CASE REPORT

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A particular case of cytomegalovirus infection in infancy

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Abstract

The clinical spectrum of perinatal infection varies from asymptomatic infection or mild disease to severe systemic involvement. The aim of this paper is to present a severe intrauterine infection, which led to difficulties in diagnosis and unfavorable evolution. *Case presentation*: M.E., 6-weeks-old, born small for gestational age, was admitted in our Hospital for gastrointestinal signs: diarrhea, abdominal distension, observed three days earlier. Clinical and biological exams revealed hepatic disease related with hepatic cytolysis and cholestasis. Abdominal ultrasound showed large amounts of ascitic fluid, cirrhotic liver, enlarged portal vessel with hepatopetal flow, normal gallbladder and biliary tract. Computed tomography (CT) angiography revealed a wide hepatic artery, the presence of portal vein and absence of splenic vein. Serology detected IgM anti-cytomegalovirus antibodies. Postmortem histological exam confirmed the liver cirrhosis; cell free cytomegalovirus (CMV) antigens were found among alveoli with atelectasis. *Discussion*: The onset of hepatic disease was acute or chronic? Anamnesis offered reliable diagnostic criteria for intrauterine infection (flu during first trimester of pregnancy, intrauterine growth restriction, prolonged jaundice). The mother had been tested for all TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) infections other than CMV. The strict liver cell tropism raised questions regarding virulence, host immunology or the existence of other disease (vascular?) *Conclusions*: Liver cirrhosis at this age is very rare; the most frequent etiology is viral. The late diagnosis of this case led to the impossibility of etiological treatment.

Keywords: congenital cirrhosis, cytomegalovirus, intrauterine infection, absence of splenic vein.

Introduction

Cytomegalovirus (CMV) is the largest member of the herpesvirus family, with a double-stranded DNA genome, capable of encoding more than 200 potential protein products. CMV induces the most common congenital viral infection, occurring in 0.4–2.3% of all live births, and is probably a common cause of mental retardation and nonhereditary sensorineural deafness in children [1].

Infants may acquire CMV infection from the mother because of intrauterine infection, perinatal infection or postnatal infection [2]. Postnatal acquired CMV infection in immunocompetent patients is generally subclinical but may sometimes give rise to mild and self-limited mononucleosis-like syndrome [2].

The clinical spectrum of perinatal infections varies from asymptomatic infection or mild disease to severe systemic involvement. CMV hepatitis is relatively common in early ages, especially early infancy, and, during this period, is associated with cholestasis [3]. CMV infection in infancy is important since it might result in cirrhosis and even death [4]. Severe neonatal symptoms of congenital CMV occur more often in infants born to mothers with primary infection in pregnancy. Typical clinical findings can only be found in about 10–15% of newborns from mothers with primary CMV infection [5, 6]. These clinical findings include intrauterine growth restriction (IUGR), microcephaly, petechiae, hepatosplenomegaly, chorioretinitis, jaundice, cytopenia, causing a mortality rate of about 10–30% in infants with neonatal manifestations of congenital CMV [7].

Aim

The aim of this paper is to present a severe intrauterine infection, which led to diagnosis difficulties and an unfavorable evolution. Consent was obtained from the parents and the Ethical Committee of the Hospital.

Case presentation

M.E., 6-weeks-old, male, born small for gestational age (birth weight 2350 g <3 percentile, birth height 47 cm <3 percentile, head circumference p35–50), was admitted in "Louis Ţurcanu" Emergency Hospital for Children, Timişoara, Romania, in July 2014, for gastrointestinal signs: diarrhea, abdominal distension, observed three days earlier. The mother had been diagnosed with viral pneumonia and treated with symptomatic medication at 20 weeks of pregnancy. Clinical examination at admission revealed weight <3 percentile, pallor, jaundice, cutaneous trophic alterations, tachypnea, tachycardia (190–210 bpm), abdominal distension with a positive fluid wave test, accelerated intestinal transit – seven stools/day, enlarged liver and spleen, left inguinal hernia, somnolence and incomplete archaic reflexes. Biological exams showed hepatic disease with cytolysis [aspartate transaminase (AST) 82 U/L, alanine transaminase (ALT) 201 U/L] and cholestasis [direct bilirubin (DB) 102 μmol/L, total bilirubin (TB) 136 μmol/L, gamma-glutamyl transferase (GGT) 160 U/L, alkaline phosphatase (ALP) 1064 U/L]. Hypoproteinemia with hypoalbuminemia (proteins 37.7 g/L, albumins 20 g/L) and alteration of coagulation was observed [prothrombin time 34 s, prothrombin index 20.2%, activated partial

thromboplastin time (APTT) 42/30 s, international normalized ratio (INR) 3.24]. Complete blood count (CBC) showed a hemoglobin level of 10 g/dL and low platelet count (120 000/mm^3). Stool analysis results were normal. Protein was found in urine with red blood cells (RBCs) 3–4/high-power field (HPF), white blood cells (WBCs) 8–10/HPF. Peritoneal fluid obtained by paracentesis was culture negative transudate. Abdominal ultrasound revealed large amounts of ascites, nodular echo texture of the liver characteristic of cirrhosis, enlarged portal vessel with hepatopetal flow, normal gallbladder and biliary tract. Computed tomography (CT) angiography revealed a wide hepatic artery (Figure 1), the presence of portal vein and absence of splenic vein (Figure 2).

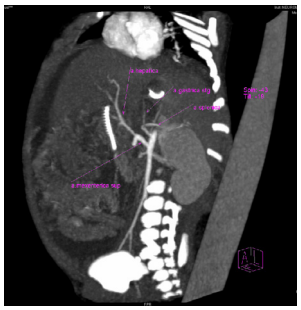

Figure 1 – ***CT angiography, arterial phase: increased diameter of the hepatic artery, micronodular structure of the liver, ascites.***

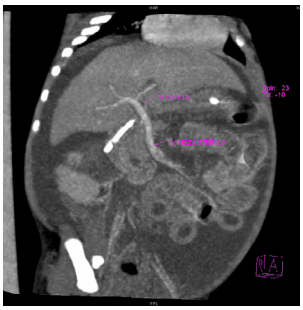

Figure 2 – ***CT angiography, portal phase: absence of the splenic vein, ascites, hepatomegaly.***

Markers were sero-negative for infection with hepatitis viruses A, B or C and positive for CMV (both IgM and IgG). The patient received albumin, fresh frozen plasma (FFP) and packed cell during the admission. Further treatment included fat-soluble vitamins. Ganciclovir therapy was not instituted, given the rapid, unfavorable evolution. Postmortem macroscopy revealed important liver enlargement, micronodularity, green discoloration due to marked cholestasis, all elements of primary biliary cirrhosis, end stage (Figure 3).

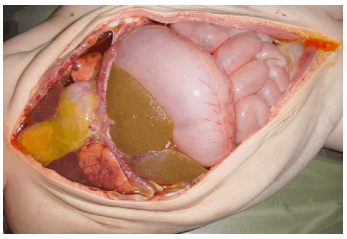

Figure 3 – ***Postmortem macroscopy: important liver enlargement, micronodularity, green discoloration due to marked cholestasis – elements of primary biliary cirrhosis, end stage.***

Histopathological (HP) analysis showed specific morphological changes: primary cirrhosis (necrosis, fibrosis and regenerative hyperplasia in the form of nodules), destruction of the liver structure by necrosis. Periportal and periseptal fibrosis with degeneration marked by ballooned or bile-stained hepatocytes, in piles of cholesterol stones was observed. 90% of the intrahepatic bile ducts were destroyed because of necrosis, with aspects of congenital ductular hypoplasia. Infected cells in or near the inflammatory foci showed HP manifestations of CMV infection; cytoplasmic and nuclear enlargement could be observed. The liver cells contained a large intra-nuclear eosinophilic inclusion, surrounded by a clear halo. The chromatin was pushed to the periphery toward the nuclear membrane (Figure 4, A–C).

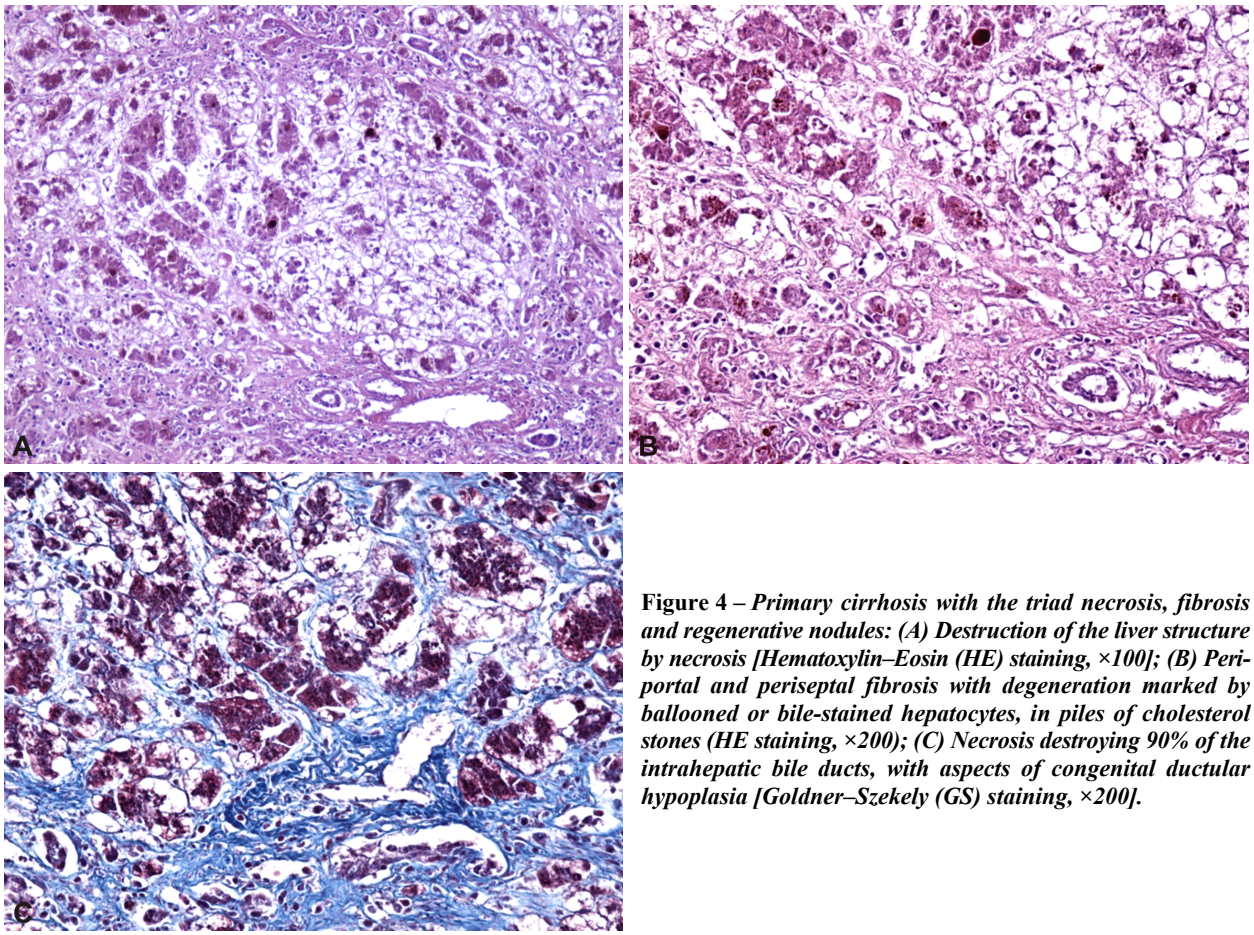

Figure 4 – ***Primary cirrhosis with the triad necrosis, fibrosis and regenerative nodules: (A) Destruction of the liver structure by necrosis [Hematoxylin–Eosin (HE) staining, ×100]; (B) Periportal and periseptal fibrosis with degeneration marked by ballooned or bile-stained hepatocytes, in piles of cholesterol stones (HE staining, ×200); (C) Necrosis destroying 90% of the intrahepatic bile ducts, with aspects of congenital ductular hypoplasia [Goldner–Szekely (GS) staining, ×200].***

Examination of the pulmonary parenchyma showed interstitial mononuclear infiltrate with foci of necrosis. The hyaline membranes were most clearly seen just beneath the pleura. Many of the alveoli contained edematous fibrous tissue, indicative of an organization of inflammatory exudate. Scattered throughout the pulmonary parenchyma were numerous large cells showing oval basophilic intranuclear inclusions with a surrounding clear halo. Cell free CMV antigens were found in the spleen (Figures 5–7).

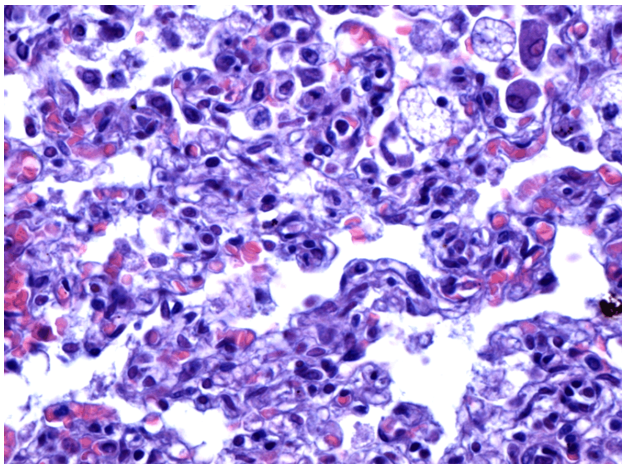

Figure 5 – ***Lung presenting interstitial mononuclear infiltrate with foci of necrosis develops, accompanied by the typical enlarged cells with inclusions of CMV, among alveoli with atelectasia (HE staining, ×400).***

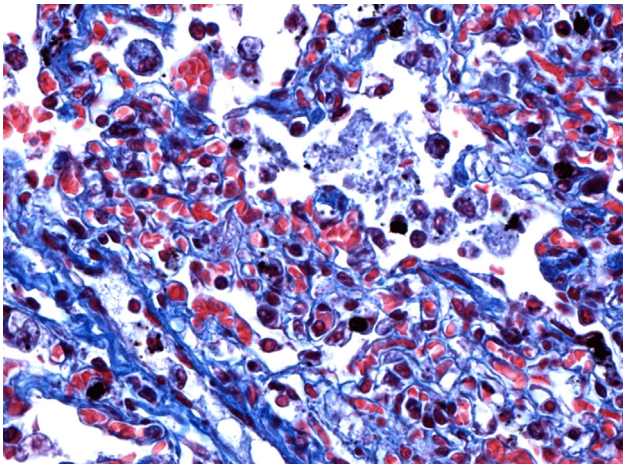

Figure 6 – ***Atelectatic alveoli, necrosis, fibrosis, interstitial mononuclear infiltrate with enlarged cells with inclusions of CMV (GS staining, ×400).***

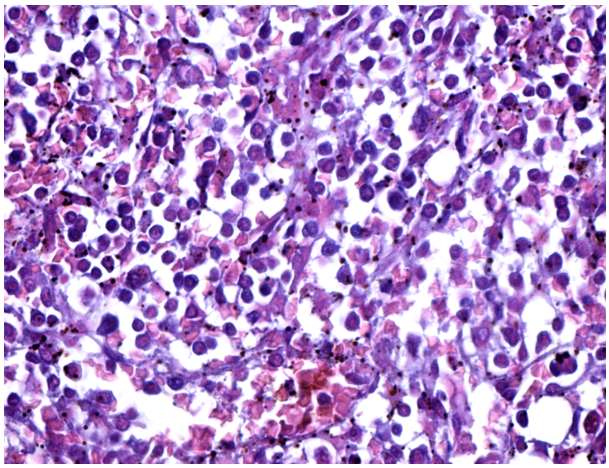

Figure 7 – ***Focal necrosis, islands of hemosiderin and enlarged splenic cells with inclusions of CMV, near a penicillar arteriole (HE staining, ×400).***

Discussion

According to studies, 10% of cases of cirrhosis in children are caused by viral infections [8, 9]. Although CMV infection during infancy is usually associated with mild manifestations, it may be fatal [4]. It has been reported that hepatic CMV infection could lead to portal hypertension and cirrhosis [10–12]. Hepatitis is a frequent complication of CMV infection and occurs either as part of multiple system involvement or isolated, such as neonatal hepatitis or cholestasis [13]. Only 5% of cases of congenital CMV infection present with severe cytomegalic inclusion disease [14, 15], while other 5% have a mild involvement; the remaining develop subclinical disease [16]. Petechiae, hepatosplenomegaly and jaundice are the most common presenting features seen in 60–80% of cases [17]. Microcephaly with or without cerebral calcifications, intrauterine growth restriction and prematurity are seen in about 30–50% of cases [18]. Inguinal hernia and chorioretinitis are less common [19]. The prognosis of severely infected infants is poor, with a mortality rate of 20–30% [20, 21]. Our case featured intrauterine growth restriction, hepatosplenomegaly, ascites and inguinal hernia. No microcephaly or cerebral calcifications on transfontanellar ultrasound were detected.

Current understanding of the pathogenesis of hepatic CMV infection is limited. CMV is known to replicate thoroughly in both hepatocytes and cholangiocytes [22]. CMV affects the fetus directly, inducing cellular injury (particularly in the brain), and has a role in placental dysfunction, leading to oxygen and substrate transport inefficiency [22, 23].

Thrombosis associated with acute CMV infection has been frequently reported in literature since 1984 [23–26]. Certain theories suggest that CMV triggers thrombosis by enhancing platelets and leukocytes adhesion to infected endothelial cells [27] and by activating factor X [28]. Other authors suggest that CMV increases the circulatory levels of factor VIII involved in the pathogenesis of thrombosis [29–31]. According to the most accepted theory, CMV induces production of anti-phospholipid antibodies. In our case, we consider that the absence of the splenic vein was the consequence of intrauterine thrombosis caused by CMV infection during the second trimester of pregnancy, when the mother had developed viral pneumonia. The mother had been tested for all TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) infections except CMV.

The diagnosis was established at six weeks after birth, when decompensated cirrhosis had already developed. The patient had not been subject to intrauterine monitoring. The late diagnosis and the presence of complications made starting antiviral therapy impossible in this case. HP exam confirmed the severity of the CMV infection, with systemic infiltration (liver, spleen, lungs).

Despite the existence of CMV in the lung, confirmed by postmortem HP exam, the patient showed no clinical symptoms of pulmonary infection.

Conclusions

Liver cirrhosis at this age is very rare; the most frequent etiology is viral. Only 5% of congenital CMV infection present with severe cytomegalic inclusion disease. The late diagnosis in this case led to the impossibility of etiological treatment. During pregnancy, screening methods for detection of infections have to be performed in all patients.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Whitley RJ, Cloud G, Gruber W, Storch GA, Demmler GJ, Jacobs RF, Dankner W, Spector SA, Starr S, Pass RF, Stagno S, Britt WJ, Alford C Jr, Soong S, Zhou XJ, Sherrill L, FitzGerald JM, Sommadossi JP. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis, 1997, 175(5):1080–1086.

[2] Horwitz CA, Henle W, Henle G, Snover D, Rudnick H, Balfour HH Jr, Mazur MH, Watson R, Schwartz B, Muller N. Clinical and laboratory evaluation of cytomegalovirus induced mononucleosis in previously healthy individuals. Report of 82 cases. Medicine (Baltimore), 1986, 65(2):124–134.

[3] Rosenthal P. Chapter 10: Neonatal hepatitis and congenital infections. In: Suchy FJ, Sokol RJ, Balistreri WF (eds). Liver disease in children. 2nd edition, Lippincott Williams and Wilkins, Philadelphia, 2001, 239–252.

[4] Ho M. Chapter 12: Acquired cytomegalovirus infection in immunocompetent patients. In: Ho M (ed). Cytomegalovirus: biology and infection. 2nd edition, Springer Science + Business Media, Plenum Publishing Corporation, New York, 1991, 229–247.

[5] Gaytant MA, Steegers EAP, Semmekrot BA, Merkus HM, Galama JMD. Congenital cytomegalovirus infection: review of the epidemiology and outcome. Obstet Gynecol Surv, 2002, 57(4):245–256.

[6] Alford CA, Stagno S, Pass RF, Britt WJ. Congenital and perinatal cytomegalovirus infections. Rev Infect Dis, 1990, 12(Suppl 7):S745–S753.

[7] Ornoy A, Diav-Citrin O. Fetal effect of primary and secondary cytomegalovirus infection in pregnancy. Reprod Toxicol, 2006, 21(4):399–409.

[8] Santos JL, Choquette M, Bezerra JA. Cholestatic liver disease in children. Curr Gastroenterol Rep, 2010, 12(1):30–39.

[9] Pinto RB, Schneider ACR, da Silveira TR. Cirrhosis in children and adolescents: an overview. World J Hepatol, 2015, 7(3): 392–405.

[10] Berenberg W, Nankervis G. Long-term follow-up of cytomegalic inclusion disease of infancy. Pediatrics, 1970, 46(3):403–410.

[11] Boeckh M. Complications, diagnosis, management, and prevention of CMV infections: current and future. Hematology Am Soc Hematol Educ Program, 2011, 2011:305–309.

[12] Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev, 2013, 26(1):86–102.

[13] White FV, Dehner LP. Viral diseases of the liver in children: diagnostic and differential diagnostic considerations. Pediatr Dev Pathol, 2004, 7(6):552–567.

[14] Varani S, Landini MP. Cytomegalovirus as a hepatotropic virus. Clin Lab, 2002, 48(1–2):39–44.

[15] Cheeran MCJ, Lokensgard JR, Schleiss MR. Neuropathogenesis of congenital cytomegalovirus infection: disease mechanisms and prospects for intervention. Clin Microbiol Rev, 2009, 22(1):99–126, Table of Contents.

[16] Enders G, Daiminger A, Bäder U, Exler S, Enders M. Intrauterine transmission and clinical outcome of 248 pregnancies with primary cytomegalovirus infection in relation to gestational age. J Clin Virol, 2011, 52(3):244–246.

[17] Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol, 2007, 17(4):253–276.

[18] Nijman J, van Loon AM, de Vries LS, Koopman-Esseboom C, Groenendaal F, Uiterwaal CS, Verboon-Maciolek MA. Urine viral load and correlation with disease severity in infants with congenital or postnatal cytomegalovirus infection. J Clin Virol, 2012, 54(2):121–124.

[19] Barkovich AJ, Girard N. Fetal brain infections. Childs Nerv Syst, 2003, 19(7–8):501–507.

[20] Leung AKC, Sauve RS, Davies HD. Congenital cytomegalovirus infection. J Natl Med Assoc, 2003, 95(3):213–218.

[21] Coll O, Benoist G, Ville Y, Weisman LE, Botet F, Anceschi MM, Greenough A, Gibbs RS, Carbonell-Estrany X; WAPM Perinatal Infections Working Group. Guidelines on CMV congenital infection. J Perinat Med, 2009, 37(5):433–445.

[22] Bristow BN, O'Keefe KA, Shafir SC, Sorvillo FJ. Congenital cytomegalovirus mortality in the United States, 1990–2006. PLoS Negl Trop Dis, 2011, 5(4):e1140.

[23] Atzmony L, Halutz O, Avidor B, Finn T, Zimmerman O, Steinvil A, Zeltser D, Giladi M, Justo D. Incidence of cytomegalovirus-associated thrombosis and its risk factors: a case-control study. Thromb Res, 2010, 126(6):e439–e443.

[24] Sherman S, Eytan O, Justo D. Thrombosis associated with acute cytomegalovirus infection: a narrative review. Arch Med Sci, 2014, 10(6):1186–1190.

[25] Schreiner M, Barck T, Foroutan B, Baumgarten U. A rare cause of portal vein thrombosis in a previously healthy young man with acute hepatitis. J Clin Virol, 2011, 51(3):152–154.

[26] Poon ML, Tang JW, Chee YL. Case report: cytomegalovirus-induced thrombosis in an immunocompetent patient. J Med Virol, 2012, 84(1):116–118.

[27] Span AH, van Dam-Mieras MC, Mullers W, Endert J, Muller AD, Bruggeman CA. The effect of virus infection on the adherence of leukocytes or platelets to endothelial cells. Eur J Clin Invest, 1991, 21(3):331–338.

[28] Van Dam-Mieras MC, Bruggeman CA, Muller AD, Debie WH, Zwaal RF. Induction of endothelial cell procoagulant activity by cytomegalovirus infection. Thromb Res, 1987, 47(1):69–75.

[29] Schambeck CM, Hinney K, Gleixner J, Keller F. Venous thromboembolism and associated high plasma factor VIII levels: linked to cytomegalovirus infection? Thromb Haemost, 2000, 83(3):510–511.

[30] Kalaitzis J, Basioukas P, Karzi E, Markakis C, Liarmakopoulos E, Hadjimarkou A, Rizos S. Small-bowel necrosis complicating a cytomegalovirus-induced superior mesenteric vein thrombosis in an immunocompetent patient: a case report. J Med Case Rep, 2012, 6:118.

[31] Van Moerkercke W, Pauwelyn K, Brugman E, Verhamme M. Cytomegalovirus-associated superior mesenteric vein thrombosis treated with systemic and *in-situ* thrombolysis. Eur J Gastroenterol Hepatol, 2009, 21(5):587–592.

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