

WHAT IS YOUR CALL?

Severe edema and elevated CA 125 in a 56-year-old woman

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A 56-year-old woman of Chinese ethnicity presented to hospital with worsening shortness of breath. She had an 18-month history of progressive generalized edema with ascites. She reporting having no chest pain, abdominal pain, nausea, vomiting, diarrhea, urinary symptoms, joint pain or rash, and the remainder of the functional inquiry was unremarkable.

Systemic lupus erythematosus had been diagnosed five years earlier on the basis of arthritis, photosensitivity, pericardial effusion, markedly elevated titres of antinuclear antibodies (ANAs) and the presence of antibodies against double-stranded DNA (dsDNA). She was taking a stable daily dose of prednisone (5 mg) and azathioprine (100 mg). She had been receiving weekly infusions of albumin and oral diuretics without improvement of the edema or ascites.

One year before presentation, investigations performed to determine the cause of the ascites showed an elevated level of cancer antigen 125 (CA 125), and an ovarian mass was detected by computed tomography. There was ovarian cancer in the patient's family history. She underwent hysterectomy and bilateral salpingo-oophorectomy because of concern that the ascites was caused by ovarian carcinoma. Pathologic specimens obtained at the time of surgery revealed a benign ovarian cyst and no evidence of malignant disease.

The patient worked in an office, but she had been unable to work for the past year because of severe edema. Her dietary history was unremarkable. She had no history of smoking or excessive alcohol intake, and she did not use street drugs.

Physical examination showed a heart rate of 93 beats/min, blood pressure of 118/78 mm Hg, oral temperature of 37.0°C, respiratory rate of 30 breaths/min with increased respiratory effort, and oxygen saturation of 93% on 3L supplemental oxygen. She had normal jugular venous pressure and soft heart sounds without any murmurs. She had reduced breath sounds on the left side without crackles or wheezing. There were moderate

ascites, grossly edematous chest and abdominal walls, and severe pitting edema of her upper and lower extremities. She was not cachectic.

The patient had normocytic anemia with a hemoglobin level of 95 (normal 120–140) g/L and a mean corpuscular volume of 88 (normal 82–97) fL. Her leukocyte and platelet counts were normal. Her erythrocyte sedimentation rate was elevated (133 [normal < 20] mm/h), and her C-reactive protein level was 4.3 (normal < 5.0) mg/L. Her serum albumin level was low (< 10 [normal 35–50] g/L), as was her total protein level (34 [normal 60–80] g/L). Her serum creatinine level was 62 (normal 42–102) μ mol/L. The levels of liver enzymes and total bilirubin were normal. Her thyroid stimulating hormone level was 1.40 (normal 0.40–5.50) mU/L. Her international normalized ratio was 0.89, and her CA 125 level was above normal (278 [normal < 34] U/mL). Urinalysis showed 3+ protein and moderate blood. A radiograph of her chest showed a large pleural effusion on the left side without any other major abnormalities. An electrocardiogram showed normal sinus rhythm and low voltages.

What is your diagnosis?

- Occult ovarian cancer
- Severe hypoalbuminemia
- Heart failure
- Liver cirrhosis
- Venous obstruction

The differential diagnosis for this patient's presentation is broad. However, the most likely diagnosis is (b) severe hypoalbuminemia, which would account for the generalized edema, pleural effusion and ascites. Her dyspnea can be attributed to the large pleural effusion on the left side.

The triad of ascites, pleural effusion and an ovarian mass has classically been associated with benign ovarian tumours (Meigs syndrome), ovarian carcinoma or metastatic gastrointestinal malignancy (pseudo-Meigs syndrome).¹ The

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patient's elevated level of CA 125 and the ovarian mass detected one year earlier were suggestive of cancer. However, it is important to recognize that an elevated level of CA 125 in conjunction with ascites and pleural effusion can occur in patients with active systemic lupus erythematosus in the absence of malignant disease.^{2,3} The increased synthesis of CA 125 has been attributed to activated peritoneal mesothelial cells. This mechanism is the likely explanation for the patient's elevated CA 125 level, which persisted long after surgical removal of her ovaries. The ovarian cyst was, therefore, almost certainly an incidental finding.

The diagnoses of heart failure and liver cirrhosis are relatively unlikely given the patient's lack of typical risk factors for these conditions, her clinical course and the findings of the physical examination. Nonetheless, further investigations to rule out these diagnoses are indicated. A cardiac assessment is particularly relevant because systemic lupus erythematosus is associated with an increased risk of coronary artery disease as well as verrucous (Libman-Sacks) endocarditis causing valvular insufficiency and embolization.

In this patient's case, transthoracic echocardiography showed normal left ventricular function, normal heart valves and a small pericardial effusion without echocardiographic evidence of tamponade. Abdominal ultrasonography showed that her liver appeared normal; it also showed

moderate to severe ascites and bilateral echogenic renal cortices consistent with medical renal disease. The results of serologic tests for hepatitis B were negative.

The patient underwent thoracentesis, with notable improvement in her dyspnea after the removal of 1.5 L of fluid. The results of pleural fluid analysis were consistent with transudate. A 24-hour urine collection resulted in 0.82 grams of protein per 24 hours and a creatinine clearance of 40 mL/min.

Further investigations showed that her ANA level was elevated at 14.1 (normal < 1.0) and that her complement 3 (C3) and 4 (C4) levels were low (C3: 0.38 [normal 0.79–1.52] g/L; C4: 0.10 [normal 0.16–0.38] g/L). An extractable nuclear antigen screen was strongly positive for anti-SSA (Ro), anti-Smith and anti-ribonucleoprotein antibodies. An enzyme-linked immunosorbent assay (ELISA) showed that her anti-dsDNA level was elevated (127 [normal < 25] IU/mL). A test for anti-tissue transglutaminase IgA was negative, and she had normal levels of total IgA.

What is the cause of the patient's hypoalbuminemia?

- Decreased synthesis of albumin because of malnutrition
- Decreased synthesis of albumin due to hepatic dysfunction
- Loss of albumin due to nephrotic syndrome
- Loss of albumin because of protein-losing enteropathy

The patient's history and the results of the clinical examination were not consistent with malnutrition, and there was no evidence of hepatic dysfunction. The presence of proteinuria and hematuria suggest the possibility of active lupus nephritis, which, in some patients, can be associated with nephrotic syndrome and hypoalbuminemia. However, the modest degree of proteinuria seen in this patient's case (less than 1 g/d in the non-nephrotic range) cannot account for her profound hypoalbuminemia. A normal adult liver is capable of synthesizing albumin at a rate of at least 15 g/d. The cause of her hypoalbuminemia was, therefore, (d) loss of albumin due to protein-losing enteropathy.

Protein-losing enteropathy can be caused by many conditions, which can be broadly classified into three main categories: mucosal inflammation with ulcers or erosions; increased mucosal permeability without ulcers or erosions; and loss of lymphatic fluid due to lymphatic obstruction (Box 1).

Box 1: Major causes of protein-losing enteropathy^{4,5}

Erosive mucosal inflammation

- Inflammatory bowel disease
- Malignant disease (e.g., gastric cancer, lymphoma)
- Severe chronic peptic ulcer disease
- Severe *Clostridium difficile* infection
- Acute graft-versus-host disease

Increased mucosal permeability without ulcers or erosions

- Celiac disease
- Hypertrophic gastropathy
- Connective tissue diseases (e.g., systemic lupus erythematosus, mixed connective tissue disease, intestinal vasculitis)
- Tropical sprue
- Collagenous colitis
- Lymphocytic gastritis
- Eosinophilic gastroenteritis
- Amyloidosis
- Infections (e.g., bacterial overgrowth, Whipple disease, parasitic infections)

Lymphatic obstruction with increased interstitial pressure

- Primary intestinal lymphangiectasia
- Secondary lymphatic obstruction (e.g., right-sided heart failure, Fontan procedure, constrictive pericarditis, retroperitoneal lymph node disease, portal hypertension)

How would you confirm the diagnosis?

- Fecal clearance of α -1-antitrypsin
- Direct endoscopic visualization
- Intestinal biopsy
- Tc 99m radiolabelled albumin scintigraphy
- Magnetic resonance imaging of the abdomen and pelvis

The diagnosis of protein-losing enteropathy can be made based on the results of (a) fecal clearance of α -1-antitrypsin or (d) Tc 99m radiolabelled albumin scintigraphy. Alpha-1-antitrypsin does not undergo enzymatic degradation in the gut, has a molecular weight similar to that of albumin and is not actively absorbed or secreted. These properties allow it to be used to provide a reliable estimate of enteric protein loss through simultaneous measurement of plasma and fecal levels of α -1-antitrypsin. In our patient's case, the 24-hour fecal clearance of α -1-antitrypsin was abnormally elevated (35 [normal < 22] mL per 24 h) and her serum α -1 antitrypsin level was low (0.74 [normal 0.89–1.92] g/L). Tc 99m radiolabelled albumin scintigraphy was not performed because of difficulty obtaining this agent.

Endoscopic visualization of the gastrointestinal tract and intestinal biopsy can identify many of the possible causes of protein-losing enteropathy, but this test usually does not provide a definitive diagnosis in patients with lupus. Our patient underwent upper endoscopy and colonoscopy, which showed punctate red lesions in the sigmoid and transverse colon. Biopsies of her stomach, duodenum, cecum and multiple sites in the colon were unremarkable.

The diagnosis of protein-losing enteropathy due to systemic lupus erythematosus was made. Her proteinuria was attributed to coexisting lupus nephritis, but a renal biopsy was not felt to be indicated. The patient's dose of prednisone was increased to 60 mg/d. Within two weeks, her edema and ascites had almost entirely resolved, and her dyspnea had greatly improved.

Discussion

The diagnosis of protein-losing enteropathy should be considered for patients with hypoalbuminemia that cannot be explained by malnutrition, hepatic dysfunction or nephrotic syndrome. The absence of gastrointestinal symptoms does not rule out protein-losing enteropathy. Delays in making this diagnosis can lead to substantial morbidity, as was the case for our patient.

Protein-losing enteropathy is an uncommon manifestation of systemic lupus erythematosus and

has an estimated prevalence of 3.2% among Chinese patients with systemic lupus erythematosus.⁶ Protein-losing enteropathy is classified under the category of increased mucosal permeability without ulcers or erosions.⁶ This condition may be part of the initial presentation of systemic lupus erythematosus, or it may occur years after the diagnosis is made. About half of all patients with protein-losing enteropathy do not experience diarrhea.

Several pathophysiologic mechanisms have been proposed, including increased mesenteric vascular permeability from intestinal vasculitis, immune complex- and cytokine-mediated vasodilation, and lymphatic dilatation; however, histologic evidence of these mechanisms is often absent.

Treatment

Treatment of protein-losing enteropathy is directed at the underlying cause.^{4,5} In most cases, protein-losing enteropathy will resolve if the underlying condition can be successfully treated or controlled. Recommendations for supportive therapy with intermittent albumin infusions and a high protein diet with medium-chain triglyceride supplementation are based on expert opinion and case reports; there have been no randomized trials of therapy.⁵

Evidence regarding treatment of protein-losing enteropathy in patients with lupus is based on small observational studies.⁶ These studies indicate that this condition has an excellent prognosis, with more than 90% of patients responding to high-dose corticosteroids alone or in combination with azathioprine or cyclophosphamide.⁶

This patient's case illustrates the fact that elevated CA 125 levels in the context of systemic lupus erythematosus must be interpreted carefully and that elevated CA 125 does not necessarily indicate the presence of malignant disease.

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