Published in final edited form as:
Mov Disord. 2007 April 15; 22(5): 728–731.

Severe Hypokinesis Caused by Paraneoplastic Anti-Ma2 Encephalitis Associated with Bilateral Intratubular Germ-Cell Neoplasm of the Testes

Lumine Matsumoto, MD[1], **Tomotaka Yamamoto, MD, PhD**[1,*], **Mana Higashihara, MD**[1], **Izumi Sugimoto, MD**[1], **Hisatomo Kowa, MD, PhD**[1], **Junji Shibahara, MD, PhD**[2], **Koichiro Nakamura, MD, PhD**[1], **Jun Shimizu, MD, PhD**[1], **Yoshikazu Ugawa, MD, PhD**[1], **Jun Goto, MD, PhD**[1], **Josep Dalmau, MD, PhD**[3], and **Shoji Tsuji, MD, PhD**[1]

1*Department of Neurology, The University of Tokyo, Tokyo, Japan*

2*Department of Pathology, The University of Tokyo, Tokyo, Japan*

3*Department of Neurology (Division Neuro-Oncology), University of Pennsylvania, Philadelphia, Pennsylvania, USA*

Abstract

We report a 40-year-old man with severe hypokinesis as paraneoplastic manifestation of a microscopic "carcinoma *in situ*" of the testis. The young age of the patient, along with progressive neurologic deterioration, detection of anti-Ma2 antibodies, and ultrasound findings of bilateral microcalcifications, led to bilateral orchiectomy, revealing the tumor in both testes. After orchiectomy, neurological symptoms stabilized, but the patient eventually died of systemic complications caused by his severe neurological deficits. Anti-Ma2 paraneoplastic encephalitis should be considered in patients with severe hypokinesis, and intensive investigation and aggressive approach to treatment is encouraged to prevent progression of the neurological deficits.

Keywords

anti-Ma2 paraneoplastic encephalitis; hypokinesis; Parkinsonism; intratubular germ-cell neoplasia

Paraneoplastic anti-Ma2-associated encephalitis usually results in limbic, diencephalic, and brainstem dysfunction. Predominant hypokinesis, however, has been rarely reported.[1] We report a patient with this disorder who developed severe hypokinesis as predominant clinical features, and whose underlying neoplasm was a microscopic "carcinoma in situ" of the testis.

CASE REPORTS

A 40-year-old Japanese man developed diplopia and unsteadiness of gait in July 2004. Within the next 2 months he developed progressive difficulty in moving his extremities, and by the middle of August, he could not get out from bed. His facial expression became markedly reduced and the voice barely audible. He also developed severe micrographia. The patient was initially seen by a psychiatrist who prescribed antidepressants, without significant improvement of symptoms. By the end of August, he had difficulty in swallowing, and tremor when holding objects. He looked anxious, irritable, and became very sensitive to auditory stimuli. In September, the patient was seen at a local hospital and found to have reduced

*Correspondence to: Tomotaka Yamamoto, MD, PhD, Department of Neurology, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-Ku, Tokyo 113-8655, Japan. E-mail: tyama-tky@umin.ac.jp

spontaneous speech with inaudible voice, limitation of eye movements, hypokinesis, and rigidity of the limbs. He became bedridden and was transferred to our hospital for further investigation in October 2004.

On admission, the patient was alert and able to follow verbal commands, although all movements were extremely slow. It took him a few minutes to raise his left arm without any weakness. The voluntary eye movements were limited in vertical and horizontal directions, but the oculocephalic reflex was intact. Intermittent conjugated or skewed deviation of the eyes to alternating directions was observed. Verbal output was extremely reduced and barely audible. He managed to answer questions by opening his eyes, mouth, or protruding his tongue. Severe rigidity, spasticity, and fluctuating dystonic postures of the limbs and neck were observed. Reflexes were hyperactive and he had bilateral upgoing toes. Episodes of diaphoresis with tachycardia and tachypnea were sometimes observed, but he did not develop generalized seizures. Owing to the long-term bedridden status, the patient had developed upper and lower limb contractures.

CSF examination showed increased protein concentration (70 mg/dl), with normal cell count (1/mm3) and glucose concentration (72 mg/dl). IgG index was elevated to 0.89. Cytology was negative for malignant cells. The EEG showed background activity of 8 to 10 Hz α wave, intermixed with frequent 6 to 7 Hz θ waves. No epileptic activities were detected. Brain MRI showed hyperintense abnormalities in pons, bilateral globus pallidi, medial thalami, pulvinars, and medial temporal lobes on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. These abnormalities were not enhanced with contrast (Fig. 1A).

Based on the clinical and MRI findings, the following possible diagnoses were considered: viral encephalitis, metabolic encephalopathy including Wilson's disease, mitochondrial encephalopathy, lymphoma, Creutzfeldt-Jakob disease, and paraneoplastic disorders. Antibodies to Japanese encephalitis, Mumps, Epstein–Barr, Varicella–Zoster, and West-Nile viruses were all negative. Serum copper, ceruloplasmin, pyruvate, and lactate levels were in the normal ranges. Prion gene analysis showed only a polymorphism of Glu/Lys at codon 219. The 14-3-3 protein level in CSF was in the borderline level.

Paraneoplastic antibody studies revealed the presence of anti-Ma2 antibodies in serum and CSF; Ma1 antibodies were not detected. This finding led to extensive investigations to identify a tumor, particularly focusing on a testicular cancer. Tumor markers such as CEA, CA19-9, CA125, SCC, Pro-GRP, NSE, SLX, sIL-2R, and α-FP were all negative. β-HCG and highly sensitive PSA were slightly elevated to 0.4 mIU/ml (<0.3 mIU/ml) and 5.45 ng/ml (<4.0 ng/ml), respectively, but they were normalized on the following examinations. Whole-body CT and FDG-PET studies were negative. While the screening for cancer was performed, the patient was empirically treated with intravenous immunoglobulin, which did not result in improvement. Repeated testicular ultrasonogram showed bilateral equivocal microcalcifications. Given these subtle abnormalities and the high prevalence of testicular cancer in young men with anti-Ma2 immunity, we performed bilateral orchiectomy with approval of the IRB and consent of family members.

Histopathological studies showed that both testes were atrophic, but no nodules were noted at macroscopic examination. The microscopic evaluation revealed atrophic seminiferous tubules with reduced spermatogenesis, and dysplastic cells that expressed placental-like alkaline phosphatase (PLAP), which has a diagnostic value for carcinoma in situ or intratubular germ-cell neoplasia (IGCN) (Fig. 2). There were numerous infiltrates composed of lymphocytes, neutrophils, and macrophages, surrounding the seminiferous tubules. Neoplastic cells and inflammatory infiltrates were identified in both testes. The neoplastic cells were reactive with anti-Ma2 antibodies on immunohistochemical analysis (data not shown).

A follow-up MRI obtained 10 months after the onset of symptoms showed a reduction of the signal hyperintensities with progressive atrophy of the affected regions (Fig. 1 B). After orchiectomy, the neurological symptoms stabilized for a few months, but the patient's poor general condition resulted in multiple systemic complications and infections; he died of septic shock seven and a half months after orchiectomy. Autopsy was not performed.

DISCUSSION

The anti-Ma2 antibody is a well-known, specific marker of paraneoplastic limbic, diencephalic, and brainstem encephalitis.[1] The target antigen, Ma2, is a 42-kDa protein predominantly expressed in the nuclear paraspeckles of neurons and at a lesser degree in the cytoplasm. It has been postulated that Ma2 plays a role in mRNA biogenesis.[2] The expression of Ma2 is restricted to brain in normal tissues and in tumors of patients with paraneoplastic anti-Ma2 encephalitis.[3] In men younger than 50 years, the tumor is almost always in the testis.[1,3,4]

The main clinical feature of our patient was severe hypokinesis with reduced verbal output. So far, two patients with anti-Ma2 encephalitis and severe hypokinesis have been reported,[1] which is a very rare presentation of paraneoplastic encephalitis, and an additional case has been identified recently.[5] Neurological, radiological, and oncological features of these three cases and our patient are summarized in Table 1.

Except for patient no. 2, the other three cases have several common clinical features such as young age, male gender, testicular tumor, and temporal stabilization of symptoms after the treatment, including orchiectomy. In these patients, the MRI showed multifocal abnormalities, including in all cases substantia nigra or globus pallidus or both. It has been well documented that bilateral lesions of globus pallidus can cause Parkinsonism.[6-8] Thus it is reasonable to attribute the hypokinesis and slowness of initiation or completion of movement identified in our patient to the damage of this major output structure of basal ganglia.

The most remarkable finding in our case is that the neurological symptoms were a paraneoplastic manifestation of an occult cancer. Although we strongly suspected that the patient had a testicular tumor, we were unable to demonstrate the tumor before the orchiectomy. The reasons for orchiectomy were relentless progression of neurological symptoms, young age of the patient, detection of anti-Ma2 antibodies, and detection of microcalcifications in the follow-up ultrasound. Testicular microcalcifications have been reported with a variable incidence (from 0.6% to 18.1%),[9,10] among individuals undergoing ultrasound and associates with development of germ-cell tumors in 40% to 45% of patients.[9]

IGCN is considered a precursor of most testicular germ-cell tumors. It consists of enlarged cells with clear cytoplasm that are aligned along the basal portion of the seminiferous tubules.[11] Immunostaining discloses PLAP-positive cells in most of the patients with IGCN. It should be noted that nonneoplastic spermatogenic cells are almost always PLAP-negative. Therefore, the identification of dysplastic PLAP-positive cells in seminiferous tubules, as in our patient, is confirmatory to the diagnosis of IGCN.

The prognosis of anti-Ma2-associated encephalitis depends on prompt treatment of the tumor, and some patients appear to respond to immunosuppressants (corticosteroids or intravenous immunoglobulin).[1] Factors associated with improvement or stabilization include male gender, young age, testicular tumor with complete response to treatment, absence of anti-Ma1 antibodies, and limited central nervous system involvement.[1] In our case, the neurological symptoms showed a rapidly progressive course, and the diagnosis was established several months after the symptom presentation. Because there was severe involvement of the CNS and the affected brain regions were already atrophic at the time of orchiectomy, it resulted in only stabilization of symptoms, but not improvement. We conclude that anti-Ma2 encephalitis

should be considered in patients with sub-acutely progressive severe hypokinesis. If the patient is a young man without evidence of a tumor, a microscopic IGCN should be strongly considered. In these patients, orchiectomy can be the only way to reveal the tumor at very early stages. Early diagnosis and treatment should be encouraged because of its beneficial effects when compared with other paraneoplastic neurological syndromes.[1,3]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES

1. Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. Brain 2004;127:1831–1844. [PubMed: 15215214]
2. Rosenfeld MR, Eichen JG, Wade DF, Posner JB, Dalmau J. Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. Ann Neurol 2001;50:339–348. [PubMed: 11558790]
3. Voltz R, Gultekin SH, Rosenfeld MR, et al. A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. N Engl J Med 1999;340:1788–1795. [PubMed: 10362822]
4. MathewRMYamamotoTNakamuraKDropchoETsujiSDalmauJOrchiectomy for suspected microscopic tumor in patients with paraneoplastic anti-Ma2 encephalitis. Contemporary Clinical Issues and Case StudiesPlenary Session: 58th Annual Meeting AANSan Diego, CAApril 5, 2006 Available athttp://www.abstracts2view.com/aan/view.php?nu=AAN06L_PL01.001
5. Castle J, Sakonju A, Dalmau J, Newman-Toker DE. Anti-Ma2-associated encephalitis with normal FDG-PET: a case of pseudo-Whipple's disease. Nat Clin Pract Neurol 2006;2:566–572. [PubMed: 16990830]
6. Feve AP, Fenelon G, Wallays C, Remy P, Guillard A. Axial motor disturbances after hypoxic lesions of the globus pallidus. Mov Disord 1993;8:321–326. [PubMed: 8341296]
7. Bhatia KP, Marsden CD. The behavioral and motor consequences of focal lesions of the basal ganglia in man. Brain 1994;117:859–876. [PubMed: 7922471]
8. Aizawa H, Kwak S, Shimizu T, et al. A case of adult onset pure pallidal degeneration. II. Clinical manifestations and neuropatho-logical observations. J Neurol Sci 1991;102:76–82. [PubMed: 1856734]
9. Hobarth K, Susani M, Szabo N, Kratzik C. Incidence of testicular microlithiasis. Urology 1992;40:464–467. [PubMed: 1441049]
10. Middleton WD, Teefey SA, Santillan CS. Testicular microlithiasis: prospective analysis of prevalence and associated tumor. Radiology 2002;224:425–428. [PubMed: 12147838]
11. Montironi R. Intratubular germ cell neoplasia of the testis: testicular intraepithelial neoplasia. Eur Urol 2002;41:651–654. [PubMed: 12074783]

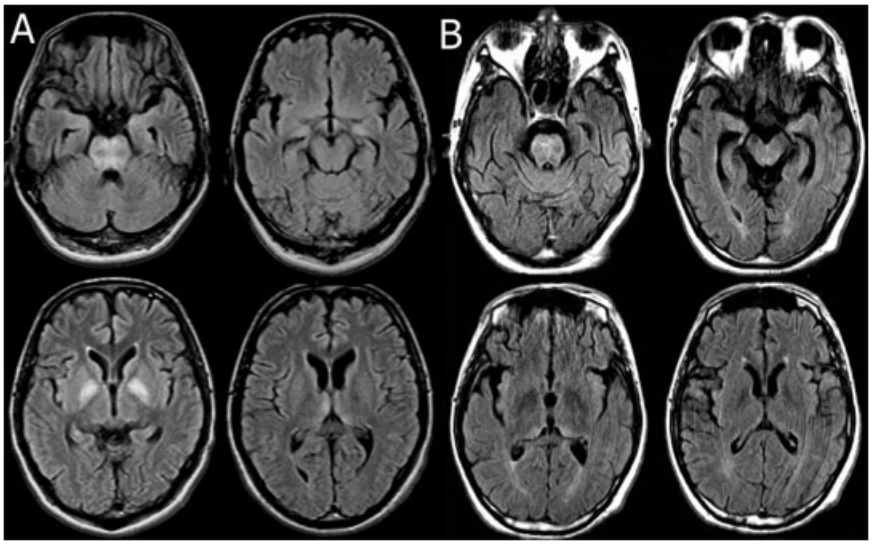

FIG 1.

Consecutive brain MRI. **A**: MRI on admission showing FLAIR hyperintensities in pons, bilateral globus pallidi, medial thalamic nuclei, pulvinars, and medial temporal lobes (TR: 9999.00 ms, TE: 105.00 ms). These abnormalities did not enhance with gadolinium. **B**: MRI FLAIR images (TR: 8002.00 ms, TE: 146.12 ms) obtained 10 months after the onset of neurological symptoms. Residual FLAIR hyperintensities are present in bilateral middle cerebellar peduncles, pons, and thalamic pulvinars. Brainstem and globus pallidi are atrophic.

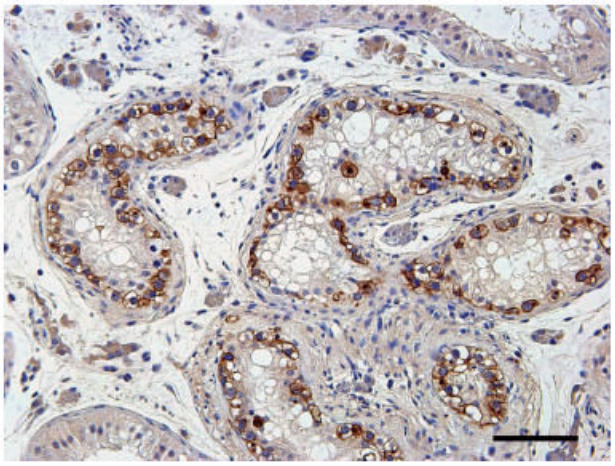

FIG 2.

Pathological findings at orchiectomy. Microscopic findings in the testis. The seminiferous tubules are atrophic and with hypospermatogenesis. The brown cells correspond to the neoplastic cells immunolabeled with PLAP, a marker of germ-cell neoplasms. Note that the neoplastic cells are restricted to the seminiferous tubules and not invasive. Scale bar is equivalent to 100 μm.

TABLE 1

Cases with anti-Ma2 encephalitis presenting with severe hypokinesis

Case	Age, gender	Clinical features (other than hypokinesis)	MRI	Type of tumor	Treatment	Outcome
1 (Dalmau et al.1)	38, M	Lethargy, loss of libido, diabetes insipidus, hypothyroidism, severe spasticity and rigidity, reduction of verbal output, excessive daytime sleepiness, tendency to continuous eye closure	Bilateral hippocampi, amygdala, midbrain (substantia nigra), internal capsule, globus pallidi	Seminoma of the testis	Orchiectomy, corticosteroids, IVIg, plasma exchange	Stabilization, 8-month follow-up
2 (Dalmau et al.1)	69, M	Loss of self-confidence, unexplained sense of fear and diplopia, excessive daytime sleepiness, vertical gaze paresis, tendency to continuous eye closure, reflex blepharospasm, hypophonia, able to follow commands, short-step gait, reduction of verbal output	Bilateral hippocampi, dorsal midbrain, colliculi + medial thalami (later)	PET + in colon and prostate (no tissues obtained for histological diagnosis)	Corticosteroids, IVIg	Progressive deterioration, died in nursing home 10 months after symptom presentation
3 (Castle et al.5)	39, M	Personality change, social withdrawal, bradykinesia and rigidity, hypophonia, narrow-based gait, retropulsion, vertical and horizontal supranuclear gaze palsy, autonomic dysfunction	FLAIR hyperintensity of right substantia nigra and left temporal lobe (frontal encephalomalacia secondary to remote head injury)	Embryonal carcinoma of the testis	Orchiectomy, corticosteroids, IVIg, mycophenolate mofetil, plasmapheresis, chemotherapy, muscle relaxants	Transient stabilization; died ~14 months after symptom presentation (see autopsy findings below)[a]
4 (our case)	40, M	Hypokinesis, vertical and horizontal supranuclear gaze palsy, rigidity and spasticity, fluctuating dystonia, reduction of verbal output, hyperreflexia and upgoing toes, paroxysmal diaphoresis	Bilateral globus pallidi, medial thalami, thalamic pulvinars, pons	Bilateral testicular, IGCN	IVIg (not effective), orchiectomy	Transient stabilization; died ~16 months after symptom presentation (7.5 months after orchiectomy)

[a]Autopsy findings: Reactive astrocytosis in the amygdala, basal forebrain, and septum. Microglial nodule in the basal forebrain and mild perivascular cuffing. The midbrain showed inflammatory changes with microglial nodules and perivascular cuffing. The pons and medulla had mild microglial proliferation and perivascular cuffing.