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Research Article

CLINICAL AND ETIOLOGICAL PROFILE OF MALIGNANT ASCITES WITH SPECIAL REFERENCE TO SAAG CRITERIA AND BIOLOGICAL MARKERS

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ABSTRACT

Objective: The aim and objective of the study are to the analysis of the various patterns of malignant ascites (MA) in our setup.

Methods: This prospective observational study was conducted from November 2008 to August 2010 in the Postgraduate Department of General Medicine, S.C.B. Medical College, Cuttack. Diagnosed patients with ascites due to malignancy (intra-abdominal or extra-abdominal) were enrolled into the study. A thorough history and clinical examination were recorded. Patients underwent abdominal paracentesis in the first 24 h after the admission. Ascitic fluid was obtained from the left lower abdominal quadrant and samples were sent for biochemical, cytological, and microbiological analysis.

Results: Among 62 patients, male predominance was 71% and mean age of presentation was 55±20.5 years. Histopathological study revealed malignant cells in 32 cases in their ascitic fluid and was classified as MA or peritoneal carcinomatosis. In 30 patients, the ascitic fluid was negative for malignant cells and was classified as malignant-related ascites (MRA). The most common cancers causing MA were gastric (62.5%) followed by ovarian (25%). The most frequently associated cancers in MRA were hepatobiliary (53.3%) and ovarian (13.3%) cancers. Biomarkers were positive in total 32 cases. All 32 patients with carcinomatous peritonitis demonstrated a low (<1.1 mg/dL) serum ascites-albumin gradient (SAAG) and all 30 patients with MRA had high SAAG (>1.1 mg/dL).

Conclusion: The incidence of MA was 51.61% and MRA was 48.39%, and highest incidence was seen in the elderly males. SAAG was diagnostic in differentiating MA from MRA with an accuracy of 100%.

Keywords: Malignant ascites, Malignant-related ascites, Biomarkers, Serum ascites-albumin gradient.

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INTRODUCTION

The accumulation of fluid in the peritoneal cavity caused by an imbalance of plasma flow into and out of the blood and lymphatic vessels is called ascites (abdominal dropsy). Many diseases are complicated by the accumulation of fluid in the abdominal cavity. According to Runyon *et al*., approximately 80% cases of ascites are caused by cirrhosis of the liver [1,2] whereas diseases such as heart failure, nephrotic syndrome, and pancreatitis play a minor role (1–3%).

About 10% of patients suffering from ascites are due to malignancy. Malignant ascites (MA) is a manifestation of end-stage events in a variety of cancers and is associated with significant morbidity and mortality. Previously, it was assumed that cancers almost always cause ascites by lining the peritoneal cavity with tumor cells that exude proteinaceous fluid; however, now, it is known that malignancy causes ascites by multiple mechanisms. Peritoneal carcinomatosis or MA is caused by lining the peritoneal cavity with tumor cells. Malignancy-related ascites (MRA) may be due to portal hypertension, lymph node obstruction due to malignancy, with an overflow of lymph into the peritoneal cavity, or Budd-Chiari syndrome, resulting from tumor occluding hepatic vein.

MA has varied clinical presentations and diverse etiology. The onset and progression of the MA are associated with deterioration in quality of life and carry a poor prognosis. Various previous studies have been undertaken to detect, diagnose, and classify MA, but most have confusing results and render non-specific facts. With this background, the following study was undertaken to study the various patterns of MA in our setup.

METHODS

The present study was a prospective observational study conducted over a period of 2 years from November 2008 to August 2010 at the Postgraduate Department of General Medicine, S.C.B. Medical College and Hospital, Cuttack. The study was conducted with the aim to study the clinical pattern of ascites due to malignancy. The primary objective was to study the serum-ascites albumin gradient (SAAG), serum albumin and total proteins, ascitic fluid albumin and total proteins, and the various biomarkers of malignancy. The secondary objective was to correlate the types of malignancy-causing ascites with the SAAG and the various biomarkers. Ethical clearance was obtained from the Institutional Ethics Committee of SCB Medical College and Hospital before the start of the study. Written informed consent was taken from all the participants before enrolling them into the study, and strict confidentiality was maintained over relevant patient information throughout the study. The study was executed in accordance with the principles of International Conference on Harmonization-Good Clinical Practice and Declaration of Helsinki.

Patients admitted to the Department of Medicine and Medical Oncology, S.C.B. Medical College and Hospital, Cuttack, and diagnosed to have ascites due to malignancy (intra-abdominal or extra-abdominal) were the study population. Malignant origin of the ascites in these patients was usually confirmed by one or more of cytological, histological, biochemical (biomarkers), imaging, or laparoscopic study. All patients with MA with primary or secondary cancer were included in our study. Ascites due to cirrhosis of the liver, congestive heart failure,

nephrotic syndrome, and other transudative and exudative ascites due to non-malignant causes were excluded from our study. A thorough history and clinical examination were undertaken and the details were recorded in a case-record form. Routine hematological and biochemical investigations of serum were performed in all patients. Patients underwent abdominal paracentesis in the first 24 h after the admission. Ascitic fluid was obtained from the left lower abdominal quadrant and samples were sent for biochemical, cytological, and microbiological analysis. Its glucose, albumin, and total protein content were determined by standard methods. At the same time, blood samples were collected and sent for determination of total protein, albumin, glucose, adenosine deaminase, and other biochemical parameters. Serum samples were also sent for the determination of biological markers of tumor.

The data were analyzed using Instant 2006 software. Quantitative variables were expressed as mean±standard deviations. Fisher's exact test or Chi-square test was used when appropriate, to compare between categorical groups. Results were considered significant if $p<0.05$. Accuracy of the test results was investigated using positive predictive value (PPV) and negative predictive value (NPV). To calculate the PPV and NPV of SAAG, a value of <1.1 g/dL was assigned as diagnostic for MA. Thus, results <1.1 g/dL were considered as positive and >1.1 g/dL were considered as negative.

RESULTS

The study comprised of 62 patients with ascites. There was a male predominance (71%) and most of the study subjects (61.3%) were aged above 50 years. Only 22.6% of the subjects belonged to the middle age group (31–50 years) and 16.12% (10 patients) were young adults (21–30 years). The mean age of presentation was 55±20.5 years (Table 1). Abdominal swelling due to ascites was the most common clinical presentation in this study and was the first presentation in 31 patients.

The histopathological study revealed that 32 out of 62 cases had malignant cells in their ascitic fluid and were thus classified as MA or peritoneal carcinomatosis. In the remaining 30 patients, the ascitic fluid was negative for malignant cells and was classified as MRA. Most common cancers causing MA were gastric (62.5%) followed by ovarian (25%). The most frequently associated cancers in MRA were hepatobiliary (53.3%) and ovarian (13.3%) cancers. Overall, the most common cancers producing MA were gastric, hepatobiliary, ovarian, colorectal, bladder cancers, and lymphoma, in decreasing order of frequency (Table 2).

In the present study, 28 patients were anemic, with the overall mean hemoglobin (Hb) level being 9.23±2.63 g/dL. Anemia was more prevalent with MRA as compared to MA (53.3% vs. 37.5%). However, there was no statistically significant difference in the average Hb levels ($p=0.31$) between the two groups (Table 3). The total serum protein was higher in MA than MRA ($p=0.0043$). The total ascitic fluid protein was significantly lower ($p=0.0001$) in the MRA group. The difference in serum albumin was significant ($p=0.0056$) between the two groups of patients but was not significant as far as ascitic fluid albumin levels were concerned ($p=0.3155$). SAAG was 0.813±0.126 in MA group and 1.62±0.35 in MRA group with a $p<0.0001$. This indicates that SAAG was <1.1 in MA group and it was >1.1 in MRA group.

Biomarkers were positive in total 32 cases (Fig. 1). CA125 was detected in 8 cases of ovarian cancer and CEA in 2 cases of colorectal carcinoma, AFP was raised in 10 cases of hepatocellular carcinoma (HCC) and in 8 cases of ovarian cancer and LDH was positive in 2 cases of HCC and 2 cases of lymphoma. Biomarkers were, thus, helpful in identifying the etiology. However, they could not be utilized to differentiate between MA and MRA.

DISCUSSION

The present study conducted with 62 patients aimed at investigating the clinical and etiological profile of MA with special reference to SAAG and biomarkers. Out of 62 patients, 32 (51.16%) patients had MA and 30 (48.38%) patients had MRA. There was a male predominance with 70.96% of the study subjects being males while females constituted the remaining 29.04%. Our findings are contrary to the previous studies by Khan [3] (54.5% females vs. 45.5% males) and Ayantunde and Parsons [4] (67% females vs. 33% males) which showed female predominance. The present study showed male predominance due to the fact that the most common cancer causing ascites in our study was gastrointestinal in origin. In the previous studies, the origin was from ovarian and breast cancers predominantly. The most common

Table 1: Baseline characteristics of the study subjects (n=62)

Characteristics	Frequency (%)
Age distribution (in years)	
21–30	10 (16.1)
31–40	4 (6.5)
41–50	10 (16.1)
51–60	16 (25.8)
61–70	8 (12.9)
71–80	14 (22.6)
Average age	55±20.5
Gender distribution	
Male	44 (71)
Female	18 (29)
Clinical profile	
Abdominal swelling	48 (77.4)
Abdominal pain	30 (48.4)
Anorexia and dyspepsia	36 (58.8)
Weight loss	28 (45.2)
Nausea and vomiting	26 (41.9)
Jaundice	6 (9.6)
Anemia	34 (54.8)
Hematemesis and melena	6 (9.7)
Lymphadenopathy	12 (19.4)
Menorrhagia and amenorrhea	8 (12.9)
Dyspnea	16 (22.6)

Table 2: Types of cancer associated with malignant ascites

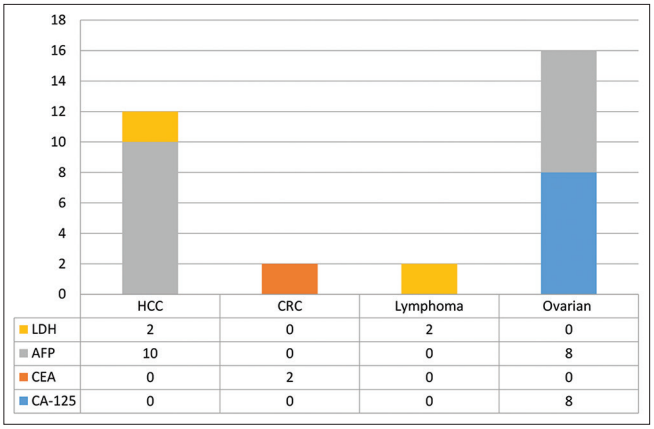
	MA	MRA	Total frequency
Frequency (%)	32 (51.6)	30 (48.4)	62
Gender distribution			
Male	22	22	44 (71)
Female	10	8	18 (29)
Cancer type			
Ovarian	8 (25)	4 (13.3)	12 (19.4)
Gastric	20 (62.5)	2 (6.6)	22 (35.5)
Hepatocellular	0	8 (26.6)	8 (12.9)
Gall bladder	0	8 (26.6)	8 (12.9)
Colorectal	2 (6)	2 (6.6)	4 (6.5)
Pancreatic	2 (6)	0	2 (3.3)
Lymphoma	0	2 (6.6)	2 (3.3)
Bladder	0	4 (13.3)	4 (6.5)

MA: Malignant ascites, MRA: Malignant-related ascites

Table 3: Comparison of serum and ascitic parameters

Laboratory parameters	MA	MRA	p-value*
Serum			
Hb (g/dL)	9.06±2.6	9.72±2.44	0.31
Total protein	5.84±0.51	2.97±0.296	0.0043
Albumin	2.52±0.36	2.84±0.61	0.0056
Ascitic fluid			
Total protein	5.025±0.55	2.23±0.24	0.0001
Albumin	3.06±0.36	1.73±0.43	0.3155
SAAG	0.813±0.126	1.62±0.35	<0.0001

*Student's t-test; *P* is significant at<0.05. SAAG: Serum-ascites albumin gradient, MA: Malignant ascites, MRA: Malignant-related ascites



	HCC	CRC	Lymphoma	Ovarian
LDH	2	0	2	0
AFP	10	0	0	8
CEA	0	2	0	0
CA-125	0	0	0	8

Fig. 1: Various biomarkers detected among the study population

age group of patients affected was elderly age group (51–80 years), i.e., 61% of total cases. 14 cases were aged between 31 and 50 years, followed by only 10 cases which belonged to 21–30 years. The mean age of presentation in this study was 55±20.5 years. This is consistent with previous studies where the mean age was 52±14.75% years. The most common presentation in the present study was abdominal swelling (77.41%), followed by anorexia and dyspepsia (58.8%), anemia (54.83%), abdominal pain (48%), weight loss (45%), nausea and vomiting (41%), dyspnea (22%), lymphadenopathy (19%), and jaundice (9.6%). Studies by Khan [3] and Ayantunde and Parsons [4] also showed similar results where abdominal swelling (55%), abdominal pain (53%), anorexia (36%), nausea and vomiting (37%), and weight change (15%) were the most frequently encountered clinical presentations. Ascites as initial presentation was found in 54% cases by Khan study; 59% cases reported by Ayantunde and Parsons study and Runyon *et al*. study [1,2]. In the present study, ascites was the initial presentation in 50% cases. This also confirms with a study by Parsons *et al*. where ascites was the initial presentation in 45–64% cases [5].

In the present study, the most common types of cancer-causing MA included gastric (62.5%) and ovarian (25%), followed by colorectal and pancreatic (6.25% each) cancers. HCC and gall bladder carcinoma constituted about 53% of cases causing MRA followed by ovarian, gastric, colorectal, lymphoma, and bladder cancer. Overall, gastric carcinoma was the leading cause of MA comprising of about 35% cases followed by hepatobiliary (25.8%), ovarian (19%), and colorectal cancers (6%). In a study by Khan [3], ovarian cancer (33.3%) was the major cause of MA followed by gastric and colorectal cancers (16.7% each), whereas gall bladder cancer (50%) was the main cause of MRA. According to a study by Ayantunde and Parsons [4], ovarian cancer (36.7%), breast cancer (13%), gastric cancer (16%), colorectal cancer (14%), and bladder and renal cancer (8% each) were the major causes of MA. On the other hand, pancreaticobiliary (31%), gastric (18%), breast (21%), and bladder and thyroid cancer were the main causes of MRA. In both the previous studies, about 8–10% cases were found to have undiagnosed primary origin of cancer. The present study, however, demonstrates that all cases were diagnosed to have some form of primary cancer. This could be possible due to the improved diagnostic facilities.

Out of the total 62 cases, anemia was present in 54.83% of cases, with a mean Hb level of 9.06±2.54 g/dL. Among the patients who presented with anemia, 6 patients had hematemesis and melena and 6 patients presented with jaundice. Anemia was a major presentation in the present study, which was not described in previous studies. Cytopathological study shows positive result in 45–60% cases. Johnson [6] and Cardozo study [7] found ascitic fluid cytology positive in 45–52% cases. This is also confirmed observations by Bhanvadia *et al*. [8]. Runyon *et al*. reported 53.3% positive ascitic fluid cytology [1,2]. In the present study, 51.16% cases were positive for malignant cells in the ascitic fluid. The sensitivity of ascitic fluid cytology was 100% for MA or carcinomatous peritonitis. The mean ascitic fluid total protein in the present study was 5.025±0.55 in MA group and 2.23±0.24 in MRA group. The positive correlation was 0.0001, which was statistically significant. Study by Khan showed the same result, but the positive and NPV were 91.6% and 90%, respectively [3]. The mean SAAG in the present study was 0.813±0.126 in patients with MA and 1.62±0.35 in patients with MRA. In accordance with the previous studies, ascitic fluid analysis of our study also revealed that all 32 patients with carcinomatous peritonitis demonstrated a low SAAG (<1.1 mg/dL) and all 30 patients with MRA had high SAAG (>l.l mg/dL). This observation confirmed that SAAG shows high accuracy for the diagnosis of MA and differentiating it from MRA, as it has positive and NPV of 100% and 100%, respectively; compared to the positive and NPV of 91.2% and 90%, respectively, for ascitic fluid total protein.

CONCLUSION

The incidence of MA was 51.61% and MRA was 48.39% in our study. Overall, the highest incidence was seen in the elderly males and the most common cause was cancers of gastrointestinal tract origin. Cytology study was diagnostic in differentiating MA from MRA with 100% accuracy. Likewise, SAAG was diagnostic in differentiating MA from MRA with an accuracy of 100%.

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AUTHOR'S CONTRIBUTION

All the authors equally contributed in making this manuscript.

CONFLICT OF INTEREST

Nil.

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