Case report

Primary peritoneal clear cell carcinoma. A case report and literature review

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Abstract

Primary peritoneal malignant tumors are exceptional. Among them, clear cell carcinoma is extremely rare, being only thirteen cases previously reported in the literature since 1990. We report a case of a 48-year-old Caucasian woman who was treated at the University General Hospital of Alicante. She consulted because of progressive abdominal pain over the last seven months, with the initial diagnosis of renal-ureteral colic. Ultrasound and computed tomography of the abdomen and pelvis revealed a 25 × 15 cm, well-defined cystic lesion with papillary projections, centrally located in the abdomen. The radiology report suggested a primary ovarian tumor versus peritoneal implant as the first option. The patient underwent an exploratory laparotomy showing a large cystic mass located in the urinary bladder peritoneum, firmly attached to the mesentery. The entire abdominal tumor was completely excised, and total hysterectomy with bilateral salpingo-oophorectomy and infra-colic omentectomy were performed. The final histological study revealed a new case of primary peritoneal clear cell carcinoma located in the urinary bladder peritoneum, firmly attached to the mesentery. grossly, it was well-circumscribed and multicystic with papillary growth involving part of the inner wall. Microscopically, it showed tubulocystic and papillary patterns with highly atypical tumor cells. After an extensive immunohistochemical analysis, the most relevant finding was an ARID1A loss that was corroborated by molecular analysis showing an ARID1A deletion. The patient received systemic chemotherapy with carboplatin and paclitaxel protocol (Å 4 cycles). Patient follow-up after the eighth month showed peritoneal implants predominantly in the right diaphragmatic cupule that were histologically confirmed as recurrence. She has just received another six cycles of chemotherapy with carboplatin and paclitaxel. Recognition of primary peritoneal clear cell carcinoma in this uncommon location, and exclude metastasis from the ovary, represents a diagnostic challenge.

1. Introduction

Extraovarian primary peritoneal carcinoma is a rare malignant epithelial tumor that develops from the peritoneum that lines the pelvis and abdomen. Clinically it is presented as an abdominal tumor without or minimal involvement of the ovaries and no identifiable primary tumor elsewhere (Meinhold-Heerlein et al., 2016). The most frequent histological types are malignant mesothelioma and epithelial tumors of müllerian type, with only anecdotal reports of clear cell carcinoma (CC). Only thirteen cases have been previously reported in the literature since 1990 (Shigeta et al., 2014; Insabato et al., 2015). In this report, we present a case of primary peritoneal clear cell carcinoma (PPCCC), as well as a review of the literature.

2. Case presentation

A 48-year-old Caucasian woman consulted in our hospital because of progressive abdominal pain over the last seven months, with the initial diagnosis of renal-ureteral colic. She had no history of medical or surgical issues. Menopause was at 42 years of age, and she had two pregnancies that ended in a cesarean section. A transcervical myectomy and tubal sterilization were also performed. She did not
receive hormone replacement therapy, and familial history was uneventful. The patient had no history of endometriosis. On physical examination, she presented extreme obesity (BMI 45). An elastic, non-painful tumor was palpable, reaching the left costal margin, with no signs of ascites. The gynecological examination of external genitals was normal, and transvaginal ultrasound showed normal atrophic internal genitals.

The patient was admitted to the hospital for further examination. Serum tumor markers CA-19.9 and HE4 were negative, and the CA-125 level was 57 U/ml. The ROMA was a low risk for detecting ovarian epithelial cancer. Ultrasound and CT of the abdomen and pelvis (Fig. 1) revealed a 25x15 cm, well-defined cystic lesion with papillary projections, centrally located in the abdomen, with no evidence of pelvic or retroperitoneal lymph node metastasis. A moderate amount of ascites was evident (< 300 ml), and the examination of the gastrointestinal and genitourinary system was negative. The radiology report suggested a primary ovarian tumor versus peritoneal implant as the first option.

The patient underwent an abdominal xiphopubic laparotomy that showed a large smooth cystic mass of 25–30 cm that occupied practically the entire abdomen (Fig. 2), firmly attached to the urinary bladder peritoneum and to the root of the mesentry. No more abdominal disease was seen, and there was no evidence of endometriosis. Both ovaries and fallopian tubes were grossly normal in appearance. The entire abdominal tumor was completely excised, with no visible residual disease. After its opening, approximately 3 L of serous fluid emanated and a multilocular tumor with papillary growth was evidenced. An intraoperative frozen section was taken from the papillae showing a papillary adenocarcinoma. Surgery was completed with a total hysterectomy with bilateral salpingo-oophorectomy and infra-colic omentectomy.

The postoperative period was normal, and the patient received the hospital discharge after 72 h. No further complications were reported. After an extensive sampling of the lesion, tissue was formalin-fixed paraffin-embedded and stained with H&E. Immunohistochemistry was performed on tumor sections using the Dako Omnis G1100 Advance staining system (Dako/Agilent, Copenhagen, Denmark) by the standard avidin–biotin method (EnVision FlexTM detection system; Dako/Agilent Technologies; Carpinteria, CA) using a panel of primary antibodies (Table 1). We further performed next generation sequencing (NGS) analysis to detect molecular alterations using a custom gene panel previously published (Rosa-Rosa et al., 2019). Target genes were: MMR associated genes (MLH1, MSH6, MSH2, PMS2), 44 genes related to ovarian and endometrium cancer (PTEN, PIK3R1, CTNNB1, ARID1A, KRAS, TP53, PPP2R1A, BRCA1, BRCA2, etc.), and regions in chromosomes 8 (targeting MYC amplification), 12 (CHD4 amplification), 3 (PIK3CA amplification), 17 (ERBB2 amplification) and 19 (CCNE1 amplification).

![Fig. 1. Preoperative CT scan image.](image1)

**Fig. 1.** Preoperative CT scan image.

**Fig. 2.** A large cystic mass located in the urinary bladder peritoneum, firmly attached to the mesentry.

| Table 1 | Panel of antibodies for the immunohistochemical analysis. |
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| Antibody | Vendor | Clone | Dilution |
| CK7 | Dako | OV-TL 12/30 | Predilute |
| CK20 | Dako | Ks 20.8 | Predilute |
| CK34BE12 | Dako | 34BE12 | Predilute |
| Ber-EP4 | Dako | Ber-EP4 | Predilute |
| CEA | Dako | 11–7 | Predilute |
| Calretinin | Dako | DAK-calret1 | Predilute |
| WT1 | Dako | 6F-H2 | Predilute |
| p53 | Dako | DO-7 | Predilute |
| ER | Dako | EP1 | Predilute |
| NapsinA | LeicaNovocastra | IP64 | 1:100 |
| AMACR | Dako | 13H4 | Predilute |
| PAX8 | ProteinTech | Polyclonal rabbit | 1:200 |
| Vimentin | Dako | V9 | Predilute |
| p16 | BD Biosciences | G175-405 | 1:100 |
| PTEN | Dako | 6H2.1 | 1:100 |
| ARID1A | Sigma | HPA065456 | 1:1500 |
| PD-L1 | Dako | 22C3 | Predilute |
| MLH1 | Dako | ES05 | Predilute |
| MSH2 | Dako | E11 | Predilute |
| MSH6 | Dako | EP51 | Predilute |

Dako, Copenhagen, Denmark; Leica Biosystems/Novocastra, Barcelona, Spain; ProteinTech, Manchester, UK; BD Biosciences, San Jose, CA (USA). Sigma; San Luis, USA.
The external surface of the tumor was smooth, of 25x23x17 cm in size. After completing its opening, we observed a multilocular tumor (0.1–20 cm) with papillary growth involving part of the inner wall of the largest cyst. The uterus and ovaries were grossly normal (right 2 × 1.6 × 0.7 cm and left 2.3 × 1.8 × 0.6 cm) as well as the fallopian tubes. Microscopically, the tumor displayed tubulocystic and papillary patterns with occasional solid areas. Tumor cells showed pale to clear and occasionally eosinophilic cytoplasm, with large atypical nuclei and prominent nucleoli. Serum tumor markers were negative. The patient underwent a diagnostic laparoscopy and biopsy of the right ovary, which showed normal histology, and both ovaries were atrophic without malignant neoplasia but bilateral serous adenofibromas (1 cm).

Immunohistochemical stainings showed positivity for CK7, NapsinA, AMACR, PAX8, vimentin, CK34BE12, Ber-EP4, p16, and CEA. Negative results were seen for CK20, calretinin, WT1, p53 (Wild-type), ER, and ARID1A (loss of expression in tumor cells; Fig. 3). These results supported the macroscopic and microscopic findings of a PPCCC. Furthermore, PD-L1 was negative, and PTEN and mismatch repair proteins (MLH1, MSH2, PMS2, and HSH6) were preserved. NGS results showed a pathogenic deletion in ARID1A -p.Ala162GlyfsTer234 (c.485_495del). In addition, two germline mutations were observed in both MKI67 (L1806V) and BRCA2 (T1915M), and somatic mutations in GSDMB (V197A) and KMT2C (S772L/K339N/T316S/L291F).

The final diagnosis was PPCCC, FIGO stage IIIIC (T3c-N0-M0) (Prat, 2015). The clinic case was discussed in our multidisciplinary committee to decide the adjuvant treatment plan.

The patient received systemic chemotherapy with carboplatin (6 AUC) and paclitaxel (175 mg/m²) every 3 weeks (×4 cycles). The computed tomography (CT), after a follow-up of eight months since the last cycle of chemotherapy, showed suspicious images of peritoneal implants predominantly in the right diaphragmatic cupule. Serum tumor markers were negative. The patient underwent a diagnostic laparoscopy that corroborated the CT findings, and the recurrence was confirmed histologically. Currently, the patient has just completed another 6 cycles of chemotherapy with carboplatin (6 AUC) and paclitaxel (175 mg/m²) every 3 weeks. The last CT (28 months after initial surgery) provided the radiological stability of the implants.

3. Discussion and conclusions

We report the clinicopathological and immunohistochemical findings of a new case of PPCCC. Histologically, this tumor showed the typical features of a CCC, being the ovary or endometrium, the most frequent locations. In fact, they would be the primary tumor location to exclude due to the rarity in the peritoneum. The current case fulfills the diagnostic criteria for primary peritoneal tumors (Meinhold-Heerlein et al., 2016).

According to previous literature (Shigeta et al., 2014; Insabato et al., 2015), the average age of the patients was 53 years (range from 37 to 67 years), and about one third had a past gynecological history of endometriosis. They usually present with progressive abdominal pain and distention, as a single mass with an average size of 11 cm.

Several tumors and tumor-like lesions share origin from the so-called secondary müllerian system, that is, the pelvic and lower abdominal mesothelium and the subjacent mesenchyme of females (Kurman, 2014). Currently, the most accepted theories regarding the origin of CCC in the peritoneum are müllerian metaplasia and endometriosis with malignant transformation. However, the latter occurs at extratopic sites in only 1.6% of the cases (Thomas and Campbell, 2000). Also, estrogen dependence has been suggested due to its association with endometriosis, adenosomyosis, and endometrial carcinoma (Wunctal and Lawrence, 2013). In the current case, despite extensive sampling of the resected specimens, we were not able to demonstrate endometriosis.

Our case presented a pathogenic deletion in ARID1A, leading to a loss of ARID1A expression. In addition, two germline mutations in MKI67 and BRCA2, which appear in the databases as benign, although the population frequency of both is less than 1%. Finally, it also presented a series of somatic mutations in GSDMB and KMT2C, which appear as unreported or of uncertain significance. Of note, in none of the previously published PPCCC cases, these molecular analyses were performed; therefore, no comparison is possible.

Recent studies support the key role of the immune system in modulating tumorigenesis and tumor clearance in several neoplasias, including endometrial and ovarian CCC (Willis et al., 2017). One main immune checkpoint pathway is mediated by programmed cell death 1 (PD-1), which is expressed on activated lymphocytes and its ligand (PD-L1). It is upregulated on antigen-presenting cell types in response to cytokine mediators in a normal immune response. The success of PD-1 and PD-L1 inhibitor therapy in numerous malignancies has led to recent studies in ovarian and endometrial tumors, including cancers with clear cell histology. The results support the role of PD-L1 expression as a potential biomarker for PD-1/PD-L1 inhibitor response regardless of mismatch repair (MMR) status (Willis et al., 2017). In the current case, we also assessed the expression of PD-L1 and MMR genes labeling in tumor cells showing negativity for PD-L1 and the MMR proteins preserved. Therefore, targeted immunotherapy was not an option for our patient.

Histologically, the main differential diagnosis should be made first with peritoneal serous carcinoma, especially at younger ages due to genetic predisposition (germinal mutations in BRCA1/2) in patients with a personal family history of ovarian or breast carcinomas.

Previous PPCCC patients received treatment similar to ovarian carcinoma showing diverse clinical responses (Shigeta et al., 2014; Insabato et al., 2015). Despite a few reported cases, it is considered a tumor with poor prognosis (recurrence or death from the disease...
between 4 and 32 months), depending on the clinicopathological stage and the amount of residual tumor after treatment. In support, our patient presented peritoneal recurrence eight months after completing chemotherapy despite non-residual tumor after debulking surgery. In conclusion, CCC is a very rare tumor in the peritoneum. It may also be influenced by its lack of recognition, being diagnosed as another neoplasia more frequent in this location. Therefore, in addition to the typical histological findings, immunohistochemistry is a very useful tool for the main differential diagnosis.

Currently, promising data is available regarding response to PD-1/PD-L1 inhibitor therapy in a subset of patients with CCC. However, further research addressing novel biomarkers and treatment strategies are necessary to improve local control and decrease mortality for these patients.

Compliance with ethical standards

This manuscript is a report of a case with a review of the literature. Research work with human and animal subjects was not conducted in preparation of this manuscript.

Authors’ contribution

G.P. and S.S-O. provided the histopathological data and wrote the manuscript; C.G-E. provided the radiological data, and wrote the manuscript; M.S-F., S.P-V. and J.M-S. provided the clinical and surgical data and wrote the manuscript; E.C-M. performed IHC stainings: All authors revised and approved the final manuscript.

Informed consent

Written informed consent was obtained from the patient to publish this data.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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