A Pain in the Neck

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A previously healthy 16-year-old girl presented to her physician because of a two-day history of sore throat, fatigue, fever, headache, and vomiting; she had not had rhinorrhea or a cough. On examination, her temperature was 36.7°C, and she appeared fatigued. She had mild erythema and white plaques on her tonsillar pillars and mild tenderness of the anterior neck, without lymphadenopathy.

The signs and symptoms on presentation are consistent with the presence of acute pharyngitis. Infections with rhinovirus, adenovirus, influenza virus, and parainfluenza virus are among its most common causes. Infection with mycoplasma or Epstein–Barr virus (EBV) is also possible, but diagnostic efforts should initially focus on the identification of group A streptococcal infection, if present, since treatment can prevent serious sequelae. The tonsillar exudates, fever, anterior cervical adenopathy, and absence of cough in this case are highly suggestive of streptococcal pharyngitis. The vomiting, however, is more commonly seen in younger children with group A streptococcal pharyngitis.

I would obtain a swab from her pharynx for a rapid streptococcal-antigen test and treat the patient with antibiotics if the test result was positive. Rapid streptococcal-antigen tests are, at best, 80 to 90 percent sensitive, so if the result was negative I would send the throat swab for culture and await the results before prescribing antibiotics.

The result of a rapid streptococcal-antigen assay was negative. Viral pharyngitis was diagnosed. Treatment with analgesics and adequate fluid intake were advised.

Four days later, the patient returned to her physician with a worsening sore throat. She was having difficulty swallowing and reported dizziness while standing. She continued to feel fatigued, chilled, and achy but stated that she had not had further fever. She described a bifrontal headache and some mild stiffness of the neck. She stated that she had not vomited since the previous visit and that she did not have abdominal pain or diarrhea. The streptococcal culture obtained during the previous visit was sterile.

Although group A streptococcal infection is still possible, the sterile culture, combined with the new and worsening symptoms, leads me to broaden my differential diagnosis. Most symptoms due to viral or streptococcal pharyngitis should be improving or resolved by the sixth day of illness. The patient’s throat pain and difficulty swallowing may be due to a complication such as a peritonsillar abscess or to a less common cause of pharyngitis, such as acute human immunodeficiency virus (HIV) infection, EBV infection, or gonococcal infection. Her headache and neck stiffness raise the possibility of meningitis. Bacterial meningitis would be unlikely without fever and severe clinical deterioration, although viral or aseptic meningitis remains a possibility.

The patient had a history of depression and childhood asthma. She was taking paroxetine and trazodone, as well as ibuprofen for her sore throat; she had no allergies to...
medication. She was a junior in high school and did not smoke, consume alcohol, or use illicit drugs. She stated that she had never been sexually active.

On examination, she was thin and pale and appeared ill. Her temperature was 36.3°C, her blood pressure 93/64 mm Hg, her pulse 120 beats per minute, her respiratory rate 22 breaths per minute, and her oxygen saturation 98 percent while she was breathing room air. She had some difficulty fully opening her mouth and protruding her tongue, but there was no anatomical distortion. Her oropharynx was dry, and there was right tonsillar erythema. Her anterior cervical lymph nodes were tender, especially on the right side; otherwise, her neck was supple. The findings on a cardiovascular examination were normal except for tachycardia, and her lungs were clear. The findings on an abdominal examination were normal, and she had no rash.

Her appearance and vital signs are alarming. Her blood pressure alone would not be cause for concern in an adolescent, but in this case it is associated with tachycardia and orthostatic symptoms. She also has trismus, as well as some asymmetric tonsillar erythema and cervical adenopathy, which may explain her neck stiffness. I am concerned that this patient has an undiagnosed bacterial infection, in particular a deep-tissue infection. Ludwig’s angina could explain the findings, but this disorder is usually associated with gingivitis, dental infection, and foul-smelling breath. Peritonsillar abscesses are often visualized on examination of the throat, but a parapharyngeal or submandibular infection might be harder to diagnose.

The white-cell count was 9000 per cubic millimeter, the hemoglobin level 11.6 g per deciliter, and the platelet count 10,000 per cubic millimeter. Examination of a peripheral-blood smear confirmed the thrombocytopenia and showed that the white-cell differential count included 89 percent segmented neutrophils and 10 percent band forms. No schistocytes were seen. The urea nitrogen level was 125 mg per deciliter (44.6 mmol per liter), the creatinine level 2.1 mg per deciliter (185.6 µmol per liter), the serum aspartate aminotransferase level 90 U per liter, the alkaline phosphatase level 270 U per liter, the total bilirubin level 1.7 mg per deciliter (29.1 µmol per liter), and the lactate dehydrogenase level 451 U per liter. Urinalysis revealed three to five nondysmorphic red cells per high-power field and occasional hyaline casts.

Given these laboratory findings, I would search for a soft-tissue infection; streptococcal toxic shock syndrome could cause any of these abnormalities. The patient’s thrombocytopenia is profound, and given the relative preservation of her other cell lines, I would focus on platelet-specific destruction rather than on sequestration or a bone marrow process. In the setting of bacterial infection, destruction would most likely be a result of disseminated intravascular coagulation. Thrombocytopenia and elevated aminotransferase levels may have a viral cause, such as infection with EBV, cytomegalovirus, parvovirus, coxsackievirus, acute HIV, or acute hepatitis. Many of these infections, however, are associated with a rash and with lymphocytosis or the presence of atypical lymphocytes. This patient’s renal failure probably represents a preglomerular process, since the ratio of urea nitrogen to creatinine is high in the setting of orthostasis and ibuprofen use. On urinalysis, there are no dysmorphic red cells or cellular casts, which would suggest glomerulonephritis.

I would stop the ibuprofen and begin aggressive rehydration. Given the possibility of meningitis, a lumbar puncture should be performed, but not before the thrombocytopenia is corrected, preferably to a level above 50,000 platelets per cubic millimeter. Although infection is the most likely explanation for the illness in this case, lymphoma is a remote possibility in an ill-appearing adolescent with adenopathy, unexplained thrombocytopenia, and an elevated lactate dehydrogenase level.

Chest radiographs showed several ill-defined nodular opacities within the right lower lobe and retrocardiac region (Fig. 1). Posteroanterior and lateral plain-film radiographs of the neck showed a normal tracheal air column and no evidence of retropharyngeal abscess. An abdominal ultrasound study showed sludge in the gallbladder but otherwise no abnormalities. Computed tomography (CT) of the head, performed without the use of intravenous contrast material, showed no abnormalities. Aggressive rehydration was begun, and the patient’s tachycardia and hypotension resolved. Lumbar puncture was deferred because of her thrombocytopenia. Administration of vancomycin, gentamicin, and piperacillin–tazobactam was begun after blood cultures were obtained.
Nodular opacities on chest radiography are found in a variety of disorders, but most commonly they are associated with septic emboli, disseminated fungal infection, and cancer — primarily lymphoma or metastatic disease. In a patient with a history of pharyngitis and findings signaling a possible deep-tissue infection of the neck, Lemierre’s syndrome — septic thrombophlebitis of the jugular vein — should be considered. The absence of abnormalities on plain films of the patient’s neck argues against the presence of a large obstructing abscess but would not rule out a smaller, parapharyngeal infection complicated by extension to the jugular veins. I would carefully palpate the tender areas of her neck for an affected vein and would request CT studies of her neck with the use of contrast material. Like endocarditis, this syndrome can be associated with multiorgan involvement, which might explain the abnormalities on her liver-function tests and her hematuria and which would put her at risk for meningitis.

Over the next 12-hour period, the patient reported that her headache and neck pain were becoming increasingly severe. Her renal function improved with rehydration; however, she became progressively acidemic and hypoxemic.

The erythrocyte sedimentation rate was 60 mm per hour. The prothrombin and partial-thromboplastin times were normal. The fibrinogen level was elevated, at 1027 mg per deciliter (normal range, 150 to 450); the D-dimer level was 0.2 to 0.4 µg per milliliter (normal range, <0.2). Serologic studies for hepatitis viruses A, B, and C were negative, as were antibody tests for EBV (tests for IgG and IgM antibodies to viral capsid antigen and for antibodies against early antigen and Epstein–Barr nuclear antigen). There was no detectable antinuclear antibody, and the levels of complements C3 and C4 were normal. Tests for urinary histoplasma antigen, HIV antibody, and antineutrophil cytoplasmic antibody and measurement of von Willebrand factor antigen were ordered. The streptococcal-antibody screen was positive, at a titer of 1:400.

These laboratory results, combined with the absence of a microangiopathic process on the blood smear, argue against disseminated intravascular coagulation as the sole cause of the patient’s thrombocytopenia. At present, she has no evidence of splenic sequestration (since no splenomegaly was detected on examination or on abdominal imaging) and no evidence of bone marrow failure or of a nonspecific consumptive process, such as thrombotic thrombocytopenic purpura; thus, her thrombocytopenia is most likely an immune-mediated process. In the absence of potential offending drugs, I would continue to look for an infection that might be associated with the production of antiplatelet antibodies. Examination of a bone marrow biopsy specimen would probably show large megakaryocytes; this procedure may be indicated if an infectious source is not identified soon.

The elevated erythrocyte sedimentation rate is nonspecific; the streptococcal-antibody screen, however, shows that the patient has recently had a streptococcal infection and suggests a causative role for this organism in her pharyngeal process. The HIV antibody test, if negative, would not rule out the presence of acute HIV disease; a viral-load assay would be more helpful. The patient's worsening acidemia and oxygenation are reasons for concern because they may indicate that she has sepsis or the acute respiratory distress syndrome. The patient should be monitored closely in an intensive care unit. Given her worsening headache and neck pain, a lumbar puncture should be performed after platelet transfusion, in addition to CT study of her neck.
CT scans of the patient’s neck, chest, abdomen, and pelvis were obtained to evaluate the possibility of lymphoma. Multiple ill-defined pulmonary masses, small bilateral pleural effusions, and widespread air-space disease were seen (Fig. 2). There was asymmetric thickening of the right pharyngeal soft tissues, and the right internal jugular vein was occluded to the level of the thoracic inlet (Fig. 3). The rest of the vasculature was normal, and there was no lymph-node enlargement. The abdomen and pelvis were unremarkable. Blood cultures grew gram-negative rods and gram-positive cocci in chains.

These findings are consistent with a diagnosis of septic thrombophlebitis of the internal jugular vein, or Lemierre’s syndrome. The gram-negative rods, if anaerobic, are likely to be a fusobacterium species; I expect that a beta-hemolytic streptococcal species will also be identified. Polymicrobial causes are not unusual in deep-tissue pharyngeal infections. The antibiotics that the patient is currently receiving provide appropriately broad coverage, but at this time I would stop the vancomycin, since infection with methicillin-resistant *Staphylococcus aureus* or highly penicillin-resistant *Streptococcus pneumoniae* is unlikely. She does not appear to have an organized abscess that requires drainage, but she does need antibiotic therapy of at least four weeks’ duration. The role of anticoagulation is controversial, but in this case, given the patient’s thrombocytopenia, I would reserve it for use if there is clot progression or perhaps for use later in her clinical course, as the acute embolic phase resolves. She will need careful monitoring and evaluation for septic complications of the disease, including meningitis, empyema, and septic arthritis.

Because her illness was rapidly progressing, the patient was urgently taken to the operating room for exploration of the right side of the neck. Extensive thrombosis of the right jugular vein extended from the base of the skull to the clavicle. Surrounding phlegmon adhered to but did not invade the carotid artery or the deep muscles of the cervical neck. No frank abscess was identified. The internal jugular vein was ligated.

Postoperatively, vasopressor support was required because of the development of the acute respiratory distress syndrome and hypotension. Organisms from the blood were identified as *Eikenella corrodens*, *S. milleri*, and *Fusobacterium necrophorum*. Anticoagulation was initiated when magnetic resonance imaging with venography showed propagation of thrombosis into the intracranial venous sinuses. The patient recovered with supportive care, including intravenous antibiotics for six weeks and anticoagulant therapy for six months. At follow-up one year later, she had moderate rightward deviation of the tongue as a result of hypoglossal-nerve weakness but no other stigmata of her infection.

**Commentary**

A sore throat is one of the most common symptoms for which patients seek medical care and ac-
counts for at least 12 million ambulatory visits annually. In the majority of cases, the sore throat is caused by a common viral pathogen; approximately 15 to 30 percent of sore throats in children and 5 to 10 percent in adults are caused by group A beta-hemolytic streptococci. The growing use of antibiotics for upper respiratory infections has fostered increasing antimicrobial resistance, and efforts to promote the judicious use of these drugs have meant that fewer patients with pharyngitis have been receiving them. Most episodes of pharyngitis are benign and self-limited. However, when symptoms do not remit, the clinician must consider other causes of the illness, such as infectious mononucleosis, acute HIV infection, or a suppurative complication such as cervical adenitis or a peritonsillar or retropharyngeal infection. Symptoms suggesting the presence of a deep pharyngeal infection include neck pain and limited mobility of the jaw, neck, or tongue. Trismus develops when the muscles of mastication are inflamed or reflexively irritated as a result of infectious spread to the lateral pharyngeal space.

Despite this patient’s clinically significant oro-pharyngeal findings, her physicians did not initially attribute her systemic symptoms to an underlying, deep pharyngeal infection. As her care shifted from an outpatient to an inpatient setting, her presenting symptom — pharyngitis — became secondary, and her systemic findings took priority. The multiple pulmonary nodules, acute renal failure, liver-enzyme abnormalities, and thrombocytopenia framed the differential diagnosis and led to such discordant possibilities as thrombotic thrombocytopenic purpura, vasculitis, and lymphoma. The context in which physicians frame a diagnostic question helps to generate the differential diagnosis and guides the subsequent evaluation. In this case, the inpatient clinicians initially marginalized the neck-related symptoms, whereas the discussant in this article placed the systemic findings into the context of an antecedent pharyngitis and arrived relatively easily at the correct diagnosis.

In 1936, André Lemierre, a Parisian bacteriologist, described 20 cases of anaerobic thrombophlebitis of the internal jugular vein with metastatic infection. Most cases of Lemierre’s syndrome occur in adolescents and young adults with tonsillopharyngitis, or less commonly, those with an odontogenic infection, mastoiditis, or sinusitis. Oral anaerobes invade the peritonsillar tissue, and infection spreads to the adjacent lateral pharyngeal space, which contains the internal jugular vein. F. necrophorum, an anaerobic, gram-negative rod that commensally inhabits the oral cavity and gastrointestinal and female genital tracts, is identified in 82 percent of the cases. It is not known why fusobacterium species invade the mucosa; antecedent EBV infection may promote the invasion, possibly by inducing immunosuppression. From the neck, the infection spreads hematogenously, most commonly to the lungs, but also to the joints, liver, spleen, bones, kidneys, and meninges.

Patients with Lemierre’s syndrome usually present with systemic findings within one week after the onset of the inciting oropharyngeal infection. Ipsilateral neck pain and swelling occur in only half the patients; a minority will have trismus or evidence of a thrombosed jugular vein on examination. Signs of metastatic infection include pulmonary infiltrates, hepatosplenomegaly, hyperbilirubinemia, elevation in liver-enzyme levels, hematuria, and disseminated intravascular coagulation with thrombocytopenia. Thrombocytopenia in the absence of disseminated intravascular coagulation has been reported, although the exact pathogenic mechanism of thrombocytopenia in the current case is not entirely clear.

The diagnosis of Lemierre’s syndrome is usually made after a variety of infectious and noninfectious illnesses have been considered. The diagnosis may first be suggested when F. necrophorum grows in blood culture; contrast-enhanced CT studies of the neck can confirm the diagnosis. Although the optimal treatment is unknown, antimicrobial therapy effective against anaerobic pathogens is critical. Penicillin, cephalosporins, clindamycin, metronidazole, chloramphenicol, and tetracyclines all have efficacy against fusobacterium species. Since anticoagulation may facilitate embolic spread, it is usually reserved for cases of retrograde propagation of thrombus. Ligation of the internal jugular vein is rarely required, although it may help to prevent further embolism if the infection spreads despite appropriate medical therapy. Before antibiotics became available, the mortality rate approached 90 percent; even with systemic antimicrobial therapy, up to 18 percent of patients may die.

In the era before antibiotics, Lemierre’s syndrome was common, but reports declined in the 1960s and 1970s as the use of antimicrobial agents for pharyngitis became increasingly common. In the past decade, the frequency of Lemierre’s syn-
Drome has again increased,11,15 and some have attributed this change to the increasingly judicious use of antibiotics.9,11,14 Because the number of physicians familiar with its dramatic signs and symptoms is diminishing, Lemierre’s syndrome has been referred to as the “forgotten disease.”8,9,11 Changes affecting the neck may be subtle or absent at the time of a patient’s presentation with metastatic infection, and the diagnosis may be overlooked. In their search for a unifying diagnosis, the clinicians caring for the patient in the current case would have been well served to remember her chief symptom: a pain in the neck.

Supported by a Career Development Award from the Health Services Research and Development Program of the Department of Veterans Affairs and a Patient Safety Developmental Center Grant (P20-HS11540) from the Agency for Healthcare Research and Quality (both to Dr. Saint).

We are indebted to Peter Strouse, M.D., for assistance with the radiographic images and their interpretation.

References


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