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Anti–NMDAR encephalitis in a patient with Crohn disease receiving adalimumab

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Anti–tumor necrosis factor alpha (TNF-α) therapies have been a significant advance in the treatment of autoimmune and rheumatologic diseases. Early preclinical and clinical studies of anti–TNF-α therapies emphasized infection and malignancy as serious adverse events associated with these agents.[1] However, subsequent clinical experience has increasingly recognized a rare and seemingly paradoxical risk of autoimmunity with agents targeting the TNF-α pathway, most notably psoriatic eruptions,[2] but also autoimmune processes associated with autoantibody production, including systemic vasculitis and lupus erythematosus.[3,4] The development of neurologic diseases in association with anti–TNF-α therapy has been documented in case series and small prospective studies,[5] with the most commonly reported associations being demyelinating diseases of the CNS and peripheral nervous systems. Here, we report a patient who developed anti–NMDA receptor (NMDAR) encephalitis while being treated with adalimumab for Crohn disease.

The patient was a 58-year-old woman diagnosed with Crohn disease at 36 years of age. She was treated with 5-aminosalicylates for many years, followed by azathioprine 100 mg daily beginning 3 years before her presentation. Six months before presentation, adalimumab 40 mg every other week was added, which she initially tolerated well. In the 3 weeks leading up to her presentation, the patient developed a progressive encephalopathy, beginning with headache and fatigue, followed by perceptual disturbances with disequilibrium and hyperesthesia, and then development of confusion and word finding difficulty. She was admitted to an outside hospital during this time with episodes of tachycardia for which a workup was unrevealing.

On presentation to our hospital, she was anxious and perseverative. Her general medical examination and basic laboratory testing were unremarkable. On neurologic examination, she was found to have poor attention and was unable to spell "world" backward or follow embedded commands. Her language was stuttering, and she had some anomia for low-frequency objects. During her hospitalization, the patient continued to have intermittent episodes of dysautonomia with tachycardia and hypotension. MRI of the brain with and without contrast and routine EEG performed on hospital day 2 were unremarkable. A lumbar puncture on hospital day 4 was significant for elevated CSF protein levels (63 mg/dL) with normal cell counts and glucose. CSF testing for NMDAR antibodies was positive in the clinical laboratory of the Hospital of the University of Pennsylvania. Research studies using screening against brain sections and CSF NMDAR cell-based assays were positive following our reported methods.[6] An MRI of the pelvis with and without contrast obtained before discharge showed no evidence of an ovarian teratoma or other pelvic malignancy. Adalimumab and azathioprine were discontinued, and she was treated with IV methylprednisolone 1,000 mg daily and IV immunoglobulin 0.4 g/kg daily for 5 days (hospital days 5 through 9) without significant clinical improvement, followed by rituximab 1,000 mg × 2 doses starting on hospital day 11. Her symptoms started improving

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several days after the first rituximab dose. She was discharged to a rehabilitation facility on hospital day 15.

The patient made a full functional recovery over 3 months and returned to work as a skilled professional. A repeat MRI of the pelvis performed 1 year after her initial presentation was again negative for pelvic malignancy. Now at 2 years after her initial presentation, the patient continues to do well without clinical relapses of anti–NMDAR encephalitis or Crohn disease. She has not received any further immunomodulatory treatments for anti–NMDAR encephalitis but was recently started on vedolizumab for Crohn disease.

Anti–NMDAR encephalitis has previously been reported in 2 patients treated with the immune checkpoint inhibitors nivolumab and ipilimumab.[7] Here, we have described a patient developing autoimmune encephalitis in association with anti–TNF-α-targeted therapy. Although causality in this instance cannot be proven, the patient's age at onset, the absence of a concurrent ovarian teratoma, and temporal association argue that adalimumab may be the inciting event. The mechanism by which anti–TNF-α therapy might lead to autoimmune disease is unknown. In the case of anti–TNF-α-triggered psoriasis, there is speculation that a systemic cytokine imbalance, with relative overproduction of interferon alpha in the setting of TNF-α suppression, leads to dysregulated T_H1-mediated immune responses.[2] In the case of autoantibody production, which would be expected to involve a T_H2-driven response, it may be that TNF-α suppression in complex cytokine environments such as the intestinal mucosa creates microenvironments within which local aberrant priming and expansion of a self-reactive B-cell population may occur. Regardless, neurologists should be aware of the potential for paradoxical autoimmune phenomena to occur with novel immunotherapies and to consider these medications as potential etiologic agents in patients who develop new neurologic complaints.

Author contributions

G.P. Noble: writing of the manuscript. E. Lancaster: study concept and critical revision of the manuscript.

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Disclosure

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