Obstructive Uropathy as a Major Presentation of Ovarian Clear Cell Adenocarcinoma

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Clear cell carcinoma of the ovary is rarely seen. It comprises 7.4% of all ovarian carcinomas and 2.4% of ovarian epithelial neoplasms. Patients are usually diagnosed between the ages of 40 and 70 years, with the peak incidence at the age of 52 years, and approximately 1/3 to 2/3 are nulliparous [1]. In previous reports, the presenting symptoms were typically related to an enlarging abdominal mass [2], and some cases were associated with endometriosis, vascular thrombotic events or paraneoplastic hypercalcemia. Hydronephrosis was demonstrated at urography in 11% of cases with carcinoma of the cervix and ovary [3]. It is unusual for acute renal failure to be a presenting symptom [4–6]. Herein, we report a 60-year-old female who was found to have a hidden end-stage clear cell carcinoma of the ovary with primary manifesting symptoms of obstructive nephropathy with acute renal failure.

A 60-year-old diabetic, menopausal woman, gravida 4, para 3, abortus 1, who had undergone oral hypoglycemic agent treatment for 10 years, came to our emergency room because of nausea and vomiting for the past 2 weeks. She had visited another hospital 2 weeks previously because of the same symptoms. A panendoscopy had been performed and peptic ulcer diagnosed. Proton pump inhibitor drugs were given. Unfortunately, the symptoms persisted, and progressive oliguria (from 3,600 mL to 400 mL per day) and bilateral lower leg edema had developed over the following days, although no other abdominal symptoms were present.

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The patient was admitted to another local hospital in August 2006 because of the aforementioned symptoms. Without symptom relief, she was found to have acute renal failure secondary to obstructive uropathy. At this time, an emergent bilateral double-J insertion and right percutaneous nephrostomy were performed to relieve the obstructive symptoms. Non-contrast computed tomography showed a retroperitoneal mass and a right ovarian mass. CA-125 was noted to be elevated to 23,812.8 U/mL, prompting a diagnosis of ovarian cancer.

After 14 days, the patient was transferred to our emergency room. Her renal function had improved (blood urea nitrogen [BUN], 10 mg/dL; creatinine, 0.7 mg/dL) compared with the results 2 weeks previously (BUN, 114 mg/dL; creatinine, 9.15 mg/dL). Abdominal ultrasonography and computed tomography scan disclosed a suspected malignant pelvic mass (5.2 × 3.8 cm) with retroperitoneal lymph node metastasis and bilateral obstructive uropathy. Encasement of the right distal ureter was noted, and the left distal ureter was also involved (Figure 1). On admission, her vital signs were stable and the physical examination was unremarkable except for grade II bilateral lower leg edema. Laboratory tests showed a normal blood cell count and biochemistry data. Other than an elevated CA-125 level (26,000 U/mL), tumor markers including CEA, CA-199, α-fetoprotein, human chorionic gonadotropin and lactate dehydrogenase were within normal ranges. Pelvic ultrasonography with color Doppler revealed a right adnexal cystic mass (5.22 × 3.8 cm) with papillary growth and low vascular resistance of blood flow (resistance index, 0.5; pulsatility index, 0.75) (Figure 2).

A staged operation was performed after the sixth day of hospitalization. Intraoperatively, a cystic mass with an intact surface was found over the right ovary, with a small amount of ascites. Frozen section biopsy of the

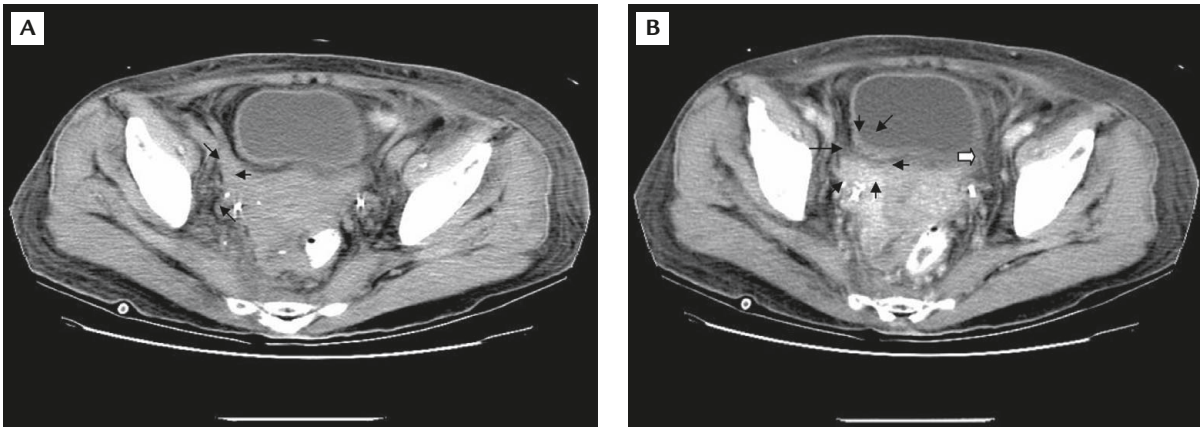

Figure 1. (A) Before contrast medium injection, soft tissue density is present in the right adnexal region. The right distal ureter is encased by the mass. The hyperdense ureteral stents identify (arrows) the position of the ureter. (B) Post-contrast enhanced computed tomography scan showing enhancement of the right ovarian malignancy (black arrows) surrounding the right distal ureter. There are also cancer lesions on the contralateral side causing left ureteral obstruction (white arrow).

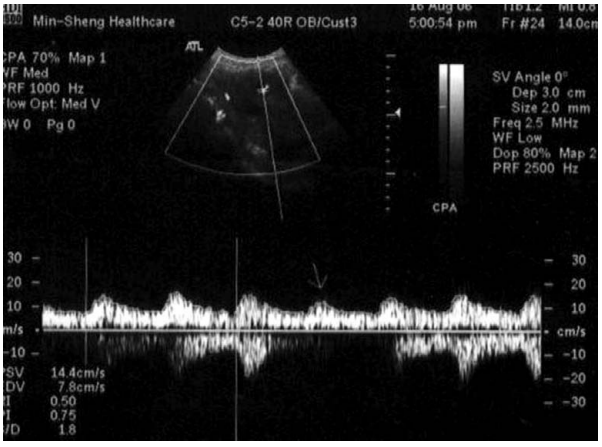

Figure 2. Pelvic color Doppler revealing a right complex heterogenous mass of about 5.22 × 3.8 cm with vascularity (resistance index, 0.5; pulsatility index, 0.75).

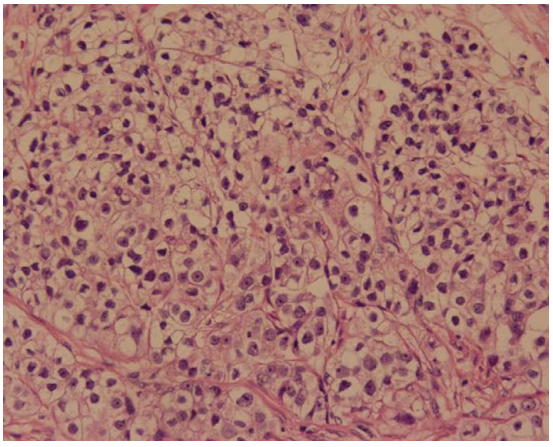

Figure 3. The neoplasm has a solid pattern and is composed of polygonal cells with abundant cytoplasm. Most cells have clear cytoplasm but some are eosinophilic. Nuclei exhibit pleomorphism, irregular nuclear membranes, distinct nucleoli, and abnormal chromatin patterns (hematoxylin and eosin, 100×).

bilateral ovarian tumor showed an ovarian malignancy with adenocarcinoma. Surgery consisted of a total hysterectomy and bilateral salpingo-oophorectomy, partial omentectomy, appendectomy and bilateral pelvic lymph node dissection. Para-aortic lymph node sampling was not performed because of severe retroperitoneal fibrosis. The pathology report revealed high-grade clear cell carcinoma of bilateral ovaries with diffuse miliary tumor seeding (0.5–1.0 cm in size) over bilateral fallopian tubes, uterus, cul-de-sac and omentum. The liver surface and diaphragm were not involved. Cytologic examination of the ascites was positive for malignant cells. Thus, the final diagnosis was clear cell carcinoma of the ovaries, histologic grade 3, poorly differentiated and FIGO stage IIIc (Figure 3).

The patient received one course of postoperative chemotherapy with carboplatin (area under the curve, 563; creatinine, 0.7 mg/dL; total 560 mg) and paclitaxel (175 mg/m^2) with no complications. Unfortunately, during the next chemotherapy course, progressive ileus and poor control of blood sugar occurred. An attack of hypoglycemia led to a vegetative status, followed by upper gastrointestinal bleeding and pleural effusion. The patient died of respiratory failure 2 months after surgery.

Although clear cell carcinoma of the ovary comprises less than 5% of all ovarian malignancies, it has received attention because of controversy regarding its historical classification, poor prognosis and distinctive clinical characteristics. This tumor was first described in 1939 by Schiller [6], who coined the term "mesonephroma" to describe an ovarian neoplasm composed of clear

and hobnail cells with a pattern resembling immature glomeruli. Another doctor, Teilum, suggested that Schiller's original tumors were composed of two distinct populations [7], one of germ cell origin with more aggressive malignant tendencies and occurring in younger women, and another less aggressive tumor, shown ultimately to be of müllerian origin and occurring in older women [8]. The less aggressive variety was subsequently categorized in 1946 as clear cell ovarian tumor, an epithelial neoplasm. In 1973, the World Health Organization defined clear cell carcinoma of the ovary as a lesion characterized by clear cells growing in solid, tubular or glandular patterns, as well as hobnail cells lining tubules and cysts [9]. The obvious and distinctive behavior of this tumor will become clearer after more cases are detected and studied.

Previous studies demonstrated a tendency for clear cell carcinoma to be detected at an early stage. The proportion of stage I/II tumors ranged from 59% to 71%. One series showed that 50% of cases were stage I at the time of diagnosis and 15% were stage II. One of the reasons for early detection is explained by the slow-growing behavior of the tumors and frequent presentation as large pelvic masses [10]. Most cases (60%) were unilateral, and only 4% of early stage cases were bilateral. The typical gross appearance was that of a large uniocular cyst (15–20 cm) with one or more white, yellow or light brown solid areas of tumor protruding into the lumen. Variable amounts of hemorrhage and necrosis might be present. The most representative symptoms were usually related to an enlarging abdominal mass. Nevertheless, some might equally be associated with endometriosis, vascular thrombotic events, and paraneoplastic syndromes such as hypercalcemia [2–6]. As the early symptoms are always vague, there is a great likelihood of delay in diagnosis by physicians until the patient presents with marked abdominal distension and/or complaints of abdominal pain. In contrast, our case initially presented with nausea and vomiting, and gastrointestinal symptoms due to uremia from obstructive uropathy, rather than due to compression by the mass.

Clear cell adenocarcinoma is one of the unfavorable prognostic features of early stage disease that might lead to a recommendation for further therapy, including surgical removal of the bulk of the tumor, chemotherapy or radiation. The survival rate of patients has dramatically improved with the prescription of platinum-based chemotherapy after surgical intervention. However, there still exist a large number of patients who show no response to these treatments. Although response to anticancer drugs is not easy to predict, *in vitro* studies suggest that acquired resistance to cisplatin has been associated with increased levels of glutathione and glutathione S-transferase activity, increased metallothionein, and decreased accumulation of cisplatin [10].

Cervical cancer is the gynecologic malignancy most commonly associated with urinary tract obstruction, while ovarian cancer rarely causes this problem [11]. Pathoanatomic bases of obstructive uropathy most frequently present as extramural compression or direct ureteral invasion of a primary localized advanced tumor in the small pelvis and/or retroperitoneum (lymph nodes metastases). The final result of obstructive uropathy is hydronephrotic atrophy, renal insufficiency, and uremia. Although immediate release of the obstruction is essential, the intactness of the urinary tract and complete relief from the obstruction are dependant on the definitive treatment of the cancer [12]. Baker et al recognized that ureteral obstruction at the time of disease diagnosis was associated with a poor prognosis [13].

To our knowledge, this is the first report in Taiwan of clear cell adenocarcinoma of the ovary initially presenting as obstructive uropathy. There is only one other such case report, which was published in India in 1994 [11]. Our case, a 60-year-old woman without prior abdominal complaints from the mass effect, was eventually diagnosed with a hidden clear cell carcinoma of the ovary that led to severe retroperitoneal fibrosis and obstructive nephropathy. We should bear in mind that clear cell adenocarcinoma of the ovary should be placed on the list of differential diagnoses when we encounter a patient who has ovarian cystic lesions but presents with symptoms of obstructive uropathy, without clinically recognizable abdominal manifestations.

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