Annals of Surgical Case Reports

Case Report
Published: 10 Apr, 2023

A Benign Ovary Pathology with Utmost Consequences

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Abstract

We present the case of a 33-year-old patient without any comorbidity, who was presented at the psychiatric emergency department with her husband and her mother. Physical examination showed no meningismus. Strength, coordination and reflexes were unchanged and physiological. There was no evidence of apraxia. A cerebral MRI and a CT thoracic abdomen were organized to complete the diagnosis. The cerebral MRI showed no ischemia or cerebral hemorrhage.

Objectives: To report a rare case of NMDAR encephalitis causing by a benign ovarian teratoma.

Keywords: Teratoma; Ovary; Anti-NMDA receptor; Encephalitis

Background

Anti-N-Methyl D-aspartate Receptor (anti-NMDAR) encephalitis is a rare autoimmune disease. His incidence is around 1 to 5 per million per year [1]. It caused by the presence of anti-NMDAR antibodies in the Cerebrospinal Fluid (CSF) [2]. It can occur at any age, but it is most prevalent in young women [3,4] with a median age between 21 years [1,5], and 23 years [6], 37% are younger than 18 years [1]. Around 80% [3,5,7] of sufferers is female.

The NMDA receptors are ionotropic receptors activated by glutamate and glycine under physiological conditions and are crucial for synaptic plasticity [2,5-8]. They are located more likely post-synaptically and transmit the electrical signals that are important for learning, memory and psyche [9].

This pathology was discovered in 2007 [5,9] by Prof. J. Dalmau. He proved that IgG antibodies attack the NR1 subunits of NMDA receptors [3,5,6,9,10]. Antibody binding blocks the interaction between the NMDA receptor and the tyrosine kinase-active receptor Ephrin B2 (EphB2), so that the NMDA receptor is internalized [1,8] and degraded. EphB2 normally binds to NMDA receptor *via* the extracellular region of NR1 and is necessary for its synaptic anchoring [5,8,9]. Neurons of the hippocampus and cerebrum are particularly affected [6-9].

Anti-NMDAR encephalitis is characterized by rapidly progressive psychiatric symptoms such as memory problems, delusion, hallucination or confusion [1,3,6-8]. 70% of patients [3,5,7,10] experience prodromes [6,9] such as headache, fever or gastrointestinal discomfort. Psychiatric symptoms are observed on average less than 2 weeks later. These symptoms are usually accompanied or followed with neurological complications. Patients alternate between states of agitation and catatonia [3]. Abnormal movements and autonomic instability are common manifestations in this phase [1,3,5,8]. It may worsen to central hypoventilation requiring intubation or even coma [3,5,7,8].

Clinical improvement occurs with slow kinetics [1,7] in the reverse order of the observed onset of the syndrome [5,7]: Neurological symptoms disappear first, psychiatric manifestations last.

Known triggers of NMDAR encephalitis are ovarian teratomas [1,4-6,10,11]. causing approximately 60% of all cases [6,7]. Rare cases with associated tumors other than ovarian teratoma include testicular germ cell tumor [3,7,10], teratoma of the mediastinum [8], small cell lung cancer [7], Hodgkin's lymphoma [7,10], ovarian cystadenofibroma, and neuroblastoma [10].

Mature teratomas contain differentiated tissues of ectodermal, mesodermal and endodermal origin and therefore may also contain nervous tissue [2]. The anti-NMDA receptor antibodies that cause the paraneoplastic neurological symptoms are produced in ovarian tissue [5]. The antigens, normally found only in the CNS, cause an autoimmune response with formation of IgG antibodies. The IgG travel through the bloodstream to the CNS [4] with activated T and B cells. These will excite

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Received Date: *21 Mar 2023*
Accepted Date: *05 Apr 2023*
Published Date: *10 Apr 2023*

Citation:
Infanger C, Fadinger N, Ndarugendamwo A, Faoro D, Montani M, Mueller. A Benign Ovary Pathology with Utmost Consequences. Ann Surg Case Rep. 2023; 6(2): 1072.

intrathecal IgG-producing plasma cells [1,5,8]. The autoimmune reaction now turns to the central nervous tissue with the known consequences.

Although literature on treatment and outcome is scarce, immediate tumor removal with subsequent immunotherapy [2-5,7,10,11], is widely recommended. Patients receiving early tumor treatment have better outcomes and fewer relapses [3,6]. In cases with tumor removal within 4 months of the onset of neurologic symptoms, mild residual deficits were observed or fully recovery was accomplished in almost 90% [9].

Case Presentation

We present the case of a 33-year-old patient without any comorbidity, who was presented at the psychiatric emergency department with her husband and her mother. The week before, she noticed exhaustion, disorderly sleep, and being progressively unfocused. She currently complained about increasing confusion and listlessness since the previous day. Her relatives reported intermittent phases of disorientation, partly associated with anxious restlessness, as well as frightening visual hallucinations with marked restlessness for one week. External anamnesis revealed a change in character, slowing down, and delusions that had gradually worsened over the previous two days. She was admitted as an inpatient due to the derealization phenomenon and mnestic deficits. The next day, she was transferred to the neurology department for somatic evaluation of the subacute psychosis.

On admission to the neurology department, the patient was hemodynamically stable and in good general and nutritional condition. Clinically, she showed a pronounced delusional syndrome, executive and attention disorders. She was temporally and spatially disoriented, and psychomotor slowed. Because of these limitations, the Glasgow coma score was assessed at 14. The patient was able to converse fluently, without aphasia. Intermittent fluctuation of symptoms with even spontaneous improvement was observed. Over time, however, the patient became suddenly dangerous not only to herself but also to others, mainly because of recurrent hallucinations.

Physical examination showed no meningismus. Strength, coordination and reflexes were unchanged and physiological. There was no evidence of apraxia.

As encephalitis was suspected, a lumbar puncture was performed. The results showed an increased number of mononuclear leukocytes. The cause of the acute psychosis could be a viral infection or chronic process.

Clarifications for Lyme disease, herpes and lues were able to exclude neuroborreliosis, herpetic meningoencephalitis, and neurosyphilis. A COVID infection could be eliminated from the list of suspicions by a negative nasopharyngeal PCR test. An antibody analytic was drawn and showed positive for N-methyl-D-aspartate receptor.

A cerebral MRI and a CT thoracic abdomen were organized to complete the diagnosis. The cerebral MRI showed no ischemia or cerebral hemorrhage. The brain parenchyma was assessed as unremarkable, with no evidence of space-occupying lesions. CT scan thorax abdomen revealed a cystic inhomogeneous lesion of the right ovary with suspicious fatty components (Figure 1).

Therefore, a gynecological consultation was requested to evaluate the adnexal mass. A transvaginal ultrasound showed an unilocular

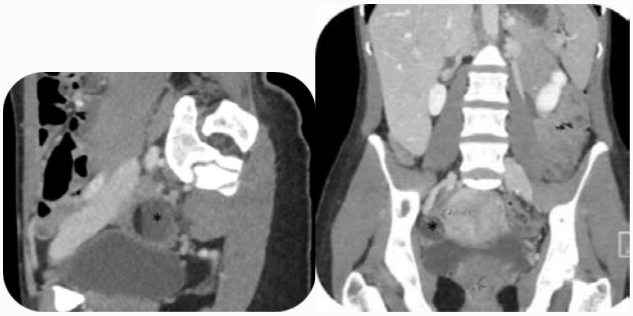

Figure 1: Teratoma (*) in CT-scan, described as a cystoid lesion of the right ovary with inhomogeneous internal structure and suspicious fatty components.

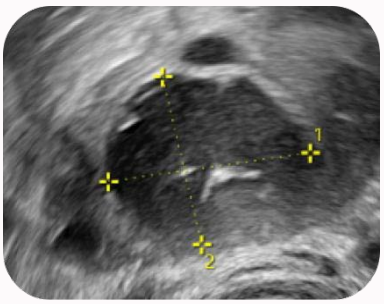

Figure 2: Teratom in transvaginal ultrasound. Voluson S8, GE, 25Hz, D1: 24.9 mm; D2: 20.7 mm.

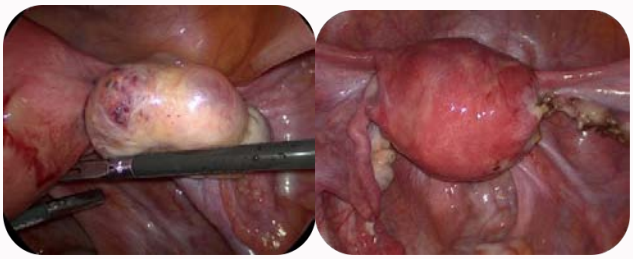

Figure 3: Pelvic situs during and after laparoscopy.

tumor with mixed echogenicity and acoustic shadows, suggestive of benign cystic teratoma (Figure 2). A performed EEG was pathological after the patient was suspected to have epileptic seizures, therefore antiepileptic therapy with lacosamide was started. Plasmapheresis was started, followed by surgical removal of the adnexal tumor the following day. The right adnexectomy was performed without any complications (Figure 3). The histological examination confirmed the suspected diagnosis and showed an adult teratoma with neural tissue (Figure 4).

After surgery the patient still suffered from visual, acoustic hallucinations and fluctuating confusion in all qualities. Psychotic episodes were treated with antipsychotics. After five cycles of plasmapheresis over a duration of nine days, the CSF was tested negative for anti-NMDAR antibodies.

Besides mnestic and executive function deficits, the patient showed no more symptoms and was released in neuropsychological rehabilitation. After gradually reducing antipsychotic medication no more psychotic episodes occurred. After four weeks of neurorehabilitation the patient was released in ambulant care with normal executive functions and minor residual mnestic deficits. Two

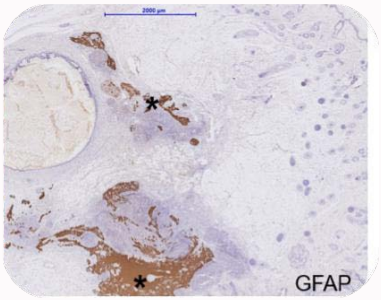

Figure 4: Teratoma showing the aggregates of lymphocytes being adjacent to neural tissue strongly expressing glial fibrillary acidic protein (GFAP) (*).

months later immunotherapy with Rituximab was started, after a routine follow-up showed recurrence of anti-NMDAR antibodies in the CSF. One year after diagnosis, the patient was still in ambulant care with psycho- and ergotherapy, prophylactic antiepileptic therapy and intermittent immunotherapy with Rituximab. She was still suffering from fatigue and lack of concentration.

Discussion

Teratoma is a common and mostly benign adnexal tumor. Sometimes it can result in serious complications like the anti-NMDAR encephalitis. In case of warning signs of autoimmune encephalitis such as sudden onset of psychosis, vegetative dysfunction, epileptic seizures, rapid deterioration, physicians should always look for teratomas, especially in young female patients. Timely diagnosis and removal are crucial to a favorable outcome. Furthermore, physicians should keep in mind that anti-NMDAR encephalitis may resurface or even manifest after teratoma removal.

Acknowledgement

We would like to thank our colleagues from the neurological department for their insights and the colleagues of the pathology department for the especially prepared GFAP-stained photos.

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