Primary clear cell carcinoma of the peritoneum: report of two cases and a review of the literature

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Summary

The most common neoplasms of the peritoneum are malignant mesothelioma and serous papillary adenocarcinoma. Clear cell carcinoma (CCC) is mostly derived from the ovary and often associated with endometriosis. We describe the clinicopathologic features of two cases diagnosed as CCC of the peritoneum origin. Case 1, a 53-year-old woman, presented with upper abdominal and pelvic tumors. Case 2, a 66-year-old woman, presented with massive ascites and abdominal tumor. The ovaries and uterine endometrium of these cases were not affected, and the tumors were diagnosed as Stage IIIc CCC of the peritoneum origin. Pathologically, endometriosis was not observed in either case. Adjuvant chemotherapy using irinotecan and cisplatin was effective in one case. The cases and a review of the literature suggested that residual tumor volume size determines the survival of these patients, and that the tumors show resistance to conventional platinum-based chemotherapy.

Key words: Clear cell carcinoma; Peritoneum; Surgery; Irinotecan; Cisplatin.

Introduction

The most common neoplasms of the peritoneum are malignant mesothelioma and serous papillary adenocarcinoma [1, 2]. Rarely, mucinous and clear cell adenocarcinomas (CCC) can be observed. A review search of Medline over 20 years revealed only four cases of clear cell carcinomas of peritoneal origin [3-6]. Our two case series of CCC of peritoneal origin are presented with a review of the reported four cases.

Case reports

Case 1

A 53-year-old postmenopausal woman presented to our hospital with the complaint of abdominal distension and mild abdominal pain. Vaginal examination revealed no abnormal findings in the uterus and adnexa, however, a small amount of ascites was observed in the pelvis. Computed tomography (CT) images revealed the largest tumor was located between the right lobe of the liver and diaphragm, and other small tumors less than 2 cm in diameter were observed in the omentum and peritoneum of the abdomen. An enhanced tumor approximately 13 x 5 cm in diameter was observed by magnetic resonance (MR) images of the upper abdomen (Figure 1A). Tumor origin was not suggested by positron emission tomography (PET) images. The patient had no history of dysmenorrheal or pelvic pain suggesting endometriosis, or other medical history. The serum level of CA125 was elevated to 467 U/ml (normal range, below 35 U/ml). Serum levels of LDH, carcinoembryonic antigen (CEA) and CA19-9 were within normal range. At surgery, the largest tumor located on the upper abdomen was severely adhered to the liver and diaphragm, and the patient underwent biopsy of this tumor and the disseminated tumors. The uterus and bilateral ovaries were not affected with disseminated tumors. Pathologically, all tumor cells showed papillary structures and a hobnail appearance (Figure 1B). Some of the tumor cell had clear cytoplasm and hyperchromatic nuclei. There were no tumor cells in either ovary microscopically, and endometriosis was not observed in any resected samples. The tumor was diagnosed as clear cell carcinoma of peritoneal origin.

The patient received one course of postoperative chemotherapy using irinotecan hydrochloride and cisplatin, but the disease progressed. Next, she received one course of chemotherapy with paclitaxel and carboplatin, however, the tumor continued progression. Subsequently, she received the best supportive care and died of disease five months after surgery.

Case 2

A 66-year-old postmenopausal woman presented with the complaint of mild abdominal pain. Clinical examination revealed a large cystic and solid tumor of the abdomen. She had no past medical history. MR images of the lower abdomen showed a large cystic and solid tumor approximately 20 x 15 cm in diameter and a small amount of ascites (Figure 2A). The serum levels of CA125 and CA19-9 were elevated to 347 U/ml and 1918 U/ml (normal range, below 37 U/ml), respectively. Serum levels of LDH and CEA were within normal range. There were no abnormal findings by CT in other organs including the kidney. At surgery, the large tumor was located on the infracolic omentum and part of the tumor was adhering to the peritoneum of the right abdominal wall, and three cystic tumors approximately 4-5 cm in diameter were disseminated in the abdominal cavity. There were no abnormal findings in the uterus or bilateral adnexa. The patient underwent tumorectomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and paraaortic lymphadenectomy. There were no macroscopic residual tumors left. The pathologic find-

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Fig. 1

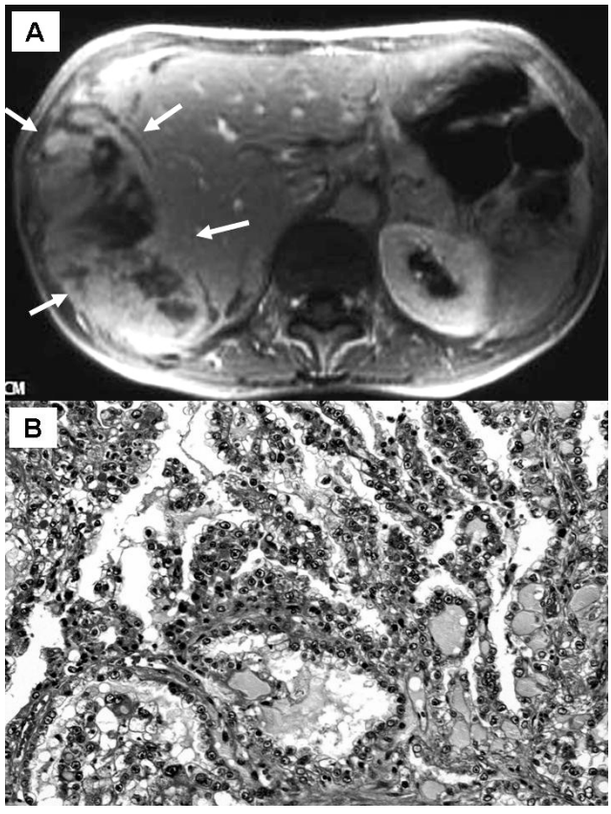

Figure 1. — A. Enhanced magnetic resonance (MR) images of the upper abdomen revealed an enhanced tumor approximately 13 x 5 cm in diameter. B. High power view of the tumor located between the liver and diaphragm. The tumor cells showed papillary structures and hobnail appearance. Some of the tumor cells had clear cytoplasm and hyperchromatic nuclei (hematoxylin & eosin; original magnification x 100).

Fig. 2

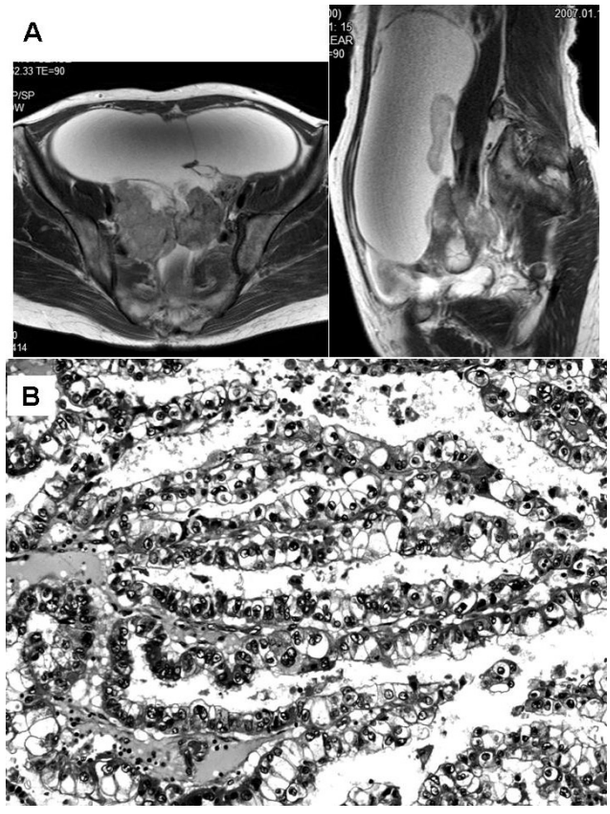

Figure 2. — A. Magnetic resonance (MR) images of the lower abdomen showed a large cystic and solid tumor about 20 x 15 cm in diameter and a small amount of ascites. B. High power view of the tumor. Tumor cells were polygonal in shape and arranged in a solid nest, and had clear cytoplasm, hyperchromatic nuclei, and clear cell boundaries (hematoxylin & eosin; original magnification x 100).

ings of the tumor revealed that tumor cells were polygonal in shape and arranged in a solid nest, and had clear cytoplasm, hyperchromatic nuclei, and clear cell boundaries (Figure 2B). The tumor was diagnosed as clear cell carcinoma of peritoneal origin. The patient received six courses of combination chemotherapy with irinotecan hydrochloride and cisplatin. She was well without evidence of disease 20 months after surgery.

Discussion

The first case of a peritoneal adenocarcinoma was reported in 1959 [7], and since then many reports have described tumors of this entity. Histologic subtype of most reported cases is serous papillary adenocarcinoma, and clinical behavior of the tumor is similar to that of Stage III ovarian epithelial adenocarcinoma [8-10]. On the other hand, adenocarcinomas with other histogy including clear cell and mucinous subtypes have rarely been observed.

CCC of the female genital tract derives mostly from the ovary, and the association with endometriosis has been well established. Advanced cases with CCC have a worse prognosis compared with those with serous adenocarcinoma of the ovary, mainly due to chemotherapy-resistant characteristics [11, 12]. CCC tumors occasionally developed from extra-ovarian endometriosis [13, 14], and showed loco-regional growth and favorable prognosis. A search of MEDLINE over the last 20 years showed only four cases of CCC deriving from the peritoneum. The characteristics of the reported four cases and the present two cases are shown in Table 1. In all six cases, there was no pathological or macroscopical coexistence of endometriosis; however, two cases had a past history of endometriosis. It might be possible that these tumors were derived from a peritoneal lesion of endometriosis implantation. Interestingly, two of the six cases had a previous history or concurrent existence of endometrial endometrioid adenocarcinoma. A study analyzing endometrial CCC tumors coexistent with endometrioid adenocarcinma suggested that CCC of the endometrium was derived from putative precursor lesions which were isolated glands or surface epithelium showing cytoplasmic

Table 1. — *Clinical profiles of four reported cases and two current cases of peritoneal clear cell carcinoma.*

Case	1	2	3	4	5	6
Author	Case 1	Case 2	Evans H. *et al.*	Lee K.R. *et al.*	Ichimura T. *et al.*	Terada T. *et al.*
Publication year	–	–	1990	1991	2001	2005
Age (years)	53	66	54	67	45	49
Past history or concurrent disease	none	none	bilateral endometrial cyst (18 and 16 years before), endometrial hyperplasia (18 years before), type II diabetes	grade 1 endometrioid adenocarcinoma of uterine corpus Stage Ic (concurrent)	bilateral endometrial cysts (17 months before)	grade 3 endometrioid adenocarcinoma of uterine corpus (15 months before)
Tumor size	5 cm	15 cm	18 cm	6 cm	NA	3 cm
Location	upper abdomen	peritoneum of right abdominal wall	sigmoid mesocolon	pelvis	pelvis	great curvature of stomach
Residual tumor diameter	> 2 cm	0 cm	0 cm	> 2 cm	0 cm	0 cm
CA125	467 IU/l	277 IU/l	NA	2218 μ/ml	28 IU/l	NA
Clinical outcome	DOD (5 months)	NED (20 months)	NA	NA	Recurrence at lymph node (32 months)	NED (6 months)

NA, not available; AWD, alive with disease; NED, no evidence of disease; DOD, died of disease.

clarity and/or eosinophilia with varying degrees of nuclear atypia [15]. It is possible the previous reported two cases of peritoneal CCC tumors were metastatic lesions of endometrial carcinoma which potentially harbored a precursor lesion of CCC disease. In the present two cases, there was no evidence of coexistent endometriosis and endometrial carcinoma both macroscopically and microscopically. However, it can not be ruled out that the cases had these precursor lesions of CCC disease.

Combination chemotherapy using irinotecan and cisplatin (CPT-P) was administered to the present two cases; one evaluable case (case 1) showing progressive disease. Although case 2 had advanced stage CCC tumors, the patient was well without evidence of disease 20 months after operation after six courses of adjuvant chemotherapy with CPT-P. CPT-P showed obvious effectiveness in the adjuvant setting for case 2. On the other hand, Ichimura *et al*. demonstrated that a combination with paclitaxel and carboplatin (TC) showed a partial response for recurrent peritoneal CCC tumor [5]. These two regimens, TC and CPT-P, are now being evaluated as the postoperative chemotherapy for clear cell adenocarcinoma of the ovary in a worldwide prospective randomized clinical trial, GCIG/JGOG3017. The regimen selected by this trial would also be a candidate for CCC of peritoneal origin.

Conclusion

The prognosis of the cases with CCC of peritoneal origin seemed to be determined mainly by the extent of the surgery, and there might be less impact of conventional chemotherapy upon survival. Although it is emphasized that the completion of optimal cytoreductive surgery is recommended for peritoneal CCC cases, investigation of chemotherapeutic regimens including molecular targeting agents are needed for further improvement of prognosis of these patients.

References

[1] Gompel C., Silverberg S.G. (eds.). Pathology in Gynecology and Obstetrics, 4th edition, Philadelphia, Lippincott, 1994, 414.
[2] Eltabbakh G.H., Piver M.S.: "Extraovarian primary peritoneal carcinoma". *Oncology* (Williston Park), 1998, *12*, 813.
[3] Evans H., Yates W.A., Palmer W.E., Cartwright R.L., Antemann R.W.: "Clear cell carcinoma of the sigmoid mesocolon: a tumor of the secondary müllerian system". *Am. J. Obstet. Gynecol*., 1990, *162,* 161.
[4] Lee K.R., Verma U., Belinson J.: "Primary clear cell carcinoma of the peritoneum". *Gynecol. Oncol.,* 1991, *41,* 259.
[5] Ichimura T., Ishiko O., Nishimura S., Kojima T., Shimura K.: "Primary peritoneal clear cell carcinoma: excellent results from paclitaxel and carboplatin combination chemotherapy". *Oncol. Rep*., 2001, *8,* 1243.
[6] Terada T., Kawaguchi M.: "Primary clear cell adenocarcinoma of the peritoneum". *Tohoku J. Exp. Med.,* 2005, *206,* 271.
[7] Swerdlow M.: "Mesothelioma of the pelvic peritoneum resembling papillary cystadenoma of the ovary". *Am. J. Obstet. Gynecol.,* 1959, *77*, 197.
[8] Bloss J.D., Liao S.Y., Buller R.E., Manetta A., Berman M.L., McMeekin S. *et al*.: "Extraovarian peritoneal serous papillary carcinoma: a case-control retrospective comparison to papillary adenocarcinoma of the ovary". *Gynecol. Oncol.,* 1993, *50*, 347.
[9] Bloss J.D., Brady M.F., Liao S.Y., Rocereto T., Partridge E.E., Clarke-Pearson D.L., Gynecologic Oncology Group Study: "Extraovarian peritoneal serous papillary carcinoma: a phase II trial of cisplatin and cyclophosphamide with comparison to a cohort with papillary serous ovarian carcinoma-a Gynecologic Oncology Group Study". *Gynecol. Oncol.,* 2003, *89*, 148.
[10] Ayhan A., Taskiran C., Yigit-Celik N., Bozdag G., Gultekin M., Usubutun A. *et al*.: "Long-term survival after paclitaxel plus platinum-based combination chemotherapy for extraovarian peritoneal serous papillary carcinoma: is it different from that for ovarian serous papillary cancer?". *Int. J. Gynecol. Cancer,* 2006, *16*, 484.
[11] Goff B.A., Sainz de la Cuesta R., Muntz H.G., Fleischhacker D., Ek M., Rice L.W., Nikrui N. *et al*.: "Clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in Stage III disease". *Gynecol. Oncol.,* 1996, *60*, 412.
[12] Sugiyama T., Kamura T., Kigawa J., Terakawa N., Kikuchi Y., Kita T. *et al*.: "Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy". *Cancer,* 2000, *88*, 2584.

[13] Modesitt S.C., Tortolero-Luna G., Robinson J.B., Gershenson D.M., Wolf J.K.: "Ovarian and extraovarian endometriosis-associated cancer". *Obstet. Gynecol.,* 2002, *100,* 788.
[14] Benoit L., Arnould L., Cheynel N., Diane B., Causeret S., Machado A. *et al.*: "Malignant extraovarian endometriosis: a review". *Eur. J. Surg. Oncol.*, 2006, *32*, 6.
[15] Fadare O., Liang S.X., Ulukus E.C., Chambers S.K., Zheng W.: "Precursors of endometrial clear cell carcinoma". *Am. J. Surg. Pathol.*, 2006, *30,* 1519.

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