

UTERINE MÜLLERIAN ADENOSARCOMAS: ABOUT A RETROSPECTIVE CASE SERIES ANALYSIS OF 13 PATIENTS.

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Abstract

Aim: The purpose of this study is to identify the incidence of uterine adenosarcomas in Lower Normandy. In addition, we sought to better define the clinical, morphological, and immunohistochemical features of this uncommon mixed mesenchymal tumors.

Patients and methods: 13 cases of uterine adenosarcomas were retrieved in the last 23 years from the archives of the François Baclesse Cancer Center and from the cancer registries of the department of Manche and Calvados in Lower Normandy (France). All cases were reviewed by the authors.

Results: 13 cases were observed beginning with the first case reported in our geographic area in 1989. Follow-up was available in 11 cases, only one young patient died, but from another non related previous carcinoma. All other patients are actually alive with no evidence of disease with a median follow-up of 10 years; only one patient with short follow-up shows a very ominous local evolution with a massive intraabdominal evolution in the context of an heterologous adenosarcoma with a rhabdomyosarcomatous component.

Key words: Adenosarcoma; Uterus; Cervix.

Introduction

Müllerian adenosarcomas are rare mixed tumors of low malignant potential that occur mainly in the uterus.

In the region of Lower Normandy (FRANCE) the authors have encountered recently several cases of adenosarcomas arising from either the cervix or uterine corpus.

Because of the rarity of this entity, we decided, with the help of both cancer registries of Lower Normandy (the registries of the Calvados and Manche), to report all cases that have occurred in this region.

The authors also reviewed the relevant literature about this seldom occurring entity.

Material and methods

We performed a retrospective review of patients undergoing primary evaluation and treatment for uterine adenosarcoma from February 1989 (when the first case was diagnosed in our geographic area)

through December 2012, and we have identified 13 patients.

Thanks to the data obtained from the charts of François Baclesse Cancer Center, the Caen University Hospital, and the data obtained from both cancer registries from departments of the Calvados and the Manche, we could retrieve all 13 reported cases, and obtain follow-up for 11 of the 13 cases.

Results

The patients' demographic and clinical features are summarized in **Table I**.

These 13 adenosarcomas have occurred during a period of 23 years. The region of Lower Normandy has a population of about 1 460 000 inhabitants. The global incidence in this region is rated at 0.37 cases per million per year.

4 cases (30%) occurred in the cervix and **9** cases (70%) in the uterine corpus. The cervical cases ranged in ages from 29 to 83 years, whereas uterine corpus cases ranged in ages from 34 to 89 years.

The usual symptom was abnormal vaginal bleeding. Most tumors were polypoid masses (**Figure 1**) ranging from 1 to 9 cm, usually filling the endometrial cavity; less commonly, the tumors were confined to the endocervix or the myometrium.

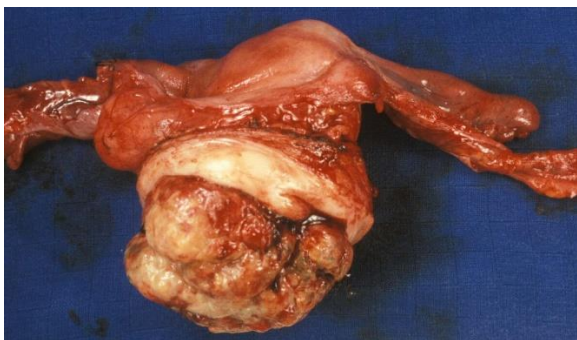


Figure 1: Gross image of Müllerian adenosarcoma of the uterine cervix. The mass has a yellow-tan, exophytic appearance.

Histologic examination revealed benign or atypical neoplastic glands within a sarcomatous stroma, which typically formed periglandular cuffs of increased cellularity, intraglandular polypoid projections, or both (**Figures 2,3**). Half of the cases were of low grade.

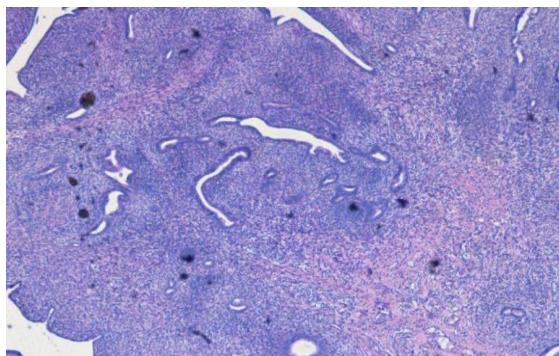


Figure 2: Section of uterus showing a polypoid proliferation with phyllodes-like architecture and cleft-like spaces (hematoxylin-eosin; x40).

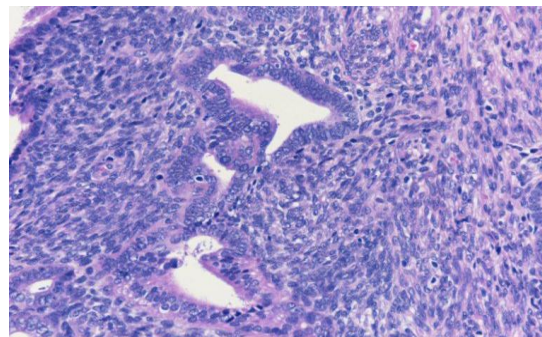


Figure 3: Glanduliform structures lined by benign epithelium and surrounded by low-grade malignant stroma (hematoxylin-eosin; x200).

In most of the cases, the histological diagnosis was relatively easy, because the sarcomatous nature was quite obvious, despite the fact that half of the cases were of low grade.

Only 3 cases (23%) showed a quite obvious heterologous sarcomatous component, one with low grade cartilaginous component and the two others with a rhabdomyosarcomatous component.

Of the 11 patients with follow-up (with a median of 10 years), one died but from an unrelated malignant Sertoli-Leydig ovarian tumour.

Table I: Demographic, clinical and pathological characteristics, treatment and outcomes for patients with müllerian adenocarcinoma.

Case	Age	Localisation	Histological diagnosis	Year of occurrence	Primary treatment	Status at last follow-up
1	88	Uterine corpus	Adenocarcinoma	1994	Radical hysterectomy	Died of other cause (hematemesis)
2	82	Uterine corpus	Adenocarcinoma	1997	Radical hysterectomy + radiation therapy	No evidence of disease (2008)
3	55	Cervix	Endocervical adenocarcinoma extended to the uterine isthmus	1997	Radical hysterectomy	No evidence of disease (2010)
4	82	Uterine corpus	Adenocarcinoma	2000	Radical hysterectomy + Intravaginal brachytherapy	No evidence of disease (2011)
5	83	Uterine corpus	Adenocarcinoma with heterologous element (Rhabdomyosarcoma)	2001	Radical hysterectomy	No evidence of disease (2011)
6	89	Uterine corpus	Adenocarcinoma	2001	Radical hysterectomy + radiation therapy	No evidence of disease (2010)
7	55	Cervix	Adenocarcinoma	2001	Radical hysterectomy + radiation therapy	No evidence of disease (2012)
8	83	Cervix	Adenocarcinoma with a sarcomatous component showing cartilaginous differentiation.	2004	Radical hysterectomy + radiation therapy	No evidence of disease (2010)
9	60	Uterine corpus	Low grade Adenocarcinoma	2005	Radical hysterectomy	No follow-up
10	69	Uterine corpus	Adenocarcinoma	2009	Radical hysterectomy + radiation therapy	No evidence of disease (2012)
11	39	Uterine corpus	Adenocarcinoma with heterologous element (Rhabdomyosarcoma)	2011	Radical hysterectomy + Chemotherapy (Doxorubicine) after peritoneal recurrence	Alive (peritoneal recurrence in 2012)
12	34	Uterine corpus	Low grade Adenocarcinoma	2011	Tumour removal only (no hysterectomy)	No follow-up
13	29	Cervix	Adenocarcinoma	2011	Tumour removal only (no hysterectomy)	No evidence of disease (2012)

Discussion

Clement and al. reported in 1974 a series of tumors of the female genital tract that were described as "... mixed tumors of the uterus, in which the stromal component has been malignant, but the epithelial elements, benign" and proposed naming these entity adenocarcinoma [1]. In 1979, a subsequent study [2] added a few cases to the original series, and the term *Müllerian adenocarcinoma* has since become universally recognized.

Müllerian adenocarcinoma is an uncommon entity. It is defined as a biphasic malignant mesenchymal tumor composed of a benign glandular component intimately associated with a sarcomatous stroma [1, 3].

The incidence of this rare neoplasm appears to be increasing in the last years, with a growing number of cases reported (now considerably more than 200) in the literature. This is probably due both to a better understanding of different anatomo-pathological aspects of uterine sarcomas (especially with the

development of the immunohistochemistry) and to a possible exposure to other different predisposing factors (pelvic irradiation, hyperestrogenism...) [3, 4]. The molecular pathogenesis of these tumors, however, remains to be elucidated.

Uterine endometrial adenocarcinomas occur typically in post-menopausal women with the median age at presentation of 58 years [5]. Compared with them, cervical adenocarcinomas tended to appear more often in younger women with the average age at presentation of 31 years [1, 5, 6]. These numbers are close to our results.

The most common site is the uterine corpus but adenocarcinoma also occurs in the cervix and ovary and more rarely in the vagina, fallopian tube, arising from peritoneal surfaces, or outside the female genital tract [3, 7]. Pelvic pain and abnormal vaginal bleeding are the presenting symptoms [7, 8].

Clinically, they arise as polypoid masses with a quite wide implantation as in our series. Most uterine cases have a polypoid gross appearance, sometimes resulting in the formation of multiple polyps [9]. Macroscopically, the average size is 5 cm, although

tumors up to 50 cm have been reported [3, 17]. Histologically, adenosarcoma is composed of benign glands with a sarcomatous stroma, which typically formed periglandular cuffs of increased cellularity, resulting in the formation of a cambium layer. At low-power magnification, "phyllodes-like" architecture with broad leaf-like projections can be observed [6, 7, 9]. In the majority of our cases, we did not observe such mimicry, because the benign endocervical glands were of rather normal architecture, without significant deformation or compression by the sarcomatous stroma.

Using the World Health Organization definition, stromal mitotic activity of 2 or more per 10 high-power fields is required for a diagnosis of adenosarcoma [7, 11]. The mitoses are usually most pronounced in areas of periglandular cuffing. Atypical mitotic figures are in general absent except in the presence of sarcomatous overgrowth [12].

Sarcomatous overgrowth is defined as the presence of pure sarcoma (without any epithelial component) comprising at least 25% of the tumor [12]. Sarcomatous overgrowth is an important prognostic factor and should be assessed in all tumors [12].

The stromal component is usually morphologically "low-grade". Sometimes it is high grade, resembling undifferentiated sarcoma. Additional histological features that are sometimes present include heterologous stromal elements, most notably rhabdomyoblastic differentiation, or sex cord-like differentiation. Heterologous elements, have no prognostic significance alone, although they occur most commonly in the presence of sarcomatous overgrowth [7, 9].

Concerning the immunophenotype, expression of CD10 in the stromal compartment is seen in adenosarcomas and highlights the periglandular cuffing. Immunoreactivity for estrogen and progesterone receptors is also seen in most cases, both in the glandular and stromal components. Mesenchymal markers, such as smooth muscle actin (SMA), CD34 and desmin can have variable positivity in the stromal component [7, 13].

The differential diagnosis of adenosarcoma is broad and should be made with caution. It consists predominantly of tumors that also have a biphasic (epithelial and mesenchymal) appearance. It includes mainly benign entities, such as adenofibroma, adenomyoma, and atypical polypoid adenomyoma [3].

Adenosarcoma can be easily distinguished from adenofibroma (both epithelial and stromal components benign) using the criteria defined as unique to adenosarcoma such as, a marked degree of atypia of mesenchymal cells, a histological malignant element, the presence of myometrial invasion, and two or more mitotic figure per 10 HPF.

Adenomyomas can be distinguished from adenosarcoma by the presence of well-defined myomatous stroma [5].

In the presence of high-grade sarcoma and/or sarcomatous overgrowth, the main diagnosis to exclude is carcinosarcoma, although undifferentiated uterine sarcoma, endometrial stromal sarcoma (ESS), and leiomyosarcoma should also be taken into consideration in the differential diagnosis [3].

Total abdominal or laparoscopic-assisted vaginal hysterectomy is the treatment of choice for uterine adenosarcoma, with or without bilateral salpingo-oophorectomy [14].

Local excision has been curative in rare cases, and could be preferred especially in young patients [15]. There is no standardized chemotherapy, hormonal therapy, or radiation therapy in adenosarcoma, but standard sarcoma chemotherapy regimens, such as doxorubicin, ifosfamide, or gemcitabine/docetaxel, and newer drugs, such as trabectedin, appear to have some efficacy in adenosarcoma with sarcomatous overgrowth [14, 16].

In the literature, systemic metastases are reported in about 5% of the cases. No systemic metastases were reported in our series. Myometrial invasion, sarcomatous overgrowth, heterologous elements and vascular invasion seem to be principle prognostic factors [17].

Uterine adenosarcoma can recur many years after initial diagnosis, and thus prolonged surveillance of patients with this disease is necessary.

Conclusion

Müllerian adenosarcoma is a relatively uncommon entity and a distinctive uterine neoplasm in gynecologic pathology that has particular clinical and histological characteristics.

It is important for pathologists to be aware of the morphologic features of these neoplasms to distinguish them from other biphasic (epithelial and mesenchymal) tumors, both benign and malignant.

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