An 82-Year-Old Woman With a 25-cm Abdominal Mass

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An 82-year-old white woman presented with progressive leg edema and low back pain. Six months later, she developed abdominal swelling. Her past medical history included hypertension and simple hysterectomy for leiomyomata 40 years previously. An abdominal ultrasound demonstrated a 25-cm, solid, partially cystic mass in her right lower abdomen. Her pertinent laboratory workup showed a serum CA 125 level as high as 2100 U/mL (2100 kU/L) (normal, <35 U/mL [<35 kU/L]) and a serum calcium level of 9.2 mg/dL (2.3 mmol/L) (reference range, 8–10.2 mg/dL [2.05–2.54 mmol/L]). The patient underwent bilateral salpingo-oophorectomy, lymph node dissection, omentectomy, and excision of a Meckel diverticulum.

The specimen received for pathologic examination was a 1010-g, 25.0 × 15.0 × 11.0-cm mass, designated ''right ovary.'' External examination revealed a solid, lobulated, but well-encapsulated mass with a rough surface; it was associated with a few thin-walled cysts filled with clear fluid (Figure 1, A). The largest cyst was multiloculated and had a granular, variegated lining (7.0 × 4.0 cm). A section of the mass had a focal ''honeycomb'' appearance (3.0 × 4.0 cm) (Figure 1, B).

The solid component of the tumor (arrows, Figure 1, B) was composed of dense fibrotic stroma with scattered glands lined by either bland-appearing clear cells or by clear cells showing variable degrees of cytologic atypia. Amorphous pink material was focally present within the cytoplasm and lumen of the glands (Figure 2, A and B). No evidence of invasion was identified. The grossly cystic areas (double arrow, Figure 1, B) consisted of papillary and tubulocystic growth patterns. The cells were highly atypical with pleomorphic nuclei, clear cytoplasm (Figure 3), and characteristic peglike hobnail cells (Figure 4). Multiple foci of stromal invasion were present. The lymph node dissection, omentum, and a segment of small bowel were free of tumor. The left ovary was unremarkable. Immunohistochemical studies demonstrated strong positivity for cytokeratin 7, CA 125, and α_1-antitrypsin, and were negative for cytokeratin 20, human chorionic gonadotrophin, carcinoembryonic antigen, and α-fetoprotein. The pink material in the lumen and intracytoplasmic eosinophilic globules was positive for periodic acid–Schiff.

What is your diagnosis?

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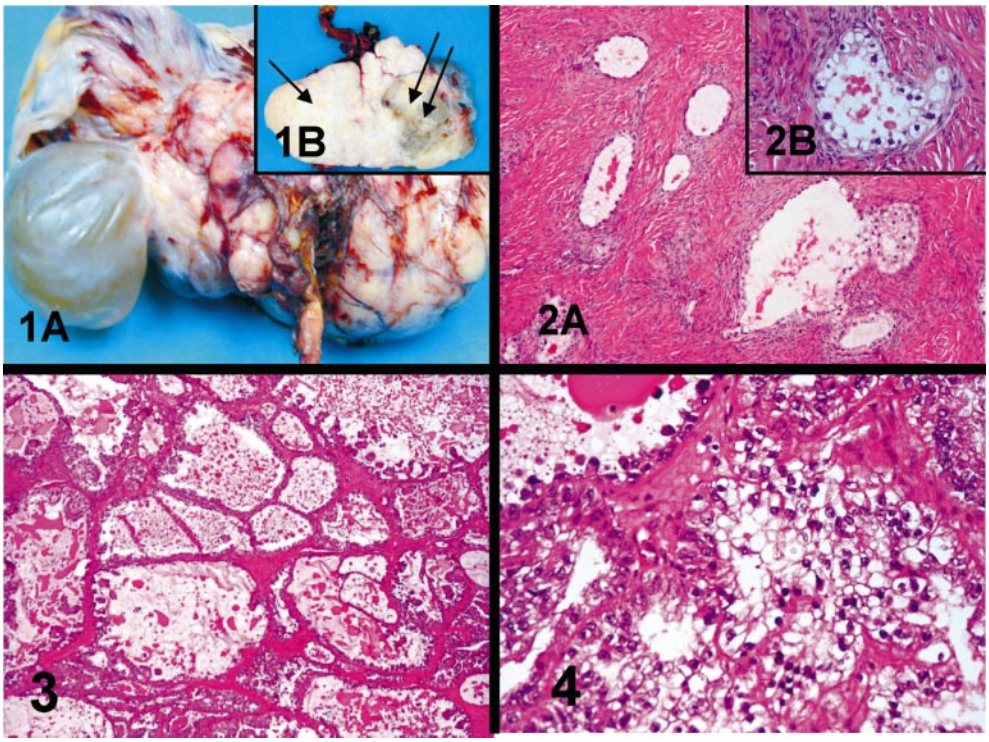

Pathologic Diagnosis: Clear Cell Carcinoma of Ovary Associated With Clear Cell Adenofibroma

Clear cell tumors of the ovary are relatively uncommon. Three main subtypes are recognized: clear cell adenofibroma, clear cell adenofibroma of borderline malignancy (also called borderline clear cell tumor or proliferating clear cell tumor), and clear cell carcinoma.[1] Most clear cell tumors are clear cell carcinomas with either prominent epithelial or fibromatous components.[2] When the fibromatous component is prominent, the tumor should be properly sampled to rule out malignant epithelial cells and invasion. Furthermore, other primary or secondary tumors of the ovary with clear cell change, such as dysgerminoma, yolk sac tumor, steroid cell tumor, endometrioid carcinoma with secretory change, and metastatic renal cell carcinoma should be excluded before a diagnosis of clear cell carcinoma is established.

Patients with clear cell adenofibroma, clear cell adenofibroma of borderline malignancy, and clear cell carcinoma may have a similar clinical presentation. They can be asymptomatic until the tumor grows to a certain size. Pleural effusion, ascites, and swelling of lower extremities are more commonly seen in the late stages of clear cell carcinoma. Most clear cell tumors are unilateral and confined to the ovary (stage I) at presentation.[1] Clear cell tumors may be similar both grossly and microscopically, showing solid and cystic areas with clear and hobnail cells. Although these similarities exist, there are distinct pathologic features that distinguish benign, borderline, and invasive clear cell neoplasms.

A pure clear cell adenofibroma is extremely rare, and clear cell adenofibromas of borderline malignancy constitute less than 1% of borderline tumors of the ovary.[3] Microscopically, borderline clear cell tumors may have the same fibromatous stroma as adenofibromas, but they also show a variable degree of glandular proliferation with cytologic atypia. Mitotic activity (≤3 mitosis/high-power field) may be found.[1] Capsular, stromal, and lymphovascular invasion should always be absent. Clear cell carcinomas constitute about 5% to 10% of all primary ovarian malignancies.[1] They often occur at a mean age of 57 years and have strong association with endometriosis and hypercalcemia. Clear cell carcinomas are uniloculated or multiloculated cysts that may have solid nodules protruding into the lumen. Microscopically, clear cell carcinomas are distinct from benign or borderline tumors by showing various growth patterns and tumor invasion into a prominent hyalinized stroma. Papillary and tubulocystic patterns are the most common, and epithelial elements predominate. Also, sheets of polyhedral cells with clear vacuolated cytoplasm, hyperchromatic nuclei, prominent nucleoli, and dissecting connective tissue septa are commonly present. The tumor cells contain ''targetoid'' hyaline cytoplasmic inclusions, which are positive for periodic acid–Schiff. Hobnail cells with big hyperchromatic nuclei may also be present. Cysts can be lined by flat epithelium. A combination of different histologic patterns and cytologic features are not uncommonly found in the same specimen.

Differential diagnoses of clear cell tumors mainly include yolk sac tumor, dysgerminoma, and metastatic renal clear cell carcinoma. Clear cell tumors can have a loose edematous stroma similar to the reticular pattern of yolk sac tumor. In general, yolk sac tumor or dysgerminoma are more common in a younger age group. Findings of elevated serum α-fetoprotein levels as well as characteristic ''Schiller-Duval bodies'' are helpful diagnostic tools in identifying yolk sac tumors. Solid sheets of clear cells in clear cell tumors may suggest the diagnosis of dysgerminoma. A dense fibrocollagenous stroma in dysgerminoma can mimic the solid component of clear cell carcinoma. However, the presence of lymphocytic infiltration into groups of tumor cells is a unique clue for the diagnosis of dysgerminoma. Also, the cells in dysgerminoma are more rounded and uniform in size and have more centrally placed, prominent nuclei. Dysgerminomas are strongly immunoreactive for placental alkaline phosphatase and lactate dehydrogenase and are negative for epithelial membrane antigen, while clear cell tumors are negative for placental alkaline phosphatase and lactate dehydrogenase and are only focally positive for epithelial membrane antigen. Renal clear cell carcinoma (clear cell type) can metastasize to the ovary, but in contrast to clear cell carcinoma, metastatic tumors are most commonly bilateral. A new marker, an antibody that can identify a proximal renal tubule antigen present at the brush border (RCC Ma or renal cell carcinoma marker) can be useful in differentiating the clear cells of renal origin from other tumors with clear cell features. Renal cell carcinomas also stain positively for CD10 and negatively for cytokeratin 7.[4] Although it is not common, heterologous components, such as rhabdomyosarcoma, may be present in clear cell carcinoma of the ovary.[5]

The prognosis for patients with pure clear cell adenofibroma or borderline clear cell tumor is favorable.[2,6] However, when these tumors are associated with invasive clear cell carcinoma, they often display a more aggressive behavior. Clear cell carcinomas seem to have a worse prognosis than other types of ovarian carcinomas, especially in advanced stages.[7] A platinum-based chemotherapy in 336 cases of ovarian tumors (101 cases of clear cell carcinoma and 234 cases of serous adenocarcinoma) demonstrated that the 3-year and 5-year survival rates for patients with stage III clear cell carcinoma were significantly lower than those observed in patients with stage III serous adenocarcinoma.[8] Clear cell carcinomas are also more chemoresistant than other ovarian carcinomas. A 43-case study showed a greater rate of chemoresistance in clear cell carcinomas of the ovary (88.9%) than in serous adenocarcinomas of the ovary (57.1%).[9]

In summary, our patient developed clear cell carcinoma associated with clear cell adenofibroma and clear cell adenofibroma of borderline malignancy. Although the association of clear cell adenofibroma of borderline malignancy with clear cell carcinoma has been reported previously, it is not yet clear whether clear cell carcinoma can arise from a borderline tumor.

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