



Intravascular Hemolysis as a Presenting Feature of Acute Cytomegalovirus Infection in an Immunocompetent Patient

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Abstract

Acute Cytomegalovirus (CMV) infection seldom presents with hemolytic anemia in an immunocompetent host. When hemolysis does occur, it is typically immune mediated and extravascular, but can be intravascular with the degree of anemia ranging from mild to severe. We report a case of a healthy 27-year-old woman who presented with jaundice and non-immune mediated intravascular hemolysis as an initial feature of acute CMV infection. Viral etiologies (including CMV) should be considered in the differential diagnosis of patients with Coombs negative intravascular hemolysis.

Keywords

Cytomegalovirus, Intravascular hemolysis, Gilbert's disease

Introduction

Hemolysis is the premature destruction or removal of Red Blood Cells (RBCs) from circulation. Extravascular hemolysis results in erythrocyte degradation in the reticuloendothelial system, while Intravascular Hemolysis (IVH) occurs when RBCs lyse in circulation secondary to shear stress, cell membrane abnormalities, or antibody mediated complement activation. Typical causes of IVH include paroxysmal nocturnal hemoglobinuria, erythrocyte enzyme deficiencies, blood transfusion with ABO incompatibility, microangiopathic hemolytic anemia, medications and infections. Bacteria, parasites, and viruses have all been found to cause IVH [1]. Mechanisms leading to hemolysis include direct invasion of erythrocytes by the organism (*Plasmodium falciparum*), release of hemolytic toxins that cause RBC phospholipid membrane degradation (*Clostridium perfringens*), or autoantibody development and immune destruction (*Mycoplasma pneumoniae*, Epstein Barr virus (EBV)) [2]. The degree of hemolysis ranges from mild to severe and is dependent on the immune status of the host.

Immunocompetent patients exposed to primary Cytomegalovirus (CMV) are typically asymptomatic or complain of a mild flu like syndrome. Less commonly, CMV infection may result in hematological complications including hemolysis, thrombocytopenia, disseminated

intravascular coagulation and pancytopenia [3,4]. CMV induced hemolysis is typically immune mediated and extravascular, occurring more often in immunocompromised hosts. However, studies have described hemolysis in immunocompetent individuals with primary CMV infection [5-8]. We report a case of acute CMV infection presenting with Coombs negative IVH in an immunocompetent host.

Case Presentation

A previously healthy 27-year-old Caucasian woman of Italian, Belgian, and German descent was referred to Mayo Clinic for further evaluation of acute jaundice which began three weeks earlier. She was mildly fatigued and noted a slight darkening of her urine. On exam, she was afebrile, with marked jaundice of skin and conjunctivae. Her spleen tip was barely palpable with deep in-

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spiration. There was no lymphadenopathy, hepatomegaly or stigmata of chronic liver disease. The patient had no prior medical history other than two uncomplicated pregnancies with vaginal delivery. She had no prior history of jaundice. She denied any viral prodrome, travel history, or infectious exposures prior to the onset of her symptoms. There was a family history of anemia in two sisters, but the etiology was unknown. She denied alcohol consumption or illicit drug use, and she was taking oral contraceptives but no other medications including nonprescription medications.

Laboratory evaluation revealed indirect hyperbilirubinemia (indirect 6.2 mg/dl (normal 0.1-1.0 mg/dl), direct 0.2 mg/dl (normal 0-0.3 mg/dl)), elevated reticulocyte count of > 160,000 μ L (normal 50,000-150,000 μ L), absolute reticulocytes 4.3% (normal 0.5-1.5%), LDH 660 U/L (normal 105-333 U/L) and undetectable haptoglobin, suggesting intravascular hemolysis. Twenty-four hour urine copper was normal. Her Complete Blood Count (CBC) was normal except for mild neutropenia (1.4×10^3 μ /L; normal $1.8-7.0 \times 10^3$ μ /L). Schistocytes were not present on peripheral smear. Her AST and ALT were normal and Hepatitis A, B, and C serologies were all negative. CMV serologies, both IgG and IgM were positive, as was her CMV DNA (7,000 copies), all consistent with acute CMV infection. Her EBV and Parvovirus B19 serologies were consistent with prior exposure, and HIV testing was negative. An abdominal ultrasound confirmed splenomegaly.

An extensive laboratory evaluation was undertaken to delineate the cause of the intravascular hemolysis including RBC enzymatic assays and hemoglobin electrophoresis, which were normal. Coombs testing including monospecific DAT and anti-complement were negative, as were cold agglutinins, Donath-Landsteiner, and ANA testing. The infectious disease team recommended expectant close observation without anti-viral therapy for CMV as she was immunocompetent and improving clinically. Nine days after diagnosis her total bilirubin had dropped to 4.7 mg/dl and her jaundice markedly improved. At one month follow up, her CMV DNA level was undetectable signaling resolution of active infection. Her neutropenia resolved. At six months the total bilirubin was 3.3 mg/dl, and her reticulocyte count to 2.4%. At last follow up, she remained completely asymptomatic, although her indirect bilirubin continued to be slightly elevated. This was evaluated by Hepatology and considered consistent with an underlying diagnosis of Gilbert's Disease. Genetic testing for confirmation was however not performed.

Discussion

Hemolytic anemia is a well-recognized complication

of primary CMV infection, most commonly affecting infants and immunocompromised patients. However, it can also occur in the immunocompetent patient, with hemolysis ranging from mild to severe [9]. A review of the literature by Rafailidis, et al. [4] has reported a total of 290 immunocompetent patients with serious manifestations of CMV infection, including gastrointestinal, central nervous system, hematological, and ocular. Of this group of patients, 25 experienced hematological manifestations such as hemolytic anemia, thrombosis, disseminated intravascular coagulation, pancytopenia, or splenic rupture [4].

CMV induced hemolysis is typically extravascular, with Coombs antibody, Anti-Nuclear Antibodies (ANA), cold agglutinins, cryoglobulins, and rheumatoid factor present [7]. However, CMV can also cause IVH and present with negative Coombs testing. The underlying mechanism of IVH is hypothesized to be direct effect of CMV viral replication on circulating erythrocytes [10], however, presence of IgG bound to RBCs in a titer too low to be detected by Coombs testing and identified only by immunoradiometric assay has also been described [11]. Non-immune mediated hemolysis is the most likely mechanism in the case we report given the negative autoimmune laboratory studies (monospecific Coombs, anti-complement, cold agglutinins, Donath-Landsteiner antibodies, and ANA) and the clinical improvement seen without steroid therapy.

Anemia secondary to CMV-induced hemolysis can range from mild to severe, often requiring transfusion. In published case reports of CMV induced hemolysis in immunocompetent hosts, all patients presented with moderate to severe anemia (hemoglobin values between 5.1-7.9 g/dL) [4,10,12,13]. Interestingly, our patient was not anemic (hemoglobin 13.7), despite presenting with jaundice, splenomegaly, indirect hyperbilirubinemia, and low haptoglobin. Close review of prior CBC's during her pregnancies confirmed that she was not polycythemic before acute CMV infection. Most likely, the simultaneous presence of Gilbert's Disease contributed to her hyperbilirubinemia and jaundice and the degree of CMV induced IVH was not severe.

Conclusions

IVH secondary to CMV infection usually occurs in immunocompromised hosts, is immune mediated and causes moderate to severe anemia. However, testing for CMV in immunocompetent patients that present with jaundice and laboratory features consistent with IVH and negative Coombs test should be considered. Future studies into the mechanism of non-immune mediated CMV induced IVH is warranted, and may help guide therapeutic strategies.

References

1. Berkowitz FE (1991) Hemolysis and infection: categories and mechanisms of their interrelationship. *Rev Infect Dis* 13: 1151-1162.
2. Crumpacker C (2000) Cytomegalovirus. In: Mandell and R Dolin, JEBGL, Principles and practice of infectious diseases. Philadelphia, Churchill Livingstone, 1586-1599.
3. Eddleston M, Peacock S, Juniper M, et al. (1997) Severe cytomegalovirus infection in immunocompetent patients. *Clin Infect Dis* 24: 52-56.
4. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, et al. (2008) Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. *Virology* 47: 47.
5. Salloum E, Lundberg WB (1994) Hemolytic anemia with positive direct antiglobulin test secondary to spontaneous cytomegalovirus infection in healthy adults. *Acta Haematol* 92: 39-41.
6. Gavazzi G, Leclercq P, Bouchard O, et al. (1999) Association between primary cytomegalovirus infection and severe hemolytic anemia in an immunocompetent adult. *Eur J Clin Microbiol Infect Dis* 18: 299-301.
7. van Spronsen DJ, Breed WP (1996) Cytomegalovirus-induced thrombocytopenia and haemolysis in an immunocompetent adult. *Br J Haematol* 92: 218-220.
8. Horwitz CA, Skradski K, Reece E, et al. (1984) Haemolytic anaemia in previously healthy adult patients with CMV infections: report of two cases and an evaluation of subclinical haemolysis in CMV mononucleosis. *Scand J Haematol* 33: 35-42.
9. Notter J, Plack A, Wirz S, et al. (2016) Coombs-Negative Severe Hemolytic Anemia and Possible Autoimmune Disease in an Adult Following Cytomegalovirus Infection. *Hematol Transfus Int J* 3: 1-6.
10. Taglietti F, Drapeau CM, Grilli E, et al. (2010) Hemolytic anemia due to acute cytomegalovirus infection in an immunocompetent adult: a case report and review of the literature. *J Med Case Rep* 4: 334.
11. Kaneko S, Sato M, Sasaki G, et al. (2013) Case of cytomegalovirus-associated direct anti-globulin test-negative autoimmune hemolytic anemia. *Pediatr Int* 55: 785-788.
12. Veldhuis W, Janssen M, Kortlandt W, et al. (2004) Coombs-negative severe haemolytic anaemia in an immunocompetent adult following cytomegalovirus infection. *Eur J Clin Microbiol Infect Dis* 23: 844-847.
13. Hwang N, Kim EH, Han SY, et al. (2015) Severe cytomegalovirus colitis with hemolytic anemia mimicking travelers' diarrhea. *Int J Infect Dis* 37: 104-106.