Digestive Diseases and Sciences, Vol. 33, No. 10 (October 1988), pp. 1208–1212

Usefulness of Serum–Ascites Albumin Difference in Separating Transudative from Exudative Ascites

Another Look

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The serum–ascites albumin difference is reported to be superior to ascitic total protein, ascitic-to-serum total protein ratio, lactic dehydrogenase, and ascitic-to-serum lactic dehydrogenase ratio in differentiating between ascites from liver disease and malignant ascites, S-A > 1.1 reflecting portal hypertension. We analyzed ascitic fluid from 46 consecutive patients with chronic liver disease, 28 patients with ascites associated with malignancy, 10 patients with right-sided heart failure, 4 patients with hypothyroidism, and 6 patients with miscellaneous causes of ascites to determine if this albumin difference is indeed a more valuable parameter. Analysis of our data confirms with a larger number of patients that the serum–ascites albumin difference is a more reliable indicator of transudative ascites, better termed portal hypertensive ascites. Malignant ascites without liver metastases had features of nonportal hypertensive ascites, and the serum–ascites albumin difference confirms this. The characteristics of malignant ascites associated with liver metastases, however, resemble those of the portal hypertensive ascites complicating liver disease. This new parameter is also helpful in distinguishing congestive heart failure with high protein ascites and portal hypertensive ascitic features from malignant ascites without liver metastases. Of particular note, myxedematous ascitic fluid, classically categorized as exudative, had an S-A > 1.1, indicating the possible role of portal hypertension in the development of ascites in these patients.

KEY WORDS: ascites, serum-ascites albumin difference; exudate; transudate; myxedematous ascites.

Ascitic fluid accumulations associated with increased hydrostatic pressure, decreased serum oncotic pressure, or both are called transudative. Conventionally, parameters such as ascitic fluid total protein <3.0 g/dl, ascitic fluid-to-serum total protein ratio (TP_R) <0.5, and ascitic fluid-to-serum lactic dehydrogenase ratio (LDH_R <0.6 have been consistent with a transudate (1–5). Despite the emergence of these many parameters, the differential diagnosis is not always clear. More recently, a difference of more than 1.1 between the concentration of albumin in serum and ascitic fluid (S-A) has been reported to be a superior index of transudative ascites (6–8) reflecting portal hypertension. Indeed, the terms "portal hypertensive ascites" and

Manuscript received November 23, 1987; revised manuscript received April 4, 1988; accepted April 7, 1988.

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Presented in part at the American Federation for Clinical Research, Washington, D.C., May 1986.

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0163-2116/88/1000-1208$06.00/0

TABLE 1. TYPES OF MALIGNANCY ASSOCIATED WITH ASCITES

Tumor type	*Number*
Metastatic to liver	
Cholangiocarcinoma	3
Pancreatic	2
Gallbladder	1
Breast	1
Bladder	1
Small cell lung	1
Unknown primary	4
Without liver metastases	
Ovary	2
Breast	1
Colon	1
Gallbladder	1
Lymphoma	1
Thyroid	1
Lung	1
Lieomyosarcoma	
Cervical cancer	1*
Unknown primary	2

*With liver cirrhosis.

"nonportal hypertensive ascites" have been adopted in recent years since they more clearly state what the gradient is showing. We will use them here. The purpose of this study was to test the reliability of this new criterion in a larger number of patients with more varied causes of ascites.

MATERIALS AND METHODS

Patients. Ninety-four consecutive patients with ascites were studied prospectively. In addition to diagnostic paracentesis, all patients underwent noninvasive radiographic studies such as ultrasound, CT scan, or radionulide scintigraphy to evaluate the liver and peritoneal cavity. A clinical diagnosis of chronic liver disease was made in 46 patients. The diagnosis was confirmed by biopsy in half.

Twenty-eight patients had malignancy and ascites. Of these, three had a tissue diagnosis of primary hepatocellular carcinoma with cirrhosis, and 13 had metastatic disease to the liver shown by noninvasive studies and confirmed by biopsy or autopsy in nine. Four of these patients also had peritoneal involvement with tumor. Twelve patients with malignancy had no gross evidence of liver involvement. Peritoneal carcinomatosis was noted at surgery or autopsy in eight and on CT or ultrasound in five. The types of malignancies are illustrated in Table 1.

Ten patients presented with severe right-sided heart failure manifested by jugular venous distension and leg edema (valvular disease in two, pulmonary hypertension in two, constrictive cardiomyopathy in two, ischemic cardiomyopathy in four). The remaining 10 patients consisted of: hypothyroidism in four, pancreatic ascites in one, nephrotic syndrome in three, liver abscess in one, hypoalbuminemia with candidal sepsis in one.

Methods. Serum and ascites samples were collected within 24 hr of each other and before therapeutic intervention such as intravenous fluids or new diurectic therapy was instituted. Total protein was measured by biuret reaction and albumin with bromocresol green dye-binding assay. LDH concentration was determined using a lactate to pyruvate spectrophotometric method. (Aminco Rotochem centrifugal fast analyzer, Chicago, Illinois). Amylase was measured by an amyloclastic method (Biomedix, West Springfield, Massachusetts). Cytology was determined on stained smears made from sediment of centrifuged ascitic fluid.

Means were compared by unpaired, two-tailed Student's t test, and results are expressed as mean ± standard deviation. Predictive values and efficiency were determined according to Galen and Gambino (9).

RESULTS

The results are summarized in Table 2. Two of 16 patients in the group with malignancy and liver involvement who had bloody ascites were excluded from the calculations. One of the 12 patients with malignancy without liver metastases had coexistent liver disease and was also excluded. These exclusions will be addressed later and separately. As a whole, the group with chronic liver disease fit the criteria for "transudate" or portal hypertensive ascites; however, there were six or fewer patients who did not meet the definition when each parameter was examined individually. Six patients (13%) had a high ascitic fluid total protein (TP). Only two patients with CLD had a serum-ascites (S-A) albumin difference less than 1.1. Cytology was negative in all patients.

The total group with malignant ascites, traditionally classified as an "exudate," had significantly higher ascitic fluid total protein ($P < 0.001$), TP_R ($P < 0.001$), ascitic fluid LDH ($P < 0.01$), and LDH_R ($P < 0.001$) when compared to the chronic liver disease group. However, the S-A did not distinguish the two groups as has been previously reported (7, 8). However, when patients with malignant ascites were separated into two subgroups, those with liver involved with tumor and those without, the following was observed: all patients with malignant ascites and liver involvement met the criteria for portal hypertensive ascites with respect to TP, TP_R, and S-A with the exceptions of the two patients with bloody ascites. In contrast, those with malignant ascites and no liver involvement all met the criteria for nonportal hypertensive ascites when these parameters were examined with one exception. The LDH and LDH_R were significantly higher in those with malignant ascites whether or not liver involvement was present, although there was considerable overlap in these groups.

TABLE 2. SUMMARY OF RESULTS OF DIAGNOSTIC PARAMETERS*

	CLD (46)	TM (28)	MM (16)	MO (12)	CHF (10)
TP	1.38 ± 1.05	3.13 ± 1.57	2.06 ± 0.61	4.21 ± 0.65	3.64 ± 0.51
TP_R	0.21 ± 0.13	0.53 ± 0.29	0.33 ± 0.11	0.74 ± 0.12	0.52 ± 0.06
LDH	105.85 ± 100.97	494.3 ± 955.79	182.69 ± 192.65	953.73 ± 1391.92	366.67 ± 757.86
LDH_R	0.37 ± 0.33	1.04 ± 1.04	0.64 ± 0.55	1.70 ± 1.27	0.48 ± 0.15
S-A	1.74 ± 0.44	1.34 ± 0.79	1.91 ± 0.60	0.63 ± 0.44	1.67 ± 0.33
Proportion of patients with "transudative" parameters and positive cytology					
TP < 3.0	39/45	14/25	14/14	0/11	1/10
TP_R < 0.5	40/45	14/25	14/14	0/11	7/10
LDH < 400	43/46	15/24	11/13	4/11	8/9
LDH_R < 0.6	41/46	8/24	7/13	1/11	7/9
S-A > 1.1	44/46	14/25	14/14	0/11	10/10
Positive cytology	0/46	12/25	5/14†	7/11	0/10

*CLD: chronic liver disease; TM: total malignancy group; MM: malignancy with liver involvement; MO: malignancy without liver involvement; CHF: congestive heart failure; TP: total protein g/dl; TP_R: total protein ratio; LDH: lactic dehydrogenase units/liter; LDH_R: LDH ratio; S-A: serum ascites albumin difference. Number in parenthesis indicates total number of patients in each group.
†Four of these patients also had peritoneal implants with tumor. One had primary hepatocellular carcinoma.

When patients had a mixed picture of both liver disease and peritoneal metastases, as was the case in a patient with cervical carcinoma with cirrhosis and no liver metastases and in four patients with both liver metastases and peritoneal carcinomatosis, the S-A albumin difference was >1.1. In both patients with bloody ascites (one with hepatoma and one with small cell carcinoma metastatic to the lung), the S-A albumin difference was less than 1.1.

Nine of 10 patients with heart failure had ascitic fluid TP greater than 3.0 g/dl and all had S-A > 1.1. There was some overlap in other criteria, but most had TPR less than 0.5 and LDH_R close to or less than 0.6. Thus, this group with "transudative" ascites had high ascitic fluid total protein. In comparison to the group with malignant ascites without liver involvement, who also had high ascitic fluid total protein, all patients with heart failure had S-A > 1.1.

In Table 3 we examine each parameter's ability to distinguish a portal hypertensive ascites from non-portal hypertensive ascites. When malignant ascites as a whole is compared to the group with chronic liver disease, in contrast to the observations of Pare et al (7), no parameters stand out as diagnostically superior. If the chronic liver disease group is compared to the group with malignant ascites without liver involvement, the S-A gradient has the best combination of predictive values (100%) and efficiency (96%) for differentiating transudate from exudate. The total protein and TP_R were also 100% predictive, but not as efficient (89% and 91%, respectively). In separating ascites in patients with malignancy who have liver involvement (portal hypertensive) from those without liver involvement (nonportal hypertensive), the S-A gradient, ascites TP, and TP_R have superior predictive values (100%) and efficiency (100%). Those patients who had positive cytology in either malignant group usually had peritoneal carcinomatosis with the exception of one patient with hepatoma.

TABLE 3. PREDICTIVE VALUES AND EFFICIENCY FOR SEPARATING ASCITES FROM CLD AND MO

	CLD	MO	Predictive value (%) +	Predictive value (%) −	Efficiency (%)
Number	46	11			
TP < 3.0	39/45	0/11	100	65	89
TP_R < 0.5	40/45	0/11	100	69	91
LDH < 400	43/46	4/11	91	70	88
LDH_R < 0.6	41/46	1/11	98	67	89
S-A > 1.1	44/46	0/11	180	85	96

Four of the remaining patients had hypothyroidism. All four of the patients with hypothyroidism have S-A greater or equal to 1.1 without any other consistent pattern in the parameters measured (Table 4). This differs from the "exudative" pattern previously reported in myxedema and may bring into question the postulated mechanism of its formation (10–12). Ascitic fluid data in the four other miscellaneous patients were too few in number to comment on.

DISCUSSION

Our study has confirmed and extended the observation in prior studies (7, 8) that the serum ascites

TABLE 4. ASCITIC FLUID VALUES IN HYPOTHYROID PATIENTS

Total protein (g/dl)	*Total protein ratio*	*LDH (units/liter)*	*LDH ratio*	*S-A albumin gradient*
2.2	0.42	87	0.40	1.5
3.3	0.56	113	0.52	1.7
0.7	0.13	6	0.03	1.7
4.4	0.66	9	0.12	1.1

albumin difference is a superior parameter in distinguishing portal hypertensive from nonhypertensive ascites because it best reflects the forces in the Starling hypothesis (13). Indeed, in patients with chronic liver disease, the S-A was most predictive of a portal hypertensive ascites even in those patients with high total protein ascites (14). We believe that, in keeping with prior studies, the S-A parameter best reflects elevated hydrostatic pressure, contributing significantly to the development of portal hypertensive ascites, even in patients with low serum albumin.

High protein cardiac ascites is not unusual (5, 8, 15, 16) especially when patients are on diuretic therapy (17). This was the case in nearly all the patients in this study. Cardiac cachexia with protein wasting into the ascitic fluid may mimic malignant cachexia. Indeed, the S-A albumin difference could help to differentiate the two, provided liver metastases are absent.

All patients with peritoneal metastasis without liver involvement behaved like nonportal hypertensive ascites having high ascites total protein, total protein ratio, and S-A albumin gradient of <1.1. If, however, there was concomitant liver disease, such as cirrhosis or diffuse liver metastases, the ascitic fluid behaved more like portal hypertensive ascites with low ascitic total protein and TP_R and a high S-A albumin gradient. Prior studies (7, 8) alluded to this, and we have confirmed this observation with a larger number of patients. The high S-A in patients with liver metastases probably reflected high portal pressures, although these were not measured. In the two patients with bloody ascites, S-A was <1.1. Without bloody ascites, one could expect a value >1.1 in these patients. In these situations, because of the blood leak, the S-A albumin difference cannot be expected to reflect the presence of increased hydrostatic pressure.

Of particular interest in this study were the observations made in patients with ascites from hypothyroidism. Ascites associated with hypothyroidism is classically categorized as "exudative," in the older terminology. Although the mechanism of its formation is not completely clear, increased capillary permeability has been implicated (10–12). Kocen and Atkinson (12) reported three cases with high ascites total protein values (>3.0 g/dl) and a low gradient of colloid osmotic pressure between serum and ascitic fluid. These patients lacked any evidence of cirrhosis, had no clinical evidence of congestive heart failure (ie, distended neck veins), and all improved with thyroid replacement. If the S-A albumin gradient is calculated, all three patients had values >1.1. Combining our four patients with those above reveals ascitic total protein values of >3.0 g/dl in five of seven by an S-A of 1.1 or greater in all seven patients. This finding would seem to indicate an element of increased hydrostatic pressure in the genesis of the ascitic fluid, and the term portal hypertensive ascites fits. The apparent resolution of ascites with thyroid replacement is consistent with a reversible defect of some kind. Given that the profile of those patients most closely resembles those with heart failure, perhaps a subclinical cardiomyopathy is playing more of a role than previously recognized, although another unrecognized mechanism is still possible.

We conclude that the S-A albumin difference is a reliable and superior indicator of portal hypertensive ascites. It is particularly helpful in distinguishing congestive heart failure with high total protein from malignant ascites without liver metastases. The characteristics of malignant ascites associated with liver metastases resemble those of ascites complicating liver disease, indicating that portal hypertension played a role in its pathogenesis. Indeed, S-A albumin difference of 1.1 in a patient with malignant ascites should prompt a search for liver metastases. Myxedematous ascitic fluid classically catagorized as "exudative" had an S-A > 1.1, fitting the classification of portal hypertensive ascites. This evokes the possible role of portal hypertension in the development of ascites in patients with hypothyroidism. Further studies are needed to confirm this.

ACKNOWLEDGMENTS

This study was approved by the Committee on Clinical Investigation of the Albert Einstein College of Medicine.

REFERENCES

1. Boyer TD, Kahn AM, Reynolds TB: Diagnostic value of ascitic fluid lactic dehydrogenase, protein, and WBC levels. Arch Intern Med 138:1103–1105, 1978

2. Foor AG, Youngberg GE, Westmore V: The chemistry and cytology of serous fluids. J Lab Clin Med 14:417–427, 1929
3. Paddock FK: The diagnostic significance of serous fluids in disease. N Engl J Med 223:1010–1015, 1940
4. Rovelstad RA, Bartholomew LG, Cain JC, McKenzie BF, Soule EH: The value of examination of ascitic fluid and blood for lipids and for proteins by electrophoresis. Gastroenterology 34:436–450, 1958
5. Spak I: On the clinical value of chemical analysis of ascites: A study of the main proteins and some enzymes in ascites of different etiology. Acta Chir Scand 261:7–13, 1960
6. Hoefs JC: Serum protein concentration and portal pressure determine the ascites fluid protein concentration in patients with chronic liver disease. J Lab Clin Med 102:260–273, 1983
7. Pare P, Talbot J, Hoefis JC: Serum–ascites albumin concentration gradient: A physiological approach to the differential diagnosis of ascites. Gastroenterology 85:240, 1983
8. Rector W, Reynolds T: Superiority of the serum-ascites albumin difference over ascites total protein concentration in separation of "transudative" and "exudative" ascites. Am J Med 44:83–85, 1984
9. Galen RS, Gambino SR: Beyond Normality—The Predictive Value and Efficiency of Medical Diagnosis. New York, John Wiley & Sons, 1975
10. Danilewitz M, Barbezat GO, Helman CA, Bank S: Myxedema presenting with ascites. S Afr Med J 52:895–896, 1977
11. Clancey R, Mackay I: Myxedematous ascites. Med J Aust 2:415–416, 1970
12. Kocen RS, Atkinson M: Ascites in hypothyroidism. Lancet 1:527–530, 1963
13. Starling EH: On the absorption of fluids from the connective tissue spaces. J Physiol 198:213–242, 1985
14. Sampliner ME, Iber FL: High protein ascites in patients with uncomplicated hepatic cirrhosis. Am J Med Sci 267:275–279, 1974
15. Witte CI, Witte MH, Dumont AE: Protein content in lymph and edema fluids in congestive heart failure. Circulation 40:623–630, 1969
16. Lindsay KL, Reynolds TB, Hoefs JC, Sanmarco ME: Ascites—University of Southern California and Rancho Los Amigos Hospital, Downey, California (Specialty Conference). West J Med 134:414–423, 1981
17. Hoefs JC: The mechanism of ascitic fluid protein concentration increase during diuresis in patients with chronic liver disease. Am J Gastroenterol 76:423–431, 1981