Cytomegalovirus Gastritis In Immunocompetent Patient: Case Report And Review Of Literature

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Citation

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Abstract

We report a case of an adult woman admitted with nausea and vomiting secondary to cytomegalovirus gastritis and then summarize the state-of-the-art knowledge on diagnosis, pathogenesis, clinical picture, treatment and prevention of cytomegalovirus (CMV) infection in humans. The patient was a 76-year-old lady who presented to the hospital with worsening symptoms. An upper GI endoscopy with biopsy revealed histopathologic changes consistent with Cytomegalovirus (CMV) induced gastritis. During her hospitalization, the patient's symptoms and biochemical profile improved. Physicians need to remain alert to the varied presentations of CMV gastritis also in immunocompetent patient.

INTRODUCTION

Human cytomegalovirus (HCMV) is an ancient virus closely linked to its natural host, human beings. Over the generations, the pathogen and the host have adapted to each other and in most cases they live in symbiosis. Only in the last years, the scientists succeeded to discover the strategic weapons, which are used by the virus to evade the human immune system. In the future, because of the progress of the modern medicine, still more immunocompromised patients will live and thus CMV will have more potential victims.

Detailed understanding of the CMV biology and pathogenicity is therefore necessary to be successful in the fight against this pathogen. In this report the most up to date knowledge about the pathogenicity and immune defense against CMV are presented.

CASE REPORT

76-year-old lady was admitted to the hospital with complaints of worsening epigastric discomfort, nausea and reduced oral intake for one week. She described pain as intermittent, across epigastrium, well localized, and aggravated by food and sometimes awakening her from sleep as well. During several months before admission, the patient reported increasing fatigue, weight loss of almost 10 pounds and loss of appetite. She denied any change in bowel habits, no melena, and no hematochezia. The patient's past medical history was remarkable for hypertension, dyslipidemia, peripheral vascular disease, osteoporosis, hemorrhoids and stroke with residual aphasia in 2001. She denied smoking, drinking alcohol or any other substance of abuse.

The patient's medication history included an ACEi, hydrochlorothiazide, B- blocker, statins, and proton pump inhibitor and calcium tablets. She had a colonoscopy in 1999 that showed hemorrhoids. She denied allergies to any medication.

Physical examination on admission revealed a well developed, chronically ill appearing woman. She was afebrile, had a heart rate of 78 beats per minute, and a blood pressure of 150/80 mm Hg. She was breathing at a rate of 18 breaths per minute. She had a moderate epigastric discomfort, no rebound tenderness or guarding, and dark brown heme negative stools. Rest of physical examination was unremarkable.

At the time of admission, her serum alanine aminotransferase level was 60 U/L (normal, 0–45 U/L), aspartate aminotransferase was 44 U/L (normal, 0–45 U/L), and alkaline phosphatase was 125 U/L (normal, 0–45 U/L). Her complete blood counts, electrolytes and coagulation profile were within normal range.

The patient tested negative for serologic markers for HIV, hepatitis A, B, and C viruses. Additionally, her T-lymphocytes count came back as CD4 of 588 and CD8 of 1649. Thyroid tests were normal.

The patient's admission chest radiograph was non contributory. Computed tomography scan of abdomen and pelvis showed mild thickening of distal stomach and proximal duodenum, small amount of pelvic ascites and small scattered hepatic cysts. No intra or extrahepatic biliary dilatation was seen. Liver, gallbladder, adrenal glands, pancreas, spleen and kidneys were unremarkable. There was no evidence of paraaortic or pelvic retroperitoneal lymphadenopathy. There were no pelvic masses noted and urinary bladder was also unremarkable. Abdominal sonogram showed hepatocellular disease and/ or fatty infiltration of the liver with cholelithiasis. The intrahepatic and extrahepatic biliary systems were not dilated. Echocardiogram showed Ejection fraction of 69%, with normal wall motions, mild aortic regurgitation mild tricuspid insufficiency. The focus of the patient's evaluation then turned to the possibility of gastric malignancy. Upper GI endoscopy with biopsy of antral mucosa demonstrated erythematous, friable and eroded antral mucosa along with erosive esophagitis. Histopathologic findings were consistent with acute gastritis associated with Cytomegalovirus infection.

Figure 1

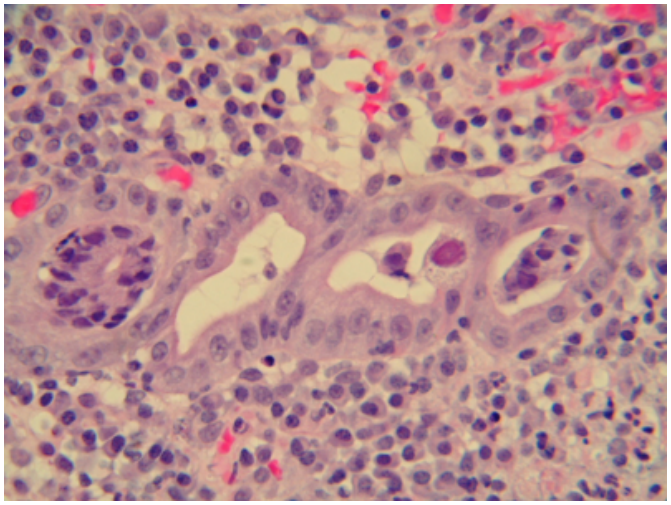
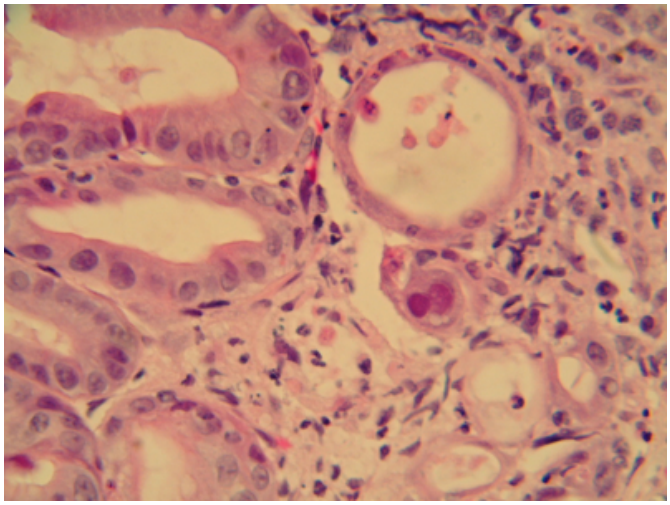


Figure 2



She was started on valganciclovir that she responded very well. Patient also underwent colonoscopy that revealed hyperplasic polyp with inflamed stroma and non specific chronic inflammation. No Cytomegalovirus identified.

Throughout her hospital stay, gradual clinical and biochemical improvements were noted. Physical therapy evaluation was obtained for deconditioning and eleven days after admission, she was discharged home.

DISCUSSION

CMV is a DNA virus of the betaherpesviridae family, for which a very slow growth is typical. With the diameter of 2G0nm it is the largest member of the herpesvirus family.

The mature virion consists of a 64-nm core containing the viral DNA enclosed by a 110-nm icosahedral capsid made up of 162 capsomeres. An envelope consisting of at least 25 to 30 virion-encoded proteins and glycoproteins enclose the complete particle. The linear double stranded DNA of CMV is approximately 240 kb in size. It has unique long and short sequences, both of which are bounded by homologous repetitive sequences. It encodes about 200 open reading frames. Until now only 33 structural proteins and some infected cell proteins are known [$_1$]. Following adsorption, possibly through 2-3 specific cell-surface receptors, the virus uncoats within the cytoplasm and a number of activation events in the cell are triggered. A rapid induction of the transcription of fos, jun and myc genes is observed within minutes of infection. Interestingly, also non-infectious viral particles and dense bodies (both of which contain many viral structural proteins, but no viral DNA) can trigger this activating cascade [$_2$].

Subsequent events on the host require viral and cellular gene expression. Following entry of the viral particle into the host cell, virion components, including the viral genome, are rapidly transported to the nucleus, where viral transcription and replication take place. The replication is detectable as early as 12 hours post infection and is quite slow, lasting some 24 hours. The replicative cycle has been divided into three independent time periods - immediate-early (IE), early (E), and late (L) - based on the appearance of different classes of CMV-specific proteins during each interval. The -IE period is routinely defined up to 2 to 4 hours postinfection. It is characterized by the restricted transcription of specific segments of the genome and the production of regulatory IE proteins, which are required for the further transcription of the CMV DNA and the transition into the E phase of CMV replication. The E period is defined as beginning after the IE period and persisting through the long eclipse phase of CMV replication. Much larger portions of CMV genome are transcribed continuously during this period. In addition, a distinct class of infected-cell proteins are synthesized, presumably many of the proteins necessary for viral DNA replication. The L period occurs from 36 to 48 hours after viral infection and coincides with the production of virion structural proteins and the release of infectious virus [3].

EPIDEMIOLOGY

The first CMV infection in humans was probably recorded in the year 1881 by Ribbert [4]. In 1920 Goodpasturi; and falbol [5] hypothesized that the swollen cells or “cytomegalia”, described in the course of the infection, were host cells injured by a virus. In 1960 Weller proposed the descriptive name cytomegabvirus. CMVs are ubiquitous agents that commonly infect animals as well as humans. They are strictly host-species-specific. The HCMV infects only humans. Various strains of HCMV, that can consequently infect the same patient, exist [6]. Because of the lability of HCMV to various environmental factors close or even intimate contact is believed to be required for horizontal spread.

Sources of virus include oropharyngeal secretions, urine, cervical and vaginal secretions, spermatic fluids, breast milk and blood. Vertical spread is transplacental. An important route of infection is iatrogenic -solid organ (SOT) and bone marrow transplantation (BMT) and blood transfusion [7, 8]. The incubation period in primo infection is 6-8 weeks; in reactivation it is 5-6 weeks. After infection, the virus persists in the host's organism for the whole life. The infection can be reactivated in immunocompromised host. Some 1-2% of newborns are infected with HCMV [9, 10], until puberty, 10-40% of children are infected, and 50-90% of adult population is seropositive for HCMV. There are three peak ages for acquisition of infection: infancy and early childhood, early adulthood and the childbearing years [8, 11].

DIAGNOSIS

Following studies help in making the diagnosis

Antigen detection: Specimens can be stained by specific immunofluorescent antibodies to detect viral antigens or viral DNA [13].

Culture techniques: The most commonly used technique is the shell viral assay of cultured cells, in which immediate early antigens are detected by use of monoclonal antibodies. This reduces the time to positivity to 24-72 hours, whereas other cultures take days to weeks [14].

Other diagnostic studies: Other studies, such as antibody tests, qualitative or quantitative polymerase chain reaction, or studies of blood or other body fluids, yield less diagnostic information for CMV esophagitis and may not indicate current active infection [13, 15].

Imaging Studies: Findings from imaging studies are nonspecific.

Procedures: The study of choice is EGD, which allows direct visualization and allows for biopsies that aid in diagnosis.

A definitive diagnosis is established in more than 70% of cases. Not uncommonly, large solitary shallow ulcers or multiple discrete lesions appear; however, ulceration is not necessary.

The biopsy specimen should be taken from the base of the ulcer. Studies have shown that at least 10 biopsy specimens should be obtained to yield a significant result. Specimens should be submitted for histologic examination, antigen detection, and viral culture studies [14, 16]

Histologic Findings: Histology of affected specimens may show acute and chronic inflammation, vasculitis, and/or mucosal ulceration. Deep biopsy specimens are preferred. Histologic staining with Papanicolaou or hematoxylin and eosin stains may reveal classic findings that include giant cells (typically 25-35 µm) with cytomegaly and large, ovoid, or pleomorphic nuclei with basophilic inclusions. These inclusions are known as owl's eyes because of the separation

from the nuclear membrane by a halo. Immunochemistry is more specific than standard staining techniques [19].

TREATMENT AND PREVENTION

In the management of CMV gastritis, currently available data is not sufficient for when to treat and for how long in immunocompetent patient. Currently, treatment options for CMV infection include the CMV DNA polymerase-inhibitors ganciclovir, foscarnet and cidofovir [17]. Although these agents potently inhibit CMV replication, they exhibit toxicity (nephrotoxicity, myelotoxicity, neurotoxicity, hepatotoxicity, teratogenity) and intravenous administration is required to obtain therapeutic drug levels, both of which limit their use for long-term treatment. Although an oral formulation of ganciclovir is also available, the bioavailability is low.

Several new antiviral agents are currently under clinical development, including lobucavir, adefovir-dipivoxil and antisense oligonucleotides [18]. Lobucavir is a nucleoside analogue with activity against a broad-spectrum of viruses. It has good bioavailability and is generally well tolerated. Cross-resistance to ganciclovir is uncommon and it does not cause myelosupression. Adefovir-dipivoxil is a prodrag of adefovir with 40% oral bioavailability and a long half-life. It is a nucleotide-monophosphate analogue, which inhibits the viral DNA polymerase. The mutations in the CMV DNA polymerase gene do not confer cross-resistance to the other respective drugs. Because of different mechanism of action, they are effective against ganciclovir-resistant strains [12, 18].

CONCLUSIONS

At present, the progress of medicine allows to successfully treat an increasing number of immunocompromised patients. However, development of CMV in immunocompetent patients is quite rare though challenging. Therefore, prevention and therapy of CMV infection will deserve special attention. Despite of increasing knowledge about the pathogenesis of HCMV infection, we are still not able to fight successfully against the immunological events those are triggered by CMV infection. Broader use of sensitive CMV detection methods will certainly bring about more detailed understanding to the pathogenesis of the early stages of infection. Nowadays, with the use of less sensitive methods, a lot of infected patients are not properly diagnosed and treated. The development of new antiviral drugs seems very promising, because some of them are able to prevent the immunopathologic events, triggered by the virus, and thus able to prevent later health injury.

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