Cytomegalovirus infection in a T-cell lymphoma patient presenting with multiple gastrointestinal ulcers: a case report

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ABSTRACT
Background and study aims Gastrointestinal ulcers are responsible for a wide spectrum of diseases. Infection, drug-induced enteritis, malignancy, vasculitis and inflammatory bowel disease are the most common causes; their clinical expression often varies according to the site and severity of intestinal involvement. We report on a 68-year-old male presenting with dyspepsia and melena and multiple gastrointestinal ulcers on endoscopy. We could not establish diagnosis of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) despite multiple biopsies taken on several endoscopic sessions, and cytomegalovirus (CMV) infection was documented by presence of inclusion bodies on pathology. The immunohistochemical study showed a mixture of B lymphocytes and predominantly T lymphocytes, negative for cluster of differentiation (CD)7. Southern blot gene rearrangement was positive for T-cell receptor beta. Our patient eventually expired from a massive gastrointestinal hemorrhage following four cycles of chemotherapy. We wish to emphasize that a CMV infection, as a comorbidity, can potentially mask and delay diagnosis of PTCL-NOS, especially in cases with aberrant immunophenotype presentation.

Introduction
Gastrointestinal ulcers are caused by a wide spectrum of diseases. Infection, drug-induced enteritis, malignancy, vasculitis and inflammatory bowel disease are the most common afflictions. Diagnosis of the above diseases, especially peripheral T-cell lymphoma, is often very challenging, with non-specificity of clinical symptoms and radiologic findings complicated by presence of comorbidities; thus, diagnosis relies on yield of tissue biopsy.

Cytomegalovirus infection (CMV) in immunocompromised patients has been extensively documented in the medical literature, but relatively less in apparently immunocompetent patients. We report a case of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) presenting with multiple gastrointestinal ulcers, which was difficult to diagnose with conventional pathology and concomitant cytomegalovirus (CMV) infection.

Case report
A 68-year-old male patient with a past history of hypertension and coronary artery disease was admitted with dyspepsia and melena and a weight loss of approximately 4 kg for the past 2 months, exacerbated with melena for the last 10 days and denying symptoms of night sweats or fever.

Physical examination was unremarkable. His initial blood work revealed a white blood cell (WBC) count of 10.7 ×10^9/L, with 87% neutrophils, mild anemia (99 g/L) and high platelet count (391 ×10^9/L). Lactate dehydrogenase and tumor markers were within normal limits. C-reactive protein (CRP) was mildly elevated.

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raised (23.8 mg/L). The patient was initially treated with fluid therapy and intravenous proton pump inhibitors (PPI). Esopha-
gastroduodenoscopy (EGD), initially performed due to mel-
ena, revealed multiple duodenal ulcers, atypical of peptic ulcer
disease and refractory to PPI (Fig. 1a–c). Distal ileal ulcers
( Fig. 1j–l) were visible on colonoscopy performed the next
day. Taking into account the high prevalence of tuberculosis in
China, the patient was tested for antibodies for Mycobacterium
tuberculosis (TB) and the Mantoux test was performed, both of
which were negative. TB T-SPOT was weakly positive and HIV
2 kg. Blood tests showed an elevated WBC count (10.48 ×10^9/L). Testing was negative. Given poor specificity of endoscopic findings, a computed tomography scan was performed which demonstrated inflammatory changes involving the greater curvature of stomach, duodenal bulb, the descending part of the duodenum and proximal ileocecum, with enlarged retroperitoneal and mesenteric lymph nodes (Fig. 2).

Microscopic examination of multiple biopsies of the ulcers revealed CMV inclusion bodies and infiltration of the muscularis propria with predominantly neutrophils and moderate infiltration of eosinophils and lymphocytes, with no significant evidence of lymphoma. CMV was negative for IgM but positive for IgG, with a CMV DNA viral load of 2.31 ×10^3 copies/mL. Prompt therapy for presumed gastrointestinal CMV disease was initiated, consisting of intravenous (IV) administration of ganciclovir 5 mg/kg every 12 hours for the first 2 weeks and IV immune globulin 500 mg/kg for 3 days, along with gastroprotective treatment with PPIs and antacids. The patient was then discharged on oral ganciclovir 1 g, TID for 2 weeks after repeat endoscopy showed mucosal healing. (Fig. 1d–f, Fig. 1m–o).

However, 1 week after finishing the course of antivirals, the patient was readmitted for watery diarrhea and a weight loss of 2 kg. Blood tests showed an elevated WBC count (10.48 ×10^9/L) and CRP (64.7 mg/L) while the stool bacillus/coccus ratio was normal and fecal examination for fungi and parasites was negative. Testing for Clostridium difficile was not performed. Repeat EGD and colonoscopy showed mucosal congestion with ulcer of relatively decreased severity. Because the superficial lymph nodes located deeply and not palpable were not amenable to biopsy, a bone marrow trephine biopsy was done. It displayed no evidence of lymphoma.

Temporary relief and further decrease of superficial lymph nodes were achieved after prednisone was added due to increased severity of the patient’s symptoms, with a decrease in WBC count (7.85 ×10^9/L) and CRP (3.8 mg/L). Thereafter, gastrointestinal vasculitis with CMV superinfection was strongly suspected.

Endoscopic assessment was repeated three more times on a monthly interval, revealing progressively healing duodenal ulcers (Fig. 1g–i) and ileal ulcers (Fig. 1p–r) and appearance of new lesions (Fig. 1g). The immunohistochemical study showed an admixture of B lymphocytes and predominantly T lymphocytes. Lymphoid cells were negative for CD7 and CD56 and strongly positive for CD2, CD3, CD5, CD79a and CD20 and partially positive for CD30 (Fig. 3). The proliferation fraction, as measured by Ki-67 nuclear staining, was 40%. The Epstein-Barr virus-encoded small RNAs (EBER) by in situ hybridization stain was equivocal.

After liaising multiple times with the pathologists, who could not establish a definite diagnosis of lymphoma, it was recommended to perform a Southern blot gene rearrangement, which was positive for T-cell receptor beta (TCR). A positron emission tomography scan revealed hypermetabolic cells in the duodenum, ileum, Waldeyer’s ring and spleen (Fig. 4).

Finally, we diagnosed the patient as suffering with peripheral T-cell lymphoma, with a PIT (prognostic index for PTCL-NOS) score of 2, belonging to the risk group 3. Subsequently, the patient was started on a CHOP (cyclophosphamide, Adriamycin, vincristine, prednisone) chemotherapy regimen, based on standard non-Hodgkin lymphoma protocol. Sadly, after four cycles, the patient expired from massive gastrointestinal hemorrhage, presumed to be due to vascular destruction and tissue necrosis associated with progression of malignancy, with new lesions appearing despite chemotherapy (Fig. 1g).

Discussion
Gastrointestinal ulcers are responsible for a wide spectrum of diseases. Based on the abdominal CT and endoscopic findings, the differential diagnosis should include Crohn’s disease, vasculitis, tuberculosis and CMV colitis. Taking into consideration the patient’s age, endoscopic findings, tissue biopsy results and our inability to induce substantial remission with both antiviral and steroid therapy, Crohn’s disease was excluded. Similarly, vasculitis, especially Behcet’s disease, was also ruled out with lack of other systemic organ involvement, normal immunoglobulin levels and negative testing for anti-neutrophil cytoplasm antibody (ANCA). Intestinal tuberculosis was ruled out with a negative Mantoux test, weakly positive T-SPOT for TB, no antibodies for TB, lack of evidence on endoscopy and pathology and no evidence of pulmonary lesions found on chest CT. Both characteristic serpiginous wel-demarcated and infiltrative ulcerations as described in CMV colitis by TH So, JH Kim, SY Ko, et al [2] were found on endoscopy. A CMV DNA viral load of 2.31 × 103 copies/mL, endoscopic and immunohistochemical staining evidence were suggestive of CMV colitis. In our case, latent CMV reactivation was assumed to be caused by poor immune status due to older age and poor feeding status.

CMV infections have traditionally been associated with immunosuppressive states such as AIDS, malignancy and transplantation and in patients under treatment with immunosuppressive drugs such as glucocorticoids or chemotherapeutics [3]. Recently, an increasing number of cases [3, 4] have been
published, suggesting that CMV infection can also be observed in apparently immunocompetent individuals, especially the elderly, with most patients older than age 55. This has been attributed to impaired cellular and humoral immunity as well as the relatively higher prevalence of comorbidities [5] such as diabetes, chronic renal failure, ischemic heart disease [2], chronic obstructive pulmonary disease [6] and rheumatic diseases.

Our case demonstrates how CMV infection can potentially mask and delay diagnosis of PTCL, although the exact mechanism is still unknown. T-cell–mediated immunity is regarded as the host’s major defense against CMV, as evidenced by increased prevalence of life-threatening CMV disease in HIV patients with low CD4 levels [5, 7]. Both Hodgkin disease (HD) and NHL lead to decreased host CMV-directed cellular immunity [8, 9]. Both B-cell and T-cell NHL can lead to a relative state

▶ Fig. 3 a–f Diffuse infiltration of the lamina propria, accompanied by a mixed infiltrate of neutrophils, eosinophils and plasma cells and moderate to large lymphoid cells with prominent nucleoli and mitotic figures (a). Histological appearance with Hematoxylin and Eosin (H&E stain) and corresponding immunohistochemical staining (b–j) using the immunoperoxidase method. The immunostains demonstrated infiltrating lymphocytes to be strongly positive for CD2, CD3, CD5 and pan B cell markers CD20 and CD79a, partially positive for CD30 and negative for CD7. Intranuclear inclusions typical of cytomegalovirus infection were also found (i).
of immunosuppression, which facilitates opportunistic CMV infection. Such CMV superinfection is not an uncommon finding in patients with lymphoma; a retrospective study by Torres et al [8] screened 83 cases of NHL, of whom 76 (93%) had CMV antigenemia or CMV disease, while out of 82 cases of HD, only 6 (7%) were positive. CMV infection is hence significantly more common among patients with NHL, while it was also reported to be highly predominant in patients with active (88%) stage III/IV lymphoma (84%). This may be because as NHL often presents clinically at a relatively more advanced stage, incidence of opportunistic CMV infection may thus increase when the general condition of the patient deteriorates, which is usually seen in active and advanced disease. Moreover, gastrointestinal involvement was documented in six out of 44 patients (13%) with CMV disease compared to studies involving immunocompetent patients, where the gastrointestinal tract was the most common site of CMV infection [7].

In the current case, proper diagnosis could not be established without performing multiple biopsies at multiple intervals, establishing a multiple disciplinary team and gene rearrangement studies. Despite the clinical picture of an elderly patient presenting with multiple gastrointestinal ulcers and extensive lymphadenopathy, we had minimal evidence of lymphoma, because the patient presented with mild weight loss, no history of fever and sweating, and normal LDH and globulin levels.

**Conclusion**

The fact that PTCL-NOS has been associated with protean clinical, genetic, and immunophenotypic features mirrors our poor understanding of lymphomas and the immune system. We recommend ruling out comorbidities associated with immune dysfunction, especially active advanced lymphoma in elderly patients presenting with gastrointestinal ulcers who are positive for CMV infection. We report herein on a rare case of PTCL-NOS and wish to highlight the range of difficulties and challenges faced by modern clinicians in establishing a diagnosis of lymphoma; in particular, cases with aberrant immunophenotypes can easily be missed if the biopsied tissue pathology is atypical.

**Competing interests**

None
References