

Aggressive ovarian adenocarcinoma with high grade sarcomatous and chondrosarcoma components in a young patient

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Abstract. Mullerian adenocarcinoma (MA) was first defined as a special malignancy of uterine corpus in 1974. Although a few hundred cases were reported about uterine adenocarcinomas, extrauterine adenocarcinomas (EMA) are very rare. Thus, clinic and pathologic knowledge about extrauterine adenocarcinomas are limited.

This case report represents an ovarian mesodermal (mullerian) adenocarcinoma, which contains dominantly high grade sarcomatous components along with chondrosarcoma components and very limited classical adenocarcinoma areas in a 25 year-old female. To our knowledge, this is the first case report in the literature reporting the combination of features as diffuse presentation of sarcomatous overgrowth (SO) areas, scarcity of classical adenocarcinoma areas, existence of chondrosarcoma areas in such a young patient.

Key words: Ovary, extramullerian adenocarcinoma, chondrosarcoma, sarcomatous overgrowth

1. Introduction

The term "mullerian adenocarcinoma" was coined for a distinctive uterine tumor characterized by a malignant, usually low grade stromal component, and a generally benign, but occasionally atypical glandular epithelial component (1). Sarcomatous overgrowth (SO) is defined as partial overgrowth of an otherwise typical adenocarcinoma by pure sarcoma. Uterine mullerian adenocarcinomas without SO generally have good prognosis. In the published case series, tumor recurrence was reported as 20% often after 5 years follow up with a fatal outcome in 10% of cases (2-5). However, tumors containing SO have worse prognosis with tumor recurrence rates of 62% and mortality rates of 54% (2, 6).

Extrauterine adenocarcinomas have been reported in ovaries, peritoneum, intestinal endometriosis, vaginal apex and fallopian tubes (7-12). Cases with ovarian adenocarcinomas are quite scarce. The largest case series that has been reported included forty cases (3). Ovarian adenocarcinomas have worse prognosis comparing with their uterine counterparts (3, 7, 9). The main reason is probably related to the location of the tumors. The tumors in the abdominal cavity have the lack of an anatomic barrier against peritoneal dissemination that may lead to larger size, higher stage, and higher frequency of rupture of the tumors (3).

2. Case report

A 25-year old nulliparous woman was admitted to our hospital complaining of abdominal pain and a palpable mass at right inferior abdominal quadrant. She had an ultrasound examination three months ago which revealed a cystic ovarian mass in 3x3 cm diameters and she was recommended follow up in every two months. On the follow up examination, a pelvic mass located in the right abdomen was diagnosed and confirmed by ultrasound scan as a solid mass in 10x10 cm diameters with cystic areas. Her tumor markers were all in normal range.

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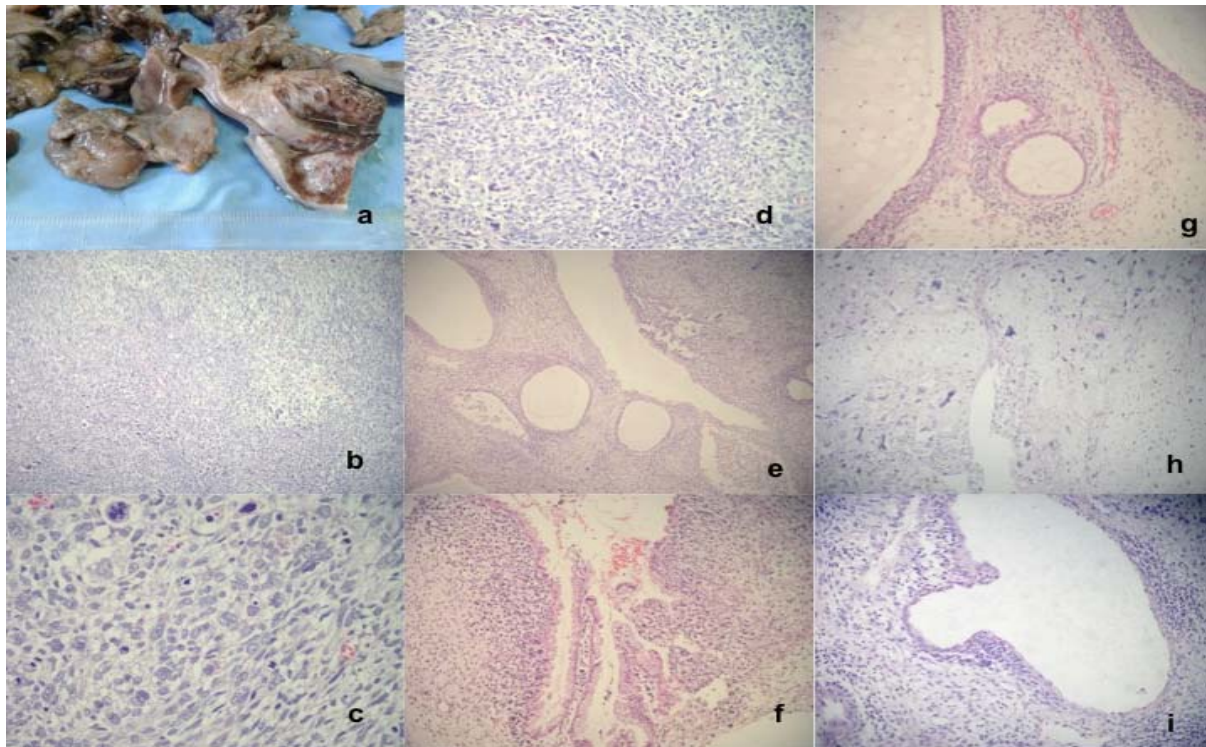


Fig. 1a. Tumor fragments composed of cystic and fragile components.
Fig. 1b. High grade sarcomatous overgrowth areas. (HEX40)
Fig. 1c. Severe atypia on sarcomatous areas. (HEX200)
Fig. 1d. Frequent atypical mitotic activity areas. (HEX400)
Fig. 1e. Benign laying epithelium and cystic glands in the stroma which was composed of diffuse proliferation of spindle cells in classical adenosarcoma areas. (HEX40)
Fig. 1f. Benign mucinous laying epithelium in classical adenosarcoma areas. (HEX200)
Fig. 1g. Periglandular cuff in classical adenosarcoma areas. (HEX200)
Fig. 1h. Stromal protrusions in classical adenosarcoma areas.(HEX200)
Fig. 1i. Chondrosarcomatous areas as heterologous elements. (HEX200)

In the intraoperative evaluation, it was noted that the mass was located only in the right adnexal area and had intense adhesions to adjacent tissues, occasionally to the uterus. According to frozen section evaluation, the tumor was malignant and a germ cell neoplasm could not completely be ruled out. With respect to the informed consent taken before the operation, a fertility preserving approach including sample from peritoneal washing fluids, right salphingo-oophorectomy, omentectomy and bilateral pelvic lymphadenectomy were performed and adhesions between uterus and the mass were excised.

For the histopathological evaluation, totally forty paraffin blocks were settled from right ovarian cyst wall and its ingredient for three separate times. For the immune histochemical investigation, stainings with vimentin, cytokeratin, estrogen receptor (ER), progesterone receptor (PR), CD10, p53, Ki 67 were performed.

In macroscopic evaluation of the right ovarian cyst, a 10x10cm mass with 2 cm wall thickness

and impaired capsule integrity was detected. The cut surface of cyst wall was yellowish- white and had irregular appearance with areas of hemorrhage and necrosis. A hemorrhagic, soft, solid, bright, partially necrotic and fragile tumor mass in 10x10x3 cm diameter was detected in the cyst (Figure 1a). Totally twenty lymph nodes were detected from bilateral pelvic and para aortic lymph node samples.

In histopathological evaluation of the first sections from the right ovarian cyst wall, solid and fascicular proliferations of the spindle cells were determined (Figure 1b). At low-power magnification (x40); nucleomegali, hyperchromasia, pleomorphysm and severe atypia could be detected (Figure 1c). Mitotic count was ranging between 20 and 30 at 10 high-power fields (Figure 1d). The necrotic areas were expansive. At two sections of last samples, benign laying epithelium and cystic glands were detected in the stroma which was composed of diffuse proliferation of spindle cells, and which

had lower cellularity, lower atypia and fibromatous appearance (Figure 1e). Epithelium was endometrioid and mucinous type (Figure 1f). There were periglandular cuffs, increased stromal cellularity in periglandular area, and rare stromal protrusions (Figure 1g, 1h). Mitotic index was lower (5-10) at those areas per 10 high-power fields. Those areas are considered as classical adenosarcoma areas. As heterologous elements, benign chondroid and frequent chondrosarcomatous areas were identified (Figure 1i). There was no sex-cord like element. In the sections taken from outer side of the tubes, omentum and outer layers of the uterus, metastasis comprised of only sarcomatous component were detected. All lymph nodes were reactive and no atypical cells were found in peritoneal washing fluids.

In immune histochemical investigation; the stromal cells showed diffuse and intense positivity with vimentin (vim) at sarcoma areas (Figure 2a). Focal, poor positivity with estrogen receptor (ER), progesterone receptor (PR), desmin and CD 10 was detected. Positivity with S100 was detected only in the areas with chondroid and chondrosarcoma components (Figure 2b). The positivity of p53 and labeling index of Ki 67 for the sarcomatous cells were %90 and %60 respectively (Figure 2c and 2d). At classical adenosarcoma areas, epithelium was positive for AE1/3 cytokeratin. Vimentin was positive at stromal cells.

Regarding all these pathologic findings, ovarian adenosarcoma with high grade sarcomatous and chondrosarcoma components was diagnosed. Only three weeks after the operation, when the multidisciplinary team decided to administer chemotherapy, the patient reapplied with swelling in the abdomen. Ultrasound examination revealed excessive ascites in the abdomen with a left ovarian mass in 2x4 cm diameters, which had not been existed in the first operation. Paracentesis was performed for patient relief. Multidisciplinary team did not recommend second operation not to increase morbidity and recommended six cycles of chemotherapy with doxorubicin and ifosfamide. The PET-CT just before the chemotherapy revealed the same left ovarian metastasis and another one in the liver parenchyma, which supported that this was an extremely aggressive tumor. At present, she is receiving chemotherapy, however her performance status is not satisfying.

3. Discussion

Extramullerian adenosarcoma (EMA) is diagnosed mostly in younger patients comparing with uterine mullerian adenosarcomas. Our patient was 25 year old and to our knowledge, she is the youngest in the literature. Usually the average tumor size of EMA is bigger than its uterine counterpart. The average size of the MA of uterus and ovary is reported as 5 cm and 14 cm respectively (3). In our case, the mass was 10 cm

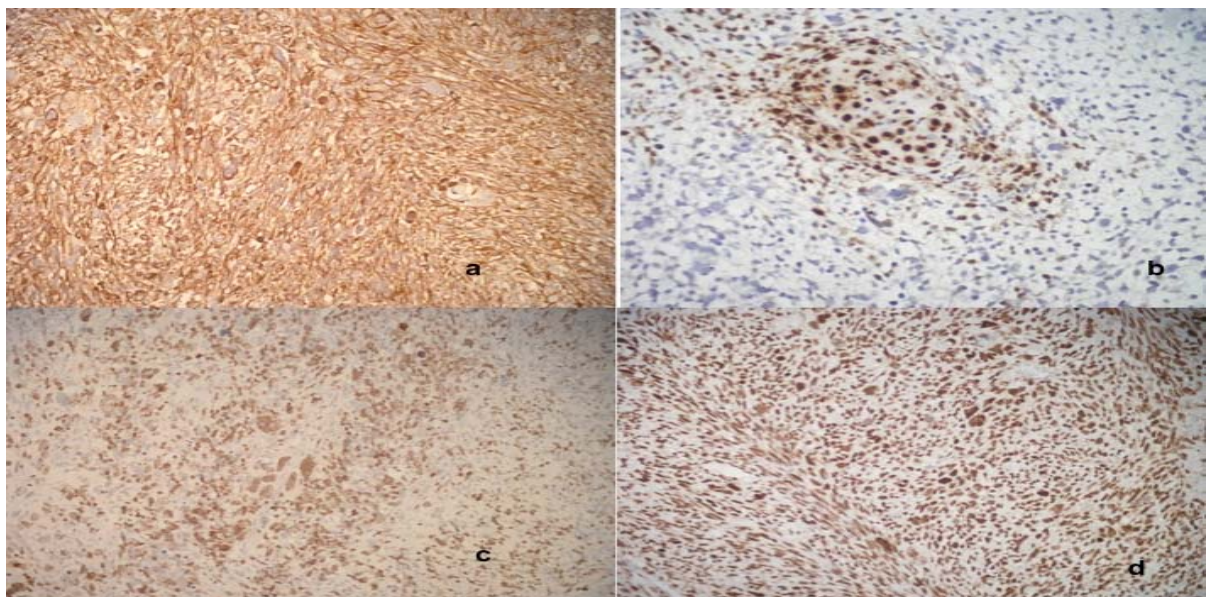


Fig. 2a. Intense positivity with vimentin (vim) in sarcomatous areas. (Vimentinx200)

Fig. 2b. Intense positivity with S100 in chondroid differentiation areas. (S100X200)

Fig. 2c. Intense positivity with Ki 67 in the tumor cells in sarcomatous areas. (KI67X200)

Fig. 2d. Intense positivity with p53 in the tumor cells in sarcomatous areas. (P53X200)

in diameter. Eichhorn et al. (3) reported that the majority of the masses in their series were composed of predominantly solid components, however, some of them were entirely solid and some were entirely cystic. Necrosis and fragility were identified at solid areas. Our case had cystic component predominantly and there were frequent fragility and necrosis at solid areas.

Sarcomatous overgrowth (SO) is defined as partial overgrowth of an otherwise typical adenocarcinoma and must be comprising at least 25% of the tumor mass. In ovarian müllerian adenocarcinomas, SO is seen at higher rates comparing with uterine MAs. Grading of these tumors are performed according to mitosis and atypia. If nuclear enlargement, pleomorphism and hyperchromatism at stromal areas are similar to low grade ESS, it can be described as mild atypia. If it can be seen at low power magnification (x40), it can be described as severe atypia.

The count of mitosis and atypia are evaluated on the area where the most mitotic activity is seen. Ten or less mitosis at 10 HPF as well as mild atypia is defined as low grade; more than 10 mitoses as well as severe atypia is defined as high grade sarcomas. SO areas are graded regarding to the same criteria (3).

Our case had 80% SO. To our knowledge, this is the highest SO rate in the literature and these areas are high grade (severe atypia and mitotic index was 20-30 at 10 HPF). The only case in the literature, which reports such a mitosis rate and atypia belongs to Hirakawa et al. (13) (30 and more mitosis at 10 HPF). Typical adenocarcinoma regions were minimal. In contrast to literature, in our case, stroma was seen as nonspecific sarcoma, resembling neither endometrial stroma nor fibromatous stroma. Epithelium was mucinous and endometrioid. Tubal, hobnail clear cell and squamous epithelium were also reported in the literature (3, 7, 14). Periglandular cuff which is diagnostic for MA was detected. However leaf-like configuration was not detected and stromal protrusions were rare.

In uterine MA; most commonly seen heterologous element is striated muscle (rhabdomyosarcoma) following with cartilage and fat. Likewise, in ovarian MA, rhabdomyosarcomas are the most common elements (3, 15). This case report is unique in the literature regarding to chondrosarcoma component in an ovarian MA.

The diagnostic role of immunohistochemistry and knowledge about this issue is limited (10). Studies are usually about uterine adenocarcinomas. It is reported that ER, PR and CD10 staining is very limited at stromal components of classical

adenocarcinoma areas in high grade tumors comparing with low grade tumors (7, 9, 10). In our case staining of these antigens was poor and focal as well. The high grade SO areas were strongly positive only with vimentin. ER, PR and CD10 reactivity was not existed in these SO areas. In the study reported by Rekhi et al. (7) Vimentin was diffuse positive in all cases. Moreover, Ki67 and p53 positivity are more frequent in the cases that contain SO (7, 10, 13). In our case Ki67 and p53 positivity were 60% and 90%, respectively. To our knowledge, these rates are the highest rates in the literature.

Poor prognostic factors for ovarian MA's are; high grade, sarcomatous overgrowth, <53 of age, tumor rupture and ovarian location (3, 8). Our case carries all of these factors. Furthermore, common peritoneal metastases were detected at first diagnosis.

Differential diagnosis of the adenocarcinomas can be difficult due to coexistence of variable components such as classical adenocarcinoma areas, SO, homologous or heterologous components and sex cord-like elements in different proportions. In our case, adenofibroma which may be a problem in differential diagnosis of low grade adenocarcinomas was never considered because high grade sarcomatous components were quite common. Malign mixt müllerian tumors were also excluded because epithelial components were benign. The existence of adenocarcinoma areas excluded primary sarcomas as well. Regarding to age of our patient, immature teratomas and sarcomas which generate from mature teratomas can have a place in differential diagnosis. However neither embryonal neuroectodermal nor endodermal derivatives were identified and existence of the classical sarcoma areas also eliminate teratomas.

Ovarian adenocarcinomas are quite rare tumors. They can exhibit various histopathological features and can pretend primary sarcomas. In conclusion, to make an accurate diagnosis, increased number of sampling should be performed in order to define all of the components before labeling a mass as a primary sarcoma.

References

1. Clement PB, Scully RE. Müllerian adenocarcinoma of the uterus. A clinicopathologic analysis of ten cases of a distinctive type of müllerian mixed tumor. *Cancer* 1974; 34: 1138-1149.
2. Clement PB. Müllerian adenocarcinomas of the uterus with sarcomatous overgrowth. A clinicopathological analysis of 10 cases. *Am J Surg Pathol* 1989; 13: 28-38.

3. Eichhorn JH, Young RH, Clement PB, Scully RE. Mesodermal (müllerian) adenosarcoma of the ovary: a clinicopathologic analysis of 40 cases and a review of the literature. *Am J Surg Pathol* 2002; 26: 1243-1258.
4. Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. *Hum Pathol* 1990; 21: 363-381.
5. Clement PB, Scully RE. Müllerian adenosarcomas of the uterus with sex cord-like elements. A clinicopathologic analysis of eight cases. *Am J Clin Pathol* 1989; 91: 664-672.
6. Krivak TC, Seidman JD, McBroom JW et al. Uterine adenosarcoma with sarcomatous overgrowth versus uterine carcinosarcoma: comparison of treatment and survival. *Gynecol Oncol* 2001; 83:89-94.
7. Rekhi B, Deodhar KK, Maheshwari A et al. Clinicopathological spectrum of 19 adenosarcomas of female genital tract, including uncommon clinical associations and immunohistochemical profile, reviewed at a single institution. *Indian J Pathol Microbiol* 2012; 55: 326-332.
8. Gallardo A, Prat J. Mullerian adenosarcoma: a clinicopathologic and immunohistochemical study of 55 cases challenging the existence of adenofibroma. *Am J Surg Pathol* 2009; 33: 278-288.
9. McCluggage WG. Mullerian adenosarcoma of the female genital tract. *Adv Anat Pathol* 2010; 17: 122-129.
10. Soslow RA, Ali A, Oliva E. Mullerian adenosarcomas: an immunophenotypic analysis of 35 cases. *Am J Surg Pathol* 2008; 32: 1013-1021.
11. Valdez VA, Planas AT, Lopez VF, Goldberg M, Herrera NE. Adenosarcoma of uterus and ovary: a clinicopathologic study of two cases. *Cancer* 1979; 43: 1439-1447.
12. Verschraegen CF, Vasuratna A, Edwards C et al. Clinicopathologic analysis of mullerian adenosarcoma: the M.D. Anderson Cancer Center experience. *Oncol Rep* 1998; 5: 939-944.
13. Hirakawa E, Yamamoto Y, Fujimoto C et al. Aggressive adenosarcoma of the ovary. *Histopathology* 2003; 42: 202-203.
14. Kao GF, Norris HJ. Benign and low grade variants of mixed mesodermal tumor (adenosarcoma) of the ovary and adnexal region. *Cancer* 1978; 42: 1314-1324.
15. Lack EE, Bitterman P, Sundeen JT. Müllerian adenosarcoma of the uterus with pure angiosarcoma: case report. *Hum Pathol* 1991; 22: 1289-1291.