Myxedema ascites with high CA-125: Case and a review of literature

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INTRODUCTION

Of the many nonspecific clinical manifestations of hypothyroidism, ascites is one of the least frequently reported and it accounts for less than 4% of cases[1]. Isolated cases of myxedema ascites have been reported in the absence of cardiac, hepatic and renal failure or peritoneal inflammation.

Frequently, other obvious signs of hypothyroidism are lacking and an inflammatory or malignant disease is suspected. Usually such patients are subjected to diuretic therapy, diagnostic laparotomies and paracentesis for long periods before hypothyroidism is diagnosed[2]. In such cases, the use of thyroid hormone replacement usually leads to a progressive decrease in ascites, which will ultimately disappear[3]. Therefore, when any patient presents with ascites of uncertain etiology, hypothyroidism should be considered as a differential diagnosis.

In some cases of ascites, CA-125 levels can be as high as those seen in patients with cancer, suggesting that any patient with ascites and a raised CA-125 concentration should have thyroid function measured as part of their initial evaluation. Here we describe a case of a patient with refractory ascites of unknown etiology, who was found to have severe hypothyroidism with high CA-125, that was diagnosed as myxedema ascites and

Abstract

Ascites appearing in a previously healthy female patient is usually ascribed to a variety of causes, among which, is a cancerous process, especially if it comes with a raised CA-125 level. Although the CA-125 antigen is present on more than 80% of malignant epithelial ovarian tissue of non-mucinous type, it is also found on both healthy and malignant cells of mesothelial and non-mesothelial origin. Myxedema ascites which is caused by hypothyroidism is a rare entity, but on the other hand is easy to treat. It is one of the differential diagnoses when the ascites is refractory to treatment and no other obvious cause can be identified. If the diagnosis is delayed, patients will frequently receive unnecessary procedures, while treatment has very good response rates and ascites resolve with serum CA-125 normalization after adequate hormonal treatment.
that responded to thyroid hormone replacement therapy.

**CASE REPORT**

A 78-year-old female was referred to our hospital because of a hip fracture after a fall. In the emergency room she was found to have severe abdominal distention due to ascites which she mentioned had been present for eight months; for this she had multiple abdominal paracentesis with recurrence of the ascites that the medical treatment prescribed failed to resolve.

Her past medical history was positive for acute right lower limb ischemia 4 years previously, for which she was treated with a vascular shunt. She did not smoke or consume alcoholic beverages.

On physical exam, her blood pressure was 130/80, her pulse 110 beats/min, her weight was 55 kg and her height was 163 cm. She was conscious, cooperative and well oriented. She was afebrile. Neck examination was normal. Cardio-pulmonary exam was normal. The abdomen was soft, distended, with a circumference of 101 cm. There was shifting dullness and fluid waves evident on palpation indicating the presence of ascites but without any stigmata of chronic liver disease. The liver and spleen were not palpable. No pretibial edema.

Complete blood count was normal. C-reactive protein was 28 mg/L. The prothrombin time and the activated partial thromboplastin time were normal. The liver function tests were normal. Amylase, lipase, total cholesterol, triglycerides, urea, creatinine and electrolytes were normal. The total protein level was 6 g/dL and albumin 2.9 g/dL. The urinalysis result showed numerous red blood cells, white blood cells and epithelial cells. Urine culture was negative. Hepatitis B and C serologies were negative. Cortisol 18.41 mg/dL (normal 5-25); Tumor markers (CEA, CA 15-3, CA 19-9) were negative except for an elevated CA-125 of 1255 U/mL (normal 0-35); negative Protein Purified Derivative (3 mm).

Chest radiology, electrocardiogram and Doppler ultrasound of the abdomen were normal. Abdominal ultrasound and computed tomography scan of the abdomen and pelvis (Figure 1) were performed showing marked ascites.

A diagnostic abdominal paracentesis yielded turbid yellowish, transparent ascitic fluid with a protein concentration of 4.1 g/dL, sugar 110 mg/dL and albumin 1.9 g/dL. The white blood cell count in the fluid was 100/mm³ and 90% of the cells were lymphocytes. Serum-to-ascites albumin gradient (SAAG) was 1 g/dL. On histological exam, no malignant cells were found. Gram staining and cytology were negative. Bacterial, fungal and mycobacterial cultures were also negative.

Gynecological evaluation showed no abnormalities. Echocardiography showed normal sized cardiac chambers, and an ejection fraction of 65%. With the high protein component of the ascites fluid, we performed thyroid function tests. These showed the following values: free T3 0.56 pg/mL (normal 2.2-4.4 pg/mL), free T4 < 0.08 ng/dL (normal 0.7-1.6 ng/dL) and thyroid-stimulating hormone level (TSH) > 100 mIU/mL (normal 0.2-5.0 mIU/mL). These findings necessitated further thyroid tests. The anti-thyroxin peroxidase was negative.

Ultrasoundography of the thyroid gland showed that both lobes were enlarged in size. Thyroid hormone replacement therapy was started with gradually increasing doses of levothyroxine, from 0.05 to 0.15 mg daily. Over the following three months, she became euthyroid with complete resolution of her ascites and CA-125 returned to normal. Her body weight decreased by 8 kg and the abdominal circumference was reduced by 12 cm. One year later, there had been no recurrence of ascites and her euthyroid condition was maintained.

**DISCUSSION**

Hypothyroidism is a relatively rare cause of ascites. However, the importance of its diagnosis is that use of thyroid hormone replacement results in complete resolution. If there is new onset ascites, diagnostic workup should begin with the analysis of ascitic fluid. Usually total protein in the ascitic fluid and the SAAG value give a useful framework for analysis. Of the various causes, peritoneal malignancies, tuberculous peritonitis, pyogenic peritonitis and pancreatic ascites can all lead to high-protein ascites. Patients with liver cirrhosis and congestive heart failure show low protein ascites. The SAAG corre-
lates directly with portal pressure. Ascitic fluid associated with portal hypertension shows a low total albumin level, and the SAAG is greater than 1.1 g/dL. (high gradient). SAAG is usually high in patients with liver cirrhosis and congestive heart failure. A gradient of < 1.1 g/dL. (low) usually suggests that the ascites is not caused by portal hypertension. The SAAG is low in patients with peritoneal malignancies, tuberculous peritonitis, pyogenic peritonitis and pancreatic ascites.

Portal hypertension secondary to liver cirrhosis is the leading cause of ascites (more than 80% of cases) and peritoneal involvement in patients with malignant diseases is the second at about 10%[6]. Therefore, if the composition of ascitic fluid and ultrasonography are not consistent with portal hypertension or other specific diseases, the physician should consider peritoneal malignancy. If the ascitic fluid shows a high protein content, then hypothyroidism should be considered as a differential diagnosis. In this patient, the ascitic fluid analysis revealed a high protein content (SAAG was < 1.1 g/dL) and there was a lack of esophageal varices or gastropathy on esophagogastroduodenoscopy without portal hypertension on abdominal ultrasound, we performed thyroid function testing, which proved decisive.

Prompt recognition of myxedema ascites prevents the inappropriate use of diuretics and unnecessary procedures, including repeated paracentesis, liver biopsies and exploratory laparotomies[10]. A constant feature was the positive response to thyroid hormone replacement therapy, which led to elimination of the ascites in every instance.

There has been a suggestion that the SAAG may exceed 1.1 in patients with myxedema ascites, based on a review of eight patients[9]. Because so few cases have been studied and portal hypertension or heart failure do not seem to be the mechanisms causing ascites in patients with myxedema, we cannot conclude that a high SAAG is a typical feature in this disease[10]. Moreover, the patient reported here showed a low SAAG.

The mechanism of ascites fluid formation in patients with myxedema is unclear. There are two main hypotheses. The first is that low levels of circulating thyroid hormones cause increased extravasation of plasma proteins because of abnormal capillary permeability and the lack of a compensatory increase in lymph flow and protein return rate[2]. The second hypothesis is that hyaluronic acid accumulates in the skin and produces edema by a direct hygroscopic effect. However, hyaluronic acid has only been found in minute quantities in patients with myxedema ascites; not large enough to exert a direct hygroscopic effect. It could, however, interact with albumin to form complexes that prevent the lymphatic drainage of extravasated albumin[5].

Although the CA-125 antigen is present on more than 80% of malignant epithelial ovarian tissue of non-mucinous type, it is also found on both healthy and malignant cells of mesothelial (pleural, pericardial, peritoneal, and endometrial) and non-mesothelial (amniotic membrane, tracheobronchial and cervical epithelium) origin. Raised serum CA-125 levels have therefore been reported in various conditions involving these cells, including pleural and pericardial effusions and ascites[10].

The mechanism of elevated CA-125 is not yet understood. Several theories have been proposed. One theory is that stretching of the peritoneum with ascites is a cause since paracentesis alone leads to a decrease in the serum value of CA-125. The other theory is that peritoneal cells shed a lot of CA-125 antigen and that it enters the blood via lymphatic absorption of ascites[4].

In conclusion, myxedema ascites is rare but easy to treat. Treatment with thyroid hormone replacement therapy leads to complete regression of the ascites. Once routine evaluation of ascites excludes common causes such as liver cirrhosis, peritoneal malignancies, infections, congestive heart failure and pancreatic ascites, thyroid function tests should be performed on patients with high protein levels in the ascitic fluid. A high CA-125 makes the diagnosis more difficult, but with extensive workup to rule out malignancies, it can be attributed to ascites. Early diagnosis is important to prevent inappropriate use of diuretics or even unnecessary laparotomies to determine the cause.

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