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Occult Growing Teratoma as the Cause of Protracted Symptoms in a Patient with Anti-NMDA-Receptor Encephalitis and Prior Ovarian Teratoma Removal: Implications for Continued Monitoring and Treatment

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Dear Editor,

Anti-NMDA-receptor encephalitis (NMDARE) is largely a monophasic, infrequently relapsing autoimmune condition, with most patients improving after the initial episode and returning to their premorbid functional status if timely and appropriate treatment is administered.[1] In a small proportion of cases, the initial episode may be followed by relapses and cumulative deterioration that persist despite continued immunosuppressive and immunomodulatory treatment.[1] Such a malignant course occurs less frequently in patients with ovarian teratomas that have been successfully and promptly resected.[2] We report a case of NMDARE in which persistent symptoms refractory to continued treatment completely disappeared after the discovery and removal of a second teratoma. Our case highlights the importance of continued monitoring for teratomas and other neoplasms in patients with persistent symptoms of NMDARE.

An 18-year-old female presented with headache, altered mental state, and seizures to the emergency room, where pleocytosis was detected in the cerebrospinal fluid (CSF). A course of acyclovir was administered, but there was no clinical response and the patient quickly succumbed to a comatose mental state that was accompanied by excessive salivation, oromandibular and whole-body dyskinesia, and hypoventilation. Electroencephalography revealed an extreme delta-brush pattern. A suspected diagnosis of NMDARE was confirmed with CSF and serum antibody testing. A right ovarian teratoma found on CT was removed, and the absence of remaining teratoma tissue was confirmed in a follow-up abdominopelvic CT. She promptly received intravenous immunoglobulins (IVIg), intravenous steroids, rituximab, tocilizumab, and low-dose interleukin-2, electroconvulsive therapy, and up to five antiseizure medications (ASMs) during her first hospitalization, which lasted for a little over 1 year (Fig. 1).

She regained alertness during the course of her treatment, but her fluency remained limited to single words when she was discharged. She continued to receive ASMs during 2 years of outpatient follow-up, as well as further immunotherapy consisting of bortezomib and IVIg boosts due to persistent breakthrough seizures and cognitive symptoms. Although she was able to speak in sentences of a few words, she continued to complain of short-term memory impairment and emotional lability.

She reported menstrual irregularity at 4 years after the start of her illness and so was referred to the gynecology department. MRI of her pelvis revealed a sizable teratoma causing left ovarian torsion, which was resected. Remarkably, in the neurology outpatient clinic 2 weeks after her surgery, she reported the complete resolution of all of the cognitive and mood symp-

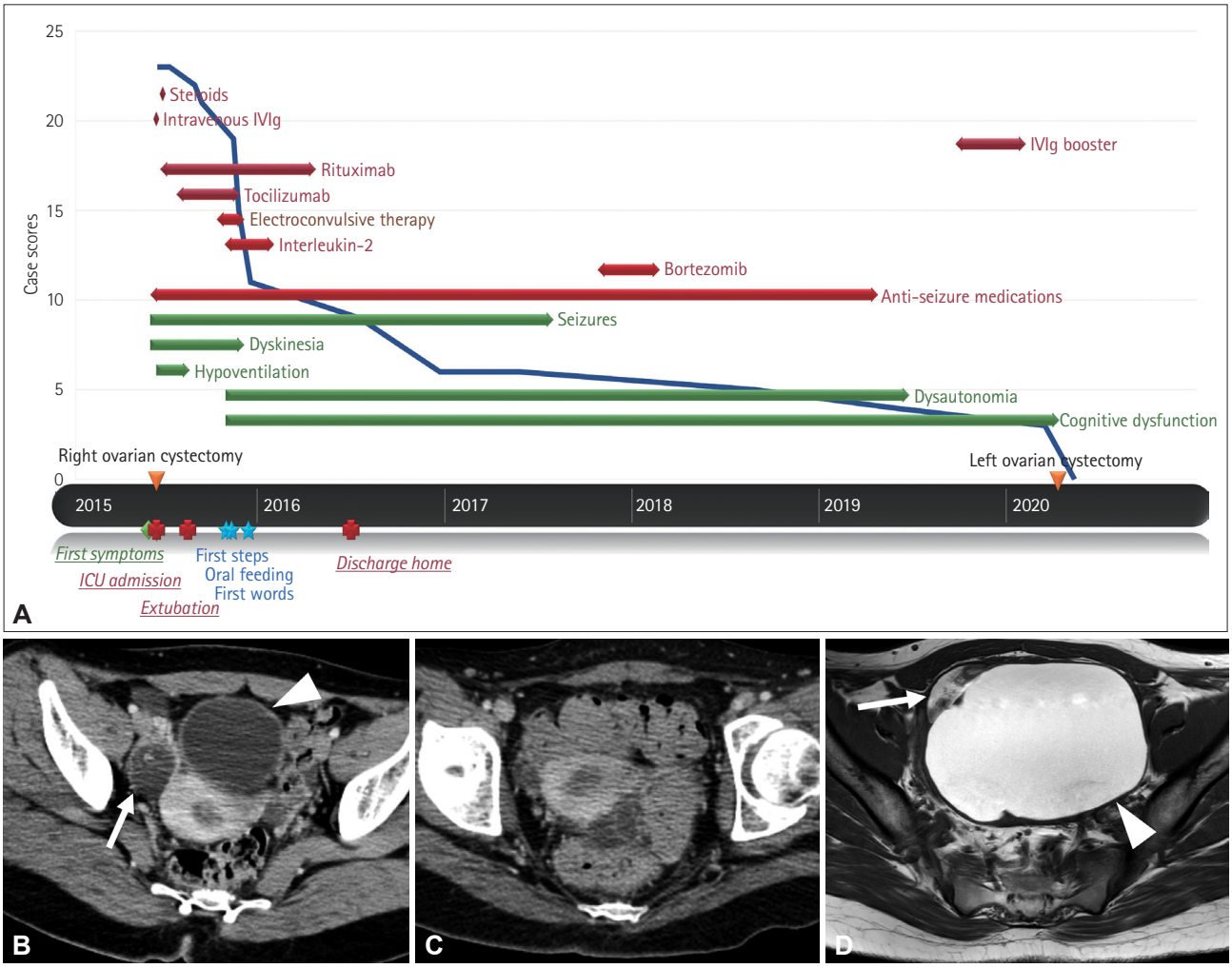

Fig. 1. Clinical course and radiologic findings of ovarian teratoma. A: Timeline of the clinical course of the patient showing her symptoms and the treatments received. The patient was assessed using a clinical assessment scale for autoimmune encephalitis consisting of nine items (seizure, memory dysfunction, psychiatric symptoms, consciousness, language problems, dyskinesia/dystonia, gait instability and ataxia, brainstem dysfunction, and weakness). The highest possible score was 27, with 27 indicating the greatest severity. B: Initial contrast-enhanced CT image of the pelvis revealing an ovarian teratoma (arrow) and cyst (arrowhead). C: Contrast-enhanced CT scan of the pelvis after the first ovarian cystectomy. No remnant cystic lesion is discernible in either adnexa. D: T1-weighted MRI of the pelvis obtained at a 4-year outpatient follow-up. A fat-containing mass (arrow) is evident, as well as a huge ovarian cyst (arrowhead). ICU: intensive care unit, IVIg: intravenous immunoglobulins.

toms that had persisted prior to the surgery. She discontinued all medications and did not experience any further symptoms.

The exact steps via which ovarian teratomas contribute to the pathogenesis of NMDARE are not yet clear, but pathologic and functional studies have provided a few hints. One study found histologic markers of atypical glioneuronal cells—resembling cells from gangliogliomas or ganglioneuroblastomas—in teratoma tissue from NMDARE patients but not from controls,[3] which suggests that specific neural antigens present in ovarian teratomas initiate a pathogenic immune response. Although the presence of such atypical glioneuronal cells was not confirmed in the second teratoma of the present patient, her clinical course indicates that it probably contributed to the continuation of symptoms despite receiving treatment. One hypothesis is that in a patient who is already sensitized for a culprit atypical neuronal antigen, the peripheral presence of similar antigens is sufficient to elicit continued symptoms.

An occult teratoma was previously shown to be associated with relapse.[4] A second occult teratoma may be responsible for a persistent clinical course with very slow improvement despite optimal treatment, and so screening for its presence may be warranted in slow-to-improve NMDARE patients who do not experience a relapse event. Although occult teratomas may be seen in CT, contrast-enhanced pelvic MRI might be more sensitive since it is more reliable in identifying all three mesenchymal layers.[5] Discovering an occult teratoma in treatment-refractory NMDARE patients may provide an alternative therapeutic option, since its resection may lead to the rapid

resolution of all symptoms.

Author Contributions

Conceptualization: all authors. Data curation: Sang Bin Hong, Yong-Won Shin. Supervision: Kon Chu, Sang Kun Lee. Visualization: Sang Bin Hong. Writing—original draft: Sang Bin Hong. Writing—review & editing: all authors.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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