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Peritoneal washing in gynecological neoplasias

Lavado peritoneal em neoplasias ginecológicas

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ABSTRACT

Introduction and objective: Peritoneal washing cytology is part of pathological staging of adenocarcinomas of the endometrium and ovary. The objective of this study was to verify the prevalence of cytology positive for malignancy in patients diagnosed with adenocarcinoma of the endometrium or ovary, as well as to verify the association between the positive cytology and the variables age of the patient, histological type of the neoplasm and degree of tumor differentiation. **Method:** A retrospective and prospective cross-sectional study was carried out through the analysis of peritoneal washing cytology reports and the anatomopathological reports of 43 patients diagnosed with ovarian or endometrial adenocarcinoma, provided by the Pathology Center of Curitiba. **Results:** In relation to endometrial adenocarcinoma, the prevalence of positive cytologies was 7%. Neither the degree of tumor differentiation ($p = 1$) nor age ($p = 0.233$) demonstrated association with such positivity. In relation to ovarian adenocarcinoma, the prevalence of positive cytologies was 20%. The degree of tumor differentiation showed a significant positive association with this positivity ($p = 0.044$). Age did not show association ($p = 0.804$). It was not possible to verify association with the histological type of neoplasms due to non-applicability of the statistical test. **Conclusion:** The prevalence of peritoneal lavage cytology positive for malignancy was 7% in endometrial adenocarcinoma and 20% in ovarian adenocarcinoma. Only the degree of tumor differentiation of ovarian adenocarcinomas showed a significant association with peritoneal washing positivity.

Key words: endometrial neoplasms; ovarian neoplasms; peritoneal lavage.

RESUMO

Introdução e objetivo: *A citologia de lavado peritoneal faz parte do estadiamento patológico dos adenocarcinomas de endométrio e ovário. O objetivo deste trabalho foi verificar a prevalência de citologias positivas para malignidade em pacientes com diagnóstico de adenocarcinoma de endométrio e/ou ovário, bem como a associação entre a positividade da citologia e as variáveis idade da paciente, tipo histológico da neoplasia e grau de diferenciação tumoral.* ***Método:*** *Foi realizado um estudo transversal retrospectivo e prospectivo por meio da análise dos laudos de citologia de lavado peritoneal e dos laudos anatomopatológicos de 43 pacientes com diagnóstico de adenocarcinoma ovariano ou endometrial, disponibilizados pelo Centro de Patologia de Curitiba.* ***Resultados:*** *Em relação ao adenocarcinoma de endométrio, a prevalência de citologias positivas foi de 7%. Nem o grau de diferenciação tumoral (p = 1) nem a idade (p = 0,233) demonstram associação com a positividade. Em relação ao adenocarcinoma de ovário, a prevalência de citologias positivas foi de 20%. O grau de diferenciação tumoral demonstrou associação positiva significativa com essa positividade (p = 0,044); a idade não demonstrou associação (p = 0,804). Não foi possível verificar a associação com o tipo histológico das neoplasias por não aplicabilidade do teste estatístico.* ***Conclusão:*** *A prevalência de citologias de lavado peritoneal positivas para malignidade foi de 7% no adenocarcinoma de endométrio e de 20% no adenocarcinoma de ovário. Somente o grau de diferenciação tumoral dos adenocarcinomas ovarianos demonstrou associação significativa com a positividade do lavado peritoneal.*

Unitermos: *neoplasias do endométrio; neoplasias ovarianas; lavagem peritoneal.*

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RESUMEN

Introducción y objetivo: *La citología del lavado peritoneal es parte de la estadificación de los adenocarcinomas de endometrio y ovario. El objetivo de este trabajo es estimar la prevalencia de citologías positivas para malignidad en pacientes con diagnóstico de adenocarcinoma de endometrio y/u ovario, así como la asociación entre positividad de la citología y las variables edad del paciente, tipo histológico de la neoplasia y grado de diferenciación tumoral.* ***Método:*** *Se realizó un estudio transversal retrospectivo y prospectivo mediante el análisis de los reportes citológicos de lavado peritoneal y hallazgos anatomopatológicos de 43 pacientes con diagnóstico de adenocarcinoma ovárico o endometrial, puestos a disposición por el Centro de Patología de Curitiba.* ***Resultados:*** *En cuanto al adenocarcinoma de endometrio, la prevalencia de citologías positivas fue 7%. Ni el grado de diferenciación tumoral (*p = *1) ni la edad (*p = *0,233) mostraron asociación con la positividad. En cuanto al adenocarcinoma de ovario, la prevalencia de citologías positivas fue 20%. El grado de diferenciación tumoral mostró asociación positiva significativa con esa positividad (*p = *0,044); la edad no mostró asociación (*p = *0,804). No fue posible verificar la asociación con tipo histológico de las neoplasias por cuanto el test estadístico no sería aplicable.* ***Conclusión:*** *La prevalencia de citologías de lavado peritoneal positivas para malignidad fue 7% en el adenocarcinoma de endometrio y 20% en el adenocarcinoma de ovario. Solamente el grado de diferenciación tumoral de los adenocarcinomas ováricos demostró asociación significativa con la positividad del lavado peritoneal.*

Palabras clave: *neoplasias del endometrio; neoplasias ováricas; lavado peritoneal.*

INTRODUCTION

According to American statistics, the endometrial malignancy is the most prevalent among the pelvic neoplasms of the female genital tract (around 24/100,000 women). Its mortality rate reaches up to 16%. It affects especially postmenopausal women – aged 60-85 years[1]. The major implicated risk factors are obesity, hyperlipidic diet, nulliparity, and hormone replacement therapy (HRT)[2].

Ovarian cancer is the least prevalent (around 12/100,000 women); however its outcome is much more unfavorable – more than 60% of the patients evolve to death[3]. Most women are diagnosed at age 60 years or older. The most commonly related risk factors are age, obesity, polycystic ovary syndrome, and genetic factors, especially mutations in the *BRCA1* and *BRCA2* genes[4].

Tumor staging has great relevance to the treatment of these patients, given that treatment depends fundamentally upon the lesion extension[5]. The system more commonly used in western countries is the TNM, recommended by the International Union against Cancer (UICC) and by the American Joint Committee on Cancer (AJCC). This system classifies tumors based on their primary size (T), the involvement of regional lymph nodes (N), and the presence of distance metastases (M)[6]. This classification can be clinical, when based on evidence obtained before definitive treatment (cTNM), or pathological (pTNM), when consisting in evidence collected by means of surgery and histopathology analysis[7].

One of the criteria used in pathological staging, both in ovarian and endometrial adenocarcinoma, is the result of peritoneal washing cytology. It is a cytological exam for intraoperative lavages, aimed at detecting subclinical metastases[8]. It was initially proposed in 1956, by Keetle and Elkins, and incorporated to the protocol of the International Federation of Gynecology and Obstetrics (FIGO) into the staging classification for ovarian cancer, in 1975, and for endometrial cancer, in 1989[9]. Although the peritoneal lavage is used in the staging of these gynecological neoplasms, the national literature is sparse on the theme.

The objective of this work was to assess the prevalence of positive peritoneal lavages in a sample of patients with ovarian and/or endometrial adenocarcinoma, as well as the association between positive lavage and the variables patient age, tumor degree of differentiation and histological type.

METHOD

The research project was approved by the Research Ethics Committee of Faculdade Evangélica do Paraná, Brazil, in October 2011. It is a retrospective and prospective cross-sectional study analyzing 43 reports of anatomopathological exams and cytology of peritoneal lavage of patients diagnosed with ovarian and/or endometrial adenocarcinoma.

These reports are dated from January 2009 through April 2012 and were obtained from electronic files of the Pathology Center of Curitiba, situated within Hospital Senhora das Graças, Curitiba, Paraná, Brazil.

The study included patients diagnosed with ovarian or endometrial adenocarcinoma that underwent surgery for lesion staging and collection of peritoneal fluid. This was processed by cytocentrifugation (Cytospin Shandon 3®), with three Papanicolaou-stained preparations being made for analysis. Those reports that did not contain all information relevant to the research were excluded. When criteria were met, the data necessary for the research were collected and catalogued in a spreadsheet.

In order to estimate the association between qualitative variables and sample positivity, Fisher's exact test was adopted. Values of $p < 0.05$ indicated statistical significance.

RESULTS

Endometrial adenocarcinoma

Reports of 28 patients were accessed, presenting mean age of 62.9 ± 13.5 years (range: 20-82 years). Among these, two presented tumor cells in cytology (**Table 1**).

Patients with positive cytology had lower mean age (60.5 ± 17.7 years) than those with negative cytology (63 ± 13.6 years). This difference, however, was not significant ($p = 0.804$).

The most common histologic type was endometrioid – with 24 out of the 28 cases –, followed by the serous type, with three cases; and the mucinous type, with just one. It was not possible to verify association with lavage positivity due to absence of positive cases in the mucinous type and of negative cases in the serous type.

Tumors were classified according to differentiation degree. No significant association was found between the degree of differentiation and the presence of neoplastic cells in the lavage ($p = 1$). Table 1 shows the distribution of cases with positive and negative cytology according to the histologic type.

TABLE 1 – Association between result of peritoneal lavage and degree of tumor differentiation of endometrial carcinoma ($n = 28$)

Degree of differentiation	Sample positivity	
	Negative	Positive
High grade	11	0
Moderate grade	9	2
Low grade	6	0
Total	26	2

p = *1.*

Ovarian adenocarcinoma

Reports of 15 patients with ovarian adenocarcinoma were analyzed, with mean age of 55.3 ± 18.2 years (range: 27-83 years). Among these, three presented tumor cells in cytology (**Table 2**).

Patients with positive cytology had higher mean age (69 ± 15.7 years) than those with negative cytology (51.8 ± 17.6 years). This difference, however, was not significant ($p = 0.233$).

The serous histological type was the most frequent, with nine cases; followed by the mucinous type, with two cases and the endometrioid type, with just one. In these patients it was also not possible to verify association with peritoneal lavage positivity due to absence of positive cases in the endometrioid type and negative cases in the mucinous type.

Of all the proposed associations, only the degree of tumor differentiation of ovarian adenocarcinomas demonstrated significant association with positivity of the peritoneal lavage ($p = 0.044$). Comparison was done between well differentiated neoplasms and a group composed of moderately and poorly differentiated neoplasms. Case distribution is listed in Table 2.

TABLE 2 – Association between result of peritoneal lavage and degree of tumor differentiation of ovarian carcinoma ($n = 15$)

Degree of differentiation	Sample positivity	
	Negative	Positive
High grade	3	3
Moderate or low grade	9	0
Total	12	3

p = *0.044.*

DISCUSSION

Endometrial adenocarcinoma

Endometrial adenocarcinoma is the seventh most frequent among women, with around 290 thousand new cases per year in Brazil[10]. The incidence of this cancer increases proportionally to life expectancy. As staging is a determining factor in prognosis and treatment of neoplasms[11], this work aimed at assessing if age, histological type and degree of tumor differentiation are factors that alter positivity of the lavage.

Positivity in peritoneal lavage is quite controversial in the literature[12]. However, it is an important tool for post-operative management in the indication of the adequate treatment when there is good cytological preparation[13]. The presence of malignant cells in the lavage raises endometrial staging to at least stage IIIC[5], however Lin states it is neither a sensitive nor a specific

method for these cases. According to the author, cells can go unnoticed by the amount of mesothelium and/or macrophages, or can even be confused with reactive mesothelial cells.

Some authors[14, 15] argue that positive lavage results depend on the correctly used technique and the observer's experience. In the researched literature, a variation in positivity was found between 2% and 33%[5, 15-19], although the present study reveals a 7.14% incidence. According to Ito *et al.* (1992)[18], a positive lavage can be related to previous hysteroscopy, as in the procedure, cell shedding can happen and, as the uterine cavity has communication with the pelvic cavity, by means of the fallopian tubes, implantation of neoplastic cells can occur in the peritoneum.

Endometrial neoplasms have two recognized subtypes: estrogen-associated type I and estrogen-independent type II. Type I is more prevalent and presents better prognosis. This implies that, in older patients, there is more exposure to estrogens[20].

For some researchers[21, 22] this disease has an incidence peak at age 55 years. However, patients included in this study had mean age of 62 years (60 for cases of positive peritoneal lavage and 63 for negative), getting close to reports by Tangjitgamol *et al.* 2010[21], in which the highest peak occurred between 61 and 64 years. It is possible that age, as an interfering factor in the result of peritoneal lavage, is more related to risk factors that coincide with increased exposure to estrogens without progesterone antagonism[11], such as obesity, HRT, late menopause and early menarche[20].

The histological type more commonly identified in endometrial neoplasms is endometrioid adenocarcinoma, in around 80% of the cases[21, 23]; followed by mucinous adenocarcinoma, in 5%; serous papillary, in 3%-4%; and clear cell adenocarcinoma, in less than 5%[11]. Our results agreed with these studies, considering that 85% (24 out of 28) of the cases were of the endometrioid adenocarcinoma type; 10% (three out of 28), mucinous adenocarcinoma; and 3%, serous papillary (one out of 28).

Endometrioid carcinomas are characterized as being more aggressive, followed by the serous carcinomas[11]. In our study, both histological types were those that presented positive peritoneal lavage. However, it was not possible to make a statistical analysis of data due to the reduced number of cases.

In general, G1 tumors, that is, those exhibiting 95% or more glandular structures (well differentiated), present higher frequency over the other categories[13, 18, 24], differing just from the results by Salvesen *et al.* (1998)[23], who found higher frequency in G2 (moderately differentiated). When this topic was compared in the present study, we verified that G1 presented frequency in 11 of the 27 patients (40.74%); G2 also presented the same percentage; while G3 (poorly differentiated), just in five of the 27 patients (22.22%).

Comparing the relationship of positivity in the peritoneal lavage and the degrees of tumor differentiation, the encountered literature shows a relationship of 14 in 50 for G1 (28%); four in 11 for G2 (36.36%); and six in 13 for G3 (46.15%)[18]. In our work we just had tumors classified as G2. For statistical tests, we grouped G1 and G2; but, even though, there was no correlation between degree of tumor differentiation and positivity of the lavage.

Although some authors[14, 16] have demonstrated utility in the procedure of peritoneal lavage as a staging factor of endometrial neoplasms, other studies[5, 19] demonstrate that peritoneal lavages can overstage neoplasias, leading to unnecessary chemotherapy.

Corroborating such findings, the International Federation of Gynecology and Obstetrics (FIGO) has recently proposed the withdrawal of peritoneal washing as a criterion for pathological staging of endometrial carcinoma[20].

Ovarian adenocarcinoma

Even though ovarian cancer is not the most prevalent among women, it is the most lethal of the tumors in the female genital tract[25]. More than 70% of patients with ovarian cancer will be diagnosed with advanced disease. This is an aggravating factor, considering that these patients' survival is directly related to the neoplasia surgical status. Thus, the use of the peritoneal lavage as a method of early detection of microscopic dissemination is of great value in reducing mortality and morbidity of the disease[26].

Knowing that the therapeutic conduct depends, at certain times, on the positive cytology of the lavage, the incidence of this behavior was verified in the sample. Zuna and Behrens (1996)[8], for example, reported 80.9% positivity. Özkara (2011)[26], in a more recent research, reported 62.2%; and Colgan *et al.* (2002)[27], 50%. In contrast, Fadare *et al.* (2004)[28] and Mulvany (1996)[29] found just 25% and 12%, respectively. The present work, confirming that by Fadare *et al*., found 20% positivity. This partially explains that the high positivity of some studies, such as those by Zuna and Behrens, and Colgan *et al*., occurs due to the inclusion of ascetic fluids in the sample, as these are known to demonstrate greater amounts of malignant cells than the pelvic lavage[28].

Considering age and positivity in the peritoneal lavage, Özkara demonstrated the absence of association between such variables, and confirmed the finding of the present study. Although it is notorious that age is an isolated risk factor for ovarian cancer[4],

it is possible that peritoneal dissemination is more related to the natural history of the disease than to the age of its onset.

Regarding the impact of histological type in the positivity of the lavage, the encountered studies were discordant. Fadare *et al*. (2004)[28] demonstrated strong positive association between serous carcinoma and positivity of the lavage. Rubin *et al.* (1988)[21] and Özkara (2001)[26], on the other hand, did not observe association among any histological type. In our sample, there was no number of cases enough for the conduction of the statistical test aimed at this comparison. The serous carcinoma is more frequently diagnosed in advanced stages, with unfavorable evolution. The mucinous and endometrioid carcinomas, on the other hand, are diagnosed, in general, at initial stages[25]. It is therefore possible that the association found by Fadare *et al*. is relevant. In our case study, the low prevalence of the less common histological subtypes may have hampered statistical analysis.

At last, when evaluating the association between degree of cell differentiation and positive cytology, the research found positive correlation ($p = 0.044$). Özkara found strong positive correlation between the variables. The author does not argue about it, but, considering that histological degree is related to tumor aggressiveness and is an independent factor in the survival of women with ovarian cancer[25], the correlation is well-founded. However, one must be attentive that the variable tumor stage can have influenced the result of the research, as the sample was not stratified.

FURTHER RESEARCH

Although the association between degree of tumor differentiation and positivity of the peritoneal lavage in ovarian neoplasms has been found, broader studies are necessary to determine the validity of the obtained results in a larger population.

CONCLUSION

With respect to endometrial carcinoma, the prevalence of positive lavages was 7.1%. Both degree of differentiation and age did not demonstrate significant association. Regarding ovarian adenocarcinoma, the prevalence of positive cytology of peritoneal lavage was 20%. The degree of differentiation demonstrated significant positive association with this positivity ($p = 0.044$). The same did not occur with patient age.

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