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ORIGINAL RESEARCH

Significance of positive malignant cells in peritoneal washings and it's clinicopathological correlation with stage of disease in patients with gastrointestinal malignancy

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ABSTRACT

Background: Gynecological malignancies account for three fourth of the female patients who present with malignant ascites. Similarly in males half of the patients with malignant cells in their peritoneal washings have malignancy involving GI tract. This study was conducted to assess free malignant cells in peritoneal cavity with varied clinicopathological profile of patients with gastrointestinal malignancies and its correlation with stage of disease.

Materials and Methods: Patients with Gastrointestinal malignancy presenting to surgical OPD during study year were assessed for clinic- pathological stage and malignant cytology. Correlation between presence of positive malignant cytology and clinicopathological stage was assessed.

Results: Out of total 34 patients with malignancies involving colorectal, gastric, esophageal and pancreas, 9 had been found to be having free malignant cells in peritoneal cavity. Advanced stage of the disease with worse clinic-pathological profile had more propensity of free malignant cells in peritoneal cavity

Conclusion: Significant correlation was found between clinicopathological stage and presence of positive malignant cytology. However, we failed to demonstrate any correlation between degree of differentiation of tumor and positive malignant cells in peritoneal cavity

INTRODUCTION

Malignant ascites is most common due to colorectal, gastric, pancreatic and uterine, ovarian cancers. Seventy five percent of women with malignant ascites i.e., presence of malignant cells in ascitic fluid have malignancy of ovary, uterus, or cervix; while only ten percent have malignancy of GI tract.[1] Whereas in men with malignant ascites more than 50% cases have malignancies of GI tract. Presence of malignant cells in ascitic fluid of patients help in arriving at diagnosis of malignancy and selecting the patients for appropriate treatment modalities.[2]

Significance of malignant cells in peritoneal washings has been recognized in gynecology and is an integral part of staging of female genital tract neoplasms at the time of initial surgery and as well as at time of follow up second look laparotomy in patients treated for gynecological malignancies.[3] It has been suggested that presence of malignant cells in peritoneal cavity in absence of involvement of serosa is due to extravasation of malignant cells via fallopian tubes in malignancies arising from cervix or endometrium. In GI malignancies dissemination of malignancies is by three routes.[4]

1. Primary cancer invades the venules, travels through the portal vein to liver. Within liver, after implantation they develop into liver metastasis. Lymphatic channels may be invaded and there is orderly progression of cancerous nodes along the nodal chain.
2. Full thickness invasion of bowel wall leading to tumor penetration through full thickness to serosa, causing seedling of cancer cells on peritoneum. Growth of these implants leads to nodule formation, which exfoliate the cancerous cells into peritoneal space, hence leading to increase in the number of nodules at exponential rate.
3. Natural dissemination of tumor cells to peritoneum requires violation of integrity of bowel wall, which may take place because of tumor pushing through bowel wall, specially thin-walled structures such as appendix.

The present study was conducted to assess clinicopathological profile of patients with GI malignancy and its correlation with presence of free malignant cells in peritoneal cavity.

MATERIALS & METHODS

A total of 34 patients of suspected or proven colorectal malignancies admitted to surgical wards during the study year were included in our study. All patients included in study were assessed on admission by recording their presenting complaints and history of complaints. Special emphasis laid on symptoms suggestive of altered bowel habits, obstruction, perforation, jaundice. History of hematochezia, melena, or hematemesis, associated abdominal mass, weight loss and anorexia were recorded.

Routine laboratory investigations of blood, urine and feces were carried out. X ray abdomen in erect and supine position were done on the patients who presented with features of intestinal obstruction. USG abdomen was done on all the patients to find out origin and extent of growth, presence of hepatic metastasis, evidence of biliary blockade, presence of ascites and intra- abdominal lymphadenopathy. Barium studies done as per requirement of each case. Endoscopic examinations done on the patients included upper GI endoscopy, side view endoscopy, endoscopic proctosigmoidoscopy and colonoscopy depending upon site of the lesion. Biopsies were taken after endoscopic examinations. Fine needle aspiration biopsies under US guidance were done in the cases where tissue diagnosis was not available. CT scans were done on cases for exact staging and planning for surgical resection.

Standard midline incision as per requirement of the surgery was given in each case with special emphasis on meticulous haemostasias before opening the peritoneum. On opening the peritoneal cavity 100 ml of normal saline was instilled into peritoneal cavity and at least 50 ml of this was retrieved in each case by plastic syringe. The peritoneal fluid in heparinized bottle was dispatched to laboratory immediately. For cytological examination, each specimen was centrifuged at a rate of 2000 rpm for 5 minutes and smears of nucleated cellular layer were prepared and dried with air. These smears were stained with Giemsa and Papanicolaou method. Slides were interpreted as (1) Positive: malignant tumor cells are present; (2) Negative: no malignant cell seen; (3) Suspicious: when suspicious looking cells are present without definite evidence of malignancy; (4) No judgement: where assessment is not possible due to lysis of cells or gross contamination with blood.

The criteria used to identify a tumor cell on conventional cytology were: (1) large hyperchromatic nuclei, (2) irregular chromatin pattern, (3) High nuclear: cytoplasmic ratio,

(4) abnormal mitosis and (5) Prominent nucleolus. Cells exhibiting all five of these criteria were classified as showing definite morphological evidence of malignancy, while cells exhibiting some but not all these criteria were classified as showing suspicious morphological evidence of malignancy.

Tumor was dealt with accordingly in each case and operative findings in terms of obvious hepatic metastasis or space occupying lesion, peritoneal nodules, ascites, enlarged lymph nodes, gross morphology and extent tumor spread were noted. Resected specimen with lymph nodes and omental nodules where present were sent to laboratory for histopathological evaluation by pathologist. Results were tabulated and analyzed.

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RESULTS

Table I Distribution of patients with positive malignant cytology

Pathology	Total Number	Malignant cells in peritoneum
Colorectal cancer	13	3
Gastric cancer	13	4
Pancreatic cancer	5	2
Cancer lower end of esophagus	3	0

Table II Correlation with clinical stage, ascites, peritoneal deposits, and histopathological differentiation in patients with positive malignant cytology

S. no.	Type of Cancer	Stage of Disease	Ascites	Peritoneal Deposits	Differentiation
1.	Colorectal	IV	No	No	moderately
2.	Colorectal	IV	No	Yes	poorly
3.	Colorectal	II	Yes	No	moderately
4.	Gastric	IV	Yes	No	moderately
5.	Gastric	IV	No	No	poorly
6.	Gastric	IV	No	Yes	moderately
7.	Gastric	III	No	No	moderately
8.	Pancreatic	IV	No	No	moderately
9.	Pancreatic	IV	Yes	Yes	moderately

Over all 9 patients out of 34 showed free malignant cells in their peritoneal cavity. Out of these 9 patients only 2 had stage II and III respectively, rest of 7 patients had advanced disease. Three patients out of 9 had peritoneal deposits, and ascites too was present in only three of these patients. 2 patients out of 9 had poorly differentiated carcinoma and remaining 7 had moderately differentiated carcinoma. Overall frequency of positive peritoneal cytology for malignant cells increased with increase in stage of disease. (X^2 value 12.49 with p value 0.009). Indicating positive association between stage of disease and presence of free malignant cells in peritoneal cavity. No association was found between differentiation and presence of malignant cells in peritoneum (X^2 value 3.03 with p value 0.22).

DISCUSSION

Malignant cells in peritoneal cavity were studied by Luke and Klebs in patients of ovarian cancer in 1867.[1] Based on same logic considerable amount of work has been done in past on significance of peritoneal cytology in GI malignancies.[5] Levels of various tumor markers, monoclonal antibodies levels and immune-cytology were studied by different workers in order to identify the malignant cells in peritoneal cavity.[6] Halsted paradigm, assumed centripetal spread of tumor i.e. primary tumor to lymph nodes and thereafter to blood stream,

hence radical en-bloc resection of tumor and draining lymph nodes should have high likelihood of success in producing cure unless distant metastasis could be shown to have already occurred.[7] Results contrary to expected as per Halsted's model have led to alternative paradigm i.e. biological predeterminism, assuming that cancer was usually a systemic disease from the outset and microscopic metastasis were assumed to have formed long before the primary tumor became clinically detectable.[8] The present study was conducted to assess clinicopathological profile of patients with GI malignancies.

Nomoto S. et al[9] in their study of peritoneal washing cytology combined with immune-cytological staining and detection of mutant K-ras in pancreatic cancer of twenty patients, studied for peritoneal washing cytology by three methods. The first method was conventional cytology, including May Grunwald and Giemsa, Papanicolaou, periodic acid schiff and Alcian blue. The second method was immunocytochemical staining, using antibodies to carbohydrate antigen (CA 19-9) and carcinoembryonic antigen. The last method, detecting K-RAS mutation, after extracting DNA from remaining pellet, by two step polymerase chain reaction and restriction fragment length polymorphism analysis. In 2 cases with macroscopic recognized peritoneal metastasis, results of all three methods were positive. Two cases without macroscopic peritoneal metastasis, judgements of conventional cytology study and K-RAS point mutation were negative.At present detecting immunocytochemical method is the most sensitive of these methods.

Florentine B.D. et al[10] studied the hyper-diploid malignant cells by fluorescence in situ hybridization (FISH) on thin prep slides from body cavity effusions. Author concluded that FISH can detect hyper-diploid malignant cells in body cavity effusions and is specifically useful when majority of cell population is malignant, which cannot be differentiated from mesothelial or atypical cells. It is less useful in detecting a small population of malignant cells hidden in an inflammatory or reactive cell background.

Nakanishi H et al[11] demonstrated CEA antigen expressing free cells in peritoneal washings in gastric cancer patients by polymerase chain reaction. The results indicated that assay is more sensitive for detection of free cancer cells in peritoneal cavity than conventional cytology.

CONCLUSION

Authors found positive association between stage of disease and presence of free malignant cells in peritoneal cavity. Advanced stage with worse clinicopathological profile has more chances of finding free cancer cells in peritoneal cavity. Further differentiation of mesothelial cells from malignant cells was a challenge. The study had limited no of sample size, hence further studies are recommended.

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