Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-019-05691-7

STANFORD MULTIDISCIPLINARY SEMINARS

Foregone Inclusion: Neonatal CMV Hepatitis and Cholestasis

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Case Presentation and Evolution

A two-month-old boy who had been born at 32-week gestation was initially evaluated by a community urgent care clinic with scleral icterus and mild respiratory distress. The patient's mother reported that she had noted repeated waking and crying cycles over the previous several weeks. He also had frequent non-projectile "spit-ups" associated with feedings. His neonatal intensive care unit (NICU) course had been remarkable for continuous positive airway pressure (CPAP) for 24 h after birth, total parenteral nutrition for approximately 20 days until he was transitioned to full enteral feeds, and phototherapy for 3 days for total bilirubin levels in the 7–8 mg/dL range. Serial head ultrasounds were notable for a tiny left-sided choroid plexus cyst. Of note, patient had failed his newborn hearing screen and was scheduled for repeat testing. He was discharged home from the NICU at 3 weeks of age. His standard newborn screening panel demonstrated elevated phenylalanine/tyrosine ratio (nonspecific for metabolic disease). Maternal prenatal laboratories were reassuring; furthermore, there was no maternal history of thyroid disorder and there was no indication for CMV testing during pregnancy.

By the time of his hospital admission, his mild respiratory distress had self-resolved and vitals were: T 36.7 °C, BP 80/68 mm Hg, HR 158 bpm, RR 32/min, O_2 saturation 98%. He was well appearing with a benign abdominal examination, but notable for an umbilical and bilateral inguinal hernias. Scleral icterus and jaundice were noted. The patient's mother described normal, pigmented stools. Labs revealed total bilirubin 8.8 mg/dL, direct bilirubin 7.1 mg/dL, alanine aminotransferase 448 U/L, aspartate aminotransferase 645 U/L, alkaline phosphatase 635 U/L, gamma-glutamyltranspeptidase 95 U/L, albumin 4.2 g/dL, international normalized ratio (INR) 1.2. He had a leukocytosis with white blood cell count 22.1/mm^3, 81.5% lymphocytes. Electrolytes and creatinine were normal. His thyroid studies were markedly abnormal: thyroid stimulating hormone (TSH) 20.92 µIU/mL, thyroxine (fT4) 1.5 ng/dL. For a one-month-old infant born at 32-week gestational age, expected TSH is 3.5 ± 3.4 mU/L [1]. Abdominal ultrasound was without biliary ductal dilation and notable for non-visualization of the gallbladder. Mild splenomegaly was noted, with the spleen measuring 7.6 cm.

Given the need for additional evaluation and risk of progression to liver failure, the patient was transferred to our tertiary care academic institution. On arrival, the patient

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Published online: 11 June 2019

was alert and his examination was consistent with what was described at the outside hospital. Repeat studies highlighted cholestasis and elevated aminotransferases, but normal liver synthetic function (albumin, INR). Repeat abdominal ultrasound with Doppler and elastography revealed mild hepatosplenomegaly, patent vasculature, and normal liver shear wave length (Fig. 1). The gallbladder was abnormally contracted despite fasting with no definite wall irregularity, no visible lumen, and normal length. The common bile duct (CBD) was visualized (Fig. 2).

Preliminary basic infectious evaluations were negative. On hospital day #2, repeat thyroid studies were: TSH 24.6 IU/mL, fT4 1.6 ng/dL. At this point, the differential diagnosis remained broad and included endocrinopathies, anatomic abnormalities of biliary tree and infectious, metabolic, and genetic causes (Table 1). Endocrinology was consulted for evaluation of his thyroid test abnormalities; differential diagnoses included congenital hypothyroidism, acquired primary hypothyroidism, and sick euthyroid syndrome, with higher likelihood of the latter. Levothyroxine therapy was initiated, given its low risk. Of note, his newborn screen was negative for congenital hypothyroidism.

On hospital day #4, he underwent percutaneous liver biopsy by pediatric interventional radiology. The gallbladder was not identified, and no cholangiogram was performed. Based on this, there was high suspicion for biliary atresia. Meanwhile, on the same day of his liver biopsy, his outside hospital serum CMV DNA PCR was 5233 IU/mL copies, raising the question of CMV hepatitis. His liver biopsy was notable for giant cell transformation of hepatocytes, mild cholestasis, focal bile ductular proliferation, focal bile duct loss, and a single viral inclusion body (Fig. 3). On hospital day #6, he underwent laparoscopic repair of his umbilical and inguinal hernias as well as a laparoscopic cholangiogram. Cholangiography revealed a hypotrophic, but present gallbladder with small lumen, but an intact extra- and intra-hepatic biliary tree without filling defects. There was good emptying of contrast into the duodenum, not consistent with biliary atresia. Since his liver biopsy CMV stain was positive (Fig. 4), he was started on valgancyclovir, following which his liver function test abnormalities substantially improved. He was discharged home and received a cumulative one-month course of valgancyclovir. Following this therapeutic course, his bilirubin is normalized and his AST and ALT down-trended significantly, remaining only

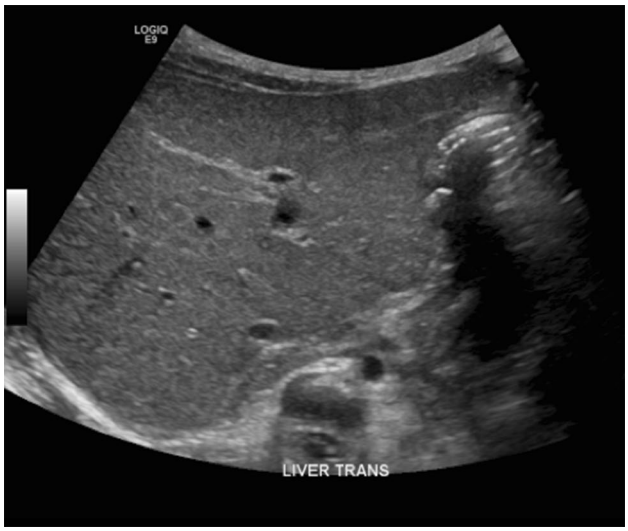

Fig. 1 Abdominal ultrasound showing uniform hepatic echotexture, a nonspecific appearance

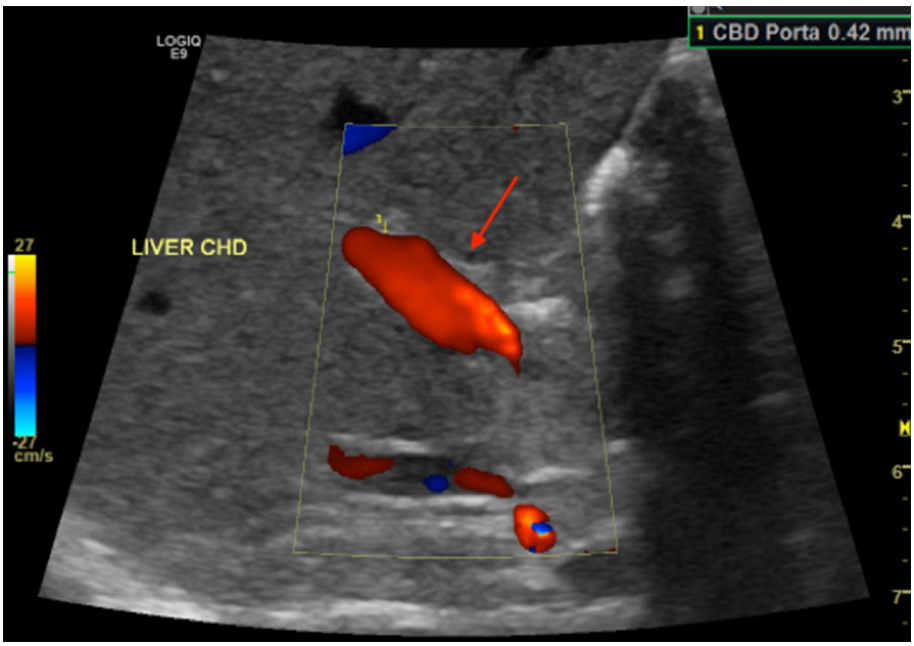

Fig. 2 Common bile duct (CBD) present making biliary atresia less likely

Table 1 Differential diagnosis of neonatal cholestasis

Infections	*Endocrinopathies*
HIV	Hypopituitarism
CMV	Hypothyroidism
EBV	*Metabolic abnormalities*
HSV	Galactosemia
Adenovirus	Tyrosinemia
Parvovirus	Disorders of bile acid synthesis
UTIs	*Toxin and drug exposures*
Syphilis	*Vascular abnormalities*
Toxoplasmosis	*Neoplastic processes*
Sepsis	*Genetic disorders*
Anatomic abnormalities of the biliary system	Alpha-1 antitrypsin deficiency
Biliary atresia	Cystic fibrosis
Choledochal cyst	Alagille syndrome
Cholelithiasis or biliary sludge	Progressive familial intrahepatic cholestasis/Byler disease
Neonatal sclerosing cholangitis	*Idiopathic*

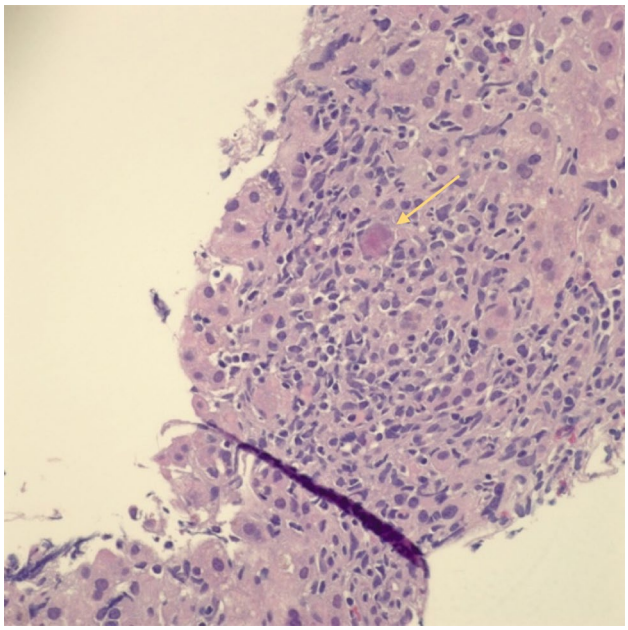

Fig. 3 CMV inclusion body (cytoplasmic)

borderline elevated. Since discharge, he has gained weight appropriately and has been developing normally.

Discussion

This case represents a unique presentation of cholestasis requiring extensive evaluation leading to the final diagnosis of CMV hepatitis. Acquired CMV in the post-natal period

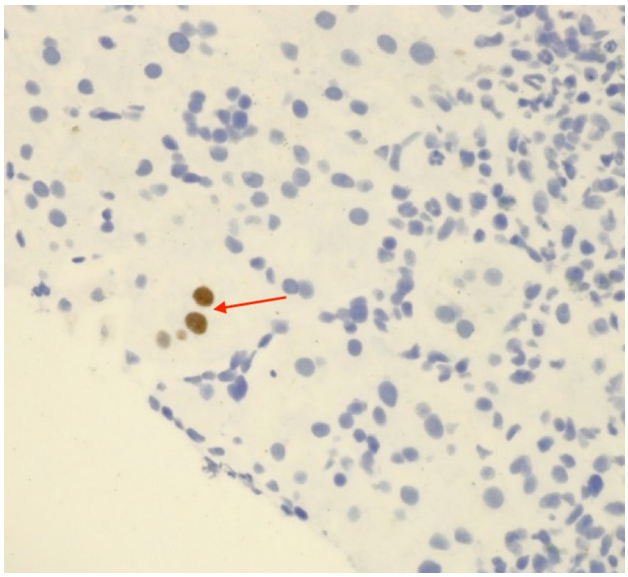

Fig. 4 CMV immunohistochemistry

in an immunocompetent infant typically does not result in symptomatic disease [2]. Nevertheless, some have hypothesized that premature infants, such as this patient who was born at 32-week gestation, are at increased risk of developing end-organ damage, such as hepatitis or chorioretinitis following perinatal infection [3]. In this infant with a failed hearing screening at birth, congenital acquisition of CMV is a possibility. Since testing for CMV was done beyond 3 weeks of age, the presentation could be due to either congenital or acquired CMV infection. This infant did not have any other stigmata for congenital CMV, such as microcephaly, periventricular calcifications, or chorioretinitis, and thus our suspicion is that he likely acquired CMV postnatally. Preterm infants appear to be at greatest risk of acquiring the virus from breast milk [2].

Hepatic manifestations of CMV most commonly involve subclinical elevations in AST/ALT in immunocompetent patients. Disease localized to a single organ and multi-organ/system fulminant presentations have been described in immunocompetent hosts [4]. Since a systematic review of CMV infection in adults revealed that severe life-threatening complications of CMV infection in immunocompetent patients may not be as rare as previously thought, treatment is recommended [5].

In pediatrics, CMV treatment recommendations and practice patterns are variable. Typically, treatment is pursued in cases of symptomatic congenital CMV infection and in patients with retinitis. Most term infants and asymptomatic preterm infants do not require antiviral treatment. Ganciclovir or valganciclovir is administered for severe symptomatic infections in premature infants. Guidelines also support treatment of immunocompromised pediatric patients [2]. Of note, a variety of CMV vaccines are under

development, but thus far have failed to reach target endpoints in clinical trials [6].

In adults, endoscopic retrograde cholangiopancreatography (ERCP) is the standard-of-care for the diagnosis and treatment of obstructive biliary disorders. ERCP has been successfully performed in newborns and infants as well. Initially reported in Europe, endoscopic diagnosis of biliary atresia by neonatal/infant ERCP has been reported, an approach that could obviate the need for surgical or interventional radiology percutaneous interventions in these young patients [7]. By doing so, this approach carries the advantage of avoiding unnecessary surgical interventions that can lead to development of adhesions and surgery-associated adverse events related to anesthesia, the surgery itself, and post-operative healing of the incision. Studies from Europe demonstrate high sensitivity and specificity rates for ERCP in the diagnosis of biliary atresia [8].

Few centers currently have high-volume therapeutic endoscopists who have the expertise to perform ERCP in infants [9]. Nonetheless, with further development and adaptation of duodenoscopes and therapeutic endoscopy tools optimized for neonatal/infant ERCP, endoscopic diagnosis of biliary atresia in high-volume tertiary care centers could become the standard-of-care. ERCP was not performed in this patient, largely due to unfamiliarity of the primary pediatrics, radiology, and surgical services with ERCP as a minimally invasive approach for evaluation and diagnosis of the etiology of pediatric cholestasis. Yet, it could have been considered prior to interventional radiology and surgical cholangiograms. With further development of endoscopes, devices and accessories for neonatal ERCP and enhanced endoscopist experience with this approach, pediatric services could be educated to include ERCP in the algorithm for evaluation of cholestasis for patients of all ages prior to interventional radiologic or surgical approaches when information from less-invasive imaging modalities (e.g. ultrasound, magnetic resonance cholangiopancreatography) is insufficient for diagnosis or when therapeutic biliary interventions are indicated.

In summary, this patient's disease initially manifested with cholestasis and transaminasemia, and after extensive evaluation was found to have CMV infection. His cholestasis and transaminasemia significantly improved after treatment with valgancyclovir. He remains on synthroid, and his TSH has normalized. His isolated TSH was thought to most likely be secondary to sick euthyroid syndrome.

Key Points

- The differential diagnosis for neonatal cholestasis is very broad
- Premature infants are at increased risk of developing end-organ damage, such as hepatitis or chorioretinitis following perinatal CMV infection.
- There is significant variability in treatment practices for both pediatric patients and adults with CMV. The indication and impact of antiviral therapy in congenital and acquired CMV infection are not well defined.
- ERCP rather than surgical or IR-based intervention may be preferable for diagnosis of pediatric/infant biliary disorders.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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