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Protracted course of disseminated adenovirus disease with necrotizing granulomas in the liver☆,☆☆,★

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ABSTRACT

A 52- year-old male with chronic lymphocytic leukemia was hospitalized with disseminated adenovirus disease. More than a month following recovery, hepatic necrotizing granulomas secondary to adenovirus were found. This case illustrates the protracted course that adenovirus disease may take and emphasizes an unusual presentation with hepatic necrotizing granulomas.

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1. Case report

A 52-year-old man presented with 3 days of fever, cough, and sweats. He had a 5-year history of untreated chronic lymphocytic leukemia (CLL) with hypogammaglobulinemia, a 33-year history of myasthenia gravis treated with prednisone 10 mg every other day, thyroidectomy for papillary thyroid cancer 12 years prior, and cryptosporidium diarrhea 15 months prior. He was taking trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis jirovecii* pneumonia which occurred a year prior and replacement levothyroxine.

On admission, he had a fever of 40.2 °C. Physical examination was unremarkable except for stable splenomegaly and peripheral lymphadenopathy. Laboratory studies revealed an absolute lymphocyte count of 12,888 per mm^3, platelet count of 74,000 per mm^3, and hemoglobin of 12.5 g/dL, unchanged from prior. The absolute neutrophil and CD4 counts were 3311 per mm^3 and 811 cells per μL, respectively. IgG level was low at 132 mg/dL, and C-reactive protein (CRP) was elevated at 73.2 mg/L. Chest computed tomography (CT) revealed 2 new

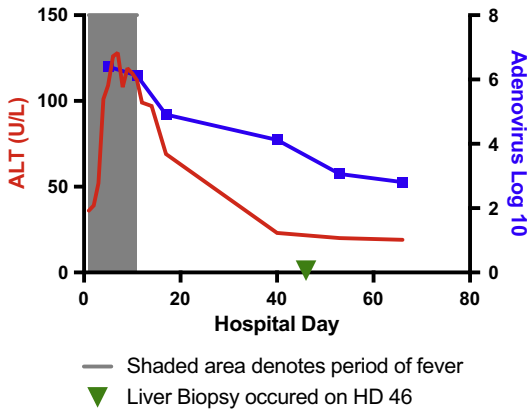

Fig. 1. Relationship between ALT (red line) and serum adenovirus load (blue line) over time. Note that both values peaked during febrile period of inpatient hospitalization (shaded area) with ALT normalized and that serum adenovirus load significantly decreased by the time liver biopsy occurred on HD46 (green triangle).

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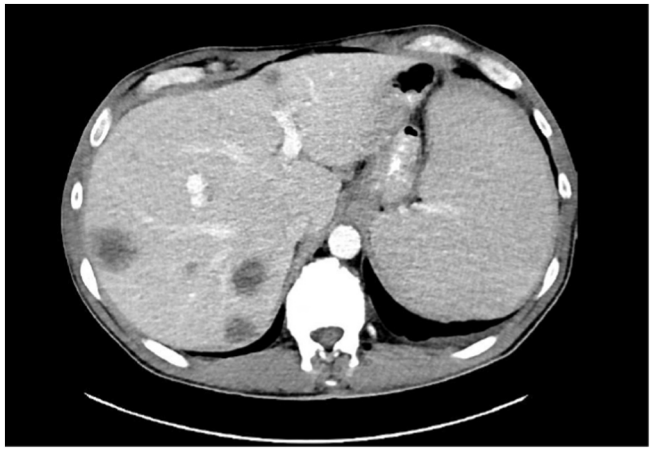

Fig. 2. CT of the liver with numerous hypodense lesions.

subcentimeter nodules in the upper lobes. Nasopharyngeal wash was negative for all pathogen targets tested by BioFire Filmarray (BioFire Diagnostics, Salt Lake City, UT). Fever continued on ceftriaxone and azithromycin, prompting a bronchoscopy on hospital day (HD) 4 and broadening of antibiotics to vancomycin and meropenem. He was given 35 g of intravenous immune globulin (IVIG) on HD3 with improvement in IgG to 540 mg/dL, and a second dose was given on HD6.

All bronchoalveolar lavage results were negative except for the detection of adenovirus and respiratory syncytial virus (RSV) by the BioFire Filmarray. Oral ribavirin (400 mg every 8 h) was started on HD5, intended to treat RSV infection, and continued for 1 week. Quantitative adenovirus PCR performed on blood drawn on HD5 demonstrated >2.5 million copies/mL (>6.4 $\log_{10}$) [Fig. 1]). CRP drawn that same day peaked at 190.9 mg/L. Liver enzymes, which had been normal on admission, began to rise on HD3, reaching a peak ALT 128 U/L and AST 201 U/L on HD 7 and alkaline phosphatase 167 U/L on HD11. The patient began to improve clinically on HD8, finally becoming afebrile on HD10. On HD12, he was discharged on no antimicrobial therapy with plans to receive IVIG every 4 weeks. Transaminases had decreased significantly by the time of discharge, and CRP had downtrended to 16.2 mg/L.

On follow-up clinic visits, plasma adenovirus load fell progressively to 81,850 copies/mL on HD16, 13,250 copies/mL on HD40, and 1150 copies/mL on HD53 [Fig. 1]. However, on HD40, he developed sore throat with tonsillitis and increased cervical lymphadenopathy. CT of the abdomen with intravenous contrast, performed because of concern for transformation of CLL, demonstrated more than a dozen hypodense lesions in the liver up to 3.5 cm in diameter [Fig. 2]. These had not been appreciated on noncontrast CT on HD3 and HD11, but in retrospect, they were present at that time. Liver enzymes and CRP were normal on HD40. Positron emission tomography–CT showed the liver lesions to be FDG-avid with a standard uptake value of 8.26. Percutaneous liver biopsy done on HD46 revealed multiple necrotizing granulomas with palisades of epithelioid cells. In the necrotic centers, cells stained positive for adenovirus by immunohistochemistry [Fig. 3]. PCR of the tissue was positive for adenovirus. Given that liver enzymes were normal, serum adenovirus load had fallen, and there were no histopathological changes consistent with active viral infection, the liver lesions were thought to represent adenovirus infection during his prior hospitalization rather than an active infection at the time of biopsy. When last seen 18 months later, there was no sign of recurrence.

Adenovirus was genotyped from plasma as species C serotype 2 using the PCR strategy introduced by La Rosa et al. (2011) with modifications. PCR was performed on DNA extracted from plasma with hexon-specific primers and 5 primer pairs targeting the fiber gene in species A-E of HAdV. Only the fiber gene primers specific to species C amplified a product of expected size. The 433-base product was sequenced and found to be a 100% match to the corresponding fiber gene sequence of

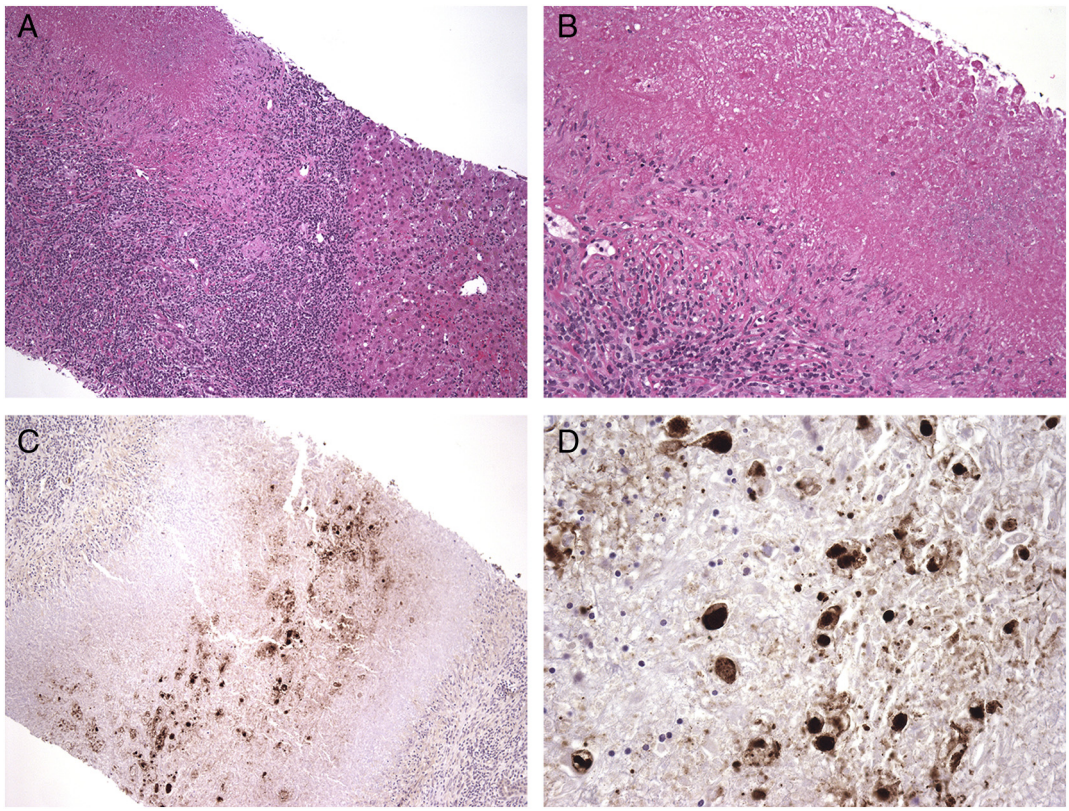

Fig. 3. Liver biopsy specimens stained with hematoxylin and eosin at 10× (A) and 40× (B) show necrotizing granulomas with palisading epithelioid histiocytes and a dense lymphoid infiltrate, and immunohistochemical stain for adenovirus at 10× (C) and 40× (D) shows numerous positive cells within the necrotic areas.

J01917.1/AC_000007, a prototype HAdV-2 virus (Davidson et al., 2003; Roberts et al., 1986).

Adenoviruses are DNA viruses classified into 7 species (HAdV-A through G), comprising at least 60 serotypes. Disseminated adenovirus disease has been defined as involvement of multiple organ systems in the presence of 2 or more HAdV-positive PCR assays of blood and other body fluids (Lion, 2014).

Liver lesions are a rare manifestation of adenovirus infection. A review in 2013 found 89 cases, 48% in liver transplant recipients, 21% in stem cell transplant recipients, 12% receiving chemotherapy, 6% with severe combined immunodeficiency, 4% with HIV, and 4% with solid organ transplants other than liver (Ronan et al., 2014). Hypodense lesions in the liver, as seen in this patient, were seen on CT in 8 of 9 cases in that series, as well as in 3 subsequent cases (Kawashima et al., 2015). Only 27% of the 89 patients survived (Ronan et al., 2014). In a 2015 review of 25 patients with allogeneic hematopoietic stem cell transplantation and adenovirus hepatitis, only 1 survived (Kawashima et al., 2015). The presence of focal necrotic lesions is typical (Kawashima et al., 2015; Wang and Wang, 2003). Necrotizing granulomas, however, as seen in this patient, are rare. A 2017 analysis of 12 cases of adenovirus hepatitis reported only 1 other case where granulomas were seen (Schaberg et al., 2017). A 2015 review of hepatic granulomas does not mention adenovirus as a cause (Lamps, 2015).

There is currently no formally approved antiviral therapy for adenovirus infection. Cidofovir has demonstrated in vitro activity (Morfin et al., 2005) and is often recommended, but usage is often limited by toxicities (Lee et al., 2016; Lenaerts and Naesens, 2006). Brincidofovir, an orally available lipid conjugate of cidofovir, has shown promise, but randomized controlled trials are lacking (Hiwarkar et al., 2017; Ramsay et al., 2017). Ribavirin has also been used, and although there have been case reports of successes, overall data are inconsistent (Lenaerts and Naesens, 2006; Ljungman, 2004), and it is not routinely recommended for use. In vitro susceptibility of adenovirus isolates to ribavirin has been shown to be species specific, with species C (which this patient had) being generally susceptible (Morfin et al., 2005). It is unknown whether this susceptibility correlates with clinical response. Given that disseminated adenovirus disease is often a fulminant process, it appears possible that ribavirin may have ameliorated this patient's disease course. However, given that IVIG had also been administered in the setting of hypogammaglobulinemia, it is difficult to determine what caused him to improve.

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