Case Report
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Atypical Proliferating Clear Cell Adenofibroma of the Ovary: A Case Report

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Abstract

Clear cell adenofibromas of borderline malignancy are extremely rare tumors of the ovaries. They may be associated with ovarian clear cell adenocarcinomas which typically present as large adnexal masses and are generally considered highly malignant. We describe the case of a postmenopausal female with an ovarian mass diagnosed as atypical (borderline) proliferating clear cell adenofibroma. The patient is alive and well without signs of recurrence three years after surgery.

Keywords: Ovary, Adenofibroma, Clear cells

Introduction

Ovarian adenofibromas are characterized histologically by a prominent fibrous tissue component in addition to epithelial elements. They are classified by the World Health Organization according to epithelial type into serous, endometrioid, mucinous, clear cell and mixed categories and according to the degree of epithelial proliferation and atypia into benign, borderline and malignant variants.[1] The epithelium is usually of the serous type. Tumors with epithelium composed of hobnail, cuboidal or columnar cells with abundant clear or eosinophilic cytoplasm are classified as clear cell type. Clear cell changes in ovarian tumors are usually associated with a malignant process; benign and borderline clear cell tumors are quite uncommon.[1] There are only a few documented cases of clear cell adenofibromas, particularly with atypical histologic changes in the tumor epithelium. Compared to clear cell adenocarcinomas, borderline (atypical) clear cell tumors are very rare.[2-5] Clear cell changes in adenofibromas have diagnostic implications as other ovarian tumors with clear cell changes, such as carcinomas, can be associated with these tumors and have to be considered in the differential

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diagnosis. Clear cell adenofibroma has been suggested as a precursor for clear cell adenocarcinoma.[6,7] We describe here a 57-year-old postmenopausal woman with an ovarian mass that was diagnosed as an atypical proliferating clear cell adenofibroma.

Case Report

A 57-year-old female presented with complaints of postmenopausal bleeding and a lump in the left side of her abdomen for two months. The patient was afebrile. There was no jaundice or lymphadenopathy. Systemic examination was normal except for mild pallor. On local examination, a large well-defined solid, non-tender mass was palpable in the abdomen as well as in the pouch of Douglas. The mass did not appear to be associated with the uterus as the uterus was of normal size. Investigations revealed a hemoglobin of 10 gm% and total cell count of 8000 cells/cu.mm. Chest X-ray was normal. CA-125 was 90 IU/ml Abdominal ultrasound showed a 10 cm large, solid mass in the left adnexa. The patient underwent a hysterectomy with bilateral salpingo-oophorectomy along with resection of the lymph nodes and a section of the omentum. The specimen was sent for histopathological examination.

On gross examination, the uterus and cervix was 6×4×3 cm with an endometrial thickness of 2 mm. The tumor mass was 10 cm in size with solid white nodular outer surface. Cut surface was also nodular, firm and white. The right ovary was remarkable except for a 2 cm hemorrhagic corpus luteum. Omental tissue was 30×10×2 cm. Common iliac, internal and external lymph nodes were also evaluated.

Light microscopy of the tumor showed glands and small cystic spaces regularly distributed in dense fibrous stroma (Figure 1a). Stroma was condensed around the glands. These glands and spaces were lined by polyhedral eosinophilic cells with focal tufting. Periodic acid-Schiff positive secretions were present in the lumen of the cystic spaces (Figure 1b). Nuclei were round, enlarged, hyperchromatic, with nucleoli. Mitosis was less than 2/10 high power field (HPF) (Figures 2 a,b). There was no stromal invasion or metastases in the omentum and lymph nodes. A diagnosis of atypical (borderline) proliferating clear cell adenofibroma was made on the basis of these histological findings. The patient has come for follow-up regularly and remains alive and well without signs of recurrence three years after surgery.

Discussion

Ovarian adenofibromas are subclassified according to the degrees of cytological and architectural atypicality of the epithelial component and the presence or absence of stromal invasion into benign, borderline and malignant groups. Tumors composed of simple glands lined by one to two layers of epithelium that show no significant atypia are classified as benign. Those

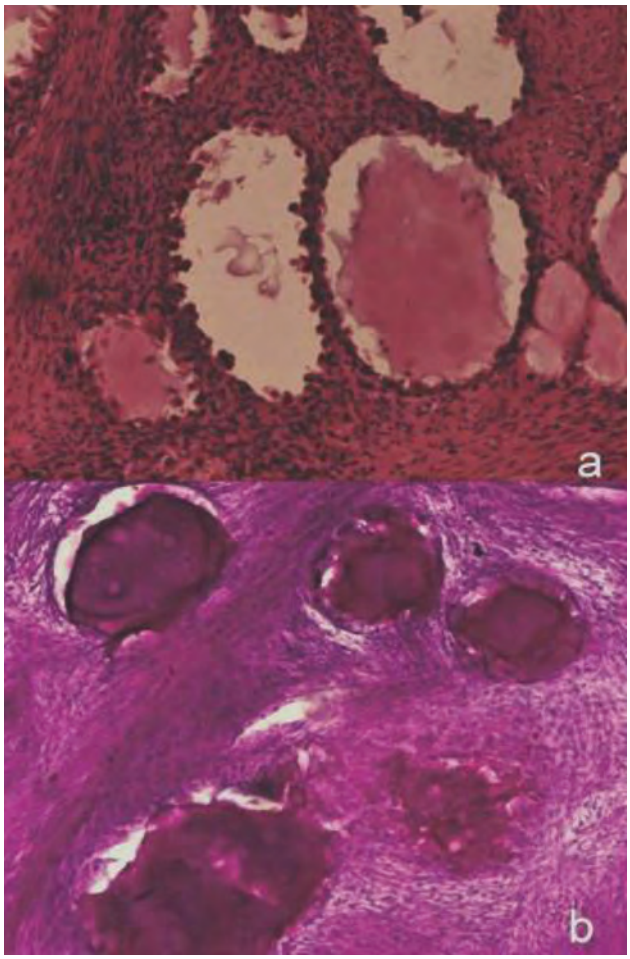

Figure 1a. Clear cell adenofibroma showing fibrous stroma and small glands lined by atypical cells with prominent tufting. (H&E, 10x) b. Clear cell adenofibroma ovary showing a periodic acid-Schiff positive secretion. (PAS,10×)

that contain glands or small solid nests composed of cells with nuclear characteristics of low-grade malignancy without invasion of the stroma are designated as borderline.[1,3] The present case had similar features of an atypical (borderline) adenofibroma ovary. Most ovarian tumors with clear cell change are carcinomas; benign and borderline clear cell tumors are uncommon.[1] The differential diagnosis of ovarian clear cell adenofibroma with atypical epithelial features should include clear cell adenocarcinomas, as well as serous, yolk sac and metastatic tumors.[8]

The most important differentiating feature from a carcinoma in this case was the absence of stromal invasion. Other microscopic features which identify the tumor as malignant are epithelial proliferation and architectural complexity, high nucleo-cytoplasmic ratio, nuclear atypia and high mitotic activity with atypical mitotic figures. Characteristic features in clear cell carcinoma include papillary architecture, a prominent clear eosinophilic cytoplasm and nuclear hobnailing.

Clear cell adenofibromas can be pure or mixed with malignant clear cell carcinomas.[8] Clear cell adenofibroma has been suggested as a precursor for clear cell adenocarcinoma. It has been determined that loss of heterozygosities on 5p, 10q and 22q are frequently present in both clear cell adenofibroma and clear cell adenocarcinoma. Clear cell adenofibromatous components, particularly the borderline type coexist in ovarian clear cell adenocarcinomas.[6,7] Clear cell carcinomas have also been divided into cystic and adenofibromatous groups. The adenofibromatous group, often diagnosed at a more advanced stage, shows less frequency with endometriosis and has a less favorable outcome.[9] Recently a study has proposed that endometriosis is the underlying precursor for both the cystic and the adenofibromatous types of clear cell carcinoma.[10] The evidence implies that there are two different pathogenetic pathways for ovarian clear cell adenocarcinomas; endometriosis-associated and adenofibroma-associated. The present case had no associated endometriosis or foci of clear cell carcinoma.

Since clear cell adenocarcinoma sometimes is accompanied by benign and borderline adenofibromas, therefore it is important to sample the tumor carefully and judiciously search for indicators of malignant change. Identification of the foci of stromal invasion can be difficult. Small solid masses of clear cells in the stroma raise the question of invasion. Bell et al. have proposed certain criteria for detecting the presence of invasion, such as the presence of glands, small solid nests of malignant cells, or single malignant cells that extend irregularly into the stroma and the presence of a desmoplastic, myxoid or edematous stromal reaction.[3] Occasionally minute foci of invasion can be identified and these tumors are designated 'microinvasive'.[1] In the present case, no evidence of stromal invasion was observed.

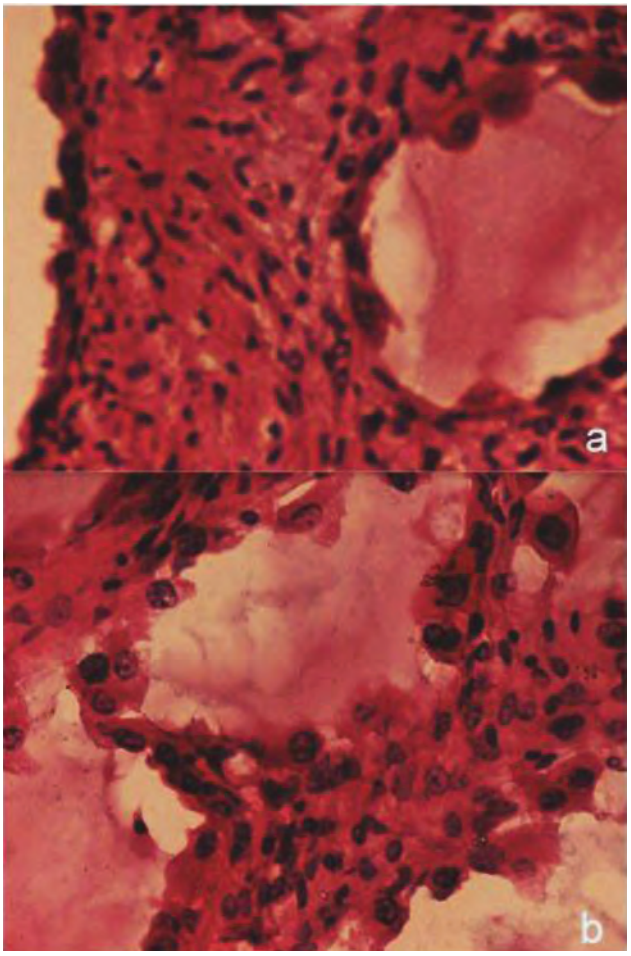

Figure 2a. Glands lined by cells with eosinophilic cytoplasm, atypical nuclei and hobnailing. (H&E, 40x) b. Cells with nuclear atypia, increased nuclear-cytoplasmic ratio, coarse chromatin and prominent nucleoli. (H&E, 40×)

When nuclear atypia is more marked with coarse chromatin clumping, prominent nucleoli and increased mitotic activity then the tumor is best designated as a 'borderline clear cell adenofibroma with intraepithelial carcinoma'.[1,3]

The largest series of borderline clear cell adenofibroma has been reported by Bell et al.[3] in a series of 11 patients whose mean age was 61 years. Patients' tumors ranged in diameter from 6.5 to 23 cm (mean: 14 cm). Presenting complaints were non-specific and included irregular vaginal bleeding, abdominal fullness and pelvic pain. Tumors were unilateral in 10 out of 11 cases. The clinical features of the present case was similar to those in the above study, except that the mass on local examination was non-tender. This was a new finding compared to previous case reports and has implied that clear cell adenofibroma in a postmenopausal female can be either tender or non-tender.

Borderline adenofibromatous tumors have a benign course following removal of the ovary. Only one patient was reported to have a questionable lung metastasis four years after presentation. Another patient with microinvasive tumor had a pelvic recurrence 3.3 years postoperatively.[1,3] The present case has no signs of recurrence three years following surgery.

Conclusion

Borderline clear cell adenofibromas of the ovaries are extremely rare tumors. The tumor mass on local examination can be either tender or non-tender. Because of common association with clear cell adenocarcinomas, extensive sampling of the tumor mass is advised. Identification of the foci of micro-invasion is also important to alert the clinician for long-term follow-up of the patient.

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