The Presentation of Multiple Perforations in the Small Bowel as Cytomegalovirus Related Immune Reconstitution Inflammatory Syndrome in an HIV-infected Patient: a Case Report

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Case Report

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Abstract

Background: Multiple perforations in the small bowel as cytomegalovirus (CMV) related immune reconstitution inflammatory syndrome (IRIS) in an human immunodeficiency virus (HIV)-infected patient is very rare. Up to now, only five IRIS-associated cases including our case were reported. We performed pathological examination, metagenomic next-generation sequencing (mNGS), CMV and immune cells immunohistochemical staining for rapid diagnosis and differential diagnosis.

Case presentation: We describe a case with multiple perforations in the small bowel as CMV related IRIS in an HIV-infected patient. The patient appeared multiple perforations in the small bowel after 26 days of antiretroviral therapy (ART). The patient underwent exploratory laparotomy. Partial resection and surgical repair of small intestine were performed. CMV enteritis was confirmed by immunohistochemistry staining and other opportunistic infections were excluded by mNGS. However, he died from intestinal obstruction and septic shock at 55 days after surgery.

Conclusions: Perforations due to CMV related IRIS are very rare, and usually lack the prodromal period symptoms of abdominal pain and diarrhea. It is not easily foreseen and appears shortly after ART. The condition of intestinal perforations is lethal, and early identification and surgical treatment are lifesaving.

Background

Multiple perforations in the small bowel as CMV related IRIS in an HIV-infected patient is very rare. Up to now, only five IRIS-associated cases including our case were reported. The patient in our case appeared multiple perforations in the small bowel after 26 days of ART. After partial enterectomy, we performed pathological examination, mNGS, CMV and immune cells immunohistochemical staining for rapid diagnosis and differential diagnosis. CMV enteritis was confirmed and other opportunistic infections were excluded.

Case Presentation

A 28-year-old Chinese man found several purple blue nodules on the face and neck for one month. He was detected positive antibody of HIV. His nadir $CD4^+$ T cell count was 25cells/μL. After skin lesion biopsy, he was diagnosed with Kaposi's sarcoma. The cytomegalovirus (CMV)-DNA load was 6.0×10^4 copies/ml. CMV antibody (IgM) was less than 8U / ml (0-18 U / ml), CMV antibody (IgG) was 12.3 U / ml (0-12 U / ml). No abnormalities were found in the funduscopic screening examination. Specific antibody of treponema pallidum (TP) was positive. Rapid plasma reagent (RPR) test titer demonstrated 1:2 positive. The patient was treated with benzathine penicillin for three weeks. He started ART with the regimen of lamivudine (3TC) 300 mg daily, tenofovir disoproxil (TDF) 300 mg daily, and nevirapine 200mg twice a day. After 16 days of ART, the patient complained of fever and was admitted to our hospital. His highest temperature is 38. 9 centigrade accompanied by chills. He had no abdominal pain, diarrhea, and hematochezia. Blood routine test of the patient showed leukocyte 5.76×10^9/L (3.5-9.5 $\times10^9$/L), lymphocyte 1.29×10^9/L (1.1-3.2 $\times10^9$/L), granulocyte 4.04 $\times10^9$/L (1.8-6.3 $\times10^9$/L), hemoglobin (Hb) 87g/L (130-175g/L),and platelet (PLT) 348×10^9/L. The level of C reactive protein (CRP) was 88.7 mg/L (0-8 mg/L), and procalcitonin (Pct) was 0.66 ng/mL (0-0.05 ng/mL). Toxoplasma antibodies of IgG and IgM were negative. Liver function and kidney function were normal. His

$CD4^+$ T cell count has already increased into 75cells/μL. CMV-DNA load was 1.3×10^4 copies/ml. He was treated with intravenous ganciclovir. Ten days later, his fever disappeared. However, the patient presented persistent left lower abdominal pain which was spastic and tolerable. He had no abdominal distension, nausea, vomiting. The patient was conscious and had normal blood pressure(BP) 115/65mmHg, respiratory rate (R) 16 times / min, pulse frequency (P) 88 times / min and body temperature(T) 36.8℃. Abdominal examination showed that the abdomen was soft and flat, left upper abdominal tenderness, without rebound pain and muscle tension. Bowel sounds were 4 times / min. A standing x-ray of the abdomen in a tertiary level hospital revealed bilateral moderate intraperitoneal free air (Fig 1A). Intestinal perforation was considered. However, he and his family members declined surgical treatment and temporarily agreed with conservative treatment. Patients were given gastrointestinal decompression, proton pump inhibitors, ertapenem combined with levofloxacin, and nutritional support. Twenty four hours later, the vital signs were T 38.4℃, BP 110 / 70mmHg, P 130 times / min, R 18 times / min. The patient had tenderness pain in the left upper abdomen and right lower abdomen and whole abdominal rebound pain and muscle tension. We rechecked the standing x-ray of the abdomen found bilateral massive intraperitoneal free air (Fig 1B). Abdominal color ultrasound showed pneumoperitoneum and pelvic effusion. The images of abdomen computed tomography (CT) showed free gas with a low diaphragm (Fig 1C). Retested blood showed leukocyte 8.74×10^9/L, lymphocyte 0.65×10^9/L, granulocyte 7.96×10^9/L, Hb 103 g/L, and PLT 338×10^9/L. Alanine transaminase (ALT) was 102U/L (9-50 U/L) and creatinine (Cr) was 92 μmol/L (59-104 μmol/L). An exploratory laparotomy was performed. A total of 1000 ml of suppurative peritoneal fluid was cleared. Multiple perforations (40,50,65,140,240 cm proximal to the terminal ileum) were found at the anti-mesenteric border of small bowel. The largest diameter of holes was 1cm. Furthermore, multiple localized discolorations on the serosal surface of small intestine were presented indicating multiple deep ulcers (20,80,100,220 cm proximal to the terminal ileum). Partial enterectomy(35cm) and
surgical repair of small bowel were performed. Histopathological showed the mucosa, submucosa and muscular layer were destroyed, neutrophil infiltration and granulation tissue formation were observed (Fig 2A). The serosa and myometrium showed pyogenic necrosis and a large number of neutrophils infiltrated (Fig 2B). There were intranuclear and intracytoplasmic inclusions typical of cytomegalovirus (Fig 2C). CMV enteritis was confirmed by hematoxylin-eosin staining and immunohistochemistry staining (Fig 2D). There were a variety of inflammatory cell infiltration, including MUM1 positive plasma cells (Fig 2E), CD68 positive tissue cells (Fig 2F), CD8 positive lymphocytes (Fig 2G), and a small amount of CD4 positive lymphocytes (Fig 2H). Kaposi's sarcoma was firstly excluded. In order to identify other possible co-infectious pathogens, formalin-fixation and paraffin-embedded (FFPE) samples from a section of the resected bowel were sent to BGI PathoGenesis Pharmaceutical Technology (BGI-Shenzhen) for metagenomic next-generation sequencing (mNGS), which indicated CMV mono-infection without co-infections such as salmonella, tuberculosis, histoplasmosis, non-tuberculous mycobacteria, cryptococcosis, amebiasis, microsporidium, schistosomiasis. Intravenous ganciclovir at 5 mg/kg twice per day for another 2 weeks followed by 5 mg/kg/day for 1 month was applied. His CMV-DNA load was already less than 500 copies/mL. The patient had no fever and abdominal pain. He discharged home at 17 days after surgery and continued to take oral medication of ART without taking oral ganciclovir for secondary prophylaxis. One month after discharge, the patient was admitted again for abdominal pain and vomiting. The patient was conscious. The vital signs were T 36.5℃, BP 110 / 76mmHg, P 103 times / min, R 16 times / min. A standing x-ray of the abdomen did not show free gas and liquid gas level (Fig 1D). However, 24 hours later, the condition of this patient aggravated with a fever and decreased blood pressure. The vital signs were T 38.4℃, BP 90 / 48mmHg, P 140 times / min. Blood routine test showed

leukocyte 5.52×10^9/L, lymphocyte 0.38×10^9/L, granulocyte 4.35 ×10^9/L, Hb 88 g/L, PLT 158 ×10^9/L. Amylase, lipase, myocardial enzyme, liver function and renal function were normal. We rechecked the standing x-ray of the abdomen showed visible dilated intestines and liquid gas level (Fig 1E). Adhesive intestinal obstruction and septic shock was diagnosed. The patient received meropenem, rehydration transfusion, dopamine, gastrointestinal decompression. Unfortunately, the patient's condition deteriorated and died at 55 days after surgery.

Discussion And Conclusions

The multiple small bowel perforations in this case were associated with CMV related immune reconstitution inflammatory syndrome (IRIS). Up to now, only five IRIS-associated cases including our case were reported[1-4] (summarized in Table 1). Most cases lacked prodromal symptom of diarrhea. The durations from ART initiation to develop bowel perforation were totally within two months. It is noted that these cases were exclusively associated with men especially with homosexual contact history. Among IRIS-related cases, small bowel perforations were common involved. Differently, our patient demonstrated severe secondary purulent peritonitis pre-operation which was the cause of short-term death. Shortening interval to operation once perforation was essential for survival. Therefore, it is actually challenging for us to make an early diagnosis and an early treatment. Non-traumatic small bowel perforation is rare[5-6]. The common causes in the general population are tuberculosis, Crohn's disease, and malignancies [7]. The most common cause in HIV-infected population is CMV infection though there has been a dramatic decrease at ART era.

The most common presenting symptoms of CMV gastroenteritis are fever, abdominal pain and diarrhea, while disease limited to the small bowel could be asymptomatic. CMV enteritis presenting as perforation in HIV-infected population showed a high mortality due to high postoperative complications including reperforation, bowel obstruction and severe sepsis complicated by multi-organ failure [8]. CMV colitis could be a manifestation of unmasking or paradoxical IRIS[9-11]. The pathogenesis of gastrointestinal CMV disease is believed to be submucosal vasculitis with thrombosis resulting in ischemia, ulcers, thinning of the intestinal wall with subsequent perforation and gangrene [12]. Histologic examination showed multiple areas of mucosal ulceration with acute and chronic inflammation. Transmural inflammation and necrosis was found at the perforation sites. The gold standard for diagnosis is the discovery of cytomegalic cells with viral inclusions bodies in epithelial, endothelial, smooth muscle, and inflammatory cells [13,14]. Infection is confirmed by immunohistochemistry for immediate early antigen of CMV. Real-time PCR and CMV culture are alternative laboratory method. As an important diagnostic tool, the significance of mNGS using FFPE samples of lesions for this case could help us to make differential diagnosis among various co-infections such as tuberculosis, non-tuberculous mycobacteria, histoplasmosis, and salmonella, which all might be associated with bowel perforations in HIV-infected patients.

In conclusion, bowel perforations shortly post-ART could be considered as CMV related IRIS in HIV-infected individuals. Up to now, in HIV-infected patients with asymptomatic CMV viremia, preemptive anti-CMV therapy was not recommended in HIV-infected population. However, preemptive anti-CMV therapy in advanced HIV-infected patients in some studies proved to be effective [15-16]. Routine enteroscopy and capsule endoscopy screening were not recommended. In order to prevent life-threatening CMV colitis, taking ART early and maintaining high $CD4^+$ T cell counts are feasible. Alerting atypical manifestations of the disease and rapid

initiating individualized therapy are crucial. Last but not least, identifying high-risk individuals and the use of preemptive anti-CMV therapy may be lifesaving. Intensifying education in assessment and monitoring to patients should be achieved among HIV specialists. Among the sickest individuals, clarifing the high risk factors correlated with mortality may guide us to take up the optimal interventions as soon as possible.

List Of Abbreviations

CMV, cytomegalovirus; IRIS, immune reconstitution inflammatory syndrome; ART, antiretroviral therapy; mNGS, metagenomic next-generation sequencing; HIV, human immunodeficiency virus; TP, treponema pallidum; RPR, rapid plasma reagent; 3TC, lamivudine; TDF, tenofovir disoproxil; Hb, hemoglobin; PLT, platelet; CRP, C reactive protein; Pct, procalcitonin; BP, blood pressure; R, respiratory rate; P, pulse frequency; T, body temperature; CT, computed tomography; ALT, alanine transaminase; Cr, creatinine; mNGS, next-generation sequencing;

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Written informed consent for patient information to be published was provided by the patient.

Availability of date and materials:

Not applicable (no datasets were generated or analyzed during the current study)

Competing interests:

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Yanli Wang, Article writing

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Table

Table 1.

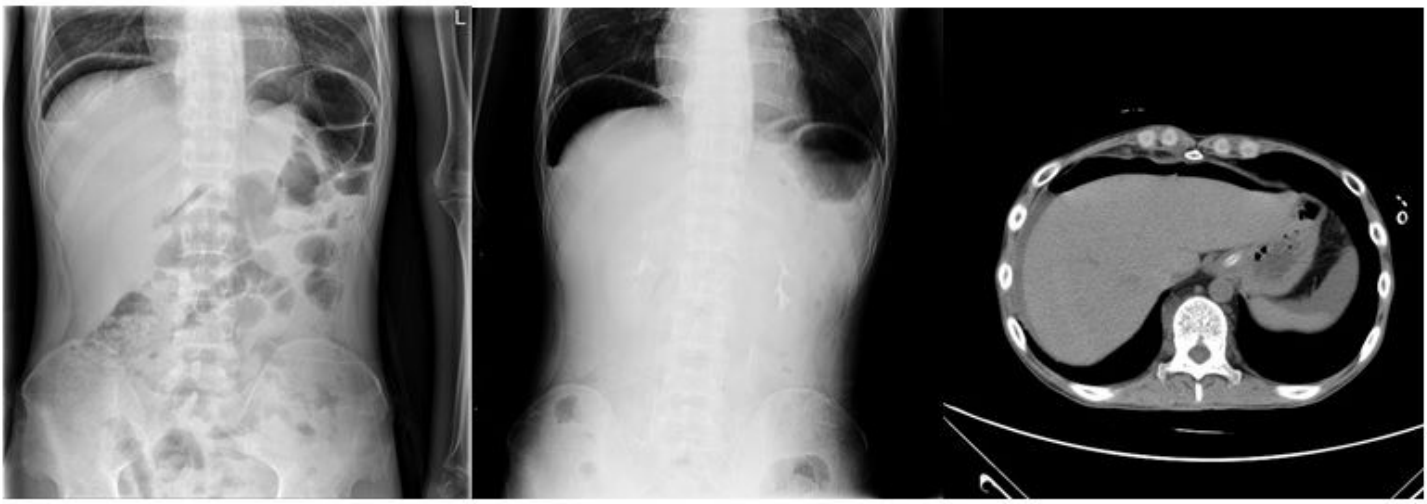
Summary of reported cases with bowel perforation due to cytomegalovirus related immune reconstitution inflammatory syndrome in HIV-infected patients

Case	Age	Gender	CD4 cell count	CMV retinitis	Duration post-ART	Manifestations and prognosis	Treatment
Gutiérrez-Delgado EM et al,2016	40	M gay	54	Y	1m Unmasking IRIS	Without diarrhea A perforation in the jejunum discharged home at 17 days after surgery and readmitted 15 days later A colonic perforation Discharged home without mentioning further follow-up	oral valganciclovir A side-to-side anastomosis colostomy Intravenous ganciclovir□ART restart colostomy and a mucocutaneous fistula Intravenous ganciclovir
Lee YC et al,2019	32	M	From 25 to 33	NM	53 d Unmasking IRIS	Post-ART diarrhea and CMV colitis Free air below the left-sided hemidiaphragm A perforation in the jejunum Survive when 30 months follow-up	Intravenous ganciclovir oral valganciclovir Surgical repair with peritoneal toileting ART was resumed
Ulrich von Both et al,2008	40	M gay	164	NM	14d Paradoxical IRIS	diarrhea at pre-ART and acute ulcerous colitis Pneumoperitoneum Perforation Survive when 24 months follow-up	subtotal colectomy ganciclovir
DeRiso AJ 2nd, et al,1989	40	M	From 135 to 395	NM	2m Unmasking IRIS	without diarrhea Without air on abdominal radiograph Murky free peritoneal fluid Three perforations in jejunum	Partial enterectomy and enteroenterostomy repair ganciclovir

						Discharged on 21st postoperative day without further follow-up	
Our patient	28	M gay	From 25 to 75	NM	26d Unmasking IRIS	Without diarrhea Five perforations in ileum Discharged on 21st postoperative day and readmitted 30 days later due to bowel obstruction and severe sepsis Die	Partial enterectomy and enteroenterostomy repair ganciclovir

M-male; F-female; NM-not mentioned or not done; DR-drug resistance of ART;

Figures



1A 1B 1C

1D 1E

Figure 1

1A. A standing x-ray of the abdomen in a tertiary level hospital revealed bilateral moderate intraperitoneal free air. 1B. Standing x-ray of the abdomen revealed bilateral massive intraperitoneal free air. 1C. The images of abdomen CT showed free gas with a low diaphragm. 1D. Standing x-ray of the abdomen revealed there was no free gas under the diaphragm and liquid gas level. 1E. Standing x-ray of the abdomen showed visible dilated intestines and liquid gas level.

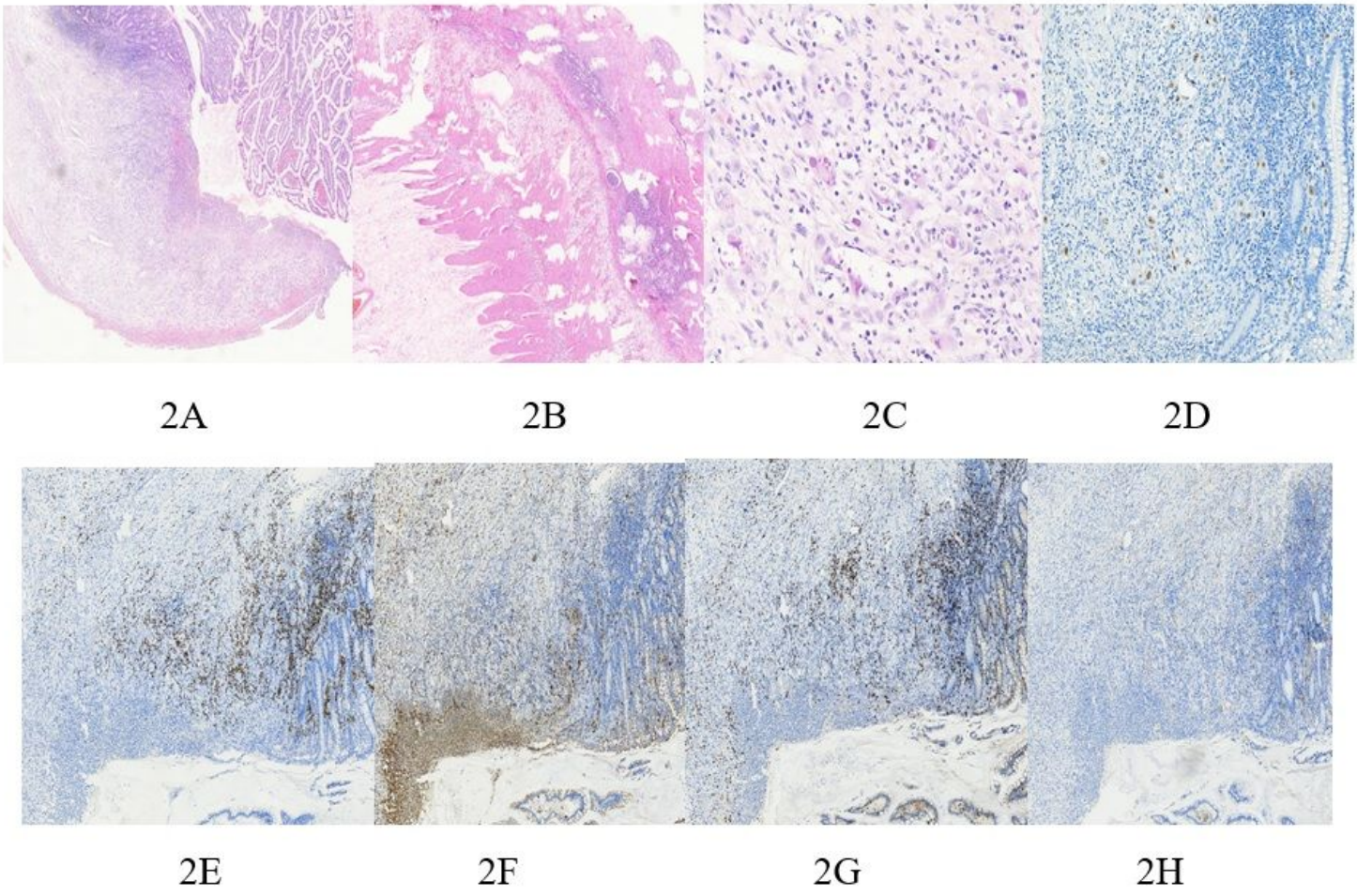


Figure 2

2A. The mucosa, submucosa and muscular layer were destroyed, neutrophil infiltration and granulation tissue formation were observed (x200 HE). 2B. The serosa and myometrium showed pyogenic necrosis and a large number of neutrophils infiltrated (x20 HE). 2C. There were intranuclear and intracytoplasmic inclusions typical of cytomegalovirus (x200 HE). 2D. Mucosa and submucosa macrophages express CMV antigens (x100 immunohistochemistry). 2E. MUM1 positive plasma cells infiltration (x40 immunohistochemistry). 2F. CD68 positive tissue cells infiltration (x40 immunohistochemistry). 2G. CD8 positive lymphocytes infiltration (x40 immunohistochemistry). 2H. CD4 positive lymphocytes infiltration (x40 immunohistochemistry).

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