VALUE OF ASCITIC FLUID CHOLESTEROL AND SERUM - ASCITES ALBUMIN GRADIENT IN DIFFERENTIATING CIRRHOTIC AND MALIGNANCY RELATED ASCITES

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ABSTRACT

In a perspective study, the ascitic fluid and serum concentration of total cholesterol, total proteins and albumin in a group of 45 patients was studied. Patients with non-malignant or cirrhotic ascites were compared with patients having malignancy related ascites and it was proved that the ascitic fluid cholesterol and the serum ascites albumin gradient helped to differentiate cirrhotic from malignant ascites. These two parameters showed a remarkable relationship to the presence/absence of malignancy. Non malignant ascites patients had ascitic fluid cholesterol values of 19.41 ± 8.33 mg/dl, as against the malignancy related ascites patients, who showed levels of 95.87 ± 12.4 mg/dl. Similarly, the serum - ascites albumin gradient levels were 2.89 ± 0.65 in non malignant ascites patients, while the malignancy related ascites cases had 0.86 ± 0.50 . The discrimination values for cholesterol were taken as 45 mg/dl while that for serum ascites gradient was taken as 1.1. Levels of serum cholesterol, total protein and albumin were not significantly altered.

KEY WORDS : Malignancy related ascites, nonmalignant ascites, cholesterol, serum – ascites albumin gradient.

INTRODUCTION

Ascites is the accumulation of free fluid in the peritoneal cavity. About 50 ml of fluid is normally present in the peritoneal cavity for the purpose of lubrication, but to become clinically evident at least 1500 ml of fluid has to accumulate. Ascites is most often caused by either chronic liver disease or malignant neoplasms. The differentiation between malignancy related ascites (MRA) and non-malignant ascites (NMA) is important for diagnostic and therapeutic purposes. Several components of the ascitic fluid have been analyzed for their differential diagnostic usefulness.

Presently, the differentiation of NMA and MRA is done following cytological studies of ascitic fluid. Though cytology is still deemed to be the best marker of MRA, recent studies report a 57 % (1) and 62 % (2) sensitivity of cytology in detecting MRA. Cytological

investigation, despite its high specificity, has been found unreliable in many cases due to the high percentage of false negative results (2). The need for the development of more sensitive and reliable parameters to differentiate MRA from NMA, initiated this study involving 45 patients with clinically evident ascites. They were classified as NMA if cirrhosis was the cause of ascites and MRA if ascites was associated with malignancy.

MATERIALS AND METHODS

Patients

Inclusion and exclusion criteria : Patients aged between 40 and 60 were included. Two groups were made – cases with cirrhotic or non malignant ascites (NMA) and cases of malignancy related ascites (MRA) This study did not include patients with tuberculous ascites.

NMA was identified in patients in whom malignancy was ruled out by ultrasonography / CT and the diagnosis of cirrhosis was confirmed by liver biopsy.

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MRA Patients with malignancy related ascites had a primary in the abdomen or pelvis and the diagnosis was made on the basis of ultrasonography/CT findings, followed by a positive biopsy for malignancy of the respective tissues. To maintain uniformity patients with secondaries in the liver were excluded.

Fluids and serum samples : Ascitic fluid samples were obtained by abdominal paracentesis. 10 to 20ml of ascitic fluid was drawn and EDTA was added to each of the vials before the collection. The ascitic fluid was centrifuged at 3000 rpm for 10 minutes and the supernatant was separated for analysis. Serum samples were collected from the left cubital vein using scalp vein sets no.23 and were similarly processed. Both these samples were stored at -20°C till analysis.

Cholesterol was determined using Zak's method (3). Total protein was estimated by the Biuret method (4). Albumin in serum and ascitic fluid was determined by the dye binding method using bromocresol green (Bartholomew and Delaney) (5).

All chemicals used were of Analytical Reagent Grade (Analar / AR) supplied by E.Merck London., Loba Chemie., BDH., etc.

The results obtained were statistically analyzed and their normal distribution, range, the mean, and standard deviation were calculated. The mean values of the two groups were compared by probability values according to the student's 't' test. A 'p' value of <0.05 was considered statistically significant.

RESULTS

The total protein levels in the serum ranged from 4 gm/dl to 7.4 gm/dl with a mean $\pm$ S.D of 5.97 ± 0.76 gm/dl in ascites due to cirrhosis as against the range of 4.4 gm/dl to 8.4 gm/dl with a mean $\pm$ S.D of 6.0 ± 1.04 gm/dl in ascites due to malignancy. The 'p' value being > 0.05 , shows that serum protein levels are not altered. In fact the levels are lower in cirrhotic patients than in MRA, due to the liver being affected to a greater degree. The albumin levels in serum also showed a

similar pattern. For the NMA cases, the range is 2.7gm/dl to 4.6 gm/dl with a mean $\pm$ S.D of 3.53 ± 0.56 gm/dl while for MRA the serum albumin shows a range of 2.1 gm/dl to 5.1 gm/dl with a mean $\pm$ S.D of 3.46 ± 0.75 gm/dl. The results indicate that the protein parameters in serum are not significantly changed in ascites due to malignant conditions. The observed values of total cholesterol was 134.8 mg/dl to 244.5 mg/dl with a mean $\pm$ S.D of 176.73 ± 26.82 mg/dl in ascites due to cirrhosis as against 102.7- 243.4 mg/dl with a mean $\pm$ S.D of 188.8 ± 31.33 mg/dl in malignancy related ascites. The 'p' value in this case being > 0.05 shows statistical insignificance (Table1). Examination of peritoneal fluid of ascites due to malignancy revealed a different picture. Values in almost all parameters showed moderate to gross elevations in malignancy related ascites when compared to non-malignant or cirrhotic ascites. Total protein in ascitic fluid of patients with cirrhosis associated with ascites ranged from 0.3 gm/dl to 2.0 gm/dl with a mean $\pm$ S.D of 1.09 ± 0.45 gm/dl, while that in patients with malignant ascites had a range of 3.2gm/dl to 5.6 gm/dl with a mean $\pm$ S.D of 4.22 ± 0.68 gm/dl. The albumin levels estimated in ascitic fluid for non-malignant ascites cases were in the range of 0.12 gm/dl to 1.24 gm/dl with a mean $\pm$ S.D of 0.65 ± 0.3 gm/dl. The levels in malignancy related ascites were in the range of 1.6 gm/dl to 3.9 gm/dl with mean $\pm$ and SD of 2.58 ± 0.63 gm/dl (Table1).

Another very significant parameter calculated was the serum-ascites albumin gradient. The gradient had a mean $\pm$ S.D. of 2.87 ± 0.65 in NMA as against 0.86 ± 0.51 in MRA (Table 2).

DISCUSSION

Malignancy related ascites is a heterogeneous group of conditions defined as clinically evident accumulation within the abdominal cavity associated with a disseminated malignancy in the absence of hepatic cirrhosis. In other words patients with malignant ascites have a primary or metastatic malignancy in the abdomen or pelvis. Malignancies that originate in or metastasize to the abdomen can cause ascites formation by several mechanisms. Fluid

Table 1. Parameters in Serum and Ascitic fluid

Sub - group	Cholesterol levels in mg%	Total protein in gm%	Albumin in in gm%
Ascites due to cirrhosis Serum Ascitic fluid	176.73 ± 26.82 * 19.41±8.33**	5.97 ± 0.76 * 1.09±0.45**	3.53 ± 0.56 * 0.65±0.30**
Ascites due to malignancy Serum Ascitic fluid	188.8 ± 31.3 * 95.87±12.40**	6.0 ± 1.04 * 4.22±0.68**	3.46 ± 0.75 * 2.58±0.30**

* Statistically not significant ('p' value > 0.05)

** Stastically significant (p<0.005)

Table 2. Comparison of serum – ascitic fluid albumin gradient in ascites due to cirrhosis and malignancy related ascites.

Sub – group	Serum – ascitic fluid albumin gradient
Ascites due to cirrhosis	2.87 ± 0.65 *
Ascites due to malignancy	0.86 ± 0.51 *

* Statistically significant ('p' value < 0.05)

can "exude" from malignant cells lying in the peritoneum. Portal hypertension can be caused by (i) massive liver metastasis (ii) hepatic vein thrombosis (iii) it can be associated with cirrhosis and superimposed hepatocellular carcinoma. Malignant obstruction of lymph channels can lead to lymphatic rupture with resultant leakage of chyle into the abdomen (6).

Biochemical analysis of peritoneal fluid for cholesterol, total protein, serum – ascites albumin gradient differentiates cirrhotic and malignant ascites and has shown that these two conditions present relatively distinct patterns. This study showed that ascitic fluid cholesterol and serum ascites albumin gradient to be reliable parameters to differentiate cirrhotic and MRA. A number of previous workers have shown the relation between high ascitic fluid cholesterol and the occurrence of MRA (7-10). Another study by Sood et. al. (11) showed that ascitic fluid cholesterol can also be a good parameter to differentiate malignant and tuberculous ascites. The cut off value was taken as 48 mg% (2). The possible reason for the occurrence of higher values of ascitic fluid cholesterol in MRA when compared to NMA may be due to lymphatic obstruction leading to rupture of lymphatic channel, causing increasing exudation of

chyle with a relatively high lipid content (6). Ascites formation in malignancies of the abdomen and pelvis generally has been attributed to increased rates of formation and decreased rates of removal of intra peritoneal fluid or a combination of the two. Considering the large volume of fluid which normally traverses the peritoneal cavity and the large reserve capacity of the peritoneal lymphatic to absorb excess fluid, one must assume it to be far more likely that impairment of the lymphatic drainage is the primary pathogenic factor (9). Feldman (12) conducted studies in mice and Coates (13) in humans using radio actively labeled components. They concluded that lymphatic obstruction is related intimately to carcinomatous ascites. Coates, in his studies used, as controls, patients with ascites due to hepatic cirrhosis and each of these patients demonstrated a normal lymphoscintigraphic scan, indicating that the lymphatic drainage mechanisms were functionally intact. Histologic studies were also consistent with the above findings.

Analysis of ascitic fluid for protein and albumin showed that the levels were higher in MRA than in NMA. Malignant tumours cause effusions by increasing permeability of the serosal surfaces. The ascitic fluid in cirrhosis is similar to plasma except for a lower protein content. Albumin being the major component of protein, its levels are reflected in the protein levels. More significant than albumin or total protein is the serum-ascites albumin gradient. The gradient being independent of the serum albumin concentration, is proportionate to the pressure gradient from the portal vein to the intra abdomen cavity and therefore, must be higher in patients where in the net portal pressure is expected to be elevated, as in hepatic cirrhosis, and conversely, it should be lower in cases with peritoneal malignancies where the portal pressure

is expected to be lower. A number of other workers have also shown similar results (14,15). In our study the serum ascites albumin gradient cut off was taken as 1.1. A serum ascites albumin gradient of > 1.1 suggests portal hypertension and a transudative type of ascites, as it does in cirrhotic patients (1). A value of serum ascites albumin gradient < 1.1 is almost surely indicative of the absence of portal hypertension and an exudative ascites as in MRA.

Conclusion

Here, an attempt has been made to study different biochemical parameters which may support cytological studies, to help arrive at a etiological diagnosis for ascites. This study has shown that increased levels of ascitic fluid cholesterol, the serum ascitic fluid albumin gradient are very good indicators of malignant ascites. They hold promises to be reliable and yet simple and cost effective indicative parameters.

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