CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

A History Lesson

Lindley A. Barbee, M.D., M.P.H., Robert M. Centor, M.D., Zachary D. Goldberger, M.D., Sanjay Saint, M.D., M.P.H., and Shireesha Dhanireddy, M.D.

In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

From the Department of Medicine (L.A.B., Z.D.G, S.D.) and the Divisions of Infectious Disease (L.A.B., S.D.) and Cardiology (Z.D.G.), University of Washington School of Medicine, Harborview Medical Center, and the Public Health–Seattle and King County HIV/STD Program (L.A.B.) — all in Seattle; the Department of Internal Medicine, University of Alabama at Birmingham, Huntsville Regional Campus, Huntsville (R.M.C.); and the Veterans Affairs Ann Arbor Healthcare System and Department of Internal Medicine, University of Michigan Medical School, Ann Arbor (S.S.). Address reprint requests to Dr. Dhanireddy at the University of Washington, 325 9th Ave., Box 359930, Seattle, WA 98104, or at sdhanir@uw.edu.

N Engl J Med 2015;372:1360-4.
DOI: 10.1056/NEJMcps1308900

A 34-year-old man presented to an ambulatory care center with a 3-day history of a sore throat. He reported associated subjective fevers, chills, sinus pressure, occasional coughing, and fatigue. He did not have dyspnea or headaches. He reported no weight loss, abdominal pain, or chest pain.

The patient's presentation is consistent with acute pharyngitis. Group A streptococcal pharyngitis should be considered; however, cases of pharyngitis often result from viral infections, and his cough may be more suggestive of the latter. Among possible viral causes is influenza, which is typically associated with myalgias and cough. Herpes simplex virus infection can also manifest as pharyngitis and should be considered, particularly in adolescents and young adults. His fatigue raises concern about infectious mononucleosis.

The patient's medical history was remarkable only for attention-deficit disorder diagnosed 15 years earlier, depression, and several episodes of tonsillitis as a child. His medications included methylphenidate (5 mg daily), bupropion (100 mg twice daily), and zolpidem (5 mg as needed). He had initiated over-the-counter omeprazole (20 mg daily) 1 day before presentation as treatment for his sore throat. He had a history of an adverse reaction to penicillin. He was a former smoker, having quit 7 years ago, and occasionally used marijuana; he did not currently drink alcohol or use intravenous drugs. He had a history of smoking methamphetamine but reported having quit at 19 years of age. He was training to become a radiation therapist.

The previous tonsillitis episodes do not help with the differential diagnosis, because tonsillitis is common in children and adolescents. Methamphetamine use is often associated with high-risk sexual behavior and, although reported in the distant past, raises concern about sexually transmitted diseases.

On examination, the oral temperature was 36.7°C, the heart rate 72 beats per minute, the blood pressure 110/70 mm Hg, the respiratory rate 16 breaths per minute, and the oxygen saturation 98% while the patient was breathing ambient air. There was no conjunctival pallor. Impacted cerumen was noted in the right ear, but otherwise the mastoid cavity was clear. A mobile, nontender lymph node measuring 1 cm by 3 cm was noted on the right anterior cervical chain. There was no occipital or postauricular lymphadenopathy. Oropharyngeal examination revealed normal dentition, no exudates, and no tonsillar enlargement. His lungs were clear, and he had no stridor. Cardiac examination revealed a regular rate and rhythm, with no murmurs. The esti-

mated jugular venous pressure was normal. The patient's abdomen was soft, nontender, nondistended, and without organomegaly. There was no joint swelling or tenderness. The neurologic examination was normal. The skin examination was remarkable for a flesh-colored soft nodule, 7 mm in diameter, on his left cheek (later found to be a benign intradermal nevus).

No laboratory evaluation was performed at the time. He was prescribed a 10-day course of cephalexin (500 mg every 6 hours) for presumed streptococcal pharyngitis and ibuprofen (800 mg three times a day).

The physical examination does not suggest streptococcal pharyngitis. The patient is afebrile and does not have tender lymph nodes, exudate, or tonsillar enlargement. Given that this patient has a low pretest probability of streptococcal pharyngitis, I would not have treated him initially with antibiotics. A rapid streptococcal-antigen test, to evaluate for group A streptococcal pharyngitis, should be performed in patients who meet two or more of the following criteria: a history of fever, tonsillar exudates, tender anterior cervical lymphadenopathy, and an absence of cough. He meets only one criterion (a history of fever). At this point, I would treat the symptoms and ask him to return if they worsened, especially if difficulty swallowing or fever developed. If the patient had had more findings to support a diagnosis of streptococcal pharyngitis, cephalexin would have been a reasonable choice, but 500 mg twice daily would have been sufficient.

The patient returned for follow-up 6 weeks later. Despite completion of the prescribed course of antibiotics, his symptoms had not lessened. The right anterior cervical lymph node had increased slightly in size to 1.5 cm by 3.0 cm. The findings on physical examination were otherwise unchanged. The white-cell count was 6500 per cubic millimeter, with 69% polymorphonuclear cells, 20% lymphocytes, and no atypical lymphocytes. The hematocrit was 42%, with a mean corpuscular volume of 86 fl, and the platelet count was 204,000 per cubic millimeter. Tests for heterophile antibodies and for antibodies to the human immunodeficiency virus (HIV) with the use of a third-generation enzyme immunoassay were negative.

He was referred to the otolaryngology clinic. Laryngoscopy revealed bilateral cryptic tonsillar enlargement (with visualization of the hard palate only on the right [tonsil size of 4+; values range from 0 to 4+, with higher values indicating a greater degree of enlargement] and visualization of the soft palate but not the uvula on the left [tonsil size of 3+]), without exudates. Computed tomography of the neck (Fig. 1) also showed enlarged tonsils and a large anterior cervical lymph node.

The patient's presentation now suggests chronic tonsillitis. Infectious mononucleosis could cause this presentation; testing for heterophile antibodies was negative, but false negative results are well recognized. The negative enzyme immunoassay 6 weeks after symptom onset makes HIV infection less likely. However, because seroconversion may in rare cases take more than 6 weeks, it would be reasonable to order a viral-load (HIV RNA) test to rule out the diagnosis. A fourth-generation test for HIV antibodies and p24 antigen can detect acute HIV infection before seroconversion. A detailed review of the patient's social and sexual history is also warranted, particularly given the history of methamphetamine use and its association with high-risk sexual behavior. The enlarging lymph node and enlarging

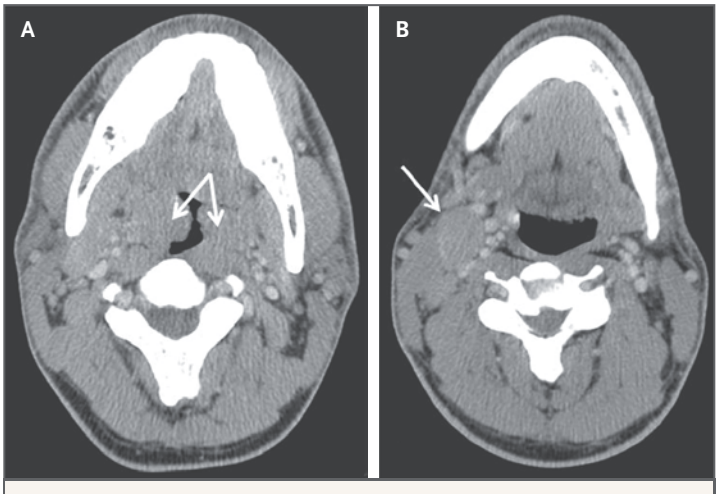

Figure 1. High-Resolution Computed Tomography of the Neck.
Panel A shows asymmetric enlargement of the right palatine tonsil (left arrow), measuring 2.1 cm by 2.2 cm (the right arrow indicates the left tonsil). The image in Panel B shows the enlarged right anterior cervical lymph node (arrow).

tonsillar size raise the possibility of tonsillar lymphoma, although this is not very likely.

The patient underwent fine-needle aspiration of a right anterior cervical lymph node. Cytologic examination revealed no malignant cells. Histiocytic necrotizing lymphadenitis (also known as Kikuchi's disease) was not present. Given the concern about cancer, he underwent a tonsillectomy. The right tonsil (4.0 cm by 3.5 cm by 2.0 cm) and left tonsil (3.8 cm by 2.2 cm by 1.8 cm) showed hyperplasia but were negative for cancer on gross inspection and flow-cytometric analysis.

The presentation is not consistent with Kikuchi's disease, which typically causes tender lymphadenopathy, so it is not surprising that evidence of this disease was not found on biopsy. The pathological findings also rule out lymphoma.

The patient continued to have a sore throat and lymphadenopathy despite tonsillectomy, and odynophagia developed after the procedure. At this point, 4 months after the onset of symptoms, he was referred to the infectious-disease clinic for consultation. Further history was obtained, particularly related to his sexual health. At first, the patient reported not having had sexual intercourse with men, but in response to further questioning, he reported that he had performed oral sex on a man approximately 6 weeks before symptom onset.

The history of oral sex raises several possibilities. Gonococcal pharyngitis may occur after oral sex but is commonly asymptomatic. Herpes simplex virus infection can cause a sore throat, but a routine oral examination should have revealed distinctive lesions. The new history of odynophagia raises concern about herpes esophagitis.

Acute HIV infection is now a greater concern, but I would expect HIV-antibody testing to have become positive by this time. If this is a case of acute HIV syndrome, early initiation of antiretroviral therapy may help control the infection and decrease transmission to partners. Other sites of lymphadenopathy should be sought on physical examination. Sore throat and odynophagia are uncommon with syphilis; however, these symptoms can occur, and a rapid plasma reagin (RPR) test should be performed. Transmission of HIV infection often occurs concurrently with the transmission of other sexually transmitted diseases such as gonorrhea and syphilis.

Physical examination revealed a diffuse maculopapular rash on the trunk, arms, and legs, with a solitary scaly lesion measuring 3 mm in diameter on the left palm; these findings were not observed previously. A nontender, right-sided anterior cervical lymph node measuring 1.5 cm in diameter was also noted. No supraclavicular, axillary, or inguinal lymphadenopathy was present. Examination of the oropharynx did not reveal any exudates.

Given the rash and the palm lesion, I have a high suspicion of secondary syphilis. The rash is characteristic of syphilis, and the time course is consistent with the patient's exposure, because secondary syphilis occurs 4 to 10 weeks after a primary infection. The incidence of syphilis has increased recently, especially among men who have sex with men. At this point, I would test for this infection and would reevaluate his reported penicillin allergy, because penicillin is the preferred treatment for syphilis.

A qualitative RPR screening test and a test of IgG antibodies to treponema were ordered; both tests were positive. The RPR titer was 1:256. The level of rheumatoid factor was less than 13 IU per milliliter, and testing for antinuclear antibodies was negative. HIV RNA was not detected.

The patient clarified that previous use of penicillin had resulted in nausea and vomiting but never a rash. He was given one dose of 2.4 million units of intramuscular penicillin G benzathine, and no adverse events occurred. On follow-up 4 weeks later, his rash had resolved, his enlarged cervical lymph node had decreased in size to less than 1 cm in diameter, and his symptoms had abated. At the 3-month follow-up visit with his primary care provider, the RPR titer had decreased to 1:4. To formally confirm the diagnosis of syphilitic tonsillitis, the initial tonsillar-biopsy sample was reexamined with Warthin–Starry staining, and the examination revealed the presence of spirochetes (Fig. 2); an investigational polymerase-chain-reaction assay indicated the presence of *Treponema pallidum*. The local public health department was notified, and contact tracing was performed.

COMMENTARY

Pharyngitis is a rare manifestation of secondary syphilis.[1-3] However, syphilis can manifest in myriad ways, as its moniker — the "great masquerader" — suggests. Infection with *T. pallidum* occurs primarily through sexual contact, but the spirochete can also be transmitted through the placenta, and direct inoculation can occur by kissing or touching an active lesion.[4] Primary syphilis is characterized by a painless ulcer at the site of inoculation; when lesions are located in the vagina, rectum, or oropharynx, they are often not noticed by the patient. Approximately 6 weeks after exposure, the chancre heals, after which signs and symptoms of secondary syphilis begin to appear. The most common manifestation of secondary syphilis is a rash, which includes skin lesions on the palms and soles, with both the rash and a palm lesion evident in this patient at the time of his referral to the infectious disease clinic. The rash is usually maculopapular but can also be pustular or a combination of the two. Lymphadenopathy, fatigue, fever, and patchy alopecia also occur in patients with secondary syphilis.[4]

Without treatment, the signs and symptoms of secondary syphilis generally resolve within 8 weeks, and the infection becomes dormant. In its latent stage, *T. pallidum* continues to occupy almost all organs of the body, and relapses of secondary syphilis may occur. Early syphilis (i.e., primary, secondary, or early latent syphilis) is more infectious than late latent syphilis. Late latent syphilis is defined by a positive syphilis test with no symptoms and a history consistent with acquisition of infection more than 12 months previously. Many years (usually decades) after untreated inoculation, tertiary syphilis, the final stage, develops and can lead to devastating neurologic and cardiac sequelae.

The treatment of choice in all stages is penicillin. For patients with early syphilis, a single intramuscular injection of 2.4 million units of penicillin G benzathine is sufficient. Patients with late latent disease should receive three intramuscular injections of 2.4 million units of penicillin G benzathine, administered once a week for 3 weeks. Doxycycline can be substituted in patients who are allergic to penicillin.[4] Particularly in patients with HIV infection, neurosyphilis should be ruled out before therapy is initiated, because first-line treatment for neurosyphilis consists of either penicillin G potassium (aqueous penicillin) or penicillin G procaine with probenecid, administered daily for 10 to 14 days.

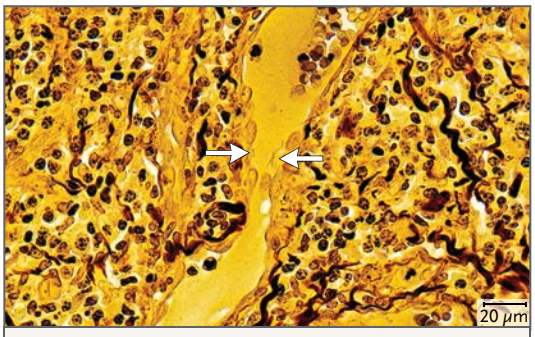

Figure 2. Tonsillar-Biopsy Specimen.
Warthin–Starry staining reveals spirochetes (arrows).

Although other antimicrobial agents have been studied for the treatment of syphilis, no others are recommended. Before the diagnosis, our patient received cephalexin, which may have some activity against syphilis. In a study performed in the 1970s, 11 of 14 patients with secondary syphilis (79%) had a good response to cephalexin, at a total dose of 30 g administered over a period of 15 days.[5] Our patient received only 20 g of cephalexin over a period of 10 days, which was not curative but which may have delayed the appearance of the rash.

Whereas syphilis rates declined between the early 1990s and early 2000s in the United States, cases of syphilis have more recently been increasing among men who have sex with men; infections in this population now comprise more than 70% of all cases of primary and secondary syphilis diagnosed in the United States. Coinfection with HIV is common. Among men who have sex with men, 40% of those who have received a diagnosis of syphilis are also infected with HIV.[6] Our patient underwent HIV testing at the second visit with his primary care physician, who recognized that a persistent sore throat and malaise may be indicative of acute HIV infection. The Centers for Disease Control and Prevention recommends that all men who have sex with men undergo testing for sexually transmitted diseases (HIV infection, gonorrhea, chlamydia, and syphilis) at least annually and that men at high risk (e.g., those with multiple or anonymous

sex partners or with a bacterial sexually transmitted disease in the previous 12 months) be tested as frequently as every 3 months.[7]

This case underscores the importance of taking a thorough sexual history. Had the patient's risk of sexually transmitted infection been recognized much earlier in the course of his symptoms, he could have been spared unnecessary procedures (including his tonsillectomy) and expense, and the risk of transmission to others would have been diminished. A survey of physicians indicated that 55% obtained a sexual history at an initial visit or annual examination, but far fewer discussed specific aspects such as the sex of the patient's partners, numbers of partners, and types of sexual activities, including anal or oral sex.[8] Physicians report a lack of time, a lack of appropriate training, cultural differences, and discomfort with discussing sexual activity as reasons for not taking a complete sexual history.[9,10] Patients may also be reluctant to divulge intimate information about sexual practices. Our patient did not initially report his sexual activity even when asked directly by the infectious diseases physician. It is possible that he did not consider oral sex to be sexual activity; a survey of heterosexual Canadian university students showed that nearly 60% did not consider oral sex as "having sex."[11]

Oral sex is common; in a 2002 national health survey in the United States, nearly 90% of men and women 25 to 44 years of age reported having had oral sex with an opposite-sex partner in their lifetime.[12] In a study involving young men who have sex with men, 80% reported having engaged in unprotected oral sex during the previous 6 months.[13] This case serves as a reminder that syphilis may be transmitted orally, as may other sexually transmitted diseases, such as gonorrhea, chlamydia, herpes simplex virus infection, and human papillomavirus infection.[14,15]

Accurate and timely diagnosis of syphilis is important not only for the patient, but also for public health. Sexually transmitted diseases are reportable diseases. In most jurisdictions, cases of syphilis must be reported to the public health department, which attempts to find and treat all sexual contacts of the index case ("partner management"). Taking a sexual history and keeping syphilis in the differential diagnosis for unexplained systemic illnesses, including unrelenting pharyngitis, are essential steps in this process.

Dr. Saint reports receiving fees for board membership from Doximity and Jvion. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Sheila Lukeheart, Ph.D., for performing molecular analysis and Rodney Schmidt, M.D., Ph.D., for providing images of tonsillar pathology.

REFERENCES

1. Kolios AG, Weber A, Spörri S, Trüeb RM, Navarini AA. Syphilitic pharyngitis. Arch Dermatol 2010;146:570-2.
2. Gedela K, Boag F. Syphilitic tonsillitis in primary care: a case report. Br J Gen Pract 2012;62:219-20.
3. Baarsma EA, Kazzaz B, Soei KI. Secondary syphilis of the tonsils. J Laryngol Otol 1985;99:601-3.
4. Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed. Philadelphia: Elsevier, 2009.
5. Duncan WC, Knox JM. Cephalexin therapy for infectious syphilis. Arch Dermatol 1974;110:77-80.
6. Sexually transmitted disease surveillance, 2011. Atlanta: Centers for Disease Control and Prevention, 2012 (http://www.cdc.gov/std/stats11/surv2011.pdf).
7. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.
8. Wimberly YH, Hogben M, Moore-Ruffin J, Moore SE, Fry-Johnson Y. Sexual history-taking among primary care physicians. J Natl Med Assoc 2006;98:1924-9.
9. Temple-Smith M, Hammond J, Pyett P, Presswell N. Barriers to sexual history taking in general practice. Aust Fam Physician 1996;25:Suppl 2:S71-S74.
10. Merrill JM, Laux LF, Thornby JI. Why doctors have difficulty with sex histories. South Med J 1990;83:613-7.
11. Byers ES, Henderson J, Hobson KM. University students' definitions of sexual abstinence and having sex. Arch Sex Behav 2009;38:665-74.
12. Mosher WD, Chandra A, Jones J. Sexual behavior and selected health measures: men and women 15-44 years of age, United States, 2002. Adv Data 2005;362:1-55.
13. Katz MH, McFarland W, Guillin V, et al. Continuing high prevalence of HIV and risk behaviors among young men who have sex with men: the Young Men's Survey in the San Francisco Bay Area in 1992 to 1993 and in 1994 to 1995. J Acquir Immune Defic Syndr Hum Retrovirol 1998;19:178-81.
14. Edwards S, Carne C. Oral sex and the transmission of viral STIs. Sex Transm Infect 1998;74:6-10.
15. Edwards S, Carne C. Oral sex and transmission of non-viral STIs. Sex Transm Infect 1998;74:95-100.

CLINICAL PROBLEM-SOLVING SERIES

The *Journal* welcomes submissions of manuscripts for the Clinical Problem-Solving series. This regular feature considers the step-by-step process of clinical decision making. For more information, please see authors.NEJM.org.