Early pathologic findings and long-term improvement in anti-Ma2–associated encephalitis

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Abstract—A 67-year-old man sequentially developed anti-Ma2–associated paraneoplastic encephalitis (PNE) and contralateral herpes simplex encephalitis (HSE). Brain biopsy 1 month before HSE revealed extensive infiltrates of T cells, B cells, and plasma cells. Most T cells expressed the cytotoxic granule–associated protein TIA-1 and the membranolytic protein granzyme-B. Although recovery was thought to be unlikely, treatment of the PNE with corticosteroids and resection of the associated lung cancer resulted in dramatic improvement for 21 months.

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Increased clinical awareness and improved tests for paraneoplastic neurologic disorders (PNDs) have resulted in early diagnosis and better outcomes for some patients. With early intervention, syndromes once considered monophasic and refractory to treatments may indeed improve or have a relapsing-remitting course.[1,2] We report the clinical and pathologic findings of a patient who, despite impressive inflammatory infiltrates in the brain biopsy, had dramatic improvement until the PND recurred 21 months later.

Case report. A 67-year-old man presented in March 2000 with diplopia noted while playing golf. He was lethargic and napping more than usual. At examination, vertical gaze paresis, horizontal saccadic pursuit, ataxia, and loss of left hand dexterity were noted. In April, an MRI revealed a nodular enhancing lesion in the right thalamus and superior collicular region (figure 1, A through C). On April 5, the CSF showed a white blood cell (WBC) count of 18/μL (89% lymphocytes, 11% monocytes), a red blood cell (RBC) count of 10/μL, a total protein concentration of 80 mg/dL, and glucose of 49 mg/dL; cryptococcal antigen, acid-fast bacilli, VDRL, herpes simplex virus (HSV), and angiotensin-converting enzyme tests were negative. CSF hypocretin levels were undetectable. On April 21, stereotactic biopsy showed extensive perivascular and interstitial lymphocytic infiltrates with numerous plasma cells (figure 2). Flow cytometry and gene rearrangement studies ruled out lymphoma. Anti-Ma2 antibodies were identified in serum (titer 1:512,000) and CSF (with intrathecal synthesis; not shown), prompting the search for a tumor (figure 3). While undergoing cancer screening, the patient received IV corticosteroids (1 g methylprednisolone per day for 3 days) followed by oral prednisone that resulted in dramatic neurologic improvement. A chest CT scan showed a small spiculated right upper lobe lesion associated with hilar adenopathy; fine needle aspirate of the lesion demonstrated an adenocarcinoma.

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On May 23, 2000, while on steroids and in preparation for surgery, the patient underwent cardiac catheterization and shortly thereafter developed seizures, confusion, and aphasia without fever. Repeat MRI showed near resolution of the contrast-enhancing abnormalities in the right temporal and thalamic regions, and a new area of fluid-attenuated inversion recovery hyperintensity in the contralateral mesial temporal lobe and insular cortex (figure 1, D through F). Repeat CSF studies demonstrated an RBC count of 10/μL, a WBC count of 10/μL (72% polymorphonuclear cells, 18% lymphocytes, 10% monocytes), and this time, the PCR for HSV was positive. The patient was diagnosed with herpes simplex encephalitis (HSE) and treated with acyclovir. After the patient was neurologically stabilized (although impaired from the HSE), a right upper and middle lobe pneumonectomy demonstrated a 1.6-cm focus of moderately differentiated infiltrating adenocarcinoma whose cells expressed the Ma2 protein (data not shown). Tumor cells were also found in 1 of 15 mediastinal lymph nodes and the pleural fluid (Stage IV lung cancer). On June 29, the patient was transferred to an extended care facility with severe deficits mainly attributed to HSE; he was bed bound and followed simple commands intermittently.

During the next 3 months, the patient's condition improved significantly, and by August 2000, he had mild expressive aphasia. By December 2000, he was functioning independently, reading and speaking normally, and had resumed golfing. His short-term memory was also improved. He had mild gait ataxia, and urinary incontinence only at night. Serum titer of anti-Ma2 was 1:16,000. Brain MRI showed resolution of the thalamic nodular enhancement, and residual HSE abnormalities (figure 1, G through I). In April 2001, neurologic follow-up demonstrated intermittent diplopia and mild cognitive deficits; the lung cancer was in "remission" despite the initial Grade IV diagnosis and the absence of any postsurgical radiation or chemotherapy.

In December 2001, 21 months after the initial presentation, the patient started reporting intermittent difficulty with downgaze, and anti-Ma2 antibodies had increased to 1:128,000 (see figure 3). Brain MRI and a chest radiograph showed no interval change. In January 2002, he had a seizure and was no longer able to remember his grandchildren's names; examination showed supranuclear downgaze paralysis, left facial weakness and hypoesthesia, mild left leg weakness, and imbalance. There was mild decreased temperature distally in the lower extremities; the left toe response was up-going, and the right was equivocal. The clinical picture was considered a recurrence of his PND, and he was treated with oral prednisone, without improvement. His status continued to decline with deterioration of cognition and worsening urinary incontinence. In June 2002, he received pulsed IV corticosteroids and immunoglobulins, without apparent effect, and by July, his gait was abnormally slowed, stiffened, and more ataxic. In August 2002, the serum titer of anti-Ma2 was 1:256,000. Plasma exchange was ineffective, and by November, he returned to an extended care facility. The patient died in March 2003 of aspiration pneumonia; no autopsy was performed.

Discussion. The patient reported here is remarkable because he had a prolonged neurologic response to corticosteroids and tumor resection despite the

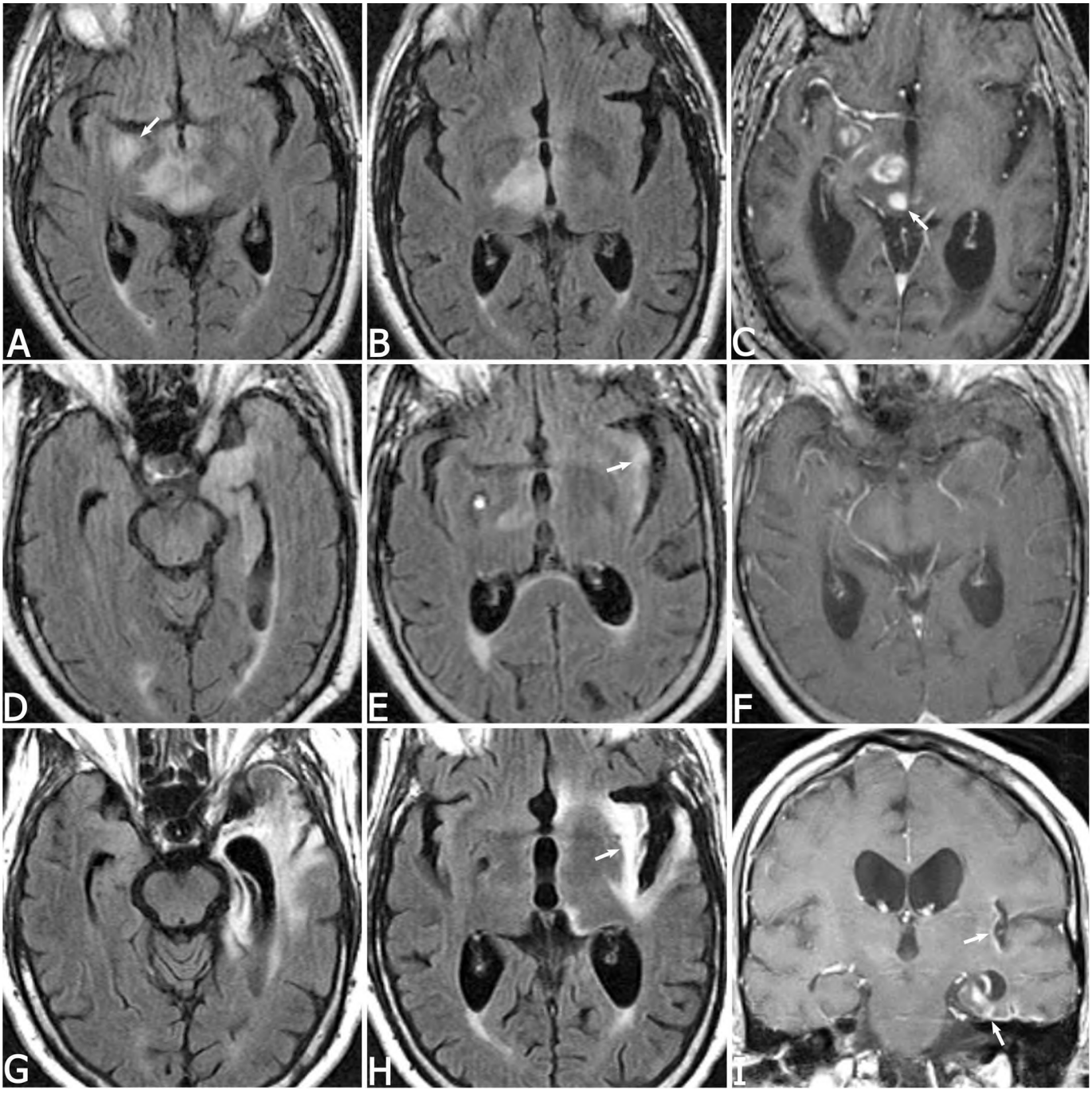

Figure 1. Brain MRI at diagnosis and follow-up. (A through C) MRI at time of paraneoplastic neurologic disorder diagnosis (April 2000). Axial fluid-attenuated inversion recovery (FLAIR) images (A and B) show abnormal hyperintensity in the midbrain, right mesial temporal lobe (arrow), and right thalamus. Axial contrast-enhanced T1 magnetic resonance (MR) image (C) from the patient's stereotactic MRI shows abnormal enhancement in the right thalamus, superior colliculus (arrow), and right mesial temporal lobe. (D through F) MRI at time of herpes simplex virus encephalitis (May 2000). Axial FLAIR images (D and E) show abnormal hyperintensity in the left mesial temporal lobe and insular cortex (arrow) consistent with the diagnosis of herpes encephalitis. The focal abnormal signal intensity in the right mesial temporal lobe is related to previous biopsy. Note the near resolution of abnormal hyperintense signal in the right mesial temporal lobe, midbrain, and thalamus. Contrast-enhanced axial T1 MR image (F) shows resolution of the previously seen enhancement in the right mesial temporal lobe, superior colliculus, and thalamus. (G through I) MRI showing the chronic effects of herpes encephalitis (December 2000). Axial FLAIR MR images (G and H) show extensive abnormal hyperintense signal in the left temporal lobe and insular cortex (arrow). There is temporal lobe volume loss with associated compensatory dilatation of the left temporal horn of the lateral ventricle and sylvian fissure. Contrast-enhanced coronal T1 MR image (I) shows abnormal T1 shortening related to blood products and subtle enhancement in the left insular cortex and temporal lobe (arrows) related to the patient's previous herpes encephalitis. Note the lack of significant enhancement of the right temporal lobe, midbrain, and thalamus.

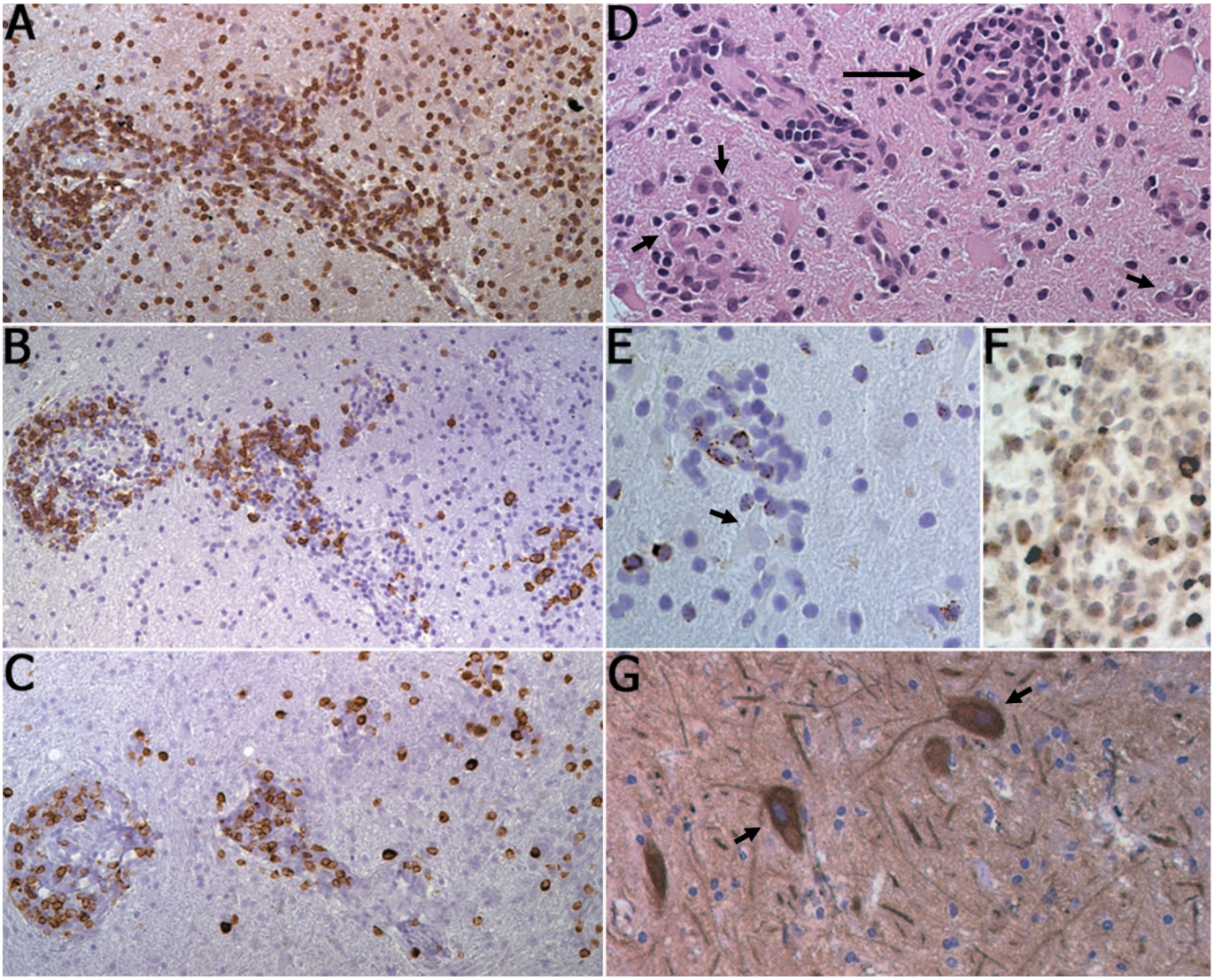

Figure 2. Inflammatory infiltrates in the mesial temporal lobe at the time of paraneoplastic neurologic disorder diagnosis. (A through C) Consecutive tissue sections immunolabeled with CD3, a pan–T-cell marker (A); CD20, a marker of B cells (B), and CD79, a marker of plasma cells (C). Note that the predominant infiltrates of T cells are accompanied by a significant number of B cells and plasma cells (×100, counterstained with hematoxylin). (D) Hematoxylin and eosin demonstrating perivascular cuffing by mononuclear cells (long arrow), and interstitial infiltrates of mononuclear cells. The short arrows point to neurons surrounded by these infiltrates (×200). (E and F) Infiltrates of T cells showing expression of TIA-1, a cytotoxic granule-associated protein (E); arrow points to a neuron in close contact with TIA-1 expressing T cells. Most of these cells use granzyme-B (and less frequently perforin, not shown), membranolytic proteins that induce target cell apoptosis (F). For these studies, deparaffined sections were incubated with commercially available antibodies to TIA-1 (diluted 1:50; Immunotech, Marseille, France) and granzyme-B (diluted 1:20; Chemicon, Temecula, CA), followed by appropriate secondary antibodies, and the reactivity developed with the avidin-biotin-peroxidase-diaminobenzidine method, as reported[7] (×400, counterstained with hematoxylin). (G) Deposits of immunoglobulin (Ig) G in neurons (arrows); this type of IgG immunolabeling was identified in approximately 10% of neurons of a small biopsy specimen; no IgM was identified. Glial cells did not contain IgG or IgM. For this study, deparaffined sections were reacted with biotinylated goat anti-human IgG or IgM (diluted 1:2,000) followed by avidin-biotin-peroxidase-diaminobenzidine[7] (×400, counterstained with hematoxylin).

severity of the brain lymphocytic infiltrates. This improvement was associated with a decrease of serum anti-Ma2 antibody titers that persisted until rising titers heralded a recurrence of the PND 21 months later. These findings and the opportunity to examine the brain inflammatory infiltrates at symptom presentation make this case notable.

To our knowledge, this is the third patient with paraneoplastic[3] or cancer-associated limbic encephalitis[4] occurring in close temporal association with HSE and the first patient in whom the PND was related to anti-Ma2 antibodies. In our patient, HSE developed 2 months after the presentation of PND, at which time the PND symptoms and MRI contrast-enhancing abnormalities had improved. It is therefore unlikely that both disorders were directly

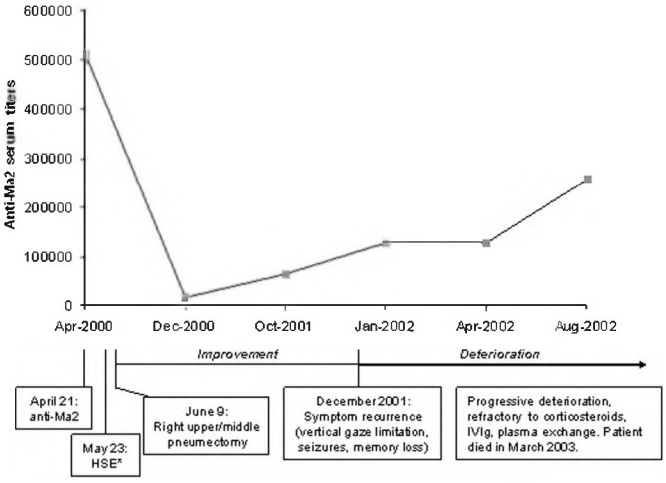

Figure 3. Correlation of serum anti-Ma2 antibody titers and neurologic symptoms. The graph demonstrates a correlation between serum antibody titers and neurologic symptoms. Two CSF samples examined for anti-Ma2 antibodies showed intrathecal synthesis of antibodies; the small number of samples precluded the determination of whether the CSF antibody titers correlated with symptoms. HSE = herpes simplex encephalitis.

related, although the use of corticosteroids probably predisposed to the viral infection. We have not found this association in 43 other patients with anti-Ma2 encephalitis.[5]

We were impressed by the extensive number of inflammatory infiltrates that were mainly composed of T cells but also included a significant number of B cells and plasma cells. The presence of brain-infiltrating plasma cells has been reported in other patients with anti-Ma2 encephalitis[6] but rarely in other types of PND.[7] These plasma cells and intraneuronal deposits of immunoglobulin (Ig) G suggest that antibodies might have contributed to the neuronal injury, but the limited amount of tissue and the fact that it was embedded in paraffin did not allow further characterization of the intraneuronal IgG. The main effectors of neuronal injury seemed to be the cytotoxic T cells that abundantly expressed TIA-1 (a cytotoxic granule-associated protein), and used granzyme B and less frequently perforin (data not shown), two membranolytic proteins that induce target cell apoptosis. We found a similar usage of granzyme-B by scattered brain TIA-1 expressing T cells in the autopsy of a patient with anti-Ma2 encephalitis who died of pulmonary embolism 2 years after partial neurologic improvement and symptom stabilization; in this patient, no intraneuronal IgG was identified (personal observation). These findings suggest that activated cytotoxic T cells may persist in the CNS of patients whose symptoms are stable or in apparent remission; they also suggest that if antibodies contribute to the neuronal injury, their role is perhaps more critical at early stages of the disorder or at symptom reactivation.

When compared with other PNDs,[8-10] patients with anti-Ma2 antibodies are more likely to improve initially with treatment of the tumor and immunosuppressants. It has been suggested that the improvement is related to the frequent association of this syndrome with tumors of the testis, which are amenable to complete resection and are highly responsive to chemotherapy.[5] This patient and another case with anti-Ma2–associated encephalitis and lung cancer (F. Graus, personal communication) indicate that neurologic improvement may also occur in patients with tumors other than germ-cell neoplasms and that it is worthwhile to treat these patients.

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