EJGO European Journal of Gynaecological Oncology

Recurrent endometriosis following tibolone hormone replacement therapy after mucinous ovarian carcinoma

B.D. de-la-Noval[1], M.D. Diestro Tejeda[1], L. Yébenes[2], I. Zapardiel[1], A. Hernández Gutiérrez[1], J. De-Santiago García[1]

[1]Gynaecology Oncology Unit, Gynaecology and Obstetrics Department, Hospital Universitario La Paz, Madrid
[2]Pathological Anatomy Department; Hospital Universitario La Paz, Madrid (Spain)

Summary

The aim is to describe an atypical clinical case of endometriosis in a young patient with surgically induced menopause due to an ovarian mucinous carcinoma. *Case Report:* A 34-year old woman with deep endometriosis developed a large mass occupying the whole abdominal cavity, without ascites or carcinomatosis. A decisional laparoscopy and complete surgical staging were performed according to a FIGO Stage IA ovarian mucinous carcinoma. The patient required hormonal replacement therapy with tibolone. A year later, an endometriotic nodule appeared in the bladder, and two years after, endometriosis on the bowel and the vaginal vault without evidence of tumoral relapse also occurred. The patient was referred to the obesity unit and discontinued tibolone, with clinical and radiological stabilization. *Conclusion.* Tibolone should be used with caution in patients with a previous history of endometriosis and it is recommended to avoid hyperestrogenic situations in gynaecological malignancies in hormone-dependent diseases.

Key words: Endometriosis; Epithelial ovarian cancer; Mucinous adenocarcinoma; Obesity; Tibolone.

Introduction

Endometriosis is a common gynecologic disease that usually affects 3–15% of premenopausal women and up to 90% of young women with chronic pelvic pain or infertility [1]. It is considered a precancerous disease, strongly associated with an increased risk of ovarian cancer [1]. Approximately 2.5% of women with endometriosis develop an endometriosis-associated ovarian cancer (EAOC), with 80% in the ovary and 20% in the extra-ovarian sites [2]. The percentage of patients with EAOC among the total of epithelial ovarian cancer (EOC) is 10-30% [3, 4]. Recurrence of endometriosis during menopause is rare, because the absence of estrogenic hormone production should prevent estrogen-dependent endometriosis. Its incidence in postmenopausal women is low and estimated to be 2-4%. It has been suggested that hyperestrogenism situations like obesity and continuous hormonal replacement therapy may promote its appearance.

The aim of this article is to describe an atypical clinical case of recurrent endometriosis in a young patient with surgically induced menopause, and history of mucinous ovarian carcinoma. The role of each of the factors involved is reviewed.

Case Report

A 34-year old woman, nulligravid, and heterozygous mutated BRCA1 carrier, complained of gastrointestinal symptoms and bloating with sudden weight gain for the last two months. The patient had endometriosis for 18 years and had undergone surgery twice (right adnexectomy and left cystectomy) without findings of atypical endometriosis or borderline lesions. There was no history of family tumor aggregation.

On physical examination, the abdomen appeared bulky, occupied by a large tumor, with no signs of ascites or peritoneal irritation. An abdominal ultrasound and a computed tomography (CT) were requested. It is described a well-defined unilocular cystic tumor of 23×33×34 cm (APxTxL) of left adnexal origin, with a solid intracavitary implant in the lower part of the anterior wall of 8×11 cm (APxTxL), with increased Doppler flow. The uterus was enlarged and heterogeneous, and lateralized to the right side of the pelvis. A lymphadenopathy of 12 mm in left common iliac bifurcation was seen. There were no signs of ascites or carcinomatosis in the radiological tests (Figure 1). Ca125 and Ca19.9 tumor markers were increased (127.9 and 61.2 IU/ml, respectively).

The authors proceeded to carry out a decisional laparoscopy observing a large tumor mass occupying the entire abdomen with no tumor spread, and the pelvic area was frozen due to deep endometriosis and many adhesions. Seventeen liters of haemorrhagic fluid were drained laparoscopically from the tumor cavity. A left oophorectomy was performed an with extraction into a sealed bag through the umbilical incision. The mass was analyzed in a deferred way due to its large size and the final histopathological result confirmed an ovarian mucinous adenocarcinoma

Revised manuscript accepted for publication August 29, 2016

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXIX, n. 2, 2018
doi: 10.12892/ejgo3859.2018

7847050 Canada Inc.
www.irog.net

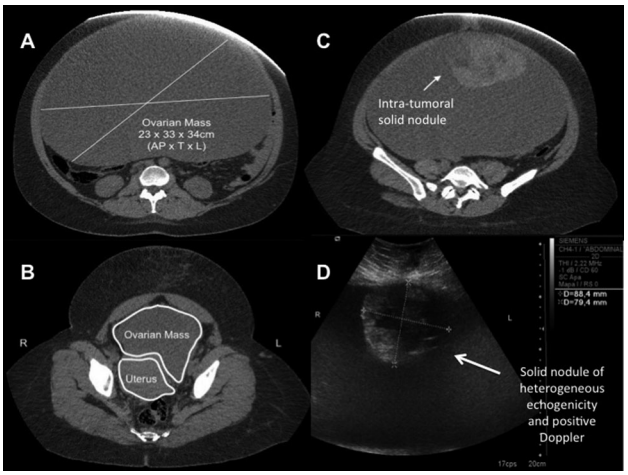

Figure 1. — CT scan: a unilocular cystic tumor of left adnexal origin that occupies the whole abdominal cavity (A). The uterus is lateralized to the right (B), and the tumor contains a solid nodule suspicious for malignancy (C, D).

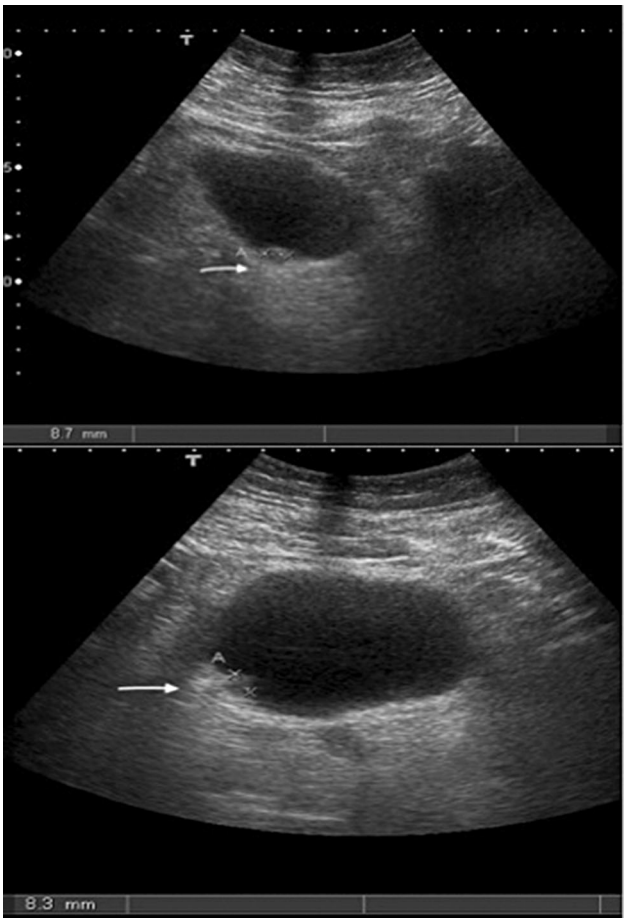

Figure 2. — Abdominal ultrasound: intracavitary 8-mm nodule in the lateral right side of the posterior wall of the bladder.

grade 2 of 26 cm. The authors then proceeded to complete an open staging surgery (hysterectomy, omentectomy, appendectomy, and pelvic and para-aortic lymphadenectomy) with no evidence of residual disease. Final International Federation of Gynecology and Obstetrics (FIGO) was Stage IA (tumor limited to one ovary, with capsule intact, or fallopian tube, no tumor on ovarian or fallopian tube surfaces, and no malignant cells in the ascites or peritoneal washings), and the patient did not require adjuvant therapy.

During follow-up, the patient began treatment with hormonal replacement therapy (HRT), tibolone 2.5 mg daily, due to severe climacteric symptoms. CT control a year after showed an increased bladder thickness. The patient complained of increased urinary frequency and discomfort. An abdominal ultrasound and cystoscopy were performed and found a 10×8-mm intracavitary endometriotic nodule in the posterior right side of the bladder (Figure 2), which was then resected. In the CT and ultrasound control, two years later, new foci of bowel endometriosis and in vaginal vault were found. There were no signs of ascites, peritoneal carcinomatosis or local pelvic relapse, the patient reported non-specific symptoms and tumor markers remained normal. It was decided to discontinue tibolone and the patient was sent to the obesity unit (BMI 42.4 kg/m^2), where she began a weight loss program with clinical improvement. Currently, there are no signs of relapse or progression.

Discussion

Endometriosis is an estrogen-dependent, chronic gynecological disorder. Although it is a benign lesion, it shares several common characteristics with invasive cancer and has an increased risk of gynecological cancer development. Endometriosis is most frequently associated with ovarian endometrioid and clear cell carcinomas. Low-grade serous or mucinous EOC were observed only in 5% and 4% of cases, respectively [3]. A recent study showed that endometriosis is not related with the risk of ovarian mucinous carcinoma, whereas it increased the risk of low-grade ovarian serous carcinoma and did not affect the risk of high-grade ovarian serous carcinoma [5].

The pathophysiological mechanism of ovarian carcinogenesis in endometriosis is related to inflammation, oxidative stress, and hyperestrogenism, that leads to malignant transformation of ectopic endometrium [6]. Also, endometriosis is characterized by genetic instability, like neoplasms. Recent data suggest that mutation of the tumor suppressor gene PTEN, TP53 or ARID1A have a role in the malignant transformation of endometriosis [7].

Atypical endometriosis is considered to be precancerous and strongly associated with EAOC. It seems to represent a transition from benign endometriosis to carcinoma [7]. Although recognition of atypical endometriosis is a pathologic diagnosis, it is rarely mentioned and clinical management remains controversial. There is no evidence that

surgery for endometriosis can reduce the risk of EAOC [3].

The risk and prognosis of ovarian cancer have not been well established in women with endometriosis, authors conclude that the presence of endometriosis in EOC is associated with a better prognosis [1, 3]. However, endometriosis may not affect disease progression (progression-free survival and overall survival were not different) after the onset of ovarian cancer [3].

Recent morphologic, immunohistochemical, and molecular genetic studies have led to a new paradigm for the pathogenesis and origin of EOC. It is based on a dualistic model of carcinogenesis that divides EOC into two categories designated types I and II (Kurman and Shih's classification) [8]. Type I tumors comprise low-grade serous, low-grade endometrioid, clear cell, mucinous carcinomas, and transitional cell (Brenner) tumors. Type I tumors are generally indolent, low-grade carcinoma diagnosed in Stage I, characterized by specific mutations, including KRAS, BRAF, ERBB2, PTEN, ARID1A, CTNNB1 or PIK3-CA, and are relatively genetically stable [8-10]. KRAS mutations occur in up to 75% of primary mucinous carcinomas [9, 11]. These mutations occur early in the evolution of type 1 ovarian tumors and are also observed in borderline tumor and endometriosis [10]. Specific mutations exhibit the continuum of tumor progression through precursor lesions between benign cystic neoplasms, borderline tumors or cystadenomas to carcinomas, as the evolution of colon cancer [9, 12]. Type I tumors rarely harbour TP53 or BRCA mutations [8, 11], therefore it is not reasonable to offer genetic counselling in this group of patients [13]. In the case reported, the genetic test was performed at another center due to epithelial ovarian cancer in a woman younger than 35 years.

Mucinous ovarian carcinomas (MOC) have been the least studied histologic types probably due to their relative low frequency. The origin of MOC is still not well established, although recent data suggest a possible origin from transitional epithelial nests located in para-ovarian locations at the tubo-peritoneal junction [8]. It is a possible option that deep pelvic endometriosis involving these transitional epithelial nests has been the trigger in this patient.

Mucinous tumors are more likely to occur in a younger women. A high proportion is confined to the ovary (FIGO Stage I) and have a good prognosis after surgery. The five-year disease-free survival is 90.8%. Symptoms are usually due to an expansive pelvic mass, which is often very large [14].

MOC is currently classified into two subtypes based on pathologic findings: intestinal type and endocervical or Müllerian type. Intestinal type MOC are much more common [2]. A retrospective review performed by Song *et al.* in 203 patients comparing intestinal-type mucinous ovarian tumors versus endocervical-like reported that the first type is usually a multiloculated cyst without papillary features and higher Ca125 and Ca19.9 levels with low relation to endometriosis in only 1.4% of all cases [2,14]; however, endocervical types are unilocular cysts with papillary projections, and are often associated with endometriosis in 30-53% of cases [2]. Carcinoembryonic antigen (CEA) is the most useful serum tumor marker to identify MOC preoperatively and to follow the progress of a patient with MOC postoperatively. CEA is elevated in 88% of MOCs than in 19% of non-MOCs [11].

The gold standard for the treatment of any suspected ovarian mass includes intact removal of the involved adnexa with intraoperative pathology evaluation. An intraoperative determination of a large tumor is difficult, so a deferred analysis is preferred in order to make decisions with a complete knowledge of the tumor histology. Surgery is the key role in the treatment of mucinous ovarian tumors, the value of adjuvant chemotherapy is unclear. Mucinous ovarian tumors are less sensitive and chemotherapy is not commonly used due to its lower effectiveness [10, 14].

Complete staging surgery includes a total hysterectomy, bilateral salpingo-oophorectomy, peritoneal biopsies, omentectomy, appendectomy, pelvic and para-aortic lymph node dissection up to the left renal veins, and close inspection of the upper and lower gastrointestinal tracts with sampling of any suspicious area [11]. Surgery is usually performed by laparotomy, but minimally invasive surgery is a feasible approach in an experienced team. However, morcellation in the peritoneal cavity is absolutely avoided and it is always necessary to use an intraperitoneal specimen bag [15].

In young women, fertility preservation is an option in early Stages IA, IB G1-G2, and selected cases of IC of MOC, but always after offering the patient comprehensive information regarding the potential risks, with preservation of the normal appearing uterus and contralateral ovary. Fertility sparing surgery most likely includes a lymphadenectomy to exclude more advanced disease [10, 14]. In this case, a conservative attitude was not possible, not only because of the genetic risk, but also because the patient did not want it.

Recurrence of endometriosis during menopause is rare, but hyperestrogenism situation may favour its appearance. Possible theories are residual ovarian functional tissue left in situ [6] or hyperestrogenism secondary to obesity or tibolone sensitization, that may have stimulated further growth of old endometrioid implants [3], such as in the bladder, or new ones, like the vaginal vault and the omentum nodules.

There is not enough evidence to ensure that HRT adversely affects patients treated for ovarian cancer. Furthermore, there is no evidence of a clinical role of hormone receptors in cells of EOC. A hypothesis against HRT is the stimulation of quiescent tumoral epithelial cells, due to hyperestrogenism; no experimental data supports this theory [16, 17].

In postmenopausal women, estrogen is produced mainly

in the skin and adipose tissue. Obese postmenopausal women produced much more endogenous estrogen than non-obese women, which may result in elevated serum estradiol levels. The use of HRT can cause an increased, although undefined, risk of recurrent endometriosis, especially in obese patients [18].

Tibolone is a synthetic anabolic steroid with weak estrogenic, androgenic, and progestagenic activities. It is recommended as a HRT in the management of postmenopausal symptoms [19] and considered safe in women with residual endometriosis [20]. A recent Cochrane review looked at pain and disease recurrence in women with endometriosis who used hormone therapy with tibolone for post-surgical menopause, with no further recurrence of disease [20]. Few studies have analysed the involvement of phytoestrogens on gynecological cancer, but there seems to be a protective effect on ovarian cancer and borderline tumors, slightly lower in ovarian mucinous carcinoma. Tibolone does not affect disease progression of ovarian cancer [21, 22].

According to the literature published, this is the second case of recurrent endometriosis with tibolone and the first in a postmenopausal young woman. Sundar *et al.* reported the first case of an endometriosis recurrence with tibolone in a 52-year-old woman [19].

In conclusion, the authors suggest that tibolone should be used with caution in patients with a history of endometriosis and an alternative to a non-hormonal treatment should be recommended in this situation. Moreover, special care must be taken to avoid situations of hyperestrogenism, especially in obese young patients. Finally, more and larger studies are needed to clarify the molecular mechanisms implied in malignant transformation of endometriosis and recurrence.

References

[1] Kim H.S., Kim T.H., Chung H.H., Song Y.S.: "Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis". *BJC*, 2014, *11*, 1878.

[2] Myung Yeo D., Eun Rha S., Young Byun J., Lee A., Kim M.R.: "MR imaging findings of extraovarian endocervical mucinous borderline tumors arising from pelvic endometriosis". *Korean J. Radiol.*, 2013, *14*, 918.

[3] Acién P., Velasco I., Acién M., Capello C., Vela P.: "Epithelial ovarian cancers and endometriosis". *Gynecol. Obstet. Invest.*, 2015, *79*, 126.

[4] Somigliana E., Vigano P., Parazzini F., Stoppelli S., Giambattista E., Vercellini P.: "Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence". *Gynecol. Oncol.*, 2006, *101*, 331.

[5] Pearce C.L., Ovarian Cancer Association Consortium: "Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies". *Lancet Oncol.*, 2012, *13*, 385.

[6] Attar E., Bulun S.E.: "Aromatase and other steroidogenic genes in endometriosis: translational aspects". *Hum. Reprod. Update*, 2006, *12*, 49.

[7] Munksgaard P.S., Blaakaer J.: "The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations". *Gynecol. Oncol.*, 2012, *124*, 164.

[8] Kurman R.J., Shih Ie M.: "Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—shifting the paradigm". *Hum. Pathol.*, 2011, *42*, 918.

[9] Cho K.R., Shih Ie M.: "Ovarian cancer". *Ann. Rev. Pathol.*, 2009, *4*, 287.

[10] Ledermann J.A., Raja F.A., Fotopoulou C., Gonzalez-Martin A., Colombo N., Sessa C., on behalf of the ESMO Guidelines Working Group: "Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Ann. Oncol.*, 2013, *24*, vi24.

[11] Brown J., Frumovitz M.: "Mucinous tumors of the ovary: current thoughts on diagnosis and management". *Curr. Oncol. Rep.*, 2014, *16*, 389.

[12] González Martín A., Redondo A., Jurado M., De Juan A., Romero I., Bover I., *et al.*: "GEICO (Spanish Group for Investigation on Ovarian Cancer) treatment guidelines in ovarian cancer 2012". *Clin. Transl. Oncol.*, 2013, *15*, 509.

[13] Song T., Choi C.H., Lee Y.Y., Kim T.J., Lee J.W., Sung C.O., *et al.*: "Endocervical-like versus intestinal-type mucinous borderline ovarian tumors: a large retrospective series focusing on the clinicopathologic characteristics". *Gynecol. Obstet. Invest.*, 2013, *76*, 241.

[14] Ledermann J.A., Luvero D., Shafer A., O'Connor D., Mangili G., Friedlander M., *et al.*: "Gynecologic Cancer Inter-Group (GCIG) Consensus Review for Mucinous Ovarian Carcinoma". *Int. J. Gynecol. Cancer*, 2014, *24*, S14.

[15] Pal T., Permuth-Wey J., Betts J.A., Krischer J.P., Fiorica J., Arango H., *et al.*: "BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases". *Cancer*, 2005, *104*, 2807.

[16] Wen Y., Huang H., Huang H., Wu M., Shen K., Pan L.: "The safety of postoperative hormone replacement therapy in EOC patients in China". *Climateric*, 2013, *16*, 673.

[17] Eeles R.A., Morden J.P., Gore M., Mansi J., Glees J., Wenczl M., *et al.*: "Adjuvant hormone therapy may improve survival in EOC: results of the AHT Randomized trial". *J. Clin. Oncol.*, 2015, *33*, 4138.

[18] Jeon D.S., Kim T.H., Lee H.H. Byun D.W.: "Endometriosis in a postmenopausal woman on hormonal replacement therapy". *J. Menopausal Med.*, 2013, *19*, 151.

[19] Sundar S.S., Gornall R.J., Kerr-Wilson R., Swingler G.R., Kinder R.B., McCarthy K.: "A case report of recurrent endometriosis following Tibolone hormone replacement therapy". *J. Obstet. Gynaecol.*, 2007, *27*, 433.

[20] Roberts A.L., Lashen H.: "Tibolone as a hormone replacement in women with endometriosis after bilateral oophorectomy". *Int. J. Gynaecol. Obstet.*, 2010, *111*, 183.

[21] Qu X.L., Fang Y., Zhang M., Zhang Y.Z.: "Phytoestrogen intake and risk of ovarian cancer: a meta-analysis of 10 observational studies". *Asian Pac. J. Cancer Prev.*, 2014, *15*, 9085.

[22] Neill A.S., Ibiebele T.I., Lahmann P.H., Hughes M.C., Nagle C.M., Webb P.M., *et al.*: "Dietary phyto-oestrogens and the risk of ovarian and endometrial cancers: findings from two Australian case-control studies". *Br. J. Nutr.*, 2014, *111*, 1430.

Corresponding Author:
B. DÍAZ-DE-LA-NOVAL, M.D.
Paseo de la Castellana, 261
28046 Madrid (Spain)
e-mail: begodelanoval@gmail.com