



CYTO-HISTOLOGIC CORRELATION OF DIAGNOSIS IN PATIENTS WITH MALIGNANT EPITHELIAL OVARIAN TUMORS

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Abstract

Introduction: The malignant common epithelial tumors of the ovary are by far the most frequently encountered malignant form of ovarian tumor and the most common cause of ascitic fluid. The cytological examination of the ascitic fluid, free peritoneal fluid and peritoneal washings is a well-accepted method for the investigation of patients with epithelial ovarian cancer. This study evaluates the role of liquid-based cytology using the ThinPrep technique, in order to investigate its accuracy in diagnosing of malignant cell in peritoneal fluid and comparison with histological diagnosis of patients with malignant epithelial tumors of the ovary.

Material and Methods: 110 consecutive abdominal cavity fluids (ascetic fluid, free peritoneal fluids and peritoneal washings) of women with malignant common epithelial ovarian tumors were investigated. All specimens were taken and prepared according to the ThinPrep technique. ThinPrep specimens were examined by cytopathologists. The cytological diagnoses were compared with the final histological diagnoses.

Results: Cyto-histological correlations were possible in 105 cases of 110; in 5 cases the cytology was inadequate. No false positive result was detected. But 4 false negative cases were detected in final cytological diagnosis. Statistical analysis was performed using the McNemar test for correlation of the final result of cytological and histological diagnosis. No statistically significant difference was observed between the ThinPrep cytological diagnosis and the final histological diagnosis ($\chi^2 = 2.25, p > 0.05$).

Conclusion: ThinPrep technique is a valid method for the pre-operative cytological diagnosis of patients with malignant ovarian tumors and can be potentially complementary to histological evaluation for further investigation of malignant lesions.

Keywords: *Micronuclei; nuclear anomalies; exfoliated cells; cervix cancer; radiotherapy*

INTRODUCTION

The malignant common epithelial tumors of the ovary are by far the most frequently encountered malignant form of ovarian tumor and the most common cause of ascitic fluid [Berek J., 2000; Jemal A. et al., 2006]. The symptoms of epithelial ovarian cancer are fairly nonspecific and often occur when the disease is already spread throughout the abdominal cavity. Most women are diagnosed as having advanced stage disease, and efforts to develop new screening approaches for ovarian cancer are a high priority [Ozols R. et al., 2004; Goff B. et al., 2007]. Standard treatment of ovarian cancer is optimal cytoreductive surgery followed by combination che-

motherapy. The first step in the management of patients with epithelial ovarian cancer is an accurate diagnosis and thorough staging, with optimal surgical cytoreduction. According to the International Federation of Gynecology and Obstetrics (FIGO), it is recommended that all ovarian epithelial tumors be classified histologically as follows: serous tumors, mucinous tumors, endometrioid tumors, clear cell tumors, Brenner tumors, undifferentiated tumors (too poorly differentiated to be placed in any other group), mixed epithelial tumors (composed of ≥ 2 of the 5 major cell types of common epithelial tumors, which are usually specified), and intraperitoneal cancer (the ovaries appear to be incidentally involved and not the primary origin, which should be classified as extraovarian peritoneal cancer) [FIGO, 1986; 1998].

The cytological examination of the ascitic fluid,

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free peritoneal fluid and peritoneal washings is a well-accepted method for the investigation of patients with epithelial ovarian cancer. The detection of malignant cells by peritoneal washing cytology may provide valuable staging and information for prognosis. Furthermore, ascitic fluid is a useful indicator of ovarian tumors which manifests in malignant ascites [Keetel W., Pixley N., 1958].

During the recent years new cytopreparatory techniques have been developed. Liquid-based cytology (LBC) was introduced in the mid-1990s as an alternative to conventional cytology screening, having as main advantages the quicker cytological interpretation, a lot fewer unsatisfactory smears and the possibility of molecular testing in the remaining fluid sample. The ThinPrep (Cytec Co., Boxborough, MA, USA) technique performed on gynecological specimens has gained popularity during the last decade, because of high quality of smears and the efficacy of the method [Hutchinson M. et al., 1992; ThinPrep, 1995]. A wide spectrum of applications in non-gynecological cases has been reported and a diagnostic sensitivity and specificity of over 90% observed. Also, many studies published on thyroid cytology, cervical and endometrial cancer with the use of ThinPrep [Vassilakos P. et al., 2000; Scurry J., Duggan M., 2000; Afify A. et al., 2001; Papaefthimiou M. et al., 2005]. Bibliography is poor about implantation of ThinPrep method in investigation of free peritoneal fluid in case of ovarian cancer. The aim of this study was to evaluate the role of liquid-based cytology using the ThinPrep technique, in order to investigate its accuracy in diagnosing of malignant cell in peritoneal fluid and comparison with histological diagnosis of patients with malignant epithelial tumors of the ovary.

MATERIAL AND METHODS

Our study was carried out in 110 patients with malignant common epithelial tumors of the ovary. The mean age of patients was 45.2 years (SD=18.35 years). One hundred and ten (n=110) consecutive abdominal cavity fluids (ascitic fluid, free peritoneal fluids and peritoneal washings) were investigated. Cytological materials were taken before or during the operation. The material collected was then transferred to a vial containing fixative (Cytolyt; Cytec, Co., Boxborough, MA, USA). After centrifugation material was transferred to a vial with cytopreservative solution (PreservCyt; Cytec, Co.). PreservCyt

solution mildly fixed the cells within 10–15 minutes and then the material was ready to be prepared by the ThinPrep 2000 Automated Slide Processor (Cytec, Co.). In cases of bloody samples, additional Cytolyt® solution washes were necessary, until the sample became clear. Finally, for each case, two ThinPrep® (TP) slides were prepared. From each case, one slide was stained with Papanicolaou stain and the remaining material was used to make additional slides for further diagnostic techniques, if necessary. ThinPrep specimens were examined by cytopathologists. Histological sections from the removed ovarian tumor were interpreted by histopathologists according to the WHO classification scheme. If the first cytological or histological slide was inadequate, a second slide was prepared. When the second one was also unsatisfactory the diagnosis was considered as “inadequate”. Finally cytological diagnosis was compared with the final histological diagnosis.

RESULTS

Cyto-histological correlations were possible in 105 cases of 110; in 5 cases the cytology was inadequate. At cytology 21 cases of stages IA, IB, IIa, IIb were negative and 80/84 cases of stages IC, IIc-IV were positive for malignant epithelial ovarian tumors.

According to the ThinPrep method, false positive results were not observed, but in 8/84 cases of stages Ic, IIc-IV, which were expected to be cytologically positive, tumour cells were not identified in the smears. Based on these data, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of diagnosis by ThinPrep cytological method were 90.47%, 100%, 100%, 72.41% and 92.37%, respectively.

Out of the eight false negative cases diagnosed by the ThinPrep method, four cases were correctly diagnosed as positive by the second review with combination of conventional cytological method. Therefore, only four cases of stages IIc-IV were cytologically false negative. Based on these data sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of final cytological diagnosis of our material were 95.24%, 100%, 100%, 84% and 96.19%, respectively. According to the histological diagnosis 79 patients had serous, 14 mucinous, 4 clear cell, 4 endometrioid, and 1 mucinous-papillary, 1 clear cell-papillary and 2 clear cell-serous cystadenocarcinomas of the

ovary. Statistical analysis was performed using the McNemar test for correlation of the final result of cytological and histological diagnosis. No statistically significant difference was observed between the ThinPrep cytological diagnosis and the final histological diagnosis ($\chi^2 = 2.25, p > 0.05$).

DISCUSSION

Epithelial cancer of the ovary is the most lethal gynecologic malignancy in developed countries. The relative lack of specific signs and symptoms of this disease, coupled with the lack of reliable screening strategies, contributes to a condition that is diagnosed at advanced stages in most patients, resulting in low overall cure rates [Yoshimura S. et al., 1984; Berek J., 2000].

The cytological examination of the peritoneal fluids is a well-accepted method for the investigation of patients with epithelial ovarian cancer [Yoshimura S. et al., 1984]. The cytological evaluation of effusions and especially peritoneal washings and ascitic fluids obtained during the laparoscopy was quite difficult and requires experienced cytopathologists [De Brux J. et al., 1968]. For this reason, the cytological examination was not widely applied in the investigation of malignant ovarian tumours, until it was incorporated in the staging of FIGO protocols. In 1975 the International Federation of Gynaecologists and Obstetricians (FIGO) incorporated results of peritoneal washing cytology into the staging classification for ovarian carcinomas [FIGO, 1986; 1998].

The adequacy of the smear is another important issue in the evaluation of cytological specimens. From 1970 until nowadays, 3000 cases have been reported in the literature without reference to insufficient smears which is characteristic of absence of criteria. Although there are some cases with the cytological diagnosis "no malignant cells are observed" it would be more appropriate, if those cases were referred like "cytological elements are not observed" [Yoshimura S. et al., 1984]. In previous studies, the diagnostic accuracy for the conventional cytology ranged from 54% to 96% [Yoshimura S. et al., 1984; Gay J. et al., 1985]. However, several investigators reported false negative cytological diagnoses of ovarian cancers, after histological confirmation of the peritoneal dissemination, to be ranged from 20% to 70%, and the most of those were

concerned peritoneal washings [Yoshimura S. et al., 1984; Pretorius R. et al., 1986]. The review of recent publications shows the high accuracy of ThinPrep method compared with the conventional cytology, with an important decrease of the screening time and good correlation with final histological diagnosis in patients with cervical, endometrial cancer, thyroid lesion, etc.

AutoCytePrep: Vassilakos et al., 2000. This was a cohort study, in which conventional screening and the AutoCytePrep method were compared with available histology and cytology follow-up data. Concerning HSIL or higher, the detection rate for the AutoCytePrep method clearly was better compared with conventional screening (0.39% vs. 0.23%, respectively), with unchanged relative specificity (1.00) [Vassilakos P. et al., 2000].

Bishop et al., 1998. This was a split-sample study, in which AutoCytePrep smears and conventional smears were compared with available histologic and cytologic follow-up data. For LSIL or higher, the detection rate was better for Auto-CytePrep screening compared with conventional screening (0.92% vs. 0.81%, respectively) [Bishop J. et al., 1998]

M. Stamataki et al., 2007. This study investigated the role of liquid-based cytology by ThinPrep technique in the detection of thyroid lesions. Specimens (n=252) for pre-operative evaluation of thyroid nodules were prepared by the ThinPrep and then examined. All cytological diagnoses were correlated to the histological ones. According to findings, a sensitivity of 87.80%, a specificity of 99.50%, a positive predictive value of 97.30%, a negative predictive value of 97.56% and an overall accuracy of 97.52% were observed in fine needle aspiration cytology in correlation to the histological diagnosis after thyroidectomy [Stamataki M. et al., 2008].

In our study we investigated ascitic fluid, free peritoneal fluid and peritoneal washings by ThinPrep method in patients with common malignant epithelial tumors of the ovary. According to our findings, 8 false negative results were observed in the first cytological diagnosis by ThinPrep method, which were correlated in second review of smears. Finally, 4 false negative cytological results were observed in final cytological diagnosis of our material and none false positive result. The McNemar test for correlation of the final result of cytological

and histological diagnosis shows no statistically significant difference between the ThinPrep cytological diagnosis and the final histological diagnosis ($\chi^2 = 2.25$, $p > 0.05$). According to our results, cytological method ThinPrep shows high accuracy and good correlation with the final histological diagnosis.

CONCLUSION

ThinPrep technique is a valid method for the pre-operative cytological diagnosis of patients with malignant ovarian tumors and can be potentially complementary to histological evaluation for investigation of malignant cells.

REFERENCES

1. Afify A.M., Liu J., Al-Khafaji B.M. Cytologic artifacts and pitfalls of thyroid fine-needle aspiration using Thin- Prep: a comparative retrospective review. *Cancer*. 2001; 25: 93(3): 179-186.
2. Berek J.S. Epithelial ovarian cancer. In: Practical Gynaecologic Oncology. Edited by Berek J.S., Hacker N.F., 3rd edn. Philadelphia, Lippincott Williams&Wilkins, 2000. P. 457-522.
3. Bishop J.W., Bigner S.H., Colgan T.J., et al. Multicenter masked evaluation of AutoCyte PREP thin layers with matched conventional smears. Including initial biopsy results. *Acta Cytol*. 1998; 42: 189-197.
4. De Brux J., Dupré-Froment J., Mintz M. Cytology of the peritoneal fluids sampled by coelioscopy or by cul-de-sac puncture. Its value in gynecology. *Acta Cytol*. 1968; 12(5): 395-403.
5. FIGO Cancer Committee. Staging Announcement. *Gynecol Oncol* 1986; 25: 383-385
6. FIGO Committee of Cynecology Oncology: Figo annual report on the results of treatment in gynaecologic cancer. *J. Epidemiol. Biostat*. 1998; 3: 1-168.
7. Gay J.D., Donaldson L.D., Goellner J.R. False-negative results in cytologic studies. *Acta Cytol*. 1985; 29: 1043-1046.
8. Goff B.A., Mandel L.S., Drescher C.W., et al. Development of an ovarian cancer symptom index: possibilities for earlier detection. *Cancer*. 2007; 109: 221-227.
9. Hutchinson M.I., Agarwal P., Denault T., Berger B., Cibras E.S. A new look at cervical cytology: ThinPrep multicenter trial results. *Acta Cytol*. 1992; 36: 499-504.
10. Jemal A., Siegel R., Ward E., et al. Cancer statistics, *CA Cancer J. Clin*. 2006; 56: 106-130.
11. Keetel W.C., Pixley N.N. Diagnostic value of peritoneal washings. *Clin. Obstet. Gynecol*. 1958; 1: 592-606.
12. Ozols R.F., Bookman M.A., Connolly D.C., et al. Focus on epithelial ovarian cancer. *Cancer Cell*. 2004; 5: 19-24.
13. Papaefthimiou M., Symiakaki H., Mentzelopoulou P., Giahnaki A. E., Voulgaris Z., Diakomanolis E., Kyroudes A. and Karakitsos P. The role of liquid-based cytology associated with curettage in the investigation of endometrial lesions from postmenopausal women. *Cytopathology*. 2005; 16: 32-33.
14. Pretorius R.G., Lee K.R., Papillo J., Baker S., Belinson J. False-negative peritoneal cytology in metastatic ovarian carcinoma. *Obstet. Gynecol*. 1986; 68: 619-623.
15. Scurry J.P., Duggan M.A. Thin layer compared to direct smear in thyroid fine needle aspiration. *Cytopathology*. 2000; 11: 104-115.
16. Stamataki M., Anninos D., Brountzos E., Georgoulakis J., Panayiotides J., Christoni Z., Peros G., and Karakitsos P. The role of liquid-based cytology in the investigation of thyroid lesions. *Cytopathology*. 2008, 19, 11-18,
17. *ThinPrep*. 2000 Operator's Manual. Marlborough, MA; Cytyc Corporation; 1995.
18. Vassilakos P., Schwartz D., de Marval F., et al. Biopsy-based comparison of liquid-based, thin-layer preparations to conventional Pap smears. *J. Reprod. Med*. 2000; 45: 11-16.
19. Yoshimura S., Scully R.E., Taft P.D., Kerrington J.B. Peritoneal fluid cytology in patient with ovarian cancer. *Gynecol. Oncol*. 1984; 17: 161-167.