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Case report

Ultrasound-guided laparoscopic ovarian preserving surgery to treat anti-NMDA receptor encephalitis

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Case report

Anti-*N*-methyl-D-aspartate receptor (NMDAr) encephalitis is a serious and potentially fatal form of antibody-mediated encephalitis, which usually affects women of reproductive age, but can affect both women and men of all ages. In 2007, it was proposed by Dalmau et al.[1] that anti-NMDAr encephalitis was strongly associated with ovarian teratoma. Ovarian teratomata have since been identified in up to 50% of adult women with proven anti-NMDAr encephalitis.[2] It is typified by a viral and psychiatric prodrome leading to reduced levels of consciousness and autonomic dysfunction.[3] If identified and treated quickly it is reversible in the majority of cases. However, it can become life-threatening, with a mortality rate of up to 10%.[4] Even with optimal management, extensive rehabilitation is necessary and recovery can take over 18 months.[4] Traditional treatment utilises a combination of steroids, intravenous immunoglobulin and plasmapheresis, with the removal of the precipitating teratoma if present.[3] Second line medical therapy includes rituximab and cyclophosphamide.[5,6] Ovarian cysts that can be visualised laparoscopically are often amenable to ovarian cystectomy. However, anti-NMDAr encephalitis has been known to arise in the context of microscopic or small cysts that are not possible to visualise laparoscopically. The removal of such cysts, which are often deeply embedded in the ovary, can be challenging and has traditionally necessitated oophorectomy. Ovarian surgery, particularly oophorectomy, has potential implications for future fertility and requires careful consideration, especially in patients who invariably do not have capacity by the time surgery is being considered. We describe the successful management of a young woman with anti-NMDAr encephalitis using ultrasound-guided laparoscopic ovarian wedge resection of a small teratoma that was not visible laparoscopically. The woman has given written consent for the case to be reported.

A 29-year-old woman presented with a 3-week history of altered behaviour culminating in her being detained by police due to agitated and aggressive behaviour. Following the onset of visual and auditory hallucinations, she was treated with haloperidol and transferred to an inpatient psychiatric unit where mental status examination was consistent with an acute psychotic episode. After becoming pyrexial (39.7°C), tachycardic and following the onset of seizure-like activity she was transferred to an acute hospital where she was commenced on intravenous ceftriaxone and acyclovir. She underwent lumbar puncture, which revealed a mononuclear pleocytosis (WCCs 23×10^9/l; 90% mononuclear cells), with normal red blood cells, protein and glucose. Due to a high clinical suspicion of autoimmune encephalitis she was started on intravenous methylprednisolone. Her cognitive function and conscious level deteriorated, which prompted transfer to the intensive care unit (ICU) for intubation, ventilation, plasmapheresis and intravenous immunoglobulin. She developed profound autonomic dysfunction, including episodes of asystole, so rituximab was commenced. Cyclophosphamide was avoided due to its possible detrimental effect on fertility.

Cerebrospinal fluid (CSF) examination was negative for bacterial organisms and polymerase chain reaction (PCR) was negative for herpes virus, varicella virus and enteroviruses. She was HIV-negative, and serum and CSF cryptococcal antigens were negative. NMDAr antibodies tested positive in blood and CSF. Magnetic resonance imaging (MRI) of the brain was consistent with an encephalitic process with hyperintense white matter change on fluid attenuation inversion recovery (FLAIR) sequences. The electroencephalogram (EEG) showed extreme delta-brush, a sign thought to be pathognomonic for NMDAr encephalitis.[7] Trans-abdominal ultrasound and computed tomography (CT) scans could not positively identify ovarian pathology and an MRI pelvis was initially reported as normal. Following persistence to identify an underlying teratoma, the imaging was discussed at the gynaecology oncology multidisciplinary team (MDT) meeting and an 8-mm dermoid cyst was identified in the right ovary. Following consultation with her family, 6 weeks into her admission, she was prepared for laparoscopic removal of the cyst under ultrasound guidance.

She underwent an uncomplicated laparoscopy. The ovaries appeared mildly polycystic with no macroscopic evidence of ovarian lesions. A transvaginal ultrasound probe was inserted and 500 ml of normal saline was instilled in the pelvis to allow intra-operative visualisation of the ovarian tissue during laparoscopy. A 1-cm dermoid cyst was identified on ultrasound in the medial aspect of the right ovary with adjacent exophytic papillary projections. The site of the lesion was marked, using monopolar diathermy, and an ovarian wedge resection was performed to remove the ovarian tissue containing the cyst. Continuous intraoperative ultrasound was used to ensure the part of the ovary containing the cyst was excised. Haemostasis was achieved and the healthy ovarian tissue was successfully preserved. There was no cyst spillage. The ovarian biopsy, measuring 30 × 15 × 10 mm, was removed transumbilically using a laparoscopic specimen retrieval bag. Histology revealed a 15 × 10 mm mature cystic teratoma with an intact capsule containing fat, neural, respiratory, odontogenic and intestinal tissues.

Postoperatively, her cognitive function significantly improved within days. Two weeks later she was transferred from ICU to a general ward where she continued to improve rapidly with neuro-rehabilitation. She was discharged 8 weeks postoperatively at which point she was fully mobile and conversant with the expectation of a complete recovery.

Discussion

Anti-NMDAr encephalitis in women needs to be managed as part of a multi-disciplinary team, involving a somewhat unusual referral pathway from neurology to gynaecology for a patient being managed on the ICU. It is imperative that gynaecologists ensure timely identification and safe removal of precipitating teratoma if present, given that prompt removal is an independent predictor of positive outcome.[4] It is a condition that is poorly understood amongst gynaecologists, exemplified by the fact that just 11% of reported cases have been published in gynaecology journals, whereas 50% are reported in neurology and psychiatry journals.[8]

Intra-operative ultrasound has been increasingly used in a wide range of specialties, since its introduction in 1961 to facilitate detection of renal calculi during urological surgery.[9] It has since been used successfully in a variety of circumstances within gynaecological practice, including surgical termination of pregnancy,[10] hysteroscopy,[11] and laparoscopic myomectomy.[12] This case demonstrates the novel application of intra-operative ultrasound to increase accuracy in the resection of ovarian lesions too small to be visualised laparoscopically. This technique minimises the risk of cyst rupture, while preserving the healthy ovarian tissue. A recent systematic review of women with teratoma-associated anti-NMDAr encephalitis showed that of 95 reported cases of mature teratoma that underwent surgical intervention, 38% ($n = 36$) underwent either unilateral or bilateral adnexectomy.[4] Given that anti-NMDAr encephalitis has a preponderance among women of reproductive age, ovarian preserving surgical techniques should be considered in all cases where benign disease is suspected. This is particularly relevant as most women lack capacity, and therefore can not consent by the time surgery is being considered.

Anti-NMDAr encephalitis can provide diagnostic difficulty for gynaecologists, with underlying teratomas so small, they do not appear using conventional imaging modalities.[13–15] Some cases have reported successful management following bilateral oophorectomy, with histological evidence of teratomas, despite not being identified on pre-operative imaging.[13] In other cases, precipitating teratomas have only been identified following a postmortem.[2,14] In another case, unilateral oophorectomy was undertaken despite 'negative imaging', with a mature teratoma being diagnosed retrospectively.[15] However 'negative imaging' did not include MRI, an imaging modality with a very high sensitivity for the presence of fat in the sebaceous component of such cysts. Furthermore, transvaginal ultrasonography found a 'minimal suspect lesion' in the same ovary that, following removal, proved to contain a mature teratoma. The sensitivity of detecting mature cystic teratomas by ultrasonography has previously been reported to be 58%.[16] Although it is likely that recent technical advances in ultrasonography have increased the accuracy of ultrasound as a diagnostic tool, expertise in gynaecological ultrasonography remains a key factor in achieving excellent diagnostic accuracy in 'difficult' ovarian lesions. It is therefore imperative that patients with anti-NMDAr encephalitis are scanned by an expert in gynaecological

ultrasonography. MRI imaging should also be used if ultrasound examination remains unconvincing, using as thin slices as possible. In treatment-resistant cases, where imaging cannot demonstrate an underlying teratoma, selective oophorectomy could be considered. Although a recent systematic review showed a slight preponderance in the right ovary (55 versus 45% on left ovary), the difference was not statistically significant.[8] In the previously described case,[14] unilateral oophorectomy was undertaken after almost a year of intensive care in the absence of clinical improvement despite intensive medical management, with subsequent improvement noted within days postoperatively. In cases with negative imaging, selective ovarian vein sampling could theoretically be undertaken to measure anti-NMDA

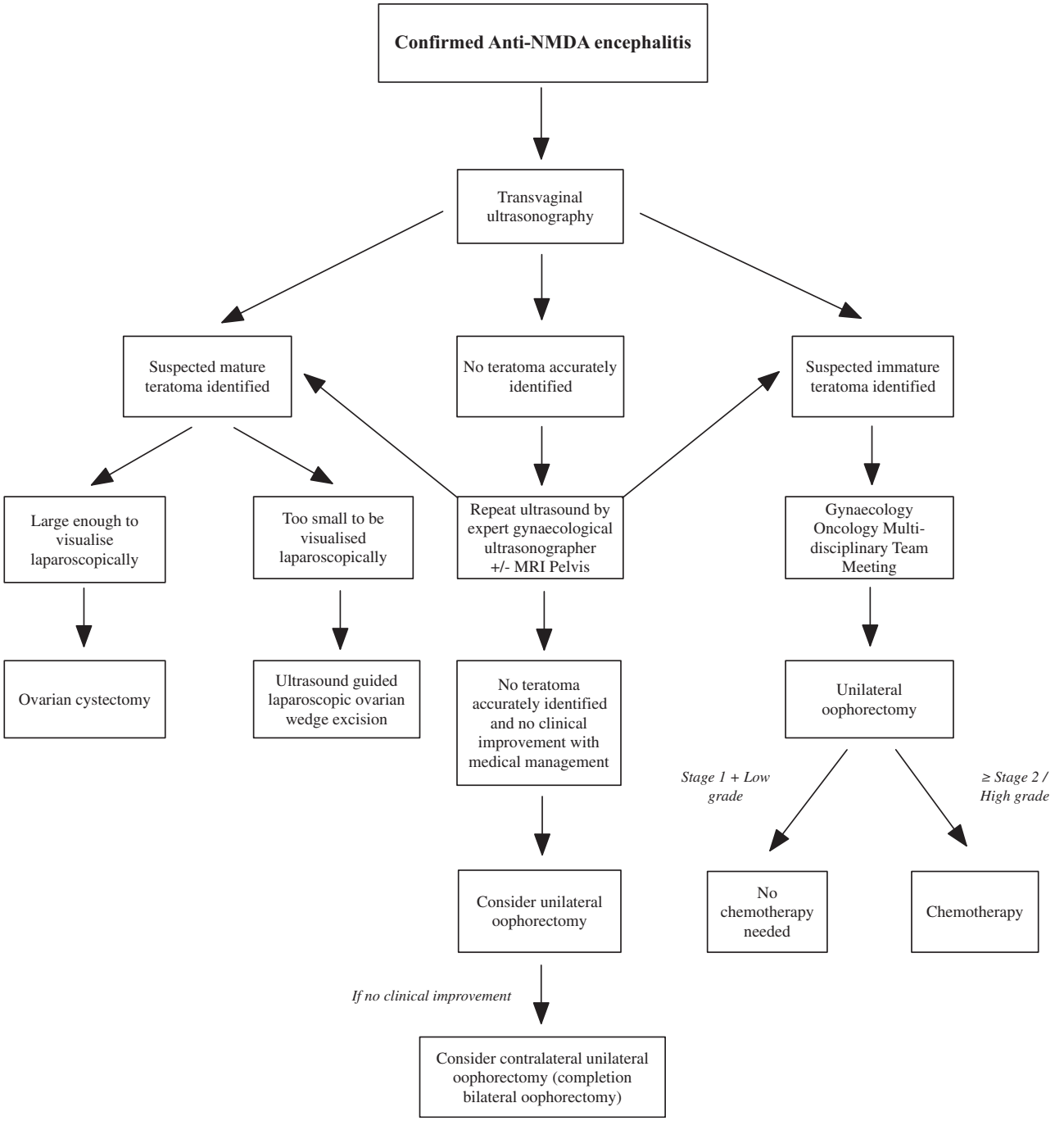

Figure 1. Suggested investigation and surgical management algorithm for anti-NMDA encephalitis associated with ovarian teratoma in women of reproductive age.

antibody assays in each ovarian vein. This could potentially identify disease laterality and reduce the risk of removing the healthy ovary. Although this technique has not been undertaken previously in cases of anti-NMDAr encephalitis, the concept can be extrapolated from a similar technique that has been used in the successful diagnosis of androgen secreting ovarian tumours that were not visible with conventional imaging modalities.[17,18] Alternatively, if such expertise is unavailable, bilateral ovarian wedge biopsies could be considered to help identify occult teratomatous tissue. If, following unilateral oophorectomy, there is no clinical improvement, subsequent oophorectomy of the contralateral ovary could be contemplated as a last resort, particularly if all medical options have been utilised.

The use of intraoperative ultrasound allows greater accuracy in delineating cyst dimensions in cysts that are too small to be visualised laparoscopically, facilitating complete cyst excision while reducing risk of cyst rupture and allowing maximal preservation of healthy ovarian tissue. This technique is also transferable to the treatment of other small tumours, which may be difficult to visualise laparoscopically, such as recurrent serous borderline ovarian tumours. Such tumours often occur in pre-menopausal women, who have often had their ovarian reserve compromised by primary treatment, further emphasising the need for ovarian tissue preservation. Objective measures of ovarian reserve, such as anti-mullerian hormone (AMH), should be taken pre- and postoperatively to help evaluate the extent of ovarian tissue damage in such cases.

Laparoscopic ultrasound is based on a similar concept to our technique, which has also been successfully used to manage a case of anti-NMDAr encephalitis, by the removal of a 10-mm mature teratoma.[19] However, laparoscopic ultrasound requires specific expertise, which is not a core part of specialty training in Obstetrics & Gynaecology, nor is it universally available. Transvaginal ultrasonography, on the other hand, is a skill that all gynaecologists should acquire. In the UK, ultrasound is an integral part of training and all trainees undertake competency-based assessments to ensure appropriate expertise is attained. Conventional ultrasound equipment is also commonplace in hospitals, making the technique demonstrated in this case both achievable and widely applicable internationally.

Another ovarian tissue-preserving technique was demonstrated by Hayashi et al.,[20] where a 7-mm mature cystic teratoma was excised, using partial resection of the ovary. Careful pre-operative planning was undertaken with detailed discussion with the radiologist to help identify the 'most likely' location of the teratoma. Following this discussion, the plan was to remove the ovary 'in pieces' and it was fortunately removed in the first piece, measuring 22 × 22 mm. Although multi-disciplinary pre-operative planning resulted in a positive outcome, the use of a blind technique potentially increases the amount of healthy ovarian tissue excised while increasing the risk of cyst rupture. The team cited lack of experience as their reason for not using laparoscopic ultrasound.

A suggested algorithm summarising the investigative pathway and surgical management of ovarian teratoma-associated anti-NMDAr encephalitis is displayed in Figure 1. Ovarian sparing surgery should be undertaken for all women with anti-NMDAr encephalitis who meet the criteria for localised ovarian mature teratoma. Ovarian cystectomy should be undertaken in those visible macroscopically, and a wedge resection should be undertaken in those too small to be visualised laparoscopically. In such cases, intra-operative ultrasound should be used to mark the ovary accurately, to minimise the risk of cyst rupture and to preserve as much healthy ovarian tissue as possible. This could be undertaken either transvaginally, as demonstrated in this case, or laparoscopically if the necessary expertise and equipment is available. Oophorectomy should be reserved for cases of suspected immature teratomas and could be considered in treatment-resistant cases where, after extensive imaging including transvaginal ultrasonography and MRI, no teratoma is identified.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

BJ helped conceive the original idea and wrote the article. RR helped write the case report. SS provided expertise and helped revise the final draft. CS and JRS both contributed to the manuscript design and participated in final draft revisions. JY conceived the original surgical concept, provided expertise throughout and helped revise the final manuscript.

Details of ethics approval

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