Autoimmune encephalitis linked with ovarian mature teratoma at a young woman – case report

Encefalită autoimună asociată unui teratom ovarian matur la o pacientă tânără. Prezentare de caz

Andreea Boiangiu[1], Cristina Vladu[1], Nicoleta Clim[1], Simona Vlădăreanu[1,2], Alexandru Filipescu[1,2]

1. Department of Obstetrics and Gynecology , University Emergency Hospital "Elias", Bucharest, Romania
2. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

All authors have equal contribution.

Abstract

Anti-NMDA receptor (NMDAR) encephalitis is an autoimmune antibody-mediated neuropsychiatric disorder known to be associated with ovarian teratoma and predominantly affecting young women. We report the case of a young woman who developed acute psychiatric symptoms, seizures, memory deficits, decreased level of consciousness, and central hypoventilation associated with ovarian teratoma (OT) and cerebrospinal fluid (CSF) inflammatory abnormalities. The ovarectomy led to a remarkable improvement. Anti-NMDA receptor antibodies were detectable in the serum and in the CSF. In cases of encephalitis associated with an ovarian teratoma, histology often shows an intense WBC infiltrate in areas of the teratoma with neural tissue. Ovarian tumour search and diagnosis are extremely important in patients presenting with neuropsychiatric disorder and a explorative laparoscopy/laparotomy and ovarectomy are justified. Prompt diagnosis and removal of the tumor are important for improving prognosis and preventing long-term neurologic sequelae.
Keywords: *encephalitis, anti-NMDA receptor, ovarian teratoma*

Rezumat

Encefalita anti-receptor NMDA reprezintă o patologie neuropsihiatrică autoimună mediată prin anticorpi ce se poate asocia cu teratoamele ovariene la o pacientă tânără. Raportăm cazul unei tinere paciente care a dezvoltat simptomatologie acută psihiatrică, deficit al memoriei de scurtă durată, convulsii, nivel al conștienței scăzut și hipoventilație centrală asociate cu prezența unui teratom ovarian (TO) și pattern inflamator al lichidului cefalorahidian (LCR). Ovarectomia a condus la o remarcabilă îmbunătățire a stării generale. Anticorpi anti-receptor NMDA au fost detectați în ser și în LCR. În cazurile de encefalită asociată cu un teratom ovarian, examenul histopatologic arată de multe ori doar un infiltrat intens inflamator în zonele cu țesut neural al teratomului. Căutarea unei tumori ovariene și diagnosticul cât mai prompt sunt extrem de importante la pacientele care prezintă tulburări neuropsihiatrice, iar o laparoscopie/ laparotomie exploratorie însoțită de ovarectomie sunt justificate. Diagnosticul prompt și indepărtarea tumorii sunt etape importante pentru îmbunătățirea prognosticului și prevenirea sechelelor neurologice pe termen lung.
Cuvinte-cheie: *encefalită, receptor anti-NMDA, teratom ovarian*

Case report

A 18-year-old G0 P0 without a significant medical past history presents for a short-term memory loss, anxiety, confusion, hallucinations started for about 1 week ago. She was first addressed to the psychiatry compartment. At the moment of psychiatric examination she complained about a severe frontal headache. The patient's symptoms progressed rapidly to delirium followed by a generalized tonic-clonic seizure. She was tachycardic at 120 bpm and hypertensive. She was minimally responsive, and had diffuse hyperreflexia. Routine laboratory tests were unremarkable. An electroencephalogram revealed findings consistent with seizure activity. She was tested for infectious diseases: HIV, HSV, cytomegalovirus, parvovirus and hepatitis, as well as autoimmune diseases - all were negative. The brain IRM revealed bilateral medial temporal lobe hyperintensity (Figure 1).

A lumbar punction was performed and showed inflammatory features, specifically a white blood cell count of 27 thousand/μL (95% lymphocytes) and pleyocitosis. The patient's symptoms progressed rapidly - her seizures became intractable and resulted in bradycardia, apnea and hypotension. She was sedated and orotraheal intubated. Serum and CSF tests for NMDAR antibodies were positive. An abdominopelvin ultrasound scan was performed and revealed a 7/6.5/6 cm right ovarian complex tumor with cystic and solid component. Se-

rum tumor markers were within normal limits CEA= 1.5 ng/ml, CA 125= 20 U/ml, CA 19-9 = 25 U/ml, AFT =3 ng/ml. An emergency exploratory laparoscopy was performed, revealing a 7-6 cm complex appearing right ovarian tumor. The left tube and ovary and the uterus appeared normal. A right salpingo-oophorectomy was performed (Figure 2).

The patient received broad-spectrum antibiotics and anti-epileptics, and was intubated and sedated for the next 24 hours. Histology showed: ovarian parenchyma and cystic structures with complex microscopic walls appearance including tridermic elements: brain tissue, muscle, adipose tissue, epithelial elements with an abundance of keratin, epidermal glands, respiratory epithelium, without immature or atypical cellular elements advocating for an ovarian dermoid cyst (Figure 3).

Post-operatively, the patient experienced rapid reversal of her neurologic impairment. She received six plasmapheresis treatments, with significant improvement in her mental status and physical limitations. The patient was discharged on post-operative day 15, hemodynamic stabile, without stiffness, motor deficits or coordination disorders, without sensitivity problems, but with short term memory impaired and visual-spatial integration impairment. Her psychometric tests showed mild cognitive impairment MoCA= 22/30 pts., MMSE=30/30 pts.

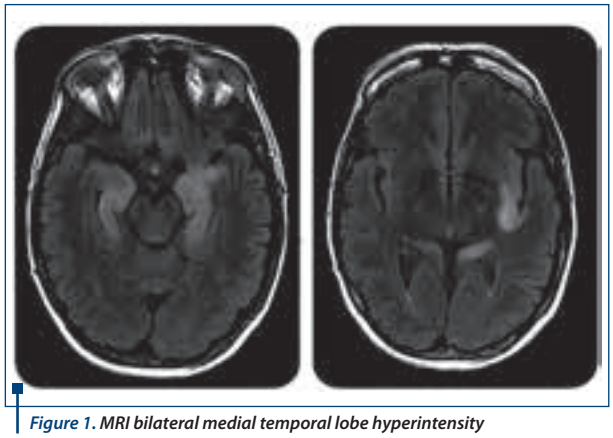

Figure 1. MRI bilateral medial temporal lobe hyperintensity

Figure 2. Right ovarian dermoid cyst

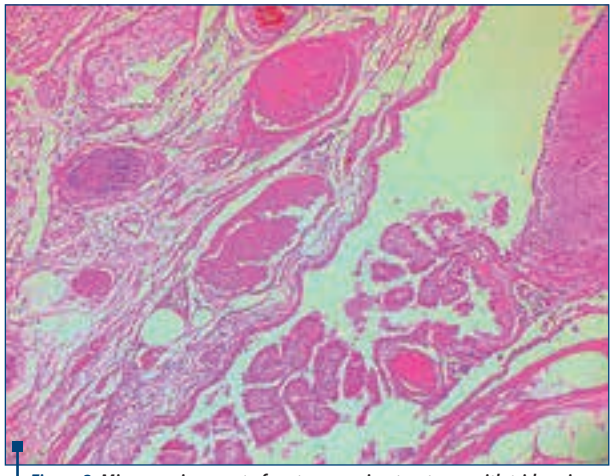

Figure 3. Microscopic aspect of mature ovarian teratoma with tridermic elements: adiopse tissue, muscular tissue, keratin, epidermal glands, staining HE ×40

Discussion

Disturbances of memory, behavior, cognition, and seizures can result from immune-mediated encephalitis. One cause of autoimmune encephalitis is the paraneoplastic manifestation of a neoplasm[1]. Until now, most paraneoplastic encephalitis have been associated with antibodies to intracellular onconeuronal proteins and cytotoxic T cells presumably against the same proteins[2]. These disorders usually associate with malignant tumors and are poorly responsive to immunotherapies or cancer treatment[3].

Despite the severity of the symptoms, paraneoplastic anti-NMDAR encephalitis has a better prognosis than most other paraneoplastic encephalitides[3,4]. Resection of the tumor appeared important to obtain final recovery or sustain the improvement that in some cases started soon after immunotherapy (corticosteroids, IVIg, or plasma exchange)[4].

In the California Encephalitis Project[5], of the 761 cases of encephalitis evaluated, the most common identifiable cause of the condition in women aged 30 years and younger was anti-NMDAR encephalitis. Enterovirus was a close second as a cause of encephalitis. Well known causes of the condition, such as Herpes simplex 1, Varicella zoster, and West Nile virus were far less common[6].

In many cases of encephalitis due to an ovarian teratoma, diagnosis is made by history, as well as physical examination consistent with: limbic encephalitis, imaging studies that show encephalitis, negative test results for viral, bacterial, and toxicologic causes of encephalitis, evidence of WBCs in the CSF, the presence of anti–NMDAR antibodies and an ovarian teratoma.

At presentation, this autoimmune encephalitis can be confounded with a psychiatric disorder and patients can often be submitted to psychiatric centers. Most patients appear confused, restless, agitated, with frequent paranoid or delusional thoughts sometimes alternating with quiet staring and dystonic or catatonic postures. In addition, most patients develop seizures and a subsequent decrease of level of consciousness, requiring antiepileptic medication, sedation, frequent mechanical ventilation, nutritional support, and management of episodes of autonomic instability and dyskinesias[7].

A constant abnormality is the presence of CSF pleocytosis or increased protein concentration that suggests an inflammatory or immune-mediated neurological process. Otherwise, extensive evaluations to identify the cause of the encephalitis are normal or unrevealing, and the associated tumors (usually appearing as "benign" ovarian cysts) are frequently considered unrelated to the disorder[7].

Encephalitis due to ovarian teratoma is treated by urgent removal of the teratoma. This is in combination with immune-modulating therapy, which may include intravenous immunoglobulin (IVIG), high-dose glucocorticoids, plasmapheresis, or rituximab (a monoclonal antibody targeted to the CD20 antigen on B lymphocytes)[8,9].

Although there is little evidence to support this clinical point, most neurologists passionately believe that once the diagnosis of ovarian teratoma-induced encephalitis is made, the teratoma should be urgently removed to help reduce the risk of permanent neurologic injury[9].

In patients with anti-NMDAR encephalitis and ovarian teratoma, surgical resection of the tumor and subsequent immunotherapy are the treatment modalities with the most significant effect on outcome[10]. Therefore, it would seem that early surgery in these patients would be of utmost importance in preventing worsening of neurologic status.

In patients with anti-MDAR encephalitis the presence of a tumor (usually ovarian teratoma) is dependent on age, sex and ethnicity, being more frequent above 18 years of age[11]. The frequency of ovarian teratomas was 56% in women >18 years old, but only 31% in women <18 years old[12].

Some patients with encephalitis have a teratoma but no detectable anti-NMDAR antibodies. In these patients, teratoma removal may be associated with improvement in the encephalitis; however, the cause of the condition may be another type of anti-neuronal antibody that has yet to be identified[13]. Women with encephalitis and an ovarian teratoma, and no evidence of infectious or toxicologic causes for the encephalitis, should be considered for teratoma removal[13].

In conclusion, anti-NMDAR encephalitis is a potentially lethal but treatable condition sometimes associated with ovarian teratomas - both mature and immature. The exact incidence of anti-NMDAR encephalitis is still unknown but it seems to be the most frequent paraneoplastic encephalitis[11].

Conclusion

Paraneoplastic encephalomyelitis (PEM) is a multifocal inflammatory disorder of the central nervous system (CNS) associated with remote neoplasia. Neurologic dysfunction probably results from an autoimmune reaction directed against onconeural antigens in the human nervous system.

Anti-NMDA receptor encephalitis is a paraneoplastic syndrome characterized by neuropsychiatric symptoms, involuntary movements, autonomic instability, and seizures.

It is more common in young females and associated with a mature ovarian teratoma[14].

Female patients presenting with new onset of psychiatric and neurologic symptoms should be thoroughly evaluated to rule out underlying neoplasm. In the event of a diagnosis of an adnexal mass, surgical resection should be performed as soon as possible in an effort to improve neurologic outcomes[15].

Pathologists encountering ovarian teratomas with reactive lymphoid elements should consider the possibility of anti-NMDAR encephalitis, particularly because the neurological symptoms may develop after tumor resection[16]. ■

References

1. Gultekin SH, Rosenfeld MR, Voltz R, et al. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain. 2000;123:1481–1494. [PubMed]
2. Darnell RB, Posner JB. A new cause of limbic encephalopathy. Brain. 2005;128:1745–1746. [PubMed]
3. Graus F, Keime-Guibert F, Rene R, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain. 2001;124:1138–1148. [PubMed]
4. Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. Brain. 2004;127:1831–1844. [PubMed]
5. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California encephalitis project. Clin Infect Dis. 2012;54(7):899–904.
6. Mangler M, Trebesch de Perez I, Teegen B, et al. Seroprevalence of anti-N-methyl-D-aspartate receptor antibodies in women with ovarian teratoma. J Neurol. 2013;260(11):2831–2835.
7. Josep Dalmau, MD, Erdem Tüzün, Haiyan Wu, Jaime Masjuan, Jeffrey E. Rossi, BA, Alfredo Voloschin, Joachim M. Baehring, Haruo Shimazaki, Reiji Koide, Dale King, Warren Mason, Lauren H. Sansing, Marc A. Dichter, MD, Myrna R. Rosenfeld, and David R. Lynch, Paraneoplastic Anti–N-methyl-D-aspartate Receptor Encephalitis Associated with Ovarian Teratoma, Ann Neurol. Jan 2007; 61(1): 25–36 [PubMed].
8. Pham HP, Daniel-Johnson JA, Stotler BA, Stephens H, Schwartz J. Therapeutic plasma exchange for the treatment of anti-NMDA-receptor encephalitis. J Clin Apher. 2011;26(6):320–325.
9. Miya K, Takahashi Y, Mori H. Anti-NMDAR autoimmune encephalitis [published online ahead of print November 5, 2013]. Brain Dev. doi:10.1016/j.braindev.2013.10.005.
10. Graus F, Dalmau J. Paraneoplastic neurological syndromes: diagnosis and treatment. Curr Opin Neurol. 2007;20:732–7. [PubMed]
11. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10:63–74. [PMC free article] [PubMed]
12. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-Methyl-D-Aspartate receptor (NMDAR) encephalitis in children and adolescent. Ann Neurol. 2009;66:118 [PubMed]
13. Armangue T, Titulaer MJ, Sabater L, et al. A novel treatment-responsive encephalitis with frequent opsoclonus and teratoma [published online ahead of print April 24, 2013]. Ann Neurol. doi: 10.1002/ana.23917.
14. Fareeha Ashraf, Kelly Janis and Benjamin Walter, Hunting for an Ovarian Teratoma in Anti-NMDA Receptor Encephalitis, Neurology April 26, 2012; 78 (Meeting Abstracts 1): P06.010
15. Janos L. Tanyi, Evelyn B. Marsh, Josep Dalmau, Christina S. Chu. Reversible Paraneoplastic Encephalitis in Three Patients with Ovarian Neoplasms, Acta Obstet Gynecol Scand. May 2012; 91(5): 630–634. Published online Mar 5, 2012. doi: 10.1111/j.16000412.2011.01365.x.
16. Dabner M1, McCluggage WG, Bundell C, Carr A, Leung Y, Sharma R, Stewart CJ., Ovarian teratoma associated with anti-N-methyl D-aspartate receptor encephalitis: a report of 5 cases documenting prominent intratumoral lymphoid infiltrates., Int J Gynecol Pathol. 2012 Sep;31(5):429-37.