65-Year-Old Woman With Confusion

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A 65-year-old woman was admitted to the hospital with new-onset confusion. She had a history of hypothyroidism, well-controlled diabetes mellitus, and hypertension. Her symptoms started 4 weeks before admission and were described by her husband as sudden onset of severe confusion with inappropriate behavior, repetitive activities, and intermittent loss of orientation to time and surroundings. Because she had symptoms of polyuria, her primary care physician initially treated her for a urinary tract infection. However, her mental status deteriorated, and she was admitted to her local hospital, where she was found to have altered mental status. Before the onset of confusion, her other medical issues were well controlled. She had no recent infections, travel, or change in her medications. Her physical examination findings were reported to be normal except for her altered mental status. No other abnormalities were noted on review of systems.

1. **At this point, which _one_ of the following is _least likely_ to explain her confusion?**
   a. Meningitis
   b. Urinary tract infection
   c. Myocardial infarction
   d. Pneumonia
   e. Bacteremia

The classic triad of bacterial meningitis consists of fever, nuchal rigidity, and altered mental status. Although these factors are not always present concurrently, a patient with no nuchal rigidity and no fever is unlikely to have meningitis. Urinary tract infection, myocardial infarction, pneumonia, and bacteremia should all be considered in the differential diagnosis of altered mental status in an elderly person. Urinalysis with microscopy is a simple test and should be performed. In the case of a myocardial infarction, electrocardiography and measurement of cardiac biomarkers would be essential in the workup. Chest radiography is warranted if pneumonia is suspected. A

history of cough productive of sputum is often present in patients with pneumonia, but this feature can be difficult to discern in a patient with altered mental status. It is appropriate to obtain aerobic and anaerobic blood cultures in an elderly patient with altered mental status.

On admission to our hospital, the patient was afebrile (temperature of 36.4°C) and had a blood pressure of 160/80 mm Hg, pulse rate of 87/min, and oxygen saturation of 95% while the patient breathed room air. On physical examination, she was noted to be nonresponsive to command, but she did not seem to be in any acute distress. Cardiac examination revealed no murmurs or other abnormalities. Findings on lung examination were unremarkable, including no evidence of abnormal lung sounds. Possible hepatomegaly was noted on abdominal examination. No lymphadenopathy was observed. Attempts to examine her oral cavity were unsuccessful. Her admission neurologic examination, which was limited given her unresponsiveness, showed no focal neurologic deficits. She was lethargic and intermittently alert, but no other abnormalities were detected. Initial laboratory studies yielded the following results (reference ranges provided parenthetically): hemoglobin, 12.7 g/dL (12.0-15.5 g/dL); leukocytes, 10.1×10^9/L (3.5-10.5×10^9/L); platelet count, 608×10^9/L (150-450×10^9/L); erythrocyte sedimentation rate, 43 mm/h (0-29 mm/h); and C-reactive protein, 14 mg/L ($\leq$8 mg/L).

Her medications on admission consisted of atenolol and valsartan-hydrochlorothiazide for hypertension, levothyroxine for hypothyroidism, metformin for diabetes, and metaxalone, methadone, oxycodone, duloxetine, and gabapentin for chronic back pain. The medication dosages were stable when her recent symptoms began, and no recent changes or history of overdose were reported.

Urinalysis showed no evidence of current urinary tract infection. Electrocardiography and cardiac biomarker sampling showed no

evidence of cardiac ischemia or any other insult. Blood cultures were obtained for aerobic, anaerobic, and fungal etiologies. The records that were received from her local hospital showed that she indeed had confirmed multiple positive blood culture results. She had experienced sepsis that resolved while she was being treated with broad-spectrum antibiotics. Her blood cultures were positive for an anaerobic organism, *Lactobacillus,* that was susceptible to piperacillin-tazobactam and was treated for 2 weeks at her home hospital.

2. **Given the presence of anaerobic bacteremia, which _one_ of the following is _most likely_ to be the source of this patient's infection?**
   a. Gastrointestinal tract infection
   b. Pelvic infection
   c. Skin and soft tissue infection
   d. Ear, nose, and throat infection
   e. The source is unknown in most cases

In reports of anaerobic bacteremia, the gastrointestinal tract has been involved in up to 70% of cases.[1] Hence, it is most likely that our patient has a gastrointestinal source. The second most common source is the female genital tract and pelvic infections. Skin and soft tissue infections and ear, nose, and throat infections are considerably less common than gastrointestinal and genitourinary tract infections, and in a small minority of cases,[1,2] the source of bacteremia cannot be identified. The records from our patient's home hospital showed that she was initially febrile on presentation. Laboratory studies had showed a mildly elevated white blood cell count but otherwise normal findings. Because the patient had abdominal pain, she underwent computed tomography (CT) that showed a possible liver abscess, which was subsequently drained. Culture of the fluid was positive for *Lactobacillus* and *Klebsiella.* She was given piperacillin-tazobactam based on culture susceptibilities. Her vital signs subsequently normalized, and her fever resolved. Although her physical examination findings were normal, her mental status worsened, and she was subsequently transferred to our hospital. Repeated CT of the chest, abdomen, and pelvis at our facility showed a decrease in the size of the hepatic abscess and no other abnormalities.

3. **Which _one_ of the following is the _most important_ factor associated with anaerobic bacteremia that should be investigated in this patient?**
   a. Diabetes mellitus
   b. Corticosteroid use
   c. Malignant neoplasm
   d. Liver disease
   e. Postsplenectomy status

Many factors have been associated with anaerobic bacteremia, including diabetes mellitus, corticosteroid use, malignant neoplasms, liver disease, and postsplenectomy state.[3,4] Our patient had a long history of diabetes, which may have contributed to the development of her bacteremia. She had no history of corticosteroid use and no known past or current malignant disease. The presence of a malignant neoplasm, however, has been the most commonly associated finding in patients with anaerobic bacteremia[3,4] and should be investigated. The presence of liver disease and postsplenectomy state are also important risk factors. Our patient did have a liver abscess but no associated liver parenchymal disease, and liver function test results were normal. She had no history of splenectomy and had an intact spleen. Other factors associated with anaerobic bacteremia include intestinal obstruction, immunosuppression, organ transplant, hematologic disorders, and alcohol abuse,[3,4] none of which were noted in our patient's history. She subsequently underwent colonoscopy that showed sigmoid diverticulosis but otherwise normal findings. Biopsy specimens taken from different parts of the ileum and colon showed no evidence of a pathologic process. Neither CT nor colonoscopy showed evidence of malignant disease. The patient underwent magnetic resonance imaging (MRI) of the abdomen and pelvis in addition to magnetic resonance cholangiopancreatography to investigate the possibility of a rare congenital biliary-venous fistula that might explain her bacteremia or visceral malignant processes that may have been missed on CT. These studies showed interval resolution of the hepatic abscess but no other abnormality.

4. **In view of the patient's *Lactobacillus* bacteremia and the diagnostic measures taken so far, which _one_ of the following is the _best_ diagnostic study to perform next to identify the source of the bacteremia?**
   a. CT of the sinuses and oral cavity
   b. Panoramic radiography of the teeth and adjacent structures
   c. Bone scan
   d. MRI with focus on deep fascial tissues of the head and neck
   e. Chest radiography

Because the patient's gastroenterology workup, which included multiple CT scans and MRI of the abdomen and pelvis, endoscopy with biopsies, and dedicated evaluation of the biliary system with magnetic resonance cholangiopancreatography, showed no abnormalities, it was unlikely that there was a breach to the gastrointestinal tract that could have led to the liver abscess. In that light, her liver abscess could have contributed to her bacteremia, but the actual source of the liver abscess and the bacteremia is yet to be determined. Her lack of mental status recovery after 2 weeks of antibiotic therapy (piperacillin-tazobactam, based on susceptibilities at her local hospital) and drainage of the liver abscess necessitated further workup. The next investigation should explore skin and soft tissue infections and ear, nose, and throat sources. However, no evidence in the patient's history or physical examination findings suggested skin or soft tissue infection.

The next step is to examine the oral cavity as a potential source. Computed tomography has become the imaging modality of choice for the assessment of suspected acute infections of the head and neck.[5] However, panorex radiography (a panoramic view of the dental and periodontal structures) is often performed for evaluation of patients presenting to the emergency department with suspected dental abscess because it gives a comprehensive single-film view of the entire maxillomandibular region.[6] It can detect some pathologic changes of the teeth including caries, occult fractures, and periodontal abscess that may be missed during a dental examination.[6] Given the uncertainty about an oral source for our patient's infection and the lack of oral symptoms, we chose panorex radiography as an initial screening study to look for periodontal disease.

A bone scan would be of great value in detecting early osteomyelitis[5] if there was high suspicion for the disorder, which was not the case with our patient. Magnetic resonance imaging with focus on deep fascial tissues of the head and neck has the advantage of higher soft tissue contrast resolution and could be of help in detecting disease that is originating in the oral cavity, including periodontal abscess.[5] This procedure, however, would not be the first imaging modality given the lack of obvious signs and symptoms of head and neck disease in addition to the time, cost, and discomfort involved when obtaining the scan. Chest radiography would not be helpful because we were looking for a source of the anaerobic bacteremia that would be less likely to be found in the lungs.

Panorex radiography showed severe changes in at least 11 teeth consistent with advanced caries and others with decayed nonrestorable dentition. The patient subsequently underwent tooth extraction of the 5 most affected teeth, with the rest to be managed conservatively with emphasis on oral hygiene measures. Shortly after the removal of the decayed teeth, she had complete recovery of her mental status. Subsequent follow-up after hospital discharge confirmed the complete recovery with no evidence of recurrence of fever or altered mental status.

5. **Which _one_ of the following risk factors would be associated with the _lowest_ mortality in our patient with anaerobic bacteremia?**
   a. Liver disease
   b. Advanced age
   c. Type of anaerobic organism
   d. Association with malignant disease
   e. Community-acquired organism

Liver disease has been shown to have a strong association with increasing mortality in patients with anaerobic bacteremia and was the most significant factor in one study.[7] Advanced age (>60 years) has also been consistently shown to be a risk factor for increased mortality.[2,3,7] The risk of mortality also varies with the type of anaerobic species isolated. For example, *Bacteroides fragilis* was

the most common organism isolated in anaerobic bacteremia in multiple previous studies and was found to have an associated mortality ranging from 24% to 31%, whereas mortality from some of the other *Bacteroides* group species was found to be higher.[2,3] Malignant neoplasms, which as noted previously are associated with the overall incidence of anaerobic bacteremia, also contribute to increased mortality when present. A review of the literature shows no known association with worse outcomes such as an increase in mortality with community-acquired anaerobic bacteremia. On the contrary, the presence of anaerobic bacteremia of nosocomial origin was associated with increased mortality.[8,9] Our patient likely contracted community-acquired anaerobic bacteremia, with the oral cavity being the likely source. The overall mortality of anaerobic bacteremia has been found to be 15% to 35%, depending on the study.[2,3]

DISCUSSION

Our case emphasizes the need to inspect the oral cavity when seeking an association with systemic disease, particularly in a patient with anaerobic bacteremia. The oral cavity is home for at least 700 species of colonizers of bacteria, including anaerobic bacteria.[10,11] These organisms commonly form a biofilm that grows above the gingival crest of the tooth.[10] An important aspect of the features of the oral biofilm is its close proximity to highly vascularized tissue beds as compared with flora of the skin, for example, which have a thick barrier to the closest vascular supply.[12] This makes the disruption of the available defenses against these colonizers a serious threat that may lead to bacteremia and other consequences depending on the host risk factors.

The oral cavity is equipped with multiple defenses to prevent the penetration of bacterial colonizers from plaque biofilms to the underlying tissue and the vascular bed.[11] These are largely composed of the surface epithelial barrier, immunologic defenses of both the innate reticuloendothelial system and the antibody-mediated lymphocytic system, and other local host-derived mechanisms such as defensins, which are locally secreted antimicrobials.[11] In the event of plaque buildup with proliferation of the biofilms, conditions such as gingivitis and periodontitis develop.[12] These

conditions and perhaps many other inflammatory disorders of the periodontal spaces lead to periodontal vascular proliferation, which increases the periodontal vasculature surface area and makes it easier for overlying bacteria to gain access to the bloodstream and cause subsequent complications.[12] These inflammatory or infectious conditions also disrupt the other defense barriers. Poor oral hygiene may lead to a substantial (2- to 10-fold) increase in the number of bacteria colonizing the teeth, which may also increase the likelihood of penetration into the bloodstream and hence establishment of a bacteremic state.[11]

The incidence of anaerobic bacteremia has been increasing since 1995 despite a prior decline.[1] Hence, anaerobes are again emerging as an important contributor to bacteremia. Multiple studies have shown that anaerobes account for 0.5% to 12% of all cases of bacteremia.[1] There are multiple possible sites for anaerobes to enter the bloodstream. The most common source of anaerobic bacteremia is gastrointestinal in 50% to 70% of cases, followed by female genital tract and pelvic infections in up to 20%. Skin and soft tissue infections and ear, nose, and throat infections make up 5% to 20% of the infections. In one study, the source was unknown in 6% of cases.[1,2] Our patient had diabetes mellitus, which is a known risk factor for periodontal disease. Diabetic patients seem to be more likely to develop periodontal disease than nondiabetic patients, presumably due to impaired innate and cellular immunity.[11] Thus, it is important to look for evidence of periodontal disease in a diabetic patient who presents with anaerobic bacteremia.

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CORRECT ANSWERS: 1. a. 2. a. 3. c. 4. b. 5. e