CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL



# Case 20-2016: A 50-Year-Old Man with Cloudy Vision, Hearing Loss, and Unsteadiness

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## PRESENTATION OF CASE

*Dr. Eric D. Gaier* (Ophthalmology): A 50-year-old man with psoriatic arthritis and human immunodeficiency virus (HIV) infection was seen at the Massachusetts Eye and Ear Infirmary because of cloudy vision.

The patient had been in his usual state of health until 3 days before this evaluation, when cloudy vision in both eyes developed gradually over the course of the day. Three days later, he sought medical attention at the emergency department of the Massachusetts Eye and Ear Infirmary. On arrival, he reported fatigue. He also reported that the rash, joint pain, and stiffness associated with his psoriatic arthritis had recently worsened.

Sixteen years before this evaluation, the patient had had laser surgery for a retinal tear in the left eye. Ten months before this evaluation, he had had an episode of *Pneumocystis jirovecii* pneumonia that led to an evaluation for and diagnosis of HIV infection, and he had begun taking antiretroviral medications 2 months before this evaluation. Six weeks before this evaluation, he had been admitted to another hospital because of hypotension, hyponatremia, pancytopenia, and acute kidney injury; the serum alkaline phosphatase level was elevated, the CD4 count and blood cortisol level were low, and blood cultures had no growth. Adrenal insufficiency, disseminated infection with *Mycobacterium avium–intracellulare*, and the immune reconstitution inflammatory syndrome were suspected. Antiretroviral medications were stopped, and azithromycin, rifabutin, ethambutol, hydrocortisone, and fludrocortisone were administered, as was trimethoprim–sulfamethoxazole three times weekly. Two weeks before this evaluation, emtricitabine, tenofovir, ritonavir, and darunavir were again initiated. The patient had no known allergies. He lived with his husband, did not smoke tobacco or use illicit drugs, and drank alcohol socially.

On examination, the patient was alert and oriented to person, place, and time. The pulse was 91 beats per minute, the blood pressure 121/77 mm Hg, the respiratory rate 20 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. Ophthalmologic examination revealed visual acuity of 20/25 in the right eye and 20/30 in the left eye. The pupils were equally round

and reactive to light; there was no relative afferent pupillary defect. The visual fields were full in response to confrontation. Examination of extraocular motility revealed full motility in both eyes. The intraocular pressure was 8 mm Hg in the right eye and 7 mm Hg in the left eye. Slit-lamp examination revealed 1+ injection of the conjunctivae, 2+ cells in the right anterior chamber, 4+ cells in the left anterior chamber, no hypopyon, and diffuse fine and large keratic precipitates on the corneas. Indirect ophthalmoscopy revealed 1+ vitreous cells and normal fundi with cup-to-disk ratios of 0.3 bilaterally.

The platelet count, red-cell indexes, anion gap, and results of renal-function tests were normal, as were blood levels of calcium, glucose, uric acid, total protein, albumin, globulin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and direct bilirubin. Other laboratory test results are shown in Table 1. The patient was discharged home with topical ophthalmic prednisolone for presumed psoriatic arthritis–associated iritis.

Five days later, the patient was seen at a follow-up visit, and cloudy vision persisted. The patient also reported that decreased hearing and difficulty balancing had developed synchronously with his ocular symptoms. On examination, visual acuity was 20/30 in the right eye and 20/40 in the left eye. Anisocoria was present in both bright and dim lighting conditions; there was a subtle relative afferent pupillary defect in the left eye. The intraocular pressure was 12 mm Hg in the right eye and 11 mm Hg in the left eye. Slit-lamp examination revealed trace injection of the superior conjunctiva of the left eye, 1+ cells in the anterior chambers, posterior synechiae at the 3 o'clock position of the right eye, extensive posterior synechiae of the left eye, and diffuse fine and large keratic precipitates on the corneas that were more abundant in the left eye than in the right eye. Indirect ophthalmoscopy revealed normal fundi, 1+ vitreous cells in the right eye, and 2+ vitreous cells in the left eye.

A diffuse rash characterized by erythematous plaques and overlying white scale was present and involved the face, abdomen, back, arms, legs, palms, and soles (Fig. 1). Results of serologic testing that had been performed during the emergency department visit 5 days earlier were received. The angiotensin-converting–enzyme level was 80 U per liter (reference range, 9 to 67), and the lysozyme level 14.9 $\mu$g per milliliter (reference range, 7.0 to 15.0). Antinuclear antibodies were absent, HLA-B27 was present, and a screening test for antibodies to *Borrelia burgdorferi* was positive. Topical ophthalmic prednisolone was continued, and ophthalmic cyclopentolate

**Table 1. Laboratory Data.**

| Variable | Reference Range, Adults* | On Presentation |
|---|---|---|
| Hemoglobin (g/dl) | 14.0–18.0 | 10.8 |
| Hematocrit (%) | 41.0–53.0 | 31.7 |
| White-cell count (per mm$^3$) | 4800–10,800 | 4400 |
| Differential count (%) | | |
| Neutrophils | 40–70 | 57 |
| Band forms | 0–10 | 3 |
| Lymphocytes | 22–44 | 23 |
| Monocytes | 4–11 | 15 |
| Eosinophils | 0–8 | 1 |
| Basophils | 0–3 | 1 |
| Erythrocyte sedimentation rate (mm/hr) | ≤20 | 105 |
| Sodium (mmol/liter) | 135–145 | 137 |
| Potassium (mmol/liter) | 3.5–5.0 | 4.3 |
| Chloride (mmol/liter) | 100–108 | 98 |
| Carbon dioxide (mmol/liter) | 23.0–31.9 | 28.1 |
| Alkaline phosphatase (U/liter) | 45–115 | 124 |
| C-reactive protein (mg/liter) | 0.0–8.0 | 18.6 |

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts Eye and Ear Infirmary are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

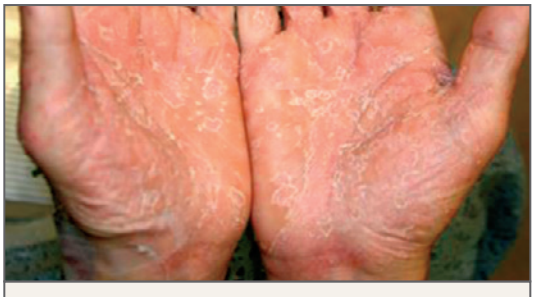

**Figure 1. Photograph of the Hands.**
The patient had a rash characterized by erythematous plaques and overlying white scale involving the face, abdomen, back, arms, legs, feet, and hands, including the palms.

was prescribed for the presumptive diagnosis of psoriatic arthritis–associated iritis.

Eleven days after the initial presentation, the patient was seen by an otolaryngologist because his hearing loss and unsteadiness had worsened. An audiogram revealed moderate sensorineural hearing loss that was worse on the left side than on the right. Later that day, the patient returned to the Massachusetts Eye and Ear Infirmary because of worsened visual cloudiness and a new floater in the right eye. On examination, the visual acuity was 20/100 in the right eye and 20/375 in the left eye. Anisocoria was present. There was no relative afferent pupillary defect. The intraocular pressure was 8 mm Hg in both eyes. Slit-lamp examination revealed extensive keratic precipitates on the corneas, 4+ cells in the right anterior chamber, and 3+ cells in the left anterior chamber. Indirect ophthalmoscopy revealed 3+ vitreous cells in the right eye with 2+ vitreous haze and 4+ vitreous cells in the left eye with 4+ vitreous haze. There were many small, yellow bilateral inferotemporal preretinal infiltrates.

Optical coherence tomography revealed shadowing from vitreous opacities and a normal foveal contour in the right eye; in the left eye, there was a poor view of the retina, and an image of the macula could not be obtained. Fluorescein angiography revealed a hazy view of the right eye with staining of the peripheral retina, particularly inferiorly, as well as a very hazy view of the left eye with some leakage and staining of the retina nasally and temporally (Fig. 2). A repeat test for *B. burgdorferi* antibodies was negative.

A diagnostic test result was received.

## DIFFERENTIAL DIAGNOSIS

*Dr. Dean Eliott:* This 50-year-old man presented with visual loss in both eyes. Notable features of the patient's medical history include psoriatic arthritis, advanced HIV infection complicated by multiple opportunistic infections, and current treatment with antiretroviral therapy and with other medications, including rifabutin for presumed *M. avium–intracellulare* infection. On examination, he was noted to have hearing loss, balance instability, rash, uveitis, and retinitis. I will formulate my differential diagnosis by first considering the patient's current diagnoses and therapies and the systemic conditions that are consistent with his clinical findings and then attempting to tie in the specific ocular findings to establish a unifying diagnosis in this case.

### PSORIATIC ARTHRITIS

Psoriatic arthritis is a seronegative spondyloarthropathy that is associated with HLA-B27 expression, which was present in this patient. He had worsening joint pain, stiffness, and rash. The rash involved the face, abdomen, back, arms, legs, palms, and soles and was characterized by erythematous plaques and overlying white scale, features consistent with this condition. Uveitis is a common finding in patients with psoriatic arthritis; however, such patients typically have nongranulomatous anterior uveitis (confined to the anterior chamber), whereas this patient had granulomatous panuveitis (involving the anterior chamber and vitreous cavity). Posterior-segment findings occasionally occur and consist of macular edema. In contrast, this patient had retinitis, with no evidence of macular edema on examination, optical coherence tomography, or fluorescein angiography. Vestibuloauditory findings can be seen in patients with psoriatic arthritis, and this patient had hearing loss and balance problems. Although there is substantial overlap between this patient's systemic findings and the features of psoriatic arthritis, this condition cannot account for all the findings.

### HIV INFECTION

HIV infection typically causes a retinal microangiopathy characterized by the development of dot–blot hemorrhages and cotton-wool spots, but it does not result in panuveitis or retinitis in the absence of an active associated opportunistic infection. This patient had a history of HIV-associated opportunistic infections with pneumocystis and *M. avium–intracellulare*. In patients with severe immunosuppression, systemic infection with pneumocystis can cause multifocal choroiditis characterized by multiple gray-white plaques that are confined to the choroid; in these cases, there is minimal or no aqueous or vitreous inflammation. In contrast, this patient had substantial intraocular inflammation and retinal involvement. Systemic infection with *M. avium–intracellulare* can also cause multifocal choroiditis characterized by multiple choroidal lesions with relatively clear aqueous and vitreous. This diagnosis would also be unlikely in this patient.

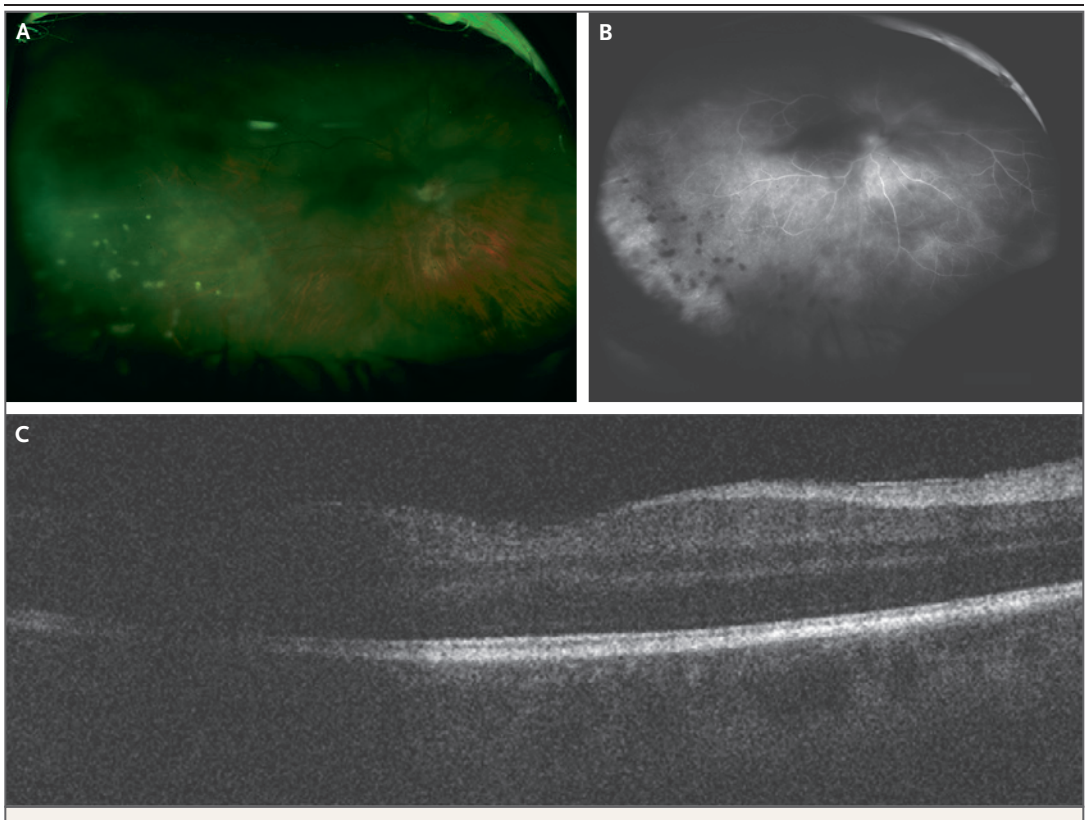


**Figure 2. Imaging Studies of the Right Eye.**

A wide-angle fundus photograph (Panel A) shows areas of vitreous haze, as well as multiple inferotemporal white dots overlying an oval area of mild, diffuse retinal whitening (the green color is an artifact). A wide-angle late frame from a fluorescein angiogram (Panel B) shows blocked fluorescence from the areas of vitreous haze and the multiple inferotemporal white dots; there does not appear to be any leakage from the disk, macula, or retinal vessels. An optical coherence tomographic image, obtained at the center of the macula (Panel C), shows a diminished signal temporally, presumably from the vitreous haze; the retinal layers appear intact, and there is no macular edema or subretinal fluid.

### CURRENT THERAPIES

Some of this patient's medications may cause ocular findings, either through immune reconstitution or toxic effects. Initiation of antiretroviral therapy occasionally causes immune recovery uveitis due to immune reconstitution. This may occur in a patient with a history of retinitis, which is usually caused by cytomegalovirus; however, this patient has no known history of retinitis or findings suggestive of previous retinitis due to cytomegalovirus or another pathogen. Immune recovery uveitis is associated with aqueous and vitreous inflammation, which was seen in this patient, and it may also be associated with retinal findings, such as macular edema and an epiretinal membrane, which this patient did not have. On the basis of this patient's history and the presence of active retinitis, we can rule out immune recovery uveitis.

The *M. avium–intracellulare* infection was being treated with rifabutin, and use of this medication has been associated with uveitis. In patients with rifabutin-associated uveitis, the inflammation of the anterior chamber typically includes the presence of a hypopyon (layered white cells in the anterior chamber), and vitreitis is often present. This patient did not have a hypopyon, and rifabutin does not account for the retinal findings; thus, rifabutin-associated uveitis is unlikely.

### CLINICAL FINDINGS

This patient had hearing loss and balance instability. In addition to psoriatic arthritis, Cogan's

syndrome is associated with both vestibuloauditory dysfunction and ophthalmic findings. Cogan's syndrome is an immunologic condition characterized by chronic inflammation, systemic vasculitis, and ocular manifestations, including interstitial keratitis, uveitis consisting of aqueous or vitreous inflammation, and retinal vasculitis. Vestibuloauditory dysfunction is a hallmark of Cogan's syndrome. However, there is no mention that this patient had interstitial keratitis, and retinitis is not associated with this condition.

Syphilis can cause hearing loss, balance problems, and ocular findings. The primary and secondary stages of syphilis are associated with dermatologic findings, as well. The rash of secondary syphilis can appear anywhere on the body; it may involve the palms and soles, and the lesions can mimic those seen in psoriasis. Syphilis can be associated with arthritis, and this patient had worsening joint pain. Syphilis can also cause uveitis and retinitis. The uveitis can be anterior, posterior, or both (panuveitis) and can occur with or without a hypopyon (usually without).

#### GRANULOMATOUS UVEITIS

This patient had granulomatous uveitis with both aqueous and vitreous inflammation (panuveitis). A variety of infectious, immunologic, and neoplastic diseases have been associated with granulomatous uveitis. Bacterial causes include *Treponema pallidum*, *B. burgdorferi*, *M. tuberculosis*, and a variety of gram-positive and gram-negative organisms that can cause endogenous endophthalmitis. Viruses that have been associated with granulomatous uveitis include herpes simplex virus types 1 and 2, varicella–zoster virus, and cytomegalovirus. Parasites (e.g., *Toxoplasma gondii*), fungi (e.g., candida, aspergillus, and cryptococcus), immunologic diseases (e.g., Vogt–Koyanagi–Harada disease, sympathetic ophthalmia, sarcoidosis, and Behçet's disease), and cancers (e.g., vitreoretinal lymphoma) may all cause granulomatous uveitis. In order to narrow the broad differential diagnosis of granulomatous uveitis in this patient, we next must consider the retinal lesions.

#### RETINITIS

This patient had retinal lesions that were described as preretinal infiltrates. Fundus photographs show vitreitis, a normal optic disk, normal retinal vessels, a normal macula, and a large, oval, gray-white area inferotemporal to the macula with a relatively uniform appearance and with a border that can be determined but is not sharply defined. This area appears to be in the retina and thus represents an area of retinitis that can be best described as having a ground-glass appearance. Multiple focal whitish opacities are present that appear to be on the retinal surface and only over the area of retinitis; these accumulations are consistent with superficial retinal precipitates. The fluorescein angiogram shows multiple focal areas of blocked fluorescence from the superficial retinal precipitates. Hence, the preretinal infiltrates can be more accurately described as an area of retinitis with a ground-glass appearance and with overlying superficial retinal precipitates.

Retinitis has a wide differential diagnosis, including infectious, immunologic, and neoplastic causes. All the infectious agents that I have listed as causes of granulomatous panuveitis can cause retinitis, with the addition of bartonella species. Immunologic causes of retinitis include sarcoidosis and Behçet's disease. Neoplastic causes include vitreoretinal lymphoma and, in rare cases, retinal metastasis.

Syphilis can affect every part of the eye and can result in a multitude of findings. It can cause retinal vasculitis, serous retinal detachment, posterior placoid chorioretinopathy, neuroretinitis, multifocal retinitis, and other findings, including ground-glass retinitis. Superficial retinal precipitates can also be present; they are presumed to be focal inflammatory accumulations on the retinal surface. In fact, superficial retinal precipitates are strongly suggestive of syphilis.[1]

Many other bacterial causes of retinitis can be easily ruled out in this case. Lyme disease may cause retinal vasculitis and neuroretinitis, findings that are not present in this patient. The serologic screening was positive for *B. burgdorferi*; however, repeat testing was negative, and the patient did not have a history of tick exposure or an erythema migrans rash, features that would be suggestive of Lyme disease. Patients with syphilis can have a false positive test for Lyme disease because of cross-reactivity, which I suspect occurred in this patient. Tuberculosis can cause choroiditis and choroidal granuloma, findings that were not present in this patient. Patients

with endogenous endophthalmitis present with a focus of vitreous inflammation overlying a retinal infiltrate, and an extraocular focus of infection is often the source. Patients with cat scratch disease may present with neuroretinitis and small, white retinal and choroidal lesions.

Patients with viral diseases typically present with severe retinitis. Acute retinal necrosis is most commonly manifested by confluent white patches of peripheral necrotizing retinitis with sharp borders, although it may be manifested by multifocal lesions and may occur in the posterior pole. Acute retinal necrosis can be associated with varying degrees of vitreitis and occlusive arteritis. The condition is most commonly caused by varicella–zoster virus but can also be caused by herpes simplex virus types 1 and 2, and affected patients may be immunocompromised or immunocompetent. This patient had no evidence of occlusive vasculitis and the appearance of his retinitis was not typical of acute retinal necrosis, although the retinal periphery cannot be seen on fundus photographs. Progressive outer retinal necrosis is a rapidly progressive, severe necrotizing retinitis caused by varicella–zoster virus. It occurs in severely immunosuppressed patients and typically occurs with only minimal vitreitis. The absence of rapid progression in this patient rules out the diagnosis. Cytomegalovirus retinitis is the most common retinal infection in patients with HIV infection and is manifested by hemorrhagic or granular areas of retinitis with very slow progression. The retinitis in this patient was neither hemorrhagic nor granular, and thus this diagnosis is unlikely.

The parasite *T. gondii* is a common cause of retinochoroiditis in both immunosuppressed and immunocompetent patients. It is typically manifested by a focal area of yellow-white retinitis with an overlying focal or diffuse vitreitis, with or without an adjacent chorioretinal scar. The retinitis in this patient was not focal and therefore not likely to be caused by this organism. Fungal infection with candida species typically produces one or more small focal areas of whitish retinochoroiditis with overlying focal vitreitis, aspergillus infection produces a large area of white retinitis with vitreitis, and cryptococcus infection commonly causes a choroiditis; none of these features were present in this patient.

Immunologic conditions are a common cause of uveitis and may include retinitis. Sarcoidosis is typically manifested by anterior uveitis, posterior uveitis, or panuveitis with one or more choroidal granulomas. This patient had an elevated angiotensin-converting–enzyme level, which may be present in patients with sarcoidosis, but the appearance of the retinitis rules out this diagnosis in this case. The elevated angiotensin-converting–enzyme level may represent widespread activation of macrophages. Behçet's disease often causes retinal vasculitis, which may include foci of inner retinal whitening, usually in association with mucocutaneous lesions. Neoplastic involvement of the uvea and retina is rare, but it often masquerades as posterior uveitis. Posterior-segment findings associated with vitreoretinal lymphoma may include white plaques under the retinal pigment epithelium and irregularly shaped, whitish, focal retinal lesions; these findings were not present in this patient.

## SUMMARY

This patient had hearing impairment, gait instability, arthritis, and a rash characterized by erythematous, scaly lesions on the palms and soles. Taking into account the patient's systemic findings and the presence of granulomatous uveitis and ground-glass retinitis with overlying superficial retinal precipitates, the most likely diagnosis is secondary syphilis with neurologic, ophthalmic, and otologic involvement. The next step would be to perform serologic tests for syphilis.

*Dr. Eric S. Rosenberg* (Pathology): Dr. Papaliodis, what was your initial impression when you evaluated this patient?

*Dr. George N. Papaliodis:* This patient's constellation of findings, including the appearance and distribution of the rash involving his palms and soles, was suggestive of syphilis. However, on further questioning of the patient, he stated that previous exacerbations of his psoriasis had been manifested by a scaly rash that had involved his palms and soles.

Given the patient's medical history and clinical presentation, our differential diagnosis included psoriatic arthritis, immune recovery uveitis, Lyme disease, and syphilis. The patient had an established diagnosis of psoriatic arthritis, and uveitis develops as an associated manifestation in approximately 7% of patients with this condition.[2] Immune recovery uveitis has been described in patients with HIV infection in whom antiretroviral therapy has been initiated[3]; this

patient had started receiving antiretroviral therapy several weeks before the onset of his ocular manifestations. Lyme disease and syphilis can both cause granulomatous uveitis and rash.

The patient's decreased hearing and disequilibrium developed synchronously with his ocular symptoms. Diseases that can induce uveitis and auditory involvement include Cogan's syndrome, Vogt–Koyanagi–Harada disease (a multisystem inflammatory disorder characterized by panuveitis and associated with neurologic and cutaneous manifestations, including headache, hearing loss, vitiligo, and poliosis), Lyme disease, and syphilis.

Testing for syphilis had been performed before I evaluated this patient. While waiting for the results, I continued to prescribe topical glucocorticoids and obtained an otolaryngologic consultation.

## CLINICAL DIAGNOSIS

Secondary syphilis.

## DR. DEAN ELIOTT'S DIAGNOSIS

Secondary syphilis with neurologic, ophthalmic, and otologic involvement.

## PATHOLOGICAL DISCUSSION

*Dr. Sarah E. Turbett:* The diagnostic tests in this patient were a fluorescent treponemal antibody absorption test, which was reactive, and a rapid plasma reagin test, which was reactive at a titer of 1:128. These findings were confirmed by the Massachusetts Department of Public Health State Laboratory with a positive *T. pallidum* passive particle agglutination assay and a repeat rapid plasma reagin test, which was reactive at a titer of 1:16. Given the patient's neurologic symptoms, a lumbar puncture was performed. Analysis of the cerebrospinal fluid revealed a total protein level of 142 mg per deciliter (reference range, 15 to 45), a white-cell count of 75 per cubic millimeter (reference range, 0 to 8), and a positive Venereal Disease Research Laboratory test at a titer of 1:4. These results, in combination with the clinical presentation, are diagnostic of secondary syphilis with neurologic, ocular, and otologic involvement.

## DISCUSSION OF MANAGEMENT

*Dr. Marlene L. Durand:* Prompt initiation of antibiotic treatment in patients with ocular syphilis is essential to prevent irreversible vision loss. A lumbar puncture is recommended for all patients with ocular syphilis or otosyphilis to determine whether there is concomitant involvement of the central nervous system, but antibiotic treatment should not be delayed if the patient declines to undergo a lumbar puncture or if the procedure cannot be performed promptly. Normal results of a cerebrospinal fluid analysis do not rule out ocular syphilis, because *T. pallidum* may infect the eye without infecting the brain or meninges. Immediate treatment for ocular syphilis should be given regardless of the results of cerebrospinal fluid analysis.

Ocular syphilis, otosyphilis, and neurosyphilis (i.e., syphilis with brain or meningeal involvement) all require treatment with a 10-to-14-day course of high-dose intravenous penicillin, which was administered in this patient. Glucocorticoids, such as prednisone, are often given concurrently with intravenous penicillin in patients with acute ocular syphilis or otosyphilis to reduce inflammation. After the course of intravenous penicillin is completed, some clinicians also give intramuscular penicillin G benzathine. Patients whose initial results of cerebrospinal fluid analysis are consistent with neurosyphilis should undergo a repeat lumbar puncture 6 months later to assess the response to treatment; some cases of neurosyphilis require retreatment.[4]

*Dr. Papaliodis:* After the rapid plasma reagin test and fluorescent treponemal antibody absorption test were reported as positive, the patient was admitted to the hospital for expedited therapy. He underwent a lumbar puncture and received a course of intravenous penicillin (4 million units every 4 hours) for 14 days, along with prednisone (80 mg daily). Otolaryngologic consultation revealed normal ear canals and drums; an audiogram showed bilateral asymmetric hearing loss that was worse in the right ear than in the left ear. Within 1 week after the initiation of treatment, the patient's visual acuity had improved to 20/30 in the right eye and 20/50 in the left eye and the intraocular inflammation had reduced. One month after treatment was completed, his visual acuity was 20/20 in the right

eye and 20/25 in the left eye, and neither eye had evidence of intraocular inflammation.

## FINAL DIAGNOSIS

Secondary syphilis with neurologic, ocular, and otologic involvement.

This case was presented at Ophthalmology Grand Rounds at Massachusetts Eye and Ear Infirmary.

Dr. Eliott reports receiving fees for serving on an advisory board from Acucela, fees for conducting an educational seminar from ThromboGenics, grant support to his institution from Neurotech and Ocata Therapeutics, and consulting fees from Alcon, Alimera, Allergan, Arctic, Avalanche, Bausch & Lomb, Biogen, Dutch Ophthalmic, Ophthotech, MacuLogix, and ThromboGenics. 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.

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