Positive peritoneal cytology in endometrial cancer: report of a case with persistence after surgery

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Background: The prognostic significance of positive peritoneal cytology in endometrial cancer remains unsettled. We previously classified malignant cell clusters on peritoneal smears into two morphologic types and found that those with irregular edges, so-called "scalloped clusters", were associated with peritoneal seeding or a poor clinical outcome. We have also reported on the use of postoperative peritoneal washings to investigate residual malignant cells in the peritoneal cavity.

Case: A 56-year-old woman underwent surgery for endometrial cancer (grade 1 endometrioid adenocarcinoma). At operation, positive peritoneal cytology was found without obvious peritoneal seeding, so a tube for cytologic studies was inserted when closing the abdomen. Washings were obtained via the tube at 7 days and 14 days after surgery, and both sets of washings were also positive for malignant cells. All three peritoneal smears showed scalloped clusters. These findings strongly suggested the presence of occult metastasis in the peritoneal cavity that had been overlooked at operation. Despite adjuvant therapy, the patient developed intraperitoneal recurrence 8 months after surgery.

Conclusion: Postoperative peritoneal washings and morphologic analysis of positive peritoneal smears are useful to determine the malignant potential of endometrial cancer with positive peritoneal cytology.

Key words: Endometrial cancer — Peritoneal cytology

I. Introduction

Although examination of peritoneal washings is now a standard part of the work-up for patients with endometrial cancer, the prognostic significance of peritoneal cytology remains uncertain. The variations in the reported prognostic significance of peritoneal cytology suggest that there may be several types of positive cytology in patients with endometrial cancer. In fact, it is very unlikely that all malignant cells will migrate via the same route and show the same behavior in the peritoneal cavity.

We recently performed two studies on this subject. In one study, morphologic analysis of positive peritoneal cytology was shown to be useful to identify a
high-risk subgroup of patients with cytology-positive stage IIIA endometrial cancer. In the other study, postoperative peritoneal washing was investigated in endometrial cancer patients who showed positive smears at surgery. These procedures are now part of our routine work-up of endometrial cancer with positive peritoneal cytology.

Here we report on a case of endometrial cancer with persistent positive peritoneal cytology and discuss the utility of our methods for such patients.

II. Case Report

The patient was a 56-year-old Japanese woman (gravida 5, para 2) who presented with vaginal bleeding for four months. There was no history of previous malignancy or tamoxifen administration. On pelvic examination, the cervix appeared normal, and there was no abnormality of uterine size or the bilateral adnexae. Endometrial aspiration cytology suggested the presence of endometrial cancer, and this was confirmed by fractional endometrial curettage. At operation, total abdominal hysterectomy, bilateral salpingooophorectomy, and pelvic/para-aortic lymphadenectomy were performed. No lymph node metastases were found in the lymph nodes resected during surgery. The peritoneal fluid in the cul-de-sac (10 ml) was aspirated when opening the peritoneal cavity. After being centrifuged, the specimen was immediately investigated by two cytologists and was found to contain malignant cells. The surgeons were informed during the operation, but no obvious site of extrauterine spread was seen in the peritoneal cavity (surgical stage IIIA). A tube for cytology was subsequently inserted into the abdominal cavity when closing the abdomen. After being centrifuged, the specimen was immediately investigated by two cytologists and was found to contain malignant cells. The surgeons were informed during the operation, but no obvious site of extrauterine spread was seen in the peritoneal cavity (surgical stage IIIA). A tube for cytology was subsequently inserted into the abdominal cavity when closing the abdomen. The peritoneal cavity was irrigated with 500 ml of physiological saline and washings were obtained through the tube at 7 days and 14 days after the operation (Fig. 1). Malignant cell clusters were found in both sets of washings. Four weeks after surgery, the patient received the first course of adjuvant chemotherapy consisting of cisplatin (70mg/m²), ifosfamide (2800mg/m²), and epirubicin hydrochloride (50mg/m²). Five courses of the chemotherapy were initially thought to be necessary for the patient, but at the end of the third course, the elevation of tumor markers, such as CA125 and CA19.9, was noted. Eight months after surgery, the patient underwent another laparotomy because of suspected intraabdominal recurrence and was found to have peritoneal seeding. Cytoreductive surgery, including total omentectomy, was performed as completely as possible, but some peritoneal lesions remained. Further chemotherapy was given after the operation, but little response was observed. The patient eventually died of her disease at 18 months after the first operation.

III. Cytologic Findings

Peritoneal smears obtained at the first operation showed numerous malignant cell clusters. Almost all of these malignant clusters had an irregular border (i.e., they were scalloped clusters) (Photo. 1). The term "scalloped cluster" indicates that the border of a malignant cell cluster is irregular and frayed due to the delicate cytoplasm or irregular nuclei of the constituent malignant cells. Isolated satellite malignant cells are often associated with this type of cluster (Photo. 1). Peritoneal smears obtained 7 days and 14 days after surgery contained similar malignant cell clusters to those seen at the time of surgery (Photo.
Photo. 1  The peritoneal smear obtained at the first operation (Papanicolaou stain, ×40). Typical cytological features of the "scalloped cluster" are present, with the malignant clusters showing peripheral scalloping and nuclear overlapping. Single cells that are becoming detached from the cluster can also be seen.

Photo. 2  The peritoneal smear obtained at 7 days after the surgery. Similar cytologic features to the smear obtained at operation are noted. In the lower part of the field, isolated satellite malignant cells are seen (Papanicolaou stain, ×40).

Photo. 3  The peritoneal smear obtained at 14 days after surgery. Scalloped clusters are still observed (Papanicolaou stain, ×40).

Photo. 4  The uterine tumor. The lesion was diagnosed as grade 1 endometrioid adenocarcinoma. The solid component accounted for less than 5% of the tumor (hematoxylin and eosin, ×4).

IV. Histologic Findings

A reddish-gray exophytic mass measuring 3.5 × 3.0 cm that filled the endometrial cavity was noted when the hysterectomy specimen was examined macroscopically. Microscopic examination of the formalin-fixed tumor revealed a diagnosis of grade 1 endometrioid adenocarcinoma of the endometrium. The depth of invasion was approximately 10% of the myometrium (Photo. 4). Neither capillary involvement nor cervical involvement was found. No abnormalities were found in the bilateral adnexae. Specimens from the second operation showed the presence of numerous recurrent lesions with similar pathological features to the primary tumor.

V. Discussion

A unique system for assessing peritoneal cytology was employed in the present case. That is, peritoneal cytology was investigated intraoperatively and the subsequent behavior of malignant cells in the peritoneal cavity was observed for two weeks postope-
In addition, morphologic assessment of each positive smear was performed. These procedures are now routinely carried out at our hospital when positive peritoneal cytology is detected in a patient with endometrial cancer. In this patient, persistence of positive peritoneal cytology was observed for two weeks after surgery. The malignant cell clusters seen during this period always had an irregular border (scalloped clusters). These findings suggested the presence of occult metastasis in the peritoneal cavity that was overlooked at operation. Continuous shedding of malignant cells from metastatic foci inside the peritoneal cavity was strongly suspected.

When the significance of positive peritoneal cytology in patients with endometrial cancer was investigated previously, most studies only assessed whether the peritoneal washings were positive or negative. However, there is considerable variation in the cytologic features of positive peritoneal smears. We previously classified malignant cell clusters on peritoneal smears into two morphologic types, which were called "well-defined" clusters and "scalloped" clusters (Fig. 2) [5,7]. The former type of cluster has a smooth border and the latter type has an irregular border. We found that the "scalloped" type was associated with poor survival. This classification was based on the finding that malignant cell clusters in peritoneal smears from patients with intraperitoneal lesions almost always show the "scalloped" pattern, whereas clusters from patients without intraperitoneal disease only occasionally have this appearance[7].

Persistence of positive peritoneal cytology in endometrial cancer patients is seldom observed when the disease is confined to the uterus. We previously reported our findings when a tube for cytologic studies was inserted on closing the abdomen in 50 cytology-positive patients with endometrial cancer[6]. None of the patients had obvious peritoneal seeding. As in the present case, the peritoneal cavity was irrigated with 500 ml of physiological saline and washings were obtained via the tube at 7 and 14 days after surgery. In 34 of the 50 patients, the tumor was confined to the uterus. Only one of them showed the persistence of positive peritoneal cytology, while cancer cells disappeared rapidly in the other 33 patients. Thus, it seems that in the majority of cytology-positive patients with disease limited to the uterus, malignant cells have little potential for implantation into the peritoneum or for metastasis.

The prognostic significance of positive peritoneal cytology remains unclear. The presence of malignant cells in peritoneal washings has been shown to be significantly associated with survival in a number of studies[1,2], but other authors[3,4], have not corroborated these findings. However, there is increasing evidence that positive cytology may only be of prognostic value when associated with other prognostic indicators, and particularly with the presence of extraterine disease[8-10].

In summary, it is most likely that the present patient had an occult metastasis in the peritoneal cavity that we were unable to detect during surgery. We eventually failed to save this patient because the tumor showed a poor response to chemotherapy. However, our system for assessment of cytology-positive endometrial cancer, i.e., cytodiagnosis during surgery followed by postoperative peritoneal washing and morphologic typing of positive peritoneal smears, provided valuable information about possible intraperitoneal disease. We believe that our system is useful for assessing the malignant potential of endometrial cancer associated with positive peritoneal cytology.
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References


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