Case Report

A rare giant borderline endocervical type mucinous ovarian tumour: A case report and review of the literature

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Abstract

Herein, we present the case of a 26 year old nulliparous female with a very large mucinous ovarian tumour. The patient presented at a late stage, when the cyst had accrued more than ten litres of fluid and when her abdomen was comparable to that of a term pregnancy. Radiological assessment confirmed the presence of a large cyst arising from the right ovary and occupying the whole abdomen, causing organ compression. The cyst was completely excised from the right ovary following cyst drainage with a Veress needle. Histology confirmed the lesion to be a borderline mucinous ovarian tumour, endocervical type. We discuss the case in detail, together with an update on pathogenesis and treatment of this uncommon disease.

Key words:

Adenocarcinoma, Borderline, Cyst, Malignancy, Mucinous, Ovary

Introduction

Malignancies of the ovary bear a complex histopathological classification system, but are largely differentiated into surface epithelial tumours (which affect the surface Müllerian epithelium), germ cell tumours (which affect the germ cells), and sex cord-stromal tumours (which affect the ovarian stroma). The surface epithelial tumours can in turn be divided, into benign, malignant, and an uncommon 'intermediate' group, referred to as borderline tumours. Borderline tumours are marked by moderate epithelial proliferation and, in some cases, may represent an intermediary stage in ovarian cancer, which will eventually progress to overt malignancy. Novel studies in the molecular pathophysiology of these tumours have revealed distinct aspects in their pathogenesis. Moreover, the clinical management of these malignancies differs significantly from that of the high grade malignancies. Until recently,

borderline malignancies were previously categorised as low-grade cystadenocarcinomas in many centres, and patients were inappropriately treated with adjuvant chemotherapy and radiotherapy, often resulting in unnecessary treatment-related morbidity and even mortality. We present a case of a 26 year old female who developed an atypically large endocervical type borderline mucinous cystadeoma. We discuss the management of this individual case in terms of imaging, surgical approach and histopathology. Moreover, we discuss the advances in the pathology of this tumour subtype, together with current guidelines in management.

Case presentation

A 26 year old nulliparous female presented with a several week history of worsening abdominal distension, which she had initially attributed to increasing weight and which had proved resistant to all weight loss efforts. Her distension had initially been treated symptomatically with antispasmodics, to little effects. She was referred to Gynaecology relatively late, when her distension became comparable to that of a term pregnancy. A full clinical assessment was taken upon her review at Gynaecology Outpatient Department. Apart from her previously described distension, she admitted to having an irregular

menstrual cycle. Her history was otherwise unremarkable apart from a personal history of β-thalassaemia trait and a strong family history of breast cancer. On examination, gross enlargement of her abdomen was immediately apparent, with distended superficial abdominal veins. The mass arose from the pelvis and extended up to the xyphoid process, filling up the whole abdomen. It was ballottable and dull to percussion. No bruits could be heard over it. She was otherwise systemically well. Ultrasound assessment of the mass was performed, which confirmed the presence of a very large mixed solid and cystic mass extending from the pelvis to the epigastrium. No focal liver lesions were detected and no signs of hydronephrosis were noted. Free fluid could not be assessed for in view of the large size of the lesion. An urgent computed tomography scan was subsequently performed, which demonstrated a large cystic lesion (Figure 1) arising from the right ovary, occupying the majority of the abdomen and measuring 28 x 20 x 33 cm. This gave the cystic structure a volume approximating 104 cm3 (roughly 10 litres of fluid). The lesion also demonstrated the presence of numerous semi-solid, but mainly cystic subcysts in its inferior aspect (Figure 2). The mass was compressing adjacent structures including the uterus, right psoas, both kidneys (without hydronephrosis), ascending and descending colon, lower aorta and inferior vena cava. However, no focal metastatic deposits or enlarged lymph nodes were demonstrable. Pre operative blood tests, including a complete blood count, urea, electrolytes, creatinine and liver function, were normal. CA-125 levels were 30.9 U/mL, whilst levels of CA-19.9, lactate dehydrogenase, alfafetoprotein and beta-human chorionic gonadotrophin were within normal limits. The patient underwent right ovarian cystectomy. A lower transverse incision was made, dissecting through skin, abdominal fat and musculofascial planes until the tense ovarian cyst wall was reached. Five mL of ascitic fluid was taken for histopathological assessment. A Veress needle was inserted through the cyst wall and attached to a vacuum pump drain. Roughly 10.5 L of straw-coloured mucinous fluid was drained. The remaining cyst wall was meticulously dissected from the right ovary. The left ovary was assessed and was completely normal. The omentum was free from deposits. Haemostasis was ensured and the abdominal wall was subsequently closed in layers. The skin was closed with subcuticular clips. Both the cyst wall and intracystic fluid were sent for histopathological review. The patient made a routine post-operative recovery and was discharged home three days after the procedure. Assessment of peritoneal fluid only demonstrated the presence of mesothelial sheets, scattered lymphocytes and neutrophils on an erythrocyte-rich background. No malignant cells were seen. Cyst fluid analysis demonstrated the presence of clusters of vacuolated epithelial cells, together with numerous macrophages, lymphocytes and neutrophils. The epithelial cells demonstrated marked size pleomorphism and atypia, consistent with a mucinous neoplasm. The cyst wall was smooth overall, apart from an area composed of numerous subcysts, which formed a conglomerate, roughly 9.5 cm in diameter, and two separate solid areas measuring 4 cm in diameter each. The cystic structures were filled with yellow viscous fluid. Sections from the cyst wall demonstrated endocervical-type mucinous epithelium, resembling that of a mucinous cystadenoma. The solid areas, however, showed moderate epithelial proliferation with cribriforming and atypia (Figure 3). Areas of haemorrhage and necrosis were also seen. However, no signs of stromal invasion were noted. A diagnosis of borderline endocervical type mucinous cystadenoma was made. The patient is currently well and experienced no complications from the surgical intervention. She is being closely followed up on an outpatient basis.

Figure 1.
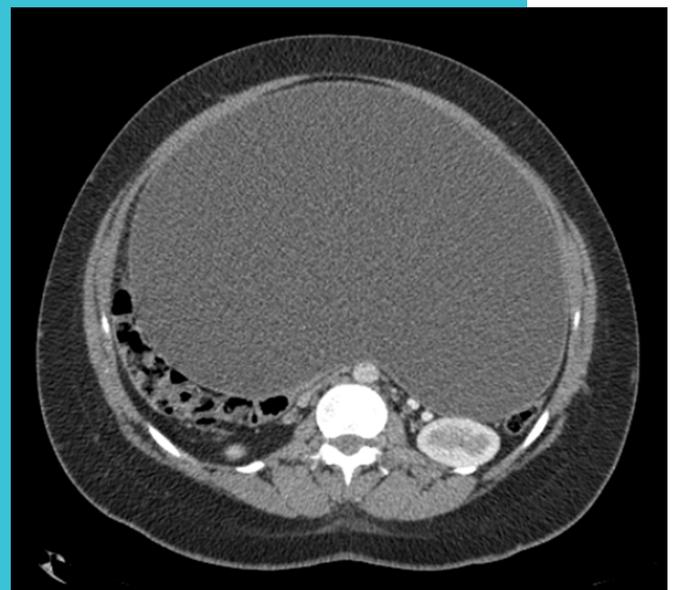
Computed tomography scan demonstrating a smooth ovarian cyst compressing the kidneys, intestines, aorta, inferior vena cava and psoas muscles.

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Discussion

Ovarian cancer accounts for 3% of all malignancies, being the sixth most commonly diagnosed tumour in females and, unfortunately, the tumour which accounts for the greatest number of deaths amongst all the tumours of the female genital tract [1]. The risk factors for this malignancy remain poorly understood, and very little evidence exists for differential risk factors according to histological tumour subtype. The main risk factors, however, include genetics (especially inheritance of BRCA1 and BRCA2, familial genetic syndromes like hereditary non-polyposis colonic cancer, and a positive family history), increasing age, nulliparity and obesity [1, 2]. Conversely, use of the oral contraceptive pill, breast feeding, hysterectomy, tubal ligation and oöphorectomy are known to be protective [1-3]. We present this case in view of the enormous size of the tumour, which, to the best of our knowledge, is the largest recorded borderline ovarian tumour in the literature. Apart from nulliparity, the patient had no other risk factors for developing ovarian malignancy. Moreover, she was outside the common age group for developing disease, which probably alludes to a significant genetic risk, which, unfortunately, was not assessed. Borderline ovarian tumours account for roughly 10% of all cases of ovarian malignancy, and occur in a younger subset of the female population [4]. They represent an intermediary subset of epithelial ovarian malignancies, frankly lying in between tumours which are unquestionably benign, and overt malignant lesions. Ovarian epithelial malignancies have been further subclassified into serous, mucinous, endometrioid, clear cell and transitional cell tumours, all of which include a further borderline subclassification [5]. Mucinous ovarian tumours account for about 30% of all ovarian tumours, with 15% of cases being malignant [6]. Borderline mucinous malignancy has been referred to by numerous nomenclatures, including atypical proliferative mucinous tumour (APMT) and mucinous tumour of low malignant potential (MTLMP). These tumours are rarer than their serous borderline counterparts, and only account for roughly 5% of mucinous malignancies of the ovary [7]. There are two further immunophenotypically distinct subclassifications of APMTs, namely the gastrointestinal type, which accounts for 90% of cases, and the endocervical (also referred to as Müllerian or seromucinous) type, which accounts for the rest [7-9]. Several gene families seem to play an important role in the pathogenesis of this disease. Amongst these are the mucin gene family, of which MUC2, MUC3 and MUC5A genes are overexpressed in intestinal-type borderline malignancies and MUC4 and MUC5B genes are overexpressed in endocervical-type disease [10]; oestrogen and progesterone receptor families, which tend to be expressed in endocervical-type tumours, and cytokeratin gene families, of which cytokeratin 20 (CK20) is overespressed in intestinal-type tumours [11, 12]. CA-125 expression tends to be more common in endocervical borderline tumours [11]. Pathological assessment of borderline mucinous tumours, especially of the intestinal subtype, heavily suggests that these lesions act as precursors to ovarian mucinous adenocarcinomas. Mutations in KRAS seems to be critical in the pathological progression in the ovarian 'adenoma-carcinoma sequence' [13-15]. Conversely, p53 mutations tend to be rare in borderline mucinous malignancy, tending to be more common in malignant adenocarcinomas. Mutations in p53 thus probably represent a stepwise progression in the progression of borderline lesions to overtly malignant tumours. This progression is seen much more frequently in the intestinal subvariant of disease [6, 16, 17]. Other studies have shown the presence of loss of heterozygosity, especially in the 5q14 and 17q11 regions of the genome. Tumours with these genetic changes have a greater propensity of progression to adenocarcinomas [18].

Figure 2.

Computed tomography scan demonstrating the inferior pole of the ovarian cyst, with numerous subcyst components.

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Intestinal-type mucinous borderline malignancy describes the 'classical' borderline mucinous malignancy, and occurs most frequently in females around 35 years of age [8]. The tumours, over 95% of which are unilateral, often take the form of a multilocular cyst, with a smooth outer surface, filled with mucinous material, which may be haemorrhagic [7, 19]. Conversely endocervical-type mucinous borderline malignancies tend to be much smaller (in stark contrast to the the cyst presented in this case), and bilaterality approaches 40% of cases. They gross morphologically resemble borderline serous malignancies, tending to be unilocular, often with prominent exophytic and intracystic papillary protruberances [7, 8, 20]. They are frequently associated with endometriosis [21, 22]. Histologically, these lesions are characteristically heterogenous in nature. With intestinal-type malignancy, the epithelium is composed of multiple goblet cells or gastric-type foveolar glands. The epithelium is often stratified into two to three layers and, in some areas, forms tufts and villous projections, possibly extending to a cribriform pattern. The individual cells bear mild to moderate degree of nuclear atypia, which is often highly focal in nature, but which may, in some cases, be quite diffuse [6, 7, 20]. Conversely, endocervical-type borderline tumours tend to be mixed in nature, with areas displaying a serous ciliated component and others exhibiting endocervical type mucinous epithelium. Once again, mild to moderate nuclear atypia may be present [6, 7, 8, 20]. Roughly 10 – 20% of borderline mucinous tumours exhibit areas of stromal microinvasion; characterised by atypical cellular clusters invading the stroma, which, by definition measure less than 5 mm in size (infiltration at depths greater than 5 mm is classified as invasive carcinoma) [7, 23]. Such microinvasion tends to be more common with endocervical variants [23]. In addition borderline mucinous malignancy, especially of the endometrial type, may be associated with foci of marked nuclear atypia, which represents an area of intraepithelial carcinoma. These areas are may easily be missed during sampling [20, 21]. Mucinous borderline tumours differ from their serous counterparts in their controversial association with pseudomyxoma peritonei. This condition is mainly connected with the intestinal subtype of mucinous tumours, particularly those with large amounts of mucin [24]. [25]. However, modern studies have shown that the vast majority of ovarian borderline tumours which present with pseudomyxoma peritonei are usually secondary deposits from a low grade appendiceal or, more rarely, pancreatic muci-

nous neoplasm with a metastatic ovarian deposit, and pseudomyxoma peritonei from an ovarian mucinous borderline tumour is, in fact, an exceedingly rare event [26, 27]. The prognosis of mucinous borderline tumours, even those with areas of microinvasion or non-invasive carcinoma, is excellent overall [28]. Even tumours with lymph node metastasis have an excellent prognosis overall [29].

Figure 3.
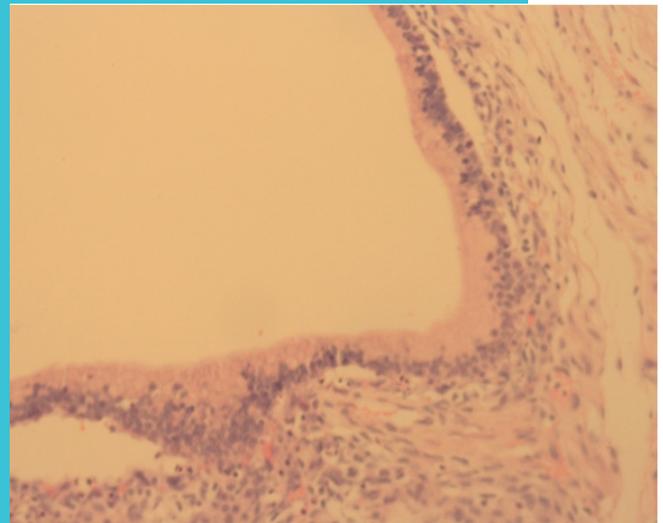
Section showing epithelial proliferation with cribriforming and atypia.

Uncommonly, the tumour is detected at advanced stages, marked by lymph node spread and/or peritoneal deposits. However, these tumours usually contain areas of high grade disease and invasive carcinoma [28, 30]. Management of disease is still controversial. All studies allude to the paramount importance of appropriate staging during surgery, ideally involving adequate exploration of the entire abdominal cavity [31]. However, stage I disease is being increasingly treated laparoscopically, often favouring unilateral salpingoophorectomy over simple cystectomy, which has, in some studies, been associated with a higher element of recurrence, especially with endocervical tumours [32]. Such fertility-conserving surgery is obviously favoured in younger individuals with the disease [33, 34]. Conversely, more aggressive high stage disease or cases which occur in women with low grade disease who have surpassed childbearing age, bilateral salpingoophorectomy with infracolic omentectomy and thorough assessment for and

excision of any peritoneal deposits may be warranted [31]. The overall survival rate for patients with stage I disease practically approaches 100%, however, this figure drops significantly with the presence of invasive disease or invasive metastatic deposits, in which case survival rates can decline to figures as low as 50%. Recurrence rates are low overall, with an estimated 0.25% recurrence for stage I disease, increasing to 2.5% with higher stage disease [28,34, 35].

In conclusion, borderline mucinous epithelial tumours are a rare pathological entity, and endocervical subvariants reaching this size are exceedingly rare indeed. They represent, however, a variant of ovarian malignancy which has an excellent overall prognosis, even when associated with epithelial invasion and lymph node metastasis. Highly conservative treatment strategies are available in fertile women, although more radical treatment is favoured in older individuals. Regular follow up is critical in these patients for early assessment of recurrence, should this occur.

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Conflict of Interest
The authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. Permuth-Wey J, Sellers TA. Epidemiology of ovarian cancer. Methods Mol Biol 2009;472:413-37.
2. McLemore M, Miaskowski C, Aouizerat B, Chen L, Dodd M. Epidemiologic and Genetic Factors Associated with Ovarian Cancer. Cancer Nurs 2009;32:281–290.
3. Tortolero-Luna G, Mitchell MF. The epidemiology of ovarian cancer. J Cell Biochem Suppl 1995;23:200-7.
4. Tropé CG, Kaern J, Davidson B. Borderline ovarian tumours. Best Pract Res Clin Obstet Gynaecol 2012;26:325-36.
5. Link C, Reed E, Sarosy G, Kohn E. Borderline ovarian tumours. Am J Med 1996;101:217-25.
6. Rosai J. Female Reproductive System. Rosai and Ackerman's Surgical Pathology 10th edition. Houston M, Mosby Elsevier, USA, 2011, 1562-609.
7. Soslow RA, Tornos C. Diagnostic pathology of ovarian tumours. 2011. New York: Springer.
8. Hart R William. Borderline epithelial tumours of the ovary. Mod Pathol 2005;18:33-50.
9. Rutgers JL, Scully RE. Ovarian müllerian mucinous papillary cystadenomas of borderline malignancy: a clinicopathologic analysis. Cancer 1988;61:340-8.
10. Borman F, Buisine MP, Wacrenier A, Querleu D, Aubert JP, Porchet N. Mucin gene transcripts in benign and borderline mucinous tumours of the ovary: an in situ hybridization study. J Pathol 2001;193:339-44.
11. Vang R, Gown A, Barry T, Wheeler D, Ronnett B. Ovarian Atypical Proliferative (Borderline) Mucinous Tumors: Gastrointestinal and Seromucinous (Endocervical-Like) Types are Immunophenotypically Distinctive. Int J Gynecol Pathol 2006;1:83-9.
12. Alaiya AA, Franzen B, Hagman A, Dyzvik B, Roblick UJ, Becker S, et al. Molecular classification of borderline ovarian tumors using hierarchical cluster analysis of protein expression profiles. Int J Cancer 2002;98:895-9.
13. Chi-Ho Mok S, Bell DA, Knapp RC, Fishbaugh PM, Wech WR, et al. Mutation of K-ras Protooncogene in Human Ovarian Epithelial Tumors of Borderline Malignancy. Cancer Res 1993;53:1489.
14. Enomoto T, Weghorst CM, Inoue M, Tanizawa O, Rice JM. K-ras activation occurs frequently in mucinous adenocarcinomas and rarely in other common epithelial tumors of the human ovary. Am J Pathol 1991;139:777–85.
15. Tsang YT, Deavers MT, Sun CC, Kwan SY, Kuo E, Malpica A, et al. KRAS (but not BRAF) mutations in ovarian serous borderline tumour are associated with recurrent low-grade serous carcinoma. J Pathol 2013;231:449-56.
16. Caduff R, Svoboda-Newman S, Ferguson A, Johnston C, Frank T. Comparison of mutations of Ki-RAS and p53 immunorecativity in borderline and malignant epithelial ovarian tumors. Am J Surg Pathol 1999;23:323-8.
17. Bell DA. Origins and molecular pathology of ovarian cancer. Mod Pathol 2005;18:19-32.
18. Nakayama K, Takebayashi Y, Namiki T, Tamahashi N, Nakayama S, Uchida T, et al. Comprehensive allelotype study of ovarian tumors of low malignant potential: potential differences in pathways between tumors with and without genetic predisposition to invasive carcinoma. Int J Cancer 2001;94:605-9.
19. Guerrieri C, Högberg T, Wingren S, Fristedt S, Simonsen E, Boeryd B. Mucinous borderline and malignant tumors of the ovary. A clinicopathologic and DNA ploidy study of 92 cases. Cancer 1994;74:2329-40.
20. Rodriguez IM, Irving JA, Prat J. Endocervical-like mucinous borderline tumors of the ovary: a clinicopathologic analysis of 31 cases. Am J Surg Pathol 2004;28:1311-8.
21. Rodriguez, I.M., J.A. Irving, and J. Prat, Endocervical-like mucinous borderline tumors of the ovary: a clinicopathologic analysis of 31 cases. Am J Surg Pathol, 2004;28:1311-8.
22. Oral E, Ilvan S, Tustas E, Korbeyli B, Bese T, Demirkiran F, et al. Prevalence of endometriosis in malignant epithelial ovary tumours. Eur J Obstet Gynaecol Reprod Biol 2003;109:97-101.
23. Riopel MA, Ronnett BM, Kurman RJ. Evaluation of diagnostic criteria and behavior of ovarian intestinal-type mucinous tumors: atypical proliferative (borderline) tumors and intraepithelial, microinvasive, invasive, and metastatic carcinomas. Am J Surg Pathol 1999;23:617-35.
24. Ronnett BM1, Kurman RJ, Zahn CM, Shmookler BM, Jablonski KA, Kass ME, et al. Pseudomyxoma peritonei in women: a clinicopathologic analysis of 30 cases with emphasis on site of origin, prognosis, and relationship to ovarian mucinous tumors of low malignant potential. Hum Pathol, 1995;26:509-24.
25. Prayson RA, Hart WR, Petras RE. Pseudomyxoma peritonei. A clinicopathologic study of 19 cases with emphasis on site of origin and nature of associated ovarian tumors. Am J Surg Pathol 1994;18:591-603.
26. Lee KR, Scully RE. Mucinous tumors of the ovary: a clinicopathologic study of 196 borderline tumors (of intestinal type) and carcinomas, including an evaluation of 11 cases with 'pseudomyxoma peritonei'. Am J Surg Pathol 2000;24:1447-64.
27. Djordjevic B, Stojanovic S, Ljubenovic N, Djordjevic I. Pseudomyxoma peritoeni and mucinous ovarian tumors. Acta Med Median 2008;47:46-8.
28. Seidman J, Kurman R. Ovarian serous borderline tumors: A critical review of the literature with emphasis on prognostic indicators. Hum Pathol 2000;31:539-57.
29. Camatte S, Morice P, Atallah D, Pautier P, Lhommé C, Haie-Meder C, et al. Lymph node disorders and prognostic value of nodal involvement in patients treated for a borderline ovarian tumor: an analysis of a series of 42 lymphadenectomies. J Am Coll Surg 2002;195:332-8..=
30. Bell DA, Weinstock MA, Scully RE. Peritoneal implants of ovarian serous borderline tumors. Histologic features and prognosis. Cancer 1988;62:2212-22.
31. Cadron I, Leunen K, Van Gorp T, Amant F, Neven P, Vergote I. Management of borderline ovarian neoplasms. J Clin Oncol 2007;25:2928-37.
32. Tazelaar HD, Bostwick DG, Ballon SC, Hendrickson MR, Kempson RL. Conservative treatment of borderline ovarian tumors. Obstet Gynecol 1985;66:417-22.
33. Borgfeldt C, Iosif C, Måsbäck A. Fertility-sparing surgery and outcome in fertile women with ovarian borderline tumors and epithelial invasive ovarian cancer. Eur J Obstet Gynecol Reprod Biol 2007;134:110-4.
34. Jones MB. Borderline ovarian tumors: current concepts for prognostic factors and clinical management. Clin Obstet Gynecol 2006;49:517-25.
35. Morice P, Camatte S, Wicart-Poque F, Atallah D, Rouzier R, Pautier P, et al. Results of conservative management of epithelial malignant and borderline ovarian tumours. Hum Reprod Update 2003;9:185-92.