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Case report

A case report of NMDAR encephalopathy - A neurologic condition that a gynecologist can cure

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ABSTRACT

Introduction and importance: Anti-NMDA receptor encephalitis is a rare autoimmune cause of acute psychosis in young women, often associated with ovarian teratomas. Surgical removal of the teratoma is a critical component of treatment.

Case presentation: A previously healthy woman was brought to the emergency department with acute psychosis, characterized by alternating episodes of catatonia and mania, regressive speech, and inappropriate behaviors such as disrobing. Despite treatment with antipsychotic medications at a psychiatric facility, her symptoms did not improve, prompting transfer to our institution. Neurological examination was non-focal, and laboratory results were unremarkable. Cerebrospinal fluid analysis showed no signs of infection, but anti-NMDA antibodies were detected. Gynecology was consulted, and a pelvic ultrasound was initially negative. However, pelvic MRI revealed an area of macroscopic fat in the left ovary, suggesting a teratoma. The patient underwent laparoscopic left salpingo-oophorectomy. Gross examination of the ovary appeared normal, but histological analysis confirmed the presence of a benign teratoma with ganglion cells and chronic inflammation. The diagnosis of anti-NMDA receptor encephalitis was confirmed. Postoperatively, the patient's mental status improved significantly, and she was discharged home.

Clinical discussion: This case illustrates the clinical, radiologic, and histopathologic features of the disease and underscores the importance of MRI in detecting ovarian teratomas when pelvic ultrasound is inconclusive.

Conclusion: Timely gynecologic intervention can be curative in these patients.

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[1] Responsible for primary data collection, drafting the manuscript, image editing, and ensuring the accuracy and integrity of the overall content. She also co-ordinated communication among the authors during the manuscript development process.

[2] Collected clinical and demographic data for the patient, assisted in the verification of patient-related information, and contributed to ensuring accurate representation of clinical details.

[3] Conducted data collection specific to the patient's clinical course and surgical outcomes. He performed the surgical procedure and provided detailed intra-operative findings to guide manuscript preparation.

[4] Performed radiological interpretation, gathered data relevant to imaging findings, and contributed to the writing and review of the radiological sections of the manuscript to ensure precision.

[5] Provided expert pathology interpretation, including detailed analysis of histopathological findings. He contributed to data gathering and drafted sections related to pathological findings for the manuscript.

[6] Served as the Principal Investigator and overall project coordinator, supervising all aspects of the study design, data analysis, and manuscript development. He provided critical revisions and ensured the scientific rigor of the final submission.

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1. Introduction

Autoimmune Encephalitis is the inflammation of the brain due to etiologies associated with different antibodies against neuronal proteins. Anti-NMDAR encephalitis occurs when Immunoglobulin G (IgG) is formed against the glutamate receptor N-Methyl-D-Aspartate (NMDA) subunit GluN1. It can affect children and adults, with a female predominance in young adults and a weaker predominance in patients older than 45 years old. Symptoms usually present a prodromal headache and fever, followed by multistage progression of symptoms such as psychiatric manifestations, sleep disorders, memory deficits, seizures, stupor with catatonic features, dyskinesias, autonomic instability (hyperthermia, blood pressure fluctuations, tachycardia, bradycardia, etc.) and language dysfunction. [1]

Despite being a rare condition, affecting only about one in 1.5 million people annually, anti-NMDAR encephalitis is the most recognized and likely the most prevalent form of autoimmune encephalitis. According to data from the California Encephalitis Project, the incidence of anti-NMDAR encephalitis surpassed that of any single viral encephalitis. [2]

Anti NMDAR encephalitis is an example of paraneoplastic syndrome, associated with ovarian or extra-ovarian teratomas in 38 % of cases [1]. A teratoma can serve as a propagator of NMDAR-antibody-producing B cells from germinal centers, causing a constant infiltration of CD20+ B lymphocytes [1,3]. Histologically, chronic inflammation surrounding neural components of the teratoma may suggest this pathology.

Ovarian teratomas are the most common type of ovarian neoplasms, accounting for 20 % of neoplastic changes in the ovary. It is most common in young women, diagnosed most often in women between the ages of 17–35. The most common presentation is asymptomatic or minimal symptoms, it is often an incidental diagnosis. Some patients may present with abdominal pain, fever and gastrointestinal, genitourinary and gynecological disturbances such as vaginal bleeding. Histologically, ovarian teratomas are found to include unilocular lesions with a cystic cavity lined by squamous epithelium plus heterogeneous contents (hair follicles, teeth, bone, etc.). This is usually unilateral and right side dominant. The vast majority of teratomas are benign, although malignant variants, an immature teratoma or cancer arising from components of teratomas, may occur. The pathophysiology behind it is still unclear, spontaneous asexual development of an unfertilized ovum after the first meiotic division or alteration of blastodermal elements in a fertilized ovum, may be the cause. On gross examination, the cystic teratoma does not have a defined shape or size as it depends on the heterogeneity of its contents. The microscopic evaluation should confirm the presence of endodermal, mesodermal and ectodermal tissue. [4]

The association of Anti-NMDAR encephalitis with ovarian teratoma is dependent on age. >45 % of patients with Anti-NMDAR encephalitis who are older than 18 years will have an ovarian teratoma. However, Anti-NMDAR encephalitis cases occurring in girls <14 years old are less likely to be associated with an ovarian teratoma [5].

2. Case presentation

A 34-year-old previously high functioning woman was taken to the local emergency department for evaluation of acute psychosis that started abruptly characterized by agitation and mania. She had no previous medical or surgical history. She exhibited regressive speech and inappropriate behavior including disrobing completely. She was admitted to a psychiatric hospital where antipsychotic therapy did not improve her symptoms. She was then transferred to our institution for further evaluations. Neurologic exam was non-focal and laboratories were unremarkable. In the next 48 h, she required spoon feeding and help with activities of daily living. She was not ambulatory. She alternated between being catatonic and not easily arousable, to overt excitement, manifested by inappropriate behavior as described previously with complete disrobing. Further investigation included a Brain MRI, and electroencephalogram (EEG) and a cerebrospinal fluid (CSF) analysis. Cerebrospinal fluid studies showed no evidence of an infectious etiology. An anti-NMDAR antibody test was positive.

At this point concerns were raised for Anti-NMDAR Encephalitis, confirmed by a positive anti-NMDAR antibody test at 1:8 dilution (normal <1:2 dilution). It was initially treated with IVIG and pulse steroids for five days. A pelvic transabdominal ultrasound at this time was negative for a teratoma, showing normal ovaries and no free fluid. When the empiric treatment finished, the patient still did not show signs of recovery or improvement. The Gynecology Department was then consulted to rule out the possibility of a paraneoplastic syndrome related to possible mature teratoma. Laboratory tests were repeated by our department showing: LDH 268 units/L, Quantitative hCG <1 mlU/mL, CA 125 < 5 U/mL. A pelvic MRI with and without contrast was then done for further evaluation of the ovary. A tiny area of macroscopic fat within the left ovary measuring 0.6 × 0.4 cm was found, suggesting a possible mature teratoma [6] (Figs. 1, 2 and 3).

After consulting with the patient's family, and shared decision making, the patient underwent a diagnostic laparoscopy with left salpingo-oophorectomy. The left ovary and all surfaces were grossly normal on gross examination. Histologic examination of the left ovary confirmed the presence of a benign teratoma (measuring about 12.5 mm greatest dimension) including fat, skin, gastrointestinal type epithelium, and collections of ganglion cells with associated interstitial and perivascular chronic inflammation (Fig. 4 and Fig. 5). The diagnosis of anti-NMDAR antibody encephalitis was confirmed. Postoperatively, she had marked improvement in her mental status and was discharged home on postoperative day 18. Five months after the diagnosis, the patient states that she is showing no physical impairment, and states that she is almost back to her baseline function but still has some short term memory deficits.

3. Discussion

Anti-NMDAR encephalitis is a common cause of autoimmune encephalitis especially in young women. It is associated with ovarian teratoma in 38 % of cases; however, it is also associated with other conditions, e.g. gonadal stromal tumors of the ovaries, extra-ovarian

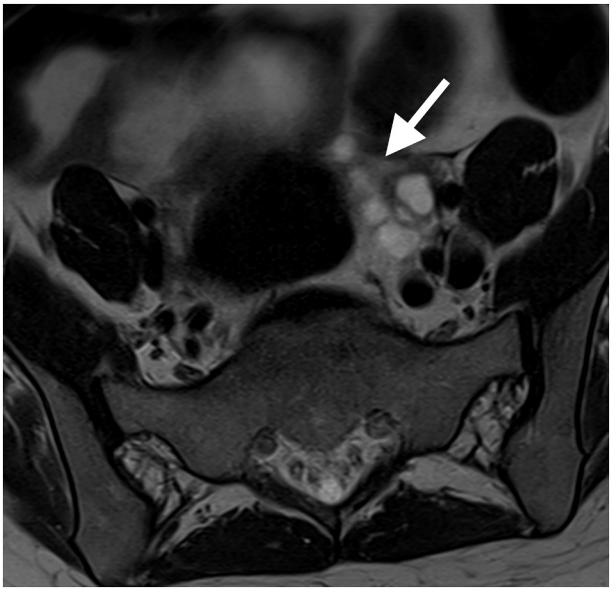

Fig. 1. Subcentimeter fat-containing ovarian teratoma on axial MRI: T2 weighted image demonstrates moderately hyperintense lesion (arrow) within the anterior left ovary and multiple adjacent T2 hyperintense fluid-containing follicles.

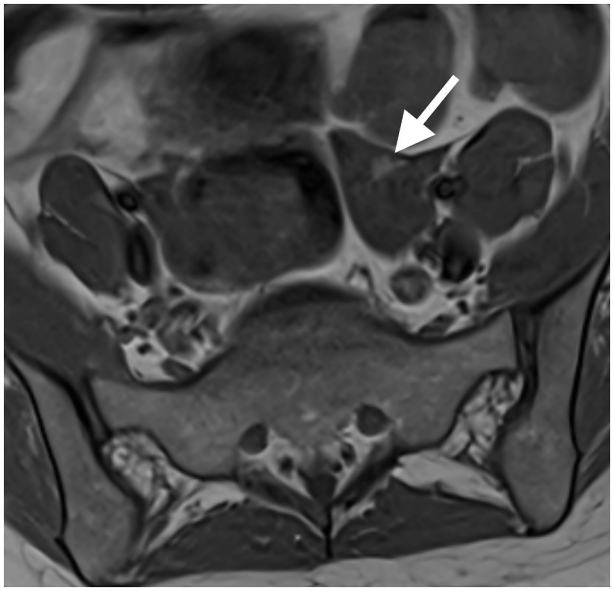

Fig. 2. Subcentimeter fat-containing ovarian teratoma on axial MRI: T1 weighted image shows hyperintense lesion (arrow) which is conspicuous relative to T1 hypointense follicles and ovarian stroma. Fat or a small hemorrhage containing cyst could have this appearance on T1 weighted imaging.

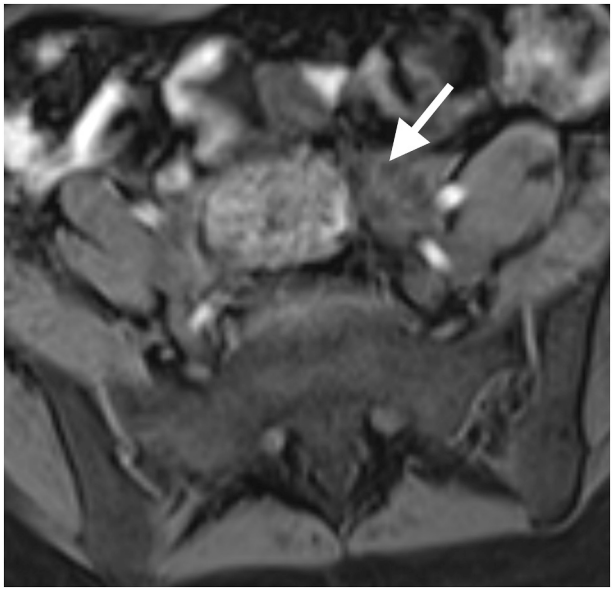

Fig. 3. Subcentimeter fat-containing ovarian teratoma on axial MRI: Fat-suppressed T1 weighted image shows lesion is now hypointense (arrow), confirming the presence of macroscopic fat.

teratoma, small cell lung cancer, or as a sequelae of herpetic encephalitis. Although it is well documented in the medical literature, it is not widely recognized among gynecologists, who are well-positioned to treat this condition effectively with surgery. This case illustrates well the importance of a multidisciplinary approach to the diagnosis and treatment of this condition with active management by both neurologists and gynecologic surgeons.

This case also presents with an excellent histologic correlation to the clinical condition, as there are collections of brain glial cells with adjacent lymphocytic infiltration. However, not all cases of teratoma with brain tissue develop surrounding inflammation. Even when inflammation does occur in the glial portion of the teratoma, the patient may not exhibit any neurologic deficits; the cause and effect of Anti-NDMAR encephalitis is still not known.

The preoperative diagnosis of ovarian teratoma is made with radiologic imaging. The imaging appearance of ovarian teratomas is based on its variable composition of soft tissue, fat, calcification (teeth or bone), and hair. Ultrasound, given its widespread availability and lack of radiation, is an excellent first line modality to screen for adnexal mass and has high specificity for teratoma [7]. However, CT and MRI are more sensitive than ultrasound. In particular, CT is more sensitive for the detection of fat and small calcifications, and MR for the detection of fat [8]. Nearly all mature ovarian teratomas contain macroscopic fat, so imaging identification of this component is key to diagnosis. However, compared to teratomas broadly, teratomas associated with anti-Anti-NMDAR encephalitis contain a smaller volume of intralesional fat [9]. The excellent soft tissue resolution of MRI can detect even small quantities of macroscopic fat which will be hyperintense on T1-weighted imaging, moderately intense on T2-weighted imaging, and hypointense upon the application of fat-suppression sequences [10]. As in this case, prompt re-investigation of the pelvis with MRI may be diagnostic when initial pelvic ultrasound and CT survey of the chest, abdomen, and pelvis do not identify a primary tumor.

In addition to surgery, Anti NMDAR encephalopathy is treated initially with immunomodulatory therapy such as immunoglobulins, corticosteroids, and plasmapheresis. Second-line therapy includes chemotherapeutic agents, e.g. cyclophosphamide or methotrexate, or targeted therapy as rituximab (monoclonal antibodies against CD20) or alemtuzumab (monoclonal antibodies against CD52) may be used. Prompt treatment is a key to success as delay in therapy is associated with poor outcomes. In a large series of 382 patients, a scoring system was used to predict poor functional outcome at 1 year. Treatment delay, admission to ICU, poor response to treatment at 4 weeks, abnormal MRI, CSF white blood cell count >20 WBC/μL were each given a point. A score of 0–1 predicts a low likelihood of poor 1 year functional status (3 % risk); however, a score of 4–5 predicts a 69 % probability of poor functional outcome. [11]

4. Conclusion

This case demonstrates the importance of prompt evaluation and diagnosis of Anti-NMDAR encephalitis as early treatment is a key to achieve a good outcome. In female patients, a search for an ovarian teratoma is a requisite part of the investigation, and a dedicated MR of the pelvis is critical to make the diagnosis, especially when an ultrasound is non-diagnostic. If an ovarian teratoma is suspected, gynecologic consultation is mandatory so that potentially curative surgery is done.

5. Methods

This work has been reported in line with the SCARE criteria [12].

Author disclosure statement

The authors declare that they have no conflict of interest. IRB approval was exempt.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

THIS STUDY IS EXEMPT FROM REVIEW AS A CASE REPORT BY

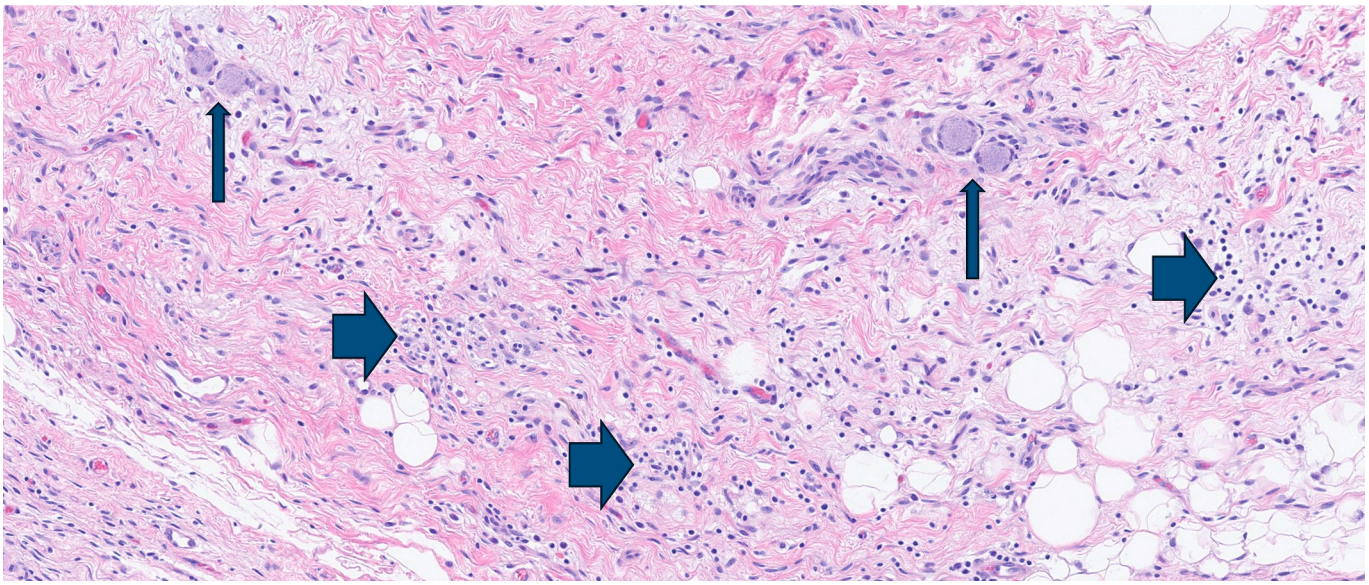

Fig. 4. The teratoma featured collections of ganglion cells (of the type seen in peripheral nervous system, with surrounding satellite cells) set in fibroadipose tissue with associated chronic inflammation. Right-pointing arrows indicate collections of lymphocytes. Upward arrows indicate ganglion cells.

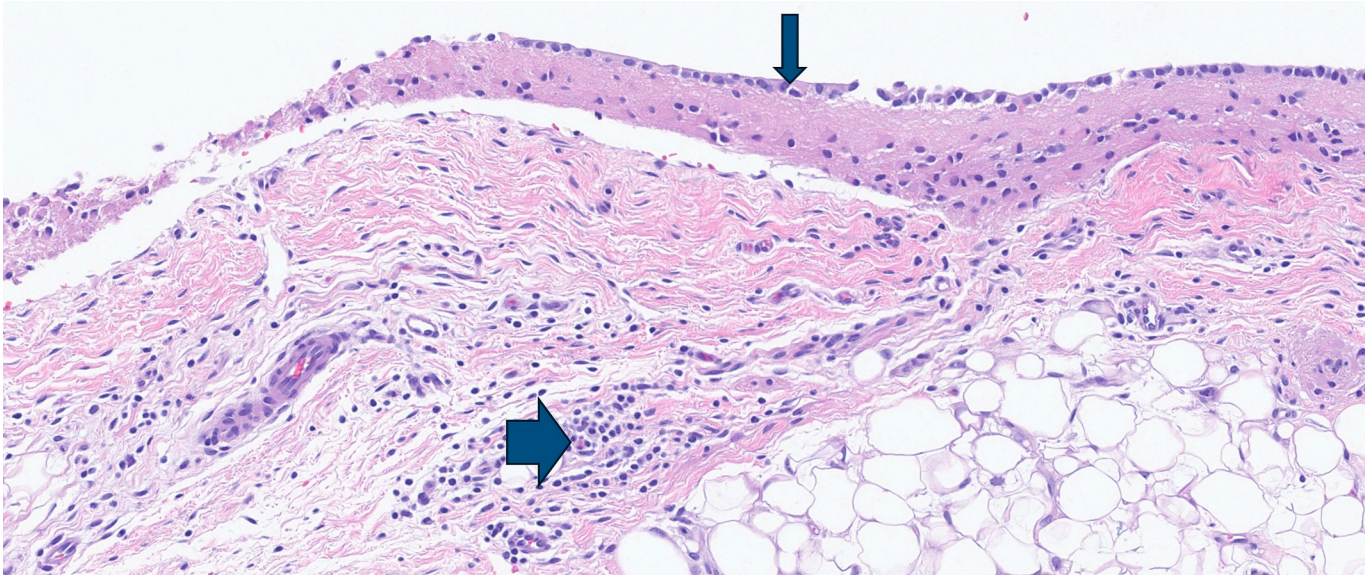

Fig. 5. A strip of mature brain tissue with an overlying ependyma (downward arrow) was free of inflammation, but nearby fibroadipose tissue was populated by lymphocytes (larger arrow).

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IRB internal policy "At Mayo Clinic single participant case studies, or a case series with multiple participants that are prepared and disseminated for educational purposes, are not systematic investigations and, therefore, are not considered research."

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Author contribution

1. Maria Paula Molina, MD: Affiliated with Mayo Clinic Florida, Department of Gynecology. Responsible for primary data collection, drafting the manuscript, image editing, and ensuring the accuracy and integrity of the overall content. She also coordinated communication among the authors during the manuscript development process.

2. Erin Drake, PA-C, MS: Affiliated with Mayo Clinic Florida, Department of Gynecology Collected clinical and demographic data for the patient, assisted in the verification of patient-related information, and contributed to ensuring accurate representation of clinical details.

3. Sherif El-Nashar, MB BCh, MS: Affiliated with Mayo Clinic Florida, Department of Gynecology Conducted data collection specific to the patient's clinical course and surgical outcomes. He performed the surgical procedure and provided detailed intraoperative findings to guide manuscript preparation.

4. Madhura A. Desai, MD, PhD: Affiliated with Mayo Clinic Florida, Department of Radiology. Performed radiological interpretation, gathered data relevant to imaging findings, and contributed to the writing and review of the radiological sections of the manuscript to ensure precision.

5. Mark A. Edgar, MD: Affiliated with Mayo Clinic Florida,

Department of Laboratory Medicine and Pathology. Provided expert pathology interpretation, including detailed analysis of histopathological findings. He contributed to data gathering and drafted sections related to pathological findings for the manuscript.

6. Tri A. Dinh, MD: Affiliated with Mayo Clinic Florida, Department of Gynecology Served as the Principal Investigator and overall project coordinator, supervising all aspects of the study design, data analysis, and manuscript development. He provided critical revisions and ensured the scientific rigor of the final submission.

Guarantor

Dr. Tri Dinh.

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3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://clinicaltrials.gov/expert-search?term=NCT06915103

Conflict of interest statement

The authors do not have any conflict of interest.

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