CASE REPORT

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Primary neurolymphomatosis with MAG antibody: a case report

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Abstract

Neurolymphomatosis (NL) is a rare neurologic manifestation of non-Hodgkin lymphoma (NHL) with poor prognosis. Investigations including MRI, PET/CT, nerve biopsy and cerebrospinal fluid (CSF) analysis can aid the diagnosis of NL. In this study, we presented a case of NL with co-existing myelin-associated glycoprotein (MAG) antibody. The patient first presented with symptoms of peripheral neuropathy involving multiple cranial nerves and cauda equina, and later developed obstructive hydrocephalus and deep matter lesions. He also had persistently positive MAG antibody, but did not develop electrophysiologically proven neuropathy and monoclonal immunoglobulin. The final brain biopsy confirmed diffuse large B cell lymphoma.

Keywords Neurolymphomatosis, MAG antibody, Rituximab, Cranial neuropathy

Introduction

Neurolymphomatosis (NL) is an uncommon syndrome of peripheral or cranial nerve root dysfunction with a poorly defined incidence and secondary to infiltration by hematologic malignancies, such as non-Hodgkin lymphomas (NHLs) and acute lymphoblastic leukemia [1]. The diagnosis of NL remains challenging, primarily as presenting symptoms are varied, conventional radiology has only modest sensitivity, and pathological diagnosis is often difficult [1, 2].

Lymphoma is a type of malignant tumors originating from different types of lymphocytes. There is a complex interrelationship between lymphoma and autoimmune diseases. It is proposed that the imbalance of immune regulation may be the basis for these immune mediated diseases in lymphoma patients [3]. Although epidemiological data were not sufficient to confirm the association with autoimmune diseases, NL seems to have a higher incidence of concomitant autoimmune diseases, including allergic purpura, systemic lupus erythematosus, hypothyroidism, celiac disease, Sjogren's syndrome, nodular erythema, recurrent chorioretinitis, peripheral neuropathy [4–6]. Peripheral neuropathy occurs in 5% of lymphoma patients. Polyneuropathy associated with IgM monoclonal gammopathy is the common clinical phenotype of peripheral neuropathy in lymphoma patients, and more than 50% of these patients have antibodies against MAG [3].

In the present study, we report a case of NL in which MAG antibody titer was progressively elevated without any clinical sign of peripheral neuropathy involvement.

Case presentation

A 64-year-old male gradually developed binocular diplopia and distal lower limb numbness and weakness from August 2021. He was diagnosed of peripheral neuropathy at the local hospital and was treated with high-dose

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IV steroids, followed by oral steroids and tacrolimus. His symptoms were partially resolved within 2 months, then worsened again during steroid tapering.

The patient was referred to our hospital in April 2022 (Fig. 1). On physical examination, he was alert and well oriented. He had bilateral facial numbness and decreased olfactory and gustatory sensations. Eyeball movement was unrestricted toward all directions. Muscle strength was decreased with MRC grading 5/5 in upper limbs and 4/5 in lower limbs. His knee reflexes were depressed. MR imaging showed enhancement of the cranial nerves (CNs) V, VIII, IX, and cauda equina (Fig. 2A-D). CSF analysis showed elevated leukocyte count, reduced glucose level, and elevated level of immunoglobulins (Table 1). CSF cytology did not find any atypical lymphocytes. Nor did flow cytometry identify monoclonal lymphocytes. Cell-based assay (CBA) showed the presence of serum Myelin Associated Glycoprotein (MAG) IgM antibody (titer 1:320, Fig. 3A). However, monoclonal immunoglobulin was absent on serum and urine immunofixation electrophoresis, and bone marrow biopsy also showed no remarkable abnormalities. Seral EB virus DNA was 3.90×10^3 copies/mL (normal range $< 4.0 \times 10^2$ copies/mL). Screening for common pathogens (herpesviruses, JC polyomavirus, mycobacterium tuberculosis, fungus, HIV and syphilis), and immune parameters (including ANA, ANCA, ENA, SSA, SSB, RF, ACPA, VEGF, GM1, GM2, GM3, GD1a, GD1b, GQ1b, GT1b, GM4, GD2, GD3, GT1a, Sulfatide, NF155, NF186, CNTN1, CNTN2, CASPR1).was all negative. Electromyography, chest CT scan, ultrasound for superficial lymph nodes and abdomin were unrevealing. The patient was suspected of a neoplastic or immune-mediated peripheral neuropathy involving cranial nerves and cauda equina. He underwent two rounds of lymphoplasmapheresis without any noticeable improvement. Then two cycles of rituximab

were administered (600 mg IV monthly). After each treatment with rituximab, his symptoms would significantly worsen to the point of being bedridden within one week, and then gradually improve (Fig. 1).

In January 2023, the patient was re-hospitalized due to recurrence of facial numbness, decreased olfactory and gustatory sensations and lower limb weakness (Fig. 1). He also had diplopia. Physical examination found that bilateral eyeball movement in upward, downward, and inward direction was restricted, suggestive of partial paralysis of bilateral oculomotor nerves. Repeated CSF investigation showed similar yet worsened abnormal findings compared to those of previous time (Table 1). Oligoclonal band (OCB) was negative. Reiber coordinate analysis showed intrathecal IgG, IgA and IgM synthesis with disruption of the blood-brain barrier (Table 1). CSF cytology and flow cytometry was unrevealing. This time the titer of sera MAG antibody was increased to 1:1000 (Fig. 3B) and the titer of CSF MAG antibody was 1:10. Repeated serum and urine immunofixation electrophoresis remained negative. On brain MRI, CN V, VIII, IX showed stronger enhancement than before (Fig. 2F-H). Moreover, CN III and ependyma of lateral ventricles was thickened and enhanced (Fig. 2I-J). Subsequent ^{18}F-FDG PET/CT scan showed hypermetabolism of lateral ventricle ependyma, anterior commissure, vertebral sacral canal and CN III, V, VIII (Fig. 3E-J). CNS lymphoproliferative disease was suspected. The patient refused brain biopsy. He was discharged after infusion of 600 mg rituximab (Fig. 1). This time his symptoms did not show any improvement. He later developed headache and intermittent nausea and vomiting.

In February 2023, the patient was hospitalized for the third time due to severe headache and frequent nausea and vomiting (Fig. 1). On physical examination, he was lethargic. Repeated MRI showed hydrocephalus and
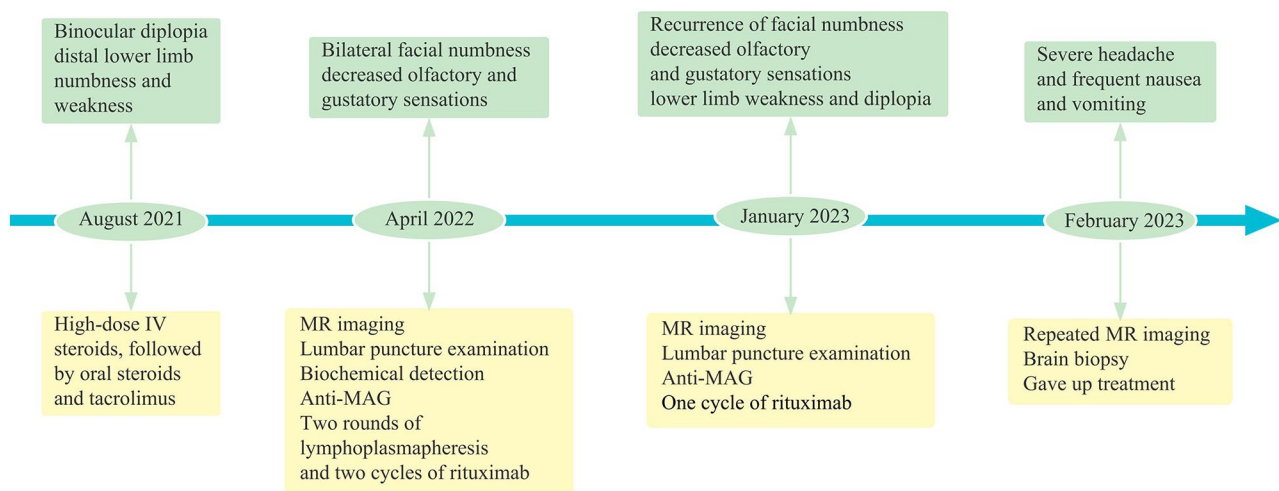
Fig. 1 Timeline of the clinical manifestations and treatment progression
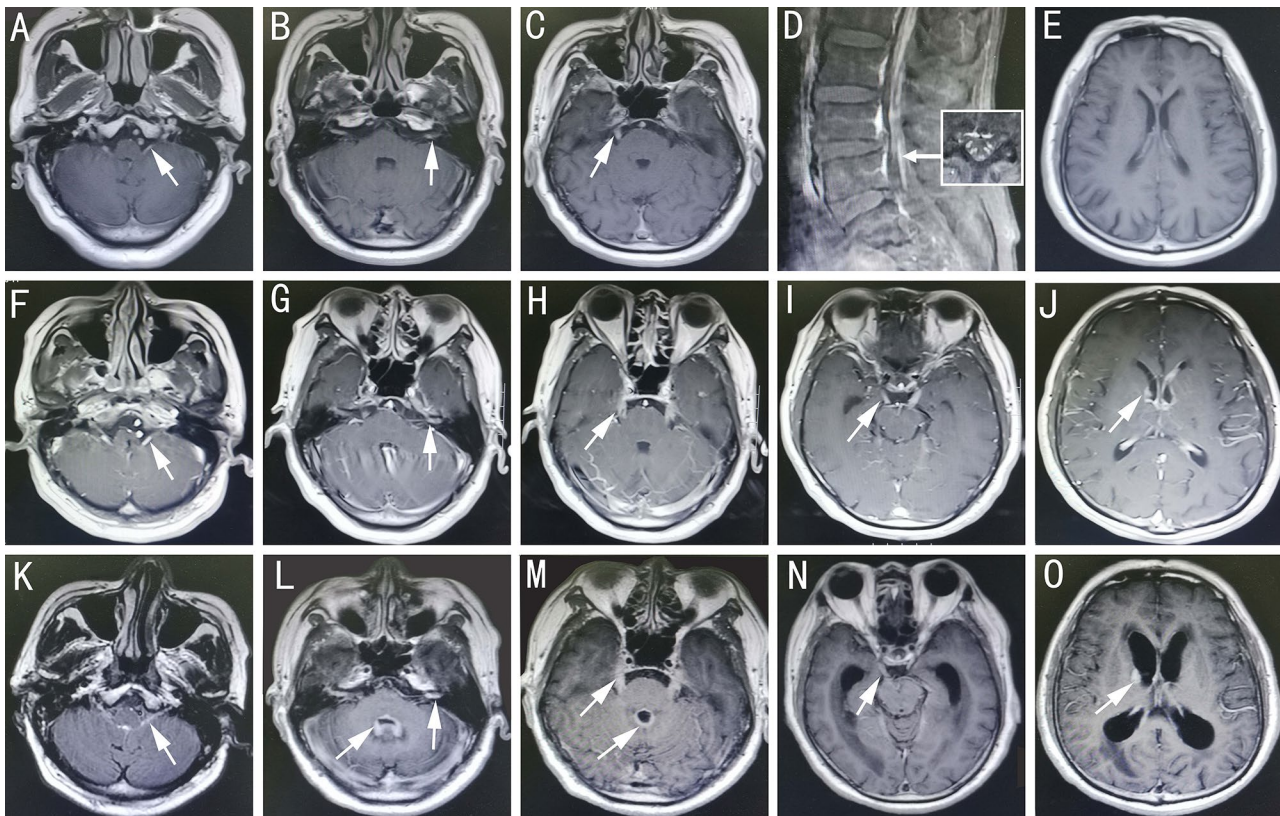
Fig. 2 MRI images of brain and spinal cord. (**A**-**E**) initial MRI 4/2022 showing enhancement of CN IX (**A**), VIII (**B**), V(**C**) and cauda equina (**D**), no enhancement in the lateral ventricle wall (**E**). (**F**-**J**) MRI 1/2023 showed that CN IX (**F**), VIII (**G**) and V (**H**) were strengthened more obviously than before. At the same time, the III cranial nerves (**I**) and the ependyma of the lateral ventricle (J) were thickened and strengthened. (**K**-**O**) Re-examination of MRI 2/2023 showed that CN IX (**K**), VIII (**L**), V(**M**), III(**N**), ependyma of the fourth ventricle (**L**, **M**) and lateral ventricle (**O**) was significantly enhanced, and severe hydrocephalus had occurred (**N**, **O**)

**Table 1** Results of serial CSF and laboratory studies

	April 2022	January 2023	Reference value
CSF cell count (×10^6/L)	90	260	< 5
CSF differential count	95% monocyte 5% multi-nuclear cells	90% monocyte 10% multi-nuclear cells	
CSF protein (mg/L)	4190.0	9210.0	150.0~450.0
CSF glucose (mmol/L)	1.73	0.68	2.50~4.4
CSF IgG (mg/L)	720.0	1250.0	0.0~30.0
CSF IgA (mg/L)	108.0	177.0	0~11.10
CSF IgM (mg/L)	57.80	59.70	0~6.94
Q_{IgG}	-	1.48	< 0.85
Q_{IgA}	-	1.03	< 0.65
Q_{IgM}	-	0.98	< 0.55
OCB	-	Negative	Negative
Serum MAG antibody	1:320	1:1000	Negative
Monoclonal immunoglobulin	Negative	Negative	Negative

more obviously enhancing lesions, especially along the lateral ventricle wall and the ependyma of the fourth ventricle (Fig. 2M-O). The patient underwent extracorporeal drainage of lateral ventricle and a stereotactic biopsy procedure of the lateral ventricle lesion. Brain biopsy confirmed diffuse large B-cell lymphoma (Fig. 3C-D). Unfortunately, the patient developed right basal ganglia and midbrain hemorrhage after surgery. His family gave up treatment and asked for discharge 10 days later (Fig. 1).

Discussion

We report a primary NL case presenting with peripheral neuropathy involving cranial nerves and spinal nerve roots, and insidious CNS lesions that eventually developed into overt periependymal lesions. He also had persistently positive MAG antibody and a very high CSF protein level. The CNS and PNS lesions were gadolinium enhancing and hypermetabolic on FDG PET/CT. The patient was transiently responsive to rituximab during disease progression.

NL is a rare type of lymphoma in which nerves are infiltrated by neurotropic neoplastic cells in the setting
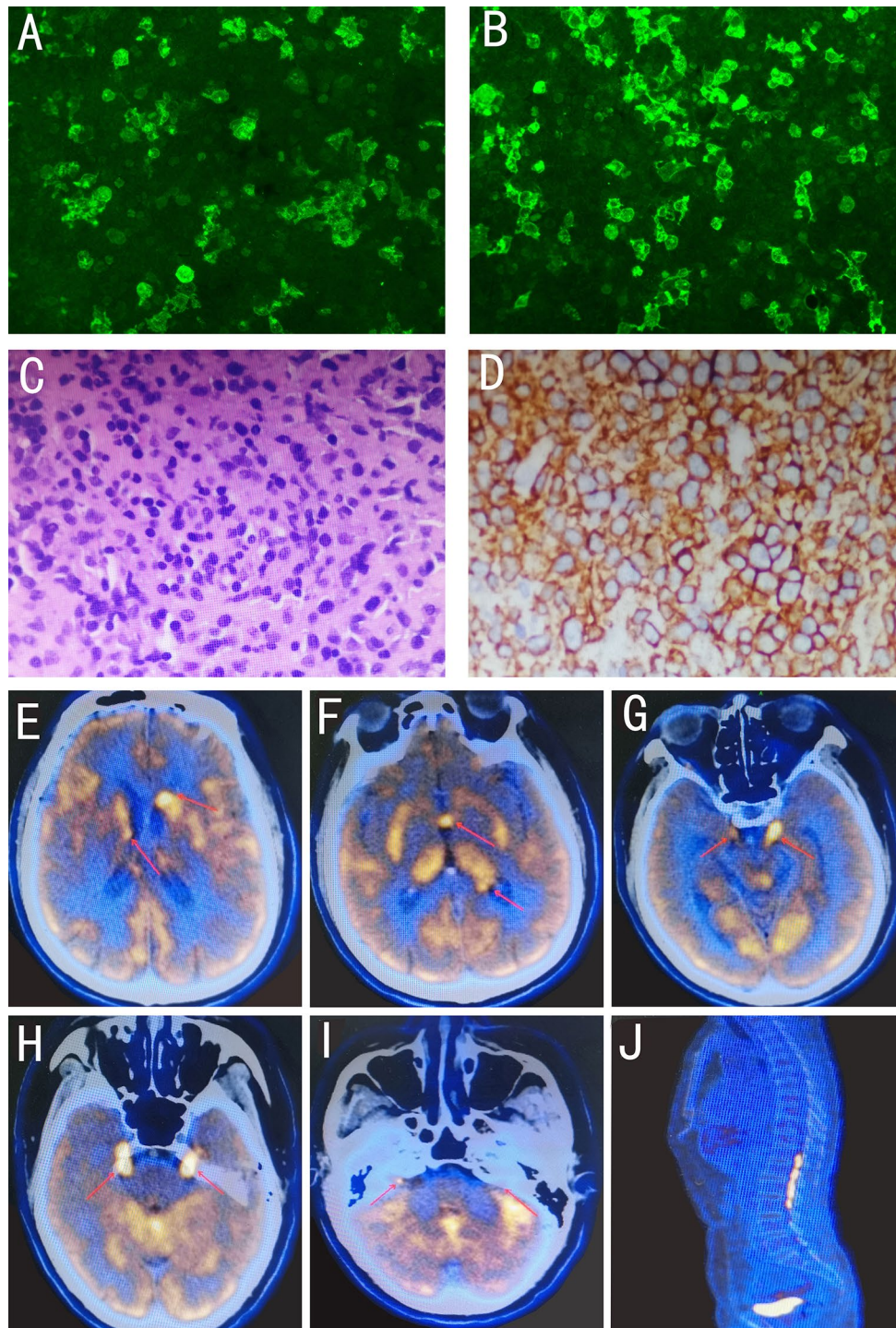
Fig. 3 Immunohistochemistry/ H&E staining and PET/CT scan. The initial (**A**, titer 1:320) and second (**B**, titer 1:1000) MAG antibody immunohistochemistry. (C-D) The tumor was composed of a diffuse infiltrate of large lymphoid cells with irregular nuclei on HE staining (**C**). The majority of tumor cells were CD20 positive shown here. Labelling with Ki-67 was > 80%. They also expressed CD10, MUM1, Bcl-2, Bcl-6 and PAX (**D**). (**E**-**J**) PET/CT scan showed hypermetabolism of lateral ventricle ependyma (**E**), anterior commissure (**F**), III (**G**), V (**H**), VIII (**I**)cranial nerves and within sacral vertebral canal (**J**)

of an unknown or a known hematological malignancies [4]. Typical NL can affect peripheral nerves, nerve roots, plexus, or cranial nerves. The most common presentations include a painful or painless polyneuropathy, mononeuropathy, mononeuropathy multiplex, and cranial neuropathy [4, 7]. B-cell NHL is the most common pathological type, whereas T-cell lymphomas are rare [1, 5]. Optimal treatment remains unknown, with

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Rituximab being effective for some NL cases [1, 5–7]. NL can be divided into primary and secondary NL. Primary NL refers to the condition in which NL is the initial and only manifestation of malignancy at the time of diagnosis. Secondary NL refers to NL occurring at the site of progression or recurrence in previously diagnosed hematological lymphoma malignancy [6]. Our patient demonstrated PNS as well as CNS involvement on presentation, although his initial symptoms were mainly PNS-related. Coexistence of CNS and PNS involvement in NL is rare. The prevalence of concomitant NL and CNS involvement is between 10–26% [1, 5, 6]. The lesions probably spread via CSF circulation. Whether the CNS or PNS lesion is the truly 'primary' disease location remains elusive.

MAG is a minor component of the myelin sheath, present at the myelin sheath and axon interface. It plays an important role in regulating adhesion and signal transduction between axons and myelin sheath [8, 9]. MAG malfunctioning, as in the presence of pathogenic mutations or anti-MAG autoantibody, may cause demyelinating or neurodegenerative diseases, with the most common phenotype being anti-MAG peripheral neuropathy [10]. MAG consists of immunoglobulin like domain and the Human Natural Killer-1 (HNK-1) carbohydrate epitope, which defines an antigen shared between human lymphocytes and neuromyelin protein. Meanwhile, the HNK-1 epitopes are recognized by anti-MAG antibody in patients with polyneuropathy [8], which offers an explanation for the phenomenon that patients with lymphatic system malignancy are prone to developing MAG antibody and peripheral neuropathy [11, 12].

There are several mechanisms involved in the production of MAG antibody in lymphoma, with the main one proposing malignant lymphocytes being the source for antibodies, which are often accompanied with monoclonal immunoglobulin [8]. Monoclonal immunoglobulin is an immunoglobulin molecule or segment with the same amino acid sequence and protein structure produced by the malignant proliferation of plasma cell disease and a small amount of B-cell lymphocytes, which is mainly diffuse large B-cell lymphoma [13, 14]. The probability of the presence of monoclonal immunoglobulin, mainly IgM, in diffuse large B-cell lymphoma is estimated to be 4.5–13.8% [14, 15], wherein more than 50% of the patients with IgM monoclonal immunoglobulin is associated with MAG antibody [12]. Although anti-MAG antibodies were described to be invariably associated with IgM monoclonal immunoglobulin, there were clinical reports that some patients with anti-MAG antibodies did not have monoclonal immunoglobulin [12]. This phenomenon may be due to (1) the low concentration of monoclonal immunoglobulin that is undetectable by immunofixation electrophoresis; (2) that the observation time is not long enough because early antigen-driven autoimmune process may be followed by late appearance of the monoclonal immunoglobulin [3, 12].

Non-lymphomatous clonal B-cell expansion due to immune "escape" mechanism which is equivalent to the imbalance of immune system regulation may be another mechanism for the emergence of MAG antibodies in lymphoma patients [3]. Some reported that lymphoma patients developed a variety of peripheral neuropathy-related IgM /IgG antibodies such as MAG, GM1, GD1a and GD1b in the absence of monoclonal immunoglobulin, which was probably the consequence of a lymphoma-induced generalized more-or-less disordered immune regulation [12, 16, 17]. In the same way, our NL case was of the diffuse large B-cell lymphoma type, and he had progressively increased anti-MAG-IgM titer but persistently negative monoclonal immunoglobulin. The production of MAG antibodies in our reported NL patient may be caused by immune dysfunction, rather than monoclonal malignant lymphoma cells. The titer of MAG antibody in CSF of this case was significantly lower than that in serum, which indicates peripheral, instead of intrathecal production of this antibody.

The HNK-1 carbohydrate epitope is not only the antigenic region of MAG, but is also present in other sulfated myelin-related proteins (such as glucuronyl paragloboside SGPG, P0, PMP-22, and phosphacan), members of the tenascin family, integrins and proteoglycans [18–20]. Thus, such glycoconjugates other than MAG may also be recognized or targeted by anti-MAG antibodies [18]. Antibodies against HNK-1 carbohydrate are detected in tumors such as meningiomas, germinomas, orbital tumors, glioblastomas, medulloblastomas, lymphoma, subependymomas, subependymomas, and medulloblastomas [19]. HNK-1 carbohydrate is functionally involved in cell adhesion, recognition, and migration. The continuous presence of antibodies and the gradual increase of titer may suggest the occurrence or progression of these tumors [19, 21]. The reason for elevated MAG antibody but not clinical sign of neuropathy involvement could be that the antibody titers did not reach a critical level or the antibody exposure time was not long enough [22, 23]. In addition, The generation of MAG antibody may also be due to targeted HNK-1 glycoproein epitope on proteins other than MAG [18, 21].

The CSF protein concentration of this patient we reported was very high and increased progressively. The main reasons for the increase of cerebrospinal fluid protein include the destruction of blood–brain or blood-nerve barrier, intrathecal synthesis, arachnoid granule absorption obstacle and cerebrospinal fluid circulation obstruction [24]. Reiber coordinate analysis indicates that both destruction of the blood–brain or blood-nerve barrier and intrathecal synthesis lead to the elevated CSF protein level. Lmphoma infilatration of cranial nerves and

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cauda equina causes the break down of blood-nerve barrier. allowing immunoglobulin entering CSF from blood. Meanwhile, the malignantly cloned B lymphocytes were recognized as antigens by immune system, thus leading to the increase of CSF immunoglobulin [25]. As in accordance with the absence of monoclonal immunoglobulin, the intrathecally synthesized protein remains polyclonal.

In conclusion, we report a NL case with both PNS and CNS involvement and persistently positive MAG antibody, which is likely to be due to immune dysfunction rather than monoclonal lymphoma cells. Meanwhile, the HNK-1 glycoprotein epitope of MAG is not necessarily the epitope recognized by MAG antibodies.

Declarations

Ethics approval and consent to participate
Informed written consent was signed by the patient.

Consent for publication
Informed consent for publication was signed by the patient's daughter.

Competing interests
The authors declare no competing interests.

Disclosure
The authors report no disclosures relevant to the manuscript.

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