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Synchronous Müllerian adenosarcomas of the uterine cervix, bilateral ovaries, left fallopian tube, and endometrium: a case report and review of the literature

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Summary

Müllerian adenosarcoma is an uncommon biphasic tumor composed of a malignant stromal component admixed with a benign glandular epithelial component. The tumor occurs mainly in the uterine corpus but also as a primary lesion in the uterine cervix, ovary, vagina, fallopian tubes, or even outside the female genital tract. While the tumor may arise from a wide range of anatomic sites, so far only two cases with synchronous occurrence of adenosarcoma have been published. Here the authors present a case of a 64-year-old woman with synchronous Müllerian adenosarcomas in the uterine cervix, bilateral ovaries, left fallopian tube, and endometrium. This case is also the first reported case with synchronous adenosarcomas involving more than two anatomic sites.

Introduction

Müllerian adenosarcoma was first described by Clement and Scully in 1974, characterized by admixed with benign-appearing epithelial elements and low-grade malignant mesenchymal components [1, 2]. The tumor usually occurs in the uterus affecting postmenopausal women, while cervical adenosarcoma tends to present in the reproductive age [3-6]. The patients with cervical adenosarcoma usually present with either recurrent polyps or abnormal vaginal bleeding [7]. Histological features of Müllerian adenosarcoma include irregularly shaped glands with prominent dense atypical stromal cells proliferation. A low power "phyllodes-like" architecture with leaf-like projections lined by a variety of benign epithelia is a characteristic picture. The benign appearing glands are surrounded by proliferative spindle cells, producing periglandular cuffs [2]. In some instances, there are areas of marked anaplastic and pleomorphic spindle cell proliferation without glandular components occupying at least 25% of the tumor, the so-called sarcomatous overgrowth [6, 7]. The mitotic count is usually low, but it is enough for this diagnosis when it exceeds 2 per 10 high power fields [2, 5]. The five-year recurrence is about 25-30% and is exclusively associated with myometrial invasion and sarcomatous overgrowth [2, 8].

Case Report

Written informed consent was obtained from the patient for publication this case report and accompanying images. The 64-year-old woman (G4P4A0) with unremarkable past medical history presented with an intermittent vaginal spotting for five years. A protruding palpable mass at the vaginal introitus had also been found for one month prior to her presentation. On pelvic examination, an irregular protruding polypoid lesion from cervix was

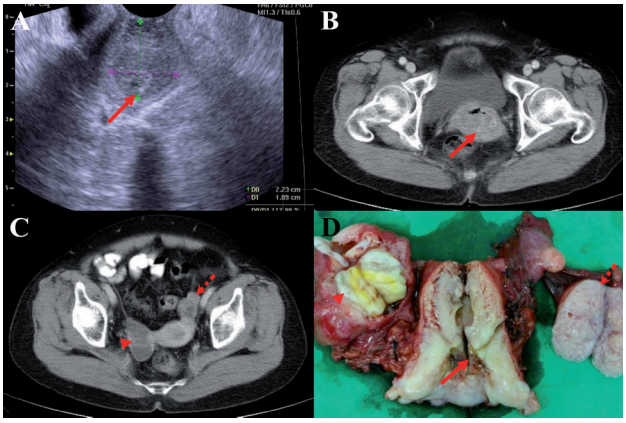

Figure 1. — Images and gross appearance. (A) A cervical mass seen with transvaginal sonogram. (B) A cervical mass seen with computerized tomography scan of the abdomen. (C) Bilateral adnexal tumors at computerized tomography scan. Arrowhead indicates the right ovary and dashed arrow labels the left ovary. (D) Status post-transection of cervical mass (arrow) with bilateral ovarian tumors (arrowhead and dashed arrow labels the right and left ovaries, respectively) and normally appearing uterus and bilateral tubes.

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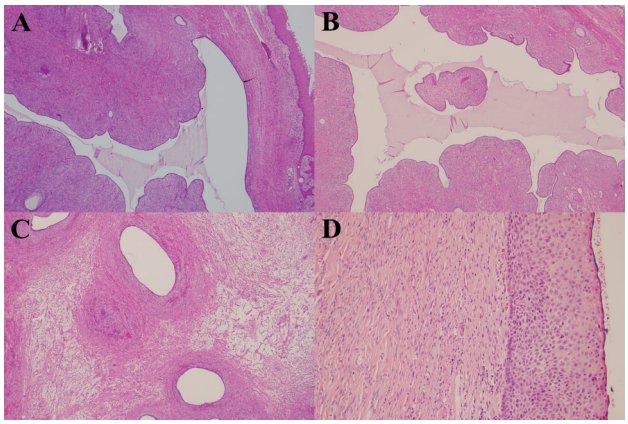

Figure 2. — Microscopic view of the uterine cervix. (A) A polypoid tumor composed of benign epithelial glands and hypercellular spindle mesenchymal components. (B) Phyllodes-like architecture. (C) Dilated benign appearing glands surrounded by hypercellular stroma, producing periglandular cuffing. (D) Moderate dysplasia of the epithelium.

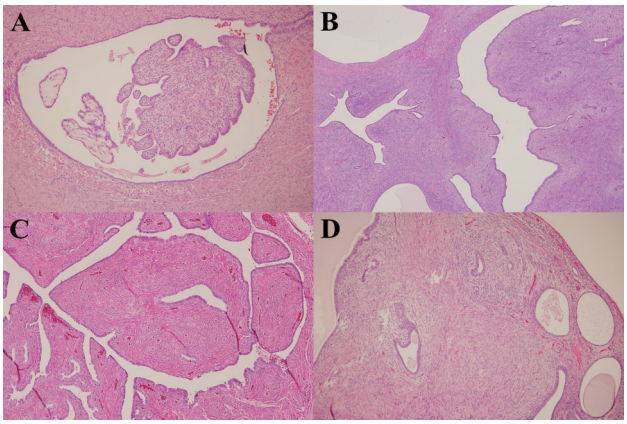

Figure 3. — Synchronous adenosarcomas. (A) Right ovary. (B) Left ovary. (C) Left fallopian tube. (D) Endometrium.

noted. Transvaginal sonogram revealed a cervical mass, measuring 3 cm in size (Figure 1A). Computerized tomography scan of the abdomen showed a cervical mass measuring around 3.9 cm in size (Figure 1B) and enhanced oval structure at the bilateral adnexae (Figure 1C). Transection of the cervical mass was performed initially and the pathology disclosed an adenosarcoma. The patient underwent subsequent extended total abdominal hysterectomy and bilateral pelvic lymphadenectomy. Pathology revealed a diagnosis of adenosarcomas involving bilateral ovaries, left fallopian tube, and endometrium. No residual tumor was found in the cervix. She then received postoperative chemotherapy at four-week intervals. She remains disease-free after treatment and has been on regular follow-up in our gynecology department.

On gross inspection, the cervical tumor showed papillary appearance measuring 4×4×3 cm in size. In the subsequent specimen of extended total hysterectomy, a normal sized uterus was revealed. The cervix showed superficial erosion with no residual tumor or definite stromal invasion. The bilateral ovaries showed enlarged with multilobulated cut surface. The endometrium and bilateral fallopian tubes grossly appeared normal (Figure 1D).

Microscopically, the cervical tumor showed a polypoid contour composed of benign epithelial glands and hypercellular spindle mesenchymal components (Figure 2A). The glandular structure was compressed by proliferated stromal cells, producing a leaf-like pattern (Figure 2B). Some glands were cystic and the stromal cells concentrated around them, forming periglandular cuffs (Figure 2C). The stromal cells showed mild atypia with increased mitotic count, measuring 4 per 10 high power fields on average. Neither heterologous mesenchymal elements nor areas of sarcomatous overgrowth were found. Moderate dysplasia was also noted in the cervical epithelium (Figure 2D).

Neoplasms with the same histological features as those in the uterine cervix were seen in both ovaries (Figures 3A and 3B), left fallopian tube (Figure 3C), and endometrium (Figure 3D). The exact tumor sizes were difficult to be well-evaluated due to their multifocality and random distribution in the parenchyma of bilateral adnexae and superficial endometrium. Foci of stromal cell proliferation in the absence of glandular elements were noted in the left fallopian tube. Endometriosis in the presence of endometrial-type glands, stroma, and old hemorrhage in the right ovary was also found admixed with the neoplasm.

Immunohistochemical stains of p16 and Ki-67 were performed on the cervix and bilateral adnexae and CD10 was done on the right ovary. The cervical epithelium showed diffuse strong reactivity of p16 (Figure 4A). Focal strong expression of p16 of glandular structure in the cervix was also found, whereas the stromal cells showed p16 negative staining (Figure 4B). Ki-67 staining was generally low (less than 5%) except the foci of periglandular cuffs (Figure 4C). Cystic glands were surrounded by CD10-positive stroma in the right ovary, highlighting the structure of adenosarcoma and endometriosis (Figure 4D).

Discussion

Müllerian adenosarcoma is an uncommon neoplasm with a low malignant potential occurring mainly in the female genital tract, comprising 1-3% of all gynecological malignancies. Differential diagnosis should include benign uterine polyp, adenofibroma [8], and malignant mixed Müllerian tumor [9]. Criteria which are applied to adenosarcoma in most cases can easily distinguish adenosarcoma from adenofibroma, such as cellular atypia of the mesenchyma, the presence of myometrial invasion, and the increased mitotic count. Malignant mixed Müllerian tumors, unlike low-grade adenosarcomas, reveal a highly aggressive behavior with frequent myometrial invasion. The carcinomatous component is most often endometrioid in type and the sarcomatous elements are usually heterogeneous [9].

The present case presented Müllerian adenosarcomas involving multiple sites of the female genital tract, raising a problem in the differentiation between primary synchronous neoplasia and metastasis. The guidelines proposed for interpreting simultaneous endometrioid cancers of the endometrium and ovary might be suitable for interpreting the relation of these tumors [10]. Although histologic similarity of the tumors and bilateral ovaries involvement sup-

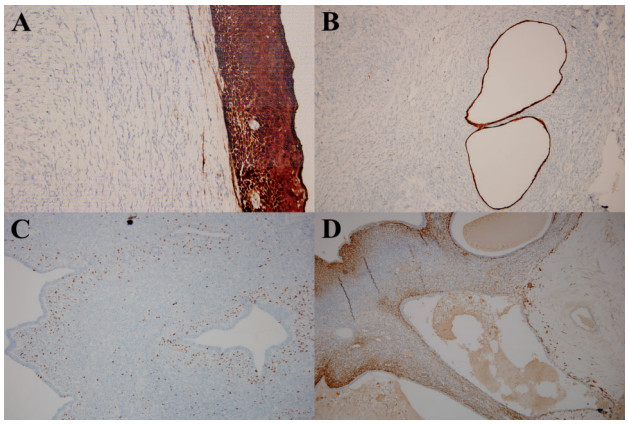

Figure 4. — Immunohistochemical stains. (A) Diffuse strong reactivity of p16 in the cervical epithelium. (B) Focal strong expression of p16 in the cervical glands. (C) Increased reactivity of the proliferation marker MIB-1 (Ki-67) in the periglandular stromal cells. (D) CD10 positive in the stroma around glands.

ported the possibility of metastasis, no vascular invasion, surface implants, or myometrial invasion of endometrial tumor, and ovarian tumors located in parenchyma favored the diagnosis of synchronous primary neoplasia. In addition, the metastasis of adenosarcoma usually involves the vagina, pelvis, and abdomen and is almost always composed of pure sarcoma [8, 11], which did not fit the presentation in the present case.

To date, only two cases of synchronous adenosarcomas have been reported in the literature [11]. One of the cases showed tumors occurred both in one side of ovary and the lumen of the appendix which appeared to arise from endometriosis [12]. The other one had an adenosarcoma located in one side of ovary and another independent primary tumor in the uterus. Endometriosis has been reported to be associated with Müllerian adenosarcoma in the gastrointestinal tract [12]. In the present case, endometriosis was also found in bilateral ovaries admixing with proliferated spindle stromal cells, suggesting a primary endometriosis with an adenosarcoma transformation. Synchronous tumors arising from endometriosis instead of metastasis are further supported by this finding. Compared with previously published two cases, the present case showed more extensive involvement of adenosarcomas in the whole Müllerian duct and bilateral ovaries.

The histogenesis of adenosarcoma has not yet been well studied. Although endometriosis was proposed to be associated with its tumorigenesis, the mechanism is still unknown [12]. The present case showed moderate dysplasia of the cervix, which may raise a question if adenosarcoma is related to HPV infection or not. Although a publication showed a contrary result, the case number was small [13]. Immunohistochemical analysis of p16 expression was performed which demonstrated a diffuse expression in the epithelium in the cervix. Focal strong expression of p16 of glandular structure in the cervix and bilateral ovaries was also noted, but the significance is uncertain. Recently by using genome-wide copy number analysis, chromosomal instability in the aggressive subgroup of adenosarcomas has been identified [14].

The immunophenotype of most adenosarcomas resembles that of endometrial stromal sarcoma, with expression of ER, PR, and CD10 in the stroma. However, cases with sarcomatous overgrowth lose the expression of the aforementioned markers but exhibit a higher Ki-67 expression and positive for p53 staining [15]. In the present case, Ki-67 staining was generally low except for the foci of stromal proliferation. Both the stroma of endometriosis and adenosarcoma in the ovaries showed positive CD10 staining, compatible with what is reported in the literature [16].

Total abdominal or laparoscopic-assisted vaginal hysterectomy is still the standard treatment for uterine adenosarcoma, with or without bilateral salpingo-oophorectomy. The prognosis of Müllerian adenosarcoma is generally favorable following primary surgery. However, local recurrences and distant metastasis may occur [8]. Thus, long-term follow-up is recommended.

Conclusion

In conclusion, Müllerian adenosarcoma is a low-grade tumor affecting a wide range of anatomic sites. Although patients with single site involvement have been well-documented, only limited cases with synchronous occurrence of this neoplasm have been published. Here the authors report a case of synchronous Müllerian adenosarcomas extensively involving multiple sites, including uterine cervix, bilateral adnexae, and endometrium. The real incidence of synchronous adenosarcomas is unknown, probably being underestimated due to their inconspicuous gross appearance, small sizes, sampling errors, or misdiagnosis. Gynecologists and pathologists should be in alert due to the possibility of multiple occurrence of this neoplasm. Thorough preoperative survey, most suitable surgical management, and extensive sampling of the specimen for pathological diagnosis and staging are thus warranted.

The case was presented at the 18th Japan-Korea-Taiwan Joint Conference for Gynecological Pathology, Taipei, Taiwan. May 24, 2014.

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