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A rare case of primary clear-cell adenocarcinoma of the bladder arising from bladder endometriosis

V. Loizzi[1,2], G. Cormio[1,2], L. Leone[1], M. Falagario[1], S. Longo[3], L. Resta[4] & L. Selvaggi[1]

[1]*Department of Obstetrics, Gynecology and Neonatology, University of Bari, Bari, Italy,* [2]*Division of Gynecology Oncology, IRCCS Bari, University of Bari, Bari, Italy,* [3]*Department of Internal Medicine, University of Bari, Bari, Italy, and* [4]*Department of Pathology, University of Bari, Bari, Italy*

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Correspondence: Vera Loizzi, M.D., Aggregate Professor, Department of Obstetrics, Gynecology and Neonatology, University of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy. E-mail: vloizzi@tiscali.it

Introduction

Endometriosis is a common benign gynaecological condition affecting 5–15% of women in their reproductive age and only 3–5% of post-menopausal women, in which endometrial tissue grows outside uterine cavity, leading to pelvic pain and infertility (Vignali et al. 2002). Even if endometriosis is a benign condition, it can spread to other organs by invading and disrupting their tissues, sharing these characteristics with invasive cancers. It is well known that ovarian cancer, especially endometrioid and clear cell types, can be the result of a malignant transformation of foci of endometriosis (Bacci et al. 2009), but even if extra-gonadic endometriosis malignant transformation was considered an exceptional event, recent studies suggested that it can also be associated with other kinds of cancer (Ness 2003; Olson et al. 2002; Scully et al. 1966).

Primary clear-cell bladder adenocarcinoma is a very rare tumour, affecting mostly women; it can be associated with bladder endometriosis suggesting a mullerian origin of this rare cancer (Lu et al. 2012).

Case presentation

A 38-year-old Caucasian woman was admitted in our department for pelvic pain, uterine fibroids and infertility. She presented with microscopic haematuria, dysuria and moderate pelvic pain that started approximately before two months.

Before 3 years the patient underwent a laparotomy with bilateral excision of endometriomas and myomectomy.

The physical examination revealed only mild tenderness in the pubic region, but no masses were palpable during transvaginal examination. Serum level of CA125 was increased (45.5 U/ml, normal range: 0–35 U/ml), while other tumour markers (CA19.9, CA15.3, CEA and AFP) were normal. Transvaginal ultrasound scans showed an irregular, solid, 7-cm large mass, possibly growing from the posterior wall of the bladder. The patient underwent a surgery with a laparotomic approach. An extended pelvic disease was observed. Only uterine fundus was visible because bladder was completely adherent to its anterior wall, and posteriorly adnexa were fixed to posterior uterine wall. An approximately 8-cm mass involving the whole bladder vault was evaluated. A partial cystectomy with removal of left ovarian cyst was performed. The final pathology report revealed a surrounding endometriosis zone in which we observed a tumour involving the bladder wall with mucosal saving (Figure 1). This tumour is composed of an aggregate of glandular structures with lining monofilament epithelial that in some areas appear flattened or cubical, whereas in others it is composed of micropapillary protrusions showing an axis more often hyaline and prominent vesicular nuclei on the epithelium and a large nucleolus. There were sporadic calcified concretions such as psammoma bodies. The periodic acid–Schiff reaction with diastase showed occasional presence of intracytoplasmic glycogen. According to Sampson's criteria, diagnosis of clear-cell adenocarcinoma (CCA) of the bladder arisen from bladder endometriosis was made. The absence of ovarian and endometrial involvement leads us to believe that neoplasm should be a primary tumour in the bladder wall.

The patient underwent 4 cycles of chemotherapy with paclitaxel, cisplatin and epirubicin (TEP). Afterwards a laparotomy with bilateral pelvic lymphadenectomy, radical Piver type II hysterectomy and bilateral salpingo-oophorectomy was performed. The pathology report revealed the presence of CCA in the pelvic lymph nodes, uterine serosa and ovaries. Other two cycles of TEP and external pelvic radiotherapy, with a total dose of 4500 cGy, were then given to the patient.

The patient started follow-up visits every two months. Five months after radiotherapy she underwent a computerised tomography scan of the abdomen, which revealed a 4-cm mass in the liver and a second-line chemotherapy with gemcitabine was given. A positron emission tomography after completion of the third cycle of chemotherapy with gemcitabine showed the presence of new lesions into the liver and an elevation of CA125 level at 458 U/ml was also observed. Thus the patient received another line of chemotherapy with topotecan, interrupted after three cycles due to progressive disease from the evidence of peritoneal metastases at the tomography scan of the abdomen and pelvis and a new increase in CA125 level to 1482 U/ml. She interrupted the medical treatment and an ileostomy due to bowel occlusion was lately performed. The patient died of progressive disease three months later.

Discussion

The most frequent sites of implantation of ectopic endometrium are ovaries, Douglas pouch, and broad and uterosacral ligaments (Schwartzwald et al. 1992). The frequency of urinary tract involvement is a rare event and was first reported by Judd in 1921; its incidence is thought to be around 1%, and 84% of all cases involve the bladder (Shook and Nyberg 1988).

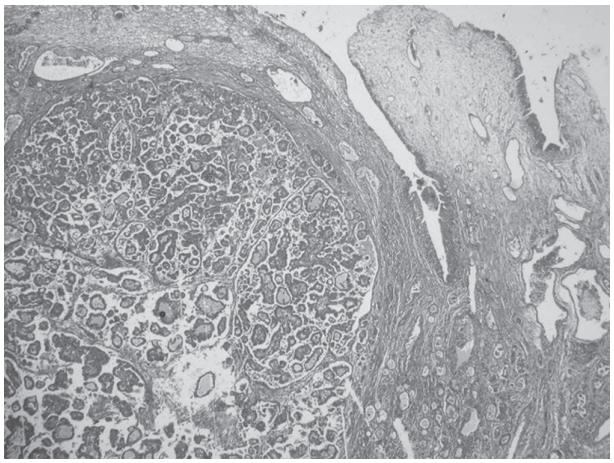

Figure 1. Pathological figure revealed a surrounding endometriosis area in which we observed a tumour involving the bladder wall with mucosal saving.

The diagnosis of bladder endometriosis can be quite difficult because the symptoms mostly described are not specific (pelvic pain, dysuria and sometimes haematuria); moreover, physical examination does not reveal any specific sign; this difficulty often results in a delay of diagnosis and in significant spread of the disease.

Pelvic ultrasound scans can be useful; foci of endometriosis look like small hyperechoic vegetations protruding in the bladder full of urine or like anechoic areas protruding from the bladder dome and posterior wall; magnetic resonance imaging can show the presence of multiple haemorrhage cystic lesions and has a diagnostic accuracy of about 98% (Maccagnano et al. 2012; Togashi et al. 1991). Cystoscopy may be helpful only when it reveals the presence of typical bluish nodules that usually change during menstrual period; laparoscopy gives a direct visualisation of the disease (Fedele et al. 1997).

When bladder endometriosis is suspected a careful differential diagnosis must be done with other benign and malignant diseases such as bladder carcinoma, leiomyomas, angiomas, amyloidosis, glandular cystitis, adenoma and a histological examination should confirm the diagnosis.

In 1925 Sampson first suggested criteria still in use to identify malignant tumours arising from endometriosis: a) clear evidence of endometriosis close to the tumour; b) the carcinoma must be seen to arise in endometriosis, and not to invade it from some other sources; and c) presence of tissue resembling endometrial stroma surrounding glands (Sampson 1925). Scott later added the histologically proven transformation of benign endometriosis into cancer as a new additional criterion (Scott 1953). The carcinoma is supposed to arise from endometriosis through phenomenon where typical endometriosis may change into severe atypia with or without hyperplasia and then into carcinoma.

To support the idea that malignant transformation of endometriosis in very rare, there is evidence that only few reports have fulfilled the application of all these criteria (LaGrenade and Silverberg 1988; Prefumo et al. 2002).

The prevalence of ovarian cancer arising in patients who underwent surgery for endometriosis has been calculated by some large retrospective series. Mostoufizadeh and Scully reported 8 cancers in 950 cases (0.8%) of ovarian endometriosis (LaGrenade and Silverberg 1988), while the prevalence of extra-ovarian cancer associated with endometriosis is not well studied. Heaps et al. reported 44 cases of malignancies arising from extra-gonadic endometriosis, which were endometrioid cell types in 66% of cases, sarcoma in 25% and only in two cases a CCA (5%). Mostly of the endometrioid cell types arose in the pelvis, the rectovaginal septum and the colon–rectum (Heaps et al. 1990). Transitional cell or urothelial carcinoma of the bladder accounts for 95% of malignant bladder tumours. The other 5% can be classified as epithelial or non-epithelial. Epithelial tumours include squamous cell carcinoma, adenocarcinoma and small cell/neuroendocrine carcinoma. Primary adenocarcinoma can be classified into different cell types such as mucinous, colloid, papillary, signet ring and CCA (Zaghloul et al. 2007). CCA is diagnosed by the presence of histological specimens of clear cells with significant pleomorphism, necrotic foci and high levels of mitotic activity, while the papillary tumour component shows characteristic hyaline stroma and monostratification of nuclei (Young and Scully 1984).

CCA mostly occurs in women (3:2 predominance) with mean age of about 60 years. Bladder CCA is a very rare disease, only one case (out of 232 cases) was observed in the four largest series of bladder carcinomas present in literature (Anderstrom et al. 1983; Grignon et al. 1991; Mostofi et al. 1955; Thomas et al. 1971). The majority of CCAs of the bladder are located in the neck of the bladder or anterior wall (Kosem and Sengul 2005). The term "clear-cell carcinoma" was introduced because the histological appearance is similar to that of clear-cell carcinoma of the female genital tract of mullerian origin (Young and Scully 1985; al-Izzi et al. 1989; Balat et al. 1996; Chor et al. 1993; Mai et al. 2000). Oliva et al. published a series of 10 patients with clear-cell carcinoma associated with bladder endometriosis, who presented with an increased serum level of CA125, which is usually considered a marker of mullerian origins, although its specificity is not high (Oliva et al. 2002; Drew et al. 1996; Koelma et al. 1987).

The differential diagnosis of CCA of the lower urinary tracts includes other carcinoma, metastatic disease and benign histologically similar tumours such as adenoma. Bladder metastases of primary CCA of the female genitalia or the kidney, extremely rare, must also be excluded.

The treatment of CCAs of the bladder is not clear. Most patients are treated with radical surgery, since invasion of the muscular wall of the bladder is almost always present. However, different surgical approaches have been proposed in the last years. Laparoscopy as well as robotic surgery have gained momentum as a minimally invasive alternative to open surgery, especially as efforts are underway to reduce morbidity due to open surgery (Bogani et al. 2014; Novara et al. 2011). Partial cystectomy, therefore, has been associated with poor outcomes (Manunta et al. 2005). Adjuvant radiotherapy is also usually administrated, while adjuvant chemotherapy mostly with cisplatin, doxorubicin and 5-fluorouracil has been reported to have a variable success (Kurosaka et al. 2005). Multidrug regimens are usually reserved for unresectable cases without clear data on tumour response.

The case presented here is a rare case of malignant transformation of bladder endometriosis into CCA. This case underlines the presence of a direct link between endometriosis and CCA, as is for CCA of the female genital tract; when the ultrasound or magnetic resonance scan is suspicious for bladder cancer in a patient with bladder involvement of endometriosis, a careful histological diagnosis must be done.

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