Journal of Neuroimmunology 337 (2019) 577084

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short communication

Multiple co-existing antibodies in autoimmune encephalitis: A case and review of the literature

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ARTICLE INFO

Keywords:
Autoimmune encephalitis
Paraneoplastic syndrome
Co-existing autoantibodies

ABSTRACT

A 66-year-old man with a history of chronic tobacco use presented with two months of progressive memory deficits, ataxia, diplopia, and opsoclonus. His brain magnetic resonance imaging (MRI) showed limbic and brainstem encephalitis, and antibody testing was positive for anti-Ma1/Ma2, anti-*N*-methyl-D-aspartate receptor (anti-NMDA-R) and anti-glutamic acid decarboxylase 65 (anti-GAD65) antibodies. His encephalitis improved with intravenous steroids, plasmapheresis, and rituximab initiation. His PET/CT was suspicious for lung malignancy, but a progressive deterioration of his respiratory status prevented full investigation. Multiple auto-antibodies may be produced in response to a malignancy and overlapping of clinical presentations may occur with multiple auto-antibodies.

1. Case report

A 66-year-old man with a history of chronic tobacco use presented with two months of worsening balance, diplopia, and confusion. He had no prior medical conditions. Neurological exam revealed short-term memory deficits, a poor fund of knowledge, ataxia, opsoclonus, restricted upgaze, restriction of right eye abduction, and a right extensor toe response. He had no myoclonus.

Brain MRI revealed an encephalitis involving the brainstem, mesial temporal lobes, and basal ganglia (Fig. 1). Cerebrospinal fluid (CSF) analysis showed a pleocytosis of 75 nucleated cells per mm^3 (reference < 6 nucleated cells per mm^3) with a lymphocytic predominance, elevated protein of 75 mg/dL (reference 15–45 mg/dL), and normal glucose. Five unique oligoclonal bands were present. In the CSF, anti-NMDA-R antibody was positive by undiluted cell-based assay (Mayo Clinical Laboratories), and anti-Ma1 and anti-Ma2 were positive (titer > 1:32, Athena Diagnostics). CSF infectious studies were negative including herpes simplex virus polymerase chain reaction. CSF cytology and cytometry were negative for malignant cells. Serum studies demonstrated low positive anti-GAD65 antibodies (0.12 nmol/L, reference ≤0.02), with the rest of the autoimmune encephalopathy evaluation otherwise negative (Mayo Clinical Laboratories). Electroencephalogram (EEG) demonstrated diffuse and intermixed slowing, but no epileptiform discharges or seizures.

Due to initial suspicion for a paraneoplastic process, malignancy screening included a negative testicular ultrasound and a computed tomography (CT) of the chest that demonstrated extensive pulmonary fibrosis, several prominent mediastinal lymph nodes, and multiple segmental pulmonary emboli. A body positron emission tomography CT demonstrated FDG uptake in a right hilar lymph node in addition to a subpleural, sub-centimeter pulmonary nodule in the left upper lobe. Biopsy of the right hilar lymph node showed benign epithelium and lymphocytes, however, without evidence of malignancy.

For treatment of a probable autoimmune encephalitis (AE), he received 5 days of 1 g intravenous methylprednisolone, followed by 5 days of plasma exchange, with improvement of his eye movements, mental status, and ataxia. He remained on an oral steroid taper and received two doses of rituximab 1 g a month apart (his second dose was delayed from the standard 1 g infusion on day 0 and day 14 due to insurance issues).

He re-presented one month after discharge with worsening dyspnea, hypoxia, and intermittent confusion. A brain MRI showed improvement, but not resolution, of his prior FLAIR hyperintensities, and a repeat chest CT showed several new subpleural, sub-centimeter/centimeter spiculated pulmonary nodules with adjacent pleural thickening. His pulmonary fibrosis and tenuous respiratory status prevented further attempts to biopsy these nodules, although there was high suspicion for an underlying lung neoplasm by his pulmonologists. The patient and his family elected for hospice care in lieu of further evaluations or treatments.

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https://doi.org/10.1016/j.jneuroim.2019.577084
Received 11 July 2019; Received in revised form 22 September 2019; Accepted 5 October 2019

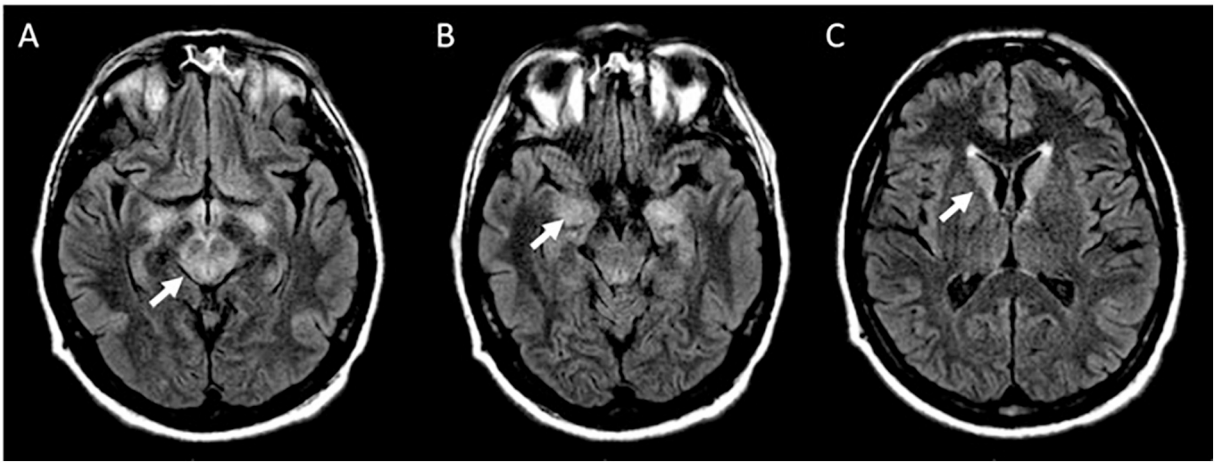

Fig. 1. Brainstem and temporal lobe encephalitis on MRI of the brain.
FLAIR hyperintensities extending from (A) the bilateral midbrain into (B) the anterior hippocampus and amygdala, (C) basal ganglia, and caudate heads. No contrast enhancement was present.

2. Discussion

This patient had co-existence of multiple auto-antibodies in the CSF (anti-NMDA-R, anti-Ma1/Ma2) and serum (anti-GAD65). Given the high suspicion for a concurrent lung neoplasm, this was concerning for an underlying paraneoplastic process. AE can occur with or without an underlying malignancy. However, the presence of multiple auto-antibodies in an older male smoker should raise concern for a paraneoplastic etiology, particularly in the setting of onconeuronal antibodies such as anti-Ma1/Ma2 (Ortega Suero et al., 2018). Anti-neuronal antibodies may be produced in the setting of an underlying malignancy through several mechanisms. The host tissue of the tumor may constitutively express antigens also seen in neurons, which are then exposed to the immune system through the breaking of immune privilege or through phagocytosis after cell death. Mutations in tumor cells may result in expression of antigens not typically seen in the host tissue, or a recombination of surface or intracellular molecules may result in molecules that mimic neuronal antigens. As multiple antigens are exposed in these processes, multiple concurrent auto-antibodies may be generated (Pittock et al., 2004; Zaenker et al., 2016). Rarely, neuronal cell surface antibodies have also been noted to form after various forms of brain injury (post-infectious, stroke, traumatic brain injury, etc) (Javidi and Magnus, 2019). One well-known example of post-infectious anti-NMDA-R encephalitis can be seen following herpes simplex virus encephalitis (Nosadini et al., 2017) The release of brain antigens following a primary autoimmune encephalitis could plausibly result in secondary generation of additional auto-antibodies, although this method of antibody generation has not been proven.

The presence of multiple anti-neuronal antibodies raises the probability of an underlying malignancy, and may be predictive of a specific malignancy (Arino et al., 2015; Horta et al., 2014; Pittock et al., 2004). For example, in one study with patients with identified tumors, the frequency of a thymoma being identified was 36% when both muscle acetylcholine receptor and striational antibodies were present. This frequency increased to 85% with co-occurrence of the collapsin response-mediator protein-5 (CRMP-5) antibody. Similarly, the co-existence of anti-Hu antibodies with either CRMP-5 or P/Q voltage gated calcium channel (VGCC) antibodies raised the frequency of small cell lung carcinoma being identified from 83% to 100%, compared with anti-Hu alone (Horta et al., 2014).

When a patient is diagnosed with an AE, appropriate and targeted malignancy screening should be undertaken, focusing on the patient's risk factors (i.e. age, sex, family or personal history of malignancy, tobacco use). Additional guidance is provided from the specific auto-antibodies discovered, as certain auto-antibodies have high associations with particular tumors (Kannoth, 2012; Pittock et al., 2004), as shown in Table 1. Paraneoplastic antibodies may predate any evidence of a primary malignancy, so continued, regular malignancy screening is necessary, recommended at least every six months for four years, depending on the antibody syndrome (Kannoth, 2012; Pittock et al., 2004; Titulaer et al., 2011).

Neuronal auto-antibodies may target intracellular or extracellular epitopes. Classic onconeural auto-antibodies (e.g. anti-Hu, anti-Yo, anti-Ri, or anti-Ma antibodies) target nuclear or cytoplasmic epitopes. Therefore, they are not directly pathogenic, but likely act as a biomarker for cytotoxic T-cell mediated neuronal damage (Dalmau and Graus, 2018). Their presence is highly associated with an underlying malignancy (generally > 95%), and generation of these antibodies is thought to occur in response to the release of intracellular antigens after the immune system has targeted and eliminated tumor cells (Kannoth, 2012). Similarly, anti-GAD65 antibodies also target a cytoplasmic neuronal protein, although these antibodies have less sensitivity and specificity for presence of malignancy, and therefore are not included as a “classic” onconeuronal antibody (Arino et al., 2015; McKeon and Tracy, 2017). The probability of malignancy with anti-GAD65 antibodies increases if the presentation fits a classic paraneoplastic syndrome (PNS) or if co-existing neuronal cell-surface antibodies are present (Arino et al., 2015). Up to 8% of the general population may have low-positive anti-GAD65 antibodies (< 2 nmol/L), with a higher prevalence in type I diabetes, autoimmune thyroid disease, and certain HLA haplotypes (McKeon and Tracy, 2017; Sørgjerd et al., 2015). Neurological syndromes are associated with the presence of auto-antibodies in the CSF, or serum antibody concentrations of at least 20 nmol/L or more, generally several orders of magnitude higher than those seen in the general population (Arino et al., 2015; McKeon and Tracy, 2017).

Antibodies to cell-surface (extracellular) antigens, on the other hand, target synaptic proteins or ion channels, such as anti-NMDA-R, anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (anti-AMPA-R), anti-γ-aminobutyric acid-A or B receptor (anti-$GABA_A$-R or $GABA_B$-R), among others. These antibodies alter neuronal function by several mechanisms, including receptor competition and internalization, and are directly pathogenic to cells. When immunotherapy is started early, before neuronal death occurs, a good recovery may be seen with the removal of the pathogenic antibody. In contrast, a lower immunotherapy response is seen in encephalitis associated with antibodies to intracellular neuronal epitopes, reflecting the degree of pre-existing neuronal injury at the time of antibody generation, as well as

Table 1
Anti-neuronal antibodies present in this case.

Anti-neuronal antibody	Type	Clinical presentation	Oncologic associations	Suggested order of oncologic screening (Titulaer et al., 2011)
Anti-Ma1/Ma2 (Ta)	Classic onconeuronal (intracellular)	Brainstem, diencephalic, and/or limbic encephalitis (Hoffmann et al., 2008; Ortega Suero et al., 2018)	Testicular tumors (anti-Ma1), lung/pleural tumors (anti-Ma1/Ma2) (Ortega Suero et al., 2018)	1. Testicular ultrasound, AFP/β-HCG (males) 2. CT +/− PET chest/abdomen/pelvis
Anti-NMDA-R	Cell surface synaptic	Psychosis, seizures, movement disorders, autonomic instability, and central hypoventilation (Dalmau and Graus, 2018)	Ovarian tumors (females), testicular germ cell tumors (males), small cell lung carcinoma (rare) (Dalmau et al., 2011)	1. Testicular ultrasound, AFP/β-HCG (males); Ovarian ultrasound (females) 2. CT +/− PET chest/abdomen/pelvis
Anti-GAD65	Intracellular synaptic	Neurologic syndromes with high-titers (> 20 mmol/L [not seen in this case]): Stiff-person syndrome, autoimmune epilepsy, autoimmune limbic encephalitis, and cerebellar ataxia (McKeon and Tracy, 2017)	Less commonly associated with cancer, but includes: lung carcinomas (small-cell and non-small cell), adenocarcinomas, and testicular seminoma (Arino et al., 2015; McKeon and Tracy, 2017)	Suggested if classic PNS or co-existing neuronal cell surface antibodies (Arino et al., 2015): 1. Testicular ultrasound, AFP/β-HCG (males) 2. CT +/− PET chest/abdomen/pelvis

the difference in immune-mediated pathogenesis (Dalmau and Graus, 2018).

Brainstem involvement is an atypical feature for anti-NMDA-R encephalitis (Dalmau et al., 2011). After careful initial consideration of our patient's clinical presentation and neoplastic risk factors, anti-Ma1/Ma2 antibodies were sent, which are not included on our institution's commercially available antibody panel (Mayo Clinic Laboratories). While auto-antibody panels can be useful in many clinical situations, sole reliance on a panel may miss antibodies critical for that specific clinical scenario, as well as newly discovered, novel neural auto-antibodies. Conversely, without the use of a panel for broad antibody screening, stepwise testing of individual auto-antibodies may result in multiple lumbar punctures and unacceptable delays in diagnosis and targeted cancer screenings. The rate of false positive results may be decreased with the use of best available testing including cell-based assays (CBA) for neuronal cell surface antibodies, which lowers the false positive rate to 0.23% as compared to older techniques and non-standard assays such as ELISA (Lang and Prüss, 2017). Given these factors, it is important that antibody testing is informed by the clinical presentation to provide an appropriate breadth to the diagnostic evaluation, which may include antibody panels and/or single antibody testing.

Co-existing (or overlapping) auto-antibody neurologic syndromes have clinical and radiographic features that may be common for each antibody-mediated disorder individually combining in a single, unique presentation that would be atypical for either antibody alone. For example, in anti-NMDA-R encephalitis, B cells producing anti-NMDA-R antibodies make up the minority of antibody-secreting cells, with the other secreted antibodies reacting with other neuronal or glial epitopes (Kreye et al., 2016). This variability in intrathecal antibodies may result in the variability seen in the clinical presentation of anti-NMDA-R encephalitis. For example, encephalitis related to anti-NMDA-R antibodies may co-exist with demyelinating disease or show gadolinium enhancement in the presence of anti-NMO, anti-MOG, or anti-GFAP antibodies (Fan et al., 2018; Flanagan et al., 2017; Titulaer et al., 2014). Limbic encephalitis related to anti-$GABA_B$-R antibodies may co-exist with a progressive sensorimotor neuropathy when anti-Hu antibodies are present (Guan et al., 2015), or demonstrate more prominent psychiatric symptoms in the presence of anti-NMDA-R antibodies (Lancaster et al., 2010). Symptoms of anti-AMPA-R encephalitis (short term memory loss, sleep changes, psychosis, or ataxia) have been noted in conjunction with stiff person syndrome (anti-GAD), optic neuropathy (anti-CRMP5), or sensory neuropathy (anti-amphiphysin) (Höftberger et al., 2015; Lai et al., 2009). The potential for a significant overlap of non-specific clinical symptoms associated with each neural auto-antibody, especially early into the clinical course, also highlights the need for antibody testing informed by the clinical presentation (Kannoth, 2012).

Our patient's brainstem and limbic encephalitis fits clinically and radiologically with a PNS associated with anti-Ma1/Ma2 antibodies. The NMDA-R antibody was present in the CSF of our patient (preferred method of testing compared to serum), where it is typically thought of as pathogenic (Dalmau et al., 2011). Although present at low levels, as a pathogenic antibody in the CSF, some component of his subacute cognitive and memory decline may be referable to this. However, no symptoms that are specific or unique for anti-NMDA-R encephalitis were noted, unlike in the co-existing antibody syndromes highlighted previously. His anti-GAD65 antibodies were present at a much lower concentration than seen in neurologic syndromes and were only found in the serum. Therefore, they are unlikely to represent true neurological autoimmunity in this setting, but are rather a marker of increased auto-antibody production in response to tumor cell breakdown and antigen release, or represent a low-titer “false positive” result as seen in 8% of the general population (McKeon and Tracy, 2017).

One disadvantage of this case is that the presence and type of lung neoplasm was not confirmed by pathology, although given the presence

of well-characterized onconeural antibodies, this case still meets criteria for a definite PNS (Graus et al., 2004). His pattern of auto-antibodies would suggest a tumor of testicular or lung origin, and there was high suspicion for a lung neoplasm given his pulmonary fibrosis, his systemic hypercoagulability, and the appearance of his lung nodules.

3. Conclusion

Initial evaluation for AE should include broad screening with antibody panels, as well as specific antibody testing informed by the clinical presentation and neoplastic risk factors. Clinical context is important in the interpretation of auto-antibody results. Co-existing antibodies may produce an overlap of clinical symptoms. In the setting of multiple auto-antibodies, a careful evaluation for occult malignancy is warranted, with initial and continued malignancy screening dictated by the antibodies present.

Funding

The authors did not receive a grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests

None declared.

Patient consent

Consent was obtained from the patient and his medical power of attorney before submission.

Financial disclosures

Ryan Kammeyer – Reports no disclosures.

Amanda L Piquet – Dr. Piquet has received research funding from the Drake Family and the Rocky Mountain MS Center. Outside of this work, Dr. Piquet reports honorarium from MedLink and consulting fees from Sanofi Genzyme and Genentech.

Acknowledgements

All authors participated in the collection of data, preparation of the final manuscript, and approval of the final manuscript.

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