

Successful endoscopic hemoclippping and conservative management for typhoid fever complicated by massive intestinal bleeding and acute pancreatitis

Case report

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Abstract

Rationale: Massive intestinal bleeding as a complication of typhoid fever has rarely been reported due to the advent of antibiotics. In addition, although several literatures have been issued on the use and success of endoscopic modalities in cases of massive typhoid ulcer bleeding, few have described hemostasis by endoscopic hemoclippping.

Patient concerns: We describe a case of a 61-year-old Korean female who presented acute episodes of massive lower gastrointestinal bleeding during admission to local hospital with a provisional diagnosis of acute gastroenteritis. She had returned from a trip to Southeast Asia 3 weeks prior to admission

Diagnoses: After the result of blood culture was identified as *Salmonella typhi*, we could make a diagnosis of typhoid fever complicated by massive intestinal bleeding and acute pancreatitis based on elevated serum lipase and computerized tomography (CT) findings.

Interventions: The patient was treated successfully by two repeat colonoscopic hemostasis procedures involving the deployment of hemoclips on ulcers in the terminal ileum and 10-day course of intravenous ciprofloxacin

Outcomes: The patient was stable and reported no further episodes of intestinal bleeding or fever during the follow-up time. In addition, acute pancreatitis, which is a rare complication of typhoid fever, resolved without complication on follow-up CT and a laboratory study.

Lessons: Considering the risk of procedure-related complications such as perforation of the small intestine wall, which become thin and friable due to ulceration, mechanical hemostasis methods, such as hemoclippping, might be safer than coagulation, when the bleeding spot can be identified and is not multiple, as in our case. In addition, our case demonstrates that *S. typhi* should be considered in the differential diagnosis of massive lower gastrointestinal hemorrhage, especially in the setting of recent travel in South or Southeast Asia.

Abbreviation: CT = computerized tomography.

Keywords: acute pancreatitis, intestinal hemorrhage, *Salmonella typhi*, typhoid fever, typhoid ulcer bleeding

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1. Introduction

Typhoid fever or enteric fever is a systemic infection caused by the gram-negative enteroinvasive organism *Salmonella typhi*. Typhoid fever is a fecal-oral transmissible disease, and thus, is prone to occur in overcrowded conditions associated with poor hygiene and untreated water.^[1] Despite effective antimicrobial agents, typhoid fever remains endemic and represents an important public health problem in most developing countries. While incidences of endogenous *S. typhi* infection have declined in most developed countries, the number of case reports issued has increased, primarily due to travel and immigration,^[2] and reflects the high global incidence of *S. typhi*,^[3,4] particularly among young children in South Asia.^[4]

Although the disease usually manifests as hectic fever with chills and loose stools, intestinal hemorrhage and perforation are well-known complications, which are normally encountered during the third week of the disease.^[5] Typhoid ulcers may penetrate intestinal wall submucosa and enlarge in size, and if

they erode a vessel, they can cause severe intestinal bleeding. Ulcers also cause bowel wall thinning, and hence, present risk of perforation. In the pre-antibiotic era, these complications were quite common, but today, given the advent of fluoroquinolones and third-generation cephalosporins, these complications are relatively rare. In the majority of cases, intestinal bleeding is usually mild and can be treated conservatively, but life-threatening massive intestinal bleeding can occur and usually requires exploratory laparotomy. Recently, modern advances like angioembolization and endoscopic therapy, have reduced rates of surgery,^[6,7] but little information is available in the literature regarding the use or success of endoscopic modalities in cases of massive typhoid ulcer bleeding.

S. typhi causes systemic infections characterized by bacterial penetration of the intestinal barrier and extraintestinal dissemination to liver and spleen, where the microorganisms survive and replicate in professional phagocytes.^[8] Thus, typhoid fever has been known to lead to diffuse organ involvement to thyroid, bone, heart, pericardium, lung, kidney, liver, and spleen.^[9] However, acute pancreatitis as a recognized complication of typhoid fever is rather rare. In fact, fewer than 10 cases of proven pancreatitis in *S. typhi* infection have been published in the English literature.^[10–15]

Recently, we experienced a rare case of typhoid fever with massive lower gastrointestinal bleeding, acute pancreatitis, and ascites. Here, we describe this case, which was treated successfully by endoscopic hemoclip hemostasis and conservative management, and extensively review relevant literature regarding the endoscopic treatment of intestinal bleeding in patients with typhoid fever. In addition, we review and discuss acute pancreatitis complicating typhoid fever. This case report was approved by the Institutional Review Board of Yeungnam University Hospital (IRB No. 2018–10–013), and the patient signed informed consent to publication of her clinical details and/or clinical images.

2. Case presentation

A 61-year-old Korean woman presented with complaints of fever, which was intermittent, high grade, and associated with chills, malaise, generalized abdominal pain, nausea, and diarrhea of 1-week duration. For about 5 days prior to onset of these gastrointestinal symptoms, she had received acetaminophen and nonsteroidal anti-inflammatory drugs (NSAID) for a persisting headache. She had no notable medical history and was non-smoker and non-alcohol drinker.

The patient was admitted to her local hospital with a provisional diagnosis of acute gastroenteritis and was started on intravenous injection of ciprofloxacin 400 mg twice daily. On initial investigation at this hospital, her liver function test results were abnormal: total bilirubin 0.9, serum aspartate aminotransferase (AST) 192 IU/L, serum alanine aminotransferase (ALT) 125 IU/L, alkaline phosphatase (ALP) 66 IU/L, total protein 6.3 g/dL, albumin 3.7 mg/dL, and lactate dehydrogenase 1459 U/L. In addition, her pancreatic enzymes were mild elevated: serum amylase 61 U/L (normal value < 80), lipase 128 U/L (normal value < 67). Other laboratory findings included white blood cells 7.7k/mL, hemoglobin 12.4 mg/dL, platelets 164 k/mL, C-reactive protein 10.1 mg/dL (normal value < 0.5) and serum glucose 121 mg/dL. Renal function, serum calcium, triglyceride, electrolytes, and coagulation screening results were normal. After initiating intravenous ciprofloxacin, her symptoms began to

improve slowly, but after 4 days at the local hospital, she began passing approximately 1 liter of fresh blood per rectum, and her hemoglobin fell from 12 g/dL to 6.1 g/dL, requiring aggressive resuscitation with approximately 3 liters of crystalloid, 6 units of packed red blood cells, and intravenous vasopressors and inotropes to maintain hemodynamic stability. Accordingly, she was referred emergently to our institution.

On arrival at the emergency center of our institution, the patient appeared acutely sick with hypotension despite continuous infusion of blood, vasopressors and inotropes. Initial vital signs were; temperature 37.9°C, blood pressure 80/50 mmHg, heart rate 91 beats/min, respiratory rate 20/min, and oxygen saturation 90% in room air. The patient had no prior history of abdominal surgery or gastrointestinal bleeding. Her abdominal physical examination revealed mild generalized abdominal tenderness with no guarding or rebound, hepatosplenomegaly, or skin rash. Nasogastric lavage was performed and aspirated water was clean. After immediate vigorous volume resuscitation, she was planned for emergent colonoscopy after enema without oral ingestion of a bowel preparation formulation.

Colonoscopy revealed the entire large bowel was filled with fresh blood and clots. After suction and irrigation, the terminal ileum was intubated, and multiple variably sized ulcers with surrounding inflammation and submucosal hemorrhages up to 25 cm from the ileocecal valve and an active bleeding spot were observed (Fig. 1A). Hemostasis was successfully achieved by applying two hemoclips precisely on the bleeding eroded vessel. In addition, multiple oval ulcers without bleeding stigmata were also seen in the cecum and ascending and transverse colon. A subsequent abdominal computerized tomography (CT) scan, which was performed immediately after the procedure, revealed segmental wall thickening of the terminal ileum, well-positioned hemoclips, and hyperdense material thought to be blood and clots in ascending colon lumen (Fig. 2A). CT also visualized several enlarged lymph nodes throughout small bowel mesentery in the right lower quadrant and ascites. In addition, peripancreatic fat infiltration with fluid collection, mild enlargement and edema in pancreatic body and tail, strongly suggesting acute pancreatitis, were observed.

After colonoscopic hemostasis had been achieved using hemoclips, intestinal bleeding ceased and the patient's vital signs stabilized without blood transfusion or inotropic infusion. Accordingly, the patient was transferred to a general ward and placed on nil-per-os, total parenteral nutrition, and intravenous ciprofloxacin and gabexate mesilate.

The day after transfer, esophagogastroduodenoscopy (EGD) and follow-up colonoscopy were performed. EGD showed multiple shallow geographic ulcers at the duodenal bulb; her rapid urease test was negative. Colonoscopy revealed multiple variably sized scattered ulcers with submucosal hemorrhage and the hemoclip site at the terminal ileum but no bleeding (Fig. 1B). In addition, it also showed multiple oval-shaped punched-out ulcers with raised margins and normal intervening mucosa in the cecum and ascending and transverse colon. These ulcers were predominantly oval or circular and were shallow, 0.5 to 1.5 cm in diameter, with whitish-pink bases. Colonoscopic biopsies were deferred due to rebleeding concerns. Based on these EGD and colonoscopic findings, we examined the patient's history of NSAIDs use in more detail. We also reexamined her travel history, which was initially denied, and found she had returned from a trip to Southeast Asia 3 weeks prior to admission. The possibility of a typhoid ulcer bleed was

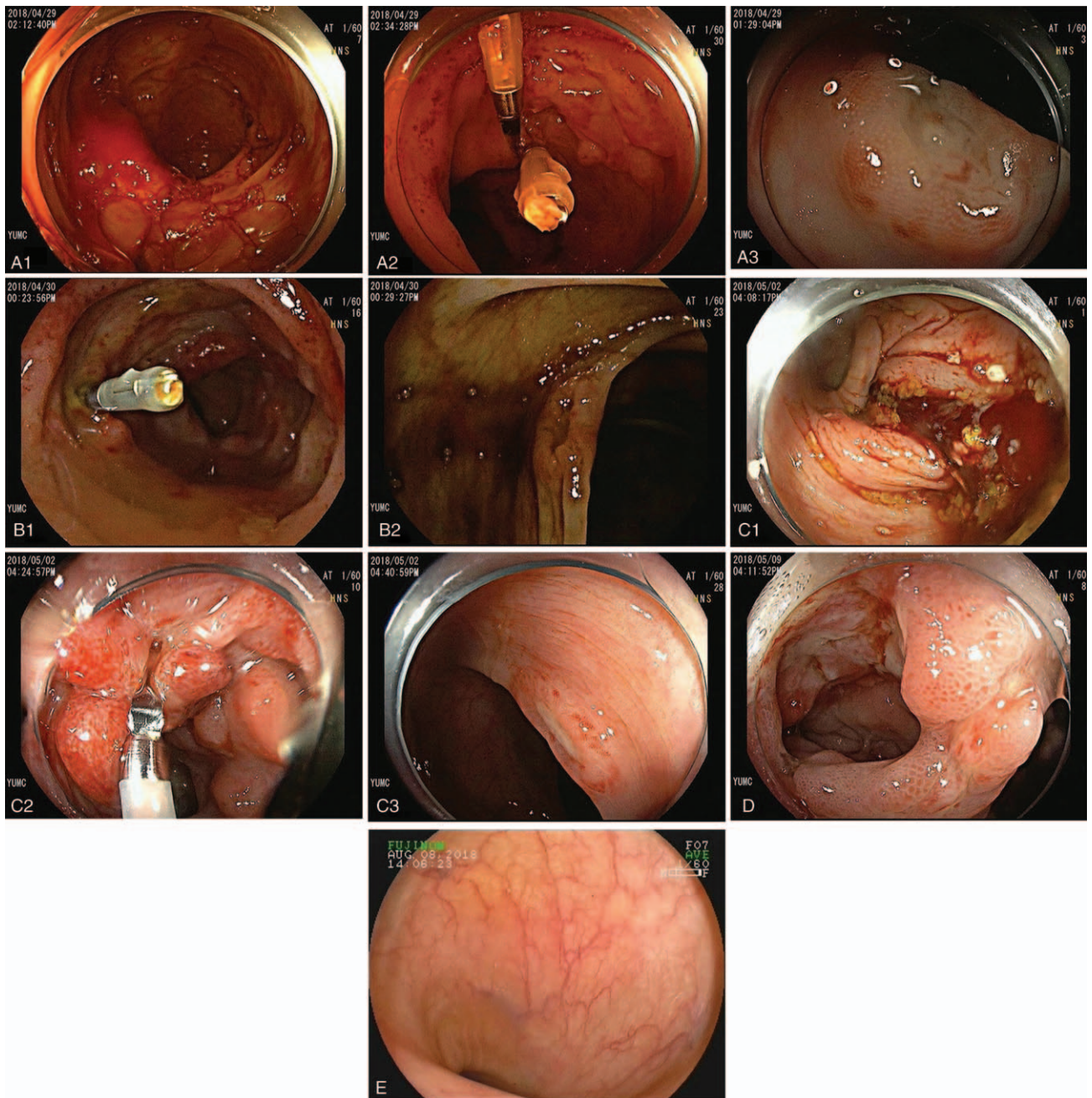


Figure 1. Colonoscopy images. (A) Initial colonoscopy images obtained at presentation showing active oozing bleeding through the ileocecal (IC) valve (A-1), multiple variably sized ulcers with mucosal edema, submucosal hemorrhages, 2 hemoclips applied on a bleeding spot in the terminal ileum (A-2), and an oval “punched-out” ulcer in the ascending colon (A-3); (B) Follow-up colonoscopy images obtained on hospital day 2 showing no bleeding from the hemoclippping site, terminal ileum (B-1) and colon ulcers (B-2); (C) Follow-up colonoscopy images at the second intestinal bleeding event on hospital day 4 showing oozing bleeding through the IC valve (C-1) and a hemoclip applied on a bleeding spot in terminal ileal mucosa, which was severely edematous with submucosal hemorrhage (C-2), and an oval healing stage ulcer with a whitish clean base in the ascending colon; (D) Follow-up colonoscopy image obtained just before discharge on hospital day 11 showing multiple circumferential ulcerations with whitish exudate and edematous friable mucosa at terminal ileum; (E) Last follow-up colonoscopy image obtained on day 100 after initial intestinal bleeding event showing no specific lesion except several ulcer scars in the terminal ileum.

considered, and angiographic localization of the bleeding vessel with coil embolization or surgical intervention, if massive intestinal bleeding with hypotension reoccurred or endoscopic hemostasis failed, was planned.

On hospital day 4, she presented intermittent slight hematochezia and repeat colonoscopy with hemoclippping was performed on the oozing site at a terminal ileal ulcer (Fig. 1C).

In addition, we judiciously performed multiple biopsies of lesions at the terminal ileum, cecum, and ascending and transverse colon due to the risk of rebleeding; however, the biopsy specimens obtained showed only ulceration, acute and chronic active inflammation. After this colonoscopic examination, we received the results of blood cultures initiated at time of admission at the local hospital, which was identified as *S. typhi* (sensitive to

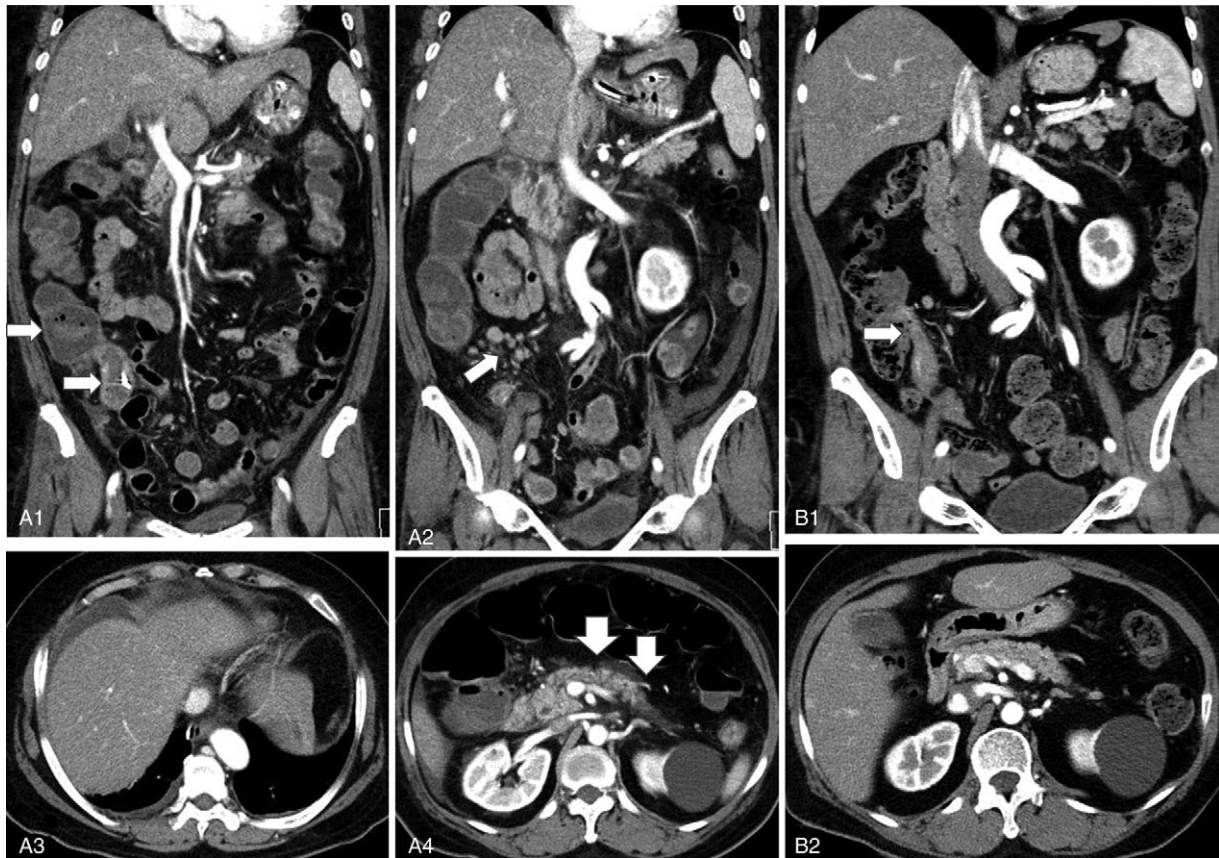


Figure 2. Abdominal computerized tomography (CT) images. (A) Initial CT images obtained at presentation showing segmental wall thickening of terminal ileum with hemoclips and hyperdense material believed to be blood and clots in ascending colon lumen (A-1), several enlarged lymph nodes in the right lower quadrant in small bowel mesentery (A-2), ascites (A-3), peripancreatic fat infiltration and fluid collection, and mild enlargement and edema in pancreatic body and tail (A-4); (B) Follow-up CT image obtained at an outpatient department 40 days after transfer showing persistent terminal ileal wall thickening (B-1), by resolution of ascites, peripancreatic fat infiltration, and fluid collection without complication (B-2).

ceftriaxone and ciprofloxacin), although blood, stool, and urine cultures and the Widal test conducted at our institution were all negative. Accordingly, a diagnosis of typhoid fever complicated by massive intestinal bleeding and acute pancreatitis based on elevated serum lipase and CT findings, and ascites was made. The patient then completed a 10-day course of intravenous ciprofloxacin and became afebrile without intestinal bleeding.

On hospital day 11, follow-up colonoscopy revealed multiple circumferential ulcerations with whitish exudate and edematous friable mucosa at the terminal ileum (Fig. 1D), and that multiple oval ulcers in cecum, ascending and transverse colon had healed leaving only subtle scars. Oral feeding was resumed, and she was discharged on hospital day 12 after completing her antibiotic course.

At her 5-day follow-up in our outpatient department, the patient was stable and reported no further episodes of hematochezia or fever and a laboratory study showed liver function tests had returned to normal; pancreatic enzymes (serum amylase 79U/L, lipase 260U/L) were higher than initial laboratory findings at our institution (serum amylase 45U/L, lipase 113U/L), but without symptoms and returned to normal levels at further follow-up laboratory study 4 weeks after discharge. An abdominal CT scan performed at our outpatient department 4 weeks after discharge (40 days after transfer) showed that terminal ileal wall thickening persisted, but that

ascites, peripancreatic fat infiltration, and fluid collection had resolved without complication (Fig. 2B). At 100 days after transfer, last follow-up colonoscopy conducted at our outpatient department revealed no specific lesion other than several terminal ileal scars (Fig. 1E). Stool samples were negative as determined by 3 consecutive cultures conducted during the month after discharge.

3. Discussion

S. typhi, which is transmitted via the fecal-oral route, modulates the host immune response to invade small intestinal mucosa.^[16] The bacterium proliferates intracellularly, initially in the Peyer's patches from where it disseminates to the liver, spleen, and reticuloendothelial system through the lymphatics and bloodstream.^[16] From the next week to third week of the infection, it proliferates further in these organs to emerge as recurrent waves of bacteremia that infect various organs, which is the hallmark of the symptomatic phase of infection. In addition, during this phase, organisms are released into bile and re-infect ileal lymphoid tissue to cause the classical bowel pathology associated with *S. typhi* infection.^[16] In the gastrointestinal tract, the terminal ileum is predominantly involved since it has abundant lymphoid follicles (Peyer's patches), in which infection induces hyperplasia leading to possibly subsequent ulceration.

The diagnosis of typhoid fever may be difficult because of its reduced incidence and atypical presentations of the disease. Therefore, important intestinal complications, such as, intestinal hemorrhage or perforation, may be the initial manifestations in some cases. In our patient, classic signs, such as, rose spots and splenomegaly, were absent, though intestinal bleeding and fever were evident. However, retrospective consideration made it clear that several clinical clues, such as relative bradycardia and a normal white blood cell count despite high fever, were overlooked. Abnormal liver functions test results and/or anemia and leucopenia are observed in nearly all patients, in whom transaminase levels are 2 to 3 times normal.^[17] Liver enzyme increases are attributable to asymptomatic hepatitis, which occurs in the majority of patients, and more than one-third of patients may manifest clinical jaundice.^[18] Blood cultures for typhoidal organisms are positive in 60% to 80% of typhoid fever cases,^[1] but blood culture positivity diminishes after the first week of the disease and becomes negative during the fourth week. Urine and stool cultures are less frequently positive. Serology tests such as Widal tests for “febrile agglutinins” are available, but none are as sensitive or specific as culture-based methods for the diagnosis of typhoid fever.^[17] In our case, the Widal test was negative, possibly because our patient was taking antibiotics before referral to our hospital.

Approaches to lower intestinal bleeding in typhoid fever have changed over past decades. Recently, colonoscopy was recommended for localizing sites of gastrointestinal bleeding in patients with typhoid fever. However, the colonoscopic characteristics of bleeding ulcers in typhoid fever have not been well established^[19]; so endoscopic examinations may give rise to other possibilities, such as intestinal tuberculosis, *Yersinia* enterocolitis, amoebiasis, or Crohn’s disease, and, when antibiotics or NSIADs are administered, can lead to misdiagnoses of pseudomembranous colitis or antibiotic-induced colitis^[20] or even NSAIDs-induced intestinal ulcers.^[21] In our case, the patient initially denied her travel history, and confirmed a history of NSAIDs use, and moreover, EGD showed multiple duodenal ulcers. Accordingly, her clinical presentation initially suggested that gastrointestinal bleeding might have been related to NSAIDs use, although massive intestinal bleeding is uncommon for NSAIDs-induced intestinal ulcers. Nevertheless, the presence of fever prompted a search for an associated infection.

Reyes et al^[6] described typical radiological findings of ulcerations in typhoid fever as round or oval oriented along the long axis of the bowel, with raised margins and a “punched-out” appearance. In a study of seven patients with hematochezia secondary to typhoid colitis, Lee et al^[22] noted that punched-out ulcers were common and the left colon was spared, which are consistent with our findings. Colonoscopy confirmed massive intestinal bleeding in the terminal ileum and the presence of diffuse typhoid punched-out ulcers from the terminal ileum to the transverse colon in our patient.

Intestinal bleeding in typhoid fever usually occurs from ulcers in the ileum and proximal colon,^[22] with terminal ileum being the most common site, and results when the wall of an adjacent enteric vessel is eroded by a necrotic Peyer’s patch. The reported incidence of intestinal hemorrhage in typhoid fever varies from 1% to 10%.^[1] In the majority of cases, bleeding is usually mild and resolves without the need for blood transfusion,^[5] but rarely, bleeding is clinically significant and can be rapidly fatal if a large vessel is involved. Few reports of massive intestinal bleeding as a complication of typhoid fever have been issued, and the majority

are of cases in developing countries or endemic areas where health care may be limited and presentation delayed.

Treatment strategies for intestinal bleeding in typhoid fever remain controversial. Most cases of mild to moderate intestinal bleeding may be treated conservatively, but massive or persistent bleeding probably require right hemicolectomy or segmental resection. Technical advances have resulted in the successful use of new modalities, such as angiographic localization of bleeding vessels with coil embolization,^[23] but it should be noted that intestinal necrosis is a fatal complication after arterial embolization. In patients with upper gastrointestinal bleeding such as gastric and duodenal bleeding, infarction and necrosis are unlikely after embolization, because of dual blood supply from the gastroduodenal and pancreaticoduodenal arteries. On the other hand, when bleeding originates from the distal small intestine or large intestine, which are distal to the Treitz ligament, the blood supply is not sufficient and the incidence of intestinal necrosis may be significantly higher.^[24] Therefore, it is an ideal method to perform embolization with “super-selection”, during which the catheter is close to bleeding blood vessels. However, due to the risks involved, this modality is available only at a few tertiary centers with a fully trained interventional radiologist and staff. Furthermore, because enteric fever is largely a disease of the developing world, many centers do not have access to radiological intervention, which probably accounts for the lack of data on this topic.

Endoscopic hemostasis is now the standard for managing these ulcer bleedings,^[22] but due to mucosal fragility in cases of typhoid fever, the safeties of colonoscopic procedures are of concern. In addition, concern has been expressed that exact bleeding foci may not be visualized by colonoscopy, especially in patients with massive intestinal bleeding, because intestinal lesions are multiple in typhoid fever and the endoscopic visualization is poor. Nevertheless, if an actively bleeding spot is identified during endoscopy, adrenaline injection, thermal coagulation, or hemoclip application may be used alone or in combination, although the latter is usually the better option.

Literature on the use and success of these endoscopic modalities for treating massive typhoid ulcer bleeding is scarce. Recently, in the largest series of typhoid ulcer bleeds reported from a single center during the typhoid fever outbreak in the Kurdistan region of Iraq,^[25] 12 of 52 patients required endoscopic hemostatic intervention by adrenaline injection with argon plasma coagulation. Treatment was effective in 11 of these 12 patients; the remaining patient died despite surgical intervention in addition of endoscopic hemostasis. In another report on typhoid ulcer bleeds in seven patients issued in South Korea,^[22] active bleeding was observed in only 1 patient, who subsequently underwent endoscopic hemostasis twice by adrenalin injection and coagulation using a heat probe. In our case, endoscopic hemoclip therapy was successfully performed for massive typhoid ileal ulcer bleeding, which has rarely been reported in the literature. Considering the risks of procedure-related complications, such as perforation of the small intestine wall, which is likely to be thin and friable due to ulceration, mechanical hemostasis methods, such as hemoclipping, might be safer than coagulation methods, if the origin of bleeding can be identified and is not multiple, as in our case. Although a small number of previous case studies have referred to endoscopic hemostasis,^[26–28] no previous report on endoscopic clipping for hemostasis being performed successfully in massive intestinal bleeding as a complication of typhoid fever has been published.

Typhoid fever is a “bacteremic” disease and many organs may be invaded by the organism; however, acute pancreatitis appears to be a rare complication. It seems that elevated pancreatic enzymes with or without clinical acute pancreatitis in patients infected by *S. typhi*, which causes typhoid fever, may differ from those elevated by *Salmonella enteritidis*, which causes *Salmonella* gastroenteritis. One explanation for the development of pancreatitis by *S. typhi* is that the bacterium invades the bile and is refluxed into the pancreatic duct, as described by the “bile reflux theory”.^[11] Direct pancreatic localization of bacteria through hematogenous and lymphatic routes has also been described,^[29] and is believed to be caused by toxins secreted or by immune response to bacteria.^[15,29] On the other hand, in non-typhoidal salmonellosis, pancreatic enzyme elevation may be due to intestinal inflammation leading to increased permeability and the reabsorption of macromolecules like amylase, as was suggested by Gnadinger et al.^[30]

Hermans et al reported a series of patients with typhoid fever that exhibited biochemical evidence of pancreatitis.^[15] Three of these 7 patients (43%) had asymptomatic pancreatitis and the other 4 patients complained of severe abdominal pain with nausea and vomiting and diffuse periumbilical tenderness. The authors suggested that the pancreas was probably affected during the secondary septicemic phase. Accordingly, the possibility of pancreatitis complicating typhoid fever must be considered in *S. typhi* infected patients, even in those without abdominal symptoms, because pancreatic enzyme changes may be observed in this patient population.^[15]

Our patient presented with abdominal pain, nausea, and vomiting, which occur with typhoid fever but are also seen in pancreatitis, although in our patient the typical clinical symptoms and signs of pancreatitis were minimal. Although there is no “gold standard” for the diagnosis of pancreatitis, elevated pancreatic enzyme levels and abdominal CT findings indicative of acute pancreatic inflammation warrant a diagnosis of acute pancreatitis. Our patient did not drink alcohol, was not taking medications, had normal triglyceride and calcium levels, and denied prior abdominal trauma. Although incidental pancreatitis cannot be completely excluded, we view this as unlikely since her laboratory and CT findings paralleled the course of typhoid fever. Thus, in the absence of other known causes of acute pancreatitis, we believe that pancreatitis in our patient was related to typhoid fever. It has been reported that asymptomatic typhoid pancreatitis is not prognostically significant.^[10,11,15] In our case patient, follow-up abdominal CT showed peripancreatic fat infiltration and fluid collection had resolved without any complication.

4. Conclusion

The authors report a case of typhoid fever complicated by massive intestinal bleeding, acute pancreatitis, and ascites. Based on an extensive review of the medical literature, this report describes an extremely rare case of successful hemostasis achieved by endoscopic hemoclippping on massive bleeding typhoid ulcer. In addition, the described case was complicated by acute pancreatitis, which is an uncommon complication of typhoid fever. We believe this case report further supports that endoscopic treatment could be considered a standard option for typhoid ulcer bleeding. In addition, our case demonstrates that *S. typhi* should be considered in the differential diagnosis of massive lower gastrointestinal hemorrhage, especially in the setting of recent travel in South or Southeast Asia. Early clinical

suspicion and the initiation of appropriate antibiotics might crucially influence the final outcomes of patients affected by this unusual complication of typhoid fever.

Author contributions

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Resources: Joon Hyun Cho.

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