

Review Article

Role of Peritoneal Fluid Cytology in Gynaecological Cancers

Tanushri Mukherjee*

Trained in Oncopathology, Command Hospital Eastern Command Kolkata, India

*Corresponding Author

Dr. Tanushri Mukherjee
Trained in Oncopathology,
Command Hospital Eastern Command
Kolkata, India
E-mail: tanujamukherjee@yahoo.com

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Abstract

Intraperitoneal dissemination of disease is an important cause of morbidity and mortality among women with genital tract cancers. Peritoneal Fluid cytology is indispensable for diagnosis, prognosis, staging and ancillary studies in gynaecological Cancers. Peritoneal fluid was examined for the presence of tumor cells in 94 patients with ovarian and endometrial cancer. The findings were correlated with the type, grade, and stage of the tumor. Fluids that were positive for malignant cells were associated with serous and endometrioid carcinomas of ovary; more often than with carcinomas of other types. Patients with high-stage tumors of all types had positive fluids more often than those with low-stage tumors. The presence of tumor cells in the fluid indicated a worse prognosis at 2 years. Analysis of other factors that influence prognosis, however, revealed that this difference was related more specifically to the stage of the disease. Since the presence of tumor cells in abdominal fluid is a factor in the sub classification of Stage I and Stage II ovarian cancer, analysis of a larger group of patients with tumors in these stages is needed to establish the prognostic significance of positive cytological findings independent of other prognostic factors.

1. Introduction

In 1956, Keettel, Pixley and Elkins proposed cytologic examination of intraoperative peritoneal washings as a means of detecting subclinical metastases. Subsequently, peritoneal washing cytology (hereafter referred to as "peritoneal cytology") has been adopted as part of the surgical work-up of such patients. In 1971, Creasman and Rutledge reported that peritoneal cytologic results correlated well with prognosis in ovarian, endometrial, and cervical cancer. In 1986 this concept was incorporated into the official staging of Ovarian Cancer by International federation of Gynaecology and Obstetrics Peritoneal Fluid Cytology used for Diagnosis which can be prospective or for confirmation and Staging of tumors. PFC can be done from Ascites/effusions - used for diagnostic purpose Washings/lavage - staging of tumors. Both types can be used for ancillary investigations and molecular studies

Positive cytology usually from ovary, tube or peritoneum. Endometrial carcinoma rare. As good as tissue biopsy diagnosis and better than random biopsies, but not as good as a decent omental biopsy. PFC can be acceptable as tissue diagnosis if cell blocks can be prepared. Often first investigation (triage patients accordingly). Need to establish carcinoma. Non-epithelial malignant cells can be present but more difficult to pick up. Correlate with radiological and clinical parameters as well as serology. Re-accumulated fluid is often a better sample for diagnosis. Cytological examination of peritoneal washings taken during surgery enables the initial as well as the second look clinical staging of the ovarian carcinoma and influences the prognosis of the disease, further management and response to therapy. The sensitivity and specificity of cytological analysis depends on the quality of the sample, histological type of the tumor and the stage of the disease.

PFC in Diagnosis of Gynaecological Cancers

- Dual population
- Single cells, sometimes similar in size to mesothelial cells
- Cell blocks and double immunostaining techniques enhance value
- Belfast preparations often equally good
- Main issue is source of malignant cells outside of the female genital tract. Hence, immunocytochemistry required.

PFC in Ovarian (+ Tubal/Peritoneal) Carcinoma

- 3D/papillary clusters or proliferation spheres
- Grouped as acini/glands or Indian file
- Vacuolation (can be targetoid)
- Psammoma bodies
- Pleomorphism

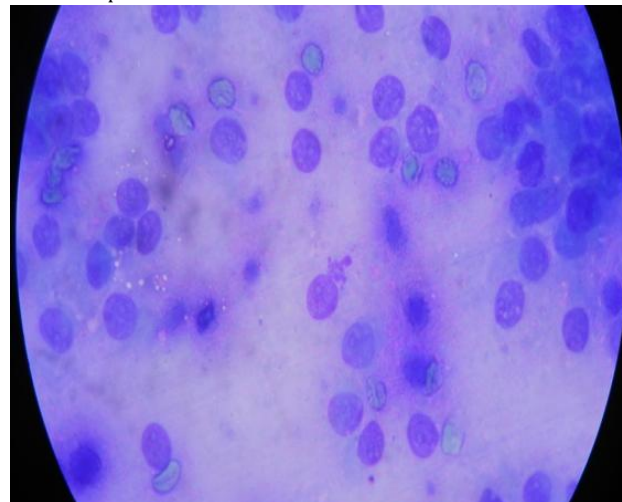


Fig 1: Showing peritoneal cytology in case of Ovarian Carcinoma.

PFC in Endometrial Carcinoma

- Grouped as acini/glands
- 3D/papillary clusters
- Can be vacuolated (clear cell carcinoma)

PFC in Gynaecological Cancers Pitfalls

- Psammoma bodies associated with benign conditions
- Ciliary tuft sex foliating from fimbrial ends of tubes
- Degenerative changes mimicking malignancy
- Exfoliation from endosalpingiosis, endometriosis and mesothelial hyperplasia ± degeneration
- Exfoliation from serous borderline tumours (can be overcalled as malignant if histology not available)

- Exfoliation of other cells such as Mullerian rests. More common with washings
- Artefactual contamination by malignant cells during sampling
- Immunocytochemistry less reliable in washings
- Other adenocarcinomas need to be distinguished requiring a large panel of antibodies
- Reactive mesothelial cells

PFC in Gynaecological Cancers Immunocyto/histochemistry

- Possible in Belfast preparations
- Ideally on cell blocks
- Useful when no or vague dual population
- Useful when no clinical/radiological findings
- Useful to distinguish mesothelial from carcinoma cells
- A small robust panel required
- Best to use in conjunction with radiological, clinical and serological parameters.

Antibodies used are:

BerEp4 (other epithelial markers, e.g. MOC-31)
 CK7, 20
 CEA, CDX2, WT1, PAX8, SMO47
 TTF, GCDFP15, mammaglobin
 CK5-6, thrombomodulin, calretinin
 Rab25
 Ki 67
 MUC4
 Claudin 1, 3, 7

- 1988 FIGO staging for ovarian cancers requires PFC analysis (1C and 2C) - ovarian carcinoma diagnosis already known. BerEp4 may be the only immunostain required.
- 2009 FIGO staging for endometrial cancers does not require PFC analysis
- Useful to record findings in histology reports if possible

PFC in Staging Endometrial Cancers

- Positive PFC - ?significance in Stage 1 & 2 malignancies
- Poor prognosis cancers usually have positive PFC
- Artefactual seeding of cells by hysteroscopy or LAVH with intrauterine balloon manipulation
- ICCR have 'recommended' that PFC findings be recorded, if available.
- Recent Advances in Ovarian Cancer PFC
- Diagnostic markers
 - CD4+/IL-17 overexpressed in ovarian carcinoma cells
 - Scavenger receptor class A, member 3(SCARA 3) raised in ovarian cancer (> breast cancer)
- Prognostic markers
 - Adhesion molecule protein signatures
 - EpCAM +ve microparticles are shed from ovarian carcinoma cells and promote migration (?implants in SBTs)
 - Osteopontin (if raised, prognosis is good) • Therapeutic target markers
 - HMGA protein expression (serous carcinoma) - Androgen receptor expression

- Comparative genomic hybridisation (CGH)
 - allows genome wide analysis (e.g. a gain of 8q24.1 predicts poor prognosis and advanced disease)
 - tumour specific hypermethylation of BRCA-1 and RAS may allow early detection of ovarian cancer

2. Method

Peritoneal fluid was examined for the presence of tumor cells in 94 patients with ovarian and endometrial cancer. The findings were correlated with the type, grade, and stage of the tumor. Fluids that were positive for malignant cells were associated with serous and endometrioid carcinomas of ovary more often than with carcinomas of other types. Patients with high-stage tumors of all types had positive fluids more often than those with low-stage tumors. The presence of tumor cells in the fluid indicated a worse prognosis at 2 years. Analysis of other factors that influence prognosis, however, revealed that this difference was related more specifically to the stage of the disease. Since the presence of tumor cells in abdominal fluid is a factor in the subclassification of Stage I and Stage II ovarian cancer, analysis of a larger group of patients with tumors in these stages is needed to establish the prognostic significance of positive cytological findings independent of other prognostic factors.

3. Conclusion

PFC is powerful tool when utilised in conjunction with clinical, serological and radiological parameters, PFC is as good as tissue biopsy diagnosis, Robust panel of antibodies required for diagnosis and subtyping, Document PFC findings in histology reports if possible, PFC allows molecular and genomic studies to indicate prognosis and therapeutic strategies as well as discovery of novel immunomarkers

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