Case report

A FEMALE WITH MALIGNANT ASCITES: A DIFFICULT CASE WITH CARCINOMA OF UNKNOWN PRIMARY

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ABSTRACT

Malignant ascites is the abnormal accumulation of fluid in the peritoneal cavity associated with several intra-pelvic and intra-abdominal malignancies. Among the gynecologic malignancies, ovarian carcinoma predominates. Of the gastrointestinal malignancies, ascites can occur with advanced colon, pancreas, gastric carcinoma, and esophageal carcinoma. Recent reports in the cytological literature suggest that 6% to 11% of malignant peritoneal effusions are due to tumors of unknown origin.[1] We reported a 62 years old female presenting adenocarcinoma ascites, which shown confusing of site of primary origin from imaging examination. First ultrasound imaging showed mass on colon area, but re ultrasound of abdominal imaging showed the possibility of endometrium carcinoma. The CA 125 level was high (2.294 u/ml). Open laparotomy showed milliar metastatic several nodule on omental, liver, and abdominal wall. There was attachment of vesica urinaria, endometrium, colon, sigmoid, and rectum. All those result conclude this patient suffered from malignant ascites of adenocarcinoma of unknown primary origin, with highly suggestive from malignant ascites of adenocarcinoma of unknown primary origin, with highly suggestive from gynecologic malignancy that difficult to differ whether from ovarian cancer or endometrium cancer. Somehow, the epidemiology, pathophysiology, clinical presentation lead the diagnosis for ovarian cancer.

Keywords: Malignant ascites, peritonitis carcinomatous, adenocarcinoma, CA 125, ovarian cancer, endometrium cancer

INTRODUCTION

Malignant ascites is the abnormal accumulation of fluid in the peritoneal cavity associated with several intra-pelvic and intra-abdominal malignancies.[1,3] Malignant peritoneal effusions come from direct extension and metastasis process is due to a reabsorption unbalanced. Break of malignant origin is usually recurrent and is often associated with an unfavorable prognosis.[2,3] Malignant ascites is defined generally as the break of peritoneal containing malignant cells. This condition was called peritonitis carcinomatous. It is indicating the presence of malignant cells in the peritoneal cavity.[3] The prevalence of peritonitis carcinomatous was 53.3% among of all ascites related to malignancies. [4]

Malignant ascites can occur in patients with colon, pancreatic, breast, and lung primaries with the development of peritoneal carcinomatosis. [4] Among the gynecologic malignancies, ovarian carcinoma predominates.[2] Recent reports in the cytological literature suggest that 6% to 11% of malignant peritoneal effusions are due to tumors of unknown origin.[1] In this report we will discuss about a difficult case of primary site assessment of adenocarcinoma ascites of a 62 years old female.

CASE REPORT

A 62 years old female complained abdominal enlargement, fever, and fatigue for a month. Sometimes, she also had abdominal pain and cramp that occurred intermittently. She had anorexia and loss body weight about 3 kg within 3 months. She also suffered from diarrhea for 3 months. There were no blood and no mucous. She already had menopause about 8 years ago, and never complaining about bloody discharge or fluor albus. She had 2 children on normal delivery, she had used pills contraception pills, and never took hormonal replacement therapy after menopause. She is a priest and a social worker of HIV patient. Her sister was dead because of gynecologic malignancy. Her father was dead because of prostate cancer

Physical examination revealed a moderately ill woman with ascites. The patient was alert; the heart rate was 100 x/min and the blood pressure 110/70 mmHg. The physical examination was unremarkable except for abdominal distension and ascites. Specifically, no abdominal dilated blood vessels were observed, and the pelvic examination was normal. Paracentesis revealed a yellowish fluid for 5 liters, and the abdominal became flatted. But 2 days later, the ascites was occurred again for 3 liters. The conformational examination revealed a mass on supraumbilical area, about 4 cm on diameter, floating, and there was no clear border. There was no abdominal tenderness on physical examination.

Laboratory finding showed the hemoglobin was 12.5g/dl, leukocyte was 9,200/mm^3, thrombocyte was 555,000/mm^3, albumin was 3.5 g/dl, SGOT 20U/ml, SGPT 38 U/ml. The bilirubin was normal with total bilirubin was 0.48 mg/dl. The BUN level was normal (8 mg/dl), and the creatinine was 1.0 mg/dl.

Analysis of ascites fluid revealed a greenish fluid with glucose level was 93 mg/dL, increased of protein 4.94 g/dl, leukocyte was 3500/mm^3, with polymorphonuclear cell (PMN) was 62.3% and mononuclear cell (MN) was 37.7%. The pathology result of ascites fluid revealed class V with adenocarcinoma.

The first USG abdomen showed ascites with suspicious of peritonitis TB. There was no mass on epigastric area detected by this imaging. The BNO result showed obstruction on 25 cm from anus. The colonoscopy revealed obstruction on 35 cm deep from anus, with external obstruction type, and the

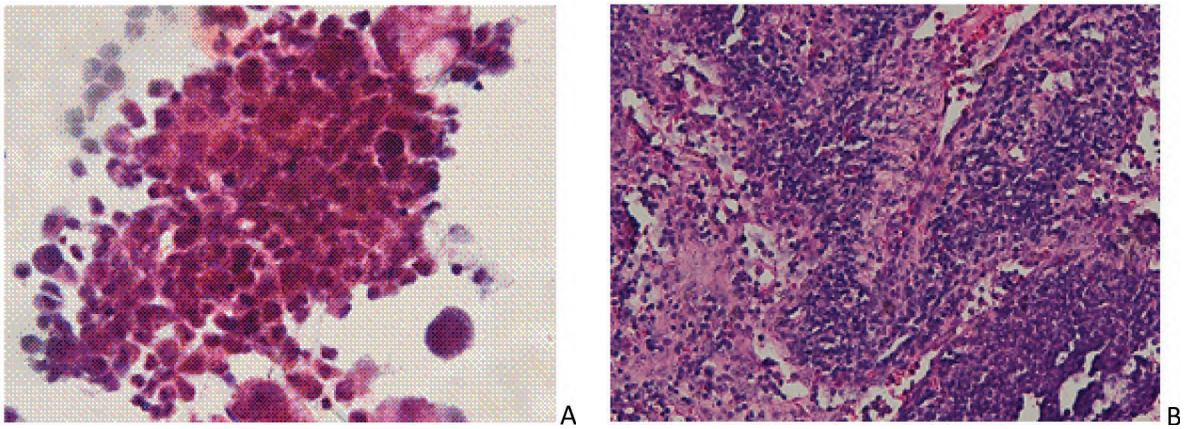
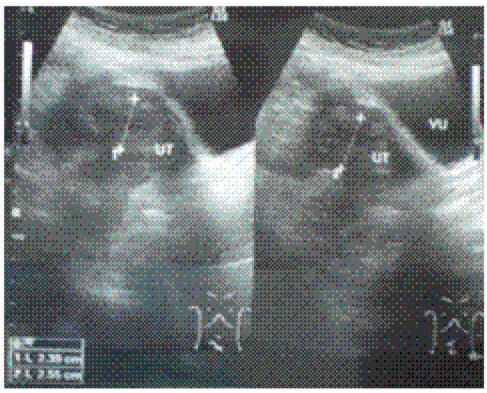


Figure 1. A. Cytology of ascites showed Class V with adenocarcinoma identify by groups of large cell, oval, with chromatin of rough nucleus, irregular margin, large cytoplasm with define margin. B. cytology of omental metastase showed adenocarcinoma identify by groups of aciny.

scope could not able inserted further. The fecal smear showed negative result of benzidine test. The tumor marker showed CEA 2.13 ng/ml, CA 19.9 was 10.5 U/ml, CA 125 was high (2.294 u/ml). The CT imaging showed there were no mass detected on genital or gastrointestinal organs. Reevaluation of abdominal USG suggests an endometrial carcinoma with ascites.

Laparotomy exploration was done, and the result showed ascites 2 l, with attachment of abdominal organs for endometrium, vesica urinaria, colon, sigmoid, and rectum. There were milliary metastatic nodules on omentum and abdominal wall. Omentum at epigastric area showed multiple nodules built mass about 6 cm on diameter. There was already metastatic nodule on liver. It was impossible to explore further because of the attachment of intra-abdominal organ, and it could not able to identify the primary site of tumor.

We conclude this patient suffered from malignant ascites as ovarian cancer and treated chemo palliative treatment using paclitaxel and cisplatine. The ascites also treated using furosemide 40 mg twice daily intravenously. We educated the patient and family about diagnosis, goal of treatment, side effect of treatment, and plan of monitoring. Monitoring was aimed to see treatment response, ascites, side effect, further progressive disease, and nutritional status.



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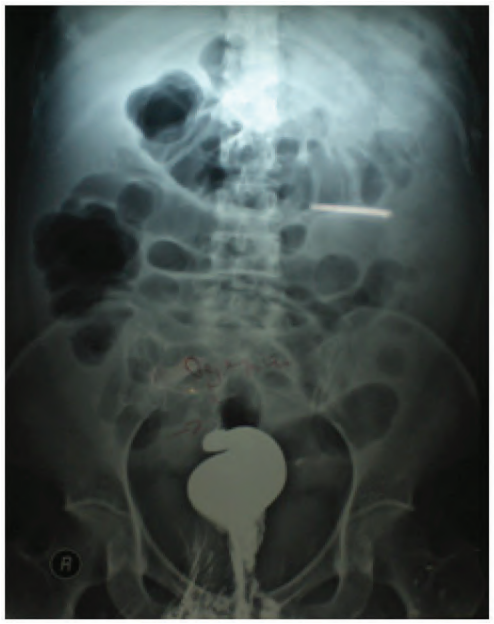

B

Figure 2. A Ultrasonography imaging showed solid tumor intra uteri with irregular margin suggest malignancy. B. Barium enema showed obstruction of colon on 35 cm from anus with obstruction sign of intestinal. Those finding brought Radiologist to conclude endometrium cancer with obstruction process to colon.

DISCUSSION

One retrospective review of causes of malignant ascites found that ovarian cancer had the highest proportion of patients who developed ascites at 37.7%, followed by pancreatic biliary cancers (21%), gastric cancer (18.3%), esophageal cancer (4.0%), colorectal cancer (3.7%), and breast cancer (3.0%). The study also found that the number of cases of malignant ascites due to an unknown primary cancer was 8.1% compared to previous reports. Previous estimates also suggest that up to 20% of cases of carcinoma of unknown primary have been associated with ascites.[4,5]

The pathophysiology of malignant ascites is not totally understood. The presence of tumor cells results in the obliteration of lymphatic drainage. Furthermore, production of locally active molecules such as *Vascular Endothelial Growth Factor* (VEGF) and *Basic-Fibroblastic Growth*

Factor (b-FGF) results in changes in Starling's law of capillary hemodynamic as shown on Table 1. VEGF is a potent growth factor that stimulates blood vessel formation as well as exerting effects on the vascular endothelial cell. A potent permeability factor, it is 50,000 times as potent as histamine. The changes in peritoneal microvasculature leading to an altered LpS product. As a result, net capillary fluid-filtration increases. Increased filtration and decreased evacuation results in ascites.[4]

Table 1. Starling's law

Net filtration
= LpS (δ hydraulic pressure - δ oncotic pressure).
= LpS[(Pcap-P1r)-s(πcap-πl f)].
Lp = the unit permeability or porosity of the capillary wall. S = the surface area available for filtration Pcap and P,t-= the capillary and interstitial fluid hydraulic pressures. ncap and nlf = the capillary and interstitial fluid oncotic pressures. s = the reflection coefficient of proteins across the capillary wall (with values ranging from 0, if completely permeable, to 1 if completely impermeable).3

Unknown primary tumor represents a heterogeneous feature of metastatic tumors, and histological presentations of cancer of unknown primary (CUP) are predominantly classified as adenocarcinomas (50 – 60%) or poorly differentiated adenocarcinomas or other carcinomas (30 – 40%).[3] The histological types of CUP are a challenge for clinicians to manage as identification of the primary sites is difficult using only routine histological examinations. [3]

Adenocarcinoma is a cancer of an epithelium that originates in glandular tissue. Epithelial tissue includes, but is not limited to, the surface layer of skin, glands and a variety of other tissue that lines the cavities and organs of the body. Epithelium can be derived embryologically from ectoderm, endoderm or mesoderm. To be classified as adenocarcinoma, the cells do not necessarily need to be part of a gland, as long as they have excretory properties. All of those kind malignancy which developed malignant ascites as mention above could be presented an adenocarcinoma.[4,6]

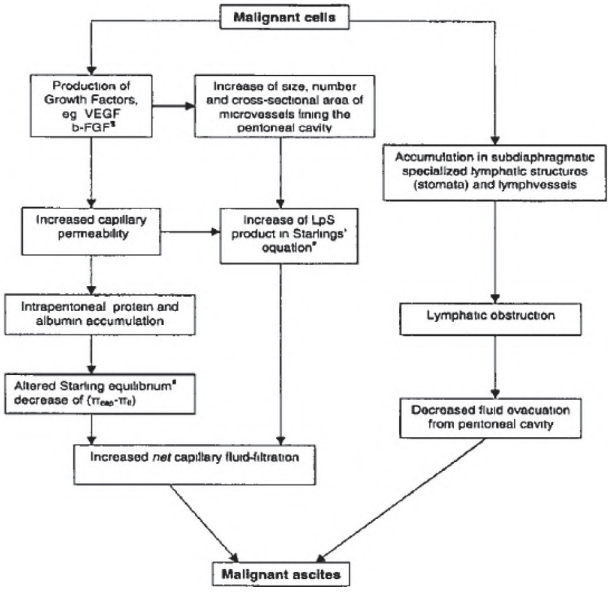

Figure 3. In this schematic drawing, the proposed pathogenesis of malignant ascites is summarized

This patient presented massive ascites, she had been evacuated 5 liter of fluid ascites on first day admission, and 3 liter on the next 2 days. The production of ascites was difficult to be controlled with diuretic and need to be evacuated periodically. This patient presented SAAG less than 1.1 showed increasing of osmolarity pressure intra peritoneal. The clinical presentations of ascites were supported diagnosis of malignant ascites and by cytology examination confirmed of adenocarcinoma ascites. According literature the most frequent causes was ovarian malignancy and gastric malignancy. [4,12] The imaging and tumor marker excluded the possibility of GI tract malignancy, then ovarian carcinoma was highly suspicious.

CA 125 was high in this patient. This data was supported to diagnosis of ovarian cancer.[8,9] But CA 125 is not specific and can be elevated in benign and physiological conditions as well as in other

Table 2. Examples of conditions associated with an elevation in serum Ca125 levels

Gynaecological	Miscellaneous
Endometriosis	Pericarditis
Fibroids	Polyarteritis nodosa
Hemorrhagic ovarian cysts	Renal disease (serum creatinine > 2.0
Menstruation	Sjogren's syndrome
PID (acute)	Systemic lupus erythematous
Pregnancy (first trimester)	
Gastro-intestinal / Hepatic	Malignancy
Acute pancreatitis	Ovary
Colitis	Breast
Chronic active hepatitis	Endometrium
Cirrhosis	Lung
Diverticulitis	Liver
	Pancreas
	Bladder
	Non-Hodgkin's lymphoma

malignancies as shown on table 2.[8,12] Goldstein, et al.[9,13] showed reactivity of CA 125 on 52% pancreatobilliary adenocarcinoma patients, whereas 82% on patient with ovarian adenocarcinoma. Vagenas, et al.[10,14] reported 5 cases of elevated CA 125 on peritonitis tuberculosis. One patient with severe condition presented high level of CA 125 (5,354 U/ml), while the other reached below 500 U/ml.

Based on Table 1, we can exclude the possibility of breast cancer, lung cancer, pancreas cancer, and bladder cancer; those because of lack evidence involved those organs, even though they could present adenocarcinoma cancer and increased level of CA 125. Analysis of imaging examination showed the negative result of CT scan, ambiguous result of abdominal USG. There were no clear clues for primary site of malignant ascites in any imaging examination. Computed tomography of the abdomen and pelvis results in the detection of a primary site for the cancer in 30 – 35% of patient's CT scans can also be helpful in evaluating the stage of the disease.[13] But abdominal CT scan may not be useful in detecting an occult primary site, because it is sometimes difficult to discern a small-mass lesion that is partly or completely submerged in a fluid of similar radiologic density. Specifically, in the evaluation of ovarian carcinoma, CT is often nonspecific for the detection of ovarian masses and small peritoneal metastases[1]

Colonoscopy and BNO showed outer obstruction of colon, this patient also suffered from chronic diarrhea, but the GI tract tumor marker was not supported to GI tract malignancy. The second USG gift clue for endometrial carcinoma with metastatic throughout the colon. This explained the outer obstruction of colon that showed from colonoscopy and barium enema. But kept in questioning whether endometrium cancer could present severe malignant ascites as this patient. The presentation of malignant ascites in endometrium cancer were rare, Wilailak, et al.[15] report only 6 cases of 65 patients (9.23%) with gynecologic malignancies who presented malignant ascites, and the opposite, the ovarian cancer had reported 80% from all gynecologic malignancies who presented malignant ascites.

Table 3. Accuracy of Invasive and Non Invasive Diagnostic Methods.[1]

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Clinical diagnosis	50%	97 %	71.4%	95%
USG diagnosis	80%	95.9 %	66.6%	97.9%
Laparoscopy / laparotomy	100%	100%	100%	100%

Clinical finding also not supported for diagnosis of endometrium cancer. She was never had history of bleeding discharge or fluor albus. The epidemiology of malignant ascites is mostly because of ovarian carcinoma rather than endometrial carcinoma. The pathophysiology leads us to achieve the explanation of ovarian carcinoma induced massive and over productive of malignant ascites. The algorithm of diagnostic and treatment also guide us to ovarian cancer. Those finding was reasonable to make the diagnosis of ovarian carcinoma. Staging must be performed for initiating treatment.

Laparotomy exploration aimed to diagnose the source of malignancy, and to define the stage of cancer. Unfortunately the progression of disease with milliary nodule metastatic and attachment of internal organ failed to identify the source of cancer.

SUMMARY

We reported a 62 years old female with malignant ascites of adenocarcinoma of unknown primary site. The data suggest this patient suffered from ovarian cancer rather than other site malignancy. The condition was improving after 5th chemotherapy.

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