Diarrhea Leads to Pneumonia and Hematuria in the Intensive Care Unit

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A 26-year-old male with a past medical history of Crohn’s disease, in remission for more than 10 years, presented to the Medical Intensive Care Unit (MICU) with diarrhea, hematuria, left-sided pulmonary infiltrates, transaminitis, and rapid-onset respiratory failure with acute kidney injury (AKI). The patient was well until 7 days prior to ICU admission, when he developed severe non-bloody diarrhea, approximately 20 times daily. Three days prior, he presented to an emergency department (ED) and was sent home after rehydration with normal saline with a reportedly normal chest x-ray (CXR). Two days prior, he presented to his primary care provider with continued diarrhea and fever to 39.4 °C, and he was sent home with anti-diarrheal medications. One day prior, he returned to the ED with chest tightness, shortness of breath, and cough productive of dark sputum, and he was found to have a new left-sided infiltrate on CXR, consistent with a pneumonia. He also reported dark urine and anorexia. He denied nausea, vomiting, abdominal pain, rash, or dysuria. In the ED, he was noted to be febrile with a temperature of 40.6 °C, tachycardic with a heart rate of 140 beats per minute, tachypneic with a respiratory rate of 29 breaths per minute and blood pressure of 115/65 mmHg, and hypoxic with an oxygen saturation of 93% on 4 L per minute of oxygen supplementation. He was transitioned to bilevel positive airway pressure (BIPAP) due to his increased work of breathing and hypoxia and received empiric antibiotic therapy and steroids, including intravenous (IV) ceftriaxone, azithromycin, and linezolid. He was then transferred to the University of Chicago Medicine MICU. His respiratory status worsened, and after about 5 h he was intubated. The patient had eaten no recent restaurant foods and had no known sick contacts. He worked as a pipe fitter. He denied having pets, unusual hobbies, or travel within the previous 6 months.

On physical examination, his heart rate was 150 beats per minute, blood pressure 100/50 mmHg, temperature 39.1 °C, and respiratory rate 28 breaths per minute. He was intubated and sedated. He did not have any cervical adenopathy, and his conjunctivae were injected. His pulmonary exam demonstrated crackles bilaterally, and cardiovascular exam revealed a normal S1 and S2 with no murmurs. Pulses were equal, but capillary refill was slow, approximately 3 s. Abdominal exam showed normal liver and spleen to palpation and was nontender. He did not have any rashes.

Initial serum laboratory results on transfer to the MICU included white blood cell (WBC) count of 11,900/μL (92% neutrophils, 3% lymphocytes), hemoglobin of 14.1 g/dL, and platelet count of 195,000/μL. The basic metabolic panel was within

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normal limits, with blood urea nitrogen of 16 mg/dL and creatinine of 1.0 mg/dL. Liver function tests showed elevated transaminases, with an alanine aminotransferase (ALT) of 1353 U/L (normal range, 8–35 U/L) and an aspartate aminotransferase (AST) of 356 U/L (8–37 U/L).

Seven hours later, his creatinine had risen to 1.9 mg/dL (normal range, 0.5–1.4 mg/dL) and the transaminases to ALT of 1877 U/L and AST of 501 U/L. He also had a markedly elevated creatine kinase (CK) of 180,620 U/L (9–185 U/L) and elevated lactate of 4.5 mmol/L (0.6–2.2 mmol/L). Urinalysis revealed 3+ blood, 3+ protein, 3–5 red blood cells (RBC), and 0 WBC, raising the question of rhabdomyolysis given the elevation in CK and the 3+ blood on urinalysis with only 3–5 RBCs. Further infectious labs known at this point are in Table 32.1; they were significant for only a positive polymerase chain reaction (PCR) for adenovirus from a nasopharyngeal swab. By this time, his chest imaging had worsened with bilateral airspace opacities and consolidations, as well as a left-sided effusion (Fig. 32.1).

Given the combination of pneumonia, diarrhea, transaminitis, and acute kidney injury (AKI), the diagnostic picture appeared to be a disseminated infection. It was clarified that the patient was not at that point, nor had he ever been treated with immunosuppressive medications for Crohn’s disease. The differential diagnosis for his constellation of symptoms is shown in Table 32.2. When a disseminated infection is found in an immunocompetent host, one should question if there is an unknown underlying immunodeficiency, and undiagnosed human immunodeficiency virus (HIV) should be considered. His HIV antibody test from blood was negative, but the question of acute HIV remained, so a serum viral load was also checked that was also negative. Given his residence in the Midwest, histoplasmosis and blastomycosis were the

### Table 32.1 Laboratory results

| Laboratory test                  | Result       | Normal values     |
|----------------------------------|--------------|-------------------|
| Blood urea nitrogen              | 24 mg/dL     | 7–20 mg/dL        |
| Creatinine                       | 1.9 mg/dL    | 0.5–1.4 mg/dL     |
| Total bilirubin                  | 0.4 mg/dL    |                   |
| Alanine aminotransferase         | 1877 U/L     | 8–35 U/L          |
| Aspartate aminotransferase       | 501 U/L      | 8–37 U/L          |
| Alkaline phosphatase             | 75 mg/dL     | 30–120 U/L        |
| White blood cell count           | 8200/μL      | 3500–11,000/μL    |
| Creatine kinase                  | 180,620 U/L  | 9–185 U/L         |
| Lactate, blood                   | 4.5 mmol/L   | 0.6–2.2 mmol/L    |
| Urinalysis                       | 3 + blood/3 + protein/3–5 red blood cells/0 white blood cells | |
| 2 blood cultures                 | No growth    |                   |
| 2 respiratory cultures           | Normal flora |                   |
| Urine culture                    | No growth    |                   |
| Stool culture                    | No growth    |                   |
| Rotavirus antigen, stool         | Negative     |                   |
| C. difficile stool polymerase chain reaction (PCR) | Negative | |
| Human immunodeficiency virus (HIV) serology | Nonreactive | |
| Respiratory viral panel, PCR<sup>a</sup> | Adenovirus positive | |
| Cytomegalovirus PCR, blood       | Negative     |                   |
| Epstein-Barr virus (EBV) PCR, blood | Negative | |
| Legionella antigen, urine        | Negative     |                   |

<sup>a</sup>Polymerase chain reaction test for the following pathogens: adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus OC43, coronavirus NL63, human metapneumovirus, human rhinovirus/enterovirus, influenza A, influenza A/H1, influenza A/H1-2009, influenza A/H3, influenza B, parainfluenza 1, parainfluenza 2, parainfluenza 3, parainfluenza 4, respiratory syncytial virus (RSV), Bordetella pertussis, Chamydophila pneumoniae, and Mycoplasma pneumoniae
endemic infections considered. Most of the diseases listed in Table 32.2 are more likely to cause disseminated disease in an immunocompromised host, but they occasionally cause disseminated disease in the absence of an immunocompromising condition.

Given the positive result of the nasopharyngeal qualitative PCR sample for adenovirus, a serum quantitative adenovirus PCR was emergently run in the microbiology laboratory. It was also positive, with 1,967,036 viral copies per mL. The patient was treated with cidofovir, and hemodialysis was initiated for what was determined to be rhabdomyolysis. Over the next week, his viral load decreased and he was extubated. He was discharged from the hospital still on hemodialysis, but with hope for recovery of renal function.

### 32.1 Adenovirus

Adenovirus was first isolated from human adenoid tissue in 1950 [1]. The virus was initially detected in military recruits in the setting of acute respiratory illnesses but was later found to have a broad spectrum of disease manifestations, including gastroenteritis, hepatitis, keratoconjunctivitis, meningoccephalitis, cystitis, upper and lower respiratory tract infections, and myocarditis [2].

Adenoviruses are non-enveloped, lytic, double-stranded DNA viruses responsible for typically self-limited illness. Children, military recruits, and college students are the most commonly affected groups [3]. Adenovirus infections occur worldwide, year-round, and infect most individuals by age 10 years. The virus is spread via aerosol droplets, by fecal-oral spread, by contact with contaminated fomites, through cervical/perinatal transmission, and by solid organ transplantation (kidney and liver). Adenoviruses are non-enveloped, so they can survive on surfaces for a prolonged period, and they are resistant to lipid disinfectants.

There are at least 54 known serotypes of human adenovirus, and the subgroups share similar disease presentations. For example, subgroup F, serotypes 41 and 42, is associated with infantile gastroenteritis [2, 3], while others typically cause respiratory disease.

Disseminated adenovirus infections occur more commonly in immunocompromised patients, in particular stem cell transplant (SCT) patients, but they have significant mortality rates in both immunocompromised and immunocompetent populations. The mortality rate for disseminated adenovirus infections in SCT patients is up to 70% [3], while in immunocompetent children it is up to 60% [4]. Importantly, immunocompro-
mised hosts can shed adenovirus in stool for an extended period of time, after symptoms of clinical disease have resolved.

Diagnosis is most commonly made using qualitative and quantitative PCR [3]. The quantitative number can be used to assess response to treatment, but one must also consider asymptomatic viral shedding and take into account the entire clinical picture. Disseminated disease is definitively diagnosed by histopathology.

Some viral infections have been associated with myositis and rhabdomyolysis, including influenza, coxsackievirus, herpes simplex virus, and Epstein-Barr virus [5]. Case reports have described rhabdomyolysis with adenovirus infection [5, 6]. In the patient described in the present case, the elevated CK and the AKI were most likely attributable to rhabdomyolysis.

Typically, treatment for adenovirus consists of supportive care. In the setting of severe adenovirus pneumonia or disseminated disease, there is some literature supporting the use of cidofovir [2, 3, 7], as was used in the patient described.

Key Points/Pearls
- Elevated CK, AKI, and gross hematuria with a urinalysis demonstrating only 0–5 RBC should prompt consideration of rhabdomyolysis.
- Adenovirus has a broad range of clinical presentations, including acute upper respiratory illness, pneumonia, diarrhea, hepatitis, keratoconjunctivitis, and disseminated disease.
- Adenovirus can also cause hemorrhagic cystitis in immunocompetent and transplant patients (in the latter BK virus and CMV are in the differential diagnosis).
- Certain serotypes of adenovirus are associated with different clinical presentations.
- In the setting of severe disease, cidofovir should be considered for treatment.

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