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Tamoxifen related Uterine Tumor Resembling Ovarian Sex Cord Tumor (UTROSCT): A case report and literature review of this possible association

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ABSTRACT

It is well known that a large number of patients treated with Tamoxifen develops endometrial pathologies ranging from benign endometrial polyps and hyperplasia to adenocarcinomas, carcinosarcomas and adenosarcomas. UTROSCT (Uterine Tumor Resembling Ovarian Sex Cord Tumor) is defined as a mesenchymal tumors of the uterine corpus that morphologically resembles ovarian sex cord tumors, without recognizable endometrial stroma. To date only 4 cases have been reported in patients treated with tamoxifen. In this article, we describe an additional case occurring in a 62-years-old patient undergoing 3 years of Tamoxifen therapy for bilateral breast carcinoma. The present work represents a further evidence of the possible association between Tamoxifen therapy and UTROSCT. A comprehensive literature review on this topic is also provided.

1. Introduction

In 1976, Clement and Scully [1] reported a series of rare tumors of the uterus resembling ovarian sex cord tumors that they divided into 2 groups: group 1 was represented by endometrial stromal tumors that showed focal epithelial-like differentiation of the type seen in ovarian sex cord tumors, while group 2 tumors were uterine mural masses with a predominant histological appearance of sex cord elements. According to the current World Health Organization (WHO) classification [2] Group I tumors are conventionally called endometrial stromal tumors with sex cord-like elements (ESTSCLE) with a particular propensity to recur or metastasize. On the other hand, Uterine Tumor Resembling Ovarian Sex Cord Tumor (UTROSCT) is the name used now for group 2 tumors, considered as a miscellaneous category, without any distinction between the different prognostic courses. The majority of group II UTROSCT behaves in a benign fashion, whereas group I behaves similarly to low-grade endometrial stromal sarcoma [3]. Although immunohistochemical studies did not delineate differential staining patterns of the sex cord-like elements between group I and II tumors, molecular investigations have confirmed the absence of JAZF1-SUZ12 gene fusion, to support the histopathological diagnosis of UTROSCT rather than ESTSCLE [4].

Tamoxifen is a nonsteroidal compound useful as adjuvant therapy in the treatment of breast cancer. However, a large number of patients treated with Tamoxifen develops endometrial pathologies ranging from benign endometrial polyps and hyperplasia to adenocarcinomas, carcinosarcomas and adenosarcomas [5].

Regarding UTROSCTs, to date only 4 cases have been reported in patients treated with tamoxifen [6–9]. In this article, we describe a new case in a 62-years-old patient undergoing 3 years of Tamoxifen therapy for bilateral breast carcinoma.

2. Materials and methods

The hysterectomy surgical samples were submitted for histological examination in neutral-buffered 10% formalin. They were dehydrated according to the standard techniques, embedded in paraffin, cut to 5-µm, and stained with haematoxylin and eosin. Immunohistochemical studies were performed with the labeled streptavidin–biotin peroxidase detection system using the Ventana automated immunostainer

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Table 1
List of immunohistochemical antibodies used in the study.

Antigen	Primary antibody	Clone	Manufacturer	Primary antiboby incubation	Time and temperature
Vimentin	Mouse monoclonal antibody	V9	Novocastra	15'	15', 37 °C
Alpha smooth muscle actin	Mouse monoclonal antibody	αsm-1	Novocastra	15'	15', 37 °C
EMA	Mouse monoclonal antibody	GP1.4	Novocastra	15'	15', 37 °C
Estrogen Receptor	Rabbit monoclonal antibody	SP1	Ventana	16'	8', 95 °C
Progesteron Reseptors	Rabbit monoclonal antibody	1.00E + 02	Ventana	16'	8', 95 °C
Inhibin	Mouse monoclonal antibody	R1	Novocastra	15'	15', 37 °C
Calretinin	Mouse monoclonal antibody	566	Novocastra	15'	30', 37 °C
CD99	Mouse monoclonal antibody	PCB1	Novocastra	15'	15', 37 °C
Desmin	Mouse monoclonal antibody	DE-R-11	Novocastra	15'	15', 37 °C
Caldesmon	Mouse monoclonal antibody	h-CD	DAKO	15'	15',37 °C
Cytokeratin 8-18	Mouse monoclonal antibody	5D3	Novocastra	15'	15', 37 °C
Cytokeratin AE1-AE3	Mouse monoclonal antibody	AE1-AE3	Novocastra	15'	15', 37 °C
CD56	Mouse monoclonal antibody	504	Novocastra	15'	20', 37 °C
Melan-A	Mouse monoclonal antibody	A103	Novocastra	20'	8', 95 °C
CD10	Mouse monoclonal antibody	56C6	Novocastra	15'	15', 37 °C
HMB45	Mouse monoclonal antibody	HMB-45	Novocastra	16'	15', 37 °C
S100	Rabbit Polyclonal antibody	S100	Dako	60'	60', 25 °C

(Ventana Medical Systems, Tucson, AZ). The following antibodies were applied: vimentin, alpha-smooth muscle actin, desmin, caldesmon, wide spectrum cytokeratins (8–18, AE1-AE3), epithelial membrane antigen (EMA), HMB45, S100 protein, Melan-A, inhibin, calretinin CD99, CD56 and CD10 (Table 1).

3. Case report

A 62-years-old woman, with a history of symptomatic multiple uterine leiomyomas, underwent clinical attention for a suspicious nodule of the right breast in 2009. A quadrantectomy was performed, with sentinel lymph node. The diagnosis was moderately differentiated invasive ductal carcinoma N.O.S with sentinel lymph node negative for metastasis. In 2010 the patient performed a controlateral quadrantectomy for another invasive ductal carcinoma of the breast N.O.S. In December of the same year the patient started the therapy with Tamoxifen. Due to non-remission of symptoms associated with uterine leiomyomas, the patient underwent hystero-annessiectomy in April of 2014.

The gross examination showed a uterus weighing 320 g, with smooth and atrophic endometrium. The myometrium showed multiple intramural nodules with regular margins, whose diameter ranged between 1 to 7 cm. Nodules with smaller dimension showed macroscopic and microscopic features of leiomyomas. The largest of these nodules (7 cm in greatest dimension) instead revealed a solid and whitish cut surface with multiple yellowish areas in its context, with a diameter varying from a few millimeters to 1.5 cm. The microscopic examination of these nodule showed a neoplastic proliferation of epithelioid cells, with both pushing and pseudo-infiltrative margins (Fig. 1A and B), surrounding by and intermixed with bundles of smooth muscle cells without atypia. The tumor was prevalently organized in anastomosing cords of 1 to 2 cells wide and in a diffuse pattern (Fig. 1C and D). Tubule formation and broad trabeculae were also observed (Fig. 1E and F). The tumor cells were small, epithelioid, with round, slightly irregular non atypical-nuclei and scant eosinophilic cytoplasm. Morphological worrisome features (necrosis, significant mitotic activity and vascular invasion) and aspects resembling endometrial stromal tumor were not seen. On immunohistochemical analysis, the neoplasm showed diffuse positivity for mesenchymal (vimentin, smooth-muscle actin) and epithelial (EMA) (Fig. 2B) markers and for estrogen and progesterone receptors (Fig. 2D). Focal immunoreactivity was detected for markers of sex cord-like differentiation (inhibin, calretinin and CD99) (Fig. 2C). Finally, the tumor cells were negative for desmin, caldesmon (Fig. 2A), cytokeratins (8–18, AE1-AE3), CD56, HMB45, Melan-A and CD10. The morphologic and immunohistochemical results were consistent with the diagnosis of Uterine Tumor Resembling Ovarian Sex Cord Tumor (UTROSCT).

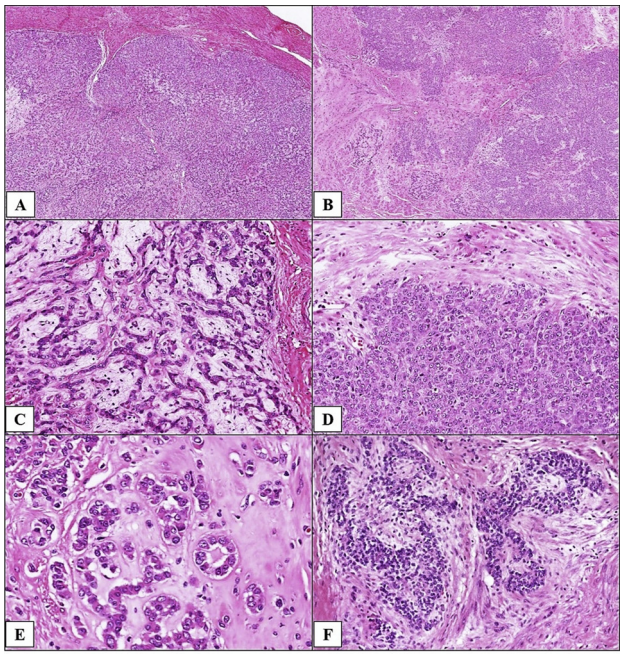

Fig. 1. Histopathological features of the reported case.
The tumor showed nodular appearance, with a mixture of pushing and infiltrative margins (A, B). Different patterns of growth were present; neoplastic cells were prevalently arranged in cords (C) or in a diffuse pattern of growth (D). Tubule formation (E) and trabeculae (F) was were also focally seen.

At the present time, the follow-up of the patient is negative regarding both breast malignancies and pelvic relapses.

4. Discussion

We presented a case of UTROSCT in a patient undergoing tamoxifen therapy as adjuvant therapy for breast carcinoma. UTROSCT is a rare type of uterine tumor, with only few small series reported in literature [10–16]. The biological behavior of this entity is indolent, with only two cases of loco-regional spread or abdominal relapse described [17,18].

In the last WHO classification [2], UTROSCT is classified in the chapter of mesenchymal tumors of the uterine corpus, defining it as a

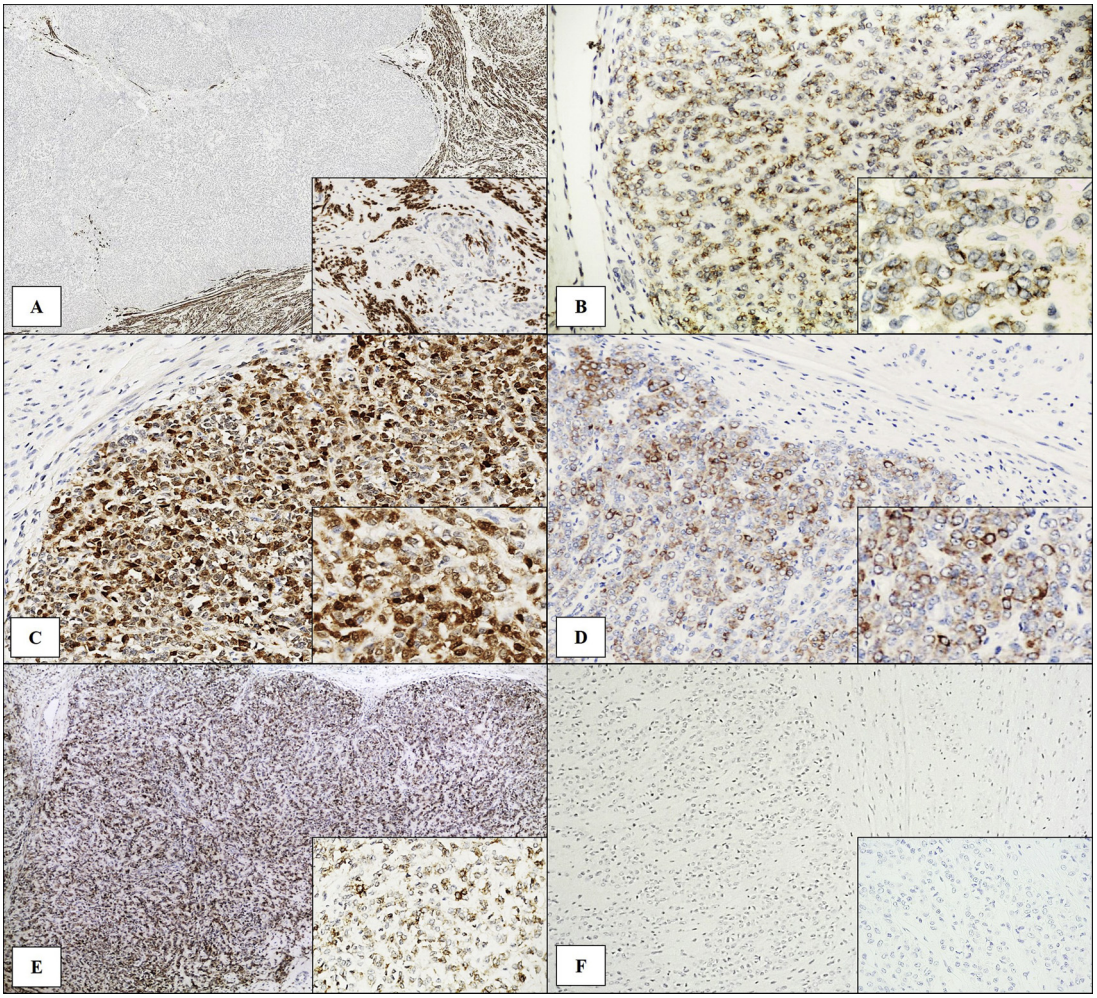

Fig. 2. Immunohistochemical features.
The immunohistochemical analysis of the tumor cells revealed a complete negativity for Caldesmon (A), whereas CD99 (B), Calretinina (C), Inhibin (D) and EMA (E) were expressed. HMB45 showed negative staining (F).

neoplasm that morphologically resemble ovarian sex cord tumors, without recognizable endometrial stroma. In fact, the first description of this tumor [1] already underlined the importance of excluding the presence of endometrial stromal tumor/sarcoma aspects that are predominant in the diagnosis and prognosis of the patient. Irving et al. suggested 50% of sex cord-like elements or more as cut-off percentage value for histological diagnosis of UTROCT [13].

Immunohistochemical studies describe in this tumor a variable expression of sex-cord differentiation markers, such as inhibin, calretinin, melan-A, CD56, CD99, WT1 and FOXL2 (10, 13, 14, 3), and the presence of both epithelial (low-weight cytokeratins, EMA) and mesenchymal (vimentin, smooth muscle actin, desmin) immunophenotypical differentiation [10,19,20]. Another immunohistochemical marker, that could be useful in differential diagnosis, is represented by CD10, being completely negative or showing only focal/patchy positive staining in UTROSCT, in this way ruling out and/or restricting the possibility of an endometrial stromal tumor [3]. However, other Authors described that the same antibody could be frequently expressed in UTROSCT [2,4,12]

The constantly negative staining for HMB45 denies the possibilities of PEComa Oliva et al. suggested the utility of caldesmon, a specific smooth muscle marker, in the differential diagnosis between UTROSCT and leiomyoma with epithelioid features [12]. In fact, in their series, six out of nine cases of epithelioid smooth muscle tumors showed at least isolated tumor cells positivity, whereas all of the seven UTROSCT cases studied were negative. In our case, the presence of a diffuse pattern of tumor cells aggregation, in the context of a smooth muscle peri-lesional overgrowth, suggests this kind of differential diagnosis. The negativity of caldesmon associated with the presence of sex-cord differentiation markers confirms the diagnosis of UTROSCT.

Generally, the majority of UTROSCTs shows a benign, indolent clinical behavior. In the literature, only few cases have been reported as malignant, with metastasis or recurrences respectively in omentum, small bowel, subcutaneous tissue, left internal iliac lymph node and epiploic appendix [3,16,18,21]

Tamoxifen is a nonsteroidal triphenylethyl compound with a selective estrogen receptor modulation. The use of tamoxifen as adjuvant therapy in breast cancer is widely known, with 5 years of treatment being considered the gold standard of hormonal therapy for breast carcinoma over the last 30 years. The efficacy of tamoxifen in breast cancer is due to its anti-estrogenic properties that are mediated by competitive binding to the estrogen receptor. However, tamoxifen may also exert a weak estrogenic effect and may act on the human endometrium [22,23]. Various studies revealed that tamoxifen causes uterine benign lesions and endometrial cancer, with a significantly higher risk for tamoxifen-related uterine sarcomas and with a positive correlation between risk and increased duration of tamoxifen use [24,25]. Moreover, some studies indicated that the tamoxifen-related risk of disease may be particularly high for certain uncommon histologic subtypes, such as carcinosarcoma compared to that of adenocarcinoma [5].

Table 2
Clinico-pathological features of stromal tumors with sex cord-like differentiation associated with Tamoxifen therapy reported in literature.

References	Diagnosis	Age (years)	Duration of Tamoxifen therapy	Clinical hypothesis	Size of the lesion (cm)	Follow-up
Present case	UTROSCT	62	3/5 months	Leiomyoma	7	10 months, A/W
Gutierrez et al.	UTROSCT	49	5 months	Leiomyoma	2	18 months, A/W
Giordano et al.	UTROSCT	46	1 month	Endometrial polyp	n.a.	n.a
Gargiulo et al.	UTROSCT	68	4/10 months	Myometrial tumor	8	n.a, A/W
Oztekin et al.	UTROSCT	58	4/10 months	Leiomyoma	6	8 months, A/W
Pang et al.	ESTSCLE	65	3/6 months	Leiomyoma	5	n.a.
Pang et al.	ESTSCLE	62	5 months	Leiomyoma	6,5	n.a.
Eddy et al.	ESTSCLE	54	3/5 months	Leiomyoma	10	n.a.
Beer et al.	ESTSCLE	61	5 months	n.a.	4	n.a.

UTROSCT, Uterine tumor resembling ovarian sex cord stromal tumor; ESTSCLE, endometrial stromal tumors with sex cord-like elements; A/W, alive and well.

In addition to the present case, four other UTROSCTs in patients treated with tamoxifen have been reported in the literature [6–9]. The clinico-pathological features of these four tumors are summarized in Table 2. The age of the four patients were comprised between 46 and 68 years, while the duration of tamoxifen use before the diagnosis varied from one to five years. The tumor size ranged from 2 to 8 cm and the location of the tumor were either submucosal-polypoid or intramural. The gross features were similar to that observed in cases not associated with tamoxifen, with a constant yellowish appearance. Two cases tested for the immunohistochemical expression of estrogen and progesterone receptors were positive, demonstrating a possible estrogenic sensitivity. One case, tested only for immunohistochemical expression of estrogen receptors, revealed a negative staining.

In conclusion, UTROSCT is a rare uterine tumor with characteristic morphological and immunohistochemical features. No specific genetic alteration is observed in UTROSCT. In particular, Wang et al. described a case of UTROSCT with t(X;6)(p22.3;q23.1) and t(4;18)(q21.1;q21.3). Various tumor-associated genes (bcl2, MALT1 and DCC at 18q21; and RAP1 at 4q21) and a gene related to gonads embryogenesis (H-Y regulator gene) are located near this translocation breakpoints [26]. Further investigations should be aimed to identify potential molecular mechanisms of tumorigenesis and genetical alteration of relevant prognostic significance.

Finally, UTROSCT might be considered as another uterine tumor related to tamoxifen therapy. This article highlights the importance of clinical follow-up in patients treated with tamoxifen, although due to the rarity of this tumor, the correlation appears difficult to demonstrate. Further studies to determining the value of ER and PgR in the characterization of this miscellaneous group of neoplasms are surely needed.

Conflict of interest

None of the authors have potential conflicts of interest relevant to this work.

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