Narcolepsy, REM Sleep Behavior Disorder, and Supranuclear Gaze Palsy Associated With Ma1 and Ma2 Antibodies and Tonsillar Carcinoma

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Objective: To describe a patient with diencephalic and mesencephalic presentation of a Ma1 and Ma2 antibody-associated paraneoplastic neurological disorder.

Design: Case report.


Patient: A 55-year-old man with a paraneoplastic neurological disorder characterized by rapid eye movement sleep behavior disorder, narcolepsy, and a progressive supranuclear palsy–like syndrome in the setting of tonsillar carcinoma.

Intervention: Immunotherapy for paraneoplastic neurological disorder, surgery and radiotherapy for cancer, and symptomatic treatment for parkinsonism and sleep disorders.

Main Outcome Measures: Polysomnography, multiple sleep latency test, and neurological examination.

Results: The cancer was detected at a limited stage and treatable. After oncological therapy and immunotherapy, symptoms stabilized. Treatment with modafinil improved daytime somnolence.

Conclusions: Rapid onset and progression of multifocal deficits may be a clue to paraneoplastic etiology. Early treatment of a limited stage cancer (with or without immunotherapy) may possibly slow progression of neurological symptoms. Symptomatic treatment may be beneficial.

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MA1 AND MA2 ARE INTRACELLULAR PROTEINS EXPRESSED IN THE TESTES AND THROUGHOUT THE BRAIN BUT ESPECIALLY IN THE BRAINSTEM, MIDBRAIN, BASAL GANGLIA, HYPOTHALAMUS, LIMBIC STRUCTURES, CRANIAL NERVE NUCLEI, FRONTAL CORTEX, AND CEREBELLAR NUCLEI.1 We report on a patient with Ma1 and Ma2 antibody–associated encephalitis characterized by distinctive sleep and movement disturbances. Squamous cell carcinoma of the tonsil was ultimately found.

A 55-year-old man presented with a 6-month history of progressive neurologic dysfunction. He has a 22–pack-year history of smoking and rarely used alcohol. Initially, for 1 month, the patient had transient hyperphagia with a 22-lb weight gain and then weight stabilization. In the second month, he developed upgaze and downgaze paresis, diplopia, and a tendency for his eyes to lock in upgaze position. By the end of the second month, he developed sleep fragmentation and daytime hypersomnolence with an Epworth Sleepiness Scale score of 24 (range, 0-24; normal score, <10). His sleep became agitated with vocalization and flailing of limbs. He sleepwalked and appeared confused. He developed brief spells of weakness of his limbs and twitching of the face in full consciousness, which were precipitated by embarrassment and nervousness. These recurred many times an hour. He did not experience sleep paralysis but did describe visual hallucinations of people and animals.

By the third month, he developed 30- to 60-second spells of recurrent freezing of gait, hand and jaw tremor, and involuntary upward gaze deviation. From the fourth month onward, dysarthria, intermittent urinary incontinence, slowness of hand function, and illegible handwriting were noted. In addition, during the prior year, the patient developed erectile dysfunction and had slightly low levels of testosterone, T4, and thyroid-stimulating hormone, but his cortisol, luteinizing hormone, follicle-stimulating hormone, and prolactin levels were normal.

Initial examination revealed vertical supranuclear gaze palsy with absent voluntary vertical saccades but preserved smooth
pursuit and improved vertical ocular range of motion with oculoucularic maneuvers. The patient’s eyes tended to lock in downgaze or upgaze position, and the patient could only bring his eyes back to primary position by tracking an object. There was no significant limb bradykinesia, rigidity, freezing of gait, or resting tremor. The patient had a mildly slow gait and a positive pull test result.

The results of cranial magnetic resonance imaging (MRI) performed from month 1 to month 17 after symptom onset were normal except for a dural-based left parietal enhancing lesion. Seven months after initial symptoms, a whole-body positron emission tomographic and computed tomographic scan demonstrated increased uptake only in the left tonsillar region and neck. Cerebrospinal fluid studies revealed a normal cell count and a normal glucose level, but an elevated protein level of 122 mg/dL and an elevated IgG synthesis rate of 15 mg/dL. Eight months after symptom presentation, the parietal lesion was removed and pathology was consistent with a grade I meningioma. Ten months after initial symptoms, serum Ma1 and Ma2 antibodies were found. The following paraneoplastic antibodies were absent in the patient’s serum and cerebrospinal fluid: antineuronal nuclear autoantibody types 1, 2, and 3, anti-glial/neuronal nuclear antibody type 1, Purkinje cell cytoplasmic autoantibody types 1 and 2, amphiphysin, and collapsin response-mediator protein 5 IgG. In serum, acetylcholine receptor (neuronal and muscle), N-type calcium channel, P/Q-type calcium channel, and voltage-gated potassium channel antibodies were also absent. A second whole-body positron emission tomographic-computed tomographic scan showed no new uptake. A poorly differentiated tonsillar squamous cell carcinoma was resected, and involvement of a single cervical lymph node was found. Thereafter, the patient underwent external beam radiotherapy. A second cranial MRI 7 months after removal of the meningioma was unremarkable.

During the investigations and treatment for the tonsillar cancer, the patient’s cognitive decline progressed, his hypersomnolence worsened (>20 h/d), and his appetite decreased, with a 20-lb weight loss likely due to mucositis from radiation therapy. Despite radiation therapy, the patient’s eye movements significantly worsened with absent downgaze, minimal voluntary upgaze, and only 50% of normal horizontal gaze range of motion. Vertical saccades were absent, and horizontal saccades were slow. The patient now demonstrated mild (left greater than right) limb bradykinesia without rigidity, more postural instability, significantly impaired short-term memory, and episodic delirium. The spectrum of clinical findings was not consistent with various atypical parkinsonian syndromes (eg, progressive supranuclear gaze palsy or corticobasal degeneration).

Polysonomography demonstrated severe disruption of sleep rhythms, absent slow wave sleep, intrusion of rapid eye movements (REM) into non-REM sleep, and complete loss of REM sleep atonia. During REM sleep, vocalization (including talking, laughing, and singing) and arm and leg movements were present. Sleep was highly fragmented (62 arousals per hour, most indeterminate in etiology). Mild positional obstructive sleep apnea was noted (apnea-hypopnea index, 10/h). A multiple sleep latency test revealed a mean initial sleep latency of 2.2 minutes during a total of 5 naps and REM sleep without atonia during a total of 2 naps within 15 minutes of sleep onset.

Fourteen months after initial symptoms, because of progressive worsening of clinical symptoms, the patient was treated weekly with 1000-mg intravenous pulses of methylprednisolone acetate for 8 weeks and monthly intravenous cyclophosphamide for 3 months. After immunotherapy, the patient’s clinical condition stabilized. Examination demonstrated no new findings and no worsening of prior abnormalities. A second polysomnogram was obtained that showed similar findings to the first, and a second multiple sleep latency test showed a mean sleep latency of 2.75 minutes with 3 sleep-onset REM periods. His Epworth Sleepiness Scale score remained high at 21. Thereafter, he commenced treatment with modafinil, which decreased his daytime somnolence. Melatonin for REM sleep behavior disorder and carbidopa-levodopa (L-dopa) for parkinsonism were administered, but these drugs were not tolerated by the patient.

**COMMENT**

We report a patient with squamous cell tonsillar carcinoma with a Ma1 and Ma2 antibody-positive paraneoplastic neurological disorder (PND) characterized by REM sleep behavior disorder, narcolepsy with cataplexy, and progressive supranuclear gaze palsy-like features. We suspect that the PND occurred in the context of the tonsillar carcinoma; meningioma is a benign neoplasm that is not associated with PND, and his symptoms progressed despite resection.

Dalmau et al found that patients who developed PNDs and who were seropositive for Ma2 antibody or for both Ma1 and Ma2 antibodies exhibited 1 or more of short-term memory deficits (63% of patients), vertical supranuclear gaze palsy (34% of patients), excessive daytime sleepiness (32% of patients), diplopia (26% of patients), dysarthria (26% of patients), unsteady gait or ataxia (18% of patients), parkinsonism or hypokinesia with vertical supranuclear gaze palsy (11% of patients), and narcolepsy with low cerebrospinal fluid hypocretin-1 levels (13% of patients). Patients who were seropositive for Ma1 and Ma2 antibodies were more likely to have brainstem encephalitis than patients who were seronegative. Similar to our patient, 32% of the patients in the study by Dalmau et al had no lesions discovered on T2-weighted MRI scans. Based on our patient’s symptoms, multifocal involvement of a variety of structures where Ma1 and Ma2 proteins are highly concentrated is likely despite the absence of lesions discovered on MRI scans. These structures include those associated with hyperphagia and narcolepsy (hypothalamus), memory (hippocampus), REM sleep behavior disorder (sublocus coeruleus and magnocellular reticular formation), sleep fragmentation (suprachiasmatic nucleus and locus ceruleus), vertical supranuclear gaze palsy (nucleus raphe interpositus and nucleus of Darkschewitsch), diplopia (abducens and oculomotor nuclei), and parkinsonism (pedunculopontine nucleus and substantia nigra pars compacta).
Seropositivity for Ma1 and Ma2 antibodies helped guide the search for occult cancer. Patients seropositive for both Ma1 and Ma2 antibodies have been previously reported to have carcinoma (lung [25% of patients], gastrointestinal tract [15%], breast [10%], salivary gland [10%], and ovary [5%]), non-Hodgkin lymphoma (10%), germ cell neoplasia (10%), renal rhabdoid neoplasia (5%), melanoma (5%), or other some other form of cancer (5%), whereas patients seropositive for the Ma2 antibody only generally have testicular carcinoma.

The use of positron emission tomography and computed tomography may help identify occult carcinoma in patients with suspected PNDs, particularly when their results were negative during the initial round of routine testing.

Our patient had ongoing neurological deterioration despite cancer remission and had no improvement with immunotherapy. The severity of these disorders may be stratified on the basis of serological findings. Compared with 6 patients seropositive for Ma2 antibody only, 44% of patients seropositive for both Ma1 and Ma2 antibodies show progressive neurological deterioration despite oncological and immunological therapies. Therefore, Ma1 antibodies may determine the type of cancer, clinical outcome, and prognosis.

In cases similar to ours, symptoms usually progressed to the point where the patient was dead within a year (Tables 1 and 2). That narcolepsy can occur in the context of a Ma antibody–associated PND is of interest in view of the hypothesis that idiopathic narcolepsy is an autoimmune disorder. REM sleep behavior disorder has been associated with paraneoplastic disorders with voltage-gated potassium channel complex autoimmunity. Although the Compta et al case most closely resembles ours, no tumor was found, and only Ma2 seropositivity was present.

In summary, clinicians should consider PND in patients with subacute onset of multifocal neurologic deficits. Ma antibody–associated PND is underrecognized; although memory deficits are the most common symptom, the disorder may present with a syndrome resembling progressive supranuclear gaze palsy, sleep disorders, or both.

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Table 1. Summary of Reported Cases With Similar Clinical Features

<table>
<thead>
<tr>
<th>Source</th>
<th>SNGP</th>
<th>Narcolepsy</th>
<th>Posture</th>
<th>REM Behavior Disorder</th>
<th>Cataplexy</th>
<th>Bradykinesia</th>
<th>EDS</th>
<th>Impaired Memory</th>
<th>Parkinsonism</th>
<th>Diplopia</th>
<th>Sleep Fragmentation</th>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Tan et al,2005</td>
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<tr>
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</table>

Abbreviations: EDS, excessive daytime sleepiness; MRI, magnetic resonance imaging; REM, rapid eye movement; SNGP, supranuclear gaze palsy.

Table 2. Summary of Serology, Lesions, Tumor Type, and Treatment for Similar Findings

<table>
<thead>
<tr>
<th>Source</th>
<th>Serology</th>
<th>Locations of Lesions on MRI Scan or at Autopsy</th>
<th>Tumor Location</th>
<th>Treatment</th>
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<tr>
<td>Our case</td>
<td>Ma1, Ma2</td>
<td>None</td>
<td>Tonsil</td>
<td>Immunotherapy, oncotherapy, _L-dopa, modafinil, melatonin</td>
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<td>Compta et al,2007</td>
<td>Ma2</td>
<td>Midbrain, hippocampus, amygdala</td>
<td>None</td>
<td>Immunotherapy</td>
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<tr>
<td>Tan et al,2005</td>
<td>Absent: Hu, Ri, and Yo. Ma2 not tested.</td>
<td>None</td>
<td>B cell</td>
<td>_L-dopa</td>
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<td>Jankovic et al,1985</td>
<td>Not tested</td>
<td>None</td>
<td>Lung Testes</td>
<td>_L-dopa, bromocriptine Immunotherapy, orchietomy</td>
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<tr>
<td>Matsumoto et al,2007</td>
<td>Ma2</td>
<td>Pons, globus pallidus, thalamus, temporal lobe</td>
<td>Testes</td>
<td>Orchiectomy, immunotherapy, oncotherapy</td>
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<tr>
<td>Castle et al,2006</td>
<td>Ma2</td>
<td>Midbrain, amygdala, basal forebrain, septum, pons, medulla</td>
<td>Testes</td>
<td>Immunotherapy</td>
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<td>Blumenthal et al,2006</td>
<td>Ma2</td>
<td>Thalamus, superior colliculus, temporal lobe</td>
<td>Lung</td>
<td>Immunotherapy</td>
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<tr>
<td>Landolfi and Nadkarni,2003</td>
<td>Ma2</td>
<td>Temporal lobe</td>
<td>Testes</td>
<td>Immunotherapy, modafinil, oncotherapy, orchietomy</td>
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</table>

Abbreviation: MRI, magnetic resonance imaging.
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Author Contributions: Study concept and design: Kumar. Acquisition of data: McKeon, Silber, and Kumar. Analysis and interpretation of data: Adams, McKeon, Silber, and Kumar. Drafting of the manuscript: Adams and Kumar. Critical revision of the manuscript for important intellectual content: McKeon, Silber, and Kumar. Study supervision: Silber and Kumar.

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REFERENCES


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