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Appearance of Tumor Cells in Cyst Fluid of Malignant Ovarian Tumor

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Abstract The significance of spillage of tumor cells into the abdominal cavity by fine needle aspiration or rupture of adnexal masses in case of malignancy is the focus. However, the appearance rate of malignant cells in cyst fluid by fine needle aspiration has been quite variable. We therefore evaluated the appearance rate of malignant cells in the cyst fluid from malignant ovarian tumors. Our study population included 29 women with malignant ovarian tumor who attended two hospitals between November 1995 and October 1998. Cyst fluid samples were aspirated from the tumors immediately after the removal of tumor. All cytologic and histologic preparations were reviewed by investigators who did not know any information of the tissues. A considerable number of viable malignant cells were found in twenty two of 26 adnexal malignancies (84.6 %). There was no significant difference in the appearance of viable tumor cells among different histologic types of tumor. Four negative cases included 3 mucinous tumors of borderline malignancy and one endometrioid adenocarcinoma (G1). The cyst fluid of most of the malignant ovarian tumor contains viable tumor cells, suggesting the risk of spillage of malignant tumor cells. On the other hand, there may be decreased risk of spillage of malignant tumor cells in mucinous tumors of borderline malignancy.

Introduction

Laparoscopic adnexectomy has been increasingly applied to the management of ovarian tumors over the last few years[1-4]. The benefits are reduced operative morbidity, hospital stay and recovery time. Although a laparoscopic approach is usually contraindicated if there is a possibility of malignancy, malignant tumor including low grade malignant tumor is occasionally encountered during this procedure. Because many clinicians remove adnexal masses by puncturing them first and their rupture can happen accidentally even during laparotomy, it is very important to know the appearance of tumor cells in the fluids. Since preoperative cytologic examination to discriminate between benign and malignant adnexal masses is considered con-

traindicated mainly because of the fear of dissemination of malignant cells, this type of study is rare. Furthermore, the reported appearance rate of malignant cells in cyst fluid by fine needle aspiration has been quite variable[5-8]. Andersen et al. recently reported that cytologic diagnoses are influenced by menopausal status, patient age, sample type, aspiration method, and cytologic quality[9]. We therefore evaluated the appearance rate of malignant cells in the cyst fluid.

Patients and Methods

Our study population included 26 women with malignant ovarian tumor excised in Yamaguchi University Hospital and Ube Industries Central Hospital between November 1995 and October 1998. Cyst fluids were aspirated by using 18-gauge needles to avoid solid regions immediately after the removal of tumor with their informed consent. The specimens were centrifuged at 220 g for 5 minutes then the sediment was smeared onto glass slides. The material was then fixed in 95% ethanol and stained with Papanicolaou and/or Giemsa stain. Cytologic and histologic preparations were reviewed by independent investigators. Histologic classification of the ovaries was done by the guidelines established by the World Health Organization and the clinical stage was classified according to the FIGO classification. A diagnosis of malignancy was established using cytologic criteria associated with cancer. These features included an increase in the nuclear/cytoplasmic ratio, prominent nucleoli, nuclear pleomorphism, granular chromatin, and the presence of mitoses[8]. Preoperative ultrasonographic assessment was performed transvaginally, combined with abdominal sonography when necessary, to document the size and characteristics of the lesion. Serum concentrations of tumor marker levels were measured by two-site immunoenzymometric assay for CA125, CEA (AIA-PACK, USA), and by a specific enzyme immunoassay for CA19-9 (IMx system, DaiNabot, Japan). The cutoff level for CA125 was 35 U/ml, for CA19-9, 37 U/ml and for CEA, 10 ng/ml. Surgical staging was determined according to the criteria of the International Federation of Gynecology and Obstetrics.

Results

Table 1 presents the characteristics of the patients. Mean ages of the patients are 56.0 years and mean size of malignant masses is 13.3 cm. The positive rate of tumor markers (CA125, CA19-9, CEA) was 79.3%, 28.6%, and 7.4%, respectively. Three of 29 tumors were completely solid including one of normal sized ovarian tumor from which fluid could not be removed. Considerable number of viable malignant cells were found in 22 of 26 adnexal malignancies (84.6%) (Table 2 & Fig. 1). Four negative cases included 3 mucinous tumors of borderline malignancy and one endometrioid adenocarcinoma (G1)(Table 3).

Table 1. Characteristics of the patients (n = 29)

Age (y)	56.0 ± 11.4 (Mean ± SD)
Size of mass (cm)	13.3 ± 6.6 (Mean ± SD)
Sensitivity of tumor markers	
CA125	23 / 29 (79.3%)
CA19-9	8 / 28 (28.6%)
CEA	2 / 27 (7.4%)
Stage	
I	13
II	1
III	15
IV	0

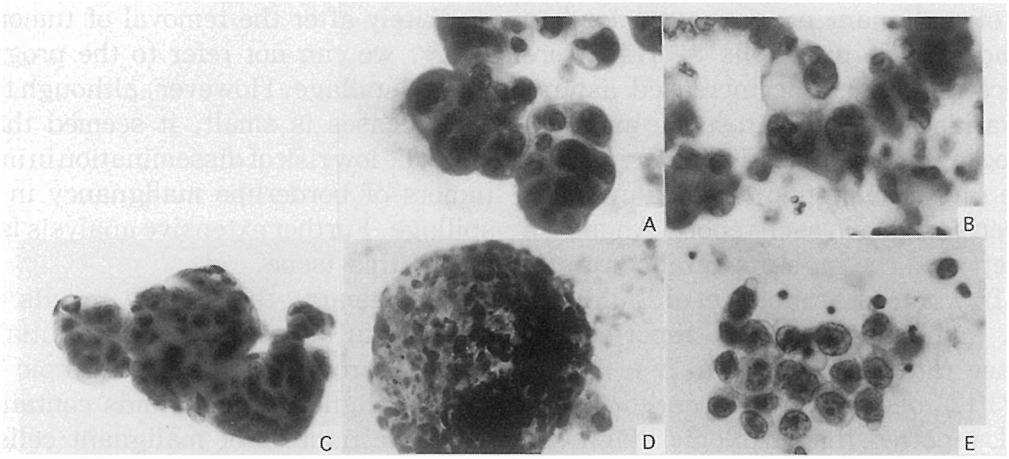

Fig 1. Typical cell pattern from aspirated tumoral fluids. (A) mucinous cystadenocarcinoma, (B) serous cystadenocarcinoma, (C) endometrioid adenocarcinoma (G1), (D) clear cell carcinoma with mirror ball formation, (E) dysgerminoma. (Papanicolaou stain, X500)

Table 2. Histologic type and the appearance rate of malignant cells

Histologic type	appearance rate
Serous cystadenocarcinoma (n = 14)	12 / 12
Mucinous cystadenocarcinoma (n = 4)	4 / 4
Endometrioid adenocarcinoma (n = 4)	2 / 3
Mucinous tumor of borderline malignancy (n = 3)	0 / 3
Clear cell adenocarcinoma (n = 2)	2 / 2
Dysgerminoma (n = 1)	1 / 1
Malignant Brenner tumor (n = 1)	1 / 1
	22 / 26 (84.6%)

Table 3. Background of negative cases

	1	2	3	4
Age	52	47	71	53
Histologic diagnosis	MTBM	MTBM	MTBM	Endometriod adenocarcinoma (G1)
stage	Ia	Ic	Ic	III b
Tumor Size (cm)	12	25	8	25
CA125 (< 35 U / ml)	43	48	33	142
CA19-9 (< 37 U / ml)	0.1	13.9	261	74.4
CEA (< 10ng / ml)	3.5	1.7	3.6	26

MTBM : mucinous tumor of borderline malignancy

Discussion

Laparoscopic approach for benign adnexal masses are now widely acceptable. This method is generally considered to be contraindicated if there is a possibility of malignancy because of the possibility of the spillage of tumor cells into the abdominal cavity. For example, Trimbos et al. have presented a case report in which laparoscopic puncture and as-

piration of malignant ovarian cysts lead to the spread of malignant cells[10]. They were very concerned about the increased aspiration of ovarian cysts by laparoscopic and even ultrasonographic guidance. However, the appearance rate of malignant cells in cyst fluid has been variable in each report. Angstrom et al[5]. reported the high appearance rate of 95% (39/41), whereas Granberg et al[6]. , Moran et al[7]. , and Higgins et al[8]. reported low appearance rate of 47% (7/15), 26% (9/35), and 25% (3/12), respectively. Recently, Anderson et al. reported that cytologic diagnoses are influenced by some factors such as aspiration method[9]. In this study, we could detect malignant cells in cyst fluid in 84.6% of malignancy after minimizing these factors. When borderline malignancy is excluded, the positive rate becomes 95.6% (22/23) which indicates that malignant ovarian tumor surely possesses a considerable number of tumor cells in cystic fluid. Therefore the possibility of the spillage of tumor cells can not be excluded during the laparoscopic approach. On the other hand, all cases of mucinous tumor of borderline malignancy indicated negative although the sample number is small. This may indicate that borderline malignancy has no or few cells in cystic fluid because of slow cellular proliferation and that the possibility of the spillage of tumor is small. Furthermore, in benign tumors, cytologic examination gave a diagnosis of benign in 90 of 91 cases (98.9%) (data not shown). One false positive was cytologically described as being suggestive of malignancy due to the presence of a psammoma body.

If the spillage of cystic fluid happens, do these findings make an influence on the prognosis? Dembo et al. indicated that tumor rupture during surgery is not a significant prognostic factor[11]. Sjövall et al. reported that patients with preoperative rupture had a worse survival rate than those with intraoperative rupture (10 year survival rate = 59% vs. 85%)[12]. Their conclusion is that the time period during which tumor spill continues is the most important and that manipulation during surgery which results in puncture or rupture does not have an influence on the outcome for the patients. Since cyst fluid samples were aspirated from the tumors immediately after the removal of tumor in this study, we can not refer to the prognosis in case of spillage. However, although the number of cases is small, it seemed that there might be low risk of dissemination in mucinous tumors of borderline malignancy in case of spillage. Further extensive analysis is needed as for this issue.

In summary, the present results indicate that careful management is essential during both laparotomy and laparoscopic surgery since malignant tumor fluids contain a considerable number of malignant cells.

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