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Differential diagnosis of massive ascites of unknown origin: An experience in a tertiary care hospital in Bangladesh

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Abstract
Background: Ascites denotes pathological accumulation of fluid in the peritoneal cavity. The word "Ascites" comes from the Greek word "Askitos", which means bladder or bag. Massive ascites of unknown origin is an uncommon condition, which represents a diagnostic challenge. Accumulation of fluid within the greater peritoneal cavity – ascites - is usually encountered in clinical practice. Ascites is a common clinical problem, which can originate from hepatic, malignant, cardiac, renal, and infectious diseases.
Aim of The Study: The aim of this review study was to discuss the current recommended diagnostic approach towards the patient with ascites and summarizes future diagnostic targets.
Material and Methods: This was a descriptive, cross-sectional, analytical, and retrospective type of study, undertaken in the department of medicine of a tertiary care hospital in Bangladesh, over a period of one year from January 2018 to December 2019. The peritoneal or ascites fluid received were processed and studied for the cell count, number, cellular features, presence, or absence of organisms if any, and malignancies.
Results: 75(50.15%) cases out of a total of 150 samples were received over a 1-year period. There was a slight male preponderance with 64(51.56%) cases and females composed of 6(48.44%) cases. The mean age of presentation among all patients was 51.6 years. A total of 13(10.24%) cases were malignancies.
Conclusion: Peritoneal or ascites fluid is one of the common body fluids to be studied in everyday practice. Meticulous cytologic evaluation is of paramount importance as numerous malignant and non-malignant pathologies can cause effusions. The medical diagnosis of ascites is broad and includes an outsized number of benign and malignant causes. A structured diagnostic approach will likely reveal the etiology within the large majority of cases and is predicated on the subsequent elements: history, physical examination, blood tests, abdominal ultrasound, and diagnostic paracentesis.

Keywords: ascites, pathogenesis, diagnosis, diuretics, paracentesis

Introduction

The word Ascites comes from the Greek word "Askitos" which means bladder or bag. Ascites which denotes pathological accumulation of fluid within the greater peritoneal sac springs from it [1]. Ascites isn't a disease rather it's a symbol provoked by physicians. Normally, as in any other cavity in the body, the peritoneal cavity is lined by its native mesothelial cell layer, is lubricated by a small amount of fluid which is considered as free fluid. Any increase in this fluid constitutes ascites. Traditionally ascitic fluid is classed as exudative and transudative supported its protein content. Ascites is a common clinical problem, which can be a result of liver cirrhosis, neoplasm, tuberculous peritonitis, pyogenic peritonitis, congestive heart failure, nephrosis and pancreatic disorders **[2].** Malignancy accounted for 10% of all the ascites. Of the malignant ascites, epithelial malignancies, in particular ovarian, endometrial, breast, colon, gastric, and pancreatic carcinomas, accounted for over 80%, while malignancies of unknown origin represented 20% [3]. Massive ascites of unknown origin is an uncommon condition with protean etiologies. In female patients, the most common causes of ascites of unknown origin were malignancies (40.3%), cirrhosis (16.7%), and tuberculous peritonitis (12.9%). Almost half of the malignant ascites of unknown origin were derived from the digestive or gynecologic systems [4]. Rarely is ascites of unknown origin a manifestation of constrictive pericarditis, which is often misdiagnosed at the first presentation of the patients, while with true reasons being overlooked for a long time. The medical diagnosis of ascites of unknown origin therefore always remains a diagnostic dilemma. Tuberculosis used to be a common cause of constrictive pericarditis. However, the clinical spectrum of constrictive pericarditis has changed considerably with an altered infectious origin. As tuberculosis has become less frequent, more common causes are previous heart operation, pericarditis, and radiation treatment [5]. Other causes may include infectious viral, tuberculous, connective-tissue disease, uremia, neoplasm, or idiopathic condition. Patients with constrictive pericarditis usually present with circulatory symptoms including dyspnea, orthopnea, or maybe coronary failure, [6]. but rarely manifest extracardiac manifestations, like massive ascites and liver cirrhosis [7]. The fibrotic or calcified pericardium is a common finding in such patients [8]. When the patient with constrictive pericarditis presents with extracardiac manifestations, they are prone to be misdiagnosed congestive heart failure, hepatic cirrhosis, or tuberculous

peritonitis. Calcified constrictive pericarditis presenting with massive ascites of unknown origin misdiagnosed as hepatic cirrhosis.

Materials and Method

This was a descriptive, cross-sectional type of study, undertaken in the department of medicine of a tertiary care hospital over a period of one year from January 2018 to December 2019. The aim of the study was to analyze the peritoneal fluids received in the department of pathology and study them with respect to clinical, demographic, and radiologic features. Findings were obtained from the cytological requisition sheets. The samples were received within 15 minutes of tapping. All the samples were centrifuged at 2500 RPM for 5 minutes. The supernatant was discarded and sediments were taken on the slides and smeared. Two slides were air-dried and stained with Leishman and two were fixed with methanol and stained with H&E stain. The slides were studied on light microscopy. Individual cases were evaluated according to the following cytological features. Cell type, number, size, architecture (Acini / Sheets/ 3D balls/ Papillae/ Rosette), nuclear and cytoplasmic, dysplasia and background features. All the data were then statistically analyzed.

Results

In our study, 128 fluids were received of which 75(50.15%) were peritoneal fluids. Male comprised of 39(51.56%) cases and females comprised 36(48.44%) cases. Slight male preponderance was noted [Table 1].

Table1: Distribution of cases according to clinical features

Parameters	Nonmalignant (68)	Malignant (7)
Mean age(51.6)	47.2 years	56.4 years
Male(39)	39(51.56%)	-
Female(36)	29(38.20%)	7(10.24%)
Gross features		
Clear (straw colored)	44(59.9%)	1(0.81%)
Hemorrhagic	23(30.04%)	4(5.36%)
Turbid	1(0.81%)	3(3.08%)

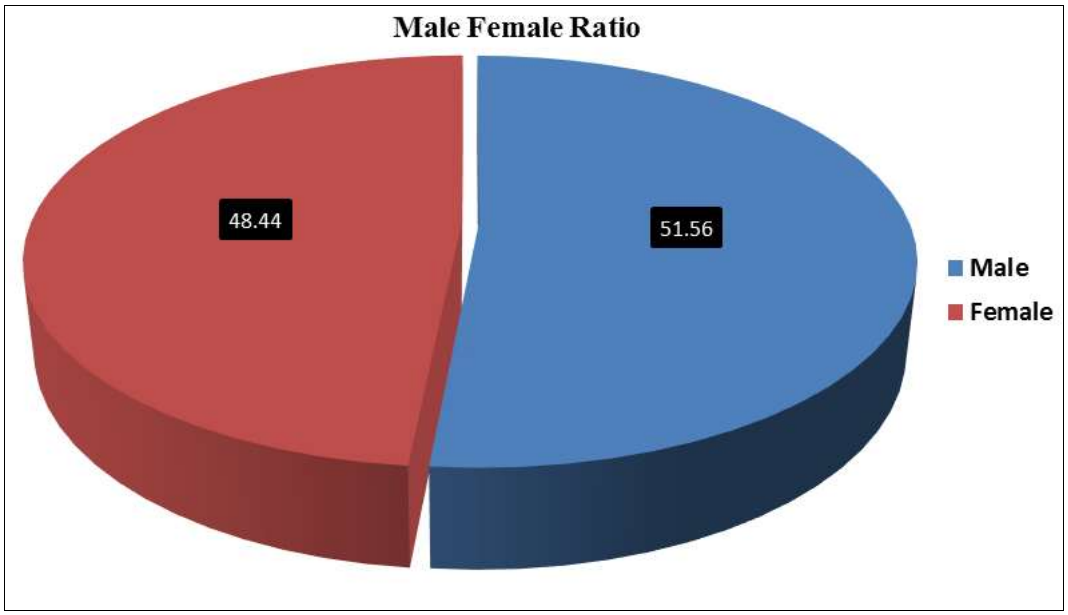

Fig 1: Male Female Ratio

Most common age group affected was 6th decade. Youngest patient was 16 years' female were as the oldest was an 84 years' male. Mean age both sexes was 51.6 years [Table 1]. Out of 75 cases, non-malignant cases formed majority of the cases 67(90%) and malignant were 8(10%) [Table1]. Mean age of non-malignant cases was 47.2 years and that in malignant cases was 56.4 years. There was not a single case of malignancy in males whereas as majority of cases of Ascites in females were non-malignant, 48(39.20%) [Table1]. Out of 75 cases, 48(63.63%) cases were transudates whereas 27(36.37%) cases were exudative in nature. When studied grossly majority of the specimens were clear that is 45(59.9%) cases followed by hemorrhagic appearance in 23(30.04%). Turbid fluids were noted majorly in malignant 1(1.16%) cases [Table 2].

Table 2: Distribution of cases according to diagnosis and nature of effusion

Aetiological factors	Number of cases (75)	
	Transudate (48)	Exudate (27)
Acute infection	-	7(10.24%)
Tuberculosis	2(3.40%)	12(15.90%)
Cirrhosis	36(47.72%)	-
CCF	6(7.38%)	-
Renal failure	3(3.97%)	1(1.16%)
Malignancy	1(1.16%)	7(9.09%)

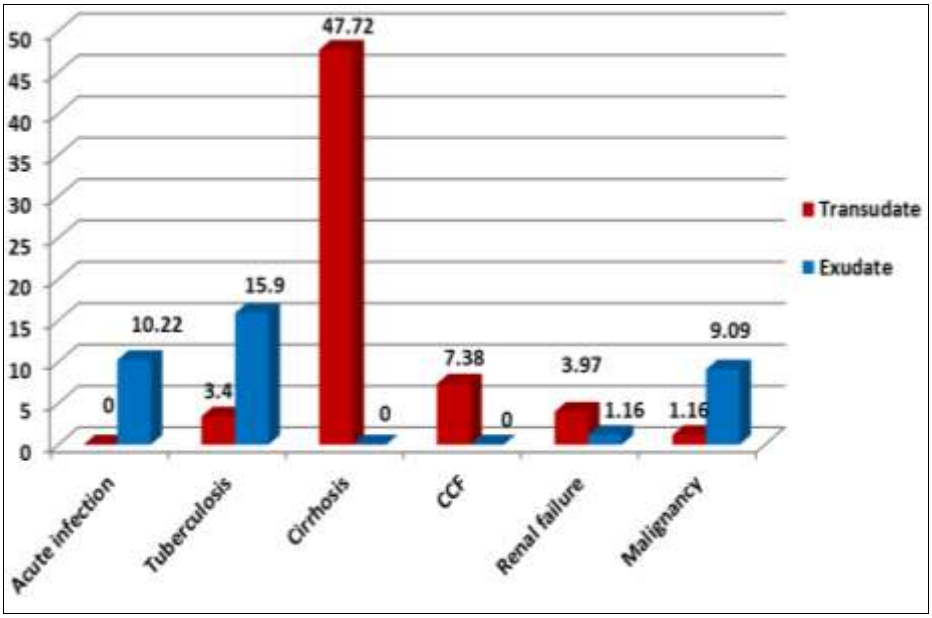

Fig 2: Various Aetiologies leading to Transudative and Exudative effusions

Various aetiologies leading to exudative and transudative effusions were noted in our study. 7(10.24%) were malignant cases, all which are seen in female patients. Among those 12(66.66%) of adenocarcinoma were noted, with 8 cases of ovarian origin and 4 of gastrointestinal origin. 4(22.22%) cases of metastatic squamous cell carcinoma and 2(11.11%) cases of hematological origin were noted.

Amongst non-malignant aetiologies, cirrhosis was the most commonly encountered cause with 36(47.72%) followed by 14(19.31%) of tuberculosis.

All the cases of cirrhosis were transudative and tuberculosis seen in 12 (15.90%) predominantly was exudative. Amongst other aetiologies of exudative nature, acute infection related ascites comprised of 13(10.24%) cases followed by malignancies with 7(9.09%) cases.

Table 3: A Sample Blood Test of Patient

Parameter	Result	Normal range
Hemoglobin (g/L)	115	113-151
Platelet (× 10^9/L)	195	110-360
Prothrombin time (s)	13.30	9-13
Total protein (g/L)	76.6	60-80
Albumin (g/L)	38.7	35-55
D-dimer (ng/L)	0.31	<0.5
Glucose (mmol/L)	3.54	3.89-6.11
C-reaction protein (mg/L)	4.67	0-8
Erythrocyte sedimentation rate (mm/h)	28	0-20
Anti-tuberculosis antibody	negative	negative
Natriuretic peptide (pg/mL)	197	0-200
Troponin I (μg/L)	0.00	0-0.06
α-fetoprotein (ng/L)	2.5	0-9
Carcinoembryonic antigen (ng/L)	2.27	0-5
CA12-5 (ng/mL)	27.21	0-5
CA15-3 (ng/mL)	3.72	0-25
CA19-9 (ng/mL)	32.96	0-27

Table 4: A Sample Ascites Test of Patient

Parameter	Result
Color	Yellow
Appearance	Turbid
Clot	Yes
Gravitide	1.020
Total protein (g/L)	47.3
Albumin (g/L)	23.9
Glucose (mmol/L)	4.85
Rivalta test	Positive
Adenosine deaminase (U/L)	10
Lactate dehydrogenase (U/L)	72
White blood cell count (× 10^6)	82
White blood cell morphology	More mononuclear cells than multinucleated cells
Red blood cell count (× 10^9)	4
Red blood cell morphology	Cell shrinkage
α-fetoprotein (ng/L)	2.1
Carcinoembryonic antigen (ng/L)	0.42
CA12-5 (ng/mL)	452.6
CA15-3 (ng/mL)	1.41
CA19-9 (ng/mL)	7.48
CA72-4 (ng/mL)	0.9

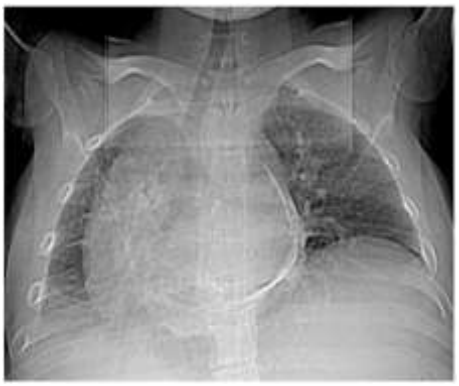

Fig 3: First frame of chest computed tomography showing the outline of calcified constrictive pericarditis and rightward-posteriorly ectopia cordis.

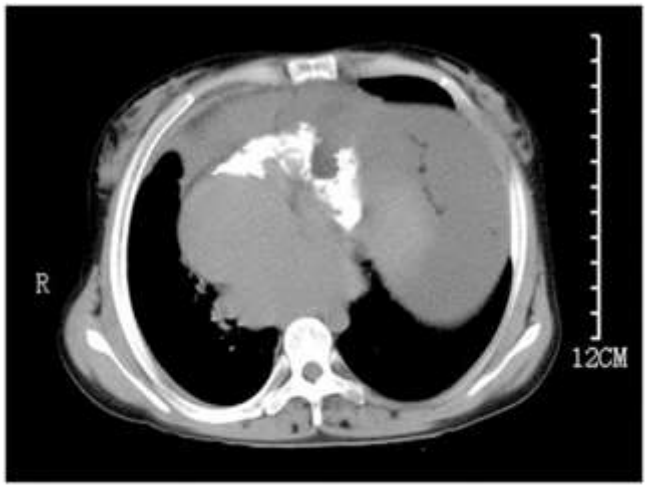

Fig 4: An axial view of chest computed tomography showing the severely calcified pericardium over the right heart.

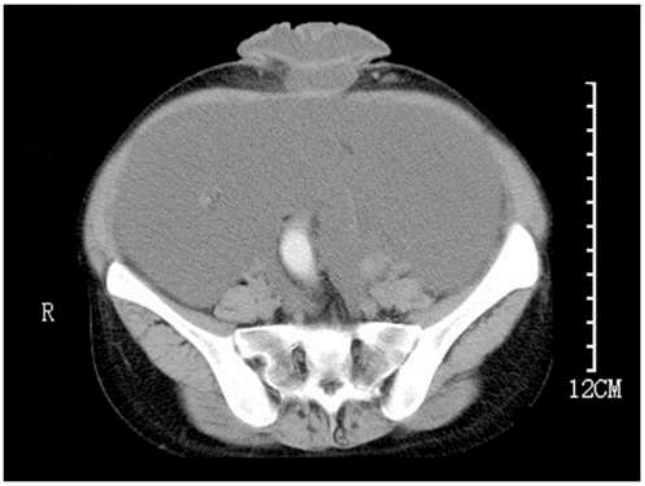

Fig 5: An axial view of abdominal computed tomography showing massive ascites, severe abdominal wall edema and an umbilical hernia.

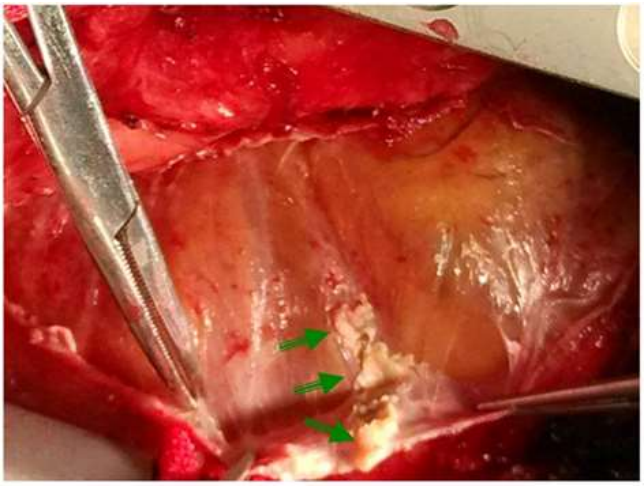

Fig 6: Pericardiectomy was performed for severe calcification covering the right ventricle, right atrium and encircling the right atrioventricular groove (arrows).

Discussion

The term "ascites of unknown origin" was firstly expressed by Ward in 1982 [9]. However, the concept of ascites of unknown origin has not been properly defined up to date. Ascites of unknown etiology cannot be determined after conventional laboratory examinations like cell count, albumin level, total protein level, gram stain, culture cytology, and further imaging investigations including ultrasound and computed tomography scan [2] Some more details have to be updated for a complete definition, which is, ascites persistent for at least more than 4 weeks; no significant improvement with multiple therapeutic paracenteses, escalating doses of diuretics, and anti-inflammatory drugs; and no causative agent could be identified after extensive laboratory investigations.[10-13] According to the course of the disease, ascites of unknown origin can be divided into acute (new-onset), sub-acute, and chronic, with a duration of the onset time of <10 days, 10 days to 3 months, and >3 months, respectively. According to the eventual discrimination of the etiologies, it can be divided into true ascites of unknown origin (with eventual recognition of the etiologies) and false ascites of unknown origin (with eventually unrecognized etiologies). For the interpretation of true ascites of unknown origin, a peritoneal reaction to repetitive inflammation, this is a process that may develop into ascites in extreme cases [14] Diagnostic evaluation of ascites of unknown origin in 129 patients, and discovered the etiologies were carcinomatosis peritonei (60.5%), tuberculous peritonitis (20.2%), cirrhosis 5.4%, and no gross abnormality (14.0%) [15]. Ascites of unknown origin may be derived from rare diseases, which include idiopathic colonic phlebitis,[16] Toxocara canis infection,[17] chronic granulomatous diseases (CGD), a rare inherited immunodeficiency syndrome that results from abnormal nicotinamide adenine dinucleotide phosphate (NADPH) oxidase function,[18] POEMS syndrome, [19] benign cystic mesotheliomas (BCM), [20] celiac disease, [21] ruptured remnants of a urachal diverticulum, [22] peritoneal carcinomatoses from desmoplastic small round cell tumor (DSRCT), [23] unknown origins irrespective of extensive investigations. [24-25] The detection rates of ultrasound scan and computed tomography scan were 94.4% and 95.6% respectively, without specificity. However, cyto morphological examination alone may provide only limited sensitivity for the detection of metastatic malignant cells [26]. Pathological examination of the omental biopsies can be helpful in determining the origin of the lesions [27]. By providing clear visualization and direct biopsy of abdominal organs, laparoscopy is a preferred technique that facilitates diagnosis, preoperative assessment, and therapy of ascites [28]. It has been utilized to confirm the diagnosis in ascites of unknown origin in terms of cirrhotic or non-cirrhotic as carcinoma peritonei, tuberculous peritonitis, or nephrogenic origin. Moreover, it is also used in peritoneal lavage cytology, preoperative assessment and staging of gastric, pancreatic and liver neoplasms, and judgment of curability of the abdominal carcinomas. Therapeutic roles were also discussed as in hemorrhagic pancreatitis, chylous ascites and catheter deployment for dialysis, and neoadjuvant chemotherapy [29]. A systematic approach to treatment using subcutaneous octreotide and a fat-free diet, resulting in complete resolution of the condition [30]. Over half of the patients with constrictive pericarditis did not show cardiopulmonary symptoms such as dyspnea and orthopnea, and therefore patients frequently present to non-cardiac physicians at their initial onset of symptoms. Ascites can be an appearance of effusive-constrictive pericarditis, [31]. Patients with untreated constrictive pericarditis sooner or later have ascites, edema, and pleural effusions. [32] Intra-

abdominal abscess, tuberculosis, bacterial peritonitis, trauma, pancreatitis, malignancies give rise to exudative effusion whereas cirrhosis, congestive cardiac failure, constrictive pericarditis, portal and hepatic vein obstruction, malnutrition and nephritic syndrome are causes for transudative ascites. [33] As widely accepted peritoneal tapping is performed to assess the tumor stage most of the time. In almost 75% of cases of malignancy ascites, the tumor cells are seen only when they lie in peritoneum so it is to be understood that patients having massive liver metastasis or hepatic cell carcinoma should not be expected to have malignant ascites. [34-36]. One of the most common primary malignancies to give rise to malignant ascites is from the ovary. [37] Presence of malignant cells in peritoneal fluid does not necessarily change the stage of the disease. But, it is definitely a poor prognostic sign which requires more intense treatment. [38] Other than ovarian malignancies, gastro-intestinal malignancies also more commonly give rise to malignant ascites. In children, hematological malignancies such as lymphomas are a cause of malignant ascites. [39] Hence an accurate and meticulous cytological evaluation of fluid obtained patients is very important to reduce morbidity and mortality.

Conclusion

The differential diagnosis of ascites is broad and includes an outsized number of benign and malignant causes. A structured diagnostic approach will likely reveal the aetiology within the large majority of cases and is predicated on the subsequent elements: history, physical examination, blood tests, abdominal ultrasound, and diagnostic paracentesis. The standard ascitic fluid analysis includes visual inspection and determination of the serum-ascites albumin gradient or gap (SAAG). In patients with suspected infection or underlying liver disease a polymorphonuclear (PMN) count and bacterial cultures are standard. According to clinical situations other well-known diagnostic studies are ascites cytology and determination of levels of amylase and triglycerides. In exceptional cases measuring urea and creatinine levels may be crucial. Adenosine deaminase (ADA) activity measurements, mycobacterium cultures, and polymerase chain reaction (PCR) for mycobacterium deoxyribonucleic acid (DNA) are indicated when tuberculosis is considered. Leucocyte esterase reagent strips are useful, in particular to rule out spontaneous bacterial peritonitis (SBP) in patients with a low a priori risk. New diagnostic markers such as viscosity, vascular endothelial growth factor (VEGF), bacterial DNA, cytokines and platelet indices have been proposed, but further research is needed to validate the value of these markers.

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