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Cytomegalovirus Related Gastrointestinal Tract Manifestation of Surgical Significance: Three Cases Presentation and Review

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This article presents three surgical cases with cytomegalovirus (CMV) infection of gastrointestinal tract in recent years (1994-1995) at Samitivej Hospital. The first patient had perforation of CMV infected duodenum with defect in cellular mediated immune response. The second patient was a six-week post renal transplanted recipient who developed CMV colitis and renal allograft infection. The third patient, with normal immune response, had massive gastrointestinal hemorrhage from CMV jejunitis. Surgical resection had to be done to control the bleeding. Only the third patient had satisfactory response to antiviral therapy.

With rising incidence of immune suppressed patients, complicated CMV infection would be more often encountered, especially in this particular group of patients. Preventive measures have been invariably used to reduce rate of CMV infection among organs transplanted patients. High index of suspecion should be the mainstay of early detection and management in the immunosuppressed patients, especially those who harbour HIV. However, patients with normal immune response but have atypical clinical presentation of CMV infection should be cautiously search for.

Cytomegalovirus (CMV) belongs to the herpes virus family, and alikes other members of herpes virus family has the characteristic of causing latent infection "Once infected, always infected".[1] Infection caused by CMV can be primary or reactive ones. While primary infection is the infection of the person who has no

previous known infection of the virus, reactive infection represents the activation of the latent virus or infection of the person who is known to have sero-positive for the virus. Most of the CMV caused infection is asymptomatic and subclinical. Clinically significant CMV infection usually occurred in newborns, patients with deliberating conditions, or immuno-suppressed patients whether they may be organs transplanted or have acquired immune deficiency syndromes (AIDS). It is uncommon for person with normal immunity to have complicated CMV infection especially if the gastrointestinal tract is involved. On the other hand some authors found it was not unusual for normal immuned person to have gastrointestinal tract CMV infection if clinicians are more alert and histopathology diagnosis is examined more carefully and extensively.[3]

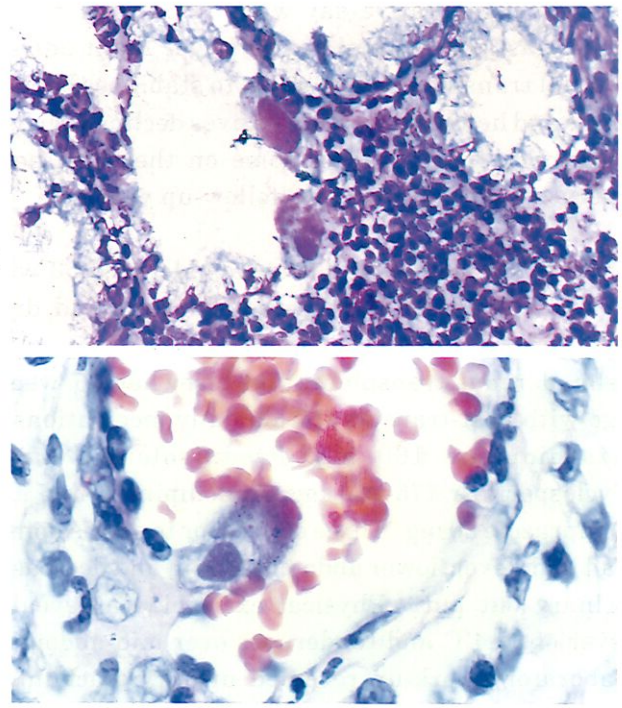

Fig. 1 Photomicrographs of CMV lesions with large inclusion bodies in infected and enlarged endothelial cell (Giemsa stain).
A. Case 1 from duodenal ulceration.
B. Case 3 from proximal jejunal ulcer.

CASE REPORTS

Case 1: A Buddist monk aged 58. He had been known to have chronic obstructive pulmonary disease with cor pulmonale for more than one year. One month ago he underwent transurethral prostatic resection (TUR-P) in a provincial hospital and received an undetermined amount of transfusion. After being discharged home, he had very poor appetite and started having melena and hematochezia 4 days prior to admission. On admission he was found dehydrated, dyspnic, hypotensive and drowsy. His abdomen was quite distended and guarded. Roentgenography of the abdomen revealed free intraperitoneal air. He was also anemic (Hct 26%) and hypoalbuminemic (albumin 2.9 gm/dl). Respiratory support by respirator was started and intravenous fluid resuscitation was done. The patient was operated upon and a perforation of 2.0 cm in diameter at anterior wall of the 2nd part of duodenum was found. The peritoneal cavity contained large amount of turbid gastric juice. The perforation was closed with double- layer sutures and omental graft. Pathology of the ulcer was chronic ulcer with cytomegalovirus inclusions in the epithelial cells of Brunner's glands (Figure 1A). His CD4 and CD8 count were 150 and 60 cells/cu.mm respectively which were suggestive of cell-mediated immune response defect. Gancyclovir was started on the

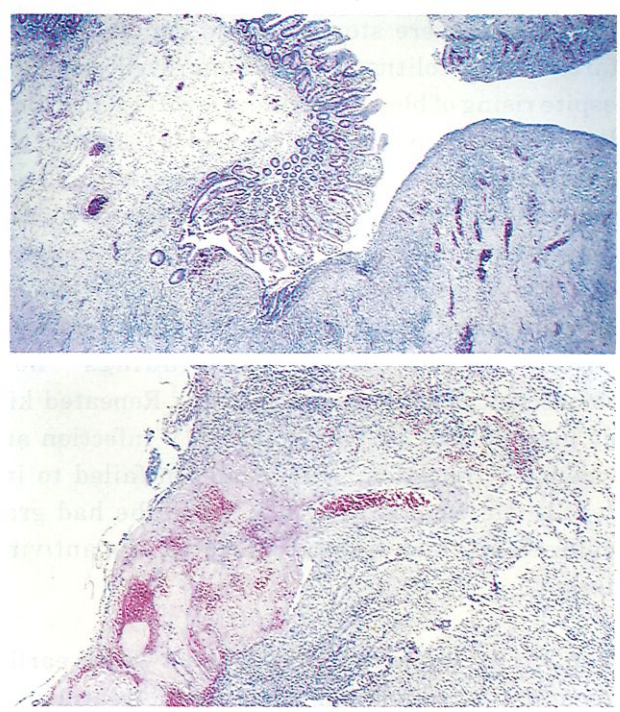

Fig. 2 Photomicrograph of the jejunal ulcer in Case 3.
A. Granulation tissue at the floor of the ulcer with many acute and chronic inflammatory cellular infiltrates. (H&E)
B. showing a bleeding arteriole with thrombus at the base of the ulceration. (H & E)

second postoperative day when he started having upper gastro-intestinal hemorrhage. Eight units of red cell transfusion were given to stabilize the vital signs and hematocrit. His relatives declined further treatment and took him home on the third post-operative day. His further follow-up was lost.

Case 2: A Hongkong Chinese male aged 53 with underlying Henoch-Schoenlein purpura and drug induced renal failure. He received a living non-related renal transplantation elsewhere 6 weeks ago with post-transplantation daily medications of Azathioprine 100 mg, Prednisolone 30 mg, Cyclosporin A 175-200 mg, Amlodipine 5 mg, and Omiprazole 20 mg. Three days prior to admission he had high fever, lower abdominal pain and decreased urinary out put. Physical examination revealed fever of 39.4°C and tenderness over mid-abdomen. Laboratory work-up revealed urinary tract infection. Appropriate antibiotics were given along with reduction of immuno-suppressant. On the fifth day, he had hematochezia which colonoscopic findings was extensive colitis of right side colon up to splenic flexor. Biopsy specimen showed severe focal necrosis with cytomegalo-virus inclusions. Azathioprine and prednisolone were stopped while gancyclovir was started. The colitic symptom improved gradually despite rising of blood creatinine level (1.6 to 3.1 mg/dl). Needle biopsy of the transplant kidney was performed on the 8th day of admission and the tissue showed cytomegalovirus inclusions without other remarkable finding. He had further improvement of his symptom except for gradual rising of creatinine level to 5.5 mg/dl. Repeated colonoscopy showed improvement of findings both colonoscopically and histologically. Repeated kidney biopsy revealed persistent CMV infection and evidence of rejection. His condition failed to improved. He went to Belgium, where he had graft nephrectomy and finally recovered an antiviral therapy.

Case 3: A Thai male aged 45 who 3 weeks earlier was admitted to another hospital for treatment of fever, vomiting, and melena. He was dehydrated and pale. His abdomen was distended but non-tender. Initial laboratory work-up revealed marked leukocytosis, hyperglycemia, acidosis, and ketosis. Computerized tomography of his abdomen showed gallbladder stones without other remarkable pathology. He was treated as diabetic ketoacidosis and influenza type-A infection (the latter with Amantadine). He had gradual improvement only to have hematochezia on the 16th day of admission. His vital signs and hematocrit had to be maintained with massive blood transfusion (18 units of whole blood and 8 units of fresh frozen plasma). Gastroscopy found no upper gastro intestinal lesion. Sigmoidoscopy and colonoscopy could not be possibly done due to the continuous bleeding. He was transferred to Samitivej Hospital and celiac and superior mesenteric angiography was done upon arrival which revealed bleeding from the second branch of the superior mesenteric artery with some degrees of hyperemia of the adjacent branches. Exploratory laparotomy was performed and a thick-walled solitary narrow segment of proximal jejunum of 45 cm was disclosed. This jejunal segment was resected and on examination its mucosa appeared hyperemic, edematous with diffuse large and small ulcerations. There were several small hemorrhagic spots and one of the ulcer was covered with fresh blood clot. Microscopic examination revealed jejunal ulcerations with polymorphonuclear and chronic inflammatory cells infiltrations (Figures 2). There were several cytomegaloviral inclusion bodies in the cellular infiltrate of the ulcers and mucosa of the jejunum (Figure 1B). Ganciclovir was started and the patient had an uneventful recovery. Upon follow-up at 4 weeks post-operation, he was in the stage of good health.

DISCUSSION

Cytomegalovirus (CMV) infection is common, with most of infection being asymptomatic or subclinical. There is a wide spectrum of CMV infection manifestations with CMV mononucleosis, pneumonitis, and hepatitis most commonly encountered. The organism is the member of herpes virus family which includes herpes simplex, varicella zoster virus, and Ebstein-Barr virus as the most commonly found pathogens. The significant characteristics of the organisms which make the infection important are:

1. Latency primary infection with each of these agents results in lifelong dormant infec-

tion capable of being reactivated by any factor that causes defect in host immune system.

2. Cell-association site of latency of CMV, though not clearly known, probably include the circulating mononuclear and polymorphonuclear leukocytes. There is no free CMV found in the circulation, rather, its DNA usually found integrated with leukocyte or lymphocyte chromosome.[4] Spreading of the virus occurs cell to cell with direct contact between the cells thus rendering neutralizing antibody ineffective and cell-mediated immunity predominant in controlling the infection.

3. Oncogenicity, all herpes group viruses must be considered potentially oncogenic.

Epidemiology

Studies of seroprevalence of CMV antibody in groups of population reveal that the infection is inapparent and wide spread. Depending on the socioeconomy of the population, the prevalence of the antibody in adults ranges from 40-100 per cent.[6] It is lower in Europe and North America, whereas higher in developing countries such as Africa and Southern Asia. There is trend for adults in high seroprevalence area to aquire CMV antibody as their age increase.[1] In Thailand, W. Kantakamalakul et al[7] found the incidence of CMV titer positivity in newborns suspected of TORCH infection was 1.7-2.5 per cent while P. Chotiwithayatharakorn found the incidence to be 10.2 per cent.[8] The incidence of adult Thai seropositivity for CMV antibody varies from 91.53 to 97.3 per cent, though there is no significant difference in age or sex as the determining factors.[9-11]

Mode of transmission of CMV infection is similar to AIDS virus. It could either be vertical transmission, perinatal contact, sexual transmission, transfusion or transplantation related infection.

Pathogenesis and Pathology of CMV Infection in the Gastrointestinal Tract

Pathognomonic appearance of CMV in microscopic examination is "owl's eye" intracellular inclusion bodiy. In infected tissue, CMV inclusion bodies are usually present in the mucosal epithelial cells, vascular endothelial cells or connective tissue stromal cells. Some authors believe CMV inclusion found in the mucosal epithelial cells does not relate to the clinical significance. CMV can affect blood vessles of variable caliber ranging from medium size artery or vein to capillaries or venules. The common vascular pathologic findings are perivascular hemorrhage, thrombosis and necrosis of the vascular wall. The gastrointestinal tract ulceration, necrosis or perforation usually strictly associated with the bowel segment of severe vascular changes. Sole presentation of CMV inclusion in mucosal epithelial cell without evidence of vascular involvement usually does not associate with mucosal ulceration or necrosis.[2,13-15]

CMV infection of the gastrointestinal tract could be found from oral mucosa to anus. The most involved portion of alimentary tract in the immuno-suppressed patient is the segment of the colon from ileo-caecal valve to splenic flexor, whereas in non-AIDS patients is the upper gastrointestinal tract. Pathologic lesion from CMV infection of gastrointestinal tract may be as minimal as superficial erosion to deep penetrating ulcer. There may be variety of lesions of CMV infection in the gastrointestinal tract; solitary mucosal lesion which mostly located in ascending colon, hemorrhagic inflammation which usually involves colon, inflammatory pseudotumour which may cause obstruction in the ileo-caecal area, neoplastic-like lesion found in antral or colon region mimicking tumour clinically and radiologically, CMV appendicitis, toxic megacolon, pseudomembrane formation, and pneumatosis intestinalis condition.[2,13-15]

Diagnosis

The diagnosis of CMV infection requires laboratory confirmation and cannot be made on clinical grounds alone. The laboratory diagnosis of CMV infection depends on either demonstration of the virus, viral components, or rising CMV serologic titer. Since seropositive adults are common in most developing society and the rise in titer of CMV antibody may not occur until 4 weeks after primary infection, the diagnosis of the infection by serology requires the comparison of serology titer before and after the

clinical manifestation of infection. If the information is not available the test for IgM titer against CMV will be helpful, but not totally reliable. Since the IgM titer may not be positive during the active infection or could be persistantly rised long after the clinical infection had subsided. Some asymptomatic homosexual male had been found to have IgM for CMV elevated.

The technique of identification of virus antigen from the circulating leukocyte (shell vial assay) had recently been devised. This permits rapid and early diagnosis of active CMV infection, especially in the early and intermediate stage of the infection. This technique is particularly important in transplant patients. It is also helpful as a marker of disease activity guiding the mode of treatment.

CMV inclusion body found in tissue histology section is a strong evidence of the infection. These may be found in the vascular endothelium, mucosal epithelium, or stromal cells of connective tissue. Atypical CMV inclusion may be found, especially when one has to distinguish from other herpes virus. In this situation, immunohisto-chemical methods prove helpful.

CMV Infection in Immune Competent Patients

In healthy adult, CMV infection is mostly asymptomatic and subclinical. The most common presentations, if ever symptomatic, is mononucleosis, pneumonitis, and hepatitis.[2] Though CMV infection in healthy adult can be presented as Guillain-Barre' syndrome, meningooencephalitis, myocarditis, thrombocytopenia or hemolytic anemia.[1] It had been evidenced that the virus itself exerts a direct immune suppressive action, through the interaction with host lymphocyte.[2]

CMV infection of the gastrointestinal tract in the immune competent patient is probably a real, albiet rare phenomenon. The presentation ranges from diarrhea, malaise, emaciation to acute colitis. There are evidences that CMV is a secondary pathogen superimposed on chronic, pre-existing diseases in gastrointestinal tract, ulcerative colitis or Crohn's disease for instance. The virus can also exacerbate the pre-existing inflammatory bowel diseases. Thus alters the couse, esppecially increases the morbidity, of the already presented bowel diseases.

CMV as Pathogen in Organs Transplantation Patients

It is known that most transplant patient will develop CMV infection clinically. The estimation is around 60-96 per cent and 20 per cent will become significantly ill.[1,5] For renal transplantation only the infection rate is about 59-100 per cent. There was more CMV infection among patients with liver and cardiac transplantation. Usually CMV infection in organ transplanted patients starts 1-6 months after initiation of immuno-suppressant with the peak occurrence at 6-8 weeks after transplantation.[1,5] Several factors risk the patients of CMV infection. The two most important are;

1. Tissue compatibility-the biologic familial relationship and HLA compatibility associated with lesser degree of CMV infection.

2. The CMV serology of both the donor and the recipient before transplantation. Primary CMV infection occurred in 83 per cent of seronegative recipients who received kidney from seropositive donors[12] whereas very few of those who received kidney from seronegative donor will develop CMV infection.

Prevention

Since a number of patients acquired CMV infection from blood transfusion. It was known that the risk was proportional to the number of units transfused, estimated as 2.4-12 per cent. The risk increased along with the increased unit of transfusion usually after massive bleeding from invasive surgery or trauma. Since it is known that seropositive donors had latent viral DNA integrated to nucleated leukocytes or lymphocytes, it is evident that risk of infection is decreased by using cryopreserved blood, leukocyte-poor blood, or blood from seronegative donors.[1] Another approach to reduce incidence of transfusion related CMV infection is to excluded seropositive donors. Since most transfusion related CMV infection is asymptomatic, its cost-benefit concern makes this approach impractical.

Since it is well proved that the incidence of post-transplantation CMV infection is higher in patients received kidney from sero-positive donors, some transplantation centers do not transplant sero-positive kidney into seronegative recipient. There is no published report to indicate the benefit of such practice. Since the incidence of sero-positivity in Thai adults is 91.53 to 97.3 per cent,[9-11] the exclusion of this group of patients will further diminish the already-insufficient renal donors pool in Thailand. Careful tissue matching of the transplant patient correlates well with the decreased incidence of transplantation related CMV infection.[4]

There are several CMV vaccines on clinical trials, one of which proved lowering the incidence of clinical disease but not of infection, and the disease tended to be less severe in vaccinated patients than in control subjects.[16] Trials of human IgG administered after transplantation in attempt to prevent transplantation related CMV infection did not prove consistently beneficial.[17,18] This could be explained by the fact that CMV organism is cell attached and usually will not be affected by circulating antibody. High-dose acyclovir administered prophylactically has been reported to reduce CMV infection and disease in bone marrow and renal transplant recipients.[19] through it has not proven to be effective enough to be generally accepted.

Treatment

Ganciclovir (dihydroxypropoxymethyl guanine, DHPG) is a guanosine derivative which is considerable active against CMV than its congener, acyclovir. Ganciclovir is selective inhibitor of CMV DNA intracellularly. Gastrointestinal tract CMV disease responds well to ganciclovir, regardless of the cause of the underlying immunosuppression.[20] Improvement or, at least, stabilization was observed in 75 to 83 percent in various groups of immunosuppressed patients treated with ganciclovir. Usually after recommended dose of 7.5 to 10 mg/kg/day in two or three divided doses, the clinical infection will be improved within 1 to 4 weeks. However, in large number of patients with persisted immunosuppression clinical and virological relapse will take place within 2 to 5 weeks of cessation of the antiviral therapy. Maintenance therapy (5 mg/kg 5 days a week) indefinitely is recommended for patients with uncorrectable cause of immunosuppression. High incidence of drug side effect prohibits long term therapy in most patients.

Forscarnet (trisodium phosphonoformat) is a pyrophosphate derivative that inhibits herpes virus DNA polymerases. It is effective against ganciclovir-resist CMV infection. Foscanet may be less well tolerated than ganciclovir because of its nephrotoxicity, electrolyte disturbance, affecting seizure and causing nausea.

Surgical intervention is usually necessary for certain CMV related gastrointestinal tract manifestation; bowel perforation, obstructive lesions, neoplastic-like lesion, and massive hemorrhage. Though there is no published data on the proper surgical management, there is report on angiographic interventional hemostasis of the CMV related massive colitic hemorrhage.[21]

This paper presented three patients with various states of immunity; normal immunity in Case No. 3, transplanted related immunosuppressant usage in Case No. 2 and immunosuppressed secondary to CMV infection or unknown cause in Case No. 1.

Case No. 1 was critical ill and had a very short hospital stay although CMV infection was recognized in the 1st day postoperation and ganciclovir was administered shortly after adminission, there was no significant improvement achieved. There is no identifiable nature or mechanism to his cell-mediated immune response defect. His immuno-suppressed condition may solely caused by the CMV infection.

Case No. 2 received a non-related living donor kidney transplantation, with pre-transplantation CMV serologic status of both donor and recipient unknown. Even in the early recognition of the CMV infection with prompt antiviral therapy, there was only partial improvement of CMV colitis but the CMV infected graft kidney deteriorated. This could be either

from drug resistance occurred initially, drug resistance developed during treatment, or over administration of immuno-suppressants. Foscarnet is the alternative of ganciclovir in situation of drug resistance. This patient finally had his graft kidney removed in Belgium to control the infection. In organs transplant patients, preventive measures should include CMV serology screening, careful tissue matching, screening blood products, prophylactic administration of CMV immunoglobulin and acyclovir. In renal transplant patient infected with CMV, ganciclovir offered clinical improvement up to 93 per cent in one study group, but significant recurrent rate of 30 percent may be anticipated.

Case No. 3 was probably an immunocompetent patient with no underlying disease except mild diabetes. After surgical control of bleeding CMV jejunitis and immediate ganciclovir therapy the patient had an uneventful recovery. There was no identifiable cause of his CMV infection, but it was more likely to be a reactive infection in his age group.

CONCLUSION

In the recent 15 months we encountered three cases of CMV infection of the gastrointestinal tract. Two cases were immunocompromised patients. We believe that with increasing AIDS patients and organ transplanted patients, the number of patients with complicated CMV infection should be more frequently encountered. With no specific clinical presentation for the infection, only high index of susspecion will bring about early diagnosis and appropriate treatment. Various serology tests at present have many drawback. Tissue diagnosis of the involved organ should be sesiously considered whenever possible for definite evidence of the infection. Rapid virus identification method permits rapid and early diagnosis of CMV infection, particularly benefitial for transplant patients. Atypical clinical presentation in gastrointestinal tract pathology should arouse the suspeion of CMV infection. Ganciclovir is still considered effective as long as prompt treatment is given.

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