Case Report

Ileum perforation due to cytomegalovirus infection in a patient with adult T-cell leukemia

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Case: A 73-year-old woman was transferred to our department due to severe abdominal pain with peritonitis. Her laboratory data showed that her white blood cell count was elevated to more than 50,000/mm³. Antibodies to HTLV-I were positive and we made the diagnosis of adult T-cell leukemia (ATL).

Outcome: Emergency laparotomy was performed and revealed two separate small perforations of the ileum, requiring bowel resection. Immunohistochemistry for cytomegalovirus (CMV) antigen revealed positive staining in the intestinal stromal cells. Despite surgery and antiviral therapy with ganciclovir, she died after 28 days.

Conclusion: Adult T-cell leukemia patients may present acute abdominal pain due to intestinal perforation caused by CMV infection. We should be aware of CMV infection as one of the pathogens causing acute abdominal crises such as massive hemorrhage or visceral perforation.

Key words: adult T-cell leukemia, cytomegalovirus, intestinal perforation

INTRODUCTION

ADULT T-CELL LEUKEMIA (ATL) is a rare T-cell malignancy associated with human T-lymphotropic virus type I (HTLV-I). ATL was first identified in Japan by Takatsuki and colleagues in 1977¹ and is most prevalently seen in the southwestern district of Japan.² A high prevalence of HTLV-I has also been reported in the Caribbean islands and countries around the Caribbean Sea.

The clinical course in acute ATL is usually poor. Death can result from pulmonary complications including *Pneumocystis* pneumonia, hypercalcaemia, cryptococcal meningitis, disseminated herpes zoster, and disseminated intravascular coagulopathies. In addition, cytomegalovirus (CMV) infection of the gastrointestinal tract is often seen in immunocompromised patients such as those with ATL.³

Although ileal perforation due to gastrointestinal CMV infection is rare, previous clinical reports have demonstrated poor prognosis when this complication occurs in ATL patients. Recently, increased survival of leukemia patients as a result of prophylaxis and treatment of other infections may result in an increase of patients with gastrointestinal CMV infection. Herein, we report a patient with ATL presenting ileal perforation, which we believe was directly attributed to CMV infection. We describe the clinical, radiological, and histopathological data of this patient and review the literature, which may help clinicians make decisions regarding treating ATL patients.

CASE PRESENTATION

A 73-YEAR-OLD WOMAN WAS transferred to our emergency department due to severe abdominal pain and nausea with a clinical diagnosis of generalized peritonitis based on free intraperitoneal air detected by abdominal X-ray and computed tomography (CT). The patient had been diagnosed with vertebral bone fractures. Physical examination revealed that her blood pressure was 56/36 mmHg, heart rate was 110 beats per minute, and oxygen saturation was 93% with 5 L per min oxygen flow. The patient was not febrile

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Fig. 1. (A) Abdominal computed tomography (CT) demonstrates pneumoperitoneum and intra-abdominal fluid, suggesting gastrointestinal perforation. (B) Intraoperative findings. Intestinal perforation in the ileum and color changes in the serous membrane along the small intestine were noted. (C) Pathological findings of the perforation site of the small intestine (H&E, $\times 100$). Microscopically, the ulcer bases and edges of perforation consisted of granulation tissue with acute and chronic inflammation, as well as necrosis. (D) Immunohistochemistry for cytomegalovirus (CMV) antigen revealed positive staining of inclusion in the intestinal stromal cells.

(36.7°C). Hepatomegaly or splenomegaly was not present. The abdomen was mildly distended with diffuse tenderness and guarding. She had no history of blood transfusion.

Her white blood cells (WBCs) were elevated to 52,820/mm³ and her platelet count was 5.0×10^4 /mm³. Giemsa (May-Grunwald-Giemsa) stain confirmed flower-like cells in the peripheral blood. Atypical lymphocytes occupied 35% of the WBCs. The serum chemistry findings were as follows: lactate dehydrogenase 385 IU/L, alkaline phosphatase 418 IU/L, C-reactive protein 7.2 mg/dL, soluble interleukin-2 receptor 58,776 U/mL. Blood gas analysis demonstrated metabolic acidosis: pH 7.15, pCO₂ 22.9 mmHg, HCO₃⁻ 7.9 mmol/L, base excess -19.3 mEq/L, lactate 11.3 mmol/L. Although serum calcium was not elevated, serum inorganic phosphorus was elevated to 5.8 mg/dL. She was seronegative for human immunodeficiency virus. Serum CMV antigen (CMV C7-HRP pp65) was positive (149 cells/50,000 WBCs). High titers of CMV immunoglobulin (Ig) M and IgG confirmed the diagnosis. Antibodies to HTLV-I were positive by CLEIA, which was confirmed by Southern blot. Lymphocyte analysis revealed CD3 (+), CD4 (+), CD8 (-), and CD25 (+). Based on these hematological data, we made the diagnosis of ATL.

Her electrocardiogram was normal, and ultrasonography showed the presence of ascites in the abdominal cavity. CT revealed pneumoperitoneum and parasplenic, perihepatic, and paracolic effusions (Fig. 1A). Based on the clinical diagnosis of diffuse peritonitis due to intestinal perforation,

emergency surgical intervention was required. At laparotomy, close observation revealed a few pinhole-like perforations in the small intestine, which were turning a white color in the serous membrane with purulent serosal exudate (Fig. 1B). An approximate 30 cm partial resection of the intestine and creation of ileostomy was performed. Pathological examination of the resected specimen showed multiple areas of mucosal ulceration with diameters ranging from 2 to 3 cm. Microscopically, the ulcer bases and edges of perforation consisted of granulation tissue with acute and chronic inflammation (Fig. 1C). Immunohistochemistry for CMV antigen revealed positive staining of inclusion in the intestinal stromal cells (Fig. 1D).

During the first six postoperative days, she seemed to remain stable until she became septic again and was stabilized with catecholamine. Multiple scenarios in which septic shock can be induced such as re-rupture of the intestinal tract, catheter-related blood stream infection, meningitis, and opportunistic infective diseases were considered. Although we did not know why her vital signs became unstable again, the etiology of mucosal impaired barrier-associated CMV infection induced by bacterial trans-located infection was hypothesized. She developed acute renal failure requiring continuous hemodialysis and had ongoing blood loss caused by intestinal hemorrhage from intestinal mucosal injury, requiring replacement with ten units of packed red blood cells. Active bleeding was not observed in gastro-duodenal endoscopy. Despite aggressive antibiotic and anti-viral treat-

ment, the patient rapidly deteriorated. To assess unconsciousness, a cerebrospinal fluid test was performed and revealed the following: glucose 109 mg/dL, protein 72 mg/dL, a cell count of 21/3 μ L, polymorphonucleocytes; 0%, mononucleocytes; 100%. No malignancy was detected in the cerebrospinal fluid. Her clinical condition gradually deteriorated after surgery as she developed acute renal failure and septic shock and died 28 days after surgery. An autopsy was not performed consistent with the family's wishes.

DISCUSSION

A DULT T-CELL LEUKEMIA is a malignant transformation of the CD4 subset of peripheral T cells caused by HTLV-1, which was first isolated by Gallo's group from cultured cells from one patient with an aggressive variant of mycosis fungoides and one with Sézary's syndrome.⁴ A definite diagnosis of ATL is based on the presence of HTLV-I proviral DNA in the tumor-cell DNA. Familial occurrence of ATL is common, as HTLV-I infection is caused by transmission of live infected lymphocytes from mother to child, from man to woman, or by transfusion.

The predominant physical findings at onset of ATL are enlargement of the peripheral lymph nodes (60% of patients), liver (26%), and spleen (22%) and skin lesions (39%). Hypercalcemia is also common (32%). The symptoms and signs include abdominal pain, diarrhea, pleural effusion, ascites, cough, sputum, and abnormal shadow on chest radiographs.

Adult T-cell leukemia shows diverse clinical features but can be divided into four subtypes: acute, chronic, smoldering, and lymphoma.⁵ The acute and lymphoma types are resistant to chemotherapy and have a poor prognosis. ATL should be treated with combination chemotherapy with the aim of achieving a cure. However, in general, the results of ATL treatment in the past have been poor, and 50% of

patients with hypercalcaemia, high lactate dehydrogenase activity, and very high WBC counts die within 6 months.⁶

Adult T-cell leukemia cells infiltrate the small intestine, stomach, and colon and cause gastrointestinal manifestation.⁷ In severe cases, malignant cells infiltrate diffusely into the lamina propria, serosa, and mesenterium. As a result of this invasion, ATL might cause gastrointestinal perforation. However, more frequently, opportunistic infections are observed in individuals with ATL, causing gastrointestinal symptoms.

In leukemia patients, infection of the gastrointestinal tract with CMV, a member of the herpes virus group, is common. The most common site is the colon, followed by the duodenum, stomach, esophagus, and rarely the small intestine, accounting for only 4.3% of all CMV gastrointestinal tract infections.⁸ Gastrointestinal tract infection with CMV typically presents with anorexia, fever, diarrhea, abdominal pain, wasting, and weight loss and is associated with a wide range of lesions, ranging from mild inflammation and erosions to esophageal and enterocolic ulcers.⁹ Typically, pathological findings of CMV infection include acute and chronic inflammation along with vasculitis and large basophilic intranuclear and intracytoplasmic inclusion bodies within macrophages and endothelial cells, which may cause bowel ischemia and perforation.

In the present case, CMV infection in the small intestine seemed to be a secondary superinfection in areas of pre-existing inflammation because it was found only in areas of ulceration and perforation. Although ATL cells are known to cause mucosal injury, apparent ATL cell infiltration was not observed in resected specimens in the present case.

To the best of our knowledge, only five cases of ATL with gastrointestinal perforation have ever been reported (Table 1). Two cases had CMV infection and one case had intestinal tuberculosis. Three of the five cases died by 15 days after surgery, indicating a poor prognosis. The remain-

Table 1. Review of adult T-cell leukemia (ATL) patients with gastrointestinal perforation. Table summarizes cases of small bowel perforation reported in ATL

Author	Year	Age	Sex	Treatment	Prognosis
Nabeshima <i>et al.</i>	1992	34	M	Operation	Died 5 days POD
Ohno <i>et al.</i>	1996	57	M	Chemotherapy + Operation	Died 15 days POD
Kasahara <i>et al.</i>	2000	67	M	Operation + Chemotherapy	Died 7 months POD
Isomoto <i>et al.</i>	2001	39	F	Operation + Chemotherapy	Died 14 months POD
Murakami <i>et al.</i>	2011	75	M	Chemotherapy + Operation	Died 15 days POD

POD, postoperative days.

ing two cases died after 7 months and 14 months. ATL patients with intestinal perforation do not seem to be able to survive for long.

CONCLUSION

ADULT T-CELL LEUKEMIA patients may present acute abdominal pain due to intestinal perforation caused by CMV infection. When treating ATL patients, we should be aware of CMV infection as one of the pathogens causing acute abdominal crises. Earlier recognition and treatment of CMV-related gastrointestinal disease may prevent the disastrous complication of gastrointestinal perforation.

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CONFLICT OF INTERESTS

NONE.

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