Kathmandu University Medical Journal (2006), Vol. 4, No. 4, Issue 16, 483-487

Original Article

Study of effusion cytology in patients with simultaneous malignancy and ascites

Jha R[1], Shrestha HG[2], Sayami G[3], Pradhan SB[4]
[1]Lecturer, [3]Head of Department, Department of Pathology, Tribhuvan University Teaching Hospital, Kathmandu, [2]Head of Department, Department of Pathology, Nepal Medical college and Teaching Hospital, Kathmandu, [4]Lecturer, Department of Pathology, Kathmandu Medical college and Teaching Hospital, Kathmandu

Abstract
Objective: To evaluate sensitivity of effusion cytology in detecting malignancy
Materials and methods: Effusion cytology was studied from 37 malignancy associated and 28 non malignancy associated ascitic fluid samples.
Results: Out of 65 cases, 44 (67.7%) effusions were reported negative, 15 (23.1%) were positive and 6 (9.2%) were suspicious for malignancy. Thus total 21 effusions (32.3%) were tumour cell positive. All 21 (100%) were true positive, none (0%) was false positive, 28 (63.6%) were true negative and 16 (36.4%) were false negative.
Thus ascitic fluid cytology had sensitivity of 56.7% and specificity of 100%. Predictive value of positive test and negative test was 100% and 63.6% respectively. Stomach was the most common primary site of malignancy associated with ascites (11 /37 i.e. 29.7%) where as adenocarcinoma was the most common type of malignancy (11/15 i.e.73.3%) in ascitic fluid cytology.
Conclusion: Ascitic fluid cytology is a simple and useful procedure with sensitivity of 56.7% and should be routinely requested.

Key words: Ascitic fluid, Effusion cytology

The word ascites is of Greek origin "askos" meaning bag or sac. Ascites denotes the condition of excessive fluid accumulation in the peritoneal cavity. Among many causes of ascites, decompensation of chronic hepatic cirrhosis accounts for 80% of the cases, followed by tumours which account for 10% of cases, congestive heart failure and inflammatory conditions account for 3% of cases each whereas other causes such as nephrotic syndrome, exudative enteropathy and chylous ascites are less common[1].

Peritoneal fluid cytology is useful for predicting the prognosis of gynaecological, gastric, pancreatic and colorectal malignancies[2,3,4,5]. However, fluid cytology shows tumour cells only when tumour cells are lining the peritoneum, not when the peritoneum is not involved. In hepatocellular carcinoma, massive liver metastasis or malignant lymphoma causing ascites by lymph node obstruction, ascitic fluid cytology is negative for malignant cells[6,7,8]. This study was carried out with the aim to evaluate sensitivity of effusion cytology in detecting malignancy in patients with simultaneous malignancy and ascites.

Materials and methods

This was hospital based prospective study carried out in Department of Pathology of Tribhuvan University Teaching Hospital (TUTH) from 1st January 2003 to 31st January 2004. Clinical charts of all the patients whose ascitic fluid samples were sent for cytological examination during the study period were retrieved for relevant information. Two Giemsa stained and two Papanicolaou stained slides were prepared from sediment obtained by centrifuging the ascitic fluid samples at 1500 rpm for 10 minutes.

Correspondence
Dr. Runa Jha
Department of Pathology,
Tribhuvan University Teaching Hospital, Kathmandu
E mail: runa75jha@yahoo.com

Histopathologic examination of tissue was used as gold standard to diagnose malignancy, in cases where this was available. Where histopathological examination was not done, diagnosis of malignancy was based on strong clinical suspicion, radiological methods (Ultrasound or computed tomography scan), direct visualization of tumour (during laparotomy or laparoscopy or endoscopy) or frankly malignant cells on fine needle aspiration cytology (FNAC). Data analysis was done with the help of software SPSS 10.0 version for windows.

Results

A total of 65 ascitic fluid samples were received during the study period from 65 different patients. Of these, 37(56.9%) patients had simultaneous malignancy and ascites. 22 of these were females and 15 were males. Remaining 28 patients (43.1%) had some non malignant cause of ascites. Most patients with malignancy (70.3%) were above 45 years of age. Effusion cytology was negative for malignant cells in 16/37 patients with malignancy (43.2%), positive in 15/37 (40.5%) and suspicious in 6/37 (16.2%).

In 17 of 37 patients with malignancy and ascites, malignancy was biopsy proven. In 11 cases radiological diagnosis was used as gold standard. In 5 cases tumour was directly visualized (3 laparotomy and 2 upper gastrointestinal endoscopy) from where biopsy was not taken due to fear of bleeding. Three patients with strong clinical suspicion of malignancy died before detail investigation could be carried out, 2 of these had malignant cells and 1 had suspicious cells in cytology. In 1 patient, FNAC of liver nodule showed frankly malignant cells. Effusion cytology findings of these cases are shown in table1.

Findings of ascitic fluid cytology

By cytologic examination of the 65 ascitic fluids, 44(67.7%) were reported "negative for malignancy", 15(23.1%) as "positive for malignancy" and 6 (9.2%) were "suspicious for malignancy". For statistical analysis, "suspicious" effusions were included in "positive" category. Thus total 21 out of 65 effusions (32.3%) were tumour cell positive.

In all cytological positive and suspicious effusions, malignancy in patient was verified by one or more of the methods mentioned above i.e. all these were true positive and none was false positive (True positive=100%, false positive=0%). Out of 44 negative effusions, 28 (63.6%) were true negative; however in rest 16 patients malignancy was present. That means these 16 cytology reports (36.4%) were false negative. All false negative effusions were re-examined and none of them showed malignant cells even after re-examination.

Thus ascitic fluid cytology had sensitivity of 56.7% and specificity of 100%. Predictive value of positive test and negative test was 100% and 63.6% respectively.

Primary site of malignancy

As shown in Table 2, overall most common primary site of malignancy associated with ascites was stomach (11/37) followed by ovary and biliary tract (7/37). Matching with these findings, most patients with positive fluid cytology had gastric malignancy (6/21). In female patients ovarian malignancy was the most common. A total of 22 females had simultaneous malignancy and ascites and 7 of these had ovarian malignancy. Accordingly, malignant cells of ovarian origin was found most commonly in effusion cytology in female patients as out of 11 female patients with positive fluid cytology , 5 had ovarian malignancy .

Type of malignancy

Typing of malignancy was attempted wherever cytology showed frankly malignant cells. Out of 15 ascitic fluid cytology signed out as "positive for malignancy", 11 were typed as adenocarcinoma (11/15 i.e.73.3%). Others were 2 lymphomas, 1 poorly differentiated carcinoma and 1 squamous cell carcinoma.

Table 1: Method of diagnosis of malignancy and effusion cytology findings in patients with simultaneous malignancy and ascites

MODE OF DIAGNOSIS OF MALIGNANCY	**EFFUSION CYTOLOGY**			**TOTAL**
	Negative	Positive	Suspicious	
Biopsy	8	7	2	**17**
Direct visualisation	3	1	1	**5**
Radiological	5	4	2	**11**
Clinical	-	2	1	**3**
FNAC	-	1	-	**1**
TOTAL	**16**	**15**	**6**	**37**

Table 2: Site of origin of primary malignancy and effusion cytology findings in males and female with simultaneous malignancy and ascites

PRIMARY SITE (number)	**CYTOLOGY POSITIVE**		**CYTOLOGY NEGATIVE**	
	Male	*Female*	*Male*	*Female*
Stomach (11)	3	3	2	3
Ovary (7)	0	5	0	2
Biliary Tract (7)	3	0	2	2
Not Known (5)	2	2	0	1
Liver (3)	0	0	1	2
Cervix (1)	0	1	0	0
Duodenum (1)	1	0	0	0
Lymph Node (1)	1	0	0	0
Pancreas (1)	0	0	0	1
	10	**11**	**5**	**11**
TOTAL (37)	**21**		**16**	

Discussion

Effusion cytology is well-accepted means to diagnose malignant tumours. After a review of the literature on diagnostic accuracy of effusion cytology, Motherby H[9] concluded that sensitivity of ascitic fluid cytology ranged from 22% to 81%, specificity from 91-100%, positive predictive value from 98-100% and negative predictive value from 56% to 91%. In this study, cytology had sensitivity of 56.7% and specificity of 100%. There are various causes of difference in sensitivity in various series. Important cause is use of "gold standard". Ideally this should be detailed histological examination[9,10] but authors often vary in the use of gold standard, thus a wide range of sensitivity and specificity is obtained.

Tumour cells are seen in effusion sediment only when tumour cells are lining the peritoneum. This occurs only in approximately 75% of the cases of cancer with ascites[6,7]. Most reliable way to exclude involvement of peritoneum by tumour is to perform histopathological examination by obtaining biopsies either by laparoscopy or during laparotomy or by thorough post mortem examination after complete follow up[6,7] but most authors often do not exclude peritoneal involvement. Patients with massive liver metastasis or lymphoma or hepatocellular carcinoma should not be expected to have positive fluid cytology[6,7,8] as ascites in these cases may not be because of involvement of peritoneum by malignancy. Peter Powaser et al[8] did not find cells diagnostic of hepatocellular carcinoma in ascitic fluid in any of the 40 cases they reviewed in a 12 year retrospective study.

Number of ascitic fluid samples also influence rate of detection of malignancy in effusion cytology. Runyon BA[7] reported 96.7% sensitivity of cytology

after examination of 3 samples, when cases only with peritoneal involvement were included. The sensitivity fell own to 82.8% when only one sample was examined. Motherby H[9] concluded that by examining only one specimen, 53.3% malignant effusions were detected cytologically whereas the detection rate increased to 66.7% by examining two specimens and to 73.3% by examining three specimens.

In this study, presence or absence of peritoneal involvement was not confirmed in any case. It was only assumed that all malignant cases with ascites had peritoneal surface involvement although this happens only in 75% cases. Thus the possibility that many cases that were labelled as "false negative" did not have peritoneal involvement and thus they were in fact "true negative" could not be ruled out. There were three cases of hepatocellular carcinoma which were "negative for malignancy" on ascitic fluid cytological examination. Only one sample was examined in this study. Sensitivity of ascitic fluid cytology in detecting malignancy would have been higher in this study if peritoneal involvement would have been confirmed, hepatocellular carcinomas without peritoneal involvement excluded and more than 1 ascitic fluid samples examined.

The problem of false negative cytology results are well recognized in examination of body cavity fluids and range from 23%-42%[10]. Johnsons WD[11] et al re-examined 107 negative effusion specimens from patients with proved malignancy and found that only 4 % of those had cells that justified neoplasia . He concluded that most negative reports were not because of inability to recognize the malignant cells but due to lack of shedding of neoplastic cells into fluid or due to fault in procedure used to convey the cells to the slides.

Primary site and type of tumour

Most common primary site of malignancy with ascites was stomach in this study .This is similar to findings of by Runyon BA[7] where as Garrison et al[13] found pancreas and Parson et al[12] found ovary to be the most common site. Stomach is the most frequent site to be involved by carcinoma in TUTH after lung/ bronchus[14]. This can be one of the reasons of gastric malignancy being found to be most commonly associated with ascites in this study. Ovary was the most common primary site shedding malignant cells in ascitic fluid in females. This is consistent with findings of Parson SL et al Wilailak et al, Monte SA et al and Karoo et al[12,15,16,17].

Most common type of malignancy detected in this study, in fluid cytology was adenocarcinoma. This is also similar to findings of other studies[9,12,16,17].

Conclusion

Ascitic fluid cytology is a simple and useful procedure with sensitivity of 56.7% and specificity of 100%. In a set up like ours where definite involvement of peritoneal surface by malignancy cannot always be proved, peritoneal fluid cytology still can detect malignant cells in over half the cases. As presence or absence of malignant cells is useful in predicting the prognosis of patients and sometimes it can be the only clue to presence of malignancy, ascitic fluid cytology should be routinely requested.

References

1. Runyon B: Approach to the patient with ascites. In: Yamada T, Alpers DH, Laine L, owyang C, Powell DW, eds. Textbook of Gastroenterology. 3rd ed. Philadelphia: lippincott Williams & Wilkins; 1999: 966-91.
2. Ikeguchi M, Oka A, Tsujitani S, Maeta M, Kaibara N. Relationship between area of serosal invasion and intraperitoneal free cancer cells in patients with gastric cancer. Anticancer Res 1994;14:2131–4.
3. Warshaw AL. Implications of peritoneal cytology for staging of early pancreatic cancer. Am J Surg 1991;161:26–30.
4. Ziselman EM, Harkavy SE, Hogan M, West W, Atkinson B. Peritoneal washing cytology: uses and diagnostic criteria in gynecologic neoplasms. Acta Cytol 1984;28:105–10.
5. Seiichiro Yamamoto, Takayuki Akasu, Shin Fujita and Yoshihiro Moriya Long-term Prognostic Value of Conventional Peritoneal Cytology after Curative Resection for Colorectal Carcinoma. Japanese Journal of Clinical Oncology Volume 33, Number 1 Pp. 33-37
6. Gulyas M; Kaposi AD; Elek G; Szollar LG; Hjerpe A. Value of carcinoembryonic antigen (CEA) and cholesterol assays of ascitic fluid in cases of inconclusive cytology.J Clin Pathol 2001 Nov;54(11):831 -5
7. Runyon BA, Hoefs JC, Morgan TR. Ascitic fluid analysis in malignancy-related ascites. Hepatology 1988; 8: 1104-09.
8. Powaser Peter and Green Linda K.: Is Cytologic Examination of Ascitic Fluid a Useful Test in Detecting Hepatocellular Carcinoma in the Veteran?: A Twelve-Year Retrospective Review . Acta cytologica september 2001 (abstracts from XIII conference)

9. Motherby H, Nadjani B, Friegel P . Diagnostic accuracy of effusion cytology. Diagnostic cytopathology Volume 26, no. 6 page 350-56.
10. Michael G, Vernick MD, Sidawy M.Cytologic Evaluation of serous effusions, processing techniques and optimal number of smears for routine preparation. American journal of clinical pathology 1993 ; 99:182-186.
11. Johnson WD . The cytological diagnosis of cancer in serous effusion . Acta cytologica 1966; 10:161-172
12. Parsons SL, Lang MW, Steele RJ. Malignant ascites: a 2-year review from a teaching hospital.Eur J Surg Oncol. 1996 Jun;22(3):237-9.
13. Garrison RN, Kaelin LD, Galloway RH, Heuser LS. Malignant ascites. Clinical and experimental observations Ann Surg. 1986 Jun;203(6):644-51.
14. Jha R, Verma S. Incidence of cancer in TUTH in one year . Book of abstracts, Fourth congress of association of clinical pathologists of Nepal, Page 3
15. Wilailak S, Linasmita V, Srivannaboon S. Malignant ascites in female patients, a seven year review. J Med Assoc Thai, Jan 1999 ; 82 (1): 15-9
16. Monte SA, Ehya H, Lang WR Positive effusion cytology as the initial presentation of malignancy. Acta Cytol. 1987 Jul-Aug;31(4):448-52.
17. Karoo RS, Llyod TDR et al, Garcea G, Redway HD, Robertson GSR How valuable is ascitic fluid cytology in detection and management of malignancy. Post graduate medical journal 2003;79: 292-299