Neurology Asia 2026; 31(3) : 1211 – 1214

A rare neurological puzzle: Anti-Ma2 encephalitis linked to lung adenocarcinoma

Ceyhun Sayman, Merve Gözüaçık, Gökhan Gölle, Şeyda Çankaya, Burak Yuluğ

Department of Neurology, Alanya Research and Education Hospital, Alaaddin Keykubat University, Antalya, Turkey

Abstract

Anti-Ma2 encephalitis is a rare paraneoplastic syndrome, mainly associated with germ cell tumors of the testis. This case report represents an atypical presentation of anti-Ma2 encephalitis in a 65-year-old female with lung adenocarcinoma. The patient presented with neuropsychiatric symptoms such as hallucinations and loss of recent memories and systemic symptoms of weight loss and night sweats. Evaluation showed bilateral hippocampal T2 hyperintensities on MRI and positivity for anti-Ma2 antibodies in serum. Initial treatment with corticosteroids resulted in partial symptomatic improvement; however, further relapses forced us to consider other immunotherapies such as rituximab and azathioprine. In spite of persistent memory deficits, the patient regained much of her general well-being. This case report points out early recognition and multidisciplinary management in this rare syndrome, especially in atypical oncological contexts. Careful malignancy workup and early institution of immunosuppressive therapy are important steps in improving patients' outcomes in paraneoplastic encephalitis.

INTRODUCTION

Anti-Ma2 encephalitis is a rare form of autoimmune, paraneoplastic neurological syndrome affecting the central nervous system (CNS).[1] Anti-Ma2 antibodies are in the spectrum of onconeuronal antibodies and usually present with limbic, diencephalic, or brainstem encephalitis. While the majority are almost exclusively found in males with germ cell tumors, particularly testicular cancer, cases related to other malignancies, including lung adenocarcinoma, had been reported.[2,3]

Patients with anti-Ma2 encephalitis typically present with a variety of symptoms, which can include memory impairments, psychiatric symptoms, ataxia, and dysfunction of the oculomotor system, depending on the involved anatomical regions.[4] Neuroimaging typically shows T2 hyperintensities in the medial temporal lobes, thalamus, or brainstem.[5] The diagnosis is based on a combination of clinical, radiological, and serological information, and antibody assays play a paramount role.

The infrequency of anti-Ma2 encephalitis associated with adenocarcinoma-related lung cancer presents considerable difficulties in diagnosis, frequently resulting in delayed diagnosis and treatment.[6] This report presents a case of autoimmune encephalitis characterized by anti-Ma2 positivity in a 65-year-old female patient diagnosed with lung adenocarcinoma, emphasizing the diagnostic methodology, clinical progression, and therapeutic strategies to highlight the necessity for prompt identification and a collaborative approach among specialists.

CASE REPORT

A 65-year-old female patient was referred to the hospital after complaints of gait instability over three months. She also reported the appearance of hallucinations, memory loss, mood swings, remarkable weight loss, and episodes of night sweats. The patient had a history of smoking for almost 30 years. Physical examinations showed gait disturbances, but there was no muscular weakness. Neuropsychological tests showed mild multimodal cognitive impairment with symptoms of depression and impairment in executive functions, memory attention, and semantic fluency.

Address correspondence to: Ceyhun Sayman, MD, Alanya Eğitim ve Araştırma Hastanesi Nöroloji Kliniği Oba, Fidanlık cad. Alanya/ Antalya, Türkiye. Email: ceysayman@yahoo.com.tr

Date of Submission: 24 April 2025; Date of Acceptance: 23 April 2026

https://doi.org/10.54029/2026yax

Cranial MRI showed bilateral T2 hyperintensities in the hippocampal region without contrast enhancement (Figure 1), and the EEG was normal. Lumbar puncture revealed cerebrospinal fluid (CSF) protein levels of 42 mg/dL, glucose levels of 80 mg/dL (with simultaneous blood glucose at 120 mg/dL), and a negative viral panel. Laboratory results were normal. Thoracic computed tomography revealed bilateral nodules suggestive of malignancy (Figure 2). After a biopsy, adenocarcinoma was pre-diagnosed. The patient received pulse methylprednisolone (1 mg/kg) for five days. A significant recovery in hallucinations and gait instability was observed. Testing for paraneoplastic neurological syndromes revealed anti-Ma2 (PNMA2) antibody positivity in the serum. Maintenance steroid therapy (1 mg/kg) was continued, and systemic chemotherapy was started in collaboration with the oncology department. Histopathological examination subsequently confirmed lung adenocarcinoma. After three cycles of platinum-based chemotherapy, follow-up thoracic computed tomography demonstrated stable disease, with no significant progression or regression of the pulmonary nodules.

When steroid treatment was slowly tapered over 3 months, a recurrence of hallucinations and a memory loss were observed. Despite clinical deterioration, follow-up MRI showed no evidence of metastasis or recurrent encephalitis (Figure 3). Rituximab therapy was initiated at a dose of 375 mg/m² administered intravenously once weekly for two consecutive weeks. Her hallucinations completely disappeared, but her memory loss persisted. Azathioprine 100mg twice daily was added for long-term immunosuppression, and the patient was placed under clinical surveillance

DISCUSSION

Anti-Ma2-associated encephalitis is a rare paraneoplastic syndrome with complex pathophysiology, mainly driven by autoimmune mechanisms against intracellular antigens.7 Its strong association with testicular germ cell tumors contrasts with the few cases linked to adenocarcinoma, as in our patient, and calls for a high index of suspicion in atypical presentations.

The patient presented with a spectrum of neuropsychiatric symptoms, including hallucinations and cognitive dysfunction, along with systemic features such as weight loss and nocturnal sweating, all of which increased the suspicion of an underlying paraneoplastic syndrome. The cranial MRI showed bilateral hippocampal T2 hyperintensities, further supporting a diagnosis of limbic encephalitis, and the cerebrospinal fluid analysis excluded common infectious etiologies. Diagnosis of anti-Ma2 encephalitis requires a high index of suspicion, particularly when the classical association with testicular tumors does not occur. The diagnosis was confirmed by the presence of the anti-Ma2 antibodies in serum, demonstrating the importance of including paraneoplastic panels in the workup of patients with encephalitis of unknown etiology.8

Anti-Ma2 encephalitis is treated with immunosuppressive therapy and therapeutic interventions against the tumors. The initial symptomatic improvement after corticosteroid therapy points out the importance of early immunosuppression.9 However, the subsequent clinical worsening, despite stable neuroimaging findings, highlights the need for adjunctive therapies. The introduction of rituximab and azathioprine was well tolerated and effective in a stepwise approach to managing refractory or relapsing disease. Although follow-up imaging showed no evidence of metastatic or recurrent disease, the persistence of autoimmune activity suggests that anti-Ma2 encephalitis may follow a relapsing clinical course. This case indicates the necessity for long-term immunological follow-up besides oncological surveillance.

This case report adds to the literature of anti-Ma2 encephalitis by highlighting its occurrence in lung adenocarcinoma, a rare association for this syndrome. It also illustrates the need for complete malignancy workup in patients with autoimmune encephalitis even when initial imaging and antibody results are inconclusive. Early recognition and early intervention are crucial to improve the outcome in paraneoplastic encephalitis. The combination of newer diagnostic modalities, including antibody testing and detailed imaging studies, with a multidisciplinary treatment approach can result in dramatic improvement in patient care.

In conclusion, anti-Ma2-associated encephalitis occurring in patients with lung adenocarcinoma is a rare occurrence. This case brings into focus the importance of increasing clinical awareness and a multidisciplinary approach in achieving a timely diagnosis and appropriate management. Moreover, the role of immunotherapy in the treatment of refractory cases emphasizes the need for personalized care in patients.

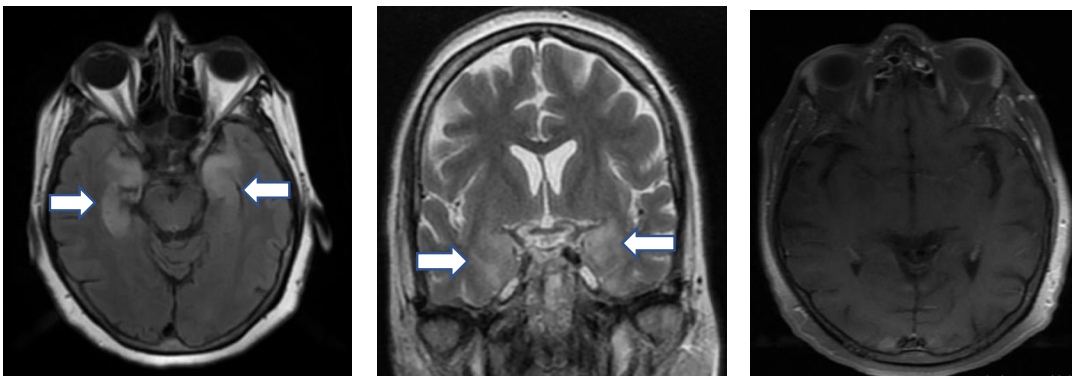

Figure 1. Fluid-attenuated inversion recovery (FLAIR) axial and coronal images demonstrating T2/FLAIR hyperintensity of the bilateral hypocampus (white arrows). Axial T1-weighted postcontrast images showing no gadolinium enhancement.

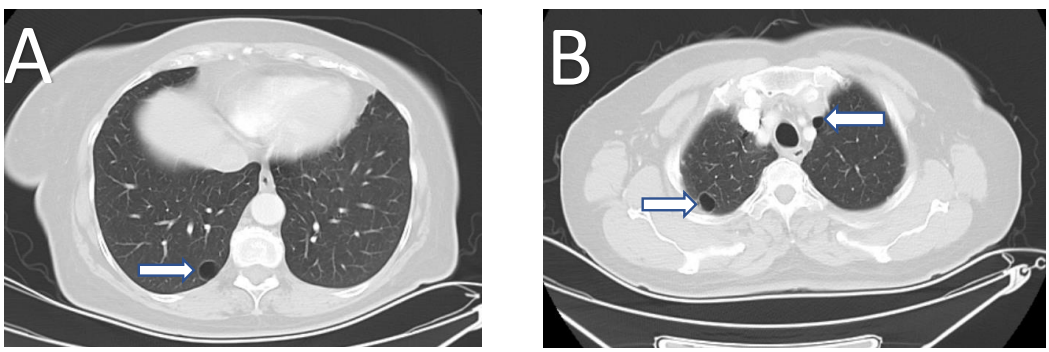

Figure 2. (A) Right pulmoner lower lobe posterolateral segmental 15mm nodule shown on torax CT (white arrow). (B) Right pulmoner upper lobe posteroapical segmental 15mm nodule and left pulmoner lobe paratracheal 5mm nodule shown on thorax CT (white arrow).

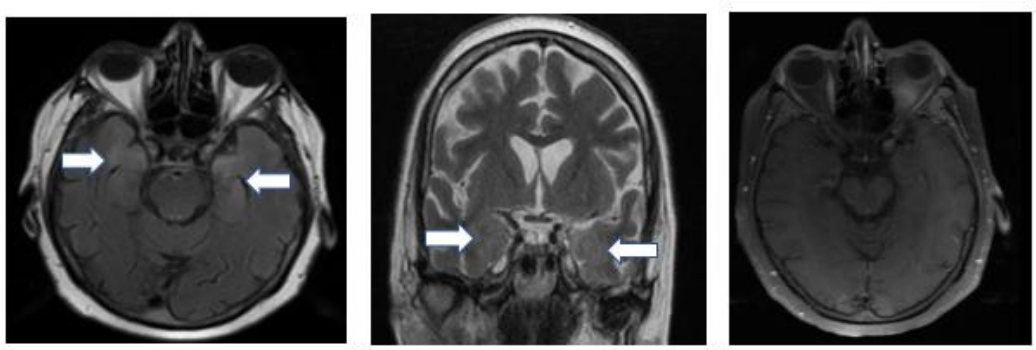

Figure 3. Fluid-attenuated inversion recovery (FLAIR) axial and coronal images demonstrating slightly T2/FLAIR hyperintensity of the bilateral hypocampus (white arrows). Axial T1-weighted postcontrast images showing no gadolinium enhancement.

REFERENCES

1. Flanagan EP, Geschwind MD, Lopez-Chiriboga AS, *et al*. Autoimmune encephalitis misdiagnosis in adults. *JAMA Neurol* 2023;80(1):30-9. doi:10.1001/jamaneurol.2022.4251.
2. Ortega Suero G, Sola-Valls N, Escudero D, Saiz A, Graus F. Anti-Ma and anti-Ma2-associated paraneoplastic neurological syndromes. *Neurologia* 2018;33(1):18-27. doi: 10.1016/j.nrl.2016.05.010.
3. Guo Y, Cai MT, Lai QL, Zheng Y, Shen CH, Zhang YX. Anti-Ma2 antibody-associated paraneoplastic neurological syndromes: A pilot study. *Brain Sci* 2021;11(12):1577. doi: 10.3390/brainsci11121577.
4. Dalmau J, Graus F, Villarejo A, *et al.* Clinical analysis of anti-Ma2-associated encephalitis. *Brain* 2004; 127:1831-44. doi: 10.1093/brain/awh203.
5. Kunchok AC, Ontaneda D, Lee J, *et al*. MRI features of anti-Ma1/Ma2 paraneoplastic neurologic syndrome. *Neurology* 2022;99(20):900-2. doi: 10.1212/WNL.0000000000201318.
6. Hoffman LA, Jarius S, Pellkofer HL, *et al.* Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients and review of previous cases. *J Neurol Neurosurg Psychiatry* 2008;79: 767-73. doi: 10.1136/jnnp.2007.118588.
7. Tüzün E, Dalmau J. Limbic encephalitis and variants: Classification, diagnosis and treatment. *Neurologist* 2007; 13:261-71. doi: 10.1097/NRL.0b013e31813e34a5.
8. Dalmau J, Graus F. Diagnostic criteria for autoimmune encephalitis: utility and pitfalls for antibody-negative disease. *Lancet Neurol* 2023;22(6):529-40. doi: 10.1016/S1474-4422(23)00083-2.
9. Vogrig A, Fouret M, Joubert B, *et al.* Increased frequency of anti-Ma2 encephalitis associated with immune checkpoint inhibitors. *Neurol Neuroimmunol Neuroinflamm* 2019;6(6):e604. doi: 10.1212/NXI.0000000000000604.