

Status Epilepticus Complicating Anti-Ma2 Antibody Associated Paraneoplastic Autoimmune Encephalitis

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ABSTRACT

Anti-Ma2 antibody associated paraneoplastic autoimmune encephalitis is a rare condition characterized by a clinical syndrome of neuropsychiatric deficits and seizures. We describe a patient with this condition who despite delay in initial diagnosis, was successfully treated with immunotherapy and removal of a testicular seminoma, but unusually developed status epilepticus after a period of remission. This case highlights that neurological sequela and medically refractory seizures can occur long after tumour resection and warrants ongoing monitoring of these patients despite initial success in treatment.

INTRODUCTION

The Autoimmune Encephalitides (AIE) are a group of autoimmune neuroinflammatory disorders that commonly have seizures as a component of their presentation [1]. There is significant overlap between seizures in AIE, autoimmune epilepsy and post encephalitic epilepsy [2] and may represent a common immune mediated epileptogenic mechanism. The following case of a patient with a paraneoplastic AIE (anti Ma-2 antibody associated) complicated by status epilepticus after initial improvement with treatment provides further insight into the interaction between AIE and post encephalitic epilepsy.

CASE REPORT

We present a case of a 40-year-old man who had presented initially with a collection of cognitive and neuropsychiatric symptoms 3 years prior. His initial symptoms and signs included narcolepsy, nocturnal hyperphagia, supranuclear palsy, dysarthria and gait ataxia, and short term memory loss. His initial work up included a normal MRI brain and an 'encephalopathic' electroencephalogram (EEG) with widespread background delta slowing. A unifying diagnosis was not made. He subsequently deteriorated 1 year later with psychosis and worsening encephalopathy resulting in a rapid decline in function. In this instance, his cranial MRI demonstrated a right temporo-insular FLAIR (fluid attenuated inversion recovery) signal abnormality (Figure 1) and his Cerebrospinal Fluid (CSF) investigation demonstrated a slightly elevated protein of 0.57g/L and $4 \times 10^9/L$ lymphocytes. There were matched oligoclonal bands detected in serum and CSF. A brain biopsy of the affected right temporal lobe demonstrated a perivascular T cell predominant lymphocytic infiltrate. Antibody testing revealed anti-Ma2 antibodies in both serum and CSF (both titers

1:160) indicating a diagnosis of anti-Ma2 associated paraneoplastic autoimmune encephalitis. Following this result, he was treated with an induction course of intravenous methylprednisolone and intravenous immunoglobulin. He also underwent an elective bilateral orchidectomy, despite normal full body PET imaging and a normal testicular ultrasound, due to concern of occult malignancy. This decision was made in conjunction with his partner and made simpler as they did not intend to have any further children. His surgical biopsy demonstrated bilateral testicular seminomas.

After his surgical treatment he received three courses of pulse cyclophosphamide therapy (750 mg/m^2) followed by two doses of Rituximab (1000 mg each, 6 months apart). His clinical state was stabilized and improved. There was also radiological improvement with a reduction in the FLAIR hyperintensity on his MRI brain (Figure 1).

One year later after the identification of the anti-Ma2 antibodies, his conscious state deteriorated abruptly. EEG at admission demonstrated frequent subclinical right temporal

lobe seizures (Figure 2), meeting the criteria for partial status epilepticus. CSF investigation demonstrated an elevated protein at 1.07 and $5 \times 10^9/\text{L}$ lymphocytes. Cell-surface antibody testing remained negative. Repeat cranial MRI demonstrated no new pathology, with stable right temporo-insular FLAIR signal abnormality. He was treated with escalating anti-epileptic therapy including a ketogenic diet. After failing to respond to a combination of 5 anti-epileptics, he was placed in the intensive care unit and sedated with a midazolam infusion. He was given 5 cycles of plasma exchange in conjunction with intravenous methylprednisolone. Due to the acuity of the patient's illness and the requirement of high dependency care plasma exchange was preferred over intravenous immunoglobulin. Repeat PET imaging revealed no evidence of metastatic tumor spread. Despite electrographic improvement of the right temporal lobe discharges on EEG, no clinical improvement was achieved and he was subsequently given palliative care after discussions with his family and he succumbed to a ventilator associated respiratory tract infection.

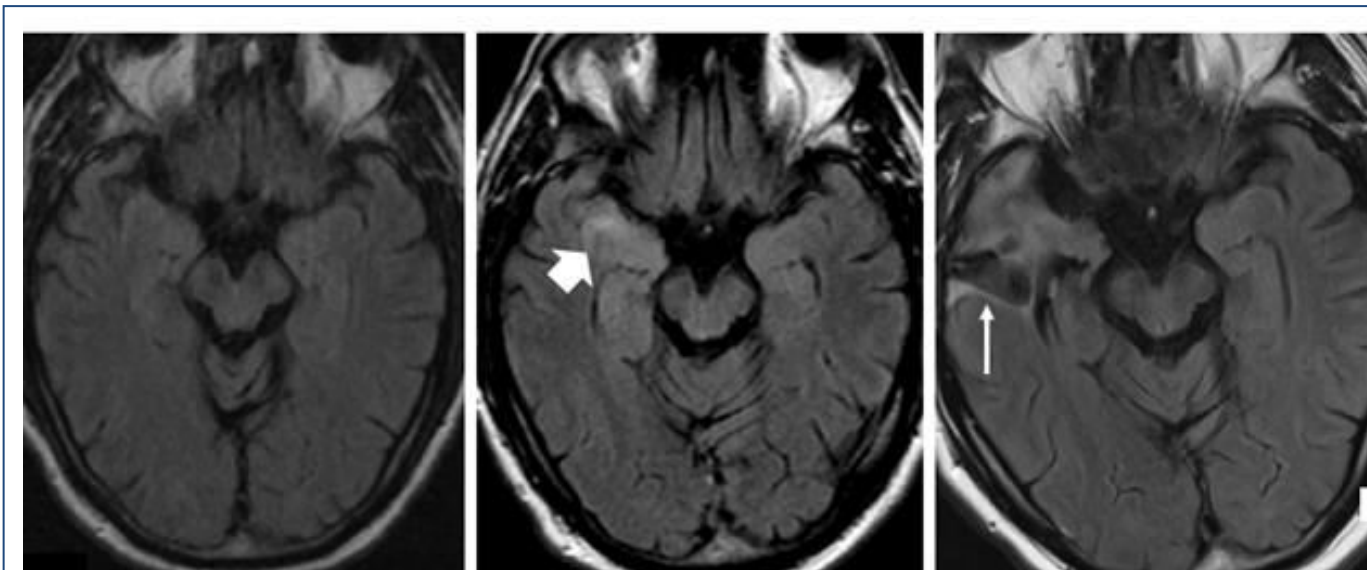
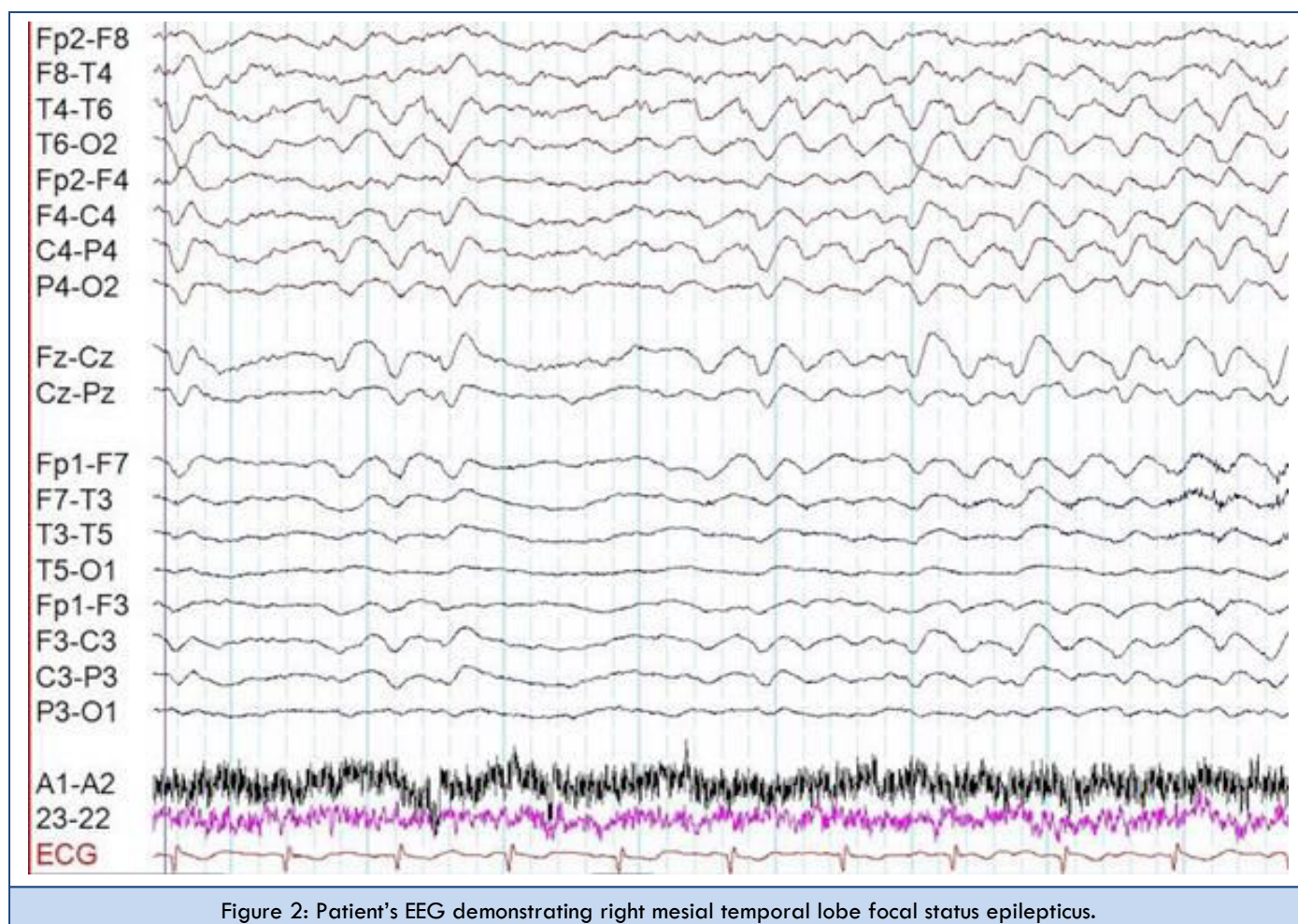


Figure 1: Patient's MRI changes. At symptom onset there is normal FLAIR signal within the mesial temporal lobes (A). By diagnosis 1 year later there is high FLAIR signal in the right mesial temporal lobe (B, thick white arrow). After treatment the FLAIR signal has improved, with some residual gliosis due to a surgical biopsy (C, thin white arrow).



DISCUSSION

Anti-Ma2 antibody associated paraneoplastic autoimmune encephalitis is characterized by antibodies against the protein Ma2, which is found in neurons as well as being expressed in testicular and other neoplasms [3]. Patients present with a variety of overlapping clinical syndromes; a Limbic Encephalitis (LE), Diencephalon (DE) involvement or a Brainstem (BS) syndrome [4]. This results in a variety of neuropsychiatric symptoms due to limbic involvement including cognitive difficulties, seizures and psychosis; diencephalon involvement including parasomnias, hyperphagia and pituitary dysregulation; brainstem syndrome including vertical gaze palsies, hypokinesia, dysarthria and ataxia [4]. This disease is most commonly associated with testicular seminoma (40%), [5] though may also be associated with lung and gastrointestinal neoplasms (both 10%). Ancillary investigations can reveal FLAIR hyperintensities on MRI in the temporal lobe, diencephalon or brainstem, and CSF investigation demonstrates

an elevated protein in 53% of patients and a mononuclear pleocytosis in 35% of patients [5]. Prognosis is dependent on the disease course and treatment choice [4]. Those with neoplasms who were treated for the neoplasm and with immunotherapy appear to improve or at least stabilise, whereas those treated with immunotherapy alone have worse outcomes [4]. A case series by Dalmau et al. demonstrated 12 patients with a disease course complicated by seizures, and 7 of those patients requiring >1 anti-epileptic medications [4]. While our case report matches the described clinical syndrome well with regards to symptoms (overlapping LE, DE and BS symptoms), presence of a testicular seminoma and response to oncological and immunological treatment, it is unusual in a number of respects: Firstly, the patient had two clearly defined clinical syndromes. The first was characterized by anti-Ma2 antibody associated paraneoplastic autoimmune encephalitis without any indication of seizures. The second was

characterized by New Onset Refractory Status Epilepticus (NORSE). Secondly, the patient had improved with initial treatment of the testicular seminoma, and appropriate immunotherapy before dramatically worsening, despite CD20 cell depletion and plasma exchange.

These unique aspects suggest two possibilities. The first is there was incomplete treatment (either immunologically or oncologically) and the patient's dramatic clinical worsening represented a relapse in his Anti-Ma2 antibody associated paraneoplastic autoimmune encephalitis. Further progression of disease after treatment has been described by Dalmau et al. in two patients within his series, although one responded to reinstatement of immunotherapy, while the other was revealed to have recurrence of their neoplasm [4]. In our case the patient neither responded to further immunotherapy, nor was identified to have recurrence of his testicular seminoma.

The second is that his NORSE was likely secondary to post-encephalitic drug resistant status epilepticus due to either structural or functional temporal lobe changes as result of his initial illness (or even due to the gliotic changes at the site of the patient's brain biopsy). Similar clinical scenarios can be seen after viral encephalitis. In a cohort of viral encephalitis cases, 10-22% developed epilepsy in the following 20 years [6]. Patients who had seizures during their acute illness were twice as likely to develop post encephalitic epilepsy [6]. A more recent study examining both infective and autoimmune encephalitis found up to 30% of patients developed post-encephalitic epilepsy, and clinical predictors included focal FLAIR changes on MRI brain and clinical focal or generalized seizures [7]. The cellular / molecular mechanism for post encephalitic drug resistant epilepsy has not been elucidated.

There has been increasing awareness that there is a relationship between neuroinflammation and epileptogenesis. Several studies have demonstrated that the pro-inflammatory cytokines interleukin1 β (IL-1 β), interleukin-6 (IL-6), tumour necrosis factor α (TNF- α) modulate susceptibility to limbic seizures in rat models of temporal lobe epilepsy [8]. These cytokines are also upregulated during seizures along with markers of monocyte activation (CD86, HLA-DR, CD14+CD16-) and T cell activation (CD25, CD69, CTLA-4 and HLA-DR) [9] in patients with temporal lobe epilepsy compared with healthy controls. Animal studies have implicated infiltrating CCR2+

monocytes as an important potential mediator of this neuroinflammation [10]. This potential mechanism has recently been a target of successful treatment with tocilizumab, an IL-6 blocker, in Rituximab refractory AIE and NORSE [11,12]. Further investigation into use of tocilizumab to prevent post encephalitic epilepsy would be of great interest.

The case presented here highlights the importance of NORSE, both as a component and complication of autoimmune encephalitis due to its impact on morbidity and mortality. It also illustrates the need for greater understanding of the immunological processes involved in epileptogenesis to instruct the use of targeted immunomodulatory therapies.

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