84-Year-Old Man With Respiratory Distress and Abdominal Distention

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An 84-year-old man presented to his local hospital after falling from his wheelchair. He had tachypnea and abdominal distention. Chest radiography revealed a right-sided pleural effusion, and abdominal radiography showed dilated loops of bowel, suggestive of bowel obstruction. The patient was then transferred to our hospital for further work-up.

The patient reported worsening of shortness of breath and abdominal distention for the past few weeks. He had a 1-year history of early satiety, nausea, and dyspepsia but had noted no weight loss. The patient was taking omeprazole for peptic ulcer disease. Recently, after positive findings on a urea breath test, metronidazole and clarithromycin were initiated for treatment of *Helicobacter pylo*ri. The patient's medical history also included type 2 diabetes, benign prostatic hyperplasia, and hypertension for which he was taking aspirin, glipizide, lisinopril, and finasteride. He was a former smoker who had quit 50 years ago.

Physical examination revealed the following: temperature, 36.4° C; blood pressure, 108/58 mm Hg; regular pulse rate, 103 beats/min; respiratory rate, 26 breaths/min; and oxygen saturation of 93% while breathing 3 L of oxygen. The patient was visibly tachypneic, with diffuse expiratory wheezing and decreased breath sounds in the right base. His abdomen was distended with bulging flanks and a positive fluid wave.

Important laboratory values on admission included the following (reference ranges provided parenthetically): hemoglobin, 10.4 g/dL (13.5-17.5 g/dL); white blood cells, 12.2 x 10^9/L (3.5-10.5 x 10^9/L); platelets, 348 x 10^9/L (150-450 x 10^9/L); sodium, 134 mEq/L (135-145 mEq/L); bicarbonate, 21 mEq/L (22-29 mEq/L); blood urea nitrogen, 35 mg/dL (8-24 mg/dL); creatinine, 1.5 mg/dL (0.8-1.3 mg/dL); chloride, 103 mmol/L (100-108 mmol/L); glucose, 160 mg/dL (70-100 mg/dL); aspartate aminotransferase, 15 U/L (17-59 U/L); total bilirubin, 0.3 mg/dL (0.1-1.0 mg/dL); albumin, 2.9 g/dL (3.5-5.0 g/dL); and lactate, 0.78 mmol/L (0.6-2.3 mmol/L).

Abdominal computed tomography without contrast medium showed a moderate amount of ascites, moderate right-sided pleural effusion, and a mildly nodular configuration of the liver. Thoracentesis resulted in removal of 1 L of serosanguineous fluid. Pleural fluid lactate dehydrogenase (LDH) was 724 U/L, total protein was 4.1 g/dL, glucose was 121 mg/dL, and pH was 7.7. The total nucleated cell count was 1196 U/L, with differential of neutrophils at 46%, lymphocytes at 5%, monocytes at 2%, and eosinophils at 2%. The serum LDH level was 200 U/L, and the serum protein level, 5.7 g/dL.

1. Which <u>one</u> of the following is the <u>most likely</u> cause of this patient's pleural effusion?

a. *Congestive heart failure*
b. *Pneumonia*
c. *Malignancy*
d. *Pulmonary embolism*
e. *Cirrhosis*

The first step in the evaluation of the pleural fluid is to determine whether it is a transudate or exudate. On the basis of criteria from Lights et al,[1] an exudate has a pleural fluid protein to serum protein ratio greater than 0.5, pleural fluid LDH to serum LDH greater than 0.6, or pleural fluid LDH greater than two-thirds the upper limit of the laboratory's normal serum LDH level. Fulfilling any of these 3 criteria indicates an exudate, and in this patient all 3 criteria are met.

Overall, congestive heart failure is the most common cause of pleural effusions,[2] but it causes a transudative effusion and is most often bilateral. Our patient had no history of heart failure, his effusion was an exudate, and it was unilateral. Pneumonia is the second most common cause of a pleural effusion,[2] and parapneumonic effusions usually have a neutrophil-predominant total nucleated cell count greater than 10,000 U/L. Our patient's cell count was 1196 U/L, and he had no cough or other symptoms suggestive of infection. Malignancy is the third most common cause of a pleural effusion.[2] Pleural fluid associated with malignancy can have an elevated total nucleated cell count, although it is usually lower than 5000 U/L and can be lymphocyte predominant. Given our patient's pleural fluid analysis and clinical symptoms, malignancy is the most likely etiology.

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See end of article for correct answers to questions.

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Pulmonary embolism is the fourth most common cause of a pleural effusion, which is almost always exudative. Such effusions are usually small, and the red blood cell count can be elevated. Cirrhosis is a less common cause of a transudative pleural effusion. Patients with cirrhosis and ascites can develop hepatic hydrothorax.[2] Although our patient did have ascites and a nodular liver, he had no history of cirrhosis, he had normal results on liver function tests, and his pleural effusion was exudative.

Because of the exudative nature of the pleural fluid, low cell count, and clinical presentation, malignancy was highly suspected. While cytologic results of the pleural fluid were pending, paracentesis was performed and resulted in removal of 5 L of serous fluid.

2. Which one of the following laboratory tests is least likely to yield useful information in the analysis of the ascitic fluid?

a. *Cell count and differential*
b. *Gram stain*
c. *Albumin*
d. *Total protein*
e. *Cytology*

Cell count and differential are very important for the diagnosis of spontaneous bacterial peritonitis, which is diagnosed by an ascitic fluid neutrophil count greater than 250 cells/mm^3. Because our patient has new-onset ascites, spontaneous bacterial peritonitis must be ruled out. Gram stain is usually not helpful in the analysis of ascitic fluid because it has low sensitivity to detect bacteria; however, it can be helpful if perforation of the gut is suspected.[3] Our patient was not experiencing abdominal pain and perforation of the gut was not a concern; therefore, a gram stain would not be helpful. The albumin value is important in the analysis of ascitic fluid because it is used to calculate the serum-ascites albumin gradient (SAAG). SAAG is calculated by subtracting the ascitic fluid albumin value from the serum albumin value. A SAAG greater than or equal to 1.1g/dL is most commonly associated with portal hypertension but can also be seen with congestive heart failure and Budd-Chiari syndrome. A SAAG less than 1.1 g/dL is associated with peritoneal carcinomatosis, peritoneal tuberculosis, pancreatitis, serositis, and nephrotic syndrome.[4] The total protein value is also helpful in narrowing the differential diagnosis of ascites. If the SAAG is less than 1.1 g/dL and the ascites protein is less than 2.5 g/dL, the fluid is most likely associated with nephrotic syndrome, whereas an ascites protein greater than 2.5 g/dL is associated with malignancy or tuberculosis.[4] Therefore, determining total protein and albumin levels is essential in the classification of ascites. Cytologic testing is not usually included in the initial screening of ascites. However, if there is high suspicion for malignancy, as in our patient, cytologic tests should be performed.

The patient's ascitic fluid showed a total nucleated cell count of 463 U/L (2% neutrophils), total protein of 3.8 g/dL, and albumin of 2.2 g/dL. Given the SAAG of less than 1.1 g/dL and total protein value greater than 2.5 g/dL, the clinical picture is consistent with abdominal tuberculosis or malignancy. Cytologic test results of the pleural and peritoneal fluid were positive for adenocarcinoma with signet ring features.

3. Which one of the following is the next best step in the care of this patient?

a. *Esophagogastroduodenoscopy (EGD) to locate the primary site of the malignancy*
b. *Positron emission tomography (PET) for staging of the malignancy*
c. *Surgical consultation for removal of the primary tumor*
d. *Oncology consultation to discuss systemic chemotherapy*
e. *Offering of symptomatic treatment only*

Ninety-nine percent of signet ring cell carcinomas originate in the stomach.[5] Because gastric cancer is the most likely diagnosis, EGD would be helpful to definitively locate the primary cancer. However, our patient has distant metastasis, and thus further invasive diagnostic testing is not absolutely necessary. After cancer is diagnosed, PET is often performed to evaluate metastatic disease; however, it is clear that the disease is advanced, and findings on PET would not change the initial management. Therefore, although performing both PET and EGD would be a reasonable next step, neither is the next best step at this point. Surgery is the primary treatment of gastric cancer. However, it is not an option in our patient because of metastatic disease. Systemic chemotherapy is an option for patients with metastatic gastric cancer and can increase survival.[6] Therefore, an oncologist should evaluate patients with newly diagnosed metastatic cancer to determine whether they would benefit from chemotherapy or clinical trials. Offering only supportive measures is inappropriate because the decision to provide palliative chemotherapy is complex and should be made in the context of discussing available options with an oncologist.

Consultation with oncology determined that the patient's functional status was poor and that he was not a candidate for systemic chemotherapy. After a discussion with his family, the patient elected to pursue best supportive care. He continued to have difficulty breathing after a few days in the hospital. Repeated chest radiography revealed reaccumulation of fluid around the right lung.

4. Which one the following is the most appropriate way to treat the patient's recurrent pleural effusions?

a. *Chest tube thoracostomy and chemical pleurodesis*
b. *Pleuroperitoneal shunt*
c. *Long-term indwelling pleural catheter*
d. *Repeated therapeutic thoracenteses*
e. *Observation and symptomatic management of dyspnea*

Chest tube thoracostomy combined with chemical pleurodesis is the most commonly used treatment of malignant pleural effusions. In this procedure, a tube is inserted into the pleural space, and a sclerosing agent is instilled. Although this procedure is highly effective, it is expensive, invasive, and associated with pain and prolonged hospitalization and therefore is not ideal for a patient with a very limited lifespan.[7] Pleuroperitoneal shunts transfer pleural fluid from the pleural space into the peritoneal cavity and are used in cases of refractory effusions that are unresponsive to chemical pleurodesis.[7] However, we do not know yet whether our patient has refractory effusions, and therefore a pleuroperitoneal shunt would be inappropriate. In addition, transferring fluid into the peritoneal space would worsen his ascites. Insertion of a long-term indwelling pleural catheter is the preferred method of treating malignant effusions in patients who request palliative care. It is less expensive and minimally invasive compared with the aforementioned methods and represents the best option in our patient. Repeated therapeutic thoracentesis is also an option for patients with a very limited life expectancy. However, it is associated with a reduced quality of life because of recurrent hospital visits and painful procedures; additionally, fluid often reaccumulates rapidly.[7] At this point in the patient's care, survival may be months, and therefore recurrent thoracentesis is not the best option. Although the patient's condition is terminal, simple observation would be inappropriate for a symptomatic malignant pleural effusion.

Therefore, an indwelling pleural catheter was placed, and the patient's dyspnea improved. However, he reported persistent nausea.

5. Which one the following is the most effective initial management for his nausea?

a. *Upper endoscopy with placement of self-expanding metal stent if indicated*
b. *Local radiation therapy*
c. *Metoclopramide*
d. *Prochlorperazine*
e. *Corticosteroids*

The most effective way to relieve nausea associated with obstruction due to gastric cancer is placement of a self-expanding metal stent.[8] This procedure is minimally invasive and often successful in relieving symptoms of obstruction. Our patient preferred this option; however, on the basis of the site and size of the tumor, a stent could not be placed. Local radiation therapy can sometimes be used as a palliative treatment of obstruction, pain, or bleeding associated with gastrointestinal malignancies. However, gastric cancer is minimally responsive to radiation, and therefore this treatment modality should be used only if response is poor to other forms of management.[8] Metoclopramide can be helpful in treating nausea associated with gastric stasis or partial obstruction, which occurs in patients with carcinoma of the stomach. However, prokinetic agents should be avoided in patients with complete bowel obstruction. Prochlorperazine is another antiemetic agent that is effective in treating nausea associated with cancer-related bowel obstruction. Both metoclopramide and prochlorperazine would be reasonable choices if stenting was not possible. Corticosteroids, such as dexamethasone, are also helpful in the treatment of nausea associated with partial or complete bowel obstruction. However, they should be considered if stenting is not an option.[9]

The patient responded to metoclopramide and prochlorperazine after stenting was unsuccessful. He remained in the hospital but continued to deteriorate. He died 8 days after gastric cancer had been diagnosed.

DISCUSSION

Gastric cancer is the fourth most common cancer worldwide, with the highest incidence in Japan, China, and South America. Gastric cancer is rare in the United States, with only 21,500 cases diagnosed each year. The incidence of gastric cancer in the United Stated is highest in African Americans, Hispanic Americans, and Native Americans. In addition, the disease is twice as common in men vs women.[10] Gastric cancer is largely asymptomatic in the early stages and therefore is often diagnosed in the late stages, with 70% to 80% of patients having lymph node metastasis at presentation.[11] The 5-year survival rate for all stages is 26%.[12]

Many lifestyle risk factors are associated with the development of gastric cancer. Patients who eat a diet high in salt and nitrates and low in fruits and vegetables are at higher risk of developing gastric cancer. Smoking also increases the risk of gastric cancer.[8] Genetic risk factors include a family history of gastric cancer and type A blood.[10]

Long-term *H pylori* infection is a predisposing factor for the development of gastric cancer. *H pylori* infection increases the risk of developing gastric cancer by 2-fold.[8] *H pylori* is thought to lead to chronic immune stimulation and chronic gastritis, which can lead to intestinal metaplasia and dysplasia. Treating the infection can decrease the

development of dysplasia.[13] Less common precursor conditions for gastric cancer include pernicious anemia, Ménétrier disease, Barrett esophagus, and hereditary nonpolyposis colon cancer syndrome.[10]

Currently, routine screening for gastric cancer is recommended in high incidence countries, such as Japan.[10] The issue of mass population screening programs for gastric cancer in the United States is controversial but is not currently recommended. Surveillance with endoscopy can be considered in high-risk patients, such as those with a family history of gastric cancer, preexisting intestinal metaplasia or dysplasia, or other precursor conditions as aforementioned.[13]

Gastric cancer is often asymptomatic with few associated physical examination findings in early-stage disease. In later stages, it can present with weight loss, abdominal pain, nausea, anorexia, dysphagia, and an abdominal mass. Additionally, late stages of gastric cancer can present with adenopathy, such as left supraclavicular adenopathy (Virchow node) or a periumbilical nodule (Sister Mary Joseph nodule). Moreover, gastric cancer can be associated with paraneoplastic manifestations, such as diffuse seborrheic keratosis (Leser-Trelat sign), acanthosis nigricans, microangiopathic hemolytic anemia, and membranous nephropathy.[10] Malignant ascites can be a late presentation of gastric cancer. Gastric cancer accounts for about 18% of malignant ascites.[14] Although gastric cancer can metastasize to the lung, it is a rare cause of a malignant pleural effusion, representing about 2% of malignant pleural effusions.[15]

Gastric cancer is diagnosed with upper endoscopy. After diagnosis, it is staged with computed tomography of the chest, abdomen, and pelvis. PET and endoscopic ultrasonography are optional. After diagnosis, the patient should be tested for *H pylori* if this has not already been done.[11] Surgery is the primary treatment of gastric cancer, with the goal being complete resection. Some patients may benefit from multimodality treatment, such as postoperative chemoradiation or perioperative chemotherapy.[16,17] However, when there are distant metastases, surgery is no longer an option for most patients; treatment depends on the patient's functional status. Patients with high performance scores may be offered palliative chemotherapy or involvement in a clinical trial.

Different strategies are involved in the supportive care of a patient with metastatic gastric cancer. The most important symptoms associated with gastric cancer are often related to gastric obstruction, including nausea, fullness, and vomiting. The preferred method of treatment for these symptoms is endoscopic placement of a self-expanding stent.[8] When malignant ascites occurs, it can worsen nausea. Therapeutic paracentesis can be performed to improve nausea, and if recurrence is rapid, a permanent drain can be placed. This procedure is usually performed in patients with a life expectancy of more than 2 to 3 months.[14] If the patient continues to experience symptoms of nausea, prokinetic agents, dopamine antagonists, and corticosteroids can he helpful.[9]

Gastric cancer is rare in the United States and often presents at a late stage. Gastric cancer should be suspected in patients older than 55 years with new-onset dyspepsia, decreased appetite, or weight loss. Because gastric cancer often presents as metastatic disease, it is important to know the appropriate diagnostic and therapeutic approach. If the cancer is known to be metastatic and the patient has a poor functional status, emphasis should be placed on supportive care and comfort.

REFERENCES

1. Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med*. 1972;77:507-513.

2. Porcel JM, Light RW. Diagnostic approach to pleural effusion in adults. *Am Fam Physician*. 2006;73:1211-1220.

3. Runyon BA, Canawati HN, Akriviadis EA. Optimization of ascitic fluid culture technique. *Gastroenterology*. 1988;95:1351-1355.

4. Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. *Ann Intern Med*. 1992;117:215-220.

5. Yokota T, Kunii Y, Teshima S, et al. Signet ring cell carcinoma of the stomach: a clinicopathological comparison with the other histological types. *Tohoku J Exp Med*. 1998;186:121-130.

6. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol*. 2006;24:2903-2909.

7. Musani AI. Treatment options for malignant pleural effusion. *Curr Opin Pulm Med*. 2009;15:380-387.

8. Catalano V, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. *Crit Rev Oncol Hematol*. 2009;71:127-164.

9. Glare PA, Dunwoodie D, Clark K, et al. Treatment of nausea and vomiting in terminally ill cancer patients. *Drugs*. 2008;68:2575-2590.

10. Fuchs CS, Mayer RJ. Gastric carcinoma. *N Engl J Med*. 1995;333:32-41.

11. National Comprehensive Cancer Network. NCCN Web Site. NCCN clinical practice guidelines in oncology- v.2.2009 Gastric cancer. Available at http://www.ccchina.net/UserFiles/2009-4/20/200942001225674.pdf. Accessed August 11, 2010.

12. National Cancer Institute. Surveillance epidemiology and end result: stomach cancer. Table 24.8: 5-year relative and period survival. Available at http://www.seer.cancer.gov/csr/1975_2007/browse_csr.php?section=24&page=sect_24_table.08.html. Accessed August 11, 2010.

13. Zivny J, Wang TC, Yantiss R, Kim KH, Houghton J. Role of therapy or monitoring in preventing progression to gastric cancer. *J Clin Gastroenterol*. 2003;36(5 suppl):S50-S60.

14. Chung M, Kozuch P. Treatment of malignant ascites. *Curr Treat Options Oncol*. 2008;9:215-233.

15. Matthay RA, Coppage L, Shaw C, Filderman AE. Malignancies metastatic to the pleura. *Invest Radiol*. 1990;25:601-619.

16. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11-20.

17. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345:725-730.

Correct answers: 1. *c*, 2. *b*, 3. *d*, 4. *c*, 5. *a*