

Anti-Ma2-associated limbic encephalitis with coexisting chronic inflammatory demyelinating polyneuropathy in a patient with non-Hodgkin lymphoma

A case report

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Abstract

Rationale: We report the rare case of a 74-year-old man with anti-Ma2-associated paraneoplastic neurologic syndrome (PNS), and review and analyze the clinical manifestations, diagnosis, and treatment of the disease.

Patient concerns: The patient presented with a 5-month history of muscle weakness, progressive body aches, and weakness and numbness in both lower extremities. Before his hospitalization, he had experienced cognitive function decline; ptosis, inward gaze, and vertical gaze palsy in the right eye; and occasional visual hallucinations. Brain and spinal cord magnetic resonance imaging (MRI) yielded normal results. Anti-Ma2 antibodies were detected in both serum and cerebrospinal fluid. A 4-hour electroencephalogram showed irregular sharp slow waves and δ waves in the temporal region. Electromyography showed peripheral nerve demyelination. Positron-emission tomography/computed tomography (PET-CT) examination revealed hypermetabolism in the lymph nodes of the whole body. Biopsy of the lymph nodes showed non-Hodgkin lymphoma.

Diagnosis: A clinical diagnosis of lymphoma and PNS was made.

Interventions: The patient was treated with intravenous dexamethasone (15 mg/day) for 3 days.

Lessons: We have presented a rare case of a PNS involving both the central and peripheral nervous systems. The clinical features of this case indicated anti-Ma2-associated encephalitis and chronic inflammatory demyelinating polyneuropathy. PET-CT played a critical role in enabling early diagnosis and prompt treatment in this case.

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy, MRI = magnetic resonance imaging, NHL = non-Hodgkin lymphoma, PET-CT = Positron-emission tomography/computed tomography, PNSs = Paraneoplastic neurologic syndromes.

Keywords: Anti-Ma2-associated limbic encephalitis, chronic inflammatory demyelinating polyneuropathy, non-Hodgkin lymphoma

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WJ and BQ contributed equally to this work.

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1. Introduction

Paraneoplastic neurologic syndromes (PNSs) can be the first symptom of a covert malignancy. Early treatment of PNS may improve the morbidity and mortality rates of cancer patients. Advances in antibody-detection techniques have enabled definitive diagnoses in patients with paraneoplastic and non-paraneoplastic autoimmune encephalitis. However, antibodies are absent in most cases of PNS associated with lymphomas, especially non-Hodgkin lymphoma (NHL).^[1] Anti-Ma2-associated encephalitis is a rare immune-mediated PNS with preferential involvement of the limbic system, diencephalon, and upper brain stem. It has been mainly described in adult men with testicular germ cell tumors.^[2] Herein, we report a newly diagnosed case of anti-Ma2-associated PNS with coexisting chronic inflammatory demyelinating polyneuropathy (CIDP) in a patient with NHL.

2. Case presentation

2.1. On admission

A 74-year-old man was admitted to our hospital because of acute worsening of body aches, numbness of all four limbs, and

weakness of the lower limbs. He reported that all of these symptoms had been slowly progressing during the past 5 months. During this period, he had sustained 2 falls during this period and felt that he was slow to react. He had also occasionally experienced visual hallucinations, and had lost almost 5 kg in 1 month.

Brain computed tomography (CT) showed lacunar infarction. Magnetic resonance imaging (MRI) of the cervical, thoracic, and lumbar spine showed degenerative changes. His sodium and chloride ion levels were slightly decreased, whereas his high-sensitivity C-reactive protein (hs-CRP) level had increased to 6.5 times the normal value (normal range, 0–3.5 mg/L), and his β_2 microglobulin level had increased to 3 times the normal value (normal range, 0.7–1.8 mg/L). Routine blood examination and a coagulation profile revealed no abnormalities. Tests for anti-streptolysin O and rheumatoid factor were negative.

On admission to our clinic, further aggravation of the clinical symptoms was observed, and right blepharoptosis and limited eyeball movements were detected, indicating right oculomotor paralysis. On examination, the patient appeared drowsy, slow to react, and poorly oriented in time and place. Tripareisis involving both lower limbs and the right upper limb was detected, the tendon reflexes had disappeared in all 4 limbs, and hypalgesia in 4 limbs was found in this patient.

A physical examination revealed that the patient could not complete the finger-to-nose test and heel-knee-tibia test with his right limbs owing to weakness. He scored 24 points on the Mini-Mental State Examination of cognitive function (orientation, 2; attention and calculation, 1; recall, 1; language, 1; ability to follow simple commands, 1).

2.2. Investigations

Serological hs-CRP was 34.50 mg/L (normal 0–3.5), erythrocyte sedimentation rate was 86 mm/hour (normal 0–15), and β_2 microglobulin level was 5.28 mg/L (normal 0.7–1.8). The serum IgA was 6.7 g/L (normal 0.7–4.0), IgG was 16.7 g/L (normal 7.0–16.0), and anticardiolipin IgG antibody level was 16 U/mL (normal 0–10). In addition, tests for IgG antibodies to herpes simplex virus, rubella virus, and cytomegalovirus were positive. The serum titers of IgG antibody of Epstein–Barr virus core antigen was 4.165 s/co (normal <1.100). The serum levels of creatine kinase and lactate dehydrogenase were normal. Serological testing for syphilis and human immunodeficiency virus was negative.

A lumbar puncture revealed albuminocytologic dissociation in the cerebrospinal fluid (CSF), specifically, the cell count was 4×10^6 cells/L (normal 0–8) with 2 lymphocytes and without any abnormal cells, and the protein concentration was 1.32 g/L (normal 0.15–0.45). Anti-PNMA2 (Ma2/Ta) was suspected to be positive in the CSF and weakly positive in the serum (antibody expression was graded as follows: $\leq 25\%$ positive cells, suspected to be positive; $>25\%$ and $\leq 50\%$ positive cells, weakly positive; $>50\%$ and $\leq 75\%$ positive cells, positive; and $>75\%$ positive cells, strongly positive).

The serum total prostate-specific antigen was mildly increased; other tumor markers were negative. A lung CT scan showed an old lesion in the superior lobe of the right lung. Abdominal Doppler ultrasonography showed prostatic hyperplasia with calcification. Scrotal Doppler ultrasonography showed a spermatocele in the head of the left epididymis. A prostatic MRI showed prostatic hyperplasia and slight enlargement of the lymph nodes in the inguinal regions and around the iliac vessels.

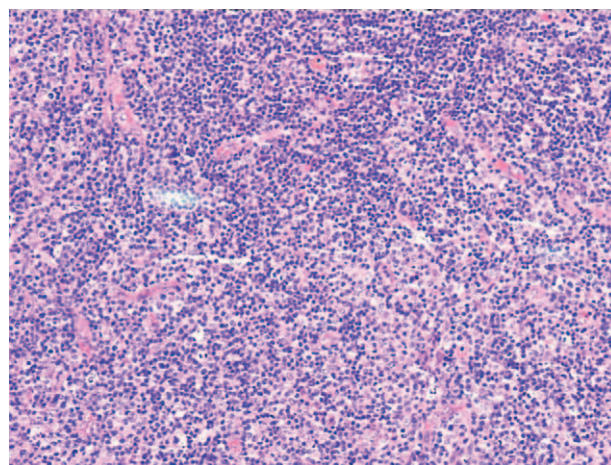


Figure 1. Histological examination using conventional techniques showed complete effacement of the epidural space by sheets of atypical lymphoid cells (magnification, 20 \times).

Positron emission tomography (PET)/CT showed that lymph nodes in multiple regions were mildly enlarged with increased metabolism, indicating a high possibility of lymphoma. Histopathological examination of the inguinal lymph nodes was suggestive of angioimmunoblastic T-cell lymphoma (AILT) or peripheral T-cell lymphoma.

Immunohistochemical examination yielded the following results: Ki-67 (+60%), CD2 (+), CD3 (+), CD43 (+), CD5 (+), CD20 (–), PAX-5 (–), CD10 (–), Bcl-6 (scattered +), CD21 (DC +), PD-1 (–), Bcl-2 (+), CD15 (–), CD30 (a few scattered +), CD7 (+), CD43 (+), CD4 (+), CD8 (partially +), granzyme B (–), TIA-1 (a few scattered +), CD56 (–), EMA (–), ALK (–), CD30 (scattered +), CD15 (–), EBER (a few scattered+). The immunohistochemical results are shown in Figures 1–4.

Brain MRI was performed twice; both MRI scans showed multiple lacunar infarctions with no suspicious signals in the brain stem and diencephalon (Fig. 5). Brain magnetic resonance angiography showed partial disappearance of the left vertebral artery, suggesting blockage. Electromyography showed that peripheral nerve conduction in all 4 limbs was significantly

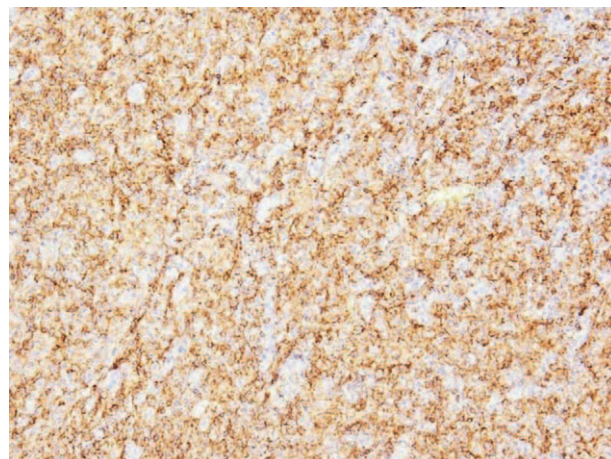


Figure 2. Immunohistochemical staining showing lymphoid cells positive for CD4 (magnification, 20 \times).

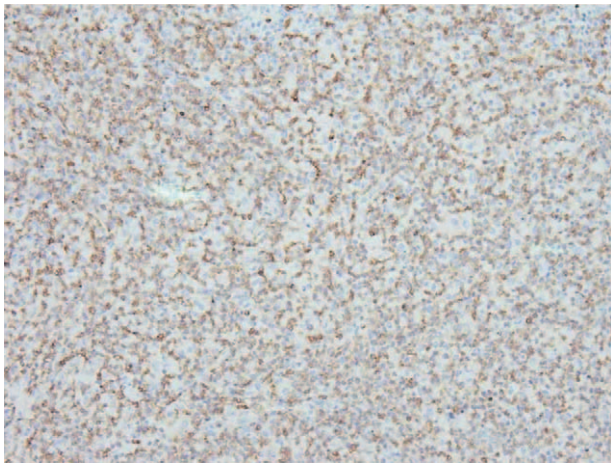


Figure 3. Immunohistochemical staining showing lymphoid cells positive for CD3 (magnification, 20×).

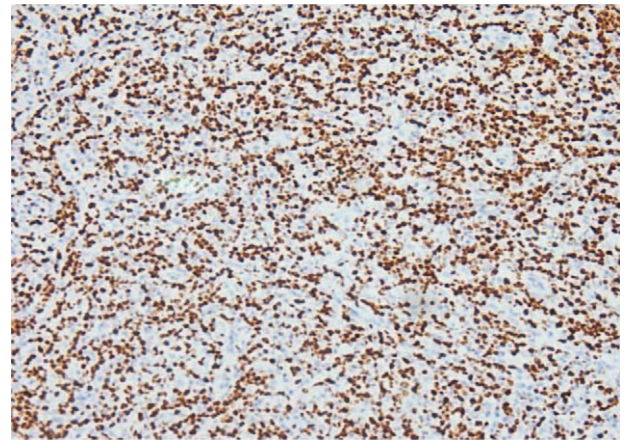


Figure 4. Immunohistochemical staining showing lymphoid cells strongly positive for Ki-67 (magnification, 20×).

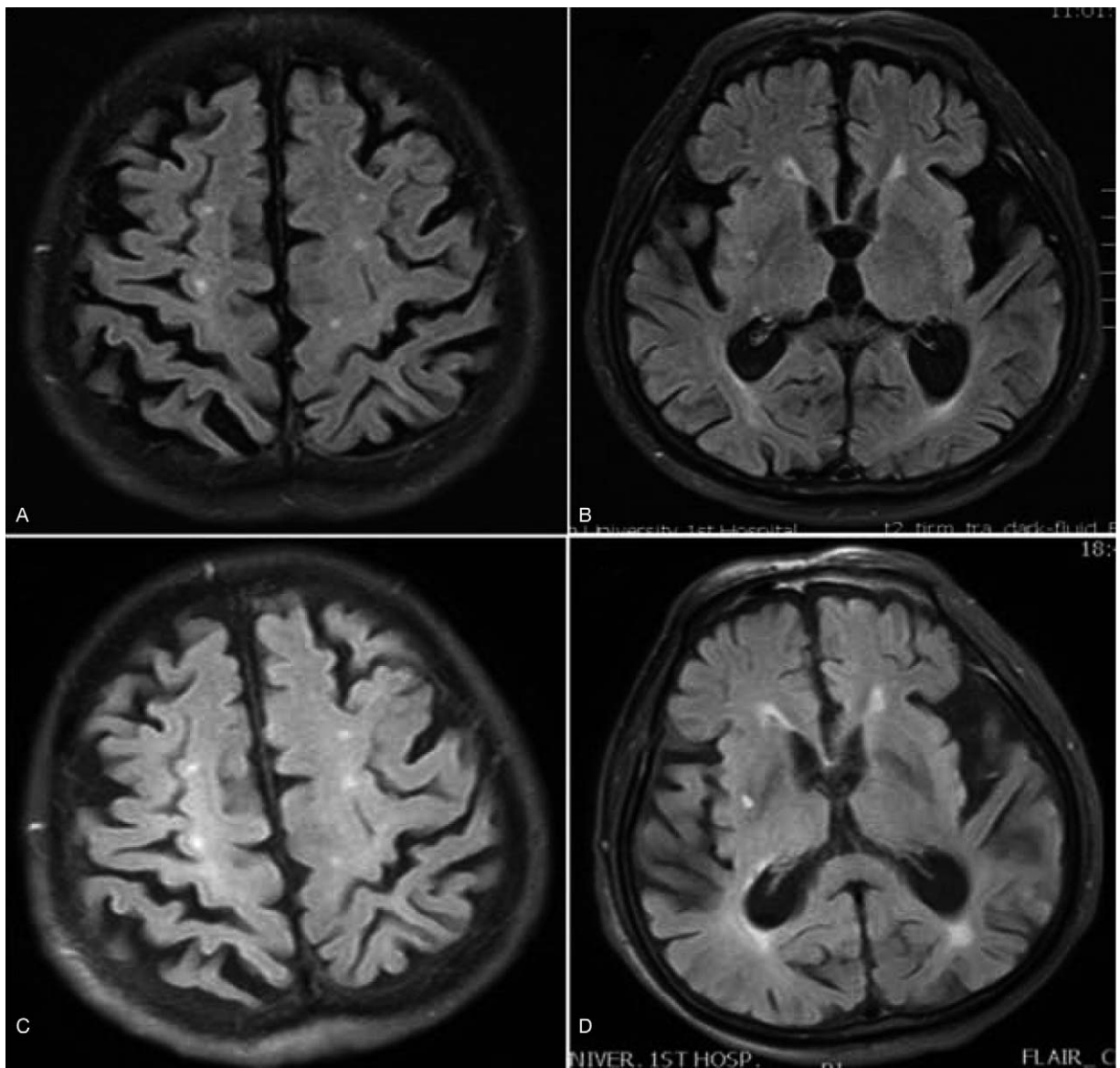


Figure 5. Brain MRI was performed twice. (A and B) MRI flair scans showed multiple lacunar infarctions. (C and D) MRI flair scans showed no difference after 20.

Electromyography						
motor never conduction velocity	latent period (ms)	amplitude (mv)	distance (mm)	conduction velocity (m/s)	average F-M latency (ms)	minimum F-wave latency (ms)
ulnar nerve motor (right)						
wrist-ADM	3.71↑	3.8↓			34.9	35.3
below elbow-wrist	8.16	3.1↓	230	51.7↓		↑
above elbow-below elbow	9.87	2.9↓	50	29.2↓		
median nerve motor (right)						
wrist-APB	7.38	2.2			30.4	37
elbow-wrist	12.3	2	250	50.8		↑
tibial nerve motor (right)						
ankle-AH	6.27	0.97↓		↓		
popliteal space-ankle	17.6	0.56↓	410	36.2↓		
common peroneal nerve motor (right)						
ankle-EDB	9.95	0.93↓				
below the knee-ankle	16	0.97↓	338	55.9		
above the knee-below the knee	17.7	1.07↓	80	47.1		
sensory never conduction velocity						
	latent period (ms)	amplitude (uv)	distance (mm)	conduction velocity (m/s)		
ulnar nerve sensory (right)						
fingerV-wrist	2.58	2.9↓	105	40.7↓		
median nerve sensory right						
fingerIII-wrist	2.61	4.7↓	120	46↓		
superficial peroneal nerve sensory right						
ankle-dorsum pedis	undetected					
right tibial nerve Hreflex						
	M-Lat (ms)	H-Lat (ms)	H/M Amp			
knee-gastrocnemius muscle	4.2	undetected				

Figure 6. Electromyography showed that peripheral nerve conduction in all 4 limbs was significantly impaired, indicating a preponderance of demyelination.

impaired, indicating a preponderance of demyelination (Fig. 6). A 4-hour electroencephalogram showed irregular sharp slow waves and δ waves in both temporal regions.

2.3. Treatment and outcome

A definitive diagnosis of CIDP was made based on the symptoms and results of auxiliary examinations. The patient's clinical condition stabilized after a cycle of enhancing immunity (intravenous immunoglobulin) and neuronutrition (edaravone injection). There were no signs of CIDP progression. In the following days, a final diagnosis of anti-Ma2-related PNS associated with lymphoma was made. The patient was treated with intravenous dexamethasone (15 mg/day) for 3 days, and all the central and peripheral nervous system symptoms improved. The patient was then transferred to the oncology department to receive systemic chemotherapy.

3. Discussion

The diagnosis of PNS represents a clinical challenge, especially when it is associated with lymphoma, which is rare. The frequency of PNS associated with lymphomas was analyzed by the PNS Euronetwork Consortium, which includes 20 European centers. Between 2000 and 2008, the Consortium identified 53 patients with PNS, 29 had NHL. Furthermore, of the 53 patients, only 11 had demyelinating neuropathies, and 9 of these were associated with NHL.^[3] Patients with NHL can present with typical CIDP or with predominantly sensory neuropathies, which are probably caused by monoclonal IgM antibodies against myelin-associated glycoproteins or gangliosides.^[4,5]

Anti-Ma2-associated encephalitis is a rare disease. As a PNS, it develops gradually, and it usually affects the limbic system, diencephalon, and/or brain stem.^[2] According to a recent review and analysis, only 68 cases of anti-Ma2-associated neurological syndromes have been reported to date.^[6] Most cases occurred in adult men with testicular germ cell tumor or non-small-cell lung cancer, whereas some were associated with tumors such as lymphoma, prostatic adenocarcinoma, gastric adenocarcinoma, and recurrent cervical cancer.^[7,8] Ma2 is an intracellular onconeural protein; anti-Ma2 antibodies recognize 2 antigens—PNMA1 and PNMA2^[9]—which are mainly expressed in neurons in the brain, spinal cord, dorsal root ganglia, and tumors.^[2,10] The mechanisms underlying selective neuronal injury in anti-Ma2-associated neurological syndromes seem to involve a cytotoxic T-cell-mediated response.

Experimental data have showed that the adoptive transfer of T-helper 1 CD4+ T-cells specific for PNMA1 induces encephalomyelitis in rats.^[9] Clinically, patients with anti-Ma2-related limbic encephalitis manifest not only the typical symptoms of limbic encephalitis—such as subacute onset of short-term memory loss, epilepsy, and psychiatric symptoms^[2,11]—but also symptoms of diencephalon and upper brain stem involvement, such as excessive daytime sleepiness and vertical ophthalmoparesis.^[12,13] Anti-Ma2 neurological disorders have been shown to even affect the peripheral nervous system, causing muscle atrophy.^[14]

In our patient, the clinical presentation and results of auxiliary examinations were consistent with the criteria for atypical CIDP according to the European Federation of Neurological Societies/Peripheral Nerve Society guidelines published in 2010.^[15] However, the symptoms of slow reaction time, depression, and

cognitive impairment are not the usual presentation of CIDP and indicate that the patient had temporal lobe involvement. Furthermore, the CSF was suspected to be positive for anti-PNMA2 (Ma2/Ta) antibodies, indicating coexisting limbic encephalitis. The brain MRI, however, was normal. Similar cases have been described in the literature.^[16]

The major characteristics of this case can be summarized as follows. First, our report shows that NHL can be associated with not only demyelinating neuropathy as a PNS but also anti-Ma2-associated limbic encephalitis. The simultaneous central and peripheral nervous system involvement observed in our patient is an extremely rare presentation of anti-Ma immunity, with only 2 reported (non-NHL-related) cases thus far.^[17] (2) Another interesting aspect of this case was the absence of lesions on brain MRI. In 2009, Blanc et al reported that brain MRI can be normal in some patients with limbic encephalitis.^[18] (3) This case shows that PET/CT is an effective and dependable examination for the diagnosis of PNS. A rapid and accurate diagnosis of PNS is essential because any delay can significantly influence clinical management, and the illness can be lethal without proper treatment.^[19] An intriguing report showed that in some cases of non-paraneoplastic limbic encephalitis with undetectable antibodies and negative findings on MRI, PET/CT may be highly suggestive of the disease.^[20]

4. Conclusion

In conclusion, clinical presentations suggestive of an immunological reaction to specific antigens should raise the possibility of a paraneoplastic syndrome. The identification of autoantibodies can guide the clinical search for a specific tumor. PET/CT and biopsy can complement the diagnostic work-up and help to confirm the diagnosis. Finding and treating the tumor are essential to improve the prognosis of patients with PNS.

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