Teprotumumab-Induced Encephalopathy: A Rare Side Effect of a Novel Therapeutic

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ABSTRACT

Introduction: Teprotumumab is a novel monoclonal antibody used for treatment of thyroid eye disease (TED). To our knowledge, this is the second reported case of encephalopathy associated with teprotumumab therapy.

Case Presentation: A 62-year-old White woman with a history of hypertension, Graves' disease, and thyroid eye disease presented with 1 week of intermittent altered mental status following her third teprotumumab infusion. Neurocognitive symptoms resolved following plasma exchange therapy.

Discussion: By using plasma exchange as first-line therapy, our patient had a shorter time course from diagnosis to symptom resolution than was reported in the previously published case.

Conclusions: Clinicians should consider this diagnosis in patients with encephalopathy after teprotumumab infusion, and our experience suggests plasma exchange is an appropriate initial treatment. Proper counseling of this potential side effect is warranted for patients prior to starting teprotumumab to facilitate earlier detection and treatment.

INTRODUCTION

Thyroid eye disease (TED) or thyroid-associated ophthalmopathy is a rare, debilitating autoimmune condition with an annual incidence of 2.6 to 16.0 cases per 10,000 population per year.[1] It is postulated that the insulin-like growth factor-1 (IGF-1) receptor is involved in its pathogenesis. Teprotumumab, a novel therapeutic monoclonal antibody approved by the US Food and Drug Administration (FDA) in 2020, inhibits IGF-1 receptor signaling and blocks the autoimmune response that exacerbates TED.[2,3] Clinical trials of teprotumumab have shown substantial and rapid improvement in proptosis reduction in patients with TED.[4] Associated side effects are typically mild and transient, such as hyperglycemia, muscle cramps, auditory disturbances, and inflammatory bowel disease.[4,5] Severe adverse events leading to hospitalization also have been reported, including diarrhea, *Escherichia coli* sepsis, and urinary retention.[6] Encephalopathy related to teprotumumab was not seen in phase 3 trials but recently has been highlighted by Hoang et al.[7] We present a second case of teprotumumab-induced encephalopathy associated with a patient with TED.

CASE PRESENTATION

A 62-year-old White woman with past medical history of hypertension and Graves' disease associated with TED presented with 1 week of intermittent altered mental status. Her husband first noticed symptoms shortly after the patient's third teprotumumab infusion. She had difficulty performing basic tasks and following instructions, extreme mood swings, and episodes of amnesia, aphasia, insomnia, tremors, and anxiety. Neurologic evaluation demonstrated significant cognitive impairment. She was fully alert and oriented but struggled forming sentences and had occasional nonsensical speech. She was able to name 5 out of 5 objects, read sentences, and follow 1-step commands but was unable to follow commands with 2 or more steps. Her Montreal Cognitive Assessment (MoCA) score version 7.1 was 22, indicating mild cognitive impairment. A continuous electroencephalogram was normal without epileptiform discharges or seizures and

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brain magnetic resonance imaging (MRI) and computed tomography of the head were both negative for signs of hemorrhage, mass, or infarct. Lumbar puncture was notable for slightly elevated protein at 46 mg/dL but otherwise had normal cell counts with negative infectious, paraneoplastic, and autoimmune testing (Table). The patient's urine drug screen was negative, as were the screening tests for syphilis, HIV, nutritional deficiencies, and metabolic derangements. Her thyroid stimulating hormone was elevated at 7.42 uIU/mL; however, a free T4 and total T3 were within normal limits. In addition to teprotumumab at the onset of symptoms, her medications included atorvastatin 40 mg daily, brimonidine 0.2% ophthalmic drops 3 times daily, vitamin D3 supplements, coenzyme Q10 100 mg daily, lisinopril/hydrochlorothiazide 10 mg daily, methimazole 10 mg daily, and nabumetone 750 mg twice daily.

Based on a single case report of a patient on teprotumumab who exhibited similar symptoms that improved with plasma exchange after failing steroid and intravenous immunoglobulin (IVIG) therapy,[7] the decision was made to start plasma exchange treatment. The patient underwent 5 plasma exchanges on alternating days, with the first exchange occurring 13 days after her last teprotumumab infusion. The plasmapheresis parameters were 1 plasma volume exchange with 5% albumin as the replacement fluid. The patient and her husband were advised of the risks of plasma exchange, including hypocalcemia or hypomagnesemia secondary to citrate chelation, hypothermia, transfusion reactions, fluid and electrolyte abnormalities, increased bleeding risk, hypotension, flushing, and gastrointestinal symptoms such as nausea and vomiting. Her confusion and mentation improved to near baseline approximately 24 hours after her first exchange, but symptoms returned by the morning of her second plasma exchange. As her treatments progressed, she would have shorter periods of altered mental status and longer periods of baseline mental status. Serial assessments throughout the hospital course demonstrated improved mental status and cognition, with less pressured speech, decreased aphasia, and better visuospatial reasoning, as evidenced by improved clock and cube drawing (Figure). She tolerated the plasma exchange treatment well without any complications. She also had remission of her neurocognitive symptoms, although she reported persistent anxiety throughout the hospital course that did not fully resolve prior to her discharge. She reported resolution of her anxiety and continued remission of her symptoms at a follow-up appointment with her ophthalmologist 3 weeks after discharge.

DISCUSSION

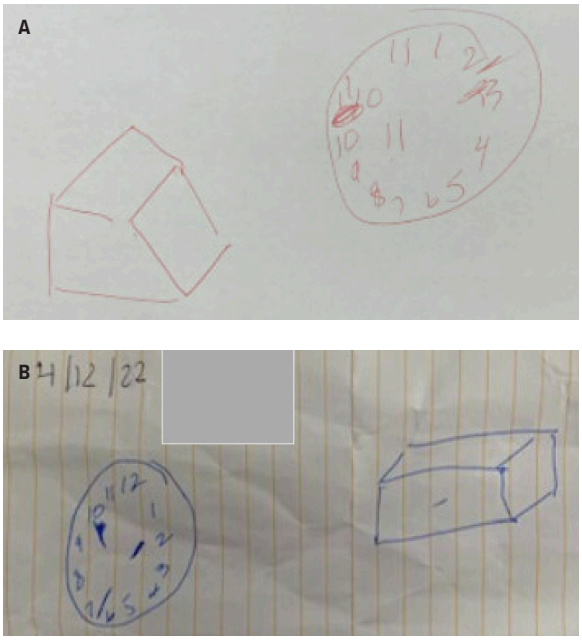
We present the case of a 62-year-old White woman with history of TED treated with teprotumumab who improved after plasma exchange therapy. To the best of our knowledge, this represents the second reported case of encephalopathy associated with teprotumumab.

Table. Serum Paraneoplastic and Autoimmune Encephalopathy Panel (Performed by Mayo Clinic Laboratories)

Result Name	Result	Reference Value
Antiglial nuclear antibody-1 (AGNA-1)	Negative	<1:2
AMPA receptor antibody CBA	Negative	Negative
Amphiphysin antibodies	Negative	<1:2
ANNA-1	Negative	<1:2
ANNA-2	Negative	<1:2
ANNA-3	Negative	<1:2
Contactin-associated protein-like 2 (CASPR2) IgG	Negative	Negative
Collapsin response-mediator protein 5 (CRMP-5) IgG	Negative	<1:2
DPPX antibody IFA	Negative	Negative
γ-aminobutyric acid ($GABA_B$) receptor antibodies	Negative	Negative
GAD65 antibody assay	0.00	≤0.02
Glial fibrillary acidic protein (GFAP) IFA	Negative	Negative
IgLON5 IFA	Negative	Negative
LGI1-IgG CBA	Negative	Negative
mGluR1 antibody IFA	Negative	Negative
VGKC antibodies	0.0	0.0 – 1.1
Neuronal intermediate filament (NIF) IFA	Negative	Negative
NMDA receptor antibody CBA	Negative	Negative
Purkinje cell cytoplasmic antibody type 1 (PCA-1)	Negative	<1:2
Purkinje cell cytoplasmic antibody type 2 (PCA-2)	Negative	<1:2
Purkinje cell cytoplasmic antibody, type Tr (PCA-TR)	Negative	<1:2

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CBA, cell-based assay; ANNA, antineuronal nuclear antibody; IgG, immunoglobulin G; DPPX, dipeptidyl-peptidase–like protein-6; IFA, immunofluorescence assay; GAD65, glutamic acid decarboxylase 65-kilodalton isoform; IgLON5, immunoglobulin-like cell adhesion molecule 5; LGI1, leucine-rich, glioma-inactivated 1 protein; mGluR1, metabotropic glutamate receptor 1; VGKC, voltage-gated potassium channel; NMDA, N-methyl-D-aspartate.

Figure. Patient's Clock and Cube Drawings



A. Initial drawing prior to plasma exchange.
B. Improved drawing after 3 rounds of plasma exchange.

Monoclonal antibodies like teprotumumab have been shown to advance treatment in several diseases; however, neurologic disorders associated with their use have been documented.[7-9] Literature shows that attenuation of IGF-1 signaling, as seen in teprotumumab use, has been related to increased risk of neurocognitive decline and psychological disorders.[7-9] In particular, teprotumumab has been shown to cause sensorineural hearing loss due to the effect IGF-1 plays in inner ear function,[10] as well as optic neuritis and Hashimoto's encephalopathy (HE).[7]

Encephalopathy related to teprotumumab therapy was first reported by Hoang et al,[7] and we approached the case under a similar hypothesis that the encephalopathy was induced by an autoimmune process related to teprotumumab. Clinical presentation and management in our case was slightly different when compared to the case reported by Hoang et al. The two patients were clinically similar in that they both exhibited behavioral changes, language deficits, inability to perform tasks requiring executive function, elevated protein in the cerebrospinal fluid, and an otherwise unremarkable workup. However, the clinical symptoms started after the fourth infusion of teprotumumab and lasted 6 weeks in the previously reported case compared to our case, where symptoms started after the third infusion and lasted 1 week before the patient sought treatment.

Our cases differ in how quickly plasmapheresis was started after the onset of symptoms. The patient in the Hoang et al case was treated with IV glucocorticoids and IVIG given their initial differential diagnosis, which included hepatic encephalopathy (HE), and literature supporting clinical improvement with these interventions.[11] However, the patient experienced progression of his neuropsychological symptoms to catatonia, mutism, and persistent memory deficits with this treatment. HE was later ruled out given that the patient had normal baseline serum thyroperoxidase antibodies (TPO) and thyroglobulin antibodies (TgAb), normal MRI/magnetic resonance angiography findings, and lack of clinical improvement with glucocorticoids and IVIG. They used plasma exchange based on the hypothesis that teprotumumab antibodies were responsible for his encephalopathy, and the patient started demonstrating clinical improvement after starting treatment. Based on the similarities between the cases and the previous patient's lack of response to IVIG and systemic steroids, our patient was treated with plasma exchange as a first line and was able to get her first round of plasma exchange within 2 weeks of her teprotumumab infusion.

Plasma exchange is the process in which a patient's blood is filtered through an apheresis machine that reinfuses red blood cells back into the patient with replacement fluid, such as plasma or albumin.[12] Given our hypothesis that the encephalopathy was an autoimmune response, plasmapheresis was deemed an appropriate intervention to remove teprotumumab antibodies from the patient in order to improve her neurological symptoms. Our transfusion medicine consulting team decided to start with 5 plasma exchanges based on the Hoang et al case report with a plan to perform more if clinical improvement was not achieved. An interesting aspect of the case was that the patient had resolution of symptoms to near baseline around 24 hours after the first plasma exchange, with symptoms returning the morning of her second plasma exchange. Although the exact physiology is unknown, perhaps residual antibodies remained in her system and required multiple plasma exchanges to be fully cleared out.

HE, a rare autoimmune vasculitis manifesting as acute or subacute encephalopathy with myoclonus and seizures, was an alternative diagnosis considered for our patient.[13] The literature shows that HE has been associated with teprotumumab, but only as a provisional diagnosis after a patient demonstrated episodic confusion with no other neurologic symptoms.[6] A limitation in our study is that we did not check antithyroid antibodies, which typically are elevated in this condition. However, we did not have a strong suspicion for HE given the absence of MRI abnormalities and seizures. In addition, an otherwise negative workup for other etiologies of encephalopathy, along with rapid improvement with plasma exchange in our previously neurologically normal patient, supports the diagnosis of teprotumumab-induced encephalopathy.

CONCLUSIONS

This case report elucidates a potentially detrimental side effect of teprotumumab and the importance of timely recognition and treatment. We provide a treatment framework with favorable results for patients who may experience encephalopathy after teprotumumab use. Proper counseling of this potential side effect is warranted for patients beginning this therapy, as it can help lead to earlier detection and treatment. This case is in the process of being reported to the FDA through MedWatch. Postmarketing surveillance efforts such as this are important to raise awareness of adverse effects that may not have been discovered during clinical trials.

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