ORIGINAL ARTICLE

Gastrointestinal Cytomegalovirus Infection in Non-Human Immunodeficiency Virus Infected Patients

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Summary

This is a retrospective study of fourteen patients who had proven *Cytomegalovirus* (CMV) infection of the gastrointestinal tract with no *Human Immunodeficiency virus* infection. The median age was 60.5 (Range 28 to 81) years. Eight patients were below (Group 1) and six above sixty five years old (Group 2). Areas of gastro-intestinal involvementw were: oesophagus (2), stomach (1), colon (10) and multiple sites (1). Seven patients from Group 1 had received immunosuppressive therapy at the time of presentation and one had diabetes mellitus. We found a high prevalence of co-morbidities such as chronic renal failure and diabetes mellitus in Group 2. At median follow up of 13.9 months, there was a mortality rate of 50%. Only four patients were treated with *ganciclovir*. Our study concludes that the gastrointestinal CMV diseases in young patients were associated with immunosuppression whereas the older patients had chronic renal failure or diabetes.

Key Words: Gastrointestinal tract, Cytomegalovirus, Human immunodeficiency virus, Co-morbidities, Immunosuppression

Introduction

Cytomegalovirus (CMV) associated disease of the gastrointestinal tract (GIT) is a well-recognised opportunistic infection in patients with Acquired Immunodeficiency Syndrome (AIDS)[1-3] and immunosuppression. Though gastrointestinal CMV disease has also been described in immunocompetent patients[4-7], descriptions and clinical course of this disorder in this group of individuals are still lacking[8-9]. In this study, we attempted to review the clinical course of gastrointestinal CMV disease in individuals who did not have *human immunodeficiency* virus (HIV) infection.

Materials and Methods

Patients diagnosed to have CMV infection on mucosal biopsies of the gastrointestinal tract were identified from our histopathology database between January 1992 and December 1999. The diagnosis was made by histological evidence of CMV infection either with haematoxylin and eosin stained for CMV inclusions bodies[10-12], or

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immunoperoxidase stained for CMV antigen[13-14]. Patients with positive *human immunodeficiency* virus serology test and those who had clinical evidence of AIDS but without HIV test were excluded[8]. The patients' case notes were reviewed for demographic data, clinical presentations, associated conditions, endoscopic findings, treatment, duration of follow up and outcome.

Results

Fourteen patients with CMV disease of GIT fulfilled our study criteria. The median age was 60.5 years (Range 28 to 81 years). There were seven male patients. We arbitrarily divided patients into two groups according to age. Eight patients were below (Group 1) and six above sixty-five years old (Group 2) (Tables I and II). Seven patients or 87.5% of patients from Group 1 had received immunosuppressive therapy at the time of presentation, the remaining patient had diabetes mellitus. Steroid was the common immunosuppressive agent. The indications for immunosuppression were bone marrow transplant (2 patients), renal transplant (1 patient), Crohn's disease (1 patient) and chemotherapy for malignancies (3 patients). Bone marrow transplant had been performed for acute myeloid leukaemia and chronic granulocytic leukaemia. Three patients with cancer had gastric lymphoma, lung cancer and laryngeal carcinoma. Only one patient in group 2 had received immunosuppression for possible ulcerative colitis. However, we found a high prevalence of co-morbidities such as chronic renal failure and diabetes mellitus. This group was not on steroid treatment. Other co-morbidities were old pulmonary tuberculosis with chronic obstructive airway disease and palatal cancer that had been treated surgically. An 81-year old patient had CMV infection with seemingly no obvious predisposing causes.

Sites of involvement and endoscopic findings are shown in Tables I and II. The most common affected site was the colon (11 cases, 78.5%). Endoscopic findings were non-specific, varying from erythematous mucosa to fresh ulceration.

Table I: Group 1 - Gastrointestinal CMV infections in non-HIV patients below 65 years

NO.	AGE	GENDER	ASSOCIATED CONDITION	SYMPTOMS	ENDOSCOPIC FINDINGS AND SITES	ANTI-VIRAL	OUTCOME
1	45	F	Renal transplant and ulcerative colitis	Rectal bleeding	Rectosigmoid colitis	None	Remission at 8 years
2	36	M	Acute myeloid leukaemia with bone marrow transplant	Rectal bleeding	Colitis	None	Death
3	60	M	Laryngeal carcinoma	Diarrhoea	Rectosigmoid colitis	None	Death
4	28	F	Chronic granulocytic leukaemia with bone marrow transplant	Diarrhoea	Colitis	None	Death
5	61	M	Diabetes 8mellitus	Diarrhoea	Multiple colonic ulcers	None	Remission at 4 years
6	53	M	Gastric lymphoma	Melaena	Gastric ulcer	None	Remission at 11 months
7	29	F	Crohn's disease	Bloody Diarrhoea	Colitis	Yes	Remission at 3 months
8	57	M	Lung Cancer	Dysphagia	Oesophagitis	None	Death

Table II: Group 2- Gastrointestinal CMV infections in non HIV patients above 65 years

NO.	AGE	GENDER	ASSOCIATED CONDITION	SYMPTOMS	ENDOSCOPIC FINDINGS AND SITES	ANTI-VIRAL	OUTCOME
1	71	F	ESRD, DM, IHD	Diarrhoea	Multiple colonic ulcers	Yes	Resolution of 4 months
2	80	F	-	Diarrhoea and rectal bleeding	Rectal ulcer	None	Resolution of 2 months
3	81	M	COLD and old PTB	Dysphagia	Severe oesophagitis	None	Resolution of 13 months
4	74	F	ESRD and IHD	Abdominal pain and diarrhoea	Pancolitis	Yes	Death
5	81	F	Carcinoma of palate	Abdominal pain and rectal bleeding	Rectosigmoid colitis	None	Death
6	78	F	Diabetes mellitus	Bloody diarrhoea and melaena	Duodenal ulcer and colitis	Yes	Death

ESRD = End stage renal disease
COLD = Chronic obstructive lung disease
IHD = Ischaemic heart disease
PTB = Pulmonary tuberculosis
DM = Diabetes Mellitus

At median follow up of 13.9 months, mortality rate was 50% in each age group. Duration of follow up varied from three weeks (as patient died soon after diagnosis) to 8 years for patients who survived. The number of patients who received antivirals was small as only four patients were treated with ganciclovir. Four patients in Group 1 died from their underlying malignancies before being treated with anti-viral therapy. The only patient with Crohn's disease had a positive outcome with ganciclovir. Despite treatment with ganciclovir, two patients from group 2 died from myocardial infarction and stroke. Five patients had spontaneous resolution (three from group 1) and were alive and well at the time of follow up. All patients with malignancy died apart from the patient with gastric lymphoma who survived without antiviral treatment. The two elderly patients without diabetes or renal failure had spontaneous resolution.

Discussion

CMV disease can involve many organs, including the retina, liver, lung and GIT[1-2, 20]. This viral disease is increasingly common because of the rising number of patients with immunodeficiency such as AIDS and organ transplant[21]. Involvement of GIT by gastrointestinal CMV disease is also not infrequently encountered in seemingly immunocompetent patients without HIV infection [6-9].

CMV is a common human viral infection, 40% to 100% of the adult population are carriers of the virus [15-16]. Once infection is acquired, it can remain latent and there is risk of reactivation when the immune system is impaired[16-19]. The sero-positivity of CMV infection among HIV patients is higher than the general population. The prevalence in the subgroup of homosexual men can be greater than 90%[22]. Despite the high rate of sero-positivity in AIDS patients, manifestations of CMV disease usually occurs after the CD4 cell count falls below 100/mm^3. CD4 cell count fall of below 50/mm^3 is the strongest factor for reactivation of CMV disease[23-25]. This fact indicates CMV disease occurs when there is profound immunodeficiency related to decreased in CD4 T-lymphocyte population. This study revealed a heterogeneous group of patients with GIT involvement of CMV infection.

Most had associated disease that resulted in immune dysfunction. The younger group had underlying malignancy or immunosuppressive therapy. The elderly group commonly had co-morbidities. Diabetes mellitus has been recognised to increase patient susceptibility to infection[27]. Ageing itself also has long been associated with relative immunodificiency. Both innate and adaptive immunity are shown to be affected by aging[28-33].

GIT CMV involvement in AIDS is extremely common, mainly affecting the oesophagus and colon although autopsy report reveals evidence of subclinical CMV disease throughout the body[1, 2, 34, 35]. One third of AIDS patients suffer from GIT CMV disease[3]. GIT CMV commonly results in inflammation, haemorrhage, erosions and ulceration of the gut mucosa[10,19]. Mucosal lesion in the GIT is probably due to vascular endothelial-cell infection leading to focal thrombosis, occlusion, ischaemia and ulceration[36]. Occasionally it causes full thickness damage and perforation of the GIT[37]. Similar pathology occurs in all the patients regardless of the underlying risk factors or disease as observed in our study.

Clinical manifestation of GIT CMV disease depends on the site of involvement [21]. For example, lower GIT CMV disease often presents as intermittent diarrhoea with crampy abdominal pain and fever[3]. We found the colon to be the commonest site, as reported by other reports. Endoscopic findings were non-specific, varying from erythematous mucosal to ulcers. The radiographic appearances of gut CMV disease also are non-specific[37-38]. Endoscopy with biopsy is the investigation of choice although the endoscopic appearance of the colonic mucosa mimics the findings as seen in other inflammatory conditions [39-42]. The best approach is to confirm the presence of CMV with histologic examination and rule out other pathogens using standard techniques[21,41]. The findings of cytomegalic cells on mucosal specimens stained with haematoxylin and eosin have been considered the "gold standard" in the diagnosis of GIT CMV disease[10-12]. The number of specimens and the diligence of the pathologist may determine the success of finding these cells[3, 42, 43]. Immunochemical techniques such as immunoperoxidase staining and in-situ DNA hybridisation are used to enhance the sensitivity of histology daignosis[11,13-14,44-47]. Application of polymerase chain reaction (PCR) or culture of mucosal biopsy specimens for CMV have not been found to be useful[21].

Serology and virus from blood, urine, stool, and throat culture for CMV are not helpful in diagnosing the presence of disease. Although CMV disease is often associated with viraemia, a positive serology or virus culture from blood is not specific or sensitive in diagnosing acute CMV disease of GIT[11, 48-51]. Advances have been made in searching for markers of CMV disease in HIV-infected hosts. Plasma PCR and leukocyte DNA have been shown to be able to identify AIDS patients with both established CMV retinitis and non-retinal CMV disease[52-54]. Prospective studies in AIDS patients prove that CMV PCR is a sensitive "surrogate marker" for active CMV disease[55]. The absolute quantity of CMV DNA also predicts disease development and high CMV loads is predictive of end-organ damage[54]. Application of these molecular investigations has not been studied in a non-HIV setting.

CMV disease of HIV infected patients is progressive with a high mortality rate in the absence of treatment[56]. One study reported a mortality of CMV colitis in immunocompetent patients was 26.7% but all deaths occurred in patients older than 65 years[9]. The mortality rate in our current study was 50% in both groups but this was mostly due to advanced malignancies or co-morbidities of our patients. We are unable to comment on the results of the treatment due to the small number of patients. One previous review suggested that treatment improved the outcome of CMV disease of GIT[21], especially in AIDS group. Introduction of ganciclovir has improved survival in AIDS patients with CMV disease[56-57]. Improvement of symptoms in about 80% and quality of life has been reported in clinical

studies[58-61]. Ganciclovir will eliminate CMV from the blood in a mean of 8 to 10 days in about 50 % of patients[62]. Foscarnet is the second effective agent in treating CMV disease. Foscarnet is the alternative agent to treat failed ganciclovir therapy patients in GIT CMV disease or relapsed post ganciclovir therapy[63-64]. Combination of these two drugs resulted in better clinical response and survival than with single agent alone[65]. Resistance to both agents has also been reported[66-67].

The role of maintenance therapy against CMV remains uncertain. CMV colitis patients were kept in remission during maintenance therapy in one study[3] but one trial concluded maintenance treatment did not prolong the time to progression or survival of GIT CMV disease patients[68]. Two other reports suggested that the relapse rate of GIT CMV disease may be less compared to retinal disease and induction treatment without maintenance may produce long term remission[68-69]. Immunologic respond to highly active anti-retroviral therapy (HAART) may enable stopping of maintenance therapy among CMV retinitis patients with AIDS[70-71]. Similarly, transplant recipients or patients receiving immosuppressive therapy may have achieved remission spontaneously when therapy is reduced or stopped8, [72-73].

In conclusion, our study showed that CMV infection of the GIT is not uncommon in patients without HIV infection or immunosuppression. These patients are elderly with multiple co-morbidities. The role of antiviral treatment is unclear as most of these patients succumbed to their underlying medical condition.

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