steroids 11 months before this referral (Fig. 1). Biochemical examination revealed increased serum immunoglobulin M (IgM) value of 62 g/L and serum protein immunofixation detected monoclonal protein of kappa type IgM. Light microscopic examination together with flow cytometry of the bone marrow disclosed infiltration of atypical lymphocytes with the surface marker expression of CD20, CD79a, IgM and monotypic immunoglobulin light chain (Fig. 2a). Taken together, the diagnosis of Waldenström macroglobulinemia was made. Six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) regimen were administered, and partial remission was achieved.

About 2.5 years after the chemotherapy, the patient began to complain of recurrent light aversion. Ophthalmologic examination and imaging survey confirmed recurrent left optic neuritis (Fig. 2b, c). At just about the same time, appearance of atypical lymphocytes in the peripheral blood was detected. These atypical cells were small and morphologically different from previously described lymphoplasmacytes (Fig. 2d). Flow cytometry disclosed that they expressed surface markers of cytotoxic T cells (surface markers positive for CD3, CD8 and negative for CD4 and CD56), and light chain deviation to kappa-type was not detected in the peripheral blood, while it was seen in the bone marrow (Fig. 2e, f). Histopathological findings of the bone marrow showed increased number of CD20, CD79a, IgM and immunoglobulin light chain deviation positive lymphoplasmacytes, which were consistent with the diagnosis of recurrent macroglobulinemia. Though the number

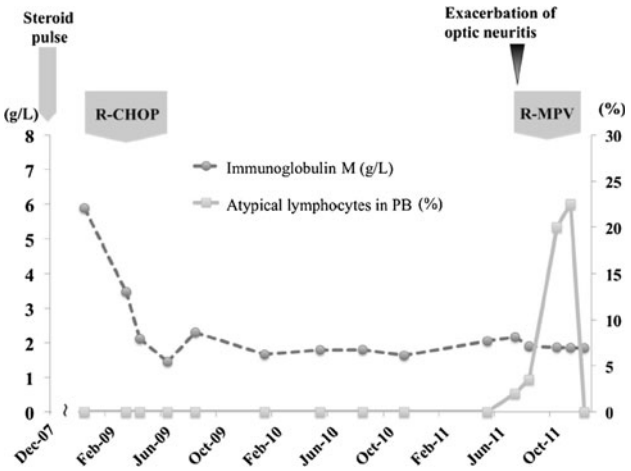

Fig. 1 Clinical course of the present case. While IgM levels were kept stable after the first chemotherapy, monoclonal expansion of T cells was observed in the peripheral blood (*PB*) at the time when optic neuritis exacerbated. These aberrant T cells disappeared as the left optic neuritis resolved after chemotherapy with R-MPV regimen

of T cells in the bone marrow had not increased, detection of T cell receptor (*TCR*) rearrangement by polymerase chain reaction (PCR) amplification suggested a possible monoclonality of these T cells (Fig. 3). Limited amount of cerebrospinal fluid discouraged us from applying Southern blot for further confirmation, however, repeated lumbar puncture and cerebrospinal fluid assessment with flow cytometry showed infiltration of both lymphoplasmacytes and T cells to the CNS (Fig. 2g, h). The risk of compromising the optic nerve discouraged us from proceeding to the biopsy of the abnormally enhanced intracranial lesions surrounding the optic nerve. While leaving a possibility of mucosa-associated lymphoid tissues (MALT) lymphoma of the orbital tissues, repeated examination detected no evidence of MALT involvement like conjunctiva, orbital soft tissue or lacrimal gland throughout the observation period. Thus we made the diagnosis of the CNS involvement of Waldenström macroglobulinemia associated with monoclonal T cells. After two cycles of rituximab, methotrexate,

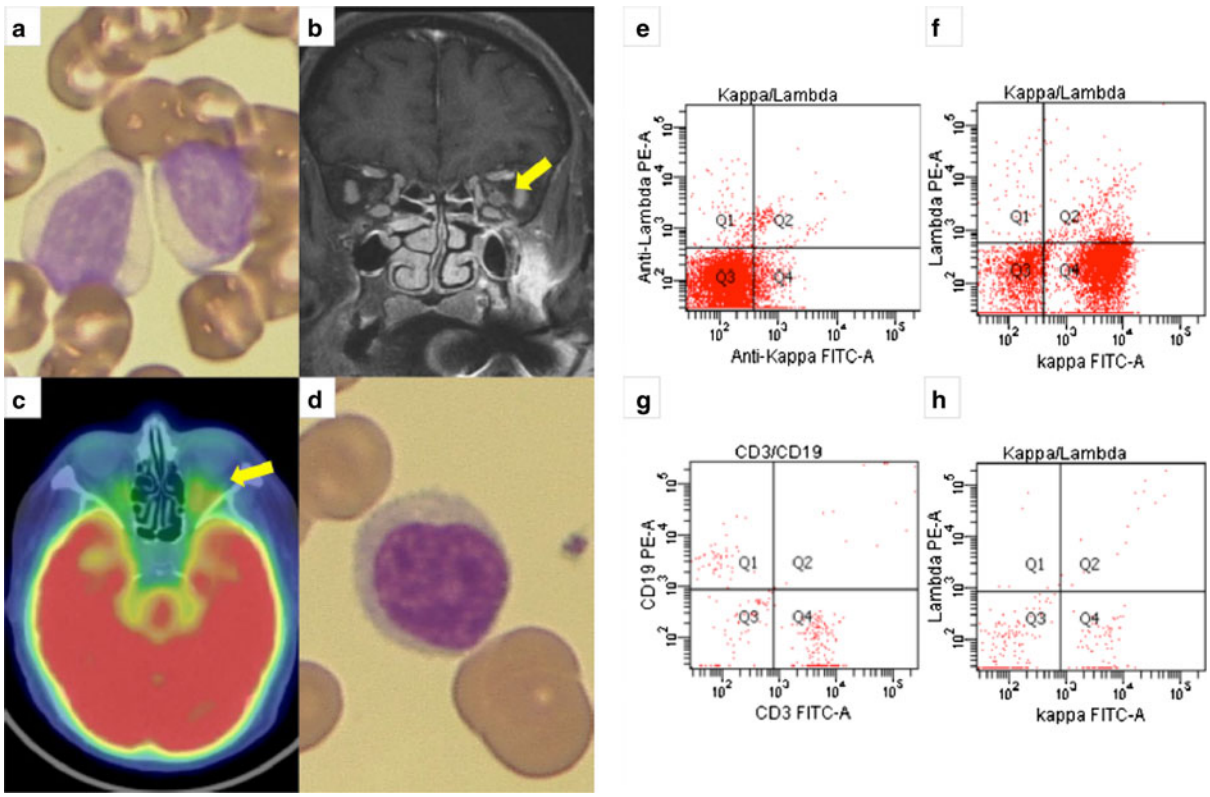

Fig. 2 Unique presentation of Waldenström macroglobulinemia with optic neuritis and monoclonal T cell expansion. **a** Lymphoplasmacytes of Waldenström macroglobulinemia in the bone marrow (×1000). **b** Brain MRI showed swollen left optic nerve with enhanced optic nerve sheath (*arrow*), compatible with recurrent left optic neuritis. **c** FDG-PET/CT demonstrated mildly increased uptakes in the left orbital nerve (*arrow*) with no other abnormal accumulations. **d** Monoclonally expanded atypical T cells in the PB (×1000). **e**, **f** Bivariate histogram of flow cytometry of patient's samples. While kappa-type light chain restriction was detected in the bone marrow (**e**), it was not seen in the peripheral blood (**f**). These findings implicated that these post-chemotherapeutically emerged atypical lymphocytes in the peripheral blood were of T cell origin. **g**, **h** Bivariate histogram of flow cytometry using a sample of the patient's cerebrospinal fluid (CSF). Every plot represents lymphocyte element. Among lymphocytes in CSF were CD3-positive monoclonal T cells as well as CD19, CD20 and light chain restriction deviation positive lymphoplasmacytes of Waldenström macroglobulinemia

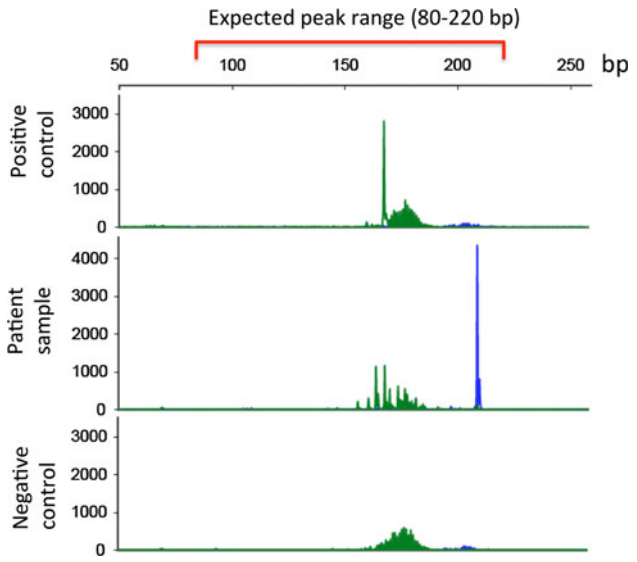

Fig. 3 Detection of T cell receptor (TCR) rearrangement in the patient's bone marrow sample. At the time recurrence, the bone marrow assessment discovered TCR beta and gamma gene rearrangement by polymerase chain reaction (PCR) method. Representative result is shown together with positive and negative controls. DNA was extracted from the sample and amplified by PCR. The PCR product was then capillary-electrophoresed with Applied Biosystems 3130 Genetic Analyzer and the rearrangement was examined by fragment analysis applications. Detected peak was considered positive when it appeared within the expected range (in this setting 80–220 bp) and its peak was higher than that of positive control. These procedures were commercially done by Mitsubishi Chemical Medience Corporation. Due to the nature of PCR method, this procedure could not rule out the possibility of false-positive results

procarbazine and vincristine (R-MPV) regimen [1], resolution of the optic neuritis with improved visual symptoms was attained, and monoclonal T cells disappeared.

Waldenström macroglobulinemia is a malignant proliferation of plasma cells secreting monoclonal IgM. Interestingly, monoclonal T cell expansion is commonly encountered among them [2]. This phenomenon was also detected in the present case concurrently with the development of optic neuritis. Although TCR rearrangement proved only by PCR method may not be sufficient to conclude that expanded T cells are definitely monoclonal, and causal association of the aberrant expansion of T cells and the optic neuropathy is a speculated one, its contribution to the development of this unique presentation of the disease might have been possible.

Neuropathy is also a frequently encountered event. The most common symptomatic neuropathy in Waldenström macroglobulinemia is symmetric peripheral polyneuropathy [3], and its pathology is attributable to autoantibody activity of IgM [4]. On the contrary, cranial neuropathy is uncommon and it could be caused by direct infiltration of lymphoplasmacytes into the CNS. This phenomenon is referred to as Bing–Neel syndrome, which was first described in 1936 [5]. To date, only case reports and several small patient series of Bing–Neel syndrome have been published. To our knowledge, only three cases of Bing–Neel syndrome with optic nerve involvement while sparing other nerves have been reported including the present case [6, 7]. Among them, two cases achieved fair neurological outcome with CNS-targeting chemotherapy, however, intensive chemotherapy combined with radiation could not prevent one patient from loosing his sight.

Thus, Waldenström macroglobulinemia with optic neuropathy is a recurrent phenomenon and we could expect fair neurological outcome in some cases by administering CNS-targeting chemotherapy.

In conclusion, we experienced a rare case of Waldenström macroglobulinemia presented with optic neuritis and monoclonal expansion of T cells. We should be reminded that, though it is a rare complication, cranial neuropathy caused by direct infiltration of Waldenström macroglobulinemia to the CNS does occur and this treatable phenomenon should carefully be ruled out.

Conflict of interest The authors have no conflicts of interest.

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