CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 24-2021: A 63-Year-Old Woman with Fever, Sore Throat, and Confusion

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PRESENTATION OF CASE

Dr. Peiyun Ni (Medicine): A 63-year-old woman was admitted to this hospital because of fever, headache, sore throat, and confusion.

The patient had been well until 2 weeks before this admission, when fever, chills, myalgias, and headache developed. She also had sore throat, odynophagia, and the feeling of a lump in the neck. The patient was concerned that she had coronavirus disease 2019 (Covid-19) and sought evaluation at an urgent care clinic of another hospital. Testing of a nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was negative, and she was instructed to quarantine at home.

Five days before this admission, the patient returned to the clinic of the other hospital because of persistent symptoms, including daily fevers. The temperature was 37.2 C, and the remainder of the physical examination was reportedly normal. Testing of another nasopharyngeal swab for SARS-CoV-2 RNA was negative, as was testing of an oropharyngeal swab for the rapid detection of streptococcal antigen.

On the day of admission, the patient s sister visited the patient and noticed that she had difficulty with word finding and performing basic tasks at home. Emergency medical services were called, and the patient was transported to the emergency department of this hospital.

On evaluation, the patient reported fevers, chills, myalgias, fatigue, generalized weakness, headaches, sore throat, and odynophagia. She acknowledged that she had mild confusion and mental slowness of 2 weeks duration. A review of systems was notable for a lump in the neck, poor appetite, unintentional weight loss of 3 kg in the past 2 weeks, and anosmia for the past year, with onset before the beginning of the Covid-19 pandemic. There was no neck stiffness, photophobia, cough, dyspnea, abdominal pain, diarrhea, or dysuria.

The patient had hypertension for which she took amlodipine and lisinopril; there were no known drug allergies. She was born in South America and had im-

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults	On Admission
Hemoglobin (g/dl)	12.0 16.0	14.2
Hematocrit (%)	41.0 53.0	42.2
White-cell count (per μl)	4500 11,000	3700
Differential count (per μl)		
Neutrophils	1800 7700	2290
Lymphocytes	1000 4800	1320
Monocytes	200 1200	60
Platelet count (per μl)	150,000 450,000	230,000
Sodium (mmol/liter)	135 145	131
Potassium (mmol/liter)	3.4 5.0	4.8
Chloride (mmol/liter)	98 108	93
Glucose (mg/dl)	70 110	127
Creatinine (mg/dl)	0.60 1.50	0.92
Urea nitrogen (mg/dl)	8 25	8
Aspartate aminotransferase (U/liter)	9 32	280
Alanine aminotransferase (U/liter)	7 33	235
Alkaline phosphatase (U/liter)	30 100	205
Total bilirubin (mg/dl)	0.0 1.0	0.3
Direct bilirubin (mg/dl)	0.0 0.4	<0.2
Albumin (g/dl)	3.3 5.0	4.5
Globulin (g/dl)	1.9 4.1	3.0
Lactate dehydrogenase (U/liter)	110 210	466

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital 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.

migrated to the United States two decades earlier. She lived in an urban area of New England with her mother and son. Her son had a brain injury and was seen by visiting nurses daily; one nurse had had a positive SARS-CoV-2 test 4 days before this evaluation. There were no other sick contacts. The patient worked in management and enjoyed gardening as a hobby. She had no recent insect bites or travel. Although she had not been sexually active for several years, she had had an episode of unprotected sexual intercourse with a new male partner 3 weeks before this evaluation. She smoked four cigarettes daily and had done so for 40 years. She did not drink alcohol or use illicit drugs. Her mother had Alzheimer s disease.

The temperature was 38.9 C, the blood pressure 160/80 mm Hg, the pulse 96 beats per minute, the respiratory rate 20 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 29.9. The patient appeared fatigued and was alert and oriented. She was unable to perform simple calculations, to list the days of the week in reverse order, or to follow two-step commands. The mucous membranes were dry, and a small nontender lymph node was palpable in the posterior neck on the left side. The white-cell count was 3700 per microliter (reference range, 4500 to 11,000); the aspartate aminotransferase level was 280 U per liter (reference range, 9 to 32) and the alanine aminotransferase level 235 U per liter (reference range, 7 to 33). Additional laboratory test results are shown in Table 1. Urinalysis revealed the presence of ketones, nitrites, and protein; there were fewer than 10 white cells per high-power field (reference range, <10). Testing of a third nasopharyngeal swab for SARS-CoV-2 RNA was negative, and blood specimens were obtained for culture.

Dr. William A. Mehan: A radiograph of the chest was normal. Ultrasonography of the abdomen showed gallbladder sludge. Computed tomography (CT) of the abdomen, performed after the intravenous administration of contrast material, showed prominent gastrohepatic, periportal, periaortic, and inguinal lymph nodes, the largest measuring 1.4 cm in diameter.

CT of the head, performed without the intravenous administration of contrast material, showed mild scattered hypodensities in the periventricular and subcortical white matter of the cerebral hemispheres. Magnetic resonance imaging (MRI) of the head, performed before and after the intravenous administration of contrast material, was notable for multifocal patchy hyperintensities throughout the juxtacortical and deep white matter of the cerebral hemispheres on fluid-attenuated inversion recovery images, without corresponding restricted diffusion or abnor-

mal enhancement (Fig. 1). The findings were unchanged from MRI findings obtained 3 months before presentation.

Dr. Ni: Empirical treatment with intravenous ceftriaxone and acyclovir was started, and the patient was admitted to the hospital.

A lumbar puncture was performed. The opening pressure was 24 cm of water; the cerebrospinal fluid (CSF) was clear and colorless. On CSF analysis, the total protein level was 201 mg per deciliter (reference range, 5 to 55) and the glucose level 43 mg per deciliter (2.4 mmol per liter; reference range, 50 to 75 mg per deciliter [2.8 to 4.2 mmol per liter]). There were 73 white cells per microliter (reference range, 0 to 5), of which 65% were lymphocytes, 29% plasma cells, and 6% monocytes. Gram s staining showed abundant mononuclear cells and no organisms. The intravenous administration of ceftriaxone and acyclovir was stopped.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Robert H. Goldstein: This 63-year-old woman presented with a progressive syndrome consisting of fever, headache, sore throat, and confusion symptoms that are common in many diseases. My differential diagnosis and clinical reasoning will be guided by the subjective history and the objective data provided in the case presentation. Subjective history includes information reported by the patient, her family, and others who directly observed the syndrome and relevant behaviors, as well as environmental and epidemiologic risk factors. On the basis of the subjective history, we can create a comprehensive differential diagnosis. Objective data include measurable, quantifiable, and observable information, specifically the findings on physical examination, laboratory evaluation, and imaging studies. By combining the subjective history with the objective data, we can form a well-reasoned interpretation of the case in order to arrive at the most likely diagnosis. This reasoned assessment will inform the diagnostic and treatment plan.

SUBJECTIVE HISTORY

I will first focus on the subjective information provided in the patient s history. She had fever,

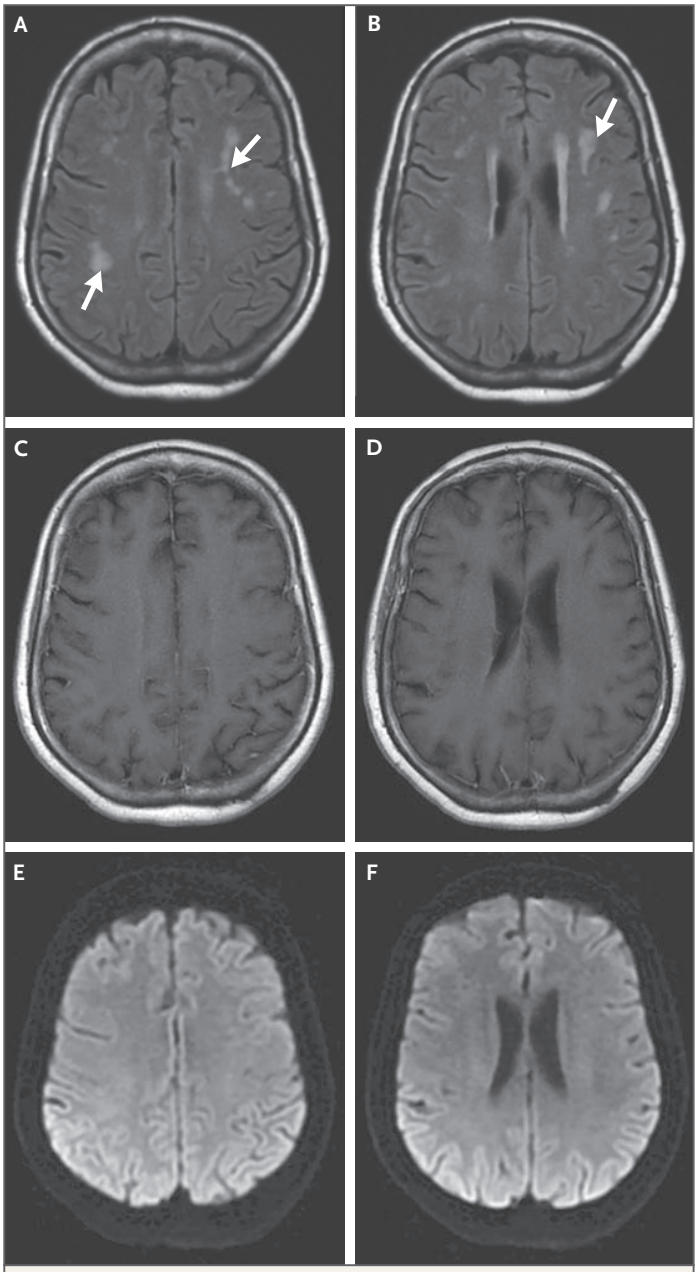

Figure 1. MRI of the Head.

Axial fluid-attenuated inversion recovery (FLAIR) images at the level of the centrum semiovale (Panel A) and at the level of the corona radiata (Panel B) show multifocal patchy hyperintensities in the cerebral white matter bilaterally (arrows). Axial T1-weighted images (Panels C and D) and axial diffusion-weighted images (Panels E and F), obtained after the intravenous administration of contrast material, show no enhancement or restricted diffusion corresponding to the white-matter hyperintensities detected on the FLAIR images.

headache, and confusion that resulted in difficulty with word finding. Our differential diagnosis must include manifestations of central nervous system (CNS) infection, namely encephalitis and meningitis. Until provided with additional information that rules out CNS infection, we should consider viral causes of encephalitis, such as herpesviruses (e.g., herpes simplex virus and varicella zoster virus) and enteroviruses (e.g., coxsackievirus).[1] We should also consider common bacterial causes of meningitis, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Listeria monocytogenes*.

In addition to symptoms associated with CNS infection, the patient reported sore throat and odynophagia, features suggestive of viral or bacterial pharyngitis, specifically streptococcal pharyngitis. She also reported myalgias, anosmia (for 1 year), and weight loss with a poor appetite, findings suggestive of a systemic viral process, including SARS-CoV-2 infection.[2] Most of these symptoms began abruptly and progressed over a period of 2 weeks, which is consistent with an acute infection or inoculation.

With respect to environmental and epidemiologic risk factors, several potential clues are provided in the history. The patient was living in New England and enjoyed gardening. Several mosquito-borne and tickborne illnesses endemic in New England are associated with encephalitis or meningitis, including Lyme meningoencephalitis, eastern equine encephalitis, and encephalitis due to West Nile virus or Powassan virus.[3] The absence of a known insect or tick bite or rash does not reliably rule out these infections; many infected patients cannot recall a bite or rash. Because this patient was born in South America, we should also consider infections endemic in some South American countries, including *Mycobacterium tuberculosis* meningitis and *Taenia solium* infection with CNS involvement (neurocysticercosis).[4]

This patient reported a history of unprotected sex with a new male partner 1 week before the onset of symptoms and 3 weeks before hospital admission. We must consider sexually transmitted infections, including acute human immunodeficiency virus type 1 (HIV-1) and infection with *Treponema pallidum* (syphilis). When acute HIV infection is included on the differential diagnosis, it is important to consider concurrent opportunistic infections. Patients with acute HIV infection often have a transient but clinically significant decrease in the CD4+ T-cell count, sometimes to a level of less than 200 per microliter, which can lead to complication by opportunistic infections such as mucocutaneous candidiasis, pneumocystis pneumonia, and reactivation of tuberculosis.[5]

OBJECTIVE DATA

Having created a differential diagnosis, we can turn to the available objective data to narrow the list. We are provided with limited findings from the physical examination, including fever, poor concentration on targeted neurologic examination, and cervical lymphadenopathy. It is important to remember the value of a physical examination, which can help to distinguish between meningitis and encephalitis (according to the presence or absence of nuchal rigidity), to identify opportunistic infections (such as mucocutaneous disease), and to differentiate between a localized CNS process and a systemic illness.[6]

Given the limited physical examination findings, we must rely on results of laboratory and imaging studies to further narrow down the differential diagnosis. The patient had a negative test of an oropharyngeal swab for streptococcal antigen and three negative SARS-CoV-2 tests, which help to rule out those infections. The elevated aspartate aminotransferase and alanine aminotransferase levels and the presence of lymphopenia suggest a systemic viral infection. The presence of diffuse lymphadenopathy on imaging supports a working diagnosis of systemic viral infection, and the findings on MRI of the head help to rule out neurocysticercosis. CSF analysis revealed a mildly elevated protein level, a slightly decreased glucose level, and lymphocytic pleocytosis, with a normal opening pressure. These results are helpful in ruling out bacterial causes of meningitis, except for tuberculosis.

The objective laboratory data and the presence of lymphadenopathy broaden the differential diagnosis to include additional systemic viral infections that can cause a mononucleosis-like syndrome. One consideration is acute infectious mononucleosis due to Epstein Barr virus, which is often transmitted in oral secretions. Affected adults present with fever, lymphadenopathy, and pharyngitis, occasionally with hepatitis and less

often with encephalitis; lymphocytosis with atypical lymphocytes, rather than lymphopenia, is often present.[7] Other considerations include acute infections with cytomegalovirus, toxoplasma, hepatitis A, B, or C virus, and HIV.

CLINICAL REASONING

Having used the objective data to focus the differential diagnosis, we must now turn to clinical reasoning, pulling in subjective findings to support the final diagnosis. The differential diagnosis includes viral encephalitis, tuberculous meningitis, and an acute systemic primary viral infection, such as acute HIV infection, with or without complication by an opportunistic infection. The discontinuation of acyclovir and ceftriaxone, which are the first-line treatments for infections with herpesviruses and tick-associated spirochetes, respectively, allows us to rule out these diagnoses.

Among the remaining possibilities, acute HIV infection (with or without a concurrent opportunistic infection) is highest on my differential diagnosis. Although the majority of new diagnoses of HIV infection in the United States are reported in cisgender men who have sex with men, 19% of new diagnoses of HIV infection in the United States in 2018 were reported in cisgender women, with nearly 85% of those attributed to heterosexual contact.[8] New incident cases of HIV infection were seen in adults and seniors; 60% of all incident cases in cisgender women occurred in those older than 35 years of age.[8]

The timeline of this case, with an episode of unprotected sex 1 week before symptom onset and with progression of symptoms for 2 weeks, is compatible with acute HIV infection. Patients with acute HIV infection often present with a constellation of viral symptoms, including CNS involvement. Over half of patients present with headaches, and more than 1 in 10 patients have symptoms of encephalitis or meningitis.[9] The presence of CNS manifestations does not have high sensitivity for the diagnosis of acute HIV infection (25%), but it does have specificity (82%), and acute encephalopathy has been recognized as a symptom of HIV seroconversion since the early days of the HIV epidemic.[5,10]

As mentioned previously, acute HIV infection can result in a clinically significant decrease in the CD4+ T-cell count, which can lead to opportunistic infections. With the exception of tuberculosis, an opportunistic infection with CNS involvement seems unlikely in this case without specific findings on brain imaging (which may suggest toxoplasmosis, progressive multifocal leukoencephalopathy, or lymphoma) and without specific findings on CSF analysis (e.g., increased intracranial pressure, which would be expected in CNS cryptococcal disease).

If the patient had acute HIV infection with a clinically significant decrease in the CD4+ T-cell count, tuberculous meningitis would be a consideration. She was born in South America, where exposure to *M. tuberculosis* may be common. In patients with acute tuberculous meningitis, CSF analysis would show neutrophilic pleocytosis, a substantially elevated protein level, and a low glucose level, with a mildly elevated opening pressure.[11] In this patient, the results of CSF analysis — including lymphocytic pleocytosis, a mildly elevated protein level, and a mildly decreased glucose level, with a normal opening pressure — are more consistent with an acute viral infection. Given these data, I will remove acute tuberculous meningitis from the differential diagnosis.

Acute systemic viral infections other than HIV infection — such as mononucleosis due to Epstein–Barr virus or cytomegalovirus, toxoplasmosis, and viral hepatitis — are possible but unlikely diagnoses in this case. Although Epstein–Barr virus and cytomegalovirus can be transmitted in oral secretions during sexual contact, acute mononucleosis due to one of these viruses is more often associated with lymphocytosis than with lymphopenia.[12] Since some patients with acute cytomegalovirus infection present with lymphopenia, this diagnosis is more difficult to rule out in this case; however, the prominent CNS manifestations make cytomegalovirus infection unlikely. The patient's history did not suggest a possible source of acute toxoplasmosis, such as consumption of undercooked food or unpasteurized milk or exposure to a cat litter box.[13] Acute hepatitis A, B, or C can be transmitted during sexual contact, but patients with viral hepatitis typically present with jaundice (an elevated bilirubin level). In addition, the average incubation period for acute hepatitis A, B, and C is 28 days, 90 days, and 14 to 84 days, respectively.[14] In this case, the onset of symptoms oc-

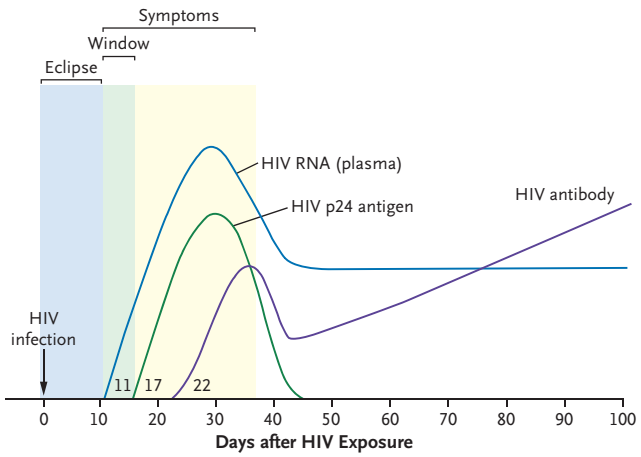

Figure 2. Temporal Appearance of HIV-Specific Biomarkers.

Shown is the expected timeline for the development of symptoms and laboratory findings associated with acute human immunodeficiency virus (HIV) infection. The time between infection (day 0) and the detection of viremia on a nucleic acid assay (approximately day 10) is called the eclipse period. The detection of viremia corresponds with the development of symptoms. Viremia leads to the production of HIV p24 antigen (detectable around day 17) and HIV antibodies (detectable around day 22). HIV p24 antigen and antibodies can be detected by standard HIV testing. The time between the first detection of viremia and the first detection of HIV p24 antigen is called the window period. Data are from Sherin et al.[15]

curred 7 days after sexual contact, which more closely aligns with the incubation period for acute HIV infection.

To establish the diagnosis of acute HIV infection, it is important to understand the temporal appearance of HIV-specific biomarkers (Fig. 2). The time between exposure to HIV and the development of viremia, called the eclipse period, usually lasts 7 to 10 days. During the eclipse period, no HIV diagnostic tests will be positive. Around 10 days after exposure, high-level viremia can be detected on an HIV nucleic acid assay and symptoms of acute infection typically develop, although a small group of patients remain asymptomatic. Approximately 1 week later (17 to 20 days after exposure), HIV p24 antigen can be detected on a standard HIV antigen and antibody assay of the blood. Around 21 to 25 days after exposure, HIV-1 or HIV-2 antibodies can be detected. The time between the first detection of viremia on a nucleic acid assay and the first detection of HIV-specific antigen or antibodies (seroconversion) is called the window period.

In this case, because the potential exposure to HIV occurred 3 weeks before hospital admission, the patient would be likely to have a detectable HIV RNA viral load and detectable HIV p24 antigen and may have detectable HIV-1 or HIV-2 antibodies; approximately 30% of patients with acute HIV infection have evidence of an evolving antibody response.

DR. ROBERT H. GOLDSTEIN S DIAGNOSIS

Acute human immunodeficiency virus type 1 infection.

DIAGNOSTIC TESTING

Dr. Bailey Hutchison: An immunoassay for HIV-1 and HIV-2 was reactive (Table 2). The assay used in this case is designed to detect HIV-1 p24 core antigen and antibodies to HIV-1 and HIV-2. Reactivity implies possible HIV infection without indicating the amount or type of targets detected in the sample or the HIV virus type (HIV-1 or HIV-2) that may be present.

In accordance with Clinical and Laboratory Standards Institute guidelines, a supplemental test should be performed to confirm the initial result. In this case, a lateral flow immunochromatographic assay was performed and revealed the presence of an antibody to only a single antigenic component of the HIV-2 envelope, glycoprotein 140 (gp140). No antibodies specific to HIV-1 antigens were detected. The detection of a single antibody is associated with imperfect specificity; at least two antibodies to either HIV-1 or HIV-2 antigens must be present for an assay to be deemed positive. Therefore, the supplemental test in this case was negative for HIV-1 antibodies and indeterminate for HIV-2 antibodies.

HIV-1 and HIV-2 have distinct but similar antigenic proteins. Because the proteins are similar, antibodies to HIV-1 antigens may show cross-reactivity to HIV-2 antigens (and vice versa), especially early in the course of infection, when the specificity of the humoral immune response to the virus is evolving. Indeterminate results on supplemental tests can also occur with late-stage acquired immunodeficiency syndrome (AIDS) and a waning anti-HIV immune response, with other infections that have cross-reactivity with HIV antibodies, with immunomodulating conditions, and with specimen contamination or testing error.[16]

Table 2. Additional Laboratory Data.*

Variable	Result
HIV-1 and HIV-2 antigen and antibody assay	Reactive
HIV-1 and HIV-2 lateral flow immunochromatographic assay	Negative for HIV-1 antibodies; indeterminate for HIV-2 antibodies
Quantitative HIV-1 nucleic acid assay (RNA copies/ml)	8,420,000
Total lymphocyte count (no. per μl)	3745
CD4+ T-cell count	
Absolute (no. per μl)	446
Relative (% of total lymphocyte count)	11.9

* HIV-1 and HIV-2 denote human immunodeficiency virus types 1 and 2, respectively.

In this case, because there was substantial clinical suspicion for acute HIV-1 infection, a quantitative HIV-1 nucleic acid assay was performed. The HIV-1 RNA viral load was measured at 8,420,000 copies per milliliter of plasma, establishing the diagnosis of HIV-1 infection. A repeat confirmatory assay performed 10 days after the initial workup showed reactivity for antibodies to four HIV-1 antigens, as well as persistence of the HIV-2 specific anti-gp140 antibody, confirming the diagnosis of HIV-1 infection.

To complete the assessment of the patient s disease status, flow cytometry was performed to assess the CD4+ T-cell count. The absolute CD4+ T-cell count was 446 per microliter (reference range, 348 to 1456), a level that is well above the threshold used to establish the diagnosis of AIDS (200 per microliter). However, the relative CD4+ T-cell count was 11.9% (based on a total lymphocyte count of 3745 per microliter), a level that falls below the AIDS threshold (14%).[17] In patients with acute HIV infection, this profound decrease in the relative CD4+ T-cell count is transient and represents depletion of CD4+ T cells concurrent with expansion of cytotoxic cells that target virally infected cells.[18]

LABORATORY DIAGNOSIS

Acute human immunodeficiency virus type 1 infection.

DISCUSSION OF MANAGEMENT

Dr. Gregory K. Robbins: Department of Health and Human Services guidelines recommend treating all patients with HIV infection, regardless of the CD4+ T-cell count. Treatment of patients with acute HIV infection may be especially important, because early initiation of antiretroviral therapy may preserve HIV-1 specific CD4+ T cells that are best able to recognize and coordinate the immune response against HIV. Early initiation of antiretroviral therapy has also been shown to preserve healthy CD4+ T-cell responses to HIV, similar to those seen in long-term nonprogressors and elite controllers.[19]

This patient s CD4+ T-cell count was notable, given the low percentage of CD4+ T cells. In some patients, the CD4+ T-cell count decreases to a level that meets the criterion for a diagnosis of AIDS (<200 cells per microliter or <14%), in which case opportunistic infections can develop.[17,20] In the era before the availability of combination antiretroviral therapy, we saw a few cases in which acute HIV infection led to opportunistic infection, AIDS, and progression to death within several months. In this patient, the absolute CD4+ T-cell count was on the low end of the normal range (446 per microliter), but the relative CD4+ T-cell count was substantially decreased (11.9%), meeting the criterion for AIDS and conferring an increased risk for the development of opportunistic infections, especially *Pneumocystis jirovecii* pneumonia. She also had a marked increase in the CD8+ T-cell count and hence lowering of the ratio of CD4+ T cells to CD8+ T cells to 0.16 (normal range, >1.00), which is commonly seen in patients with acute HIV infection.[21,22]

When we discussed the diagnosis of acute HIV-1 infection with this patient, we provided extensive counseling and education about the effectiveness of antiretroviral therapy, and we

shared with her our optimism that she would have a normal life expectancy.[23] She elected to start treatment with a single combination pill of bictegravir emtricitabine tenofovir alafenamide. Viral genotyping revealed a reverse-transcriptase gene mutation at R211T and protease gene mutations at L10I, I13V, I62V, L63P, and H69Q; none of these mutations conferred clinically significant resistance to her antiretroviral regimen. An HIV integrase inhibitor resistance test was not performed, because resistance mutations against this drug class are uncommon. Because the patient s relative CD4+ T-cell count was less than 14% and she was at risk for opportunistic *P. jirovecii* pneumonia, a blood specimen was obtained for measurement of the β-D-glucan level as a biomarker of *P. jirovecii* infection. The test was negative, and the administration of trimethoprim sulfamethoxazole was started as prophylaxis for *P. jirovecii* pneumonia.

The patient s symptoms resolved shortly after she started antiretroviral therapy. She continues to do well and understands her diagnosis and the importance of adherence to her daily regimen. This case shows the importance of obtaining a detailed sexual history; without this, the diagnosis of HIV infection in this patient would probably have been missed or delayed.

FINAL DIAGNOSIS

Acute human immunodeficiency virus type 1 infection.

This case was presented at the Medical Case Conference.

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

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