CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 31-2019: A 45-Year-Old Woman with Headache and Somnolence

Allan R. Tunkel, M.D., Ph.D., Elinor L. Baron, M.D., Karen A. Buch, M.D.,
Francisco M. Marty, M.D., and Maria Martinez-Lage, M.D.

PRESENTATION OF CASE

Dr. Elinor L. Baron: A 45-year-old woman with multiple sclerosis, seronegative inflammatory polyarthritis, and migraine was admitted to this hospital during the winter because of lethargy and decreased verbal output.

The patient had been in her usual state of health until 13 days before this admission, when a severe headache developed. The pain began insidiously, was pounding in quality, and radiated from the occiput to the retro-orbital area and forehead. The onset of pain coincided with visual aura, including blurring of the peripheral vision and oscillating flashes of light. The headache was reminiscent of the patient's previous migraine headaches, the last of which had occurred more than 10 years earlier; symptoms had typically abated with butalbital–acetaminophen–caffeine therapy.

Five days later, and 8 days before this admission, symptoms worsened, and the patient sought care at the emergency department at another hospital. On arrival, she reported photophobia, nausea, and vomiting; she had no history of head injury, and she reported no neck pain, fever, chills, numbness, tingling, weakness, or dizziness. On examination, the temperature was 37.1°C, the pulse 101 beats per minute, the blood pressure 147/98 mm Hg, the respiratory rate 20 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. She appeared uncomfortable and was lying in bed in a dark room with her eyes covered. She was alert, oriented, and able to follow commands. Her neck was supple. Ptosis and miosis of the left eye were noted; the neurologic examination was otherwise normal. The hematocrit, hemoglobin level, and blood levels of electrolytes, glucose, and thyrotropin were normal, as were the results of kidney-function and liver-function tests. Other laboratory test results are shown in Table 1.

Computed tomography (CT) of the head showed no evidence of an acute intracranial process, and there was a finding suggestive of an inferior basal ganglia cyst that appeared unchanged from that seen on imaging that had been performed

From the Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI (A.R.T.); the Department of Medicine, Newton–Wellesley Hospital, Newton, MA (E.L.B.); and the Departments of Radiology (K.A.B.) and Pathology (M.M.-L.), Massachusetts General Hospital, the Department of Medicine, Brigham and Women's Hospital (F.M.M.), and the Departments of Radiology (K.A.B.), Medicine (F.M.M.), and Pathology (M.M.-L.), Harvard Medical School — all in Boston.

N Engl J Med 2019;381:1459-70.
DOI: 10.1056/NEJMcpc1904045

Table 1. Laboratory Data.*

Variable	Reference Range, Other Hospital	7 Days before Admission, Other Hospital	3 Days before Admission, Other Hospital	Reference Range, This Hospital†	On Admission, This Hospital
Blood					
White-cell count (per mm^3)	4000–11,000	6490	8450	4500–11,000	5710
Platelet count (per mm^3)	135,000–400,000	260,000	166,000	150,000–400,000	93,000
Differential count (%)					
Neutrophils	45–68	59.8	71.3	40–70	68.1
Lymphocytes	25–44	26.8	17.3	22–44	20.0
Monocytes	2.5–8.1	10.9	9.2	4–11	7.5
Eosinophils	0.0–3.6	0.5	0.4	0–8	1.9
Basophils	0.0–1.8	0.8	0.7	0–3	0.7
Immature granulocytes	0.0–0.9	1.2	1.1	0.0–0.9	1.8
Lactate dehydrogenase (U/liter)	120–246		304	110–210	424
Erythrocyte sedimentation rate (mm/hr)	0–20	1	4	0–20	5
C-reactive protein (mg/liter)	0–8.0	6.0	48.5	0–8.0	47.3
Procalcitonin (ng/ml)	0–0.08		0.07		
Cerebrospinal fluid					
Color	Colorless		Colorless	Colorless	Yellow
Turbidity	Clear		Clear	Clear	Slight
Glucose (mg/dl)	40–70		45	50–75	107
Total protein (mg/dl)	15–45		190	5–55	572
Red-cell count (per mm^3)	0		1	0–5	68
White-cell count (per mm^3)	0–5		63		298
Differential count (%)					
Segmented neutrophils			18	0	13
Lymphocytes			46	0–100	64
Macrophages			36	0–100	18
Xanthochromia	Not present		Not present	Not present	Present

* To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† 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.

5 years earlier. Magnetic resonance imaging (MRI) and magnetic resonance arteriography of the head and neck revealed stable, scattered demyelinating plaques; no active demyelinating lesions were seen, and there was no evidence of venous sinus thrombosis or cavernous sinus thrombosis. The patient received intravenous fluids, ondansetron, diphenhydramine, metoclopramide, magnesium sulfate, and morphine, but the headache persisted. Intravenous hydromorphone, ketorolac, and methylprednisolone were subsequently administered, which led to a moderate reduction in pain. The patient was discharged home and was instructed to take diclofenac and oral methylprednisolone for 5 days.

One day after discharge, and 5 days before admission to this hospital, the headache and nausea recurred, along with intermittent episodes of vomiting. Four days before this admission, lethargy, disorientation, and decreased verbal output developed. The patient was able to follow commands, but verbal responses to questions

were limited to "yes" and "no." She had no fever, chills, chest pain, shortness of breath, cough, dizziness, loss of consciousness, convulsive movements, incontinence, facial droop, or slurred speech. The patient was taken by ambulance to the emergency department of the other hospital.

On examination, the patient was alert but confused. The temperature was 37.3°C, the pulse 110 beats per minute, the blood pressure 160/110 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 96% while she was breathing ambient air. She was able to follow commands, and the neurologic examination was unchanged from the previous examination. Levels of electrolytes and glucose were normal, as were the results of kidney-function and liver-function tests; a urine toxicology screen was positive for cannabinoids. Other laboratory test results are shown in Table 1. CT of the head was unchanged from the CT performed 3 days earlier, and a chest radiograph was normal. Intravenous ketorolac, famotidine, and pantoprazole were administered, and the patient was admitted to the other hospital.

The next morning, a fever with a temperature of up to 38.0°C developed. Repeat MRI of the head revealed no notable change from the previous MRI. A lumbar puncture was performed; the opening pressure was 28 cm of water, and 6 ml of clear cerebrospinal fluid (CSF) was removed. The results of the CSF analysis are shown in Table 1. Testing of the CSF for autoantibodies associated with autoimmune and paraneoplastic encephalopathy was performed. Specimens of blood, urine, and CSF were obtained for culture, and the patient received empirical intravenous acyclovir, vancomycin, and meropenem. That evening, nuchal rigidity was noted. During the next 3 days, the patient's mental status waxed and waned but was persistently poor overall, and she had a fever with a temperature of up to 39.0°C. She was transferred to the neurology service of this hospital for further evaluation.

On the patient's admission to this hospital, her husband reported that her verbal output had increased since admission to the other hospital, such that responses to questions now included words and phrases. The patient had a history of multiple sclerosis, which had been stable for many years with treatment with rituximab. She had seronegative inflammatory polyarthritis with progressive symptoms, despite increased use of immunosuppressive therapies. She also had a history of hypertension, depression, anxiety, and melanoma. An episode of sinusitis had occurred 10 weeks before admission to this hospital and had resolved after the administration of doxycycline. She had undergone an extended carpal tunnel release of the right wrist and radical flexor tenosynovectomy for inflammatory flexor tenosynovitis. Medications before admission included rituximab, hydroxychloroquine (started 18 months before admission), leflunomide (started 11 months before admission), methylprednisolone (started 18 months before admission), butalbital–acetaminophen–caffeine combination tablets, diclofenac, hydrocodone–acetaminophen, inhaled albuterol, duloxetine, bupropion, quetiapine, trazodone, lisinopril, nifedipine, cholecalciferol, and folic acid. She was allergic to penicillin, levofloxacin, cephalosporins, and sulfonamide-containing medications.

The patient was married and had three school-age children; she lived with her family in a suburban community in New England and spent summers on Cape Cod, in Massachusetts. She was receiving disability benefits and spent most of her time indoors. There was no recent history of travel. She had a healthy dog. She had smoked 10 cigarettes daily for 7 years and had quit 22 years before this admission. She drank alcoholic beverages in moderation and reported no use of illicit drugs. Her mother had had coronary artery disease, diabetes, and migraine; her father had had hypertension, diabetes, atrial fibrillation, and multiple sclerosis.

On examination, the temperature was 36.3°C, the pulse 90 beats per minute, the blood pressure 106/65 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 98% while the patient was breathing ambient air. She was awake, alert, and oriented to her name. The sclerae and conjunctivae were clear, and the pupils were symmetric and reactive, with no afferent pupillary defect. Repetitive blinking and squinting in the left eye were noted, but there was no definite ptosis or facial droop. No oropharyngeal exudates were present, and there was no erythema. Mild resistance to neck flexion was noted. The lungs were clear. There were ulcers on the distal fingers, but no rashes were noted. Muscle tone and strength were normal, as

was sensation to light touch. Reflexes were normal, and there was no startle myoclonus; a mild postural tremor was seen. The patient wrote "magical" when asked to write her name. She was able to follow simple, but not complex, commands. Laboratory testing revealed a blood sodium level of 133 mmol per liter (reference range, 135 to 145). The levels of other electrolytes, glucose, creatine kinase, and lactic acid were normal, as were the results of kidney-function and liver-function tests. Blood tests for human immunodeficiency virus (HIV) type 1 p24 antigen and antibodies to HIV types 1 and 2 were negative. Bacterial cultures of the blood, urine, and CSF that were obtained at the other hospital before the initiation of antibiotic agents were negative, as was testing of the CSF for autoantibodies.

Dr. Karen A. Buch: On admission to this hospital, MRI of the head, performed after the administration of intravenous contrast material, revealed subtle leptomeningeal enhancement in the posterior fossa. T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging showed signal hyperintensity in the sulci of the temporal and occipital lobes, as well as signal hyperintensity in the right posterior periatrial region that corresponded with a punctate focus of restricted diffusion (Fig. 1).

Dr. Baron: Empirical treatment with doxycycline was initiated, and the administration of intravenous acyclovir and meropenem was continued. A repeat lumbar puncture was performed, and the results of the CSF analysis are shown in Table 1. During the subsequent 2 days, the patient's mental status remained poor. An electroencephalogram showed diffuse theta slowing in the background, with no epileptiform activity. The next day, a fever with a temperature of up to 38.6°C developed, along with loss of all verbal output and an inconsistent ability to follow commands.

Dr. Buch: Follow-up MRI of the head, performed after the administration of intravenous contrast material, revealed the presence of new hydrocephalus, progressive and extensive leptomeningeal enhancement, and abnormal enhancement in the choroid plexus and ependyma of the lateral ventricles. T2-weighted FLAIR imaging showed extensive periventricular signal hyperintensity throughout both cerebral hemispheres, in the dentate nuclei, and surrounding the fourth ventricle, as well as signal hyperintensity in the bilateral basal ganglia, bilateral hippocampi, splenium of the corpus callosum, and periventricular white matter that corresponded to areas of restricted diffusion (Fig. 2).

A diagnostic test result was received.

DIFFERENTIAL DIAGNOSIS

Dr. Allan R. Tunkel: This patient, who has been immunocompromised as a result of treatment with methylprednisolone and rituximab, presents with signs and symptoms of acute meningoencephalitis. Her general laboratory studies are not particularly remarkable. Lumbar puncture reveals an elevated opening pressure, and the CSF analysis is notable for mononuclear pleocytosis, a normal glucose level, and an elevated protein level. MRI of the head reveals diffuse pachymeningeal and leptomeningeal enhancement, sulcal hyperintensity in the basal cisterns and cerebellum on T2-weighted FLAIR imaging, increased ventricular size, and a solitary 5-mm lesion in the splenium with restricted diffusion and no enhancement. Despite treatment with vancomycin, meropenem, acyclovir, and doxycycline, the patient has had progressive deterioration, a finding that may be helpful in determining a specific cause for the acute meningoencephalitis.

NONINFECTIOUS CAUSES OF ACUTE MENINGOENCEPHALITIS

CSF testing for autoantibodies associated with autoimmune and paraneoplastic encephalopathy was reported to be negative; although no information is available with respect to which specific tests were performed, I will rule out the possibility of autoimmune and paraneoplastic encephalopathy on the basis of this report. Carcinomatous meningitis should be considered, given the patient's history of melanoma; however, there are no details regarding the extent of disease, and if the patient had carcinomatous meningitis, I would have expected a more long-term presentation. Migraine or migrainelike syndromes can cause a lymphocytic meningitis, but this would not be expected to progress to meningoencephalitis. Certain medications can cause meningitis, with nonsteroidal antiinflammatory drugs being the most notable; although this patient has been treated with diclofenac, her symptoms began before initiation of therapy.

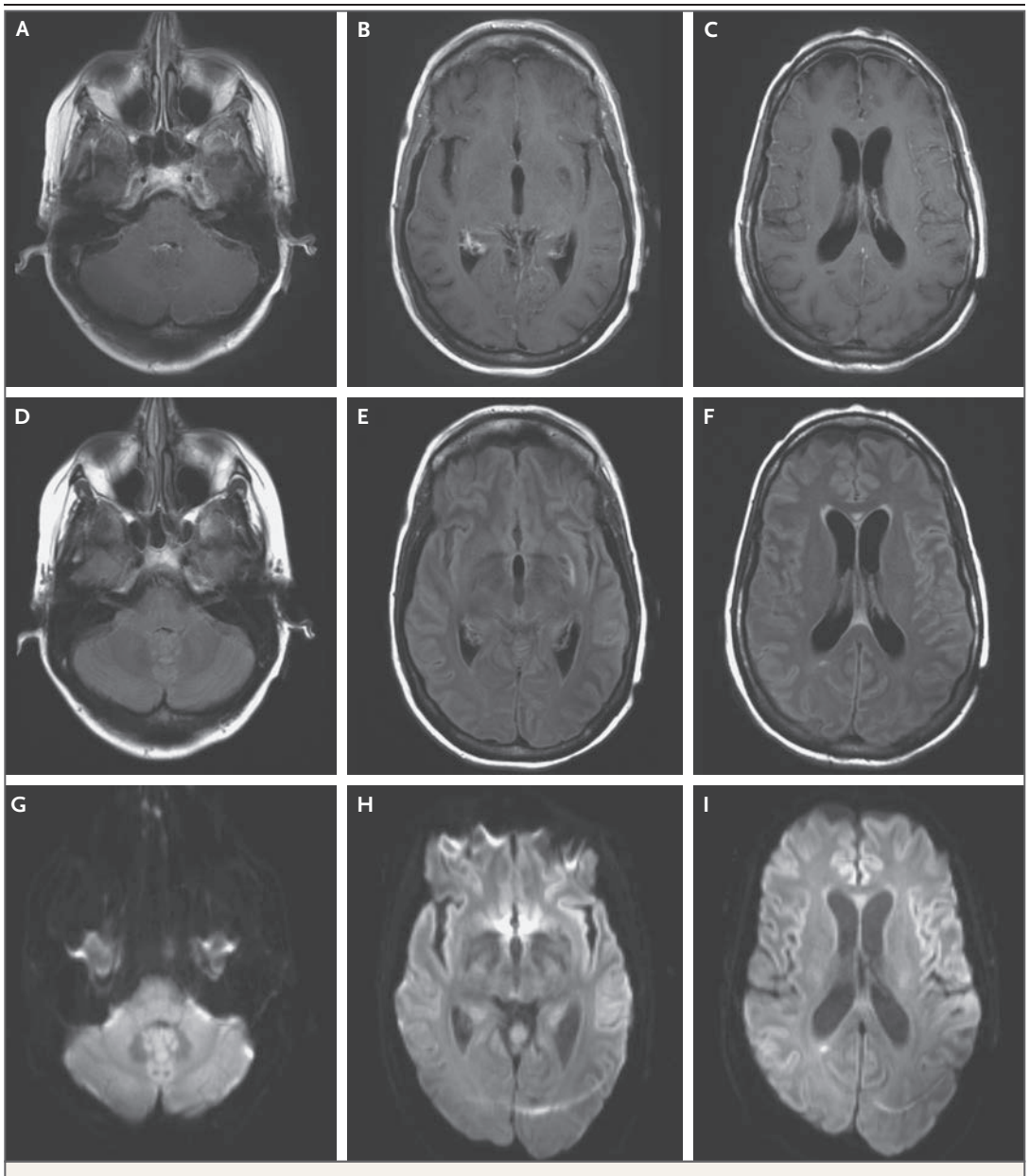

Figure 1. Initial MRI of the Head.

MRI of the head was performed on admission to this hospital. Shown are images obtained at the level of the dentate nuclei, third ventricle, and lateral ventricles (left, middle, and right columns, respectively). T1-weighted contrast-enhanced images (Panels A, B, and C) show subtle leptomeningeal enhancement in the posterior fossa. T2-weighted fluid-attenuated inversion recovery (FLAIR) images (Panels D, E, and F) show signal hyperintensity in the sulci of the temporal and occipital lobes, as well as signal hyperintensity in the right posterior periatrial region that corresponds to a punctate focus of restricted diffusion on diffusion-weighted images (Panels G, H, and I).

INFECTIOUS CAUSES OF MENINGOENCEPHALITIS

Protozoa

Certain protozoa can cause amebic meningoencephalitis. Acanthamoeba species cause disease in immunocompromised patients, and *Balamuthia mandrillaris* can affect both immunocompromised and immunocompetent patients. However, these organisms usually cause a granulomatous meningoencephalitis, with single or multiple enhancing lesions visible on MRI; such imaging find-

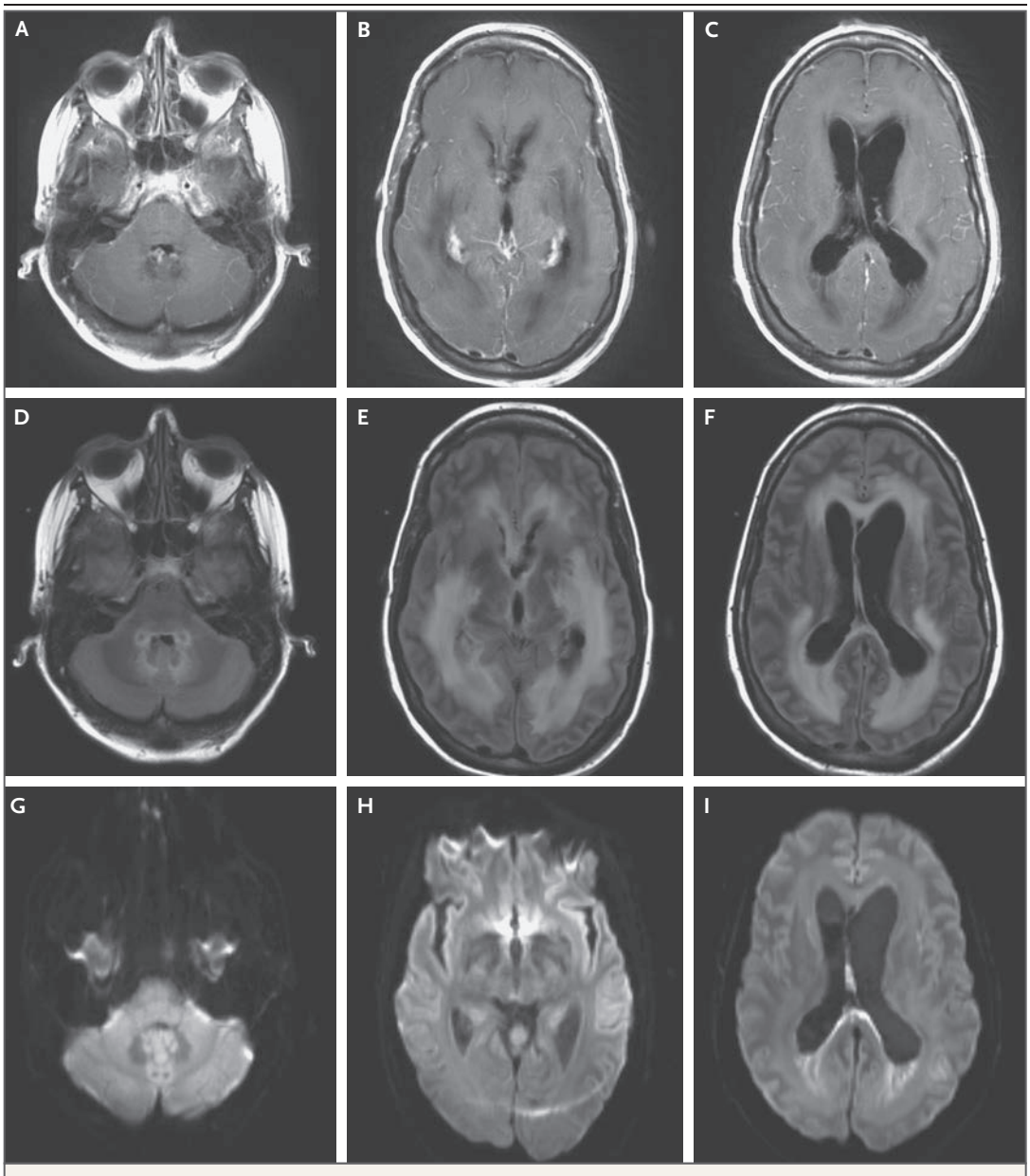

Figure 2. Additional MRI of the Head.

Follow-up MRI was performed 10 days after admission. Shown are images obtained at the level of the dentate nuclei, third ventricle, and lateral ventricles (left, middle, and right columns, respectively). T1-weighted contrast-enhanced images (Panels A, B, and C) show new hydrocephalus, progressive and extensive leptomeningeal enhancement, and abnormal enhancement in the choroid plexus and ependyma of the lateral ventricles. T2-weighted FLAIR images (Panels D, E, and F) show extensive periventricular signal hyperintensity throughout both cerebral hemispheres, in the dentate nuclei, and surrounding the fourth ventricle, as well as signal hyperintensity in the bilateral basal ganglia, bilateral hippocampi, splenium of the corpus callosum, and periventricular white matter that corresponds to areas of restricted diffusion on diffusion-weighted images (Panels G, H, and I).

ings are not present in this case. Infection with *Toxoplasma gondii*, a protozoan that can cause a nonfocal encephalitis in patients who are not infected with HIV, should be considered in any immunocompromised patient who presents with encephalitis.

Fungi

Fungal meningoencephalitis is usually subacute or chronic. A diagnosis of an endemic mycosis (histoplasmosis, blastomycosis, or coccidioidomycosis) is unlikely in this patient, given that she has no history of exposure or travel to a region in which such mycoses are endemic. Infection with *Cryptococcus neoformans* must be considered in this case, given her long-term treatment with methylprednisolone, and this entity should be ruled out by CSF testing for cryptococcal polysaccharide antigen.

Bacteria

Bacterial meningitis should always be considered in any patient who presents with acute meningoencephalitis. The most common cause in this context is *Streptococcus pneumoniae*, but CSF findings usually include a neutrophilic pleocytosis, a low glucose level, and an elevated protein level. *S. pneumoniae* and most other causes of community-acquired bacterial meningitis would respond to an antimicrobial regimen, such as that administered to this patient. However, infection with *Listeria monocytogenes* is possible; listeria meningitis is more common among immunocompromised persons than among immunocompetent persons.[1] Biologic therapies have been associated with the development of listeria meningitis. In one review of 266 reported cases of listeria meningitis in patients receiving biologic therapies, most patients (77%) had been treated with infliximab, but 4% had received rituximab therapy, as had this patient.[2] Atypical CSF findings have also been reported in patients with listeria meningitis; in one report, 23% of patients had no individual CSF findings that were indicative of bacterial meningitis.[3] Meropenem has been used successfully to treat listeriosis, which makes this diagnosis unlikely, although treatment failure associated with meropenem has been described.

Given the patient's location, in New England, other bacteria should also be considered. Infection with *Anaplasma phagocytophilum* is possible, but there is no evidence of leukopenia, thrombocytopenia, or elevated blood aminotransferase levels, thereby making this diagnosis unlikely. Infection with a spirochete, such as *Treponema pallidum*, *Borrelia burgdorferi*, or *B. miyamotoi*, may be possible, but this patient received therapies that would have been effective against these organisms. *Mycobacterium tuberculosis* is important to consider, given the patient's immunocompromised state, lack of response to antimicrobial therapy, and MRI findings of basilar meningitis, hydrocephalus, and diffuse pachymeningitis; however, most patients with tuberculous meningitis have a low CSF glucose level, and this patient's level was not low on admission to this hospital.

Viruses

Does this patient have a viral infection that is causing acute meningoencephalitis? I would rule out the viruses that are arthropod-borne. The mosquito-borne viruses that can cause disease in the northeastern United States — West Nile virus, St. Louis encephalitis virus, La Crosse virus, and eastern equine encephalitis virus — would all be unlikely, given the patient's presentation in winter, when mosquitoes are not active in this region of the country because of cold temperatures. Tickborne Powassan virus is possible but also unlikely, even though tickborne infections can occur in winter. Ticks are generally inactive if the air temperature falls below 2°C; however, if the ground is not covered by snow and the soil temperature reaches 7°C, ticks will search for blood hosts, and *Ixodes scapularis* remains active if the temperature is above freezing.

The herpes viruses are important causes of meningoencephalitis. However, this patient's progression of disease while receiving intravenous acyclovir makes herpes simplex viruses and varicella–zoster virus unlikely. Epstein–Barr virus is possible, although cerebellar ataxia and cranial-nerve palsies are usually present with this virus. Cytomegalovirus can cause central nervous system disease, most often in patients with acquired immunodeficiency syndrome (AIDS), but it is usually associated with evidence of widespread disease. Human herpesvirus 6 can cause disease in immunocompromised adults but is usually seen in patients who have undergone hematopoietic stem-cell transplantation.

Influenza viruses can cause an acute encephalopathy syndrome, such as acute necrotizing encephalopathy,[4,5] but such a condition is rare in adults and usually does not cause CSF pleocytosis; there is also no evidence of previous or concomitant respiratory tract symptoms in this patient. JC virus, which causes progressive multifocal leukoencephalopathy, has been reported in patients receiving rituximab[6,7]; however, the

MRI findings in this patient are not consistent with this diagnosis, and affected patients usually do not have clinically significant CSF pleocytosis. The nonpolio enteroviruses (e.g., echovirus and coxsackievirus) can cause meningoencephalitis, but their presence would be unusual in the winter months, because the disease is more typical in late summer and early fall. Chronic enteroviral meningoencephalitis has been reported in patients treated with rituximab,[8,9] given that prolonged rituximab therapy can produce B-cell deficiency leading to hypogammaglobulinemia. However, this entity is exceedingly rare and is usually associated with a more long-term presentation.

Finally, I would consider adenovirus meningoencephalitis as a possible diagnosis. Adenoviruses can cause meningitis or meningoencephalitis as a primary infection or as a complication of systemic or respiratory infection in immunocompromised adults. Adenovirus is a rare cause of meningoencephalitis, especially given its association with diseases of the respiratory and gastrointestinal tracts and the fact that meningoencephalitis occurs more commonly as a complication of severe pneumonia.

After considering the most common causes of meningoencephalitis in this patient, adenovirus infection is the most likely diagnosis by process of elimination. This would not be a viral infection that I would usually consider in this clinical scenario, but it might have been considered by the treating physicians, especially if adenovirus was identified in another clinical specimen (e.g., from the respiratory tract). The diagnosis of adenovirus meningoencephalitis could be confirmed by a polymerase-chain-reaction (PCR) test of blood or CSF. Although the diagnosis may also be established by culture, CSF viral cultures are generally not recommended in patients who present with meningoencephalitis.[10]

DR. ALLAN R. TUNKEL'S DIAGNOSIS

Adenovirus meningoencephalitis.

HOSPITAL COURSE AND DIAGNOSTIC TESTS

Dr. Baron: After approximately 8 days of incubation, the viral culture of CSF that was obtained during the initial lumbar puncture at the other hospital grew adenovirus type 2. Once this result was obtained, PCR testing of CSF, blood, and urine for adenovirus was performed; all the tests were positive. On the day that the result of the CSF viral culture became known, the patient received one dose of cidofovir (5 mg per kilogram of body weight). She was also treated with intravenous immune globulin (0.5 mg per kilogram per day for 5 days), which was expected to have high levels of neutralizing antibodies against common serotypes of adenovirus. Despite the use of these therapies, the patient's clinical status continued to decline. An application for the use of brincidofovir, an experimental antiviral drug, was submitted through an expanded-access protocol based on the hypothesis that brincidofovir might have higher central nervous system penetration than cidofovir. While the patient awaited the arrival of brincidofovir from the pharmaceutical company, her condition continued to deteriorate. On the 10th hospital day, the follow-up MRI of the head was performed.

Given the patient's profound neurologic deficits and worsening findings on imaging studies, she was transitioned to comfort measures only, and on the 12th hospital day, she died peacefully. An autopsy was performed.

Dr. Maria Martinez-Lage: On postmortem examination, the brain weighed 1260 g (reference range, 1250 to 1400). There was congestion of the leptomeningeal vessels and mild focal gray opacification of the subarachnoid space (Fig. 3A). The corpus callosum was friable and necrotic (Fig. 3A). Coronal sections of the hemispheres showed scattered, sharply demarcated gray lesions in the periventricular and deep white matter, findings that were consistent with demyelinating plaques. Ill-defined, bilateral, somewhat symmetric areas of softening and necrosis were present in the corpus callosum, centrum semiovale, hippocampi, cerebellar dentate nuclei, and basis pontis (Fig. 3B). The choroid plexus was prominent in the temporal horns of the lateral ventricles, and the ependymal lining was focally disrupted.

On microscopic examination, there was extensive mononuclear inflammation with microglial nodules involving the cerebral white matter, neocortex, pyramidal layer of the hippocampus, and cerebellar dentate nuclei (Fig. 3C), as well as all examined levels of the brain stem and spinal cord. Patchy infiltrates were seen in the subarachnoid space and spinal roots. In some re-

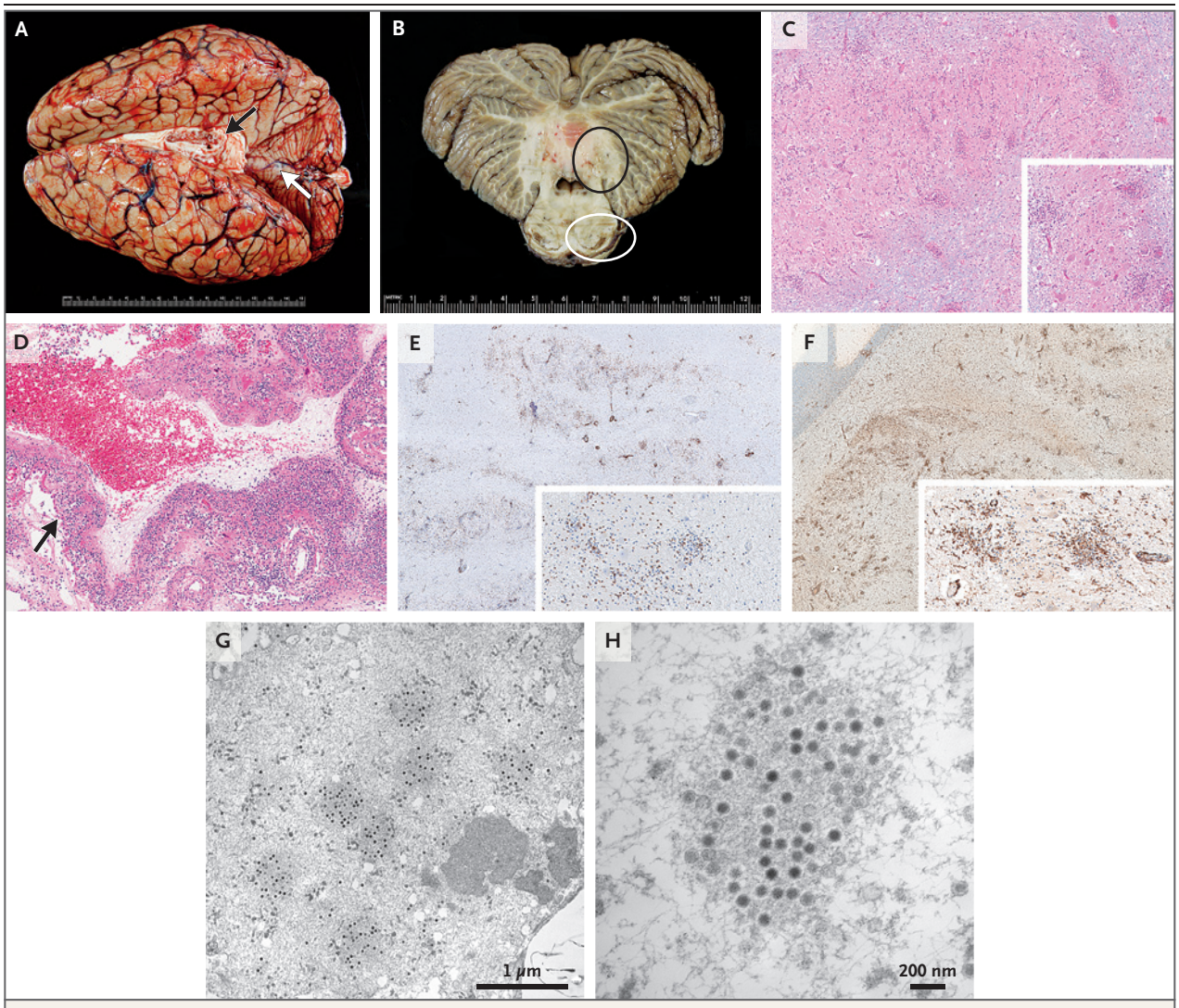

Figure 3. Autopsy Specimens of the Brain.

Panel A shows congestion of the leptomeningeal vessels and mild focal gray opacification of the subarachnoid space (white arrow); the corpus callosum is friable and necrotic (black arrow). In Panel B, ill-defined, bilateral, somewhat symmetric areas of softening and necrosis are present in the corpus callosum, centrum semiovale, hippocampi, cerebellar dentate nuclei (black oval), and basis pontis (white oval). In Panel C, hematoxylin and eosin staining shows extensive mononuclear inflammation involving the dentate nucleus of the cerebellum, with microglial nodules present in both gray and white matter (inset). This pattern of inflammation was widespread, involving multiple locations. In Panel D, hematoxylin and eosin staining shows the choroid plexus of the lateral ventricle, where there is evidence of necrosis, with numerous foamy macrophages and cellular debris (arrow indicates residual choroid plexus lining). Panels E and F show immunohistochemical staining for CD3 and CD163, respectively, in the dentate nucleus of the cerebellum (the same region shown in Panel A). The lymphocytic infiltrates are composed predominantly of CD3+ T cells, with perivascular and parenchymal distribution (Panel E; inset shows a microglial nodule in proximity to residual neurons). Abundant microglial nodules, activated microglia, and macrophages can be seen (Panel F; inset shows a microglial nodule). In Panels G and H, electron microscopy of a paraffin-embedded tissue block of the midbrain reveals icosahedral intracellular viral particles with an average diameter of 81.5 nm, findings that are consistent with adenovirus.

gions, including the corpus callosum and choroid plexus (Fig. 3D), the lesions were frankly destructive, with numerous foamy macrophages. Nuclear inclusions were not readily identified. The lymphocytic infiltrates were composed predominantly of CD3+ T cells, with perivascular and parenchymal distribution (Fig. 3E). Immunohistochemical staining for CD163 highlighted abundant microglial nodules, activated microglia, and macrophages (Fig. 3F). Immunohistochemi-

cal staining for adenovirus was negative; however, electron microscopy of a paraffin-embedded tissue block revealed many nonenveloped icosahedral intracellular viral particles with an average diameter of 81.5 nm, findings that were consistent with adenovirus (Fig. 3G and 3H). The result of immunohistochemical staining was considered to be false negative, potentially owing to sampling.

The general autopsy revealed evidence of necrotizing interstitial nephritis and focal enteritis, and immunohistochemical staining for adenovirus was positive. No other organs, including the lungs and liver, were involved.

The findings are consistent with an adenoviral meningoencephalomyelitis (with associated adenoviral nephritis and enteritis), in conjunction with multiple sclerosis. Adenovirus encephalitis is extremely rare and is seen almost exclusively in immunocompromised hosts.[11]

Among the more than 50 serotypes of adenovirus, serotype 2 (which was identified in this patient) is the most common serotype that has been reported to be associated with meningoencephalitis and disseminated disease.[12,13] Published reports of the neuropathological features of adenovirus meningoencephalitis are scarce,[14,15] but reported cases show bilateral, sometimes symmetric, necrotizing lesions with a striking predilection for medial and paramedian structures (e.g., the mesial temporal lobe,[16] basal forebrain,[17] and brain stem[15]) and the ventricular system.[18] Lymphocytic infiltrates, microglial nodules, and intranuclear inclusions are the most common microscopic findings, although intranuclear inclusions were not a salient feature in this case. Involvement of the spinal cord and roots, as seen in this patient, has been reported in a single case.[19]

DISCUSSION OF MANAGEMENT

Dr. Francisco M. Marty: There are no approved antiviral agents for the prevention or treatment of adenovirus-associated infectious diseases. An oral, live-attenuated vaccine against adenovirus serotypes 4 and 7 is available for U.S. military use only. Prevention of adenovirus-associated infectious diseases relies on personal hygiene, including hand washing, contact precautions, and water chlorination.[20]

Cidofovir has been used off label for the treatment of adenovirus-associated infectious diseases in immunocompromised hosts[21,22] since its approval for the treatment of AIDS-related cytomegalovirus retinitis.[23,24] Cidofovir therapy is frequently associated with renal tubular cellular injury and nephrotoxicity. Protocols for the administration of cidofovir include the use of aggressive intravenous hydration and the concurrent use of probenecid to prevent concentration of cidofovir in renal tubules and to minimize the risk of kidney injury. Because cidofovir enters the cells by concentration gradient with some contribution from fluid-phase endocytosis,[25] I prescribe cidofovir at a dose of 5 mg per kilogram per week, regardless of renal function, when treating patients with severe adenovirus-associated infectious diseases, until clinical signs and symptoms resolve and the blood adenovirus load becomes undetectable. With the development of molecular methods to detect adenoviruses, DNA surveillance with PCR testing and preemptive off-label treatment with cidofovir have been increasingly used in high-risk immunocompromised populations.[26,27]

Brincidofovir is an investigational lipid conjugate of cidofovir that has been developed as a bioterrorism countermeasure against smallpox.[28,29] It is administered orally and is not excreted into the renal tubules through the organic anion transporter 1, a characteristic that minimizes its potential to cause nephrotoxicity.[30] A dose-ranging trial and subsequent phase 3 trial were conducted to evaluate brincidofovir for the prevention of cytomegalovirus and other double-stranded DNA viruses in patients who had undergone allogeneic hematopoietic-cell transplantation.[31,32] The results of the phase 3 trial showed that although brincidofovir had antiviral activity against cytomegalovirus, it was associated with gastrointestinal toxic effects that were indistinguishable from gastrointestinal graft-versus-host disease.[32]

A social media campaign that was undertaken to gain expanded access to brincidofovir for a child with severe adenovirus infection[33] led to the development and Food and Drug Administration approval in 2014 of an open-label protocol for the use of brincidofovir in the treatment of adenovirus-associated infectious diseases.[34,35] Although results from some studies were encouraging,[36-38] the development of brincidofovir for the treatment of adenovirus-associated infectious diseases

was recently terminated.[39] Brincidofovir remains available through an expanded-access program for the treatment of adenovirus-associated infectious diseases in certain patients (ClinicalTrials.gov number, NCT02596997).[39] Treatment of adenovirus-associated infectious diseases with adoptive immunotherapy with the use of third-party cytotoxic T cells is being pursued but remains investigational.[40,41]

ANATOMICAL DIAGNOSIS

Adenovirus (serotype 2) meningoencephalitis.

This case was presented at the postgraduate course "Infectious Diseases in Adults."

Dr. Marty reports receiving grant support, paid to his institution, and consulting fees from Chimerix. 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.

REFERENCES

1. Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with Listeria monocytogenes: 33 years' experience at a general hospital and review of 776 episodes from the literature. Medicine (Baltimore) 1998;77:313-36.
2. Bodro M, Paterson DL. Listeriosis in patients receiving biologic therapies. Eur J Clin Microbiol Infect Dis 2013;32:1225-30.
3. Brouwer MC, van de Beek D, Heckenberg SGB, Spanjaard L, de Gans J. Community-acquired Listeria monocytogenes meningitis in adults. Clin Infect Dis 2006;43:1233-8.
4. Goenka A, Michael BD, Ledger E, et al. Neurological manifestations of influenza infection in children and adults: results of a National British Surveillance Study. Clin Infect Dis 2014;58:775-84.
5. Alsolami A, Shiley K. Successful treatment of influenza-associated acute necrotizing encephalitis in an adult using high-dose oseltamivir and methylprednisolone: case report and literature review. Open Forum Infect Dis 2017;4(3):ofx145.
6. Kelesidis T, Daikos G, Boumpas D, Tsiodras S. Does rituximab increase the incidence of infectious complications? A narrative review. Int J Infect Dis 2011;15(2):e2-e16.
7. Kartau M, Verkkoniemi-Ahola A, Paetau A, et al. The incidence and predisposing factors of John Cunningham virus-induced progressive multifocal leukoencephalopathy in Southern Finland: a population-based study. Open Forum Infect Dis 2019;6(2):ofz024.
8. Quartier P, Tournilhac O, Archimbaud C, et al. Enteroviral meningoencephalitis after anti-CD20 (rituximab) treatment. Clin Infect Dis 2003;36(3):e47-e49.
9. Grisariu S, Vaxman I, Gatt M, et al. Enteroviral infection in patients treated with rituximab for non-Hodgkin lymphoma: a case series and review of the literature. Hematol Oncol 2017;35:591-8.
10. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303-27.
11. Schmidt-Hieber M, Schwender J, Heinz WJ, et al. Viral encephalitis after allogeneic stem cell transplantation: a rare complication with distinct characteristics of different causative agents. Haematologica 2011;96:142-9.
12. Echavarría M. Adenoviruses in immunocompromised hosts. Clin Microbiol Rev 2008;21:704-15.
13. Nagasawa H, Wada M, Kurita K, Iseki C, Katagiri T, Kato T. A case of non-herpetic acute limbic encephalitis associated with a type-2 adenovirus infection. Rinsho Shinkeigaku 2006;46:322-7. (In Japanese.)
14. Chou SM, Roos R, Burrell R, Gutmann L, Harley JB. Subacute focal adenovirus encephalitis. J Neuropathol Exp Neurol 1973;32:34-50.
15. Davis D, Henslee PJ, Markesbery WR. Fatal adenovirus meningoencephalitis in a bone marrow transplant patient. Ann Neurol 1988;23:385-9.
16. Dubberke ER, Tu B, Rivet DJ, et al. Acute meningoencephalitis caused by adenovirus serotype 26. J Neurovirol 2006;12:235-40.
17. Vincentelli C, Schniederjan MJ, Brat DJ. 35-Year-old HIV-positive woman with basal forebrain mass. Brain Pathol 2010;20:265-8.
18. Anders KH, Park CS, Cornford ME, Vinters HV. Adenovirus encephalitis and widespread ependymitis in a child with AIDS. Pediatr Neurosurg 1990-1991;16:316-20.
19. Awosika OO, Lyons JL, Ciarlini P, et al. Fatal adenovirus encephalomyeloradiculitis in an umbilical cord stem cell transplant recipient. Neurology 2013;80:1715-7.
20. Centers for Disease Control and Prevention. Adenoviruses: prevention & treatment. 2018 (https://www.cdc.gov/adenovirus/hcp/prevention-treatment.html).
21. Hedderwick SA, Greenson JK, McGaughy VR, Clark NM. Adenovirus cholecystitis in a patient with AIDS. Clin Infect Dis 1998;26:997-9.
22. Ribaud P, Scieux C, Freymuth F, Morinet F, Gluckman E. Successful treatment of adenovirus disease with intravenous cidofovir in an unrelated stem-cell transplant recipient. Clin Infect Dis 1999;28:690-1.
23. Safrin S, Cherrington J, Jaffe HS. Clinical uses of cidofovir. Rev Med Virol 1997;7:145-56.
24. Lion T. Adenovirus infections in immunocompetent and immunocompromised patients. Clin Microbiol Rev 2014;27:441-62.
25. Connelly MC, Robbins BL, Fridland A. Mechanism of uptake of the phosphonate analog (S)-1-(3-hydroxy phosphonylmethoxy-propyl)cytosine (HPMPC) in vero cells. Biochem Pharmacol 1993;46(6):1053-7.
26. Legrand F, Berrebi D, Houhou N, et al. Early diagnosis of adenovirus infection and treatment with cidofovir after bone marrow transplantation in children. Bone Marrow Transplant 2001;27:621-6.
27. Lee YJ, Chung D, Xiao K, et al. Adenovirus viremia and disease: comparison of T cell-depleted and conventional hematopoietic stem cell transplantation recipients from a single institution. Biol Blood Marrow Transplant 2013;19:387-92.
28. Beadle JR, Hartline C, Aldern KA, et al. Alkoxyalkyl esters of cidofovir and cyclic cidofovir exhibit multiple-log enhancement of antiviral activity against cytomegalovirus and herpesvirus replication in vitro. Antimicrob Agents Chemother 2002;46:2381-6.
29. Hostetler KY. Alkoxyalkyl prodrugs of acyclic nucleoside phosphonates enhance oral antiviral activity and reduce toxicity: current state of the art. Antiviral Res 2009;82(2):A84-A98.
30. Tippin TK, Morrison ME, Brundage TM, Momméja-Marin H. Brincidofovir is not a substrate for the human organic anion transporter 1: a mechanistic explanation for the lack of nephrotoxicity observed in clinical studies. Ther Drug Monit 2016;38:777-86.
31. Marty FM, Winston DJ, Rowley SD, et al. CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. N Engl J Med 2013;369:1227-36.
32. Marty FM, Winston DJ, Chemaly RF, et al. A randomized, double-blind, placebo-controlled phase 3 trial of oral brincidofovir for cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2019;25:369-81.
33. Kroll D. Josh Hardy going home after getting Chimerix anti-viral drug. Forbes. July 17, 2014 (https://www.forbes.com/sites/

davidkroll/2014/07/17/josh-hardy-going-home-after-getting-chimerix-anti-viral-drug/#1633d4b73d24).
34. Ouyang H. Hashtag prescription. Harper's. June 2016 (https://harpers.org/archive/2016/06/hashtag-prescription/).
35. Moch KI. Ethical crossroads: expanded access, patient advocacy, and the #SaveJosh social media campaign. Medicine Access @ Point of Care. December 14, 2017 (https://journals.sagepub.com/doi/full/10.5301/maapoc.0000019).
36. Grimley MS, Chemaly RF, Englund JA, et al. Brincidofovir for asymptomatic adenovirus viremia in pediatric and adult allogeneic hematopoietic cell transplant recipients: a randomized placebo-controlled phase II trial. Biol Blood Marrow Transplant 2017;23:512-21.
37. Hiwarkar P, Amrolia P, Sivaprakasam P, et al. Brincidofovir is highly efficacious in controlling adenoviremia in pediatric recipients of hematopoietic cell transplant. Blood 2017;129:2033-7.
38. Ramsay ID, Attwood C, Irish D, Griffiths PD, Kyriakou C, Lowe DM. Disseminated adenovirus infection after allogeneic stem cell transplant and the potential role of brincidofovir — case series and 10 year experience of management in an adult transplant cohort. J Clin Virol 2017;96:73-9.
39. Chimerix announces first quarter 2019 financial results and strategy update. Durham, NC: Chimerix, May 9, 2019 (http://ir.chimerix.com/news-releases/news-release-details/chimerix-announces-first-quarter-2019-financial-results-and).
40. Dave H, Luo M, Blaney JW, et al. Toward a rapid production of multivirus-specific T cells targeting BKV, adenovirus, CMV, and EBV from umbilical cord blood. Mol Ther Methods Clin Dev 2017;5:13-21.
41. Tzannou I, Papadopoulou A, Naik S, et al. Off-the-shelf virus-specific T cells to treat BK virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. J Clin Oncol 2017;35:3547-57.