Primary peritoneal carcinoma with long term survival: A case report*

By Alexanderia G. Yatco-Buenaventura, MD, Jan Gayl F. Rodriguez, MD, DPOGS, Maria Roberta D. Merencilla, MD
Nephtali M. Gorgonio, MD, FPOGS, Liza Karina I. Gorgonio, MD, FPOGS and Ma. Patricia Luna-Sun, MD, FPOGS, FSGOP

Department of Obstetrics and Gynecology, Cardinal Santos Medical Center

ABSTRACT

Primary peritoneal carcinoma is rare, presents with non-specific abdominal symptoms, is usually diagnosed late and is associated with a poor prognosis.

A 51-year-old female with Primary Peritoneal Carcinoma Stage III-C, was initially treated with cytoreductive surgery and intravenous paclitaxel and carboplatin. After 28 months in remission, she developed tumor recurrence. She underwent tumor excision followed by combined intravenous paclitaxel and intraperitoneal carboplatin. The patient is alive and disease-free 5 years after the initial operation.

This case was reported to inform our clinicians that the peritoneum can be the primary site of a rare malignancy. Prognosis may be poor but long-term survival can be achieved in younger patients with good performance status. Having a tumor that is sensitive to platinum-based chemotherapy can contribute to a longer survival even if the tumor was sub-optimally reduced.

Keywords: Chemotherapy, Cytoreductive Surgery, Primary Peritoneal Carcinoma

INTRODUCTION

Primary peritoneal cancer (PPC) is cancer of the cells lining the peritoneum or abdominal cavity. The first case of Extraovarian Primary Peritoneal Cancer was reported by Swerdlow in 1959[1].

The first local report on primary peritoneal carcinoma was published in 2004 by Pacioles and Luna. After tumor debulking and chemotherapy with Paclitaxel and Carboplatin, the patient had tumor recurrence. She refused to undergo another surgery and died 13 months after her operation[2].

Optimal surgical debulking with chemotherapy offer the patient the most effective treatment. Late diagnosis and extensive peritoneal involvement lead to a poor prognosis.

This is the second locally reported case of primary peritoneal carcinoma. The patient has survived the disease 5 years after the initial surgery. We aim to present our experience in the management of PPC and its recurrence.

THE CASE

A 51-year-old G3P3 (3003) female diagnosed with Primary Peritoneal Carcinoma stage III-C, was admitted for the third time for tumor recurrence.

History of the present illness started 5 years prior to admission (PTA), when patient noted increased abdominal girth associated with constipation and dysuria. Four months after treatment for urinary tract infection, there was recurrence of dysuria with acute urinary retention, hence consult at at our institution.

On examination, the bladder was noted to be distended. An indwelling foley catheter was inserted. There was difficulty inserting the speculum due to an obstructing mass overlying the posterior vaginal wall. After a foley catheter was inserted to relieve the urinary retention, an ultrasound of the kidney, ureter and bladder to identify the cause of obstruction was done. This showed normal kidney, ureter and bladder with note of an 11 x 11 cm left adnexal complex mass. She was subsequently referred to our service. Bimanual examination revealed a hypogastric mass approximately 10 x 10 cm, tensely cystic and impacted in the cul-de-sac with the inferior pole approximately 3 cm from the introitus and anal opening. The uterus, cervix and bilateral adnexae could not be properly assessed due to mass. The patient was scheduled for surgery with an impression of ovarian new growth.

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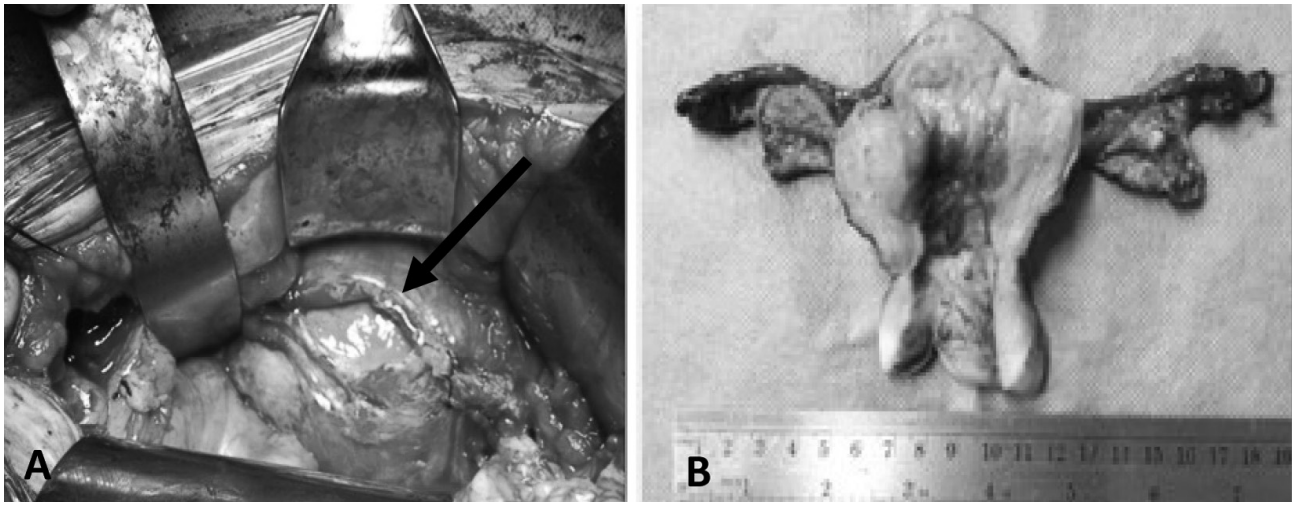


Figure 1. (A) The arrow denoted the peritoneal mass with friable and necrotic peritoneal cyst wall densely adherent to the bladder and rectal walls. (B) Uterus, cervix, endometrium, fallopian tubes and ovaries appearing grossly normal.

Intraoperative findings were as follows: the uterus, measured 7.5 x 6 x 3 cm with no gross lesions. Bilateral ovaries and tubes were grossly normal. An encapsulated mass was noted in the cul-de-sac. There was a solid mass in the infracolic omentum approximately 10 x 10 cm (Figure-1A). The intraoperative diagnosis was primary peritoneal carcinoma. After performing total abdominal hysterectomy, bilateral salpingoophorectomy, the posterior vaginal wall was opened to gain access to the cul-de-sac mass. The upper half of the mass was excised with the upper 4 cm of the posterior vaginal wall. There was an egress of 150 cc brownish red serous fluid. The inner wall was vascular and had several papillary excrescences occupying 50% of the mass. Approximately 50% of the mass was excised. Frozen section revealed poorly differentiated serous carcinoma. Bilateral pelvic lymph node dissection, para-aortic lymph node palpation and infracolic omentectomy were subsequently performed.

Histopathology of the peritoneal mass revealed poorly differentiated adenocarcinoma (Figure-2). The uterus and bilateral adnexae had no pathology. The omentum was positive for tumor, while all lymph nodes were negative.

Immunohistochemical staining of the specimen was positive for CK 7, ER and CA125 and was negative for CDX2, CK 20, and Calretin. The patient underwent nine cycles of intravenous chemotherapy with Carboplatin-Paclitaxel. Serum CA125 obtained 1 week after the first chemotherapy was 33 U/mL. CA125 showed decreasing levels, while serial transvaginal ultrasound revealed no masses.

Four years PTA, Magnetic Resonance Imaging (MRI) with contrast revealed no tumor recurrence or metastasis. CA125 was normal. Patient remained asymptomatic.

Three years PTA, transvaginal ultrasound showed a well-circumscribed hypoechoic structure at the cul-de-sac,

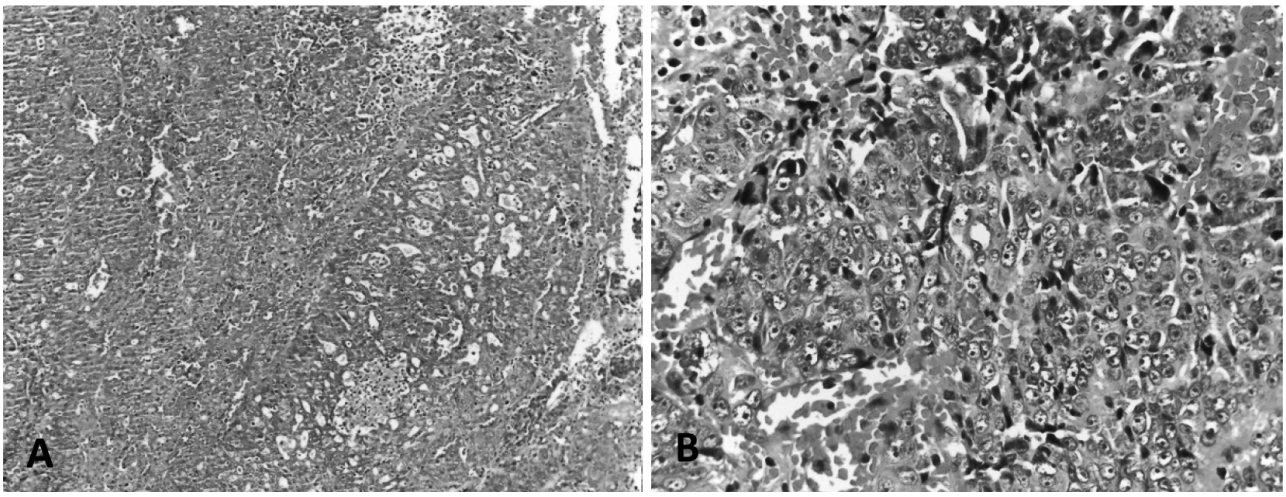


Figure 2 (A and B). Histopathology of the specimen showing tumor cells arranged in sheets and nests, with large vesicular nuclei and prominent nucleoli. Mitotic count is 3-8 per high power field.

which measured 1.15 x 0.90 x 0.80 cm and had minimal peripheral vascularity. Although the CA125 was normal (2.4 U/mL), tumor recurrence was considered and she was subsequently admitted.

The patient underwent proctosigmoidoscopy, exploratory laparotomy and excision of a 2 x 1 cm mass at the left pararectal area. Histopathology of the excised mass showed Fibrovascular and Fatty Tissue Fragments with Chronic Inflammation.

Two years PTA, transvaginal ultrasound showed a well-circumscribed hypoechoic avascular structure at the left posterior portion of the vaginal wall, which measured 0.81 x 0.84 x 0.76 cm. Three additional scans showed an increase in the size of the mass, which had reached 2.07 x 1.50 x 0.98 cm, 11 months prior to admission.

Magnetic Resonance Imaging (MRI) of the whole abdomen showed a 1.2 x 1.4 x 1.8 cm lobulated enhancing lesion with restricted diffusion at the left mesorectal fat, posterior to the vaginal stump. CA125 was 4.34 U/mL. Repeat MRI done 3 months later showed an increase in the size of the mass to 1.4 x 2.3 x 2.8 cm.

Six months PTA, patient underwent Computed Tomography Scan guided biopsy of pelvic mass and cytology showed malignant cells.

In the interim, there was further increase in the size of the mass. Tumor markers increased but were still within the normal range. On contrast MRI 3 months PTA, there was enlargement of the mass with appearance of 2 satellite nodules posterior to it. Surgery was postponed due to patient's personal matters. The patient was continually monitored with CA125, sonologic and MRI scans.

Three weeks PTA, internal examination revealed a 3 x 3 cm doughy mass at the posterolateral paravaginal area. MRI showed no significant change in the size of the mass and the 2 satellite nodules. Patient was subsequently admitted.

On laparotomy, the bowels were densely adherent to the anterior peritoneal wall. Excision of the cul-de-sac mass was done followed by infragastric omentectomy, and insertion of intraperitoneal port.

The specimen consisted of a soft 3 x 2 x 1.5 cm, mass, which on cut section revealed a 0.6 x 0.6 x 0.3 cm solid area. No areas of hemorrhage or necrosis were noted (Figure 3). Histopathology revealed poorly differentiated carcinoma with one of three lymph nodes positive for tumor.

The patient underwent combined chemotherapy with intraperitoneal carboplatin and intravenous paclitaxel. On follow-up, patient was asymptomatic with decreasing levels of CA125 from 14.59 U/mL on the first cycle of chemotherapy to 9.5 U/mL on the sixth.

DISCUSSION

The origin of PPC or primary serous papillary carcinoma of the peritoneum (PSPCP) has not been well characterized. It is better established as a neoplasm that arises from the mesothelial cells of mullerian origin. This theory explains why PSPCP is like primary serous carcinoma of the ovary, resembling the latter clinically, radiologically, and immunohistochemically. It has similar sensitivity to

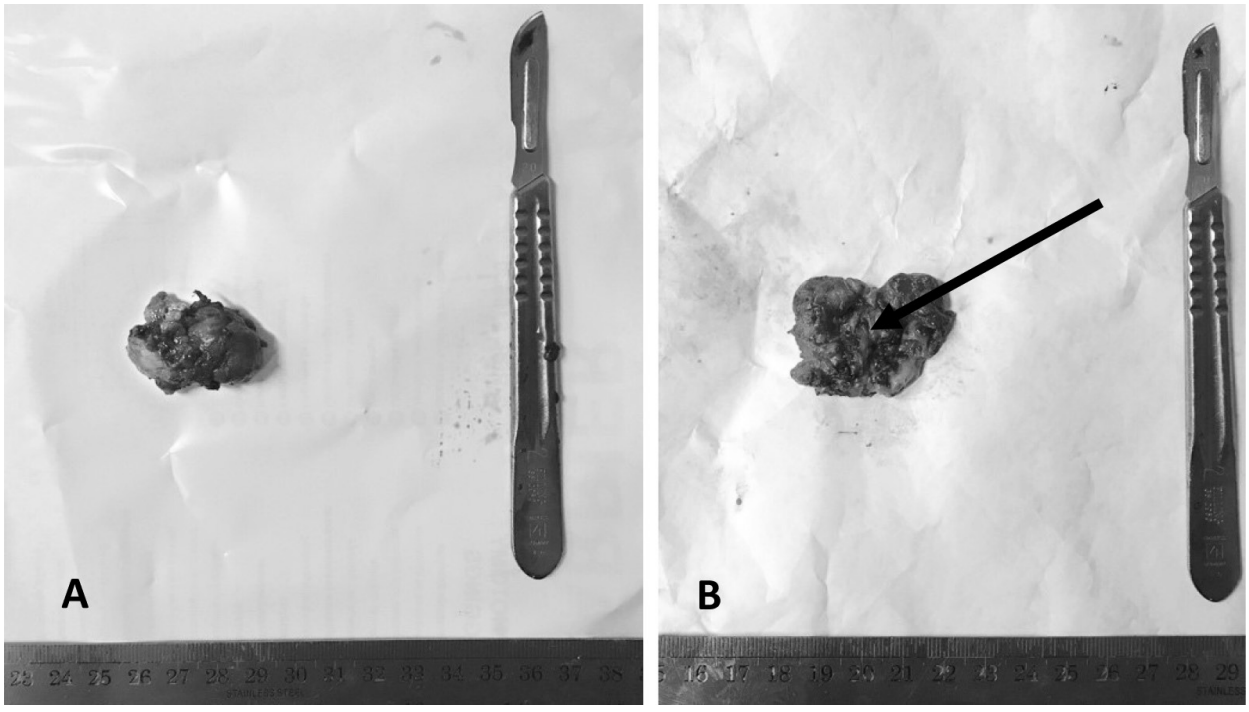


Figure 3. Tumor Recurrence Specimen. (A) Tan-yellow, soft mass located in the cul de sac measuring 3 x 2 x 1.5 cm. (B) On cut section is a solid mass within, measuring 0.6 x 0.6 x 0.3 cm.

platinum-based chemotherapy[2].

Most reported cases have been in elderly women. In majority of patients, symptoms are non-specific[3]. Our patient presented with constipation, increased abdominal girth, and dysuria with urinary retention.

Surgical exploration provides the diagnosis, staging, evaluation and treatment of patients with PPC. Primary peritoneal carcinoma is staged surgically as in ovarian cancers and since both are alike, the same staging system is used. With an omental implant that measured 2.5 cm, our case is stage IIIC.

The diagnostic criteria for PPC according to the Gynecology Oncology Group (GOG) are as follows: (1) the ovaries are either absent or normal in size; (2) extraovarian site involvement is greater than the involvement of the surface of either ovary; (3) an absence of a deep-seated invasive ovarian carcinoma or invasive disease in the ovarian cortical stroma with tumors that measure less than 5 x 5 mm2; (4) the histopathological and cytological characteristics of the tumors are similar to that for epithelial ovarian cancer. According to this criteria, our case is consistent with PPC.

Immunohistochemical analysis can differentiate between primary peritoneal carcinoma and extensive intraperitoneal disease from other organs. To date, there have been few comprehensive immunohistochemical studies for PPC.

Estrogen receptor (ER), cytokeratin 7 (CK7), and cancer antigen 125 (CA-125) stains are both positive in primary peritoneal carcinoma and primary ovarian carcinoma. Neither entity possesses cytokeratin 20 (CK20) and Calretinin[1]. CDX-2, initially thought to be specific for colon carcinoma, will be reactive in more than 50% of cases[4] (Table 1).

Immunohistochemical staining in our patient has shown that PPC and ovarian carcinoma are immunohistochemically indistinguishable from each other. The established diagnostic criteria should be used in differentiating the two disease entities. The different immunohistochemical stains used in our patient were able to rule out colon carcinoma as the primary site of malignancy.

Primary mode of treatment is surgery. For stages III to IV, as in the case presented, total abdominal hysterectomy with bilateral salpingoophorocystectomy with complete surgical staging and/or tumor debulking should be done. Since the volume of residual disease remaining after cytoreductive surgery inversely correlates with survival, all visible tumor should be resected at the initial surgical procedure[5].

Chemotherapeutic regimens used for peritoneal cancers are the same as those used for ovarian cancer. Combination of carboplatin and paclitaxel are used to treat advanced-stage disease. For women with optimally reduced disease (<1 cm of residual disease), there are two options: intravenous (IV) chemotherapy alone or a combination of IV and intraperitoneal (IP) chemotherapy (IV/IP therapy). Women with sub-optimally reduced disease (>/=1 centimeter of residual disease) are not candidates for IP therapy due to limited penetration into larger tumors. These women should therefore receive IV treatment. Radiation therapy is not routinely recommended for peritoneal cancer.

In our case, intravenous chemotherapy was given after the initial surgery since the patient had sub-optimally reduced disease. She was in complete remission for 28 months until tumor recurrence was noted on follow-up.

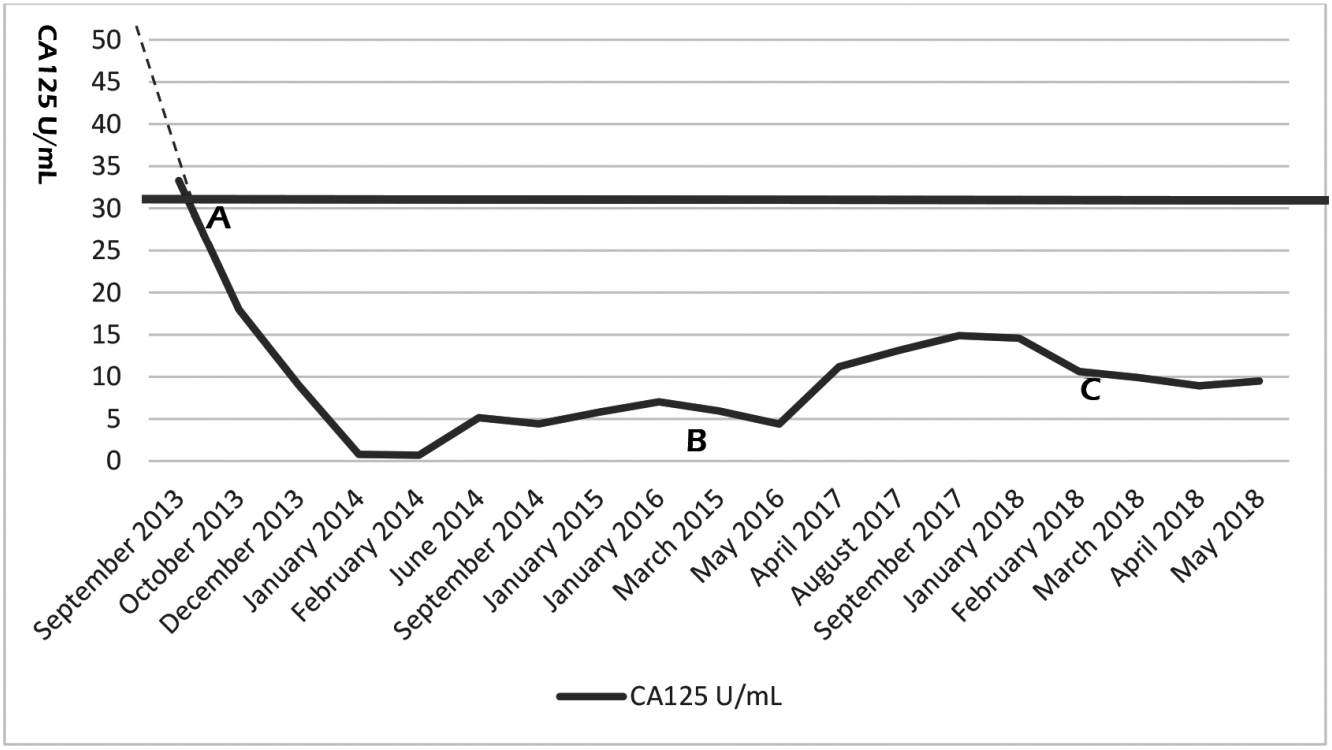
Clinicians can use the guidelines on follow-up of patients as recommended by the Society of Gynecologic Oncologists of the Philippines. Appropriate tumor markers should be determined every visit.

CA125 antigen is considered currently as the most effective tumor marker for primary peritoneal carcinoma and measurements correlate with the clinical status of the disease[5]. As in ovarian malignancy, CA125 is markedly elevated and may be used for monitoring treatment and for detecting recurrence. Once with evaluation of tumor markers, additional diagnostics may be used such as

Table 1. Comparison of patient's immunohistochemical staining to peritoneal, ovarian and colon carcinoma immunostaining

Immunohisto-chemical Stain	Ovarian Carcinoma	Primary Peritoneal Cystadeno-carcinoma	Colon Adenocarcinoma	Patient
CK7	+	+	-	+
CK20	-	-	+	-
CDX2	-	N/A	+	-
ER	+	+	-	+
CA 125	+	+	-	+
Calretinin	-	-	N/A	-

Table 2. CA125. All the values are within normal limits of 35U/mL on follow-up. (A) Decreasing levels of CA-125 during intravenous chemotherapy. (B) Increasing levels when tumor recurrence was discovered. (C) Decreasing levels during IV/IP chemotherapy. Red line denotes upper limit of normal CA125 and blue line denotes patient's CA125 levels.



ultrasound and MRI.

In our case, there was no pre-treatment CA125 done. As shown in Table 2, CA125 measurements after the operation were all within normal limits of less than 35 U/mL. There was decreasing levels of CA125 during intravenous chemotherapy. When tumor recurrence was discovered on ultrasound and MRI, the level of CA125 was increasing.

Tumor recurrence should be suspected if on serial monitoring of CA125, the level is increasing even with values still within normal limits. The normal levels of CA125 noted in our patient despite tumor recurrence can be explained by the small tumor size noted on exploration.

Disease progression or recurrence is defined as a new lesion or an increased size of the pre-existing lesion on an image or an elevated CA125 level in two consecutive tests, if no measurable lesion was present[5]. Majority of patients will relapse and require retreatment despite initial therapy. In our patient, a new lesion was noted with increasing size noted on ultrasound and MRI.

The management of relapsed disease is stratified based upon the amount of time that has elapsed between the completion of platinum-based treatment and the detection of relapse, known as the platinum-free interval (PFI). Patients with a PFI of six months or longer are considered to have "platinum-sensitive" disease, while those with PFI of less than six months are considered to have "platinum-resistant" disease. Women who experience disease progression during first-line platinum-based therapy, is often referred to as having "platinum-refractory" disease[5].

Our patient had "platinum-sensitive" disease with PFI of 37 months. She however, had tumor recurrence and underwent a second cytoreduction surgery followed by combined intravenous and intraperitoneal chemotherapy.

Patients who have undergone optimal tumor debulking should be offered intraperitoneal chemotherapy wherein the chemotherapeutic agents are directly administered into the peritoneal cavity. Due to poor blood supply to the peritoneal surface, there is low penetration of drugs into tumor nodules when systemic chemotherapy is used. Intraperitoneal chemotherapy has direct contact of the cytotoxic drugs to the tumors themselves, without reliance on blood supply to the area[6]. Intraperitoneal administration permits a several-fold increase in drug concentration to be achieved within the abdominal cavity compared with intravenous treatment.

In 1955, treatment of peritoneal tumors as a local disease with intraperitoneal chemotherapy was first introduced by Weissberger[6]. In 1978, Dedrick studied the depth of tissue penetration by different cytotoxic drugs that can penetrate 1-3 mm into tissue. This gave rise to the notion that tumor deposits need to be 2.5 mm or less for intraperitoneal chemotherapy to have some effect[7].

For this reason, a good cytoreduction is required prior to any intraperitoneal chemotherapy.

Armstrong et al., in a study of patients with stage III ovarian or primary peritoneal carcinoma with no residual mass greater than 1.0 cm, concluded that survival in patients with optimally debulked stage III ovarian cancer is improved with intravenous paclitaxel plus cisplatin, intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel[7]. For the tumor recurrence, our patient received a combined intravenous paclitaxel and intraperitoneal carboplatin for 6 cycles.

The prognosis for PPC is poor. The survival time varies between 7 and 27.8 months. Five-year survival rates range from 0% to 26.5%.[8] Our patient has survived the disease 5 years after the initial surgery.

With regard to the prognostic factors of PPC, Eltabbakh et al. suggested that age <70 at diagnosis, performance status </=1, and residual tumor size </=1 cm had significant impact on overall survival[8]. Unal et al in their analysis, concluded that performance status and optimal cytoreduction are important prognostic factors for survival rates[9].

Some investigators have reported that by univariate analysis, overall survival depends on age at diagnosis, performance status and degree of debulking achieved at the primary cytoreductive surgery. However, multivariate analysis showed that only performance status and debulking surgery correlated with overall survival and these results were statistically significant[10].

In our patient, the performance score was Zubrod scale 0 (normal activity) while the completeness of cytoreduction score was CC3 (>2.5 cm). The good performance status and age at diagnosis may have contributed to our patient's long-term survival. Although our patient had sub-optimally reduced disease, the use of platinum-based chemotherapy for which the tumor is sensitive contributed to her long term survival.

CONCLUSION

The peritoneum can be a primary site of a rare malignancy. Rare as it may seem, it should be considered in elderly females presenting with non-specific abdominal symptoms.

This report has demonstrated that primary peritoneal carcinoma and primary ovarian carcinoma have similar immunohistochemical findings. On follow-up, tumor recurrence should be suspected if CA125 levels on serial monitoring are increasing, even if the values are still within normal limits. We cannot overemphasize the importance of regular follow-up.

Long-term survival can be achieved in younger patients with good performance status. In patients with sub-optimally reduced disease, the use of platinum-based chemotherapy can contribute to long-term survival. Intravenous and/or intraperitoneal chemotherapy can be used based on the size of the tumor left after cytoreductive surgery. ■

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