We describe a patient who presented with a clinical syndrome of limbic encephalitis, narcolepsy, and cataplexy. The anti-Ma2 antibody was positive. Although there was no mass on imaging, orchiectomy was performed in this patient, and testicular carcinoma was found. This is the first known case of limbic encephalitis and anti-Ma2 antibody to be associated with cataplexy and possible narcolepsy. Neurological symptoms precede the diagnosis of cancer in 50% of patients with paraneoplastic syndromes, and clinicians are therefore strongly advised to evaluate patients with neurological symptoms for this condition.

The paraneoplastic syndrome of limbic encephalitis associated with the anti-Ma antibody is well described in patients with testicular cancer (Dalmau et al., 1999; Gultekin et al., 2000; Voltz et al., 1999). Typically, personality and mood changes develop over days or weeks, associated with severe impairment of recent memory, confusion, agitation, and seizures.

We present the case of a patient with encephalitis, narcolepsy, and cataplexy who was ultimately diagnosed with testicular cancer. This case is unique for two reasons. (1) This is the first case of paraneoplastic limbic encephalitis associated with the anti-Ma2 antibody in which an organ was removed prospectively on the basis of clinical scenario and antibody test without radiographic evidence of neoplasm. (2) This is the first known case of limbic encephalitis and anti-Ma2 antibody to be associated with cataplexy and possible narcolepsy, although hypersomnia has been reported (Voltz et al., 1999).

Case Study

This 35-year-old male presented with a 6-month history of progressive memory loss, panic attacks, anxiety, confusion, and visual hallucinations. He also had complex partial seizures on rare occasions. Other than the impairment of recent memory, the neurological exam was normal. Informed consent was obtained from the patient or guardian(s) of the patient described in this case study. MRI revealed bilateral medial temporal lobe hyperintensities on FLAIR (fluid attenuation inversion recovery) sequence. Long-term monitoring for epilepsy was consistent with subclinical electrographical seizures originating from the bitemporal regions independently during sleep. Serum tests for Lyme disease, rapid plasma reagin, and human immunodeficiency virus were negative. Data from CSF Lyme titer and viral polymerase chain reaction were also negative. CSF was significant for an elevated protein of 60. Results of immunohistochemical and Western blot studies of the serum were positive for anti-Ma2 antibodies. CT scans of the chest, abdomen, and pelvis were normal except for thickening of the right...
semenal vesicle. A testicular ultrasound and MRI showed a right hydrocele but no mass.

The patient developed symptoms of excessive daytime sleepiness and cataplexy. The cataplexy was witnessed by the authors and manifested by brief episodes of paralysis in response to emotion.

A polysomnogram was significant for a sleep efficiency of 44.3%, sleep latency of 4.5 min, and respiratory disturbance index of 23.1, with most respiratory events being hypopneas. A multiple sleep latency test (MSLT) performed on the following day showed sleep latency of 9 min with 2 episodes of REM onset. However, study results were confounded by several factors. At the time of the study, the patient needed to be on several medications that can affect sleep staging and architecture—clonidine, amitriptyline, clonazepam, valproic acid, and phenytoin (Obermeyer and Benca, 1996; Sammaritano and Sherwin, 2000), whereas standards for MSLT indicate that prior to MSLT patients should be taken off any confounding medications, such as hypnosedatives and antidepressants (Carskadon et al., 1986). Our patient was not able to stay awake between naps and in fact was observed to have several cataplectic events, whereas standards also indicate that any other causes of excessive daytime drowsiness should be treated prior to MSLT. A repeat polysomnogram with continuous positive airway pressure for treatment of sleep apnea was not successful because the patient’s dementia led to uncooperativeness.

With the patient’s history of excessive daytime sleepiness, hallucinations, and witnessed cataplexy, we made a clinical diagnosis of narcolepsy. Narcolepsy can be diagnosed without MSLT in the presence of excessive daytime sleepiness and witnessed cataplexy (Honda and Juji, 1988). Human leukocyte antigen (HLA) typing for DR2 and DQW was negative. HLA is positive in 85%–98% of patients with primary narcolepsy. However, this case of narcolepsy is probably secondary, and HLA positivity would not necessarily be expected. Family history is often negative in narcolepsy, with most cases being sporadic (Thorpy, 2001).

The patient continued to worsen with frequent seizures, excessive sleepiness, and cataplexy. He received methylprednisolone and then cyclophosphamide, but improved little. His symptoms worsened over a year with increased activity of complex partial seizure that responded poorly to medications. Cataplexy was controlled with imipramine. Modafinil in high doses (800 mg/day) did not improve excessive sleepiness.

Although no mass was evident on imaging, in paraneoplastic syndromes the tumor is often small and may elude clinical detection (Henson and Urich, 1982). Therefore, in light of the progressive worsening, we performed an elective right orchiectomy. The right side was chosen because of the prior hydrocele and the thickening of the seminal vesicle on that side. Pathology revealed an intratubular germinomatous testicular carcinoma.

Several weeks postorchiectomy, the patient was less confused. He became aware of his memory deficits, and his cataplexy improved significantly. The frequency of the complex partial seizures decreased with vagal nerve stimulator and topiramate, phenytoin, phenobarbital, and primidone. There has been no improvement in the memory impairment.

Discussion

Our patient has limbic and brainstem encephalitis associated with the anti-Ma2 antibody. Limbic encephalitis associated with the anti-Ma2 antibody occurs in patients with testicular cancer, adenocarcinoma of the lung, and breast cancer (Barnett et al., 2001; Dalmau and Posner, 1997; Gultekin et al., 2000; Sutton et al., 2000; Voltz et al. 1999). This is a unique case in that an organ was removed prospectively because of the clinical scenario and antibody testing. This is also the first report of a testicular cancer case associated with cataplexy and possible narcolepsy.

Hypothalamic involvement has been documented in a majority (70%) of patients with anti-Ma2 antibody and testicular cancer (Gultekin et al., 2000). Narcolepsy is a dysregulation of REM sleep characterized classically by excessive sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations, and disturbed nocturnal sleep. A cholinergic/monoaminergic imbalance underlying the symptomatology has been established and is most likely caused by an absence of hypocretin signaling. Hypocretin-containing cells are mapped in the hypothalamus (Oveis et al., 2001).

Paraneoplastic immune disorders manifest themselves in many ways, and a clinician who is aware of the several manifestations at initial presentation can more accurately diagnose the condition and potentially diagnose the underlying malignancy at an early stage. Treatment of these disorders still remains extremely difficult, although some patients are reported to have achieved stabilization or improvement of the neurological manifestations after removal of the underlying tumor.
References


