

FULMINANT HEPATIC FAILURE DUE TO DISSEMINATED ADENOVIRUS INFECTION IN A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction

Adenovirus infection is a common cause of upper respiratory infection in which symptoms are usually mild and transient. Rarely, adenovirus may disseminate, resulting in pneumonitis, severe hepatic necrosis, and fulminant hepatic failure.¹ Such cases have been reported in two types of patients: those with a primary immunodeficiency (eg, thymic dysplasia, severe combined immunodeficiency or AIDS) and those with a secondary immunodeficiency (eg, immunosuppressive therapy or chemotherapy).² We report a case of fulminant hepatic failure caused by disseminated adenovirus infection in a patient with Rai stage 0 chronic lymphocytic leukemia (CLL) who had not received corticosteroid or cytotoxic chemotherapy.

Case Report

A 56-year-old man developed pneumonia in 1996 and was treated with antibiotics. He was noted to be hypogammaglobulinemic, and intravenous immunoglobulin (Ig) was prescribed. During his first infusion in 1996, he had an unspecified reaction and no further administrations were given. In March 1998, he presented with recurrent pneumonia and was diagnosed with CLL by peripheral blood immunophenotyping. A chest radiograph showed bilateral

infiltrates, and a computed tomography scan of the chest demonstrated bilateral air space disease with periaortic and mesenteric lymphadenopathy. Sputum cultures grew *Proteus mirabilis*, and he was treated with intravenous antibiotics and discharged home. One month later he was readmitted for increasing dyspnea and productive cough. He was treated with intravenous antibiotics and transferred to Duke University Medical Center on April 19, 1998.

The patient was from West Virginia, worked as a mechanic, and had no significant chemical exposure. He was married, did not smoke, and had no significant history of alcohol intake and no risk factor for acquisition of HIV. On examination his temperature was 39.4°C, blood pressure 109/55 mm Hg, pulse 109 beats per minute, and respiratory rate 22. He was alert and oriented. He had no lymphadenopathy. His chest examination showed bibasilar rales and diffuse rhonchi. His cardiovascular examination was normal, and his abdomen was unremarkable without evidence of ascites or hepatosplenomegaly.

Laboratory studies on admission disclosed the following values: hemoglobin, 10.3 g/dL; hematocrit, 31%, white blood cell count, 2,200/mm³; 32% lymphocytes; platelet count, 167,000/mm³; lactate dehydrogenase, 544 IU/L;

aspartate aminotransferase (AST), 25 IU/L; alanine aminotransferase (ALT), 40 IU/L; IgG, 74 mg/dL (normal 588–1,573); IgM, 0 mg/dL (57–237); and IgA, 21 mg/dL (46–287). A bone marrow biopsy showed hypercellular marrow and patchy involvement by small lymphocytes consistent with CLL. Approximately 50% of the lymphocytes were abnormal and stained with multiple B-cell lineage antigens as well as CD5, CD23, and lambda light chain. No granulomata were seen, and cultures for bacteria, mycobacteria, and fungi were negative. Adenovirus grew slowly from the bone marrow culture, and identification of this agent occurred 2½ weeks following the patient's death.

The patient developed worsening pancytopenia over the next 72 hours. The platelet count fell to 10,000, the white blood cell count fell to 600/mm³, and hematocrit fell to 22%. He was given granulocyte colony-stimulating factor (G-CSF) and packed red blood cell transfusions. On April 24, 1998, his liver

function tests became elevated, with AST 3,680 IU/L and ALT 1,320 IU/L. Hepatitis B core antibody was positive, while hepatitis C antibody, hepatitis A IgM, cytomegalovirus IgM, and HIV enzyme-linked immunosorbent assay (ELISA) were all negative. Forty-eight hours later, his AST had risen to 11,984 IU/L, the ALT was 1,961 IU/L, total bilirubin level was 6.1 mg/dL, and prothrombin time was 18.3 seconds. His chest radiograph showed normal heart, mediastinum, and hila with heterogeneous opacities in the bases as well as bilateral basilar bronchiectasis.

He was transferred to the intensive care unit because of altered mental status and hypoxia. An hepatic Doppler ultrasound showed normal hepatic parenchyma and patent hepatic and portal veins. The patient became hemodynamically unstable and required intravenous dopamine and endotracheal intubation. He developed grand mal seizures and suffered cardiopulmonary arrest. He died of multiorgan system failure on April 27, 1998.

At autopsy, cultures of the consolidated lung tissue were positive for adenovirus and cytomegalovirus. Bone marrow cultures were positive for adenovirus, serotype 4. Liver histology showed subtotal hepatic necrosis and immunostains for adenovirus were positive (Figs 1 and 2). Immunostains of the liver tissue were negative for herpes simplex virus, cytomegalovirus, hepatitis B surface, and hepatitis B core antigen. The only other site of adenoviral infection at autopsy was a cecal ulcer. Other evidence for immune dysfunction included *Strongyloides stercoralis* infection of the jejunum and superficially invasive candidiasis at the gastroesophageal junction. B-cell CLL involved the bone marrow, thoracic and abdominal lymph nodes, the interstitium around airways of the right and left lungs, and the submucosa of the small and large intestines.

Discussion

Adenovirus is a ubiquitous double-stranded DNA virus com-

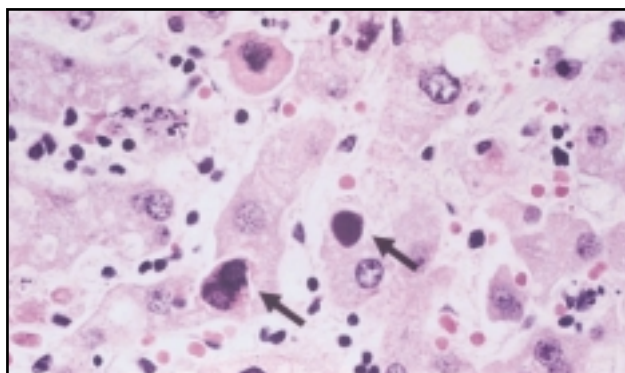


Fig 1. — "Smudge cell" inclusions of adenovirus are present within hepatocytes (arrows). These are intranuclear, basophilic inclusions without a halo that at times may encompass the entire cell. Separate intracytoplasmic inclusions are not present.

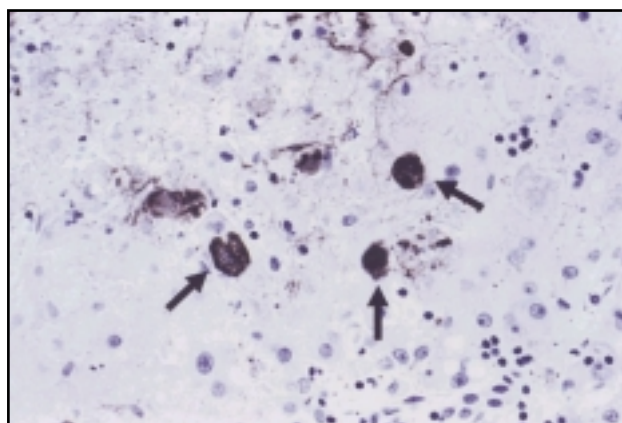


Fig 2. — Immunohistochemical stain for adenovirus shows localization of viral-specific antigen in the infected hepatocyte cell (arrows).

monly associated with upper respiratory illness.² Of the 47 known serotypes, 1, 2, 3, 5, and 7 are most commonly associated with human disease.³ Transmission typically occurs through aerosolized droplets, fecal-oral exposure, or swimming pool water.³ The incubation period ranges from a few days to 2 weeks.

The most common adenoviral illness is the familiar upper respiratory infection in the immunocompetent patient. This syndrome is transient and almost never causes medically significant problems. Outbreaks of respiratory disease are more common in the winter, although adenoviruses are endemic during the entire year. Epidemic keratoconjunctivitis is another less common presentation of adenovirus infection. It is more common in the summer months and is associated with transmission through swimming pool water. Following acute infection, the virus may be shed up to 12 weeks and may remain in lymphoid tissue for years where it can become reactivated following immunosuppression.

Detection of adenoviral infections in patients can occur through multiple methods including shell vial assay, conventional culture techniques using tissue monolayers, direct fluorescent antigen (DFA) using antibodies, enzyme immunoassay, polymerase chain reaction (PCR), immunohistochemistry (such as used in this case), and serology, whose use is mainly for epidemiological purposes. One study compared conventional and rapid culture, two antigen detec-

tion tests, and PCR for detection of adenovirus in nasopharyngeal aspirates and found PCR using Ad7 hexon-specific primers had a superior sensitivity and revealed positive cases that could not be confirmed by culture.⁴

In the immunocompromised patient, adenovirus may cause disseminated disease and death. Compared with self-limited infections, a wider spectrum of organ involvement is seen in disseminated disease. Cystitis, nephritis, pneumonitis, hepatitis, and gastroenteritis have all been reported in disseminated adenovirus infection in the immunocompromised patient.¹ Adenovirus has been isolated in 3.8% to 18% of bone marrow transplant recipients,⁵⁻⁷ in 8% to 18% of liver transplant recipients,⁸⁻¹⁰ and in 12% of kidney transplant recipients.¹¹ The most common sites of infection in these patients are urine, throat, and rectum. While the case fatality rate of disseminated adenovirus infection has been reported to be as high as 60%, not all immunocompromised patients with adenovirus infection develop disseminated disease.²

The source of adenovirus infection in the immunocompromised host is uncertain, but there are three possibilities.² The most likely cause is reactivation of latent adenovirus infection. The virus remains latent in lymphoid and renal tissue after clearance of acute infection.³ Shields et al⁵ showed that 69% of bone marrow transplant recipients were seropositive for previous adenovirus infection prior to transplantation.

This suggests that most patients were infected with adenovirus prior to transplantation and reactivated virus after administration of immunosuppressive drugs. A second possibility is the exogenous transmission of adenovirus to the immunocompromised host. This may occur through nosocomial transmission¹² or during a community outbreak.¹³ Third, there is evidence that adenovirus may be transmitted via transplanted organs. Koneru et al¹⁴ reported that 67% of liver transplant recipients who developed adenovirus hepatitis after transplant were seronegative for adenovirus before transplantation and received donor organs from seropositive donors. Varki et al¹⁵ reported a patient who developed adenovirus infection within 1 week of receiving a liver from a donor with adenovirus infection.

At least 24 cases of fulminant hepatic failure due to adenoviral hepatitis have been reported (Table). There are additional reports of patients with disseminated adenovirus infection who died of multiorgan system failure; although these patients had some degree of hepatitis, the contribution of liver disease to the overall clinical outcome was not clear.^{8,10} All of the cases of fulminant hepatic failure caused by adenovirus have occurred in patients with a well-defined primary or secondary immunosuppressive condition. Of the 24 patients listed in the Table, 9 had a primary immunodeficiency, while 15 had a secondary immunodeficiency due to chemotherapy or immunosuppressive drugs.

The most common presentation was severe pneumonitis with associated severe hepatic necrosis. The serotype of adenovirus was reported in 20 patients. The most common were type 5 (9 patients), type 2 (5 patients), and type 1 (2 patients). Types 3, 6, 7, 12, 31, and 32 were reported in one patient each. Two patients had two serotypes reported. To our knowledge, this is the first documented example of a patient with serotype 4 adenovirus having fulminant hepatitis. The frequency of isola-

tion of serotype 5 suggests this serotype may have a greater propensity to cause hepatitis. Animal experiments showing that human adenovirus type 5 causes hepatitis in hamsters³⁴ and mice³⁵ support this hypothesis.

While our patient did not have a defined primary immunodeficiency syndrome, immune dysfunction caused by his underlying CLL may have predisposed him to infections. Between one third and one half of patients with CLL will develop an

infection at some point in their disease. The most common type of infection is bacterial; fungal and viral infections are far less common. Shaw et al³⁶ characterized 50 infections in a cohort of 25 CLL patients. Bacterial infections accounted for 46 (92%) of infections, viral accounted for 3 (6%), and one episode (2%) was caused by fungus. Twomey³⁷ reported similar results in 45 CLL patients who developed 71 infections of which 54 had identified pathogens. Of these cases, 89% were bacterial, 6% were viral, 3%

Patients With Disseminated Adenovirus Infection and Fulminant Hepatitis

Case #	Underlying Condition	Adenovirus Type	Age	Maximum Aspartate Aminotransferase	Maximum Prothombin Time	Reference
1	ALL	5	19	8,830	<18%	Kitabayashi et al ¹⁶
2	ALL	5	17	8,830	25.7	Carmichael et al ¹⁷
3	BMT	2	22	>4,000	84	Bertheau et al ¹⁸
4	BMT	5, 12	13	2,070	-	Niemann et al ¹⁹
5	BMT	5	34	2,926	86.2	Johnson et al ²⁰
6	BMT	5	19	-	-	Purtilo et al ²¹
7	BMT	32	-	-	-	Charles et al ²²
8	CLL	1	45	40.6*	-	Ljungman et al ²³
9	HD	-	28	9,120	<10%	Zahradnik et al ¹
10	HIV	1	7	4,129	14.7	Krilov et al ²⁴
11	HIV	2	0.5	6,940	36.8	Krilov et al ²⁴
12	HIV	3	24	891	-	Krilov et al ²⁴
13	HIV	2 or 6	30	-	-	Dombrowski et al ²⁵
14	OLT	5	0.75	-	-	Varki et al ¹⁵
15	OLT	5	53	2,985	-	Saad et al ²⁶
16	OLT	-	46	1,070	-	Saad et al ²⁶
17	OLT	-	**	2,340	-	Cames et al ²⁷
18	OLT	-	**	1,926	-	Cames et al ²⁷
19	RT	5	56	14,900	19.6	Norris et al ²⁸
20	SCID	31	0.5	966	-	Rodriguez et al ²⁹
21	SCID	5	0.1	4,422	20	South et al ³⁰
22	TD	7	0.5	-	-	Benyesh-Melnick et al ³¹
23	TD	2	0.16	3,600	60	Aterman et al ³²
24	TD	2	0.9	-	29	Wigger et al ³³

ALL = acute lymphocytic leukemia
 CLL = chronic lymphocytic leukemia
 HIV = human immunodeficiency virus
 RT = renal transplant
 TD = thymic dysplasia
 * AST expressed as ukat/L (normal is <0.7)
 ** Pediatric patients, age not given
 BMT = bone marrow transplant
 HD = Hodgkin's disease
 OLT = orthotopic liver transplant
 SCID = severe combined immunodeficiency

were fungal, and 2% were tuberculosis. Ulmann et al³⁸ reported their experience with 60 patients with CLL of whom 23 developed infections. A total of 2,152 infection days were recorded in these patients, with 2,078 (97%) due to bacterial infection and 74 (3%) due to virus or tuberculosis. One limitation to these data is that viral cultures can be difficult to perform and therefore the true incidence of viral infections may be higher than reported.

The cause of the increased number of infections in CLL patients is thought to be due primarily to hypogammaglobulinemia. In fact, our patient had profound hypogammaglobulinemia. Shaw et al³⁶ reported that the number of infections in patients with CLL and hypogammaglobulinemia was 2.7 times higher than in patients with normal globulin levels. Ulmann and colleagues³⁸ reported an 89% incidence of infections in their patients with hypogammaglobulinemia compared to 15% in those with normal globulin levels. Furthermore, the severity of hypogammaglobulinemia worsens as the stage of CLL progresses.³⁹

In addition to defects in humoral immunity, CLL patients also have defects in cellular immunity.⁴⁰ Although the absolute number of T cells is usually normal in these patients, the CD4/CD8 ratio is decreased,⁴¹ and decreased natural killer cell activity has been reported.⁴¹ Shaw et al³⁶ showed that 83% of CLL patients exhibited decreased response to skin antigens. Chapel and Bunch⁴² found 48% of their CLL patients to be

anergic. While such defects in cellular immunity in CLL patients have been documented experimentally, no clear relationship between these defects and the occurrence of infections has been established.

Our patient had profound immune dysfunction as evidenced by his fulminant adenoviral hepatitis, adenoviral/cytomegaloviral pneumonitis, and *S. stercoralis* and candidal infections. However, the severity of immunodeficiency was far out of proportion to the extent of his underlying CLL. He had only recently been diagnosed with Rai stage 0 CLL (manifest only by an elevated absolute lymphocyte count) and had not received any cytotoxic or corticosteroid therapy. His hypogammaglobulinemia was profound and was likely an important factor in his susceptibility to viral infections, and we suspect he had severe T-cell dysfunction as well.

While no proven efficacious therapy for adenovirus infection exists, there are several case reports of successful treatment of disseminated adenovirus infection. In one case, a patient with deficient cellular immunity and disseminated adenoviral infection recovered after the administration of thymic hormone.⁴³ In another case, a patient with severe pneumonitis caused by adenovirus recovered after infusion of immune globulin with high titers of antibody directed towards adenovirus.⁴⁴ Newer agents such as ribavirin,⁴⁵⁻⁴⁷ ganciclovir^{48,49} and vidarabine¹⁶ have also demonstrated efficacy in the treatment of adenovirus infections.

The patient described here is an unusual case in that a fatal adenovirus infection developed in the absence of immunosuppressant or a primary immunodeficiency syndrome. The diagnosis was unexpected and was not made until an autopsy was performed. Although fatal viral infections are rare in patients with CLL, physicians should be aware of the possibility of disseminated adenovirus infection in this population.

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