Fever and Stiff Neck

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Editors’ Note: With this article we inaugurate a new feature of the ARCHIVES. The aim of “Clinical Problem Solving” is to demonstrate how master clinicians approach complex problems. The thinking process is more important than the final diagnosis. We thank the New England Journal of Medicine for the concept and for advice on implementation. Contributions are welcome; however, informal inquiries via e-mail to the editorial office are advised prior to preparing and submitting a manuscript.

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Clinical Presentation: An 11-month-old boy was seen in the emergency department by his pediatrician for evaluation of fever (body temperature, 38.5°C) and a stiff neck. The patient’s illness began 5 days earlier when he developed nasal congestion and fever. His pediatrician prescribed amoxicillin on the third day of illness. The fever persisted, however, and by the fifth day, the patient was irritable and refused to flex his neck.

New symptoms reported in the emergency department included decreased activity, poor intake of food and fluids, and decreased urine output. The parents also reported that after 1 day of amoxicillin therapy, the patient developed a faint red rash over his trunk, arms, and legs. The rash faded after 2 days. Symptoms of confusion, headache, conjunctivitis, cough, vomiting, or diarrhea were denied; however, the parents reported that his usual “noisy breathing” seemed worse. Medical history included a diagnosis of laryngomalacia diagnosed by bronchoscopy at age 5 months.

The infant was born at term after an uneventful pregnancy to a healthy mother. He attended a day care center while his parents worked. There was no exposure to cigarette smoke or pets. Immunizations were up-to-date, but he had not yet received pneumococcal vaccine.

Dr Green: The patient’s illness began as a common upper respiratory tract infection associated with a low-grade fever and congestion, and his condition has worsened after several days of illness. He has developed irritability, neck stiffness, lethargy, and poor intake of foods and fluid. Decreased urine output indicates dehydration.

Meningitis must first be excluded in anyone with a fever and stiff neck, but there are other concerns. The change in the patient’s breathing pattern from his usual noisy breathing is worrisome. There are several bacterial and/or viral illnesses that when combined with laryngomalacia might make the stridor worse. Fifteen or more years ago, when invasive Haemophilus influenzae type b disease was a more imminent threat, I would have greater concern about the possibility of epiglottitis in a febrile infant who does not want to move his neck or swallow. Epiglottitis may in some ways mimic meningitis. Supraglottitis is also a consideration. I am more concerned about bacterial disease than a secondary viral process because this patient seems more ill than one who simply has viral croup superimposed on laryngomalacia. Therefore, if meningitis is ruled out, I would suspect a disease that involves the airway. Extrinsic compression of the airway by a neck infection such as bacterial adenitis is possible, although it would be uncommon for this to cause airway compression. Bacterial adenitis may cause neck stiffness but would not cause the patient to be more symptomatic from his previously diagnosed laryngomalacia. However, a deep space infection could cause both neck stiffness and stridor. An unrecognized congenital cyst with a secondary bacterial infection could explain his predominant symptoms. The physical examination should reveal further information.

Physical Examination: In the emergency department the patient had a temperature of 39.3°C, heart rate, 165 beats/min; respiratory rate, 35 breaths/min; and blood pressure, 100/65 mm Hg. His height was in the 25th percentile for his age, and his weight was in the fifth percentile. He was alert, acyanotic, ill-appearing, and mildly dehydrated. There was no rash. Perfusion and pulses were normal. His neck was stiff, held in an extended position, and turned slightly to the left. Examination of the nose, ears, and throat revealed only moderate erythema of the tonsils and soft palate and dryness of the oral mucosa. One left anterior cervical lymph node was enlarged (3 cm), tender, and firm, but not red or fluctuant. Mild inspiratory stridor was present and loudest with the patient in the supine position. His chest was clear on auscultation. No cardiac abnormalities were present. The remainder of the examination findings were normal. Room air oxyhemoglobin saturation was 98%.

Dr Green: The patient has a high-grade fever and an elevated heart rate. The tachycardia is most likely owing to the fever and dehydration. It is reassuring that his blood pressure is normal although this does not guarantee that he is not bacteremic or in the early stages of sep-
Contrast-enhanced computed axial tomographic scan showing cervical adenopathy on the left and a cystic lesion at the tongue base.

At this point I want to examine the patient for a deep space neck infection by obtaining a contrast-enhanced computed axial tomographic (CAT) scan of the neck. A lateral neck x-ray film is quicker to obtain and might reveal characteristics such as a widened retropharyngeal space, but I do not think the findings will be conclusive. I would also obtain a complete blood cell count with differential and platelet counts, electrolytes, serum urea nitrogen, creatinine, and a blood culture. Even though the patient has been treated with an oral antibiotic, it is still important to obtain culture for organisms.

**Laboratory Data:** A lumbar puncture revealed clear colorless-fluid containing 0.12 x 10^6 white blood cells (0.05 neutrophils, 0.75 lymphocytes, 0.20 monocytes) and 0.43 x 10^6 red blood cells. A Gram stain of the cerebrospinal fluid (CSF) did not show bacteria. The level of glucose in the CSF was 3.33 mmol/L (60 mg/dL) and the CSF protein level was 17 mg/dL. Serum electrolyte, serum urea nitrogen, creatinine, and glucose levels were normal. A complete blood cell count revealed a white blood cell count of 10.6 x 10^6 with a predominance of neutrophils. The platelet count was normal at 301.0 x 10^9. A urinalysis revealed a specific gravity of 1.025, a pH of 6.0, and 15 white blood cells per high-power field, but no red blood cells or bacteria. Blood and a throat culture specimens were also obtained. The erythrocyte sedimentation rate (ESR) was 40 mm/h. A plain radiograph of the neck showed a widened retropharyngeal space. A contrast-enhanced CAT scan of the neck showed left anterior cervical adenopathy, mild left parapharyngeal node enlargement without abscess formation, and a round cystic lesion at the base of the tongue that was not enhanced (Figure). The results of a chest radiograph were normal.

**Dr Green:** The CSF examination, which is always indicated when there is concern for meningitis, revealed pleocytosis with a predominance of lymphocytes, normal levels of glucose and protein, and no organisms on Gram stain analysis. These findings are confounded by the fact that the patient received amoxicillin for 2 days before the spinal tap was obtained. Oral amoxicillin can partially treat bacterial meningitis, particularly if *Neisseria meningitidis* is the culprit organism. In contrast, *Streptococcus pneumoniae* usually will not respond at all to oral amoxicillin. I am skeptical that the patient has partially treated bacterial meningitis because his illness has progressed despite amoxicillin therapy. Aseptic or viral meningitis is possible since the CSF findings are consistent with those of aseptic meningitis. However, aseptic meningitis would explain neither the progression of his illness nor the worsening of his breathing.

The widened retropharyngeal space on the lateral neck radiograph suggests a deep space neck infection, specifically retropharyngeal cellulitis or abscess. Such infections are parameningeal and may be accompanied by a CSF pleocytosis that mimics aseptic meningitis. However, in contrast with what was seen on the lateral neck radiograph, the retropharyngeal space did not appear to be widened on the CAT scan. Because the CAT scan is a more sensitive imaging test, the results obtained here exclude a large retropharyngeal abscess. Often in early deep space neck infections, the scan may not be sensitive enough to detect a
small abscess or cellulitis. The adenopathy is consistent with a neck infection although it may not be the source of all symptoms. The nonenhancing cystic lesion at the base of the tongue is an unexpected finding. It is not clear whether this is an incidental finding of a congenital cyst or whether this is an infected cyst. The cyst did not enhance with contrast, which contraindicates infection.

The remainder of the findings from laboratory studies are consistent with an infection. The ESR is elevated but is not specific enough to be helpful. The urinalysis showing 15 white blood cells per high-power field is also not helpful, although a group A streptococcus infection is sometimes associated with sterile pyuria.

Dr Green: Any congenital cyst is at risk for becoming secondarily infected, which would be a potential explanation for all of the symptoms. However, 2 findings argue against secondary infection of a congenital cyst. First, there has been no change in the size of the cyst. In my experience, when cysts become secondarily infected, they invariably enlarge. Second, unless it was very early in the course of the infection, one would see enhancement by contrast on the CAT scan, which was not the case. So I must conclude that this is a congenital cyst unrelated to the current illness.

A bacterial infection seems to be the most likely diagnosis at this time; therefore, I want to consider potential etiologic organisms and contemplate therapy. Although I think the patient probably has a deep space neck infection, I would still include coverage for meningitis. Because this is a current case and the patient is immunized, I am not worried about *H influenzae* type b. The most likely pathogens in meningitis are *S pneumoniae* and *N meningitidis*. In an era of bacterial resistance to penicillin, an infant or child who attends a day care center is at greater risk for infection by penicillin-resistant streptococci. I would thus treat this patient with both vancomycin and cefotaxime sodium, using doses appropriate for a central nervous system infection. This regimen also provides coverage for pathogens that cause deep space neck infections, such as staphylococci and streptococci. Anaerobic organisms can also cause deep space neck infections. A third-generation cephalosporin would probably provide adequate coverage in anaerobic infections above the diaphragm. If I were treating this patient for just a neck infection and not meningitis, then single-drug therapy with either ampicillin sodium–sulbactam sodium or ticarcillin disodium–clavulanate potassium would be adequate. Finally, although I think it is unlikely that the cyst is secondarily infected with bacteria, treatment with vancomycin and cefotaxime will be effective against the pathogens involved in an infected congenital cyst. Infection of a thyroglossal cyst, or even the thyroid itself, would likely be caused by *S aureus*, and vancomycin would be more than sufficient coverage. Superinfection of a subglossal cyst, typically caused by mouth flora such as group A streptococcus and staphylococci, would be treated the same way.

After starting antibiotic treatment, I will admit the patient to the hospital and monitor his airway carefully. I will also consult my colleagues in otolaryngology to interpret the cystic lesion at the base of the tongue and review all of the radiographs with an attending radiologist to help define the cyst and any other abnormalities.

Hospital Course: The patient was admitted to the hospital and placed on intravenous (IV) vancomycin and cefotaxime. An otolaryngologist was consulted and subsequently recommended observation and IV antimicrobial therapy. A review of the existing hospital record revealed that during the original evaluation for stridor, magnetic resonance imaging of the chest was obtained and the findings were normal. However, when the test was reviewed, a cyst at the tongue base was clearly present and was not changed in size compared with what was currently found.

Hospital Course: Intravenous fluids corrected the patient's dehydration but his oral intake remained poor. Fever occurred (body temperature, 39°C-40°C) for the next 4 days while he was treated with antibiotics. His stridor was unchanged. Blood, throat, urine, and CSF cultures showed no growth by the third day of his hospital stay. On the fourth day of hospital admission, the patient's lips became red and cracked, and he developed swelling over the dorsum of both hands and swelling of the digits of his hands and feet.

Dr Green: The patient has not responded to our therapy, has prolonged fever, and now has new physical findings of red, cracked lips and swollen hands and feet. These factors lead me to consider 2 possibilities. First, he did not respond to the antibiotics because the neck infection has progressed to the formation of an abscess. The initial CAT scan may have missed it because it was not fully developed. If that is the case, his symptoms did not alleviate because successful treatment of an abscess includes drainage in addition to antimicrobial therapy. While an abscess could explain all of the persistent symptoms, it would not necessarily explain the new findings involving the lips, hands, and feet.

The second possibility, and the more likely one, is that the patient has Kawasaki syndrome (KS). His collective symptoms and signs meet the criteria for this syndrome, which is diagnosed on clinical grounds. He has had 9 days of fever, a single swollen lymph node, pharyngeal erythema, red and cracked lips, and swollen hands and feet. Although he does not have a rash now, the parents reported one earlier in the illness, and the rash of KS may be early and transient. The only criterion that he lacks is conjunctivitis. Irritability, lethargy, and poor eating may be seen in patients with KS, but these are very nonspecific features. Findings from the laboratory studies are also consistent with KS. His ESR is elevated and his platelet count is normal, which is expected early in the illness. Sterile pyuria is often present. Finally, CSF pleocytosis is consistent with the aseptic meningitis observed in patients with KS. What is atypical is the late onset of lip changes and hand and foot swelling. Up to that point, although he had 8 days of persistent fever, a single enlarged lymph node, and a history of a transient rash, he did not meet criteria for KS. Incomplete or atypical KS has been described in young infants, usually younger than 6 months. The other striking features that
appeared early on were distractions from the diagnosis of KS.

This patient meets criteria for KS on the ninth day of illness. Given that I do not have much more time to treat him without losing the potential benefit of IV immunoglobulin (IVlg) to prevent the development of coronary artery disease, I will start treatment with standard therapy of aspirin and IVlg. I will also obtain another complete blood cell count to see if his platelet count has increased as I would expect in a patient with KS entering the second week of the illness. He will, of course, need evaluation of his heart, including an electrocardiograph and ultrasonic cardiography. However, because of his neck stiffness, I will obtain another CAT scan of his neck to rule out a retropharyngeal abscess.

**Hospital Course:** A repeated white blood cell count revealed a platelet count of 750.0 x 10^6. Results of a second ESR were 55 mm/h. Findings from a plain chest radiograph, a 12-lead electrocardiograph, and ultrasonic cardiography were unremarkable. A second CAT scan of the neck was obtained and showed no change from the first study. Aspirin and IVlg were administered in doses standard for the treatment of KS. All acute symptoms and signs resolved within 24 hours of treatment. Antibiotics were discontinued prior to the initiation of IVlg therapy.

**Dr Green:** The rapid resolution of symptoms following the administration of both aspirin and IVlg is consistent with the diagnosis of KS, along with the elevated platelet count and ESR. In fact, this impressive response to therapy may represent the only true test of diagnosis for KS short of the development of coronary artery aneurysms. I am reassured that the infant does not have abnormal coronary arteries at this time. If this is a case of KS, prompt treatment is likely to prevent subsequent development of a coronary artery aneurysm.

I will continue administering the high-dose aspirin until he has defervesced for approximately 2 to 3 days and then lower the dose of aspirin, maintaining this treatment until his ESR is less than 20 mm/h and his platelet count is normal. Some experts recommend low-dose aspirin for a minimum of 6 to 8 weeks. He will need another cardiac ultrasound in 4 to 6 weeks. If this patient were receiving aspirin during influenza season, he would be at risk for Reye syndrome, and appropriate precautions would have to be taken. I would want to know whether he was susceptible to varicella because of the risk of Reye syndrome in patients receiving aspirin who contract the varicella virus. At age 11 months, he is too young to receive the varicella vaccine, but the IVlg has probably temporarily protected him against chicken pox. Still, the parents should be advised to call his pediatrician if their son is exposed to or develops varicella while he is receiving aspirin.

**Physical Examination:** The patient was discharged to his home with instructions for the parents to administer aspirin as prescribed. At 6 weeks' follow-up, he was well although stridor persisted. The parents reported peeling of his hands and feet. His ESR and platelet count were normal. The results of a follow-up cardiac ultrasound were also normal. After evaluation of his thyroid gland, the patient was found to have a large vallecular cyst, which was resected. The stridor resolved after surgery.

**COMMENT**

Diagnostic accuracy in clinical care depends on a complete history and physical examination. In the hospital setting, the initial assessment of a patient is typically the most comprehensive. However, patients may come into treatment at a point in the natural history of their particular illness before all salient features are evident. This patient did not meet criteria for the diagnosis of KS when he was first evaluated. Moreover, atypical or uncommon manifestations of disorders can be traps for the inexperienced or unwary clinician. This has been emphasized in the literature on KS. For example, Stamos et al described 11 children with KS whose initial symptoms suggested bacterial lymphadenitis and who developed other features of KS later. In conditions that are diagnosed only on clinical grounds, repeated interviews and physical examinations are essential.

The initial consideration of meningitis seemed wise because of the patient's symptoms and the serious consequences of failure to diagnose and treat such a life-threatening disorder. Although neck stiffness is a cardinal sign of meningitis, the physician thought carefully about other serious conditions, including epiglottitis and deep space neck infection. He wisely avoided the trap of assuming that the patient had previously been correctly diagnosed with laryngomalacia alone and thus was able to entertain the possibility that an infected congenital cyst was a cause of the patient's illness. As it turned out, the cyst was a classic "red herring," which the physician recognized and rejected as the primary cause of the patient's illness.

The experienced clinician sifts through physical findings, extracts pertinent information, and builds a factual case for the diagnosis or subsequent investigation. In this case, as the course of the illness was revealed to the physician, he used each new piece of information to expand the differential diagnoses. In the beginning, he favored a diagnosis of a deep space neck infection; as new physical evidence was disclosed, he concluded that an atypical presentation of KS was the most likely diagnosis. The clinician with an open mind allows emerging data to enhance the course of his or her thinking.

**REFERENCES**