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Original Article

Relationship between positive peritoneal fluid cytology and the type of the malignancy in patients with malignancy related ascites

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Abstract

Aim: Malignancy related ascites may be due to abdominal origin, extraabdominal origin and primary peritoneal malignancy. The relationship between positive peritoneal fluid cytology and the type of the malignancy and the burden of the tumor in the abdomen was investigated.

Materials and Methods: One-hundred eighty-nine consecutive patients with malignancy who were examined for ascites fluid cytology were retrospectively identified in the last two years. Age, gender, primary tumor site, radiologic imaging and pathology results of the patients were recorded. According to the abdominal imaging at the time of the paracentesis procedure, the extensiveness of disease in the abdomen was classified as only ascites, ascites with peritoneal carcinomatosis, ascites with liver involvement (primary tumor or metastases) and ascites with peritoneal carcinomatosis with liver involvement.

Results: Out of 189 patients, 119 patients (63.0%) were female. The primary tumor site was ovary in 49 patients, stomach in 38 patients, pancreatobiliary system in 37 patients, breast in 16 patients, colorectal in 14 patients, uterine in 13 patients, kidney or bladder in 6 patients, liver in 6 patients, lymphoma in 4 patients, malignant mesothelioma in 3 patients, lung in 2 patients and skin in one patient. Peritoneal fluid cytology revealed malignant cells in 102 patients (54.0%), while 87 patients (46.0%) had benign results. There was a relationship between primary tumor site and malignant cell detection in the fluid (p= 0.001). The detection of malignant cells was correlated with abdominal extensiveness of disease as well (p = 0.01). In multivariate analysis, only primary tumor site [(p = 0.001), risk ratio: 2.28, 95% confidence interval: 1.83-2.73] was the independent factor affecting cytologic positivity.

Conclusion: Considering primary tumor site and the extensiveness of disease in the abdomen, primary tumor site was the most important factor affecting peritoneal fluid positivity.

Keywords: Cytology; malignancy; peritoneal carcinomatosis; peritoneal fluid

INTRODUCTION

The pathologic accumulation of protein rich fluid in peritoneal cavity is described as ascites. Although benign diseases often play a role in etiology, malignancy is the underlying cause in a small proportion of cases (1,2). Malignancy related ascites may be the first finding at the time of initial diagnosis or it may develop after initial diagnosis and treatment. In addition to ascites fluid tests, cytological examination should be performed on the patients in suspicious malignancy-related ascites. The mechanism of ascites formation is quite complex and sometimes several mechanisms can be intertwined. Different malignancies cause ascites with different mechanisms and probably, the rate of cancer cell detection in ascites fluid may also differ according to this situation. Up to our knowledge, there is no study in literature about the relationship between positive peritoneal fluid cytology and the type of the malignancy. It is generally emphasized that ovarian cancer is the most common ascites producing malignancy and primary liver malignancy is the most common cancer type with ascites negative cytology (3-6). The overall sensitivity of cytology smears from malignancy-related ascites is 58 to 75 percent (7-9). The sensitivity of ascites cytology with immunohistochemistry especially in ovarian cancer is 80.6% (10).

In this study, relationship between positive peritoneal fluid cytology and the type of the malignancy as well as the burden of the tumor in the abdomen was investigated.

MATERIALS and METHODS

Ethical consideration

The data were collected retrospectively and approved by our institutional ethics committee.

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Patient selection and method

There were 233 consecutive patients who were examined retrospectively for ascites fluid cytology between January 2018 and February 2020 in our tertiary reference center. Twenty-nine patients with benign etiologic diseases (cirrhosis in 21 patients, nephrogenic ascites in 4 patients, heart failure in 4 patients), 15 patients whose result changed to malignant disease with more than two cytological evaluations (which had benign result at first but turned to malignant result with the next evaluations) and patients who received peritoneal washing cytology or cytological evaluations during surgery were excluded. Although repeated cytological evaluations were performed, 189 patients who did not have any inconsistency between test results were included in the study. Age, gender, primary tumor site, radiologic imaging and pathology results of the patients were recorded. Presence of ascites was confirmed by physical evaluation and radiological imaging. For cytological evaluation, ultrasound-guided paracentesis was performed. Immunocytochemistry for cancer-specific biomarkers was also used to confirm diagnosis in 54 patients as they did not have malignancy diagnosis at initial. The extensiveness of the disease inside the abdomen was classified to four categories according to the abdominal tomography and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) findings at the time of the paracentesis procedure as only ascites, ascites with peritoneal carcinomatosis, ascites with liver involvement (primary tumor or metastases) and ascites with peritoneal carcinomatosis with liver involvement.

Statistical analysis

Descriptive statistics (number, percentage) were used to analyze the parameters related to the patient demographic characteristics, primary tumor site and intraabdominal extension of the disease. Chi-square or Fisher's exact test was used for categorical variables to compare ascites fluid evaluation results and the primary tumor site and intraabdominal extension of the disease; and continuous variables such as the amount of ascites fluid sent for cytological evaluation was examined by Student's t-test. Multivariate Cox regression analysis was carried out to compare and to identify the factors that might have any effect on the cytologic positivity. These analyses were used to calculate the risk ratio (RR) and 95% confidence intervals (CI). P values < 0.05 were considered as statistically significant. All analyses were performed with SPSS software (version 21.0; SPSS Inc., Chicago, IL).

RESULTS

One-hundred nineteen patients (63.0%) were female out of 189 patients. Median age was 62.0 years in female, 60.5 years in male patients. Forty-seven patients had peritoneal fluid at the time of diagnosis, while ascites developed by disease progression in other patients. Peritoneal fluid cytology showed malignant cells in 102 patients (54.0%), while the cytology result was benign in 87 patients (46.0%). The median amount of ascites fluid sent for cytological evaluation in those with or without malignant cells were 1500 cc and 1300 cc respectively. This was similar in both groups (p= 0.66). The primary tumor site was ovary in 49 patients (25.8%), stomach in 38 patients (20.1%), pancreatobiliary system in 37 patients (19.6%), breast in 16 patients (8.5%), colorectal in 14 patients (7.4%), uterine in 13 patients (6.9%), kidney or bladder in 6 patients (3.2%), liver in 6 patients (3.2%), lymphoma in 4 patients (2.1%), malignant mesothelioma in 3 patients (1.6%), lung in 2 patients (1.1%) and skin in one patient (0.5%).

Abdominal tomography and/or 18F-FDG PET/CT showed intraabdominal extensiveness of the disease as follows; only ascites in 32 patients (16.9%), ascites with peritoneal carcinomatosis in 84 patients (44.4%), ascites with liver involvement (primary tumor or metastases) in 28 patients (14.9%), and ascites with peritoneal carcinomatosis with liver involvement in 45 patients (23.8%). Table 1 demonstrates intraabdominal extensiveness of malignancy according to primary site of the tumor.

Table 1. Abdominal extensiveness of malignancy according to primary site of the tumor

	Abdominal extention of the disease			
Primary tumor site	Only ascites	Ascites with peritoneal carcinomatosis	Ascites with liver involvement	Ascites with peritoneal carcinomatosis with liver involvement
Ovary	6 (12.2%)	34 (69.4%)	2 (4.1%)	7 (14.3%)
Stomach	10 (26.3%)	18 (47.4%)	4 (10.5%)	6 (15.8%)
Pancreatobiliary system	3 (8.1%)	15 (40.5%)	5 (13.5%)	14 (37.8%)
Breast	3 (18.8%)	2 (12.5%)	7 (43.8%)	4 (25.0%)
Colorectal	1 (7.1%)	4 (28.6%)	3 (21.4%)	6 (42.9%)
Uterine	4 (30.8%)	5 (38.5%)	1 (7.7%)	3 (23.1%)
Kidney or bladder	1 (16.7%)	1 (16.7%)	1 (16.7%)	3 (50.0%)
Liver	1 (16.7%)	0 (0.0%)	3 (50.0%)	2 (33.3%)
Lymphoma	2 (50.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)
Malignant mesothelioma	0 (0.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)
Lung	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
Skin	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)

The relationship between the results of ascites fluid evaluation and both primary tumor site and intraabdominal extensiveness of malignancy were given in Tables 2 and Table 3. There was a relationship between primary tumor site and malignant cell detection in the fluid (p = 0.001). Also, presence of malignant cells in ascites showed association with intraabdominal extensiveness of malignancy in univariate analyses (p = 0.01). In multivariate analysis, only primary tumor site [(p = 0.001), RR: 2.28, 95% CI: 1.83 - 2.73] was the independent factor affecting cytologic positivity.

Table 2. The relationship between the results of the ascites fluid evaluation and primary tumor site

	Cytologic Examination		
Primary tumor site	Malignant cells positive	Malignant cells negative	P values
Ovary	40 **(81.6%)**	9 (18.4%)	
Stomach	25 **(65.8%)**	13 (34.2%)	
Pancreatobiliary system	14 (37.8%)	23 (62.2%)	
Breast	8 (50.0%)	8 (50.0%)	
Colorectal	4 (28.6%)	10 (71.4%)	
Uterine	6 (46.2%)	7 (53.8%)	0.001
Kidney or bladder	1 (16.7%)	5 (83.3%)	
Liver	0 (0.0%)	6 **(100.0%)**	
Lymphoma	0 (0.0%)	4 **(100.0%)**	
Malignant mesothelioma	3 **(100.0%)**	0 (0.0%)	
Lung	1 (50.0%)	1 (50.0%)	
Skin	0 (0.0%)	1 **(100.0%)**	

Table 3. The relationship between the results of the ascites fluid evaluation and intraabdominal extensiveness of malignancy

	Cytologic Evaluation		
Abdominal extention of the disease	Malignant cells positive	Malignant cells negative	P values
Only ascites	14 (43.8%)	18 (56.3%)	
Ascites with peritoneal carcinomatosis	58 (69.0%)	26 (31.0%)	0.01
Ascites with liver involvement	8 (28.6%)	20 (71.4%)	
Ascites with peritoneal carcinomatosis with liver involvement	22 (48.9%)	23 (51.1%)	

DISCUSSION

Malignancy related ascites is mostly due to abdominal cancers such as ovarian, gastric, pancreatic, uterine, colorectal, and liver. However, it may be due to peritoneal origin such as primary peritoneal carcinoma and malignant mesothelioma, as well as extra-abdominal origin such as lymphoma, lung, and breast cancer. In a few patients, a primary tumor cannot be detected. (11-13) In 52-54% of intraabdominal malignancies, the first finding is ascites. (12,14) Primary tumor site is a factor for ascites development. In their study with 209 patients Ayantunde et al. concluded that ovarian malignancy was the most common cause (37%) followed by pancreatobiliary (21%) and gastric malignancy (18%)(12). In another study, primary malignancy was mostly ovary (47%) followed by non-Hodgkin's lymphoma (11%) and gall bladder carcinoma (9%) (15). The most frequently observed tumors which caused ascites in our series were ovarian, stomach and pancreatobiliary system tumors.

Many mechanisms play a role in ascites formation. The balance between fluid secretion into the abdominal cavity and the absorption by the peritoneum is impaired. Malignant ascites may develop via increased fluid production by tumor cells lining peritoneal cavity, obstruction of lymphatic drainage by tumor cells (14,16), increased portal pressure due to tumor metastasis, altered vascular permeability, released of inflammatory cytokines, (17-19) and vascular endothelial growth factor secreted by tumor cell due to increased capillary permeability (20). There is a relationship between these mechanisms and positive cytology. Malignant cells cannot be detected in ascites cytology developing secondary to increased portal pressure due to liver involvement (3,4). Positive ascetic fluid cytology is correlated with peritoneal carcinomatosis without liver metastases (4). In our series, while positive ascites cytology was not detected in primary liver tumor, the rate of malignant cell detection was 28.6% in metastatic liver disease. In the presence of peritoneal carcinomatosis, the rate of malignant cell detection in ascetic fluid increased (69.0%) and this finding is compatible with literature. There is a difference between the origin of the primary tumor and ascites formation mechanisms. Obstruction of lymphatic drainage by tumor cells is often seen in lymphoma and breast cancer (21,22). While malignancies of ovary and urinary bladder as well as peritoneal mesothelioma tend to cause peritoneal carcinomatosis; lung, breast and gastrointestinal malignancies may cause massive liver metastases as well as peritoneal carcinomatosis (22). In this respect, our series revealed that when primary liver malignancy was excluded, peritoneal carcinomatosis and peritoneal carcinomatosis with liver involvement were higher in intraabdominal tumors which developed ascites.

Cytologic evaluation of the peritoneal fluid is important for differential diagnoses. While the sensitivity of conventional cytological examination is lower, if immunohistochemical staining is carried, sensitivity

increases (1). The relationship of positive peritoneal cytology and primary cancer site has been shown in the literature for both ovary and primary liver tumors. It was emphasized that the most common cytological positivity was in ovary cancer with the sensitivity of 67 - 80% (9, 10). In this study, immunohistochemical staining was performed in 54 patients. Although the number of patients with malignant mesothelioma is low, the top three tumors with the highest rate of positive ascites cytology were malignant mesothelioma (100%), ovary (81.6%) and stomach (65.8%). Similarly, despite the small number of cases, ascites cytology was negative in all patients in primary liver cancer, lymphoma and skin tumor. The limitation of this study is that the intraabdominal spread of the disease can only be classified radiologically. However, most of the disease findings detected in surgery are more than radiological imaging.

CONCLUSION

Considering primary tumor site and the extensiveness of disease in the abdomen, primary tumor site was the most important factor affecting peritoneal fluid positivity.

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