DOI: 10.7860/NJLM/2018/38349:2323

Original Article

Pathology Section

Clinicopathological Profile of CMV Colitis at a Tertiary Care Center

RENUKA MALIPATEL, MALLIKARJUN PATIL

ABSTRACT

Introduction: Cytomegalovirus (CMV) infection is commonly seen in immunosuppressed individuals like Acquired Immunodeficiency Syndrome (AIDS), receiving chemotherapy/other immunosuppressive drugs, Inflammatory Bowel Disease (IBD). Rarely seen in immunocompetent individuals; CMV can involve any part of gastrointestinal tract, but commonly involves the colon.

Aim: To study the clinicopathological features of CMV colitis at St John's Medical College.

Materials and Methods: A retrospective study involving all CMV colitis patients admitted in the hospital from January 2010 to December 2017 was conducted. All histopathologically proven cases of CMV colitis were included. From the hospital records clinical, demographic and serological data were retrieved. Histopathology slides were reviewed.

Results: Eighteen patients with CMV colitis were studied. Mean age was 57 years (range 32-86). The underlying predisposing factors like AIDS, post organ transplant, IBD were seen in 10 patients. Eight patients were immunocompetent. CMV DNA data was available in eight patients. The common clinical presentation was chronic diarrhoea, bleed PR, acute exacerbation of ulcerative colitis. All patients histopathology revealed characteristic inclusion bodies except in two, which were confirmed by IHC.

Conclusion: CMV colitis is commonly seen in immunosuppressed individual but can also be seen in immunocompetent. High index of suspicion in immunosuppressed individual with typical clinical symptoms is important for early diagnosis and treatment.

Keywords: Gastrointestinal tract, Immunosuppression, Viral inclusions

INTRODUCTION

CMV is a double stranded DNA virus, which belongs to herpesviridae family [1]. It is an opportunistic pathogen, which remains dormant in healthy individuals for lifelong with the risk of intermittent reactivation [2,3]. Sero-prevalence of CMV infection in healthy adults is approximately 50-95%, which increases with the age [4,5]. CMV infection commonly involves retina, lung, kidney, central nervous system and colon [6]. The primary infection in immunocompetent individuals is asymptomatic or may manifest with mild, self limiting mononucleosis like syndrome. CMV infection is commonly seen in immunosuppressed individuals like those receiving immunosuppressive treatment, chemotherapy, AIDS patients and patients with IBD [7]. It is rarely seen in immunocompetent individuals during critical illness and extreme age groups.

The CMV infection of GI tract commonly involves colon which presents with diarrhoea, abdominal pain, fever and bleeding per rectum. In patients with IBD it may present as acute exacerbation of the disease. As effective antiviral therapy is available to treat, high degree of suspicion is important for early diagnosis and treatment. Studies done so far have emphasized on CMV colitis seen mostly in immunodeficient states like HIV/AIDS, acute exacerbation of ulcerative colitis, transplant recipients. Except a very few included immunocompetent individuals. This study was done to describe clinicopathological characteristics of CMV colitis in both immunodeficient and immunocompetent hosts, at the tertiary care center.

MATERIALS AND METHODS

This retrospective study was done from January 2010 to December 2017. All hospitalised patients with biopsy proven cases of CMV colitis were retrieved from Pathology archives. The hospital medical records were reviewed for demographic details, laboratory findings, history of medications such as immunosuppressants, immunocompromised status, history of IBD and other comorbidities.

All patients had undergone colonoscopic examination and biopsy.

CMV colitis was diagnosed histologically based on both characteristic cytomegalic cells with intranuclear (owl eye like inclusion) and cytoplasmic punctiform viral inclusion bodies

on routine Haematoxylin and Eosin (H&E) staining. In the H&E stained slide viral inclusions in a given biopsy were counted and scored from 1 to 3. Very occasional viral inclusions (1-3) found in the entire biopsy were given a score of 1, >3 inclusions were given a score of 2. When the inclusions were seen frequent and in clusters, score 3 was given [8]. In suspicious cases immunohistochemistry (IHC) using mouse monoclonal antibodies to CMV (Bio SB, clone: 8B1.2, 1G.2 & D4.2) was performed on formalin fixed paraffin embedded sections.

From the hospital records data on serological tests like CMV IgM, IgG antibodies and CMV DNA by PCR were collected wherever available.

RESULTS

There were 18 patients with CMV colitis in the eight years study period. 13 were males with a male to female ratio of 2.6:1. Mean age was 57 years (range 32-86). The underlying predisposing factors were seen in 10 patients as shown in [Table/Fig-1]. The rest of eight patients were immunocompetent without any risk factors. The clinical features at presentation were as shown in [Table/Fig-2]. Fever was present in seven patients in addition to other clinical features. The colonoscopic features were as shown in [Table/Fig-3,4]. CMV DNA by PCR was available only in eight patients, with the mean viral load of 4134 copies/mL.

Risk factor	Number of cases	%
HIV infection	5	50
Post renal transplant	2	20
Ulcerative colitis	2	20
Chronic kidney disease	1	10
Total	10	100

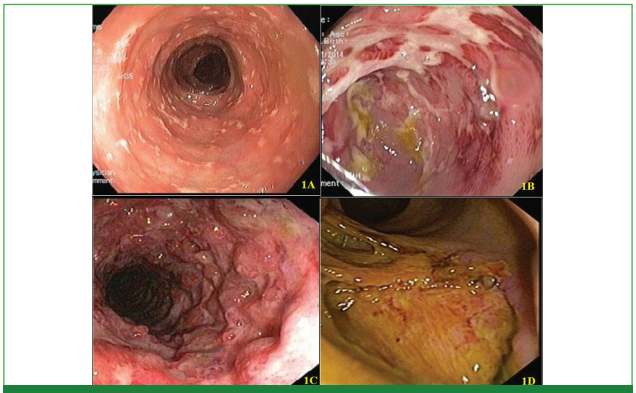
[Table/Fig-1]: Risk factors.

Clinical presenation	Number of cases	%
Diarrhoea	8	44.5
Bleed PR	3	16.6
Acute exacerbation of ulcerative colitis	3	16.6
Abdominal pain	3	16.6
Anaemia	1	5.6
Total	18	100

[Table/Fig-2]: Clinical presentation.

Colonoscopic appearances	Number of cases	%
Multiple discrete ulcers	13	72.2
Mucosal haemorrhages	02	11.1
Deep ischaemic ulcers	02	11.1
Superficial ulcers	01	5.6
Total	18	100

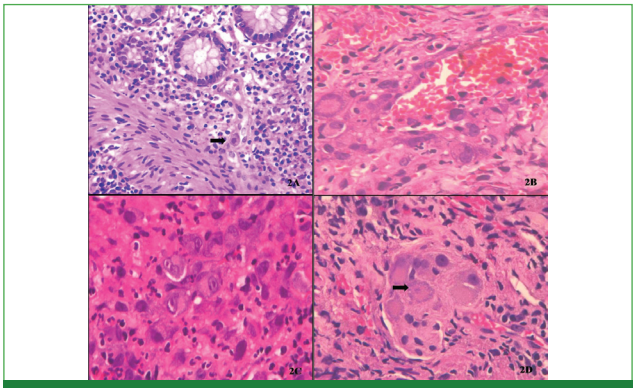
[Table/Fig-3]: Colonoscopic appearances.



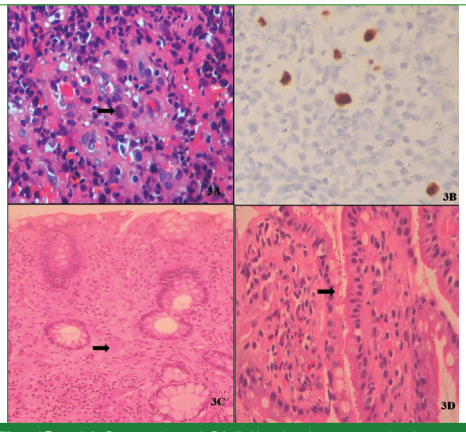
[Table/Fig-4]: Colonoscopy images showing: a) superficial ulcers; b) mucosal haemorrhages and ulcers; c) multiple deep ulcers; d) deep, necrotic ulcer. (left to right)

The histopathology findings [Table/Fig-5,6] included mucosal inflammation, superficial and deep ulcers and dense submucosal inflammation. Mild inflammation of the lamina propria with very occasional viral inclusions was observed in one case (score 1). Superficial ulceration with dense submucosal inflammation and scattered viral inclusions (score 2) were seen in six cases. The inflammatory infiltrate consisted predominantly of lymphocytes and plasma cells with admixed population of neutrophils and eosinophils. Vasculitis with fibrinoid necrosis of the wall, necrosis of the epithelium and exuberant granulation tissue formation is noted in 11 cases. In these latter cases more numbers of scattered and clustered viral inclusions (score 3) were seen. Nuclear and cytoplasmic inclusions were seen most commonly in the stromal cells/ mesenchymal cells and granulation tissue. In some cases clusters of cytomegalic cells seen mimicking ganglion cells. Conversely ganglion cells with viral inclusions were also noted. IHC for CMV highlighted viral inclusions in two suspicious cases.

One of the HIV patient had associated CMV oesophagitis and the other showed synchronous cryptosporidium infection of the colon.



[Table/Fig-5]: a) Dilated capillary with CMV inclusions in the endothelial cell (arrow) (H&E, 40X); b) CMV inclusions in the endothelial cells of a capillary with vasculitis (H&E,100X); c) Stromal cells with characteristic CMV inclusions seen in clusters (H&E, 100X); d) ganglion cells with cytoplasmic basophilic fine dot like inclusions (arrow) (H&E, 100X). (left to right)



[Table/Fig-6]: a,b) Occasional CMV inclusion seen in the granulation tissue, highlighted by CMV IHC (40X); c) colon biopsy from a case of ulcerative colitis with CMV inclusions (arrow) (H&E,40X); d) Cryptosporidium seen as basophilic round organisms along the epithelial surface (H&E, 100X). (left to right)

DISCUSSION

Human CMV is a member of family of Herpes viruses. After primary infection which is usually asymptomatic, remains dormant with risk of intermittent reactivation. Any site of gastrointestinal tract from oral cavity to the rectum can be involved by CMV infection but colon is frequently involved due to unknown reasons. CMV disease commonly seen in persons with immunodeficiency such as AIDS, recipients of organ transplants, haematological malignancies, chemotherapy and other immunosuppressive drug therapy. CMV commonly infects columnar epithelial cells, endothelial cells, monocytes and fibroblasts [9].

In the present series of 18 cases, the common clinical presentation was diarrhoea which was seen in eight patients (44.4%) similar to other studies by Einbinder Y et al., and Carter D et al., [10,11].

The other clinical features were abdominal pain, bleeding per rectum in three patients each and exacerbation of ulcerative colitis in two patients. Gastrointestinal bleeding is one of the commonest presenting symptoms reported in many studies due to deep ulceration in the colon, which may cause erosion of the surrounding blood vessels, sometimes severe enough to cause shock and requiring blood transfusions [12-14]. In the present study gastrointestinal bleeding was seen in three patients.

Among IBD patient's prevalence of CMV infection is 5-36% [15,16]. In ulcerative colitis CMV reactivation can predispose to acute exacerbation. The elevated cytokine levels such as tumour necrosis factor and interferon in patients of UC promotes the reactivation of latent CMV infection. The outcome of UC in patients with CMV infection is worse than CMV negative UC. CMV infection in UC is generally treated with ganciclovir along with tapering of immunosuppressive drugs [17].

In the present series, two patients of ulcerative colitis presented with acute exacerbation due to CMV infection. Both these patients were on steroids, were treated with Ganciclovir therapy and tapering of steroids [17]. CMV superinfection in patients of ulcerative colitis was less, similar to that observed by Kalappurayil NB et al., [18].

CMV disease in AIDS patients presents with chronic diarrhoea, fever, bleed PR and weight loss. In the presence of compatible symptoms, characteristic endoscopic appearance and typical intranuclear inclusion bodies on histology makes diagnosis of CMV disease in AIDS [19]. In the present series, five AIDS patients presented with chronic diarrhoea, abdominal pain and bleed PR.

CMV colitis is commonly seen in individuals with immunosuppression, rarely seen in immunocompetents especially in old age with other comorbidities like diabetes mellitus, chronic renal failure and ischaemic heart disease. In a study by Seo TH et al., the comorbid conditions in immunocompetent individuals with CMV colitis were diabetes mellitus(four cases), chronic renal failure (two cases) and ischaemic heart disease (two cases), out of 12 cases [12]. In the present series, among eight immunocompetent individuals except for the old age (65 years) no comorbid conditions were seen. CMV colitis in immunocompetent individuals is rare and described in literature in the form of case reports and small case series. In all these studies old age (>55 years) was the most important associated risk factor for CMV colitis and for poor outcome [20].

The colonoscopic findings in CMV colitis include colonic ulcers, erosions and haemorrhages. Rarely deep ulcers with sloughing mimicking ischaemic ulcers can be seen [21]. In the present series two patients had deep ischaemic ulcers. Since CMV infects endothelial cells which may initiate endothelial inflammation and vasculitis producing occlusive vascular ischemia.

Classical cytoplasmic and intranuclear CMV inclusions remain the gold standard for diagnosis. The biopsy specimens with disproportionate submucosal inflammation and ulceration with granulation tissue have to be examined carefully for CMV inclusions with multiple deeper sections wherever necessary. We observed that the severity of inflammation and density of infected cells were not proportionate, similar to the study by Mohanlal RD et al., [8]. Vasculitis was more common in score 3. In the present experience it was found basophilic cytoplasmic fine dot like inclusions in enlarged cells as a very helpful feature in identifying CMV infected cells, more so in the context of ganglion cells, when owl like intranuclear inclusions are not apparent. IHC is not a must in cases with classical CMV inclusions. High index of clinical suspicion, much obscuring inflammation and non-classical inclusions warrants IHC testing [22,23].

LIMITATION

Limitations of the present study are: First, it was a retrospective study involving only hospitalised patients with severe CMV infection leading to selection bias. Second data on CMV PCR was available only in eight patients but we included the patients who had characteristic inclusion bodies on histopathology which is the gold standard for the diagnosis of CMV infection.

CONCLUSION

In conclusion although CMV infection is common in individuals with immunosuppression, the present study demonstrates that it can occur even in immunocompetent individuals. In future the presence of compatible symptoms CMV colitis needs to be considered and actively looked even in immunocompetent individuals apart from immunosuppressed individuals and in patients with inflammatory bowel disease for early diagnosis and treatment.

REFERENCES

[1] Spaete RR, Gehrz RC, Landini MP. Human cytomegalovirus structural proteins. J Gen Virol. 1994;75(Pt 12):3287-308.
[2] Kalil AC, Florescu DF. Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit. Crit Care Med. 2009;37:2350–58.
[3] Osawa R, Singh N. Cytomegalovirus infection in critically ill patients: a systematic review. Crit Care. 2009;13:R68.
[4] de la Hoz RE, Stephens G, Sherlock C. Diagnosis and treatment approaches of CMV infections in adult patients. J Clin Virol. 2002;25 Suppl 2:S01-12.
[5] Li X, Huang Y, Xu Z, Zhang R, Liu X, Li Y, et al. Cytomegalovirus infection and outcome in immunocompetent patients in the intensive care unit: a systematic review and meta-analysis. BMC Infectious Diseases. 2018;18:289.
[6] Galiatsatos P, Shrier I, Lamoureux E, Szilagy A. Meta-analysis of outcome of cytomegalovirus colitis in immunocompetent hosts. Diag Dis Sci. 2005;50:609-16.
[7] Himoto T, Goda F, Okuyama H, Kono T, Yamagami A, Inukai M, et al. Cytomegalovirus- associated acute gastric mucosal lesion in an immunocompetent host. Intern Med. 2009;48:1521-24.
[8] Mohanlal RD, Karstaedt A. Cytomegalovirus infection of the gastrointestinal tract in Soweto, South Africa: a look back at the clinical and histological features over 8 years. J Infect Dis Epidemiol. 2017;3:038:01-06.
[9] Goodgame RW. Gastrointestinal cytomegalovirus disease. Ann Intern Med. 1993;119:924-35.
[10] Einbinder Y, Wolf DG, Pappo O, Migdal A, Tsvang E, Ackerman Z. The clinical spectrum of cytomegalovirus colitis in adults. Aliment Pharmacol Ther. 2008;27(7):578-87.
[11] Carter D, Olchovsky D, Pokroy R, Ezra D. Cytomegalovirus-associated colitis causing diarrhea in an immunocompetent patient. World J Gastroenterol. 2006;12:6898-99.
[12] Seo TH, Kim JH, Ko SY, Hong SN, Lee SY, Sung IK, et al. Cytomegalovirus colitis in immunocompetent patients: a clinical and endoscopic study. Hepatogastroenterology. 2012;59(119):2137-41.
[13] Cheung AN, Ng IO. Cytomegalovirus infection of the gastrointestinal tract in non-AIDS patients. Am J Gastroenterol. 1993;88(11):1882-86.
[14] Chan KS, Yang CC, Chen CM, Yang HH, Lee CC, Chuang YC, et al. Cytomegalovirus colitis in intensive care unit patients: difficulties in clinical diagnosis. J Crit Care. 2014;29(3):474.e01-06.
[15] Kandiel A, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. Am J Gastroenterol. 2006;101:2857-65.
[16] Kishore J, Ghoshal U, Ghoshal UC, Krishnani N, Kumar S, Singh M, et al. Infection with cytomegalovirus in patients with inflammatory bowel disease: prevalence, clinical significance, and outcome. J Med Microbiol. 2004;53:1155-60.
[17] Kim YS, Kim YH, Kim JS, Jeong SY, Park SJ, Cheon JH, et al. Long-term outcomes of cytomegalovirus reactivation in patients with moderate to severe ulcerative colitis: A multicenter study. Gut Liver. 2014;8:643-47.
[18] Kalappurayil NB, Thomas J, Mankuni B, Thomas V. Assessment of disease severity and role of cytomegalo virus infection in patients with ulcerative colitis. Journal of Clinical and Diagnostic Research. 2017;11(3):EC07-EC11.
[19] Mentec H, Leport C, Leport J, Marche C, Harzic M, Vildé JL. Cytomegalovirus colitis in HIV-1-infected patients: A prospective research in 55 patients. AIDS. 1994;8:461-67.
[20] Goodman AL, Murray CD, Watkins J, Griffiths PD, Webster DP. CMV in the gut: a critical review of CMV detection in the immunocompetent host with colitis. Eur J Clin Microbiol Infect Dis. 2015;34:13–18.
[21] Siegal DS, Hamid N, Cunha BA. Cytomegalovirus colitis mimicking ischemic colitis in immunocompetent host. Heart Lung. 2005:34;291-94.
[22] Juric-Sekhar G, Upton MP, Swanson PE, Westerhoff M. Cytomegalovirus (CMV) in gastrointestinal mucosal biopsies: should a pathologist perform CMV immunohistochemistry if the clinician requests it? Hum Pathol. 2017;60:11-15.
[23] Liao X, Reed SL, Lin GY. Immunostaining detection of cytomegalovirus in gastrointestinal biopsies: clinicopathological correlation at a large academic health system. Gastroenterol Res. 2016;9(6):92-98.

AUTHOR(S):

1. Dr. Renuka Malipatel
2. Dr. Mallikarjun Patil

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Pathology, St John's Medical College, Bangalore, Karnataka, India.
2. Professor Grade 2, Gastroenterology, St John's Medical College, Bangalore, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Mallikarjun Patil,
Professor, Department of Gastrenterology, St Johns Medical College, Bangalore-560034, Bangalore, Karnataka , India.
E-mail: drmalli_arjun@yahoo.co.in

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Publishing: **Oct 01, 2018**