

## Case Report

# Gastric Perforation in a 60-Year-Old Woman with CMV Gastritis and Amphetamine Abuse Led to Death

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## Keywords

Amphetamine · Cytomegalovirus infections · Intensive care units · Stomach diseases

## Abstract

Gastric perforation as a multi-etiological disease is a full-thickness injury of the stomach wall. In this case report, we presented a 60-year-old woman with a history of suicidal behavior referred to the emergency unit with a decreased level of consciousness due to the multidrug consumption (amphetamine and benzodiazepine). Passing 3 days of admission in the intensive care unit, the patient represented severe abdominal distension, lack of defecation, and the absence of bowel sound, which suggested the gastrointestinal (GI) complication. Abdominal-pelvic sonography followed by laparotomy confirmed the gastric perforation, which finally led to the patient's death. Pathological analysis showed that the vast involvement of cytomegalovirus (CMV) in the patient's GI tract resulted in several peptic ulcers. The first report of gastric perforation-related death arises from the partnership of CMV infection and drug poisoning.

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Published by S. Karger AG, Basel

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## Introduction

Gastric perforation arises from injury or insult to the gastric wall's mucosa, which leads to the disruption of the closed gastrointestinal (GI) system. This disruption exposes the GI contents to the organs within the peritoneal cavity, resulting in peritonitis as a life-threatening event. The manifestation of gastric perforation is presented by distension and abdominal pain. The most common causes of gastric perforation include infections such as cytomegalovirus (CMV), inflammation, obstruction, trauma, drug poisoning, or an invasive procedure [1].

CMV infection of GI may affect anywhere from the mouth to the anus, but the most common site is the colon (47%) and after that, the duodenum (21.7%), stomach (17.4%), esophagus (8.7%), and small bowel (4.3%) [2]. Common symptoms of infected GI with CMV are fever, diarrhea, abdominal pain, and weight loss, typically due to gastritis and enteritis. CMV may also lead to ulceration and perforation mediated by ischemia. However, CMV is often seen in immunocompromised patients, but the prevalence of CMV in immunocompetent hosts is not common [3].

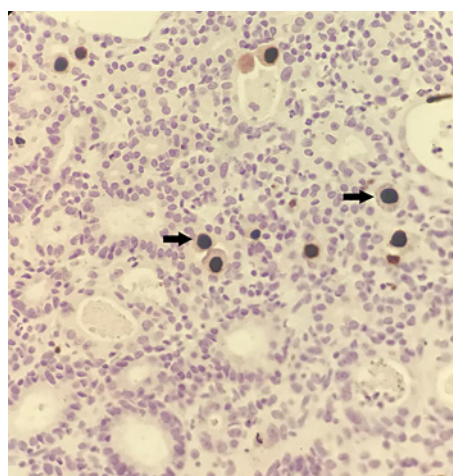
Drug-related GI toxicity is the other common cause of gastric perforation. Amphetamine, phenothiazines, antidepressants, narcotics, and calcium channel blockers are the most common pharmaceutical causes of GI perforation [4]. The agonist activity of amphetamine alpha-adrenergic receptors in the gastric and mesenteric arteries leads to intense vasoconstriction that causes focal ischemia – gangrene arising from severe ischemia results in gastric ulceration and perforation [5].

The incidence of GI perforation caused by coinciding CMV infection and drug poisoning has not been reported. However, in this study, we represent a case report in which a CMV-infected patient experienced a GI perforation due to drug poisoning. It seems that previous CMV infection underlies the GI perforation induced by drug poisoning. The concomitance of the CMV infection with drug poisoning resulted in the poor prognosis of GI perforation, which led to the mentioned patient's death.

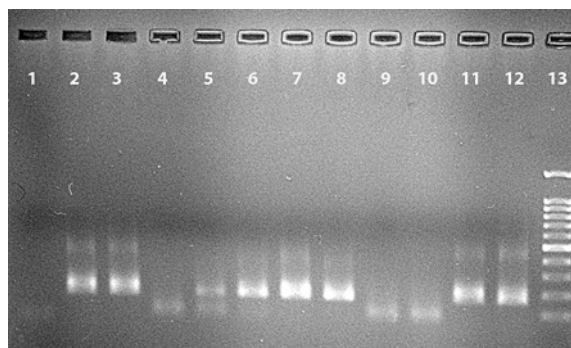
## Case Report

A 60-year-old patient who had attempted suicide was referred to the emergency department due to a low level of consciousness with a Glasgow Coma Scale score of 11. The patient's history revealed that she had been a known case of bipolar disorder, hyperlipidemia, osteoporosis, renal stone, and water pipe smoker. The scar of an electrical burning on her right hand showed that she had a history of suicidal behavior. The patient was admitted to an intensive care unit with dizziness and drowsiness due to drug poisoning. The analysis of the patient's urine demonstrated the presence of amphetamine and benzodiazepine. On the second day of admission, the Glasgow Coma Scale score decreased to nine and then completely fell to three. The cardiac analysis findings showed the right bundle branch block and complete bundle branch block resulted from amphetamine overdose. For the elimination of amphetamine from blood circulation, several rounds of therapeutic hemodialysis had been performed. On the third day of admission, severe abdominal distension, lack of defecation, and the absence of bowel sound had occurred. The first abdominal-pelvic sonography showed a multiloculated fluid collection in the abdominal-pelvic cavity, which suggested the GI perforation and severe peritonitis. Immediately, the patient was transferred to the operation room, and laparotomy confirmed the perforation of the stomach and acute peritonitis. During the surgery, the bowel adhesion and stomach perforation were repaired. Besides, retro-gastric and sub-diaphragmatic fluid collection along with generalized peritonitis were removed by drainage. A gall bladder specimen's pathological analysis showed severe acute or chronic acalculous cholecystitis with focal mucosal necrosis.

**Fig. 1.** Detection of CMV infection by IHC. A stomach tissue section stained with a monoclonal antibody directed against CMV pp65 antigen is shown. Arrows indicate IHC-positive cells. IHC staining using a monoclonal antibody against CMV pp65 antigen (>2 cells stained; magnification,  $\times 1,000$ ). IHC, immunohistochemistry.



**Fig. 2.** Agarose gel electrophoresis of the PCR products obtained from FFPE tissues using the specific primers amplified a 177-bp fragment within the coding region of gB. Lane 1: non-template control, lane 2 and 3: 177-bp CMV DNA fragment in the gall bladder, lanes 4–11: 177-bp CMV DNA fragment in gall bladder in perforation site of the gastric wall, lane 12: 177-bp positive control, and lane 13: 100-bp DNA marker.



Passing 2 weeks after the first surgery, the patient experienced severe constipation, abdominal distention, ascites, and edema. The second abdominal-pelvic sonography revealed the multicoated fluid collection and septation in the abdominal-pelvic cavity, which necessitated the second laparotomy. After the second surgery, sepsis disseminated intravascular coagulation and the increase in serum BUN and creatinine levels, resulting in renal failure, occurred. Finally, cardiorespiratory arrest led to patient death related to multidrug poisoning (alprazolam and amphetamine), metabolic encephalopathy, perforation of peptic ulcers, and sepsis. The pathology report of partial gastrectomy revealed gastric perforation with severe CMV gastritis, ulceration, and foreign body-type giant cell reaction. Immunohistochemistry staining using a monoclonal antibody against CMV pp65 antigen indicated CMV immunoreactivity with brownish areas (shown in Fig. 1). A nested-PCR [6] confirmed CMV infection for CMV DNA in gall bladder specimens and gastric wall biopsy (shown in Fig. 2).

## Discussion

Gastrointestinal perforation requires full-thickness injury of the gastric and bowel wall that causes the release of GI contents into the peritoneal cavity. The perforation may be due to various etiologies, including acid peptic disease, drugs, surgery or instrumentation (particularly with cautery), blunt or penetrating trauma, and bowel obstruction. Neoplasms are the

most common cause of perforation by direct penetration of the tumor through the GI wall. Inflammation (such as Crohn's disease), infections (CMV), drugs such as indomethacin and amphetamine, metabolic conditions (homocystinuria), congenital defects (Meckel's diverticulum), and vascular diseases (granulomatous arteritis) are rare etiologies of GI perforation. Typical perforation symptoms include severe abdominal pain, fever, constipation, nausea, and vomiting [1].

CMV has been found as the leading cause of nontraumatic perforation of the GI tract in immunocompromised patients, but it is not common in immunocompetent individuals. Other infection-related etiologies include tuberculosis, *Entamoeba histolytica*, and *Ascaris lumbricoides* [7].

CMV, as a double-stranded DNA virus, belongs to the herpes virus group. This infection is transmitted during birth, breastfeeding, sexual contact, organ transplant, or transfusion. This viral disease is prevalent in adults by involving 50–80% of the general population, representing an antibody to CMV by the age of 35 years [8].

The virus in CMV-infected healthy adults expects to remain inactive with no further symptoms. The weakening of the immune system may lead to the reactivation of CMV in an immunocompetent individual. The underlying factors of CMV-mediated GI disease in some immunocompetent patients are unclear. One hypothesis suggested that inflammation mediated by mucosal injury of GI may promote the migration of CMV-infected macrophages [9].

CMV infection causes GI ischemia due to submucosal vasculitis and thrombosis. Besides, the thinning of the GI wall may promote subsequent perforation and gangrene [7]. The diagnosis is made by histopathological analysis, but the gold standard for diagnosis is the discovery of cytomegalic cells using H&E. Cytomegalic cells have cow eye inclusions with a surrounding halo [10].

Amphetamine is a central nervous system stimulant used in the treatment of attention deficit hyperactivity disorder, narcolepsy, and obesity. Amphetamine can cause GI ischemia, thereby leading to ulceration and perforation by multiple mechanisms. The most important of these mechanisms is an agonist activity of amphetamine at the vasoconstrictive alpha-adrenergic receptors in the gastric and mesenteric arteries. Amphetamine also exerts vasculotoxicity by enhancing endothelial permeability to low-density lipoprotein, which results in the regulated expression of endothelial adhesion molecules [11]. These events subsequently lead to leukocyte migration and proliferation of adventitial mast cells. Its inhibitory effect on gastric motility augments the ulcerogenic potential of amphetamine. Delaying in gastric evacuation may increase acid exposure times, hence prompting ulcer formation [12].

It has been shown that amphetamine in a certain amount is able to deduce in thymus and spleen cellularity and in peripheral T-lymphocyte population in mice [13]. It has been found that amphetamine inhibits T-cell proliferation. Additionally, amphetamine reduced their ability to develop immunity and passively transfer it to *Listeria monocytogenes*.

There is evidence that stimulants, such as methamphetamine, suppress the host's immune system and have profound immunological effects [14]. As amphetamine can lower or inhibit immunity, it is possible that in our case CMV was activated as a result of a decrease in immunity and stimulated gastric perforation caused by the drug.

In this case, previous CMV-related ulcers worsen the prognosis of perforation mediated by amphetamine-induced toxicity. The coincidence of both these two factors resulted in full wall gastric perforation and severe peritonitis.

Surgery interventions are a recommended approach for cases with clinical signs of peritonitis or perforation [15]. Observation of free fluid in the abdominal-pelvic cavity of this patient necessitated the laparotomy. Intraoperative findings and the hemodynamic

status of the patient determine the procedure to be carried out during the surgery. These procedures may include resection with primary anastomosis as well as the bypass of the ileum or colon. However, surgery is the definitive treatment in many cases, but it carries 6% morbidity, and up to 30%, mortality depends on the etiologies of gastric ischemia [16].

Morbidity and mortality related to GI perforation resulting from CMV gastroenteritis in immunocompetent patients are high with low life expectancy. Amphetamine-associated gastric perforation also is a life-threatening event with a high mortality rate. As in the mentioned case, the coincidence of CMV gastroenteritis and amphetamine drug poisoning worsens the prognosis and leads to patient death.

### Acknowledgments

The authors are thankful to our colleagues in the division of pathology, Ali-Asghar diagnostic laboratory, Shiraz University of Medical Sciences, who provided expertise that greatly assisted the research.

### Statement of Ethics

The study was approved by the Research Ethics Committee of Shiraz University of Medical Sciences (Ref. No. IR.SUMS.REC. 1394.S371). Since this is a noninterventional, retrospective, subject-anonymized study, the Research Ethics Committee specifically waived the requirement for written patient consent.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Funding Sources

There was no funding from any sources to report for this submission.

### Author Contributions

A. Behzad Behbahani presented the original idea and designed the study. N. Seyyedi carried out the experiment and contributed to manuscript writing and editing. A. Farhadi and F. Asadian supervised experimental performance. F. Khajeha provided advice as a pathology consultant. F. Safari contributed to experimental performance.

### Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.



## References

- 1 Shin D, Rahimi H, Haroon S, Merritt A, Vemula A, Noronha A, et al. Imaging of gastrointestinal tract perforation. *Radiol Clin North Am*. 2020 Jan 1;58(1):19–44. Available from: <https://pubmed.ncbi.nlm.nih.gov/31731901/>
- 2 Kawate S, Ohwada S, Sano T, Kawashima Y, Kishikawa I, Tomizawa N, et al. Ileal perforation caused by cytomegalovirus infection in a patient with recurrent gastric cancer: report of a case. *Surg Today*. 2002;32(12):1088–90. Available from: <https://pubmed.ncbi.nlm.nih.gov/12541029/>
- 3 Barling DR, Tucker S, Varia H, Isaacs P. Large bowel perforation secondary to CMV colitis: an unusual primary presentation of HIV infection. *BMJ Case Rep*. 2016;2016:bcr2016217221. Available from: <https://pubmed.ncbi.nlm.nih.gov/28003231/>
- 4 Cappell MS. Colonic toxicity of administered drugs and chemicals. *Am J Gastroenterol*. 2004 Jun;99(6):1175–90. Available from: <https://pubmed.ncbi.nlm.nih.gov/15180742/>
- 5 Yahchouchy E, Debet A, Fingerhut A. Crack cocaine-related prepyloric perforation treated laparoscopically. *Surg Endosc*. 2002;16(1):220. Available from: <https://pubmed.ncbi.nlm.nih.gov/11961661/>
- 6 Kühn JE, Wendland T, Eggers HJ, Lorentzen E, Wieland U, Eing B, et al. Quantitation of human cytomegalovirus genomes in the brain of AIDS patients. *J Med Virol*. 1995;47(1):70–82. Available from: <https://pubmed.ncbi.nlm.nih.gov/8551263/>
- 7 Gutiérrez-Delgado EM, Villanueva-Lozano H, García Rojas-Acosta MJ, Miranda-Maldonado IC, Ramos-Jiménez J. A case report of small bowel perforation secondary to cytomegalovirus related immune reconstitution inflammatory syndrome in an AIDS patient. *Ann Med Surg*. 2016 Jan 1;13:20–3. Available from: <https://pubmed.ncbi.nlm.nih.gov/28018589/>
- 8 Makker J, Bajantri B, Sakam S, Chilimuri S. Cytomegalovirus related fatal duodenal diverticular bleeding: case report and literature review. *World J Gastroenterol*. 2016 Aug 21;22(31):7166–74. Available from: <https://pubmed.ncbi.nlm.nih.gov/27610026/>
- 9 Jun YJ, Sim J, Ahn HI, Han H, Kim H, Yi K, et al. Cytomegalovirus enteritis with jejunal perforation in a patient with endometrial adenocarcinoma. *World J Clin cases*. 2013;1(7):220. Available from: <https://pubmed.ncbi.nlm.nih.gov/24340271/>
- 10 Liao X, Reed SL, Lin GY. Immunostaining detection of cytomegalovirus in gastrointestinal biopsies: clinicopathological correlation at a large academic health system. *Gastroenterology Res*. 2016;9(6):92–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/28058077/>
- 11 Yamamoto BK, Moszczynska A, Gudelsky GA. Amphetamine toxicities: classical and emerging mechanisms. *Ann N Y Acad Sci*. 2010;1187:101–21. Available from: <https://pubmed.ncbi.nlm.nih.gov/20201848/>
- 12 Doong ML, Lu CC, Kau MM, Tsai SC, Chiao YC, Chen JJ, et al. Inhibition of gastric emptying and intestinal transit by amphetamine through a mechanism involving an increased secretion of CCK in male rats. *Br J Pharmacol*. 1998;124(6):1123–30. Available from: <https://pubmed.ncbi.nlm.nih.gov/9720782/>
- 13 Freire-Garabal M, Balboa JL, Núñez MJ, Castaño MT, Llovo JB, Fernández-Rial JC, et al. Effects of amphetamine on T-cell immune response in mice. *Life Sci*. 1991;49(16):PL107–12. Available from: <https://pubmed.ncbi.nlm.nih.gov/1910138/>
- 14 Potula R, Haldar B, Cenna JM, Sriram U, Fan S. Methamphetamine alters T cell cycle entry and progression: role in immune dysfunction. *Cell Death Discov*. 2018 Mar 19;4(1):44–13. Available from: <https://www.nature.com/articles/s41420-018-0045-6>
- 15 Vashistha N, Singhal D, Makkar G, Chakravarty S, Raj V. Management of giant gastric ulcer perforation: report of a case and review of the literature. *Case Rep Surg*. 2016;2016:4681989. Available from: <https://pubmed.ncbi.nlm.nih.gov/28050305/>
- 16 Shin R, Lee SM, Sohn B, Lee DW, Song I, Chai YJ, et al. Predictors of morbidity and mortality after surgery for intestinal perforation. *Ann Coloproctol*. 2016 Dec 1;32(6):221–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/28119865/>