CORRESPONDENCE

Bloody Diarrhea in a Patient of Aggressive Lymphoma: a Diagnostic and Therapeutic Challenge

Ankur Jain¹ · Gaurav Prakash¹ · Alka Khadwal¹ · Pankaj Malhotra¹ · Amanjit Bal² · Jasmina Ahluwalia³ · Subhash Varma¹

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Cytomegalovirus (CMV) is an important cause of morbidity and mortality in immunocompromised patients. CMV disease in an immunocompetent person is rare unless immune system is compromised by co-morbidities and necessitates a work-up for an undiagnosed underlying immunodeficiency [1]. A 40-year-old man presented to our hospital with fever (101 °F) since 1 month associated with significant weight loss and bloody diarrhea for 10 days. Personal history was negative for smoking, alcohol intake or high risk behavior. Patient was febrile (oral temperature of 101.5 °F) and his vitals were: blood pressure—110/70 mm hg and pulse rate—112/min. General examination revealed marked cachexia, pallor and bilateral axillary and inguinal lymphadenopathy.

✉ Gaurav Prakash
drgp04@gmail.com

Ankur Jain
drankur589@yahoo.in

Alka Khadwal
alkakhadwal@hotmail.com

Pankaj Malhotra
hematpgi@gmail.com

Amanjit Bal
docaman5@gmail.com

Jasmina Ahluwalia
jasminapgi@gmail.com

Subhash Varma
suvarma@hotmail.com

His blood investigation were-hemoglobin: 84 g/l, white cell counts- $6.9 \times 10^9/L$, platelets- $144 \times 10^9/l$, sedimentation rate—65 mm/h, lactate dehydrogenase—960 U/l and $\beta 2$ microglobulin-3500 mg/l. Histopathological examination of the axillary lymph node revealed infiltration by large atypical lymphoid cells (Fig. 1a, b). Immunostaining was positive for CD45, CD30 and PAX-5 and negative for CD20, CD3, ALK, CD15, C-MYC and CD3, consistent with CD30 positive diffuse large B cell lymphoma (DLBCL). Staging evaluation by contrast enhanced CT scan revealed enlarged mediastinal, hilar, axillary and retroperitoneal lymph nodes with hepatosplenomegaly and thickened caecal wall. Bone marrow aspirate showed infiltration by lymphoma (stage IVB) (Fig. 1c, d). Stool culture revealed *Shigella flexneri* and based on anti-microbial sensitivity pattern, patient was treated with a combination of oral metronidazole (400 mg q8h) and ciprofloxacin (500 mg q12h). Diarrhea persisted despite 7 days of oral antibiotics. Clostridium difficile toxin assay was negative in stool. Sigmoidoscopy was subsequently performed which revealed multiple rectal ulcers. Rectal biopsy suggested only non-specific inflammatory changes. Due to persistent bloody diarrhea and non-contributory rectal biopsy, colonoscopy was performed which revealed multiple deep ulcers in the ascending colon and caecum. Colonic biopsy revealed cryptitis and crypt abscesses (Fig. 2). Nucleocytomegalic endothelial, stromal and epithelial cells were seen with smudgy nuclear inclusions which showed positivity for CMV on immunohistochemistry (Fig. 3). CMV DNA was detected in the peripheral blood (15,600 copies/ml) by polymerase chain reaction (PCR) and a diagnosis of CMV colitis was made. Viral markers (hepatitis B surface antigen, anti-HCV antibody and HIV) were negative and immunoglobulin profile was normal. Patient was treated with parenteral Ganciclovir (5 mg/kg q12) for 2 weeks. Diarrhea resolved on day 7 of

¹ Department of Internal Medicine, PGIMER, 4th floor, Nehru Hospital, Chandigarh 160012, India

² Department of Histopathology, PGIMER, Chandigarh 160012, India

³ Department of Hematology, PGIMER, Chandigarh 160012, India

Fig. 1 Section showing neutrophilic infiltrate in lamina propria surrounding the crypts with occasional focus of cryptitis (*star*) with nuclear enlargement and smudged chromatin (*arrow*) in epithelial cells (H&E stain $\times 400$)

Fig. 2 Immunohistochemistry for CMV showing nuclear positivity (*arrow*) in the epithelial cells (Immunoperoxidase $\times 400$)

therapy and there was complete clearance of CMV infection from the colon as demonstrated by a repeat biopsy performed after 2 weeks of therapy. However, patient had worsening cytopenias due to marrow infiltration by lymphoma and succumbed as a result of septicemia. Patients with hematological malignancies may develop CMV colitis as a result of impaired T-cell function resulting from administration of chemotherapeutic drugs. CMV colitis has been reported following treatment of follicular lymphoma, relapsed mantle

cell lymphoma, myelodysplastic syndrome and adult T-cell lymphoma/leukemia [2–5]. CMV colitis in a treatment naïve patient of DLBCL has not been reported. Histological demonstration of CMV offers a specific albeit less sensitive method of diagnosing CMV colitis and has been shown to correlate with peripheral blood CMV DNA levels by PCR [1, 6]. Ison et al. [7] showed that 15% patients with Gastrointestinal (GI) CMV disease had undetectable DNA levels in blood and 4.9% with positive CMV DNA in blood had no evidence of CMV disease on histology. Therefore, a combination of biopsy and peripheral blood DNA estimation by PCR is investigation of choice for diagnosing CMV colitis. CMV may be missed on initial biopsy due to patchy involvement thereby necessitating multiple biopsies. ‘Isolated’ detection of CMV DNA in blood in a patient of colitis does not necessarily indicate CMV disease and histological confirmation is warranted before starting CMV specific treatment [1]. Our patient had bloody diarrhea for which no apparent cause was found. Colonic biopsy delineated CMV as the etiology which was supported by detection of CMV DNA in the blood. As our patient was therapy naïve, we propose that functional T-cell impairment might have predisposed him to CMV colitis. Treatment of concomitant CMV colitis and stage IV lymphoma was challenging in the current case. We opted to treat CMV colitis first due to the risk of fatal CMV disease (colonic perforation or massive bleeding) with upfront chemotherapy. We could successfully eradicate CMV from colon after 2 weeks of Ganciclovir therapy. Unfortunately, patient died as a result of progressive disease without receiving specific anti-lymphoma therapy. Lymphomagenic potential of CMV in cases of concomitant GI lymphoma and CMV disease has been described [8, 9]. Since our patient didn’t have a GI lymphoma; it is unlikely that CMV played an etiological role in lymphoma pathogenesis. CMV colitis in this case appears secondary to functional immunosuppression due to lymphoma. We emphasize that CMV colitis must be considered in the differential diagnosis of bloody diarrhea in a patient of lymphoma (even if therapy naïve) and an early colonic biopsy may allow accurate diagnosis in such cases. Treatment of concurrent CMV colitis and lymphoma is challenging and needs to be individualized.

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Fig. 3 **a, b** Section showing lymph nodal effacement with large atypical lymphoid cells scattered amidst numerous mature appearing lymphocytes. The atypical cells are 2–5 times the size of tumor lymphocytes, with large pleomorphic nuclei, inconspicuous nucleoli and scant cytoplasm. Brisk mitosis is seen along with atypical mitotic figures (H&E stain $\times 400$). **b, d** Represents bone marrow aspirate showing infiltration by the atypical lymphoid cells (H&E stain $\times 400$)

reviewed the Bone marrow aspirate of the patient, SV: provided guidance and supervision for the case management.

Compliance with Ethical Standards

Conflict of interest None.

Informed Consent Obtained from the patient prior to publication of any material.

Ethical Standards Not needed as this article does not involve any human or animal participant.

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