ORIGINAL ARTICLE

Transmission of Lymphocytic Choriomeningitis Virus by Organ Transplantation

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ABSTRACT

BACKGROUND

In December 2003 and April 2005, signs and symptoms suggestive of infection developed in two groups of recipients of solid-organ transplants. Each cluster was investigated because diagnostic evaluations were unrevealing, and in each a common donor was recognized.

METHODS

We examined clinical specimens from the two donors and eight recipients, using viral culture, electron microscopy, serologic testing, molecular analysis, and histopathological examination with immunohistochemical staining to identify a cause. Epidemiologic investigations, including interviews, environmental assessments, and medical-record reviews, were performed to characterize clinical courses and to determine the cause of the illnesses.

RESULTS

Laboratory testing revealed lymphocytic choriomeningitis virus (LCMV) in all the recipients, with a single, unique strain of LCMV identified in each cluster. In both investigations, LCMV could not be detected in the organ donor. In the 2005 cluster, the donor had had contact in her home with a pet hamster infected with an LCMV strain identical to that detected in the organ recipients; no source of LCMV infection was found in the 2003 cluster. The transplant recipients had abdominal pain, altered mental status, thrombocytopenia, elevated aminotransferase levels, coagulopathy, graft dysfunction, and either fever or leukocytosis within three weeks after transplantation. Diarrhea, peri-incisional rash, renal failure, and seizures were variably present. Seven of the eight recipients died, 9 to 76 days after transplantation. One recipient, who received ribavirin and reduced levels of immunosuppressive therapy, survived.

CONCLUSIONS

We document two clusters of LCMV infection transmitted through organ transplantation.

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LYMPHOCYTIC CHORIOMENINGITIS VIRUS (LCMV) is a rodent-borne, Old World arenavirus that has been reported to cause asymptomatic or mild, self-limited illness in otherwise healthy humans. It is a known cause of aseptic meningitis, but fatal infection is rare.[1-4] Transmission of infection from a woman to a fetus can result in hydrocephalus, chorioretinitis, or microcephaly.[5-8] Outside of vertical transmission during pregnancy, human-to-human transmission of LCMV has not been described.[9] We describe two clusters of unexplained clinical syndromes in transplant recipients and the subsequent investigations to identify donor-transmitted infection as the cause of illness.

METHODS

CASE REPORTS

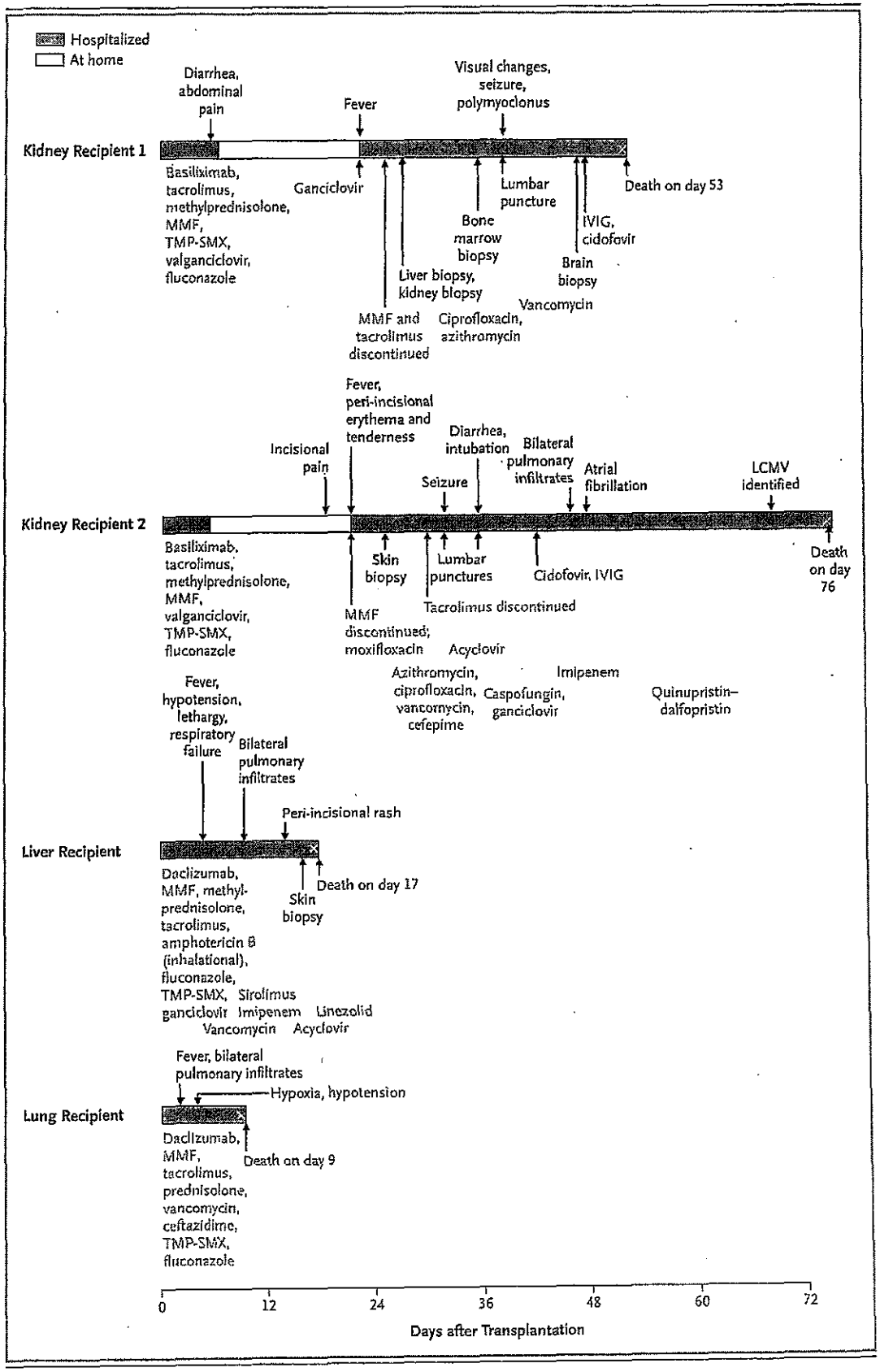
The 2003 Cluster

In December 2003, unexplained febrile illnesses developed in four recipients of solid organs from a common donor (Fig. 1; additional information on clinical symptoms and laboratory findings for each recipient is listed in Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org).[10] Kidney Recipient 1 was a 46-year-old man with diabetes. Diarrhea and mild, diffuse abdominal pain developed on post-transplantation day 5, but his condition was stable and he was discharged home the following day. He was readmitted on post-transplantation day 23 with fever, persistent watery diarrhea, and worsening abdominal pain. Laboratory studies revealed leukopenia with elevated aminotransferase and creatinine levels. Ganciclovir therapy was initiated because of concern about possible cytomegalovirus infection. Tacrolimus and mycophenolate mofetil were discontinued. Examination of kidney-, liver-, and bone marrow–biopsy specimens did not reveal an infectious cause. On day 40 after transplantation, seizures and polymyoclonus developed. The patient reported blurred vision, and chorioretinitis was noted on ophthalmologic examination. Cerebrospinal fluid studies revealed a markedly elevated level of protein (720 mg per deciliter), a normal glucose level (147 mg per deciliter [8.2 mmol per liter]), and 4 white cells and 3 red cells per cubic centimeter. Polymerase-chain-reaction (PCR) tests for cytomegalovirus, herpes simplex virus, varicella–zoster virus, Epstein–Barr virus, human herpesvirus 6, enterovirus, adenovirus, *Mycobacterium tuberculosis*, and *Borrelia burgdorferi* were negative. Magnetic resonance imaging of the brain revealed bilateral, hemispheric, subdural fluid collections and diffuse dural thickening. Examination of a specimen obtained by dural biopsy on post-transplantation day 47 showed fibrosis; cidofovir and intravenous immune globulin were initiated for the suspected presence of an unknown viral pathogen. The patient's condition continued to deteriorate, and he died on post-transplantation day 53. An autopsy revealed bronchopneumonia and hepatic congestion without inflammation.

Figure 1 (facing page). Clinical Course of Lymphocytic Choriomeningitis Virus (LCMV) Infection in the 2003 Cluster.

MMF denotes mycophenolate mofetil, TMP-SMX trimethoprim–sulfamethoxazole, IVIG intravenous immune globulin, and X death. Immunosuppressive agents are shown in red, and antimicrobial agents in blue.

Kidney Recipient 2 was a 56-year-old man with glomerulonephritis. He was discharged home on post-transplantation day 5 but was readmitted on post-transplantation day 22 with fever, leukopenia, and peri-incisional erythema and tenderness. A skin-biopsy specimen obtained at the wound edge revealed basal-cell vacuolation suggestive of viral infection; no viral inclusions were seen, and immunohistochemical stains were negative for cytomegalovirus and adenovirus. Tacrolimus and mycophenolate mofetil were discontinued. Altered mental status and seizures with myoclonus developed on post-transplantation day 31. Cerebrospinal fluid studies revealed a markedly elevated protein level (620 mg per deciliter), a low glucose level (57 mg per deciliter [3.2 mmol per liter]), and 12 white cells (48 percent lymphocytes and 22 percent monocytes) and 6 red cells per cubic centimeter. PCR testing for the same infectious agents as in the case of Kidney Recipient 1 was unrevealing. Magnetic resonance imaging showed subdural fluid collections with diffuse dural enhancement. The patient's condition continued to deteriorate, with photophobia, nuchal rigidity, diarrhea, thrombocytopenia, diffuse erythroderma, respiratory failure, and atrial fibrillation, despite empirical administration of cidofovir and intravenous immune globulin. He died on post-transplantation day 76; an autopsy revealed meningoencephalitis and acute bronchopneumonia.



The liver recipient was a 40-year-old woman with alcoholic cirrhosis whose early postoperative course was marked by fever, lethargy, and hypotension. Markedly elevated aminotransferase levels, leukopenia, and bilateral pulmonary infiltrates with respiratory failure developed. Liver biopsy revealed focal centrilobular coagulative necrosis. On post-transplantation day 14, a perincisional petechial rash was noted; skin biopsy revealed chronic inflammation and hemorrhage. She died on day 17 after transplantation. An autopsy revealed extensive hepatic necrosis without evidence of infection.

A common source of infection in these recipients was suspected, all of whom underwent transplantation at the same facility. Therefore, the Department of Public Health of the Wisconsin Department of Health and Family Services and the organ-procurement organization (OPO) coordinating the transplantations were notified for assistance.

The lung recipient, who had undergone transplantation at a different facility, was a 46-year-old man with chronic obstructive pulmonary disease who had been receiving prednisolone daily for three months before transplantation. Within four days after transplantation, hypotension, bilateral pulmonary infiltrates, and leukocytosis developed; broad-spectrum antimicrobial agents were administered. Fever (temperature, 38.3°C), hypoxia, and refractory hypotension ensued. He died on day 9 after transplantation. An autopsy revealed diffuse alveolar damage without evidence of rejection.

The donor was a 51-year-old man who had been found unresponsive, with apparent head trauma. Computed tomography (CT) of the brain revealed a large, right-sided subdural hematoma with a midline shift. There was no improvement in his neurologic status, and he was declared brain-dead on hospital day 2. He received no blood products and was afebrile throughout his hospitalization. Donor-eligibility screening and testing detected no infection precluding organ or tissue donation. His liver, lungs, kidneys, and multiple musculoskeletal and vascular tissues were recovered for transplantation. Tissue specimens from the donor and recipients were submitted to the Centers for Disease Control and Prevention (CDC) for additional testing (Table 1).

Table 1. Summary of Laboratory Evaluations for Lymphocytic Choriomeningitis Virus Infection in the 2003 Cluster.*

Patient	Outcome or Status	Immunohistochemical Staining	Serologic Testing		Culture
			IgM	IgG	
Donor†	No reported disease	–	–	–	–
Lung recipient‡	Death 9 days after transplantation	+	NT	NT	NT
Liver recipient§	Death 17 days after transplantation	+	NT	NT	NT
Kidney Recipient 1¶	Death 53 days after transplantation	+	–	–	+
Kidney Recipient 2‖	Death 76 days after transplantation	+	+	–	+

* NT denotes not tested.

† Specimens obtained at autopsy that tested negative included serum (serologic testing and virus isolation); bone marrow and blood vessel (virus isolation); and heart, stomach, tongue, thyroid gland, kidney, prostate, cerebral cortex, midbrain, pons, medulla, cerebellum, and spinal cord (immunohistochemical analysis).

‡ Specimens that tested positive by immunohistochemical analysis included lung, kidney, spleen, liver, and lymph node obtained at autopsy. No brain tissue was available for testing.

§ Specimens that tested positive by immunohistochemical analysis included skin obtained on day 15 and brain, lung, spleen, liver, heart, and adrenal gland obtained at autopsy.

¶ Specimens that tested positive included bone marrow, heart, kidney, liver, adrenal gland, and lung obtained at autopsy (immunohistochemical analysis); cerebrospinal fluid and a nasopharyngeal wash obtained on post-transplantation day 42 (viral culture); and leptomeninges in a brain-biopsy specimen obtained on post-transplantation day 47. Brain tissue obtained at autopsy tested negative.

‖ Specimens that tested positive included serum obtained on day 76 (serologic testing), skin on day 27 (immunohistochemical analysis), and blood on day 42 and cerebrospinal fluid on days 31 and 36 (viral culture). Bronchoalveolar-lavage fluid was positive on immunofluorescence assay. Brain tissue obtained at autopsy was negative.

The 2005 Cluster

Kidney Recipient A was a 48-year-old man admitted to a hospital in Rhode Island in late April 2005, 17 days after undergoing cadaveric renal transplantation (Fig. 2). He had been discharged home on post-transplantation day 7 with a creatinine level of 1.6 mg per deciliter (141 μmol per liter). At the time of readmission, he had had right-lower-quadrant pain in the area of the allograft for four or five days, as well as nausea, anorexia, diarrhea, fever, and chills. He was febrile (temperature, 38.7°C), and there was tender erythema over the area of the allograft, without incisional dehiscence or drainage. His creatinine level was 2.6 mg per deciliter (230 μmol per liter), and proteinuria, hematuria, a prolonged prothrombin time, and slightly elevated aminotransferase levels were present. Mycophenolate mofetil was discontinued, and administration of broad-spectrum antimicrobial agents was initiated. CT and ultrasonography of the abdomen and pelvis were unrevealing. Routine cultures of urine, blood, and stool were negative, as were studies of the stool for leukocytes, ova, parasites, *Clostridium difficile*, giardia, cryptosporidium, *Yersinia enterocolitica*, and rotavirus. Tacrolimus was discontinued because of concern about the worsening infection of uncertain cause. His temperature rose to 40.4°C, and he had copious diarrhea, dyspnea, and tender erythema extending from the area over the allograft to the right flank. Examination of biopsy specimens of the colon and kidney revealed no inflammation or viral inclusions.

Kidney Recipient B was a 54-year-old man who was admitted to the same hospital with fever. He had undergone cadaveric renal transplantation 17 days previously and had been discharged home on post-transplantation day 8 with a creatinine level of 3.3 mg per deciliter (292 μmol per liter). On post-transplantation day 14, mycophenolate mofetil was discontinued because of diarrhea. Fever and pain developed in the right lower quadrant over the area of the allograft, and he was readmitted for evaluation. He was lethargic and febrile (temperature, 38.4°C) and had tender erythema overlying the allograft, without incisional drainage. His creatinine level was 4.0 mg per deciliter (354 μmol per liter), with a platelet count of 113,000 per cubic millimeter and an alanine aminotransferase level of 298 IU per liter. Routine cultures of urine, blood, and stool were negative, and ultrasonography and CT of the abdomen and pelvis were unrevealing. Fever, diarrhea, and pain persisted, despite empirical use of broad-spectrum antimicrobial agents. A percutaneous liver biopsy was performed on post-transplantation day 23 because of worsening hepatitis and leukocytosis. Multiple foci of hepatocellular necrosis without inflammation or viral inclusions were noted. Later that day, he had a cardiac arrest and died. An autopsy revealed coronary artery disease and diffuse cerebral edema without meningitis or encephalitis.

A review of the records of the hospital's transplantation center revealed that the kidney recipients shared a common donor who had also been hospitalized there. The donor was a 45-year-old woman with hypertension who had presented to the emergency department with a five-day history of right-sided headache and acute left-sided weakness. She was alert and afebrile and had left-sided hemiparesis. CT of the brain revealed an infarct in the distribution of the right middle cerebral artery, and tissue plasminogen activator was administered. Throughout her hospitalization, she was afebrile and received no blood products or antimicrobial agents. She had a normal white-cell count on admission, with normal hepatic enzyme levels and platelet counts throughout her course. Intracerebral and subarachnoid hemorrhages with uncal herniation subsequently developed, and she was declared brain-dead. The donor met the screening criteria for organ and tissue donation, and surgical teams procured the lungs, kidneys, liver and associated blood vessels, skin, and corneas. Cultures of urine and blood performed at the time of organ procurement were negative. Examination of preimplantation biopsy specimens of the liver and kidney revealed no inflammation or granulomas. An autopsy revealed infarction in the distribution of the right middle cerebral artery, subarachnoid and left frontal intracerebral hemorrhages, and a patent foramen ovale. There was no evidence of infection.

The OPO coordinating the transplantations was contacted to obtain additional information about the donor. Physicians caring for the liver and lung recipients were contacted for information on their clinical status.

The liver recipient was a 54-year-old man with cirrhosis and chronic hepatitis B and C. In the initial days after the transplantation, he had head-

ache, fever (temperature, 39.1°C), and abdominal and right-shoulder pain. Leukopenia, thrombocytopenia, rising aminotransferase levels, and prolongation of the prothrombin time were noted. Administration of broad-spectrum antimicrobial agents was initiated; multiple cultures were negative. Exploratory laparotomy revealed intraabdominal hematoma without evidence of infection. The patient had a single, generalized seizure with hypotension and subsequent worsening of renal, hepatic, and respiratory function. No seizure focus was identified on radiologic imaging or electroencephalography. Examination of a liver-biopsy specimen revealed mild portal inflammation, liver-cell regeneration, cholestasis, and mild steatosis; these findings were interpreted as transplant-associated ischemia. Left bundle-branch block and atrial fibrillation developed. The patient became obtunded, with worsening coagulopathy and multiorgan failure. On post-transplantation day 21, high-dose methylprednisolone and antithymocyte globulin were administered for suspected acute graft rejection. Fever and hypotension persisted, with increases in aminotransferase and lactate dehydrogenase levels. The cause of his multiorgan failure was unclear. He had a cardiac arrest and died on post-transplantation day 26. An autopsy revealed extensive hepatic necrosis, bronchopneumonia, pulmonary edema, and subarachnoid hemorrhage.

The lung recipient was a 41-year-old man with cystic fibrosis. He was extubated on post-transplantation day 2 but became delirious the following day and had leukocytosis and thrombocytopenia. Chest radiographs revealed right-lower-lobe infiltrates. His temperature rose to 37.9°C, and diffuse abdominal pain and respiratory distress developed. CT of the chest on post-transplantation day 16 showed bilateral air-space disease, a finding interpreted as evidence of acute rejection, and high-dose methylprednisolone was administered. His creatinine level, prothrombin time, and aminotransferase levels steadily increased, and intermittent atrial fibrillation developed. On post-transplantation day 19, a pustular rash was noted on the face and trunk; examination of a skin-biopsy specimen revealed folliculitis, and aerobic, fungal, and viral cultures were negative. Symmetric effusions of the knees, elbows, and ankles developed. The hypoxemia and acidemia progressed, and the patient died on post-transplantation day 23. An autopsy revealed organizing diffuse alveolar damage and extensive geographic hepatic necrosis without inflammation or viral cytopathic changes.

Figure 2 (facing page). Clinical Course of Lymphocytic Choriomeningitis Virus (LCMV) Infection in the 2005 Cluster.

MMF denotes mycophenolate mofetil, TMP-SMX trimethoprim–sulfamethoxazole, CVVH continuous venous–venous hyperfiltration, and X death. Immunosuppressive agents are shown in red, and antimicrobial agents in blue.

Because of concern about transplant-transmitted infection in the organ recipients, the Rhode Island Department of Health, the Massachusetts Department of Public Health, and the CDC were contacted for assistance in investigating the causes of the recipients' illnesses. Causes considered included acute hepatitis A, leptospirosis, toxoplasmosis, enterovirus infection, and flavivirus infection. Tissue specimens from the donor and recipients were submitted to the CDC for additional testing.

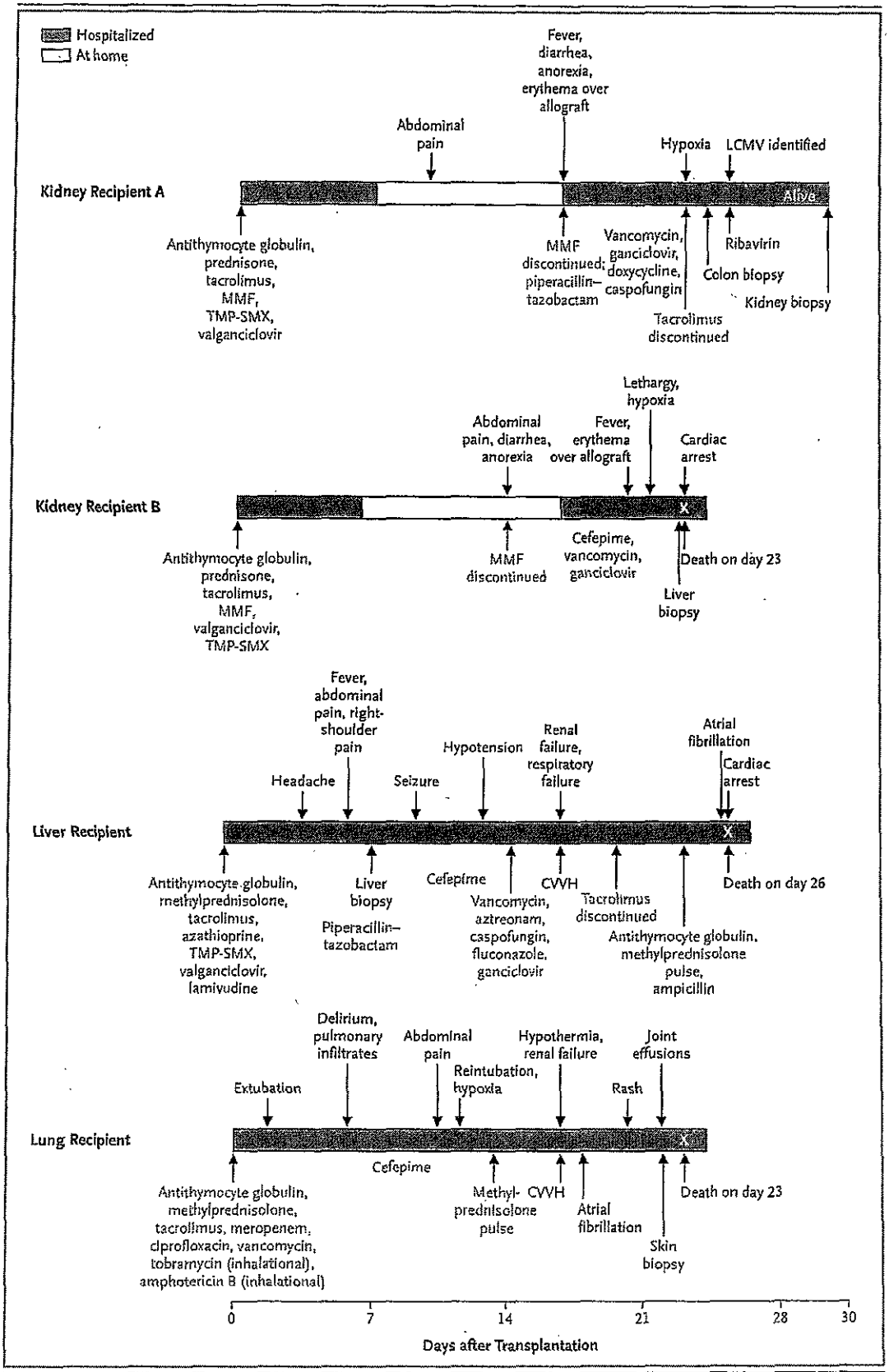
EPIDEMIOLOGIC INVESTIGATIONS

For both clusters, epidemiologic investigations were conducted at the transplantation centers and coordinating OPOs. For the 2005 cluster, epidemiologic investigations were also performed at the donor's home and workplace by state public health authorities and the CDC.

VIRUS ISOLATION AND INDIRECT FLUORESCENCE MICROSCOPY

Virus isolation was attempted by inoculation of Vero E6 cells with cerebrospinal fluid, serum, blood, and 10 percent fresh-tissue suspensions. Cultures were examined by thin-section electron microscopy. "Spot" slides of culture cells were also evaluated by indirect fluorescent antibody testing with the use of specific mouse hyperimmune ascitic fluids prepared against the Armstrong strain of LCMV.[11]

In the 2003 investigation, virus isolation was also attempted by inoculating suckling mice (*Mus musculus*) with fluid specimens (0.03 ml intracranially and 0.1 ml intraperitoneally) or with 10 percent homogenates of frozen tissue. Mice were killed by exposure to isoflurane, and tissues were fixed in 10 percent neutral buffered formalin and evaluated with the use of immunohistochemical stains for LCMV, as described below.



Studies in animals were performed at the CDC and were approved by the CDC Laboratory Animal Care and Use Committee. Animal research was conducted in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals, and it adhered to the principles stated in the *Guide for the Care and Use of Laboratory Animals*, by the U.S. National Research Council.

HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL ANALYSES

Multiple formalin-fixed, paraffin-embedded tissue specimens, including biopsy and autopsy tissues from the donors and recipients, were stained with hematoxylin and eosin and various immunohistochemical stains by means of an immunoalkaline phosphatase technique.[12] For both clusters, initial tissue specimens were evaluated with immunohistochemical stains for a number of viral agents, including flaviviruses, adenoviruses, and herpesviruses 1, 2, 3, and 5. In the investigation of the 2003 cluster, immunohistochemical testing for LCMV was performed after identification of this virus by culture, indirect fluorescent antibody testing, and electron microscopy. In the investigation of the 2005 cluster, immunohistochemical testing for LCMV was included in the initial evaluation of tissue specimens. The primary antibodies used for LCMV immunohistochemical detection included hyperimmune rabbit and mouse anti-LCMV antibodies specific for LCMV and an anti–Lassa virus monoclonal antibody reactive with both Lassa virus and LCMV.[13]

GENETIC DETECTION AND CHARACTERIZATION OF VIRUS

RNA was extracted from clinical specimens or viral isolates, and specific molecular targets were amplified by reverse-transcriptase–PCR (RT-PCR) assays with the use of broadly reactive polymerase gene–specific primers for the detection of arenavirus RNA. The resulting complementary DNA products were purified, and nucleotide sequences were determined and analyzed. In the investigation of the 2005 cluster, after LCMV-specific sequences had been obtained from PCR products amplified from clinical specimens, a more sensitive, LCMV-specific, quantitative real-time RT-PCR (TaqMan) technology was developed and used for more extensive analysis of specimens.

Figure 3 (facing page). Pathological Studies Revealing Lymphocytic Choriomeningitis Virus (LCMV) in the 2003 Cluster.

Panel A, an electron micrograph of LCMV isolated in Vero E6 cells from the cerebrospinal fluid of Kidney Recipient 1, shows highly pleomorphic, 50-to-300-nm virions containing electron-dense particles. Panel B shows immunohistochemical staining of LCMV (red) in neurons and choroid-plexus ependymal cells of a mouse inoculated with the virus (immunoalkaline phosphatase with naphthol–fast red and hematoxylin counterstain; monoclonal anti-LCMV antibody). Panel C shows immunohistochemical staining of LCMV antigens in lung tissue from the lung recipient (monoclonal anti-LCMV antibody). The image in Panel D reveals extensive hepatocellular necrosis with minimal inflammatory-cell infiltrates in the liver recipient (hematoxylin and eosin). Panel E shows immunohistochemical staining of viral antigens in the transplanted liver (monoclonal anti–Lassa virus antibody). Panel F shows immunohistochemical staining of LCMV antigens in the donor kidney of Kidney Recipient 1 (monoclonal anti-LCMV antibody). Panel G shows immunohistochemical staining of viral antigens in the skin of Kidney Recipient 2 (monoclonal anti–Lassa virus antibody). All micrographs are shown at low magnification.

SEROLOGIC TESTING

An enzyme-linked immunosorbent assay was used to detect LCMV-specific IgM and IgG. The assay was performed as previously described,[11] with some modifications in commercially available components, such as microtiter plates and conjugates.

RESULTS

INVESTIGATION OF THE 2003 CLUSTER

Results of testing in the 2003 cluster are summarized in Figure 3 and Table 1. Electron microscopy of Vero E6 cell cultures inoculated with cerebrospinal fluid from Kidney Recipient 1 revealed viral particles compatible with an Old World arenavirus. Indirect fluorescent antibody testing of these cultures confirmed the identity of the arenavirus as LCMV. Subsequently, LCMV was identified by immunohistochemical analysis of the brain tissue of mice inoculated with cerebrospinal fluid from the same patient. LCMV was identified in multiple tissues from each of the four recipients. Nucleotide analysis of PCR products revealed that the viral isolates obtained from the two kidney recipients were identical and were distinct from previously described LCMV strains (Fig. 1 of the Supplementary Appendix). Extensive