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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 4-2022: A 55-Year-Old Man with Bilateral Hearing Loss and Eye Redness

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PRESENTATION OF CASE

Dr. Mia Y. Bothwell (Medicine): A 55-year-old man was evaluated in the rheumatology clinic of this hospital because of bilateral hearing loss and eye redness.

The patient had been in his usual state of health until 8 weeks before the current evaluation, when a headache involving the left temple developed. A similar headache had occurred during an episode of shingles 15 years earlier. He received a prescription for a 1-week course of valacyclovir for the treatment of presumed shingles. No skin lesions developed, and the headache resolved.

Four weeks before the current evaluation, hearing loss in the left ear developed during an airplane flight. The hearing loss persisted after the flight, and the patient began to have intermittent tinnitus in the left ear and redness in both eyes. He was evaluated by an otolaryngologist at a clinic affiliated with this hospital. He reported no vertigo, otorrhea, rhinitis, or sore throat. On examination, there was redness in both eyes. The right and left auricles and external auditory canals were normal, as was the right tympanic membrane. The left tympanic membrane was retracted; there was no middle-ear effusion. Results of the Weber test were inconsistent. The Rinne test was positive bilaterally, with air conduction greater than bone conduction. There was no sinus tenderness. Nasopharyngoscopy revealed midseptal deviation to the left; the posterior aspect of the nasopharynx was normal. The remainder of the examination, including a cranial nerve examination, was normal.

An audiogram showed sloping mild-to-severe sensorineural hearing loss in both ears. Results were asymmetric at low frequencies, with more severe hearing loss in the left ear than in the right ear from 125 to 2000 Hz (Fig. 1A). Word recognition was 96% with the right ear and 84% with the left ear (reference range, 80 to 100). Results of tympanometry were normal in both ears. The patient received a prescription for a 12-day tapering course of oral prednisone. Magnetic resonance imaging (MRI) of the head, performed with and without the administration of intravenous contrast material, revealed no abnormal findings.

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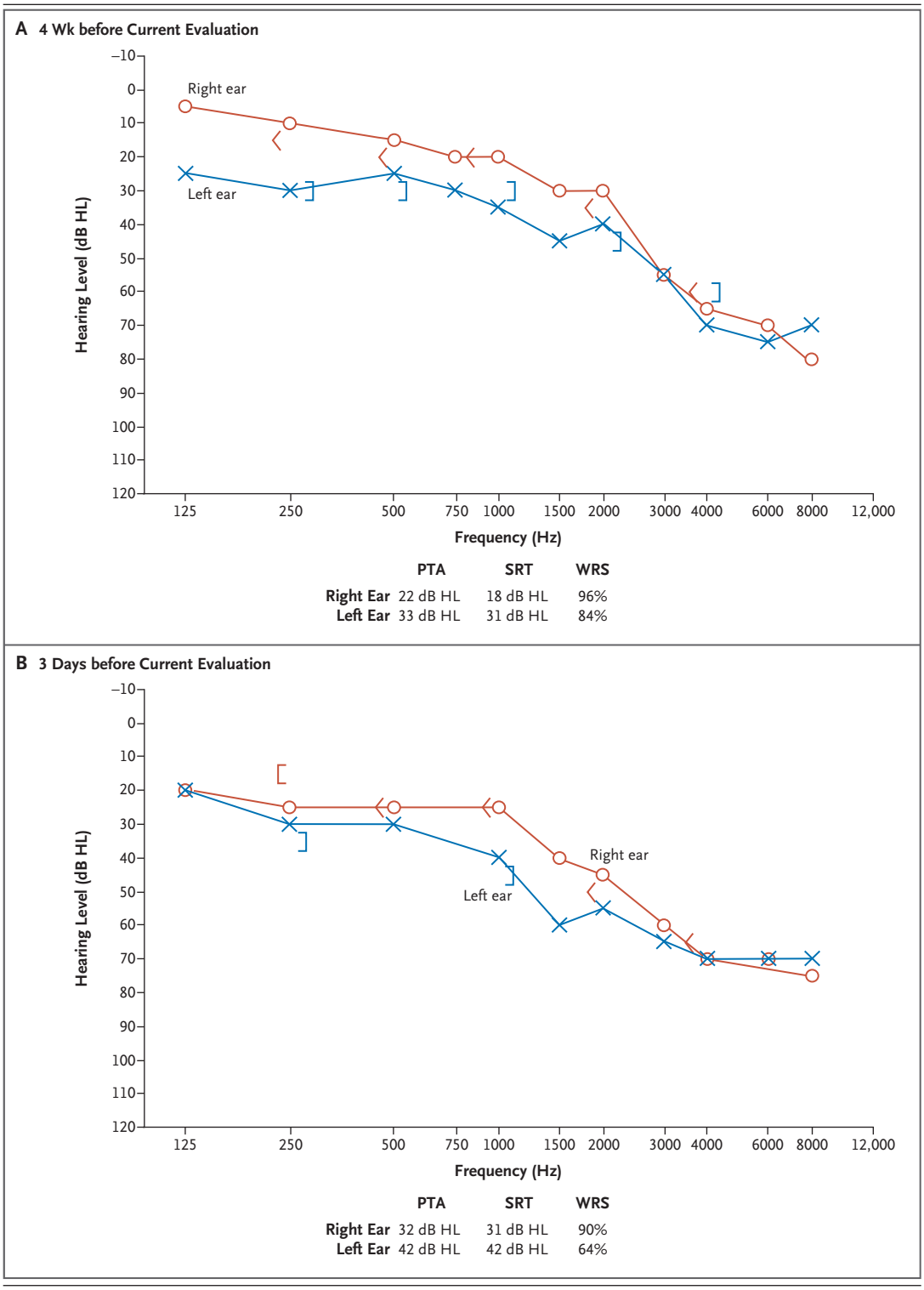

Four weeks later, the patient was evaluated by a different otolaryngologist at the clinic affiliated with this hospital. Hearing loss had progressed. Eye redness had initially decreased after prednisone therapy was started but had subsequently recurred after prednisone therapy was stopped. On examination, there was redness in both eyes. There was no spontaneous

Figure 1 (facing page). Audiograms.

An audiogram obtained 4 weeks before evaluation in the rheumatology clinic (Panel A) shows sensorineural hearing loss in both ears. The results are asymmetric, with more severe hearing loss in the left ear than in the right ear; the word recognition score (WRS) is 84% in the left ear. An audiogram obtained 3 days before evaluation in the rheumatology clinic (Panel B), after a course of prednisone therapy, shows worsening of hearing loss in both ears and reduction of the WRS to 64% in the left ear. The pure tone average (PTA) is the average of the hearing levels at three frequencies (500, 1000, and 2000 Hz) of tonal sounds (reference range, 0 to 25 dB HL). The speech reception threshold (SRT) is the softest hearing level at which the patient can repeat back spondaic words (reference range, 0 to 25 dB HL). The WRS indicates the patient's ability to repeat back words (reference range [good to excellent], 80 to 100%); the scores were obtained with words presented at a level of 72 dB HL in the right ear and 75 db HL in the left ear. The air-conduction threshold is indicated by a circle for the right ear and an X for the left ear. Bone-conduction thresholds are indicated by brackets and arrowheads, which open to the right for the right ear and open to the left for the left ear. HL denotes hearing level.

nystagmus or gait ataxia. Sinusoidal gaze tracking was normal. The head-thrust test to the left was positive, a finding that indicates vestibular hypofunction on the left side. Results of the Romberg test were normal. The Fukuda step test was positive, with the patient rotated to the left, a finding that also indicates vestibular hypofunction on the left side. A repeat audiogram showed worsening of sensorineural hearing loss and reduction of word recognition to 90% with the right ear and 64% with the left ear (Fig. 1B). Results of tympanometry were normal. The patient was referred for an urgent rheumatologic evaluation.

Three days later, in the rheumatology clinic at this hospital, the patient reported ongoing hearing loss in both ears and redness in both eyes, as well as the recent onset of imbalance. He also reported that he had had fatigue and intermittent body aches for 2 months and that he had lost 5 kg of weight over a 6-month period. There was no history of oral or genital lesions; 6 weeks earlier, a nonpruritic patchy rash had developed on his torso after he received the influenza vaccine and had rapidly resolved with the use of an oral antihistamine. There was a history of irritable bowel syndrome, diverticulosis, gastritis, allergic rhinitis, and asthma. Medications included intranasal and inhaled fluticasone, vitamin B_{12}, and omeprazole. There were no known drug allergies. The patient lived with his wife in an urban area of New England. For the past 12 years, he had been sexually active with his wife only. He was a retired construction worker. He was a nonsmoker, drank alcohol rarely, and did not use illicit drugs.

On examination, the patient appeared well. The temperature was 36.9°C, the blood pressure 115/79 mm Hg, the heart rate 95 beats per minute, the respiratory rate 15 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. There was redness in both eyes. The finger-rub test revealed grossly reduced hearing in both ears. The Romberg test was positive when the patient's eyes were open, a finding that indicates vestibular or cerebellar hypofunction. The remainder of the examination, including skin, joint, and neurologic assessments, was normal. Blood levels of electrolytes and glucose were normal, as were results of liver-function and kidney-function tests. The complete blood count with differential count was normal. The erythrocyte sedimentation rate was 55 mm per hour (reference range, 0 to 13), and the C-reactive protein level 12.3 mg per liter (reference value, <8.0). The patient was referred for an urgent ophthalmologic evaluation at this hospital, which was to take place on the same day.

On ophthalmologic evaluation, the patient reported no blurred vision, floaters, eye pain, itching, or photophobia. He wore contact lenses, which he changed daily. On examination, visual acuity was normal in both eyes. The right cornea had trace pinpoint epithelial deposits, a peripheral ring of punctate epithelial erosions, and several small confluent areas of punctate epithelial erosions centrally, with no infiltrate. The left cornea had a peripheral ring of punctate epithelial erosions and several confluent areas of punctate epithelial erosions centrally, with no infiltrate. There was evidence of anterior uveitis, with 7 cells per high-power field in the right anterior chamber and 6 to 7 cells per high-power field in the left anterior chamber. There was trace flare in both eyes.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Jeffrey P. Harris: This 55-year-old man presented with progressive hearing loss, imbalance, and

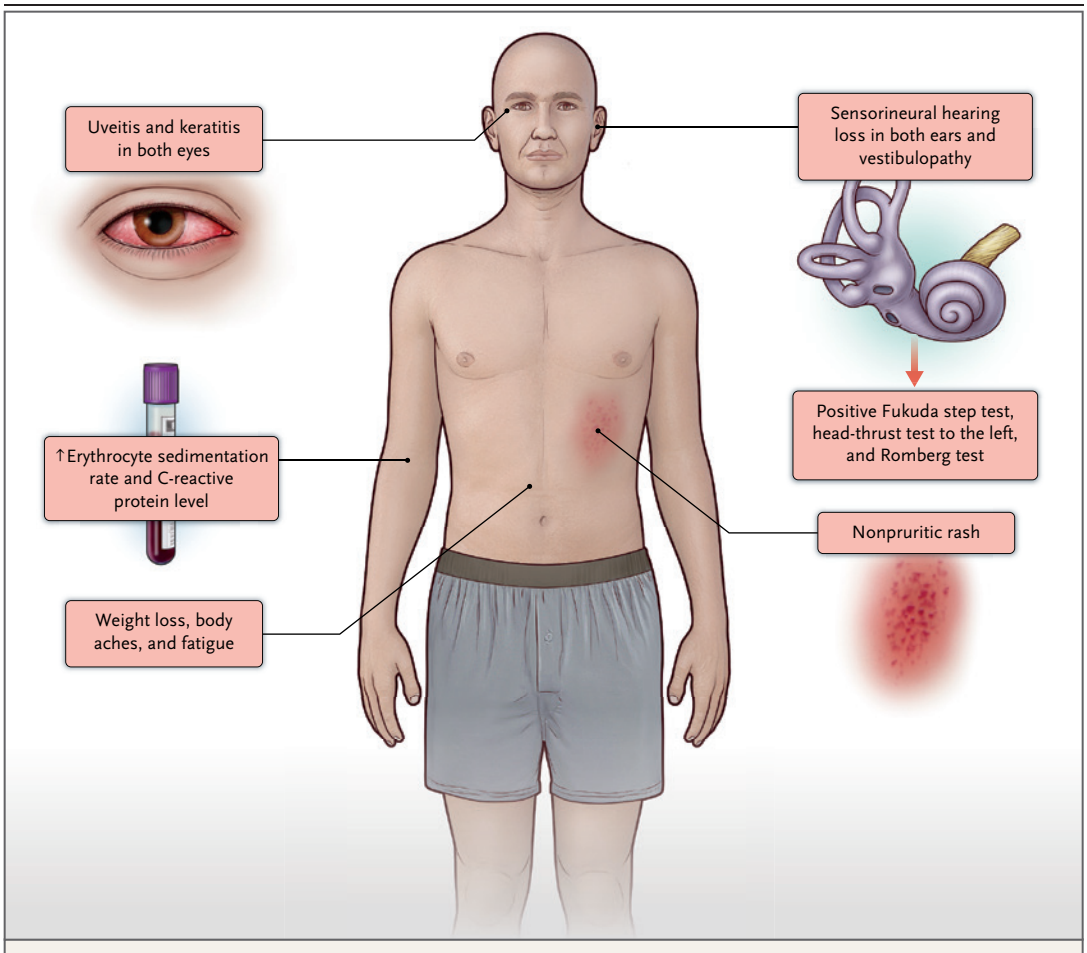

Figure 2. Salient Features of This Patient's Presentation.

ocular inflammation. A headache involving the left temple had occurred 8 weeks earlier. These symptoms were superimposed on a 6-month history of weight loss, a 2-month history of body aches and fatigue, and the occurrence of a nonpruritic rash on the torso (Fig. 2). During the evaluation, the erythrocyte sedimentation rate and C-reactive protein level were elevated. On the basis of this constellation of findings, I will focus my initial differential diagnosis on the conditions that cause temporal pain, asymmetric sensorineural hearing loss, and ocular inflammation.

TEMPORAL PAIN

The development of clinically significant temporal pain prompts consideration of temporal arteritis, a specific phenotype of giant-cell arteritis. Although hearing loss and elevations in the erythrocyte sedimentation rate and C-reactive protein level are consistent with this condition, the patient is young for the development of temporal arteritis; the mean age at onset is 72 years.[1,2] In addition, there was no jaw claudication or vision loss, and the lack of a response to glucocorticoids and the normal retinal examination make this possibility unlikely.[3]

The history of shingles suggests the possibility of a recurrence of herpes zoster oticus. However, there were no vesicles on the auricle or posterior auditory canal; the eye redness, without vesicles, crossed the midline to affect both eyes; and the rash on the torso was not in a dermatomal distribution. Audiovestibular symptoms can be a manifestation of herpes zoster oticus, but this patient did not have facial nerve

paresis, which often occurs. In addition, herpes zoster oticus does not affect both labyrinths.

ASYMMETRIC SENSORINEURAL HEARING LOSS AND DIZZINESS

Upper respiratory infection can lead to the acute onset of progressive hearing loss, known as sudden sensorineural hearing loss. However, the hearing loss would not involve both ears. A posterior fossa mass, such as a vestibular schwannoma, can cause both asymmetric sensorineural hearing loss and dizziness, and such tumors can occur bilaterally in patients with neurofibromatosis type 2. Leptomeningeal infiltration from lymphocytic leukemia, carcinomatosis, or neurosarcoidosis can also cause asymmetric sensorineural hearing loss.[4,5] However, the results of MRI in this patient rule out these possibilities. Meniere's disease involves both ears in 10 to 47% of cases.[6] However, this condition is not associated with ocular inflammation or systemic symptoms. Autoimmune inner ear disease is characterized by rapidly progressive asymmetric sensorineural hearing loss, and affected patients may have vestibular abnormalities. Autoimmune inner ear disease may occur in isolation or as part of a spectrum of rheumatologic conditions, but it would not explain this patient's ocular symptoms.[7]

INNER EAR AND OCULAR INVOLVEMENT

The patient had a positive Fukuda step test and a positive head-thrust test to the left; subsequently, a Romberg test was also positive. These findings suggest a vestibulopathy on the left side or a posterior-column disorder with altered proprioception. He had bilateral ocular inflammation, a finding consistent with keratitis and anterior uveitis, but he did not have loss of visual acuity, eye pain, or evidence of involvement of the posterior chamber or retinal artery. Conditions associated with both inner ear and ocular involvement and with systemic symptoms fall under three main categories: systemic vasculitides and rheumatologic diseases, autoinflammatory conditions, and infections.

Systemic Vasculitides and Rheumatologic Diseases

Inner ear and ocular involvement can be manifestations of several important systemic vasculitides and rheumatologic diseases.

Systemic lupus erythematosus can cause episcleritis and uveitis, but it typically affects the retinal vasculature, and such involvement was not observed in this patient. In addition, patients with lupus typically have high-frequency hearing loss, whereas this patient had low-frequency hearing loss.[8]

Patients with relapsing polychondritis can have both ocular inflammation and inner ear dysfunction. However, this patient did not have any joint involvement or inflammation of cartilage in the nose, auricle, trachea, or bronchus, features that would suggest a diagnosis of relapsing polychondritis.

Ankylosing spondylitis can cause hearing loss, but the hearing loss is usually mild and conductive in nature. In addition, patients with ankylosing spondylitis usually have uveitis in one eye at a time.[9]

Granulomatosis with polyangiitis is a disorder that causes tissue necrosis and vasculitis involving small and medium-sized vessels. Although the middle ear and nearly every structure in the eye can be involved, this patient did not have any lesions in the lungs, kidneys, or sinuses, features that would suggest a diagnosis of granulomatosis with polyangiitis.

Cogan's syndrome causes hearing loss, dizziness, and bilateral eye findings that were originally referred to as "nonsyphilitic keratitis." The eye findings include bilateral ocular inflammation, photophobia, and eye pain and may involve interstitial keratitis, episcleritis, scleritis, and uveitis. The onset of hearing loss, tinnitus, and vertigo is typically sudden and occurs within 3 to 4 months after the eye findings develop.[10] Temporal bone studies have shown osteoneogenesis of the cochlea.[11] Constitutional symptoms such as fever, fatigue, weight loss, myalgias, and arthralgias occur within 2 months after the onset of the illness. The erythrocyte sedimentation rate and C-reactive protein level are elevated.[10,12,13] Cogan's syndrome may have cardiovascular manifestations, such as aortitis. The incidence is increased in persons with HLA-B17, HLA-A9, HLA-Bw35, and HLA-Cw4. Anti-HSP70 antibodies have been reported to be present in 92.5% of patients with Cogan's syndrome and have also been found in patients with autoimmune inner ear disease and rapidly progressive sensorineural hearing loss.[14,15] This patient had

most of the signs and symptoms of Cogan's syndrome, so it remains a top consideration in this case.

Autoinflammatory Conditions

Several autoinflammatory disorders may have inner ear and ocular involvement.

Susac's syndrome causes both ocular inflammation and sensorineural hearing loss. However, the condition is characterized by encephalopathy and retinal-artery occlusion, which were absent in this patient.

Patients with Behçet's syndrome can present with anterior and posterior uveitis, hearing loss, and tinnitus. However, this patient did not have skin, oral, or genital ulcerations, which are hallmarks of this condition.

Paraneoplastic syndromes, which are due to an altered immune response to an underlying cancer, can also cause inner ear and eye deficits.[16] These syndromes occur in 8% of patients with cancer and are most frequently associated with lung, breast, hematologic, medullary thyroid, gynecologic, and prostate cancers. This patient did not have a known underlying cancer.

Infections

Several well-recognized infections can cause simultaneous inner ear and ocular involvement and must be considered.

Tuberculosis can be associated with numerous eye symptoms, ranging from lid to retinal symptoms. It can also involve the middle ear and mastoid sinus by passing through the eustachian tube. Tuberculosis can result in clinically significant destruction, including multiple tympanic membrane perforations and middle-ear inflammation, which can lead to hearing loss and dizziness. This patient had no evidence of a process involving the middle ear or mastoid.[17] In addition, if he were to have tuberculosis involving the central nervous system, I would expect him to be much sicker.

Lyme disease, which is caused by *Borrelia burgdorferi*, is a great masquerader that can mimic many of the diseases discussed. It is endemic in the Northeast region of the United States, where this patient lives, and can cause constitutional symptoms such as myalgias, weight loss, and fatigue. It can also cause sensorineural hearing loss and vertigo, as well as uveitis and episcleritis.[18] The erythrocyte sedimentation rate and C-reactive protein level may be elevated. Although erythema migrans (the bull's-eye rash) is characteristic of this infection, the rash does not develop in 20 to 30% of patients, and some patients may not be aware that they have been bitten by a tick. Joint involvement is seen in up to 60% of cases, and neurologic abnormalities such as facial nerve paralysis are reported in 15 to 20% of cases.[19] Although this patient's rash was not consistent with erythema migrans and he did not have any joint swelling, I cannot dismiss Lyme disease as a possible diagnosis.

Sir William Osler aptly said, "He who knows syphilis knows medicine." Although this patient indicated that he had been monogamous for the past 12 years, the preceding history is unknown. His constitutional symptoms of weight loss, myalgias, arthralgias, and headache and the elevations in the erythrocyte sedimentation rate and C-reactive protein level are consistent with syphilis. Neurosyphilis can cause progressive bilateral sensorineural hearing loss and vertigo; histopathological studies have shown involvement of the temporal bone and its marrow spaces, the incus, and the region of the endolymphatic sac, which can lead to endolymphatic hydrops.[20,21] Neurosyphilis is also a well-known cause of episcleritis, keratitis, and uveitis. This patient briefly had a nonpruritic rash on his torso, which could be consistent with the secondary stage of syphilis. He had a positive Romberg test, which suggests a disease process affecting the posterior column with an alteration in proprioception, a classic finding of tabes dorsalis, a complication of late-stage syphilis.

In summary, the list of systemic disorders associated with eye and ear involvement and with constitutional signs and symptoms is broad.[22] However, this patient's presentation is most consistent with Cogan's syndrome or a spirochetal infection — either syphilis or Lyme disease. Among these entities, syphilis is the best clinical fit in this case. To establish the diagnosis of syphilis, I would perform a lumbar puncture with cerebrospinal fluid (CSF) analysis to look for pleocytosis and to conduct the Venereal Disease Research Laboratory (VDRL) test and the fluorescent treponemal-antibody absorption (FTA-ABS) test.[23]

DR. JEFFREY P. HARRIS'S DIAGNOSIS

Syphilis.

DIAGNOSTIC TESTING

Dr. Elisabeth S. Tabb: Diagnosis of syphilis can be challenging because of the broad spectrum of clinical manifestations and the lack of a single definitive test.[24] Since the pathogen that causes syphilis, *Treponema pallidum*, is difficult to culture, serologic testing is the most common diagnostic approach.

The first test in our algorithm is a qualitative, automated chemiluminescence microparticle immunoassay that detects IgM and IgG to *T. pallidum* in serum, confirming the presence of *T. pallidum*–specific antibodies. The test was reactive in this patient. When the first test is positive, we then use the same serum specimen to perform a nontreponemal assay, the rapid plasma reagin (RPR) test. We perform serial dilutions to determine the end-point antibody titer. The patient's RPR test was positive at 1:512. Overall, both a treponemal test and a nontreponemal test were positive; these results are interpreted as consistent with current or past syphilis.

Laboratory testing is helpful in supporting the diagnosis of neurosyphilis. However, no single test can be used to establish the diagnosis. The diagnosis of neurosyphilis depends on the combination of CSF tests (measurement of the white-cell count and protein level and a reactive VDRL test), a reactive serologic test, and the presence of neurologic signs and symptoms. The CSF FTA-ABS test is a treponemal test that is less specific for neurosyphilis than the CSF VDRL test but is highly sensitive.[25,26] A lumbar puncture was performed in this patient. CSF analysis showed colorless nonturbid fluid, with 21 nucleated cells per cubic millimeter, 54% neutrophils, 22% lymphocytes, 24% monocytes, and a total protein level of 83 g per deciliter. The CSF VDRL test was reactive at 1:2; this result supports a diagnosis of neurosyphilis. Ocular manifestations that can be associated with neurosyphilis include syphilitic uveitis, which was present in this patient.[25]

LABORATORY DIAGNOSIS

Infection with *Treponema pallidum* (syphilis).

DISCUSSION OF MANAGEMENT

Dr. Andrea L. Ciaranello: Our colleagues at the rheumatology clinic referred this patient for an outpatient follow-up visit in the infectious disease clinic at the time that the RPR test was sent for analysis. Before his scheduled visit, we were notified of his positive RPR test by the state health department, and we asked the patient to present to the emergency department for evaluation and treatment.

On arrival in the emergency department, the patient noted unchanged eye redness and hearing loss but had no other symptoms. We performed antigen and antibody tests for human immunodeficiency virus and urinary nucleic acid tests for gonorrhea and chlamydia, all of which were negative. The patient's wife underwent antibody testing for syphilis, which was negative. Treatment with a 14-day course of intravenous penicillin was initiated in the patient.

We saw the patient for a virtual outpatient follow-up visit on the third day of therapy, and he noted a marked decrease in the eye redness. During the next 4 months, he continued to attend follow-up visits with rheumatology, otolaryngology, and infectious disease consultants. A slow, modest decrease in sensorineural hearing loss was noted. He also reported episodes of recurrent tinnitus and new vertigo that began a few weeks after therapy concluded; the episodes were brief and occurred infrequently, without improvement or worsening over the 4-month period. A follow-up assessment, which will include performing a serum RPR test and obtaining a CSF sample to measure the white-cell count and protein level and to perform a VDRL test, is planned for 6 months after the completion of therapy.

A physician: What is the proposed pathophysiological process that leads to ear involvement in patients with otosyphilis?

Dr. Harris: There is evidence that *T. pallidum* disseminates hematogenously throughout the body and presumably into the temporal bone. It is also likely that in the late stages, it gains entry to the inner ear when CSF passes through the internal auditory canal or the cochlear aqueduct. The inner ear is immunoresponsive, and *T. pallidum* should invoke both a humoral antibody response and activation of innate immunity through

proinflammatory cytokines and CD4+ and CD8+ T cells. All the necessary components for this response reside in the inner ear in the region of the endolymphatic sac.[27,28] However, it is thought that antigenic variation of the surface-exposed protein of *T. pallidum*, TprK, may contribute to the lack of a vigorous immune response.

Another physician: Would continuation of glucocorticoids after diagnosis and treatment of syphilis increase the likelihood of hearing recovery?

Dr. Harris: Patients with various forms of rapidly progressive sensorineural hearing loss are typically treated early with high-dose, and at times intratympanic, glucocorticoid therapy, which may reverse the hearing loss and dizziness. Treatment of neurosyphilis with antibiotic therapy alone may result in management of the infection, but glucocorticoids are required to reduce the inflammatory response in the inner ear and prevent irreversible fibrosis and osteoneogenesis. Therefore, if the patient received long-term antibiotic therapy consistent with recommendations of the Centers for Disease Control and Prevention, I would treat with glucocorticoids.[29]

FINAL DIAGNOSIS

Neurosyphilis.

This case was presented at Neurology Grand Rounds.

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

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