Uterine tumors resembling ovarian sex cord tumors. A case report

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Summary

Uterine tumors resembling ovarian sex cord tumors (UTROSCT) are rare, usually benign, polypoid or nodular neoplasms which generally arise in the fourth to sixth decade of life. We report a case of a 74-year-old woman who presented with vaginal bleeding and remarkable uterine enlargement. Abdominal hysterectomy with bilateral salpingo-oophorectomy was performed and a diagnosis of UTROSCT was made. Immunohistochemistry is mandatory for a correct diagnosis and a panel of at least two markers of sex cord differentiation is recommended. Differential diagnoses include leiomyosarcoma, UTROSCT and ESTSCLE, mixed müllerian tumor and metastatic ovarian sex cord tumor.

Key words: UTROSCT; Ovarian sex cord tumors; Inhibitin; Calretinin.

Introduction

Uterine tumors resembling ovarian sex cord tumors (UTROSCT) are very rare neoplasms, first described in 1976 by Clement and Scully [1]. To date, only 77 cases have been reported in the literature. Although UTROSCT are usually benign, a case with metastasis was described by Biermman *et al*. in 2008 [2] thus, at present the definition of tumor with uncertain behavior is more accepted.

Frequently, UTROSCT are polypoid or nodular masses located in the uterine fundus. They usually occur in reproductive age, although some cases arise in postmenopause. These tumors are divided into two groups based on the relative proportion of sex cord-like elements and endometrial stromal cells: endometrial stromal tumors with sex-cord-like elements (ESTSCLE; Group I), characterized by sex-cord-like areas in a leiomyomatous background; uterine tumors resembling ovarian sex cord tumors (UTROSCT; Group II), mainly or exclusively composed of cells with a proliferative pattern resembling ovarian sex-cord tumors. Group II tumors show a benign biological behaviour, whereas Group I tumors stand out due to a high risk of recurrence and metastasis [3].

Clinically, abnormal vaginal bleeding is the most common presenting symptom, though these tumors occasionally show hormone-secreting activity [4]. In most cases the diagnosis is incidental, following immunohistochemical and ultrastructural studies on surgical specimens. A total abdominal hysterectomy with bilateral salpingo-oophorectomy or a simple hysterectomy seems to be the gold-standard treatment, even though successful medical treatment with anastrazole has been reported [5]. In young patients fertility-sparing surgery with a close long-term follow-up is acceptable [6-8].

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Case Report

A 74-year-old caucasian woman presented at the Department of Obstetrics and Gynecology of San Salvatore Hospital (University of L'Aquila, Italy) with postmenopausal vaginal bleeding. On bimanual examination a hard mass occupying all the pelvic cavity and extending as far as 1 cm beyond the transversal umbilical line was detected. Pelvic ultrasound (US) and computed tomography (CT) scan showed an enlarged uterus with a 16 x 12 cm fundic, dishomogenous, ill-defined mass. Serous tumoural markers (CA 15-3; CA 19-9; CA-125) were negative. A standard total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed.

The uterus weighed 835 g and was deformed by a nodular intramural lesion of 17 cm in diameter. It was fixed in 10% buffered formalin over a 48-hour period and processed for routine light-microscopic examination. Specimens were embed-

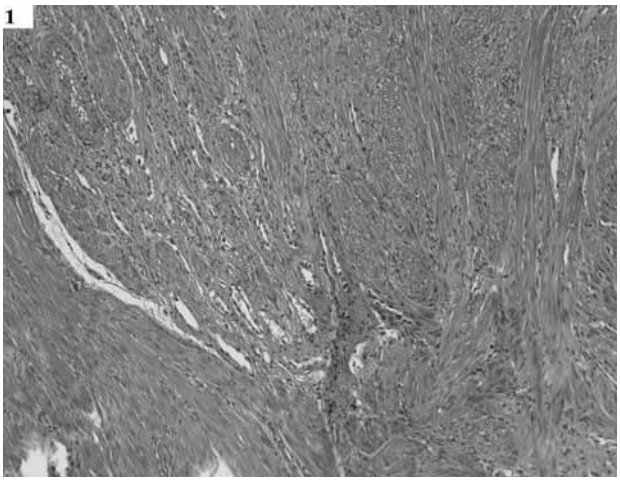

Figure 1. — Histological features of the tumor: sweeping and intersecting fascicles of smooth muscle cells surrounding diffuse proliferation of tubular and gland-like structures, lined by plump cells with indistinct cytoplasm (20 x magnification, H&E).

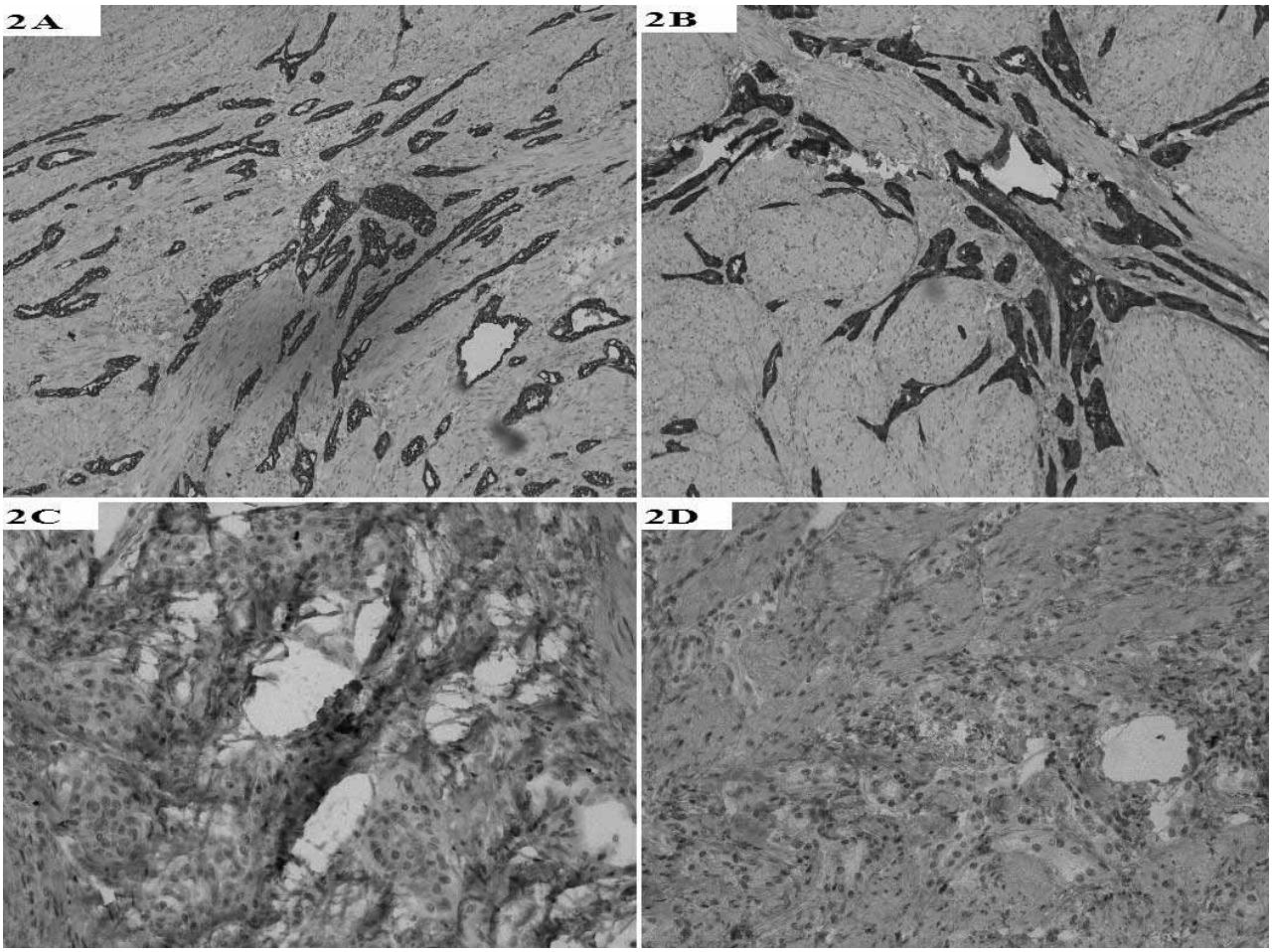

Figure 2. — Immunohistochemical positive stainings: cytokeratin AE1/AE3 postitivity of the gland-like structures (20 x magnification) (2A); calretinin postitivity of the gland-like structures (20 x magnification) (2B); CD99 postitivity of the gland-like structures (40 x magnification) (2C); alpha-inhibin postitivity of the gland-like structures (40 x magnification) (2D).

ded in paraffin, and 4-micrometer-thick sections were cut and stained with hematoxylin-eosin, and reviewed by three pathologists. Thus, histopathological and clinical findings were correlated. On histologic examination the tumor was composed of sweeping and intersecting fascicles of smooth muscle cells, surrounding a diffuse proliferation of tubular and gland-like structures, lined by plump cells with indistinct cytoplasm. Neither necrosis, nuclear pleomorphism or mitoses were observed. No lymphatic or vascular invasion was noted.

Immunohistochemistry was performed with the avidin-biotin-peroxidase complex technique. Heat-induced antigen retrieval was conducted by immersion of the sections in sodium citrate buffer (0.01M sodium-citrate monohydrate, pH 6.0). Sections previously formalin-fixed and paraffin-embedded were stained for calretinin, CD10, CD99, inhibin, actin, CAM 5.2, and estrogen receptors. The results were divided in negative, focally positive, positive and strongly positive. The tumor cells stained strongly positive for CD99, calretinin, CAM 5.2, estrogen receptors and weakly for inhibin; no reaction for actin or CD10 was observed.

Finally, a diagnosis of uterine tumor resembling ovarian sex cord tumors (UTROSCT) was made.

Eight months after the surgical procedure the patient is healthy and without recurrence.

Discussion

Morphologic and immunohistochemical findings suggest that UTROSCT arise from pluripotential uterine mesenchymal cells, which mainly differentiate into sex cord cells. Focal smooth muscle and endometrial stromal cell differentiation can also occur [3]. Because of the difficulties in recognising these structures on hematoxylin-eosin stain, immunohistochemistry is necessary for a correct diagnosis [9].

In the present case, several differential diagnoses had to be considered, such as any kind of polypoid lesion clinically, as well as leiomyosarcoma, UTROSCT and ESTSCLE, mixed müllerian tumor and metastatic ovarian sex cord tumor histopathologically [10, 11]. All UTROSCT stained positive for at least two sex cord differentiation markers, often with co-expression of cytokeratin, CD10, vimentin, estrogen receptor and progesterone receptor; desmin immunoreactivity, if present, is restricted to smooth muscle areas [3]. Inhibin is the most specific marker for these cells [12], even though some studies have shown that calretinin may be more sensitive

than inhibin, thus being useful in inhibin-negative ovarian sex cord stromal tumors [13]. However, calretinin is less specific than inhibin: in a study by Movahedi *et al*., they demonstrated positivity in approximately one-quarter of ovarian surface epithelial carcinomas tested, compared with only 2% showing inhibin positivity [13]. Inhibin is a peptide hormone normally produced by ovarian granulosa cells, that inhibits FSH production and GnRH release. The mechanism of action of inhibin is still unknown, but may involve competing with activin for binding to activin receptors and/or binding to inhibin-specific receptors [14].

Recently, Pusiol *et al*. identified a new pathologic entity, defined as "uterine leiomyoma with tubules". This lesion is characterized by sweeping and intersecting fascicles of smooth muscle cells surrounding a diffuse proliferation of tubular and gland-like structures, lined by plump cells with indistinct cytoplasm. The "uterine leiomyoma with tubules" shows UTROSCT-like histological features, but different immunohistochemical stainings. Thus, if no positivity for at least two sex cord differentiation markers is observed, a diagnosis of "leiomyoma with tubules" should be made [15].

Generally, UTROSCT show benign histological features (i.e., well-circumscribed borders, absence of vascular invasion) and a benign biological behaviour. Rarely, are infiltrative borders and focal vascular invasion [3] observed, usually in association with a malignant biological behavior [2].

Risk factors for this lesion are still unknown. Cases of UTROSCT arising in a patient with Mazabraud's syndrome [16] and, more frequently, in patients in treatment with tamoxifen [17, 11] have been reported. Since some endometrial stromal sarcomas with low malignant potential have been described in patients treated with tamoxifen, we could hypothesize that this neoplasm would occur more frequently in the future [18].

Conclusions

Since UTROSCT may be confused with several uterine adenocarcinomas or metastasis, immunohistochemistry is mandatory for a correct and accurate diagnosis with the aim of avoiding overtreatment [9]. Thus, we suggest the use of an appropriate immunohistochemical panel to facilitate this diagnosis, including at least two sex cord differentiation markers (calretinin and one of either melan A, CD99, or inhibin) [3]. Immunohistochemical stains may show positivity for vimentin, cytokeratin, actin and desmin in variable proportions. Inhibin is a more specific marker for these cells [12]. Further features, such as including necrosis, vascular invasion, mitotic index and tumour borders are relevant for the outcome of patients.

References

[1] Clement P.B., Scully R.E.: "Uterine tumors resembling ovarian sex-cord tumors. A clinicopathologic analysis of fourteen cases". *Am. J. Clin. Pathol*., 1976, *66,* 512.
[2] Biermann K., Heukamp L.C., Büttner R., Zhou H.: "Uterine tumor resembling an ovarian sex cord tumor associated with metastasis". *Int. J. Gynecol. Pathol*., 2008, *27,* 58.
[3] Irving J.A., Carinelli S., Prat J.: "Uterine tumors resembling ovarian sex cord tumors are polyphenotypic neoplasms with true sex cord differentiation". *Mod. Pathol*., 2006, *19,* 17.
[4] Organization Classification of Tumours. Pathology and Genetics of Tumours of female reproductive system. Lyon, IARC Press, 2002.
[5] Blinman P., Tattersall M.H.: "A case of uterine tumor resembling ovarian sex cord tumor responding to second-line, single agent anastrazole". *Int. Med. J.,* 2009, *39,* 617.
[6] Garuti G., Gonfiantini C., Mirra M., Galli C., Luerti M.: "Uterine tumor resembling ovarian sex cord tumors treted by resectoscopic surgery". *J. Minim Invasive Gynecol.,* 2009, *16,* 236.
[7] Berretta R., Patrelli T.S., Fadda G.M., Merisio C., Gramellini D., Nardelli G.B.: "Uterine tumors resembling an ovarian sex cord tumors: a case report of conservative management in young women". *Int. J. Gynecol. Cancer,* 2009, *19,* 808.
[8] Hillard J.B., Malpica A., Ramirez P.T.: "Conservative management of a uterine tuomur resembling an ovarian sex cordal stromal tumour". *Gynecol. Oncol*., 2004, *92*, 347.
[9] Nogales F.F., Stolnicu S., Harilal K.R., Mooney E., García-Galvis O.F.: "Retiform uterine tumours resembling ovarian sex cord tumours. A comparative immunohistochemical study with retiform structures of the female genital tract". *Histopathology,* 2009, *54,* 471.
[10] Suzuki C., Matsumoto T., Fukunaga M., Itoga T., Furugen Y., Kurosaki Y. *et al*.: "Uterine tumors resembling ovarian sex-cord tumors producing parathyroid hormone-related protein of the uterine cervix". *Pathol. Int*., 2002, *52*, 164.
[11] Oztekin O., Soylu F., Yigit S., Sarica E.: "Uterine tumor resembling ovarian sex cord tumors in a patient using tamoxifen: report of a case and review of literature". *Int. J. Gynecol Cancer,* 2006, *16,* 1694.
[12] Kuruvila S., Samarasinghe D., Thomas S.: "Uterine neoplasm resembling an ovarian sex cord tumour". *Saudi Med. J.,* 2003, *24,* 221.
[13] Movahedi-Lankarani S., Kurman R.J.: "Calretinin, a more sensitive but less specific marker than -inhibin for ovarian sex cord-stromal neoplasms. An immunohistochemical study of 215 cases". *Am. J. Surg. Pathol*., 2002, *26*, 1477.
[14] Chen Y.G., Wang Q., Lin S.L., Chang C.D., Chuang J., Chung J. *et al*.: "Activin signaling and its role in regulation of cell proliferation, apoptosis, and carcinogenesis". *Exp. Biol. Med. (Maywood),* 2006, *231* , 534.
[15] Pusiol T., Parolari A.M., Piscioli F.: "Uterine leiomyoma with tubules". *Int. Semin. Surg. Oncol*., 2008, *5*, 15.
[16] Calisir C., Inan U., Yavas U.S., Isiksoy S., Kaya T.: "Mazabraud's syndrome coexisting with a uterine tumor resembling an ovarian sex cord tumor (UTROSCT): a case report". *Korean J. Radiol*., 2007, *8,* 438.
[17] Stolnicu S., Balachandran K., Aleykutty M.A., Loghin A., Preda O., Goez E. *et al*.: "Uterine adenosarcomas overgrown by sex-cord-like tumour: report of two cases". *J. Clin. Pathol*., 2009, *62,* 942.
[18] Kunz J., Friedrich T.: "Uterine tumor resembling ovarian sex cord tumor: case report and review of the literature". *Praxis* (Bern 1994), 2007, *96,* 1177.

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