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A Rare Complication of Hypothyroidism: Myxedema Ascites

By Ramya Embar Srinivasan, MD, Susie Estes, MD, Mukta Panda MD,FACP

ABSTRACT

A 43-year-old white female with a history of hypothyroidism and not on her thyroid replacement for a year, presented with irregular periods, weight gain, hoarse voice, hair loss and abdominal distention with dyspnea. Physical exam was significant for thin hair, dry skin, decreased reflexes, non-pitting edema in her extremities, distant heart sounds and dullness on abdominal percussion. Thyroid-stimulating Hormone (TSH) level was 55 and free T4 was less than 0.4ng/dL. Four liters of straw-colored fluid removed by paracentesis revealed exudative effusion with total protein 6gm/dL, fluid white blood cell count 795 cells/mm³, lymphocytes 58%. Further evaluation to exclude other causes of high-protein ascites was negative, including malignant cells, bacterial cultures, acid fast bacilli stain and culture, urine protein and antinuclear antibody. Echocardiogram showed normal cardiac function with a large pericardial effusion without tamponade. Ultrasound of the liver was negative, as well as CT scan of the abdomen and pelvis, except for a large amount of ascites.

Discussion: The objective of this case report is to recognize that hypothyroidism causes high-protein ascites and must be included in the differential diagnosis of all high protein ascites, since it is an easily treatable condition. Ascites caused by hypothyroidism occurs in <4% of cases, thus the diagnosis is often delayed, and patients frequently receive unnecessary procedures such as liver biopsies and exploratory laparotomies. Review of the literature reveals that analyses of ascitic fluid from patients in this condition usually show high-protein (>2.5 g/dL) low white blood cell counts, with a high proportion of lymphocytes. Case reports of both high as well as low SAAG are documented. A consistent feature is the response to thyroid hormone replacement therapy, which leads to resolution of the ascites. We opted for watchful waiting with thyroid replacement once we excluded the most common causes of high-protein ascites without making the patient undergo extensive invasive workup.

INTRODUCTION

Hypothyroidism is one of the most common chronic disorders in the United States. Myxedema is defined as a disease caused by decreased activity of the thyroid gland in adults, characterized by dry skin, non-pitting edema, mental deterioration, and a subnormal basal metabolic rate. Roughly, 11 million American adults and children have this illness. It is most common in older women, affecting about 10 percent of this population. Hypothyroidism is probably greatly under-diagnosed; the 2001 Colorado health fair screening study found the condition in nearly 10 percent of 23,000 people not on thyroid medication.

Since only four percent of hypothyroid patients develop ascites as a complication, there is delay in diagnosis of myxedema-related ascites and patients may go undiagnosed for a long time. The diagnosis of myxedema-related ascites is important because thyroid hormone replacement is a definitive therapy leading to complete resolution of ascites. Therefore, when patients present with new onset ascites of uncertain etiology, hypothyroidism should be considered in the differential diagnosis.

We report a case of myxedema-related ascites and discuss the diagnostic characteristics of the ascitic fluid in hypothyroidism, and postulate a hypothesis for formation of serous cavity effusions in hypothyroidism.

CASE REPORT

A 43-year-old obese white female with a self-admitted history of hypothyroidism diagnosed in June 2010, presented to the emergency room in December 2011 with abdominal distension, dyspnea, irregular periods, weight gain, hoarseness and hair loss. She was not adherent with her thyroid replacement for over one year, and was not on any other medications.

There was no history of fever or cough, no yellow discoloration of eyes, no history of kidney disease or sick contacts. She did not smoke or consume alcohol and was a homemaker with no other significant past medical or family history. Surgical history included one cesarean section and abdominal hernia repair.

On examination, she appeared older than her stated age but not in any distress. She was afebrile, blood pressure was 132/80 mmHg, the pulse rate 56 beats/min, and she weighed 163kg with body mass index of 58kg/m².

The patient was alert and oriented. She had thin hair, dry skin and no jugular vein distension. Cardiac examination revealed distant heart sounds, no murmurs or gallops. The abdomen was markedly distended, non-tender, dull on percussion. No fluid thrill or shifting dullness could be demonstrated as the patient was obese, no distended veins noted on abdomen, and umbilicus was everted. All four extremities revealed non pitting edema with delayed reflexes. She had a yellowish tinge to her skin (Table 1).

Laboratory data revealed her white blood cell count was 7,900 cells/mm³, hematocrit 29.4% and platelet count was 268,000 cells/mm³, mean corpuscular volume 75 fL, serum alkaline phosphatase level was 52 u/L, total bilirubin 0.4 mg/dL, aspartate aminotransferase (AST) 6 U/L, alanine aminotransferase (ALT) 18 U/L, lipase 5 U/L, and serum triglycerides 275 mg/dL, low-density lipoprotein (LDL) 131 mg/dL, high-density lipoprotein (HDL) 27 mg/dL, total cholesterol 213 mg/dL, sodium 135 mmol/L. The serum total protein level was 7.1 g/dL and serum albumin 3.5 g/dL. Antinuclear antibody was negative, thyroid-stimulating hormone (TSH) 55 microIU/mL (prior level not known), free T4 was <0.4ng/dL. Urinalysis results were normal. HIV, Hepatitis B and C serologies were negative (Table 2).

Her initial chest radiograph showed findings of cardiomegaly with atelectasis on bilateral lung bases. CT abdomen and pelvis with contrast showed moderate ascites and grossly normal kidneys, liver, spleen, colon, rectum, gynecological structures (Figure 1).

Ultrasound guided paracentesis was performed and 4 liters of straw-yellow fluid was drained. Ascitic fluid analysis showed an elevated total protein (6 g/dL) and a low serum-to-ascites albumin gradient (SAAG; 0.1 g/dL) suggestive of an exudative effusion. The white blood cell count in the fluid was 795 cells/mm³, and 58% of the cells were lymphocytes, and 36% polymorphs. Gram staining and cytology were negative. Bacterial, fungal and mycobacterial cultures were also negative; adenosine deaminase (ADA) level was 42 U/L (normal range 0-24 U/L).

Transthoracic echocardiogram showed moderate pericardial effusion without significant tamponade physiology. Left ventricle was normal in size with ejection fraction greater than 55%.

Based on the above findings and review of literature, we diagnosed myxedema ascites with probable spontaneous bacterial peritonitis.

The patient had no history suggestive of coronary artery disease and was placed on thyroid replacement therapy. She was discharged home in a stable condition. A consistent feature is the response to thyroid hormone replacement therapy, which has always led to resolution of the ascites.

We opted for watchful waiting and close monitoring with thyroid replacement therapy once we had ruled out the common causes of high-protein ascites, avoiding extensive invasive workup.

DISCUSSION

Whether hypothyroidism results from hypothalamic-pituitary disease or primary thyroid disease, symptoms and signs of the disease vary in relation to the magnitude of the thyroid hormone deficiency, and the acuteness with which the deficiency develops. Hypothyroidism is less prominent clinically and better tolerated when there is a gradual loss of thyroid function (as in most cases of primary hypothyroidism) than when it develops acutely after thyroidectomy or abrupt withdrawal of exogenous thyroid hormone. The typical clinical manifestations of hypothyroidism may be modified by factors such as coexisting non-thyroidal illness.

Some of the common manifestations of hypothyroidism include constipation, anemia, decreased cardiovascular contractility, menstrual abnormalities, hypercholesterolemia, reversible increase in serum creatinine, carpal tunnel syndrome, peripheral neuropathy, skin and hair changes, and decreased drug clearance rate. Less than four percent of hypothyroid patients develop ascites as a complication.¹ Successful treatment of ascites depends on the accurate diagnosis of its cause. The most common causes of new onset ascites are cirrhosis of liver (80%), cancer (10%), heart failure (3%), tuberculosis (2%), dialysis (1%)² (Table 4). Hypothyroidism is the cause of ascites in less than one percent of new-onset ascites cases.²

Detailed history and physical examination are important in formulating a differential diagnosis for ascites and also prevent unnecessary diagnostic and invasive workups. In the current obesity epidemic, an obese abdomen can masquerade as ascites, potentially leading to inappropriate treatment with diuretics.

The description of the onset of symptoms may be helpful for distinguishing fat from ascites. Patients frequently seek medical attention within a few weeks of ascites development. The fluid usually accumulates rapidly, and patients are intolerant of the distension and the associated early satiety and shortness of breath. In contrast, the thickening abdominal wall and enlarging omentum associated with obesity develop over months or years.

History and physical examination of patients with suspected ascites must include risk factors for cirrhosis (history of liver disease, alcohol use, viral hepatitis, obesity, diabetes, hyperlipidemia, family history of liver disease). Questions need to be asked to determine history suggestive of cancer, tuberculosis, pancreatic disease, chronic kidney disease. Appropriate questioning and chart review may provide clues regarding these unusual causes of ascites formation.

Patients with ascites should be imaged to confirm or refute the presence of ascites, cirrhosis, or malignancy. Ultrasound is probably the most cost-effective modality. Another advantage of ultrasound is that it involves no radiation or intravenous access, and no risk of contrast allergy or nephropathy. Abdominal paracentesis with appropriate ascitic fluid analysis is the most efficient way to confirm the presence of ascites and diagnose its cause.

Usually total protein in the ascitic fluid and the SAAG value give a useful framework for analysis of whether the ascitic fluid is a transudate or an exudate. The total protein in the ascitic fluid is >2.5 g/dL in the exudate and <2.5 g/dL in the transudate. Of the various causes, peritoneal malignancies, tuberculosis peritonitis, pyogenic peritonitis and pancreatic ascites can all lead to high-protein ascites. Patients with liver cirrhosis or congestive heart failure show low protein ascites. SAAG of <1.1 g/dL (low) usually suggest the ascites is not caused by portal hypertension. The SAAG is low in patients with peritoneal malignancies, tuberculous peritonitis, pyogenic peritonitis and pancreatic ascites (Table 5).¹⁵

A review of the literature showed 51 well-documented cases of myxedema ascites (Tables 6, 7).¹

A consistent finding was the high total protein level (>2.5 g/dL). Total protein levels exceeded 2.5 g/dL in almost all cases, with a mean of 3.9 g/dL. The mean SAAG was 1.5 g/dL with a range of 0.8-2.3 g/dL and predominance of lymphocytes.¹

There has been a suggestion that the SAAG may exceed 1.1 in patients with myxedema ascites, based on a review of eight patients.¹ However, since the cases studied are small in number and portal hypertension or heart failure did 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. There have also been cases of myxedema ascites with low SAAG.¹

Our patient had high protein (>2.5 gm/dL) in the ascitic fluid, with low SAAG (0.1 gm/dL) and lymphocyte predominance. The other causes of high-protein and low-SAAG ascites were ruled out based on negative ascitic fluid bacterial cultures, acid-fast bacilli culture and stain, low ascitic fluid amylase level, negative malignant cells on cytology and cell block, and normal CT appearance of liver, spleen, kidneys and gynecological structures.

Interestingly, we found that this patient had probable spontaneous bacterial peritonitis based on ascitic fluid polymorph of 286 cells/mm³. There has been only one reported case of spontaneous bacterial peritonitis associated with myxedema ascites from the review of literature.⁵

Adenosine deaminase (ADA) level in the ascitic fluid was elevated in our patient and based on literature review indicated that the ascitic fluid ADA activity has good accuracy but poor sensitivity, and imperfect specificity in a United States patient population in which the prevalence of tuberculosis is low. False-positive ADA levels were noted in infection-related (non tuberculous) ascites, peritoneal carcinomatosis. Bayes Theorem predicts that a higher rate of spontaneous and secondary bacterial peritonitis in the United States further decreases the predictive values (both positive and negative) of ascitic fluid ADA activity.¹³

A review article on 51 well-documented cases of myxedema ascites noted that the consistent feature in myxedema ascites was a response to thyroid replacement therapy.¹ We started the patient on thyroid replacement therapy with levothyroxine 150 mcg daily dose and titrated the dose to 200 mcg during hospitalization, and discharged the patient home in a stable condition with this dose. The patient initially improved with resolution of abdominal distension and decrease in weight but unfortunately was non-adherent to the thyroid replacement therapy due to self-reported unaffordability of levothyroxine. She developed abdominal discomfort and abdominal distension three to four weeks after she stopped her levothyroxine. Unfortunately, the patient missed all her follow-up appointments in the endocrine clinic despite multiple phone calls informing her about the seriousness of her condition and the possibility of this worsening without thyroid replacement.

MECHANISM OF EFFUSIONS IN HYPOTHYROIDISM

The accumulation of fluids in serous body cavities in hypothyroidism is frequently recognized, the most common sites being the pleural, peritoneal and pericardial cavities. The precise mechanism of effusion formation in patients with myxedema is unclear.

Parving, et al., demonstrated that a combination of 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.³ Another 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. However, it could interact with albumin to form complexes that prevent the lymphatic drainage of extravasated albumin.⁴

Lange demonstrated that the capillary permeability increased in hypothyroidism with leakage of plasma proteins, and permeability returned to normal with thyroid replacement therapy.¹⁴

The cause for increased capillary permeability and protein extravasation in hypothyroidism is not clear. Studies have shown undetectable nitric oxide levels in congenital hypothyroid infants⁹ and decreased nitric oxide levels in thyroidectomized rats as well as hypothyroid patients.^{8, 10}

Recent studies have shown that a decrease in nitric oxide levels causes an increase in capillary permeability, increased plasma protein filtration out of the microvasculature and endothelial dysfunction.

Kubes, et al., demonstrated that inhibition of nitric oxide synthesis with the L-arginine analogue causes a rapid increase in vascular fluid filtration and vascular protein clearance and an increase in microvascular permeability.⁷ The study by Kurose, et al., suggested that the increased albumin leakage observed in postcapillary venules after inhibition of nitric oxide production involved a mechanism that included a role for cGMP, platelet activating factor, leukocyte-endothelial cell adhesion, and the endothelial cell cytoskeleton.⁶

Other studies suggest a decrease in nitric oxide levels causes oxidative stress-induced endothelial cell damage, activation of inflammatory cells like mast cells, and platelets, which release substances that increase micro vascular permeability.⁸

A decrease in nitric oxide levels has been suggested to cause endothelial dysfunction in hypothyroidism, contributing to reversible endothelial dysfunction. Nitric oxide is important for mobilization and differentiation of endothelial progenitor cell (EPC) ADMA (endothelial nitric oxide synthetase inhibitor), correlated inversely with the circulating EPC count and reduced in-vitro differentiation of EPC into endothelial tube-like structures in a dose-dependent manner in one study, whereas in another study, it was found to be increased in subclinical hypothyroidism (SCH) and significantly reduced after T4 therapy.¹¹

Vascular Endothelial Growth Factor (VEGF) also increases capillary permeability, and the levels of VEGF are elevated in patients with hypothyroidism and return to normal with thyroid replacement therapy.¹²

Based on the review of literature, we speculate that decreased nitric oxide levels and decreased endothelial progenitor cell count in hypothyroidism as well as increased activity of vascular endothelial growth factors and direct effect of TSH on endothelial cells cause increased capillary permeability and increased protein extravasation causing high-protein effusions in hypothyroidism (Figure 2).

CONCLUSION

In conclusion, myxedema ascites should be considered in the differential diagnosis of high protein ascites as treatment with thyroid hormone replacement therapy leads to complete regression of the ascites. On initial evaluation of ascites, routine investigations should be done to rule out the common causes and thyroid function tests performed on patients with high-protein ascites.

Though literature review shows no correlation between TSH level and ascites, further research focusing on measuring nitric oxide levels in ascitic fluid and other serous cavity effusions may be beneficial in better understanding the pathogenesis of effusions in hypothyroidism.

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Table 1. Pertinent physical exam findings.

Vital Signs		Pertinent Physical Findings
Temperature	98.7 F	Appeared older than stated age
Blood Pressure	132/80 mmHg	Thinning hair, dry Skin
Heart Rate	56 beats/min	Distant heart sounds

Respiratory Rate	12/min	Dullness on abdominal percussion
Oxygen Saturation on Room Air	98%	Non-pitting edema in extremities
Body Mass Index	58Kg/m ²	Delayed reflexes

Table 2. Relevant laboratory data.

Laboratory Findings	Patients results
White Blood Cell count	7900 cells/mm ³
Hematocrit	29.4%
Platelet count	268,000 cells/mm ³
Creatinine	1 mg/dL
ALT	18 U/L
AST	6 U/L
Alkaline Phosphatase	52 U/L
Total Protein	7.1 gm/dL
Serum Albumin	3.5 gm/dL
TSH	55 microIU/ml (prior level not available)
Free T4	<0.4 ng/dL
Anti Nuclear Antibody	Negative
Serum triglycerides	275 mg/dL
HIV	Negative
Hepatitis Panel	Negative

Table 3. Ascitic fluid analysis.

Ascitic Fluid Parameters	Patient's Results
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Amount	4 liters
Color	Straw Yellow
Total protein	6 gm/dL
Albumin	3.4 gm/dL
Serum Ascites Albumin Gradient (SAAG)	0.1 gm/dL
Total WBC count	795 cells/mm ³
Total RBC count	1070 cells/mm ³
Lymphocytes %	58%
Polymorphs %	36%
Malignant cells	Negative
Acid Fast Bacillus stain and culture	Negative
Bacterial gram stain and culture	Negative
LDH	345 units/L
Triglycerides	117 mg/dL
Adenosine deaminase	42 units/L (Normal Range:0-24 units/L) ¹⁵

Table 4. Causes of Ascites.

Cirrhosis	81%
Cancer	10%
Heart Failure	3%
Tuberculosis	2%
Dialysis	1%
Pancreatic Disease	1%
Hypothyroidism	<1%
Others	2%

Table 5. Causes of high and low SAAG Ascites.

High SAAG(>1.1gm/dl)	Low SAAG(<1.1gm/dl)
Cirrhosis	Tubercular Ascites
Alcoholic Hepatitis	Pyogenic Ascites
Heart Failure	Peritoneal carcinomatosis

Table 6. Characteristics of reported patients with Myxedema Ascites.

*From Ji JS, Chae HS, Cho YS, Kim HK, Kim SS, et al. Myxedema Ascites: Case Report and Literature Review. J Korean Med Sci 21(4):761-4, Aug

	# of patients	Mean	Ranges	Remarks
Ascitic protein (gm/dl)	49	3.9	1.8-5.1	48 patients(98%) showed ascites protein levels >2.5gm/dl
SAAG(serum ascites albumin gradient)(gm/dl)	11	1.5	0.8-2.3	Small sample size
Ascites WBC count (per micro L)	48	60	10-4000	Predominance of lymphocytes (mean 81%)
Duration of ascites	51	8 months		1 year to 8 years

Response to treatment	51		Regression of ascites
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Table 7. Characteristics of Ascitic Fluid in Hypothyroidism.

Parameters	Literature review	Patient Data
Ascites Protein	Usually >2.5gm/dl	6gm/dl
Ascites WBC count	Lymphocytic predominance	58% lymphocytes
Serum Ascites Albumin Gradient (SAAG)	Limited Data	0.1gm/dl

Figure 1. CT abdomen and pelvis with contrast demonstrating significant ascites, indicated by white arrows.

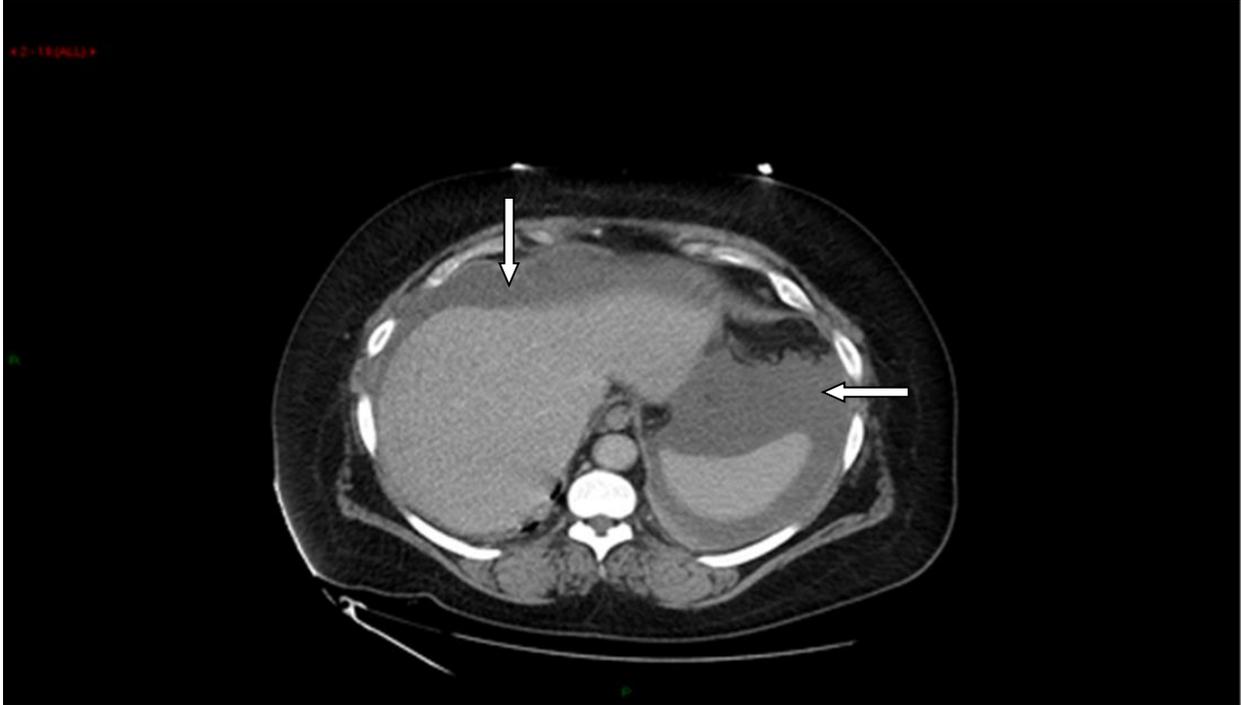


Figure 2. Probable mechanism of high protein effusions in Myxedema.

