Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Spl Issue [4] November 2022 : 177-181

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Clinicopathological features of CMV Colitis in 4 patients: A case series

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ABSTRACT
Cytomegalovirus (CMV) is a double stranded DNA virus belonging to the herpesvirus group. CMV disease is usually seen in immunocompromised patients commonly involving gastrointestinal system. The most common clinical presentation of CMV colitis is lower gastrointestinal bleeding. Other features include high grade fever, diffuse abdominal pain, watery diarrhoea, intermittent bloody stool, haematochezia, weight loss, bloody diarrhoea rarely as toxic megacolon, massive bleeding and perforation. To study clinicopathological spectrum and the colonoscopic/endoscopic features of gastrointestinal CMV disease. Written records of all patients with CMV disease pathology were entered into an electronic database. Retrospective analysis of these cases was performed from May 2020 to May 2021 at SGT Medical College and Hospital, Gurugram. Maximum number of patients with CMV colitis presented with GI bleeding. Constipation was seen one case. The type of ulcer on colonoscopy was also found to be significant. Linear esophageal ulcer noted in one case.
Conclusion-*This study describes the clinicopathological spectrum of gastrointestinal CMV disease from India.*
Keywords- Bleeding, CMV, Gastrointestinal, Ulcer

Received 04.10.2022 Revised 18.10.2022 Accepted 28.11.2022

INTRODUCTION

Cytomegalovirus is a DNA virus of the family Herpesviridae. CMV infection is a common opportunistic infection in immunocompromised patients like HIV infection, post-transplant patients, malignancy. [1,2] CMV infection can also occur in patients with increased risk factors like prolong steroid exposure, chronic kidney disease on haemodialysis, ulcerative colitis etc. [3,4,5] CMV infection in immunocompetent host generally are asymptomatic and presents as infectious mononucleosis. Symptomatic CMV colitis is a well-known condition in immunocompromised patients with significant morbidity and mortality. We hereby present cases of CMV colitis with contrasting clinical features. To study clinicopathological spectrum of gastrointestinal CMV disease and study the colonoscopic/endoscopic features of CMV disease.

MATERIALS AND METHOD

Study Design- The study was a retrospective observational study of 4 cases of CMV received at histopathology department from May 2017 to May 2018. Details of all histopathology reports were retrieved using Hospital information system (HIS) and Central laboratory information management system (CLIMS) and computerized using a Microsoft® Excel database. Each diagnosis was entered accompanied by the patient's age, gender, colonoscopy and clinical details. The data were sorted by age and gender, male to female ratio, colonoscopic details and clinical presentation.

Inclusion Criteria-All cases of CMV Disease were included in the study including cases positive by CMV IHC in symptomatic patients.

Case description-

The clinical and colonoscopic features are summarized in Table 1

Case 1-A 61-year-old female patient presented with severe bleeding per rectum following prolonged constipation with fecolith in colon. She is a known patient of chronic kidney disease on haemodialysis, coronary artery disease, hepatitis related chronic liver disease. Patient had fecolith obstruction of colon for which colonoscopy was done to relieve obstruction. On colonoscopy very large hard stool mass seen near

the splenic flexure. The scope could not be negotiated beyond the mass. Multiple attempts were made to break the mass via biopsy forceps, vigorous washing, and lactulose enema. Following colonoscopy, she continued to have severe bleeding per rectum leading to anemia for which several units of packed cell transfusion was given. Despite conservative measures patient continued to have bleeding per rectum. Repeat colonoscopy was done which showed presence of three distinct ulcers in colon with one of them was oozing. Haemostasis was achieved and biopsy was taken. Patient improved clinically. After two days she had abdominal distension with severe abdominal pain. Radiological examination suggested perforation of colon. Patient was conservatively managed as per advice of surgical team. Histopathological examination and immunostains showed presence of CMV colitis. Intravenous ganciclovir was started accordingly. Patient improved clinically and subsequently discharged from hospital on oral therapy.

38-year-old male patient presented with high grade fever with chills, vomiting, abdominal pain and diarrhoea (about 6-7 episodes/day, watery in consistency) in the last 8 days. He is a known patient of acute demyelinating encephalomyelitis, Acute Kidney Injury/Acute respiratory distress syndrome/bilateral lacunar infarct (likely embolic)/pseudomembranous colitis diagnosed recently, and was on steroid and intravenous antibiotics. He was initially treated as pseudomembranous colitis based on colonoscopy performed outside showing pancolitis. MRI brain done was suggestive of multiple acute lacunar infarcts in bilateral cerebral hemisphere likely embolic. At the time of admission, he was conscious, oriented to following all commands, power grade 3/5 in both lower limbs and 4/5 in bilateral upper limbs. His initial investigation showed Hemoglobin 12.5 g/dl, Total leucocyte count 33,400/cmm, Platelet 3,50000/cmm, Serum creatinine 2.7mg/dl, Blood urea nitrogen 58mg/dl, Prothrombin time 35.4 seconds, INR 3.1, SGOT 17, SGPT 6, Albumin 2.0g/dl, Urine R/M: Protein ++, RBC - occasional, WBC-2-3/hpf. C3 3:55 mg/dl (84-164), C4: 29.4 mg/dl (15-48). Urine C/S: Candida Tropicalis. Blood C/S: No growth. ANA/ANCA/Anti phospholipid antibody/Cardiolipin/Ds DNA: Negative. Protein Electrophoresis, IgG band - Positive, IgM & IgA - Negative, KAPPA band- Positive (132) mg/L, LAMDA band - Positive (95.30) mg/L, Beta 2 macroglobulin: 106647 ng/ml. Upper GI endoscopy also done on which revealed nodular mucosa in 2nd part of duodenum. Lower erosive esophagitis. Colonoscopy done which revealed diffuse ulceration, nodularity and friability in left part of colon with evidence of bleeding. Biopsy taken was suggestive of CMV infection. On IHC stain CMV was positive. Patient was started on hemodialysis due to rapidly deteriorating renal functions (serum creatinine 5.07, BUN 99), in view of CMV with multiple system involvement (neurological + enterocolitis + renal failure) patient was started on Ganciclovir and Intravenous immunoglobulin since 04/11/2016. GI symptoms have improved on Ganciclovir. Case 3- A 70 years old male, presented with complaints of intermittent abdominal pain (non radiating, aggravated on ingestion of food), water brash & obstipation in the last 7 days and loss of appetite in the last 2 weeks. USG done which was suggestive of cholelithiasis. At the time of admission, the patient 's pulse was 73/minute and BP was 102/53 mmHg. Patient presented with the above-mentioned complaints. Initial investigation showed Hemoglobin 11 g/dl, Total leucocyte count 14,090/cmm, Platelet 3,91000/cmm, Serum creatinine 0.73mg/dl, Blood urea nitrogen 11mg/dl, Prothrombin time 13.4seconds, INR 1.15, Sodium 131mEq/L, Potassium 4mmol/L. Amylase 27, Lipase 15.40. He was started on IV fluid, IV antibiotics, IV PPI, IV anti emetic and other supportive measures. He underwent UGIE which revealed fundal gastropathy and small D1 polyp (likely Brunner gland hyperplasia). CECT showed Fatty infiltration in liver and Cholelithiasis with acute cholecystitis. Mural thickening in segments of large bowel and terminal ileum. Findings suggestive of inflammatory etiology. Colonoscopy done which revealed colonic ulcer (nature?) Biopsy showed ulcer slough with presence of CMV inclusions.

Case 4- A 92-year-old male, known case of coronary artery disease – Post Coronary Artery Bypass Graft Surgery (2008), Atrial fibrillation with rapid ventricular rate on Cordarone, Severe aortic stenosis, left ventricular ejection fraction 20-25%, hypertension & Benign Prostatic Hyperplasia, presented with complaints of sudden onset bleeding P/R (1 episode) while passing stool in morning. Blood was bright red colour around 100-120ml. Past history of constipation present. No history of hematemesis, pain abdomen. At the time of admission, the patient 's pulse was 112/minute and BP was 106/61 mmHg.

Initial investigation showed Haemoglobin- 14g/dl, Total leucocyte count - 6.5/cmm, Platelet 1,72000/cmm, INR 1.31, Creatinine- 1.81mg/dl, Sodium- 133mEq/L, Potassium - 5.33mmol/L. Total Bilirubin - 0.93mg/dl, Direct Bilirubin - 0.14mg/dl , Albumin- 2.8g/dl. Patient was started on Intravenous fluid, IV Proton pump inhibitors, Tab. Mucomix and other supportive measures. Patient underwent Sigmoidoscopy which revealed ulcerated lesion just inside the anal verge with active bleeding - haemostasis achieved by injecting 1:20000 adrenaline. Internal haemorrhoids present (Sclerosant injected). Repeat Sigmoidoscopy was done which showed circumferential ulcerated lesion with small polypoidal proliferations in anal canal with no active bleeding. Biopsies from rectum show features of CMV colitis.

Table 1- Clinical features and colonoscopic findings of CMV Colitis patients-

Age	Site of biopsy	Histology	CMV /ml	Colonoscopy	Deep ulcer
61/ Female	Colon biopsy	Presence of CMV colitis	362.11	3 areas of ulceration likely stercoral, the one which was most proximal has some amount of erythematous area probably has bleed in recent past hence 1:20000 adrenaline was applied to achieve homeostasis in 4 quadrants. Another small ulcer about 20 cm from the anal verge which has similar erythematous areas the biggest ulcer in between these two was near the splenic flexure was white based without any evidence of recent bleed so no end therapy was done, there were few ulcers at anal verge, small external haemorrhoids	
38/ Male	Colon Biopsy	Presence of CMV colitis	887 after 13 days 5253 after 5 days 66	Upper GI endoscopy also done on which revealed nodular mucosa in 2nd part of duodenum. Lower erosive esophagitis. Linear erosion at lower part of oesophagus,	

				Nodular duodenal mucosa in D2, Diffuse colonic ulceration	
72/ Male	Colon biopsy	Active colitis with ulceration compatible with CMV Colitis		Multiple large ulcers up to 4-5 cm seen in ascending colon, transverse and descending colon	
92/ Male	Anal Canal Ulcer	Benign Anorectal mucosal tissue with ulceration -CMV Colitis		Ulcerated lesion just inside the anal verge active bleeding, internal haemorrhoids present	Circumferential ulcer with small polypoidal proliferation

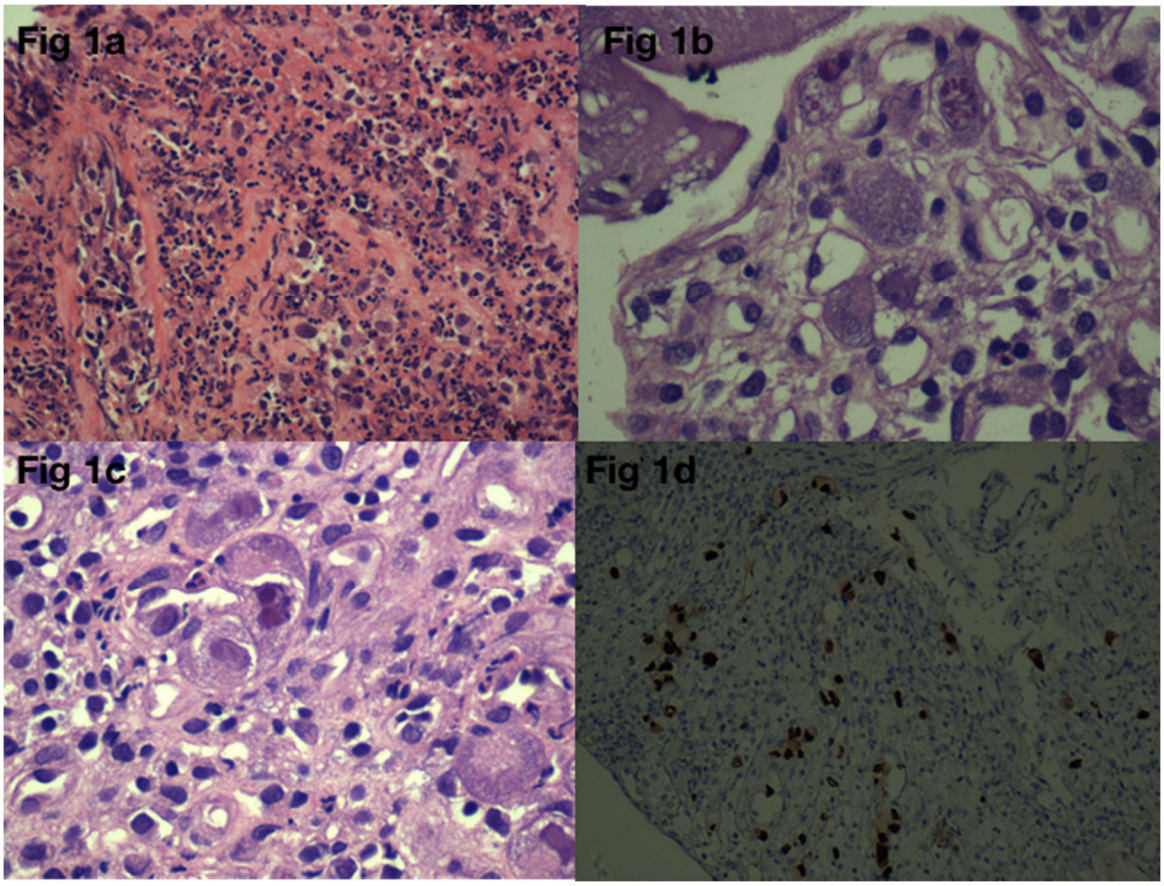

Fig 1a-CMV inclusion in ulcer slough
Fig 1b, c-Nucleomegalic CMV inclusions in endothelial cells
Fig 1d-IHC for CMV showing CMV inclusions

DISCUSSION

CMV colitis is manifestation of CMV tissue-invasive disease. The disease is usually seen in immunocompromised patients and rarely in immunocompetent patients. CMV virus or Human herpes virus

5 (HHV 5) belong to *Herpesviridae* family; is a double-stranded DNA virus capable of a wide spectrum of disease in humans.[1] Tissue-invasive gastrointestinal (TI-GI) CMV is defined as CMV disease with symptoms localized to the GI tract. Most cases of TI-GI CMV occur in patients with relative immunosuppression due to critical illness or comorbidities such as type 2 diabetes mellitus, renal insufficiency, pregnancy, autoimmune diseases, heart failure, or malignancy. [2,3,4] In our case series 3 cases were seen in immunocompromised patients and only one case was seen in an immunocompetent adult. These cases of CMV colitis presented to ICU of our hospital over last year. The most common clinical presentation of CMV colitis is lower ggastrointestinal bleeding. Other features include high grade fever, diffuse abdominal pain, watery diarrhoea, intermittent bloody stool, haematochezia, weight loss, bloody diarrhoea rarely as toxic megacolon, massive bleeding and perforation. [5,6,7] In our cases 2 patients presented with lower GI bleed while two presented with watery diarrhoea. The presenting clinical features are not specific for CMV colitis and diagnosis can only be established with typical histologic finding of "owl eye" cell and CMV inclusions on IHC. Characteristic colonic features of cmv colitis include deep irregular ulcer, punched out ulcer, geographical ulcer, longitudinal ulcers and mucosal defects. All cases in our series show presence of multiple and diffuse large ulcers. The ulcers were irregular in shape. None of the cases showed punched out ulcers. On microscopy CMV colitis is diagnosed by presence of intra nuclear inclusions also called owl's eye inclusions. The inclusion is usually seen in enlarged endothelial cells lining the vessels and also seen embedded in ulcer slough. The lamina propria usually shows moderate to dense mixed inflammatory infiltrate with areas of cryptitis and presence of apoptotic debris. The Nucleomegalic can be confirmed by immune histochemistry [8] Treatment comprises of targeted antiviral therapy with ganciclovir or valganciclovir is appropriate for severe CMV colitis.

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CITATION OF THIS ARTICLE

Y Komal , B Nalini, K Ajay, S Rajeev· Clinicopathological features of CMV Colitis in 4 patients: A case series. Bull. Env.Pharmacol. Life Sci., Spl Issue [4]: 2022: 177-181