Pathology – Research and Practice 208 (2012) 497–500

Contents lists available at SciVerse ScienceDirect

Pathology – Research and Practice

journal homepage: www.elsevier.com/locate/prp

Teaching cases

Necrotic mature ovarian teratoma associated with anti-N-methyl-D-aspartate receptor encephalitis

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ARTICLE INFO

Article history:
Received 10 March 2012
Received in revised form 15 May 2012
Accepted 24 May 2012

Keywords:
Ovary
Teratoma
Autoimmune disease
Encephalitis
Anti-N-methyl-D-aspartate receptor

ABSTRACT

A 20-year-old female with a diagnosis of autoimmune encephalitis against N-methyl-D-aspartate receptor was found to have a 13 mm teratoma in the left ovary. The tumor had undergone massive coagulative necrosis within a normal ovary, a previously unreported feature. Necrosis of a mature cystic teratoma is very rare in the absence of ovarian torsion. It is proposed that necrosis may have induced a massive liberation of neuronal antigens.

The vast majority of the tumors associated with this newly described condition are ovarian teratomas containing neural tissues. In this paper, we review their different histopathological aspects that may explain the relative incidence of various tumor types associated to this form of encephalitis. Anti N-methyl-D-aspartate receptor encephalitis has now become the most frequent autoimmune disorder associated with ovarian teratoma.

Introduction

Albeit only rarely, ovarian teratomas can be associated with autoimmune disorders; autoimmune hemolytic anemia [1] and hyperthyroidism in both benign [2] and malignant struma ovarii [3] have been reported.

Since 2005, a neurosciences research group led by Dalmau [4–6] has identified over a hundred cases of autoimmune encephalitis due to antibodies against the N-methyl-D-Aspartate receptor (anti-NMDAR), and which most frequently involves the temporal lobes and hippocampus. This clinically severe form of encephalitis is often associated with an ovarian teratoma, although in a high proportion of cases, ranging from 41 to 80%, the tumor is not detected [6,7]. Removal of the ovarian tumor and early immunotherapy often improves the outcome with full recovery or only a residual mild neurological deficit [6,8,9]. We believe that this association has now become the most frequent autoimmune disorder associated with ovarian teratoma.

The histopathology of these tumors has not been analyzed in detail, although it has been reported that the majority contain neural tissue [5,10]. We report a case of a small ovarian mature cystic teratoma with the unusual histology of a massive coagulative necrosis and which was associated with clinical anti-NMDAR encephalitis.

Clinical data

A 20-year-old female with a previous history of a presently inactive Crohn's disease and minor bronchial asthma presented with headache, hyperthermia, diarrhea and vomiting. Four days later she developed tonic-clonic seizures, agitation and hypoventilation and required intubation. An initial computerized axial tomography (CAT) scan of the head performed 48 h after the initiation of symptoms was unremarkable. The cerebrospinal fluid (CSF) showed leukocytosis with mononuclear predominance, slightly elevated proteins and a normal glucose. Microbiological stains and specific tests for mycobacteria and cryptococcus were negative. Viral serology for herpes, varicella zoster, parotiditis and enterovirus was also negative.

She was referred to San Cecilio University Hospital with a diagnosis of encephalitis. On admission, she was unconscious but with open eyes, marked dystonia and frequent seizures. Under sedation,

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http://dx.doi.org/10.1016/j.prp.2012.05.018

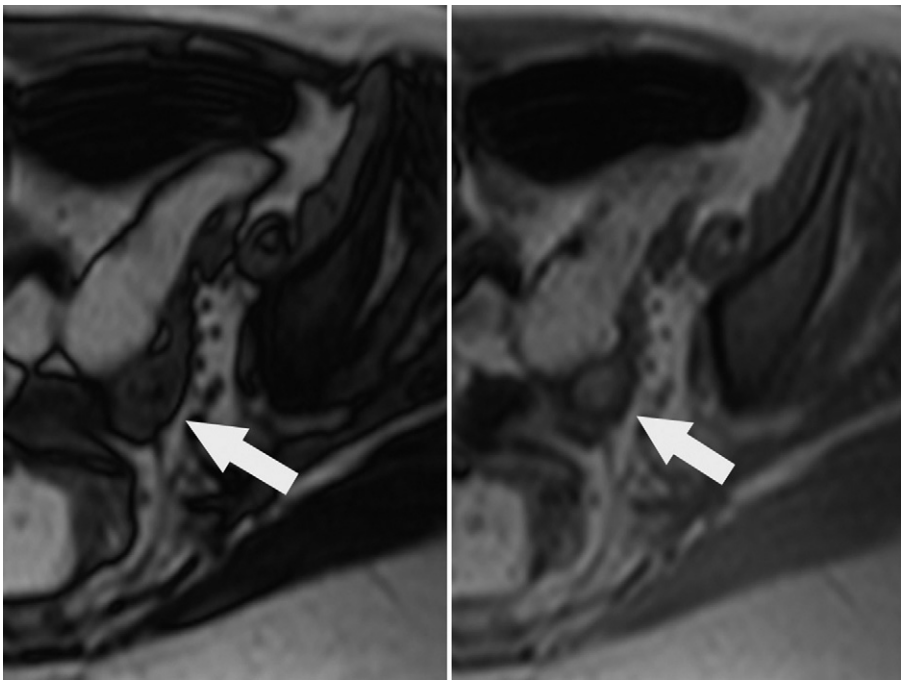

Fig. 1. Magnetic resonance imaging of left adnexum. Tumor (arrow) can be seen in both T1-weighted (T1W) *out-phase* (left) and T1W *in-phase* images (right).

both repetitive flexion of extremities and stereotyped movements in face and mouth were present. Further CAT and magnetic resonance (MRI) head scans were unremarkable. Once both neoplastic and viral aetiologies were discarded, a possible autoimmune disorder was considered and subsequently supported by the presence of positive Anti-NMDAR antibodies in the CSF, which established a diagnosis of anti-NMDAR encephalitis. Immunosuppressant treatment with corticoids and immunoglobulin followed by Rituximab and Cyclophosphamide was started but with little improvement.

Initially, further imaging studies, including abdominal ultrasonograms and a CAT scan, failed to demonstrate any pelvic tumor, however, a subsequent pelvic MRI revealed a rounded intraparenchymatous mass of 20 mm × 18 mm in the left ovary which was diagnosed as a fat-containing tumor, possibly a teratoma (Fig. 1). The right ovary was unremarkable. An abdominal laparotomy with left oophorectomy was performed.

Materials and methods

The surgical specimen was fixed in 10% buffered formalin, and the entire ovarian tissue (5 blocks) was processed for light microscopy. Immunohistochemical techniques for glial fibrillary acid protein (GFAP), (DAKO, Glostrup, Denmark, prediluted), neuron-specific enolase (NSE), (DAKO, prediluted), microtubules-associated protein 2 (MAP2), (DAKO, prediluted) and neuronal specific nuclear protein (NeuN), (Master Diagnostica, Granada, Spain, prediluted) were done.

Results

Macroscopically the ovary had an unremarkable external appearance, but a sagittal section revealed a 13 mm round, well delineated cyst filled by a mass of red, necrotic, friable tissue admixed with few hairs (Fig. 2A).

Microscopically, the cyst contained a teratomatous protuberance that had undergone massive coagulative necrosis (Fig. 2B) that only allowed identification of ghost tissues such as skin, appendages and fat (Fig. 3). Hairs and desquamated epithelium

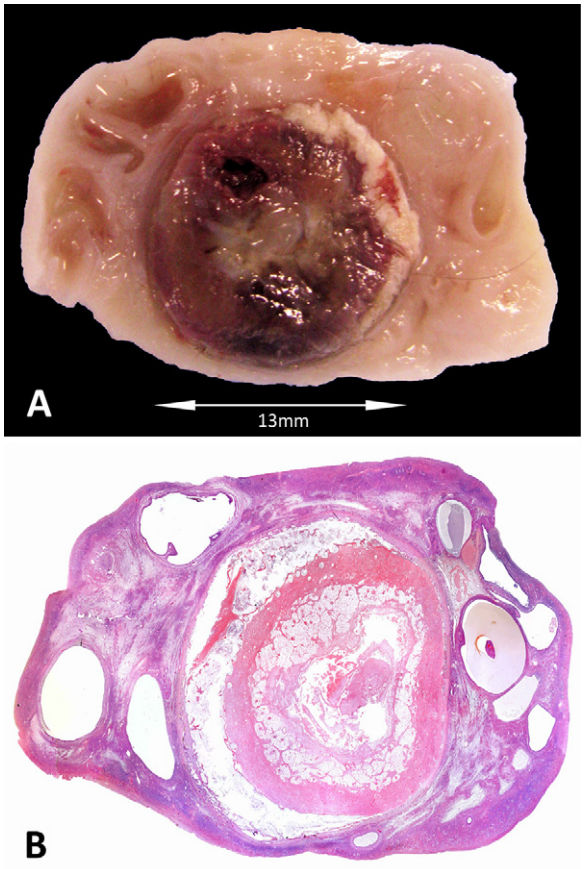

Fig. 2. Sagittal section of intraparenchymatous 13 mm necrotic teratoma (A). (B) A low power H&E stain (40×) shows a cavity containing hairs and a protuberance displaying massive infarction, where only "shadow" tissues are identifiable. The surrounding ovarian tissue is unremarkable, lacking signs of torsion.

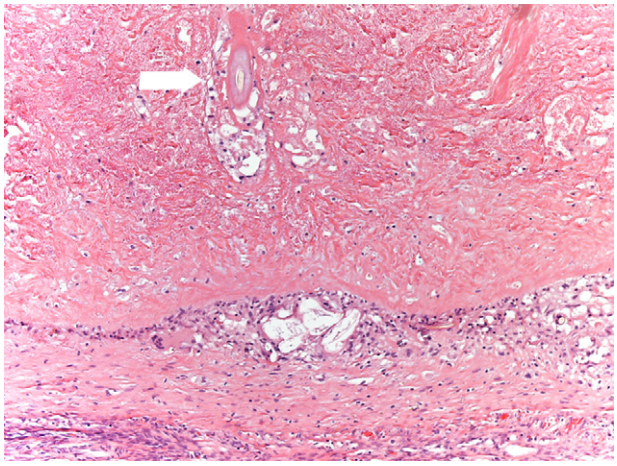

Fig. 3. A higher magnification H&E stain (400×) of the protuberance's edge showing necrotic tissue with a remaining hair (arrow).

filled the remaining cystic space. The central part was cystic and surrounded by a band of homogeneous liquefied tissue. Neither inflammatory infiltrates nor torsion-related histological features such as congestion or hemorrhage were present. The surrounding ovarian tissue was normal. Immunohistochemical attempts to demonstrate neural tissues by staining for GFAP, NSE and neuronal markers such as MAP2 and NeuN proved negative, probably due to the absence of immunoreactivity of the necrotic tissue.

Clinical follow up: There was a slight clinical improvement after surgery; dystonia was slightly reduced and the seizures stopped. The NMDAR antibody title was 1/10. Six months after the onset of symptoms and 3 months postoperatively, the patient has no more seizures, has regained consciousness, partly recovered her speech and voluntary movements and is now able to recognize family members. She is still undergoing immunosuppressant treatment.

Discussion

Most articles dealing with this new entity focus on the clinical and immunological features of the patients [5–7,11], while the histopathology of associated teratomas deals either with immunohistochemical findings of neural tissues expressing antibodies to N-methyl-D-aspartate receptors or the immunophenotype of their inflammatory infiltrates [10].

The majority of associated tumors correspond to ovarian teratomas containing neural tissues, where anti-NMDA receptor antibodies may be demonstrated in neuronal-like cells [5,10]. Only two isolated cases of testicular and mediastinal locations have been reported [6]. Unusually, this entity may take place in association with non-teratoid tumors exhibiting neuroendocrine differentiation [6,11,12]. There is only one report on a non-teratoid sex-cord stromal tumor, presumably lacking neural tissues, in the ovary [6].

63% of the ovarian teratomas reported in association with Anti-NMDAR encephalitis were mature cystic types and 27% were immature ones [6]. However, proportionally, the infrequent immature teratomas have a much higher representation in this condition than the mature cystic ones when compared with their relative overall incidence; mature cystic teratomas are the most frequent ovarian tumors in young females. The higher ratio of immature teratomas associated with this entity can be explained by the large mass of neural tissues present in them which often differentiate neurons and their precursors [13] and that are likely to be related to the formation of Anti NMDAR antibodies [5,10]. In mature cystic teratomas, neurons are present in only about 7–9% of tumors [14] which often have organoid arrangements reminiscent of central ganglia, cortex and cerebellum [15]. Furthermore, the lower frequency and smaller amounts of neural tissues present in testicular and mediastinal teratomas would partly explain their rarity in this condition.

None of the reported cases have described any particular histological features such as necrosis. The teratoma in our case had a massive coagulative necrosis, a previously unreported feature. Necrosis of a mature cystic teratoma is indeed a most unusual event in the absence of ovarian torsion, which had not occurred here as the characteristic features of venous infarction were absent. Thus, there are no objective reasons to explain the presence of necrosis in this small tumor. We do not believe that cyclophosphamide can cause necrosis of mature tissues which are identical to other adult tissues; nor is there a vasculitis phenomenon or inflammatory response that may be considered the source of ischemia. Although the advanced stage of necrosis precluded immunohistochemical identification of neural tissues that were likely to be present, since they occur in over half of cystic mature teratomas, it can be speculated that necrosis may have induced a massive liberation of neuronal antigens. Moreover, it can be hypothesized that this small necrotic tumor may eventually have been reabsorbed, leaving little imagenological evidence which could explain the poor detection rate of associated tumors in many instances. In the present case, the small size of the tumor made image diagnosis difficult, causing a delay in the final diagnosis. However, there has been a substantial improvement 3 months after surgery, consciousness has been regained and seizures have ceased. This positive response to surgery and immunosuppressant therapy stresses the fact that early diagnosis is of paramount importance, as it may result in almost complete recovery [8,9,16].

References

[1] I. Kim, J.Y. Lee, J.H. Kwon, J.Y. Jung, H.H. Song, Y.I. Park, et al., A case of autoimmune hemolytic anemia associated with an ovarian teratoma, J. Korean Med. Sci. 21 (2006) 365–367.

[2] Y. Mimura, M. Kishida, H. Masuyama, N. Suwaki, J. Kodama, F. Otsuka, et al., Coexistence of Graves' disease and struma ovarii: case report and literature review, Endocr. J. 48 (2001) 255–260.

[3] H. Kano, M. Inoue, T. Nishino, Y. Yoshimoto, R. Arima, Malignant struma ovarii with Graves' disease, Gynecol. Oncol. 79 (2000) 508–510.

[4] R. Vitaliani, W. Mason, B. Ances, T. Zwerdling, Z. Jiang, J. Dalmau, Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma, Ann. Neurol. 58 (2005) 594–604.

[5] J. Dalmau, E. Tuzun, H.Y. Wu, J. Masjuan, J.E. Rossi, A. Voloschin, et al., Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma, Ann. Neurol. 61 (2007) 25–36.

[6] J. Dalmau, A.J. Gleichman, E.G. Hughes, J.E. Rossi, X. Peng, M. Lai, et al., Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies, Lancet Neurol. 7 (2008) 1091–1098.

[7] S.R. Irani, K. Bera, P. Waters, L. Zuliani, S. Maxwell, M.S. Zandi, et al., N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes, Brain 133 (2010) 1655–1667.

[8] M. Seki, S. Suzuki, T. Iizuka, T. Shimizu, Y. Nihei, N. Suzuki, et al., Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis, J. Neurol. Neurosurg. Psychiatry 79 (2008) 324–326.

[9] A. Uchino, T. Iizuka, Y. Urano, M. Arai, A. Hara, J. Hamada, et al., Pseudopiano playing motions and nocturnal hypoventilation in anti-NMDA receptor encephalitis: response to prompt tumor removal and immunotherapy, Intern. Med. 50 (2011) 627–630.

[10] E. Tuzun, L. Zhou, J.M. Baehring, S. Bannykh, M.R. Rosenfeld, J. Dalmau, Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma, Acta Neuropathol. 118 (2009) 737–743.

[11] P. Niehusmann, J. Dalmau, C. Rudlowski, A. Vincent, C.E. Elger, J.E. Rossi, et al., Diagnostic value of N-methyl-D-aspartate receptor antibodies in women with new-onset epilepsy, Arch. Neurol. 66 (2009) 458–464.

[12] M. Hara, A. Morita, S. Kamei, M. Yamaguchi, T. Homma, N. Nemoto, et al., Anti-N-methyl-D-aspartate receptor encephalitis associated with carcinosarcoma with neuroendocrine differentiation of the uterus, J. Neurol. 258 (2011) 1351–1353.

[13] F.F. Nogales Jr., B.E. Favara, F.J. Major, S.G. Silverberg, Immature teratoma of the ovary with a neural component ("solid" teratoma). A clinicopathologic study of 20 cases, Hum. Pathol. 7 (1976) 625–642.

[14] F.F. Nogales, The pathology of germ cell tumours, in: H. Fox, M. Wells (Eds.), Haines and Taylor's Obstetrical and Gynaecological Pathology, 5th ed., Churchill Livingstone, London, 2003, pp. 798.
[15] F.F. Nogales, D. Aguilar, Neural tissue in human teratomas, in: I. Damjanov, D. Solter (Eds.), The Biology of Teratomas, Humana Press, Clifton, NJ, 1983, pp. 174–177.
[16] J. Dalmau, E. Lancaster, E. Martinez-Hernandez, M.R. Rosenfeld, R. Balice-Gordon, Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis, Lancet Neurol. 10 (2011) 63–74.