

# Clinical and Pathological Characteristics of Amoxicillin Associated Hemorrhagic Colitis

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## Research article

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## Abstract

**Background and objective:** Amoxicillin is an antibiotic with various benefits for patients. However, adverse reactions sometimes occur, and the clinical misdiagnosis rate is high because some clinicians have limited knowledge regarding this drug. Combined with literature review, this study explores the clinical pathological features of hemorrhagic colitis caused by amoxicillin to improve its diagnosis and treatment.

**Methods:** "Amoxicillin", "hemorrhagic colitis", "antibiotic-associated colitis (AAC)", "antibiotic-associated hemorrhagic colitis (AAHC)" were used as the index words to retrieve Pubmed, EMbase, Wanfang Database and Chinese national knowledge infrastructure (CNKI). Related articles were then selected and combined with the patient information obtained from our department to complete the clinical pathological files. To summarize the clinicopathological data, diagnosis, treatment of the disease.

**Results:** A total of 19 articles were included in the study. Patients may have abdominal pain, bloody stools or blood in the stool, but generally no anemia. The laboratory tests for hemoglobin (HGB) and erythrocyte sedimentation rate (ESR) are normal, and C-reactive protein (CRP) is often elevated. Abdominal ultrasound and computed tomography (CT) findings revealed that the intestinal wall was thickened and presented edema, and some parts exhibited peritoneal effusion. Upper gastrointestinal endoscopy usually has no bleeding changes. A colonoscope was used to reveal the mucosal erosion, mainly found on the right hemicolon and this finding was consistent with acute colitis. The pathology is consistent with acute hemorrhagic colitis. The symptoms were relieved after drug withdrawal and principally with supportive treatment. The patient's gastrointestinal symptoms usually did not recur.

**Conclusion:** Patients with acute colitis caused by amoxicillin generally experienced abdominal cramps and bloody stools, but treatment response was good, and follow-up monitoring revealed no recurrence. The history of antibiotic therapy and early total colonoscopy examination are important to establish the correct diagnosis. *Klebsiella oxytoca* (*K. oxytoca*) were cultured in fourteen cases, which is described as a causative organism for AAHC.

## Background

Amoxicillin plays a crucial role in disease prevention and has made important contributions to the protection of human health, but related adverse reactions and complications have increasingly occurred<sup>1,2</sup>, in which antibiotic-associated colitis (AAC) is comparatively common without clear pathogenesis<sup>3</sup>. Antibiotic-associated hemorrhagic colitis (AAHC) is a special type of AAC. After treatment with broad-spectrum antibacterial drugs such as fluoroquinolone, cephalosporin or penicillin and etc. within two to seven days, AAHC appeared and the clinical manifestations were abdominal pain, diarrhea, and finally bloody stools<sup>4</sup>. Amoxicillin and other penicillin derivatives are the most common pathogenic drugs<sup>5</sup>.

Amoxicillin, also known as ampicillin and penicillin, which is a beta lactam antibiotic that mainly acts on gram-positive bacteria and some gram-negative bacteria<sup>6</sup>. According to the reports by Toffler et al in 1978<sup>7</sup> and Sakurai et al<sup>8</sup> in 1979, this antibiotic causes hemorrhagic colitis, and adverse reactions have been reported in many countries worldwide<sup>4, 9–13</sup>. Amoxicillin-clavulanate potassium is a combination of amoxicillin and the enzyme inhibitor clavulanate potassium, which can also cause hemorrhagic enteritis<sup>14, 15</sup>. Given the lack of specificity and rapid change of the AAHC symptoms caused by amoxicillin, as well as the lack of cognition of the digestive system performance of AAHC in clinical work, early diagnosis is difficult and misdiagnosis often occurs, posing risks to patients. Therefore, this review analyzes the clinical features of AAHC in order to improve the diagnosis rate of it.

## 1 Methods

### 1.1 Literature Search strategy

The selected databases including PubMed, EMBASE, Wan Fang and Chinese National Knowledge Infrastructure(CNKI) databases were searched to select the suitable literature related to amoxicillin and related drugs induced hemorrhagic colitis. The search began in setting up the literature database and ended in April 2019. The search strategy included the following terms: "amoxicillin", "amoxicillin clavulanate potassium", "hemorrhagic colitis", "antibiotic-associated hemorrhagic colitis". The search language was limited to English. Corresponding Chinese characters were used in Chinese database. On this basis, we tried to trace the references that had been incorporated into the literature and manually retrieve the relevant conference proceedings to identify potential informations that were not retrieved. Unpublished literature was not retrieved.

### 1.2 Inclusion and exclusion criteria

Studies were included in this review if the following conditions were met: The patient was finally diagnosed with hemorrhagic colitis after treatment with amoxicillin or amoxicillin-related drugs and had detailed clinical and pathological data that could be extracted. Studies were excluded if other drugs that caused hemorrhagic colitis were others. Drug-induced diseases were eventually diagnosed as diseases other than hemorrhagic colitis. Studies on animals, human xenografts and cell lines were excluded. Studies were excluded if they were review articles, summaries, systematic evaluations, the reader letters and so on. Repeated publications were also removed.

### 1.3 Data extraction

The following information was extracted from the literature: title, first author names, the year of publication, country, symptoms and signs, accompanying symptoms and laboratory, gastrointestinal and imaging examinations, treatment plan and follow-up information, combined with the clinical data of one

patient admitted to our department and clinical characteristics of the disease. All included literature was examined by two reviewers. If any differences arose, then the final results decided through a discussion, or consultation with a third reviewer.

## 2 Results

### Literature search results

19 articles were included in the study, and the basic characteristics of the included articles were shown in Table S1 and S2. All patients were treated with amoxicillin or amoxicillin-related drugs, and other gastrointestinal diseases were excluded from laboratory and imaging examinations, and the diagnosis was hemorrhagic colitis.

### 2.1 General information

#### 2.1.1 Case report

A 43-year-old female patient presented with yellow paste stool after oral administration of 200mg amoxicillin 5 days before admission due to the upper respiratory tract infection. Three days later, the patient was admitted to the hospital with acute abdominal pain, nausea, vomiting, and 10 times bloody diarrhea. Physical examination revealed a temperature of 37.0°C, pulse of 66 beats/min, respiratory rate of 16/min and blood pressure 119/73 mmHg. Physical examination found that she had an acute painful face, slightly tense abdominal muscles, tenderness in the lower abdomen, but no rebound pain. Auscultation bowel sounded 3 times/min, but tone weakened. Other physical examinations did not show positive signs. After admission, blood routine examination: white blood cell count (WBC)  $7.18 \times 10^9$ , neutrophil value (NE, 74%), red blood cell count (RBC)  $5.14 \times 10^{12}$ , hemoglobin (HGB) 123 g/l, platelet count (PLT)  $193 \times 10^9$ ; stool routine: fecal hemorrhage, RBC full field of vision/HP, WBC+, occult blood (OB): positive (+). There were no obvious abnormalities in liver function, renal function, electrolyte, coagulation function and autoimmune disease antibody spectrum. High-sensitivity C-reactive protein (hsCRP) was 16.43 mg/L and erythrocyte sedimentation rate (ESR) was 8 mm/h. No pathogenic bacteria were found in stool culture, and *Clostridium difficile* toxin was negative. Abdominal ultrasonography detected widespread and uniform thickening of the colon wall, pelvic and intestinal spaces, and small anechoic areas. The maximum depth was approximately 9 mm. Chest computed tomography (CT) revealed small fibrotic lesions in both lungs and interstitial thickening at the edge of the lower lobe. Total abdominal CT showed extensive and uniform thickening of the colon wall, possible inflammatory lesions, a small amount of peritoneal effusion, multiple calcifications in the right posterior lobe of the liver and splenomegaly (Figure 1). Gastroscopy revealed chronic superficial gastritis with erosion and duodenitis (Figure 2). Enteroscopy was diagnosed as hemorrhagic colitis (Figure 3). Pathological results showed chronic inflammation of ascending colon mucosa with hemorrhage in the interstitium (Figure 4). This

patient presented abdominal pain and diarrhea after oral amoxicillin, consistent with AAHC. Omeprazole was administered, and rehydration and compound glutamine were provided to promote intestinal mucosal repair. On the third day of admission, the patient was relieved of yellow and soft stool. On the fifth day, the symptoms were completely relieved and the patient was discharged. Followup for 45 days after discharge showed no recurrence of abdominal pain or bloody stool. The colonoscopy results showed restoration to normal mucosal image (Figure 5).

## 2.1.2 Case characteristics

In combination with our patient, 51 patients were analyzed, 27 males and 24 females. The age of onset was 5 - 74 years, with an average of 35.3 years. The course of disease was 1-9 days, with an average of 3.9 days. No remarkable correlation existed between onset and age and gender. Amoxicillin was administered at a dose of 300-4500 mg/day. The most common cause of medication was upper respiratory tract infection (23 cases, 45.1%), followed by eradicated *Helicobacter pylori* (7 cases), gingivitis (4 cases), tonsillitis (3 cases), acute appendicitis, acute otitis media, dog bites and other diseases. Thirty patients were taking other drugs at the same time, the most common of which were metronidazole (6 cases), acetaminophen (2 cases) and nonsteroidal antiinflammatory drugs (NSAIDs) (2 cases).

## 2.2 Signs and symptoms

Abdominal pain was the most common symptom, which were present in 48 cases (94.1%). The most common symptoms were followed by distended abdomen, accompanied by diarrhea, characterized by yellow and watery consistency with frequency reaching more than 10 times per day. The patients may have nausea and vomiting at the same time. All patients had bloody stools or blood in the stool (51 cases, 100%), with a frequency of up to 20 times per day. The patients may have abdominal tenderness, but no muscle tension or rebound tenderness. The patients did not present with jaundice or anemia. Rectal examination showed bright red blood. Four patients developed fever with a maximum body temperature of 38.5°C, which returned to normal after symptomatic treatment.

## 2.3 Laboratory testing

Four patients did not mention blood routine examination, and 47 patients with blood routine analysis showed that 31 patients (66%) had elevated WBC, 16 patients (34%) had normal disease, and no patients had leukopenia. Only one patient (2.1%) showed decreased HGB. Sixteen patients reported erythrocyte sedimentation results, 13 (81.3%) of which were normal, and 3 of which showed a marked increase. Twelve patients were examined for CRP, 10 (83.3%) of which had increased CRP, and 2 of which were normal. Fourteen cases of positive *Klebsiella oxytoca* (*K. oxytoca*), 3 cases of positive *Klebsiella pneumoniae*, 3 cases of positive *Escherichia coli* (*E. coli*) were found. One case of positive

*Praefusmorgani*, 1 case of positive *Straptococcus faecalis*, and 1 case of positive *Citrobactorfreud* were found.

## 2.4 Abdominal imaging

Ultrasound examination revealed thickening of the intestinal wall and peritoneal effusion. Abdominal X-ray showed thickening of the intestinal wall, dilatation of the intestine or accumulation of gas, and there was no remarkable change. Gas angiography suggested a colonic sputum and a jagged appearance of the descending colon. Abdominal CT showed intestinal wall edema, thickening, inflammatory changes and ascites.

## 2.5 gastrointestinal examination

Total colonoscopy and biopsy revealed mucosal hemorrhage changes mainly in the right colon, rectum and sigmoid colon are completely normal. Microscopic appearance of mucosal erosion, hemorrhage, edema, and even active bleeding were found. Some patients showed ulcerative lesions and intestinal fistula. No remarkable changes in the colonoscopy lesions were found after 2-3 days of illness, but the colonoscopy lesions disappeared completely after one week. The intestinal mucosa returned to normal. Upper gastrointestinal endoscopy could be normal or showed inflammatory changes without evident hemorrhagic lesions.

## 2.6 Pathology

The disease was consistent with acute hemorrhagic colitis. Mucosal congestion and edema were observed. Inflammatory cells such as monocytes, neutrophils and lymphocytes infiltrated in the lamina propria, and red blood cells infiltrated in the interstitial. However, the gland or crypt structure showed no changes.

## 2.7 Treatment and follow-up results

The treatment principle was to stop the original oral medication, and the symptoms were relieved quickly after the medication was stopped. The main treatment for acute diarrhea was supportive treatment with focus is on rehydration and correction of electrolyte imbalance. In severe cases, intravenous short-term steroid therapy could be used. Most patients recovered quickly, with complete remission in the short term, and no complications. Gastrointestinal symptoms did not recur in patients after followup after discharge.

## 3 Discussion

The intestinal tract is one of the common target organs for drug damage<sup>16</sup>. Drug-related hemorrhagic colitis is categorized into AAHC and other drug-related hemorrhagic colitis; and 85% of AAHC is caused by amoxicillin or other penicillin derivatives<sup>17</sup>. Most cases of amoxicillin-induced hemorrhagic colitis, including clinical characteristics, occur within one to nine days of medication and can occur at all ages<sup>18–20</sup>. The history of taking amoxicillin or penicillin derivatives. Patients have bloody diarrhea, or bloody stool, with or without abdominal cramps, and other systems are rarely involved. Colonic mucosa microscopically demonstrates mild to moderate inflammatory changes, probably associated with ulcer, mucosal edema, and bleeding<sup>21</sup>. It is mainly located in the right hemicolon or transverse colon with segmental distribution<sup>22</sup>, similar to ischemic colitis<sup>3</sup>. Pathological examination revealed erythrocyte infiltration of the colonic mucosa.

Kato *et al*<sup>18</sup> regarded that colonoscopy confirms AAHC is safe and effective, whereas Hogenauer *et al*<sup>2</sup> claimed that sigmoidoscopy alone is ineffective, and colonoscopy is necessary for the diagnosis of AAHC. However, Yamada *et al*<sup>19</sup> thought that AAHC patients demonstrated remarkably improved symptoms after drug withdrawal and without implementation of invasive examination. Those who are qualified for colonoscopy are recommended to actively improve the examination. Ultrasound examination can probably provide clues for the diagnosis of AAHC and reduce the need for invasive examination<sup>23</sup>. The abdominal CT of the patients showed diffused edema of the intestinal wall with partial ascites, which should be differentiated from pseudomembranous colitis<sup>23</sup>. If colonoscopy cannot be tolerated by the patients and X-ray and CT examinations are inappropriate, then abdominal ultrasound may be feasible.

In the identification of diseases including pseudomembranous colitis or *Clostridium difficile*-associated diarrhea, infectious colitis, necrotizing enterocolitis, ischemic colitis, inflammatory bowel disease, allergic purpura, hemolytic uremic syndrome and other drug-related colitis<sup>18, 25</sup>, some patients conform to AAHC in the short term, but eventually diagnosed with other diseases, should pay attention to the identification of other diseases<sup>26</sup>.

The cause of AAHC has not been fully elucidated. In 1982, Dickinson R *et al*<sup>11</sup> discovered that the infection morbidity of most patients were caused by the drug, and the respiratory pathogens and drugs were speculated to interact with each other in a similar hypersensitivity reaction. However, approximately 50% morbidity due to respiratory tract infection was not caused by the drugs and the possibility is not high. Antibiotic intake results in flora imbalance, which increases the amount of carbohydrates that cannot be metabolized; hence, diarrhea occurs due to the infiltration of carbohydrates<sup>27</sup>. This inference may explain diarrhea in patients, but cannot explain hemorrhage. Antigen–antibody responses damage the integrity of vascular endothelium, leading to submucosal hemorrhage in the intestinal wall. Drugs can also directly or indirectly damage endothelial cells, leading to thrombosis, erythrocyte aggregation, and colonic hemorrhage<sup>28</sup>.

It is speculated that the bacterial infection may be related to AAHC, and the patient develops bacterial infection and then AAHC. *K. oxytoca* is probably the most common pathogenic bacteria of AAHC<sup>10, 19</sup>. It is

found in the intestinal tract of 1.6–10% of healthy people<sup>19, 29</sup>. Zollner-Schwetzl *et al*<sup>30</sup> regarded that *K. oxytoca* is not a pathogenic factor of hemorrhagic non-hemorrhagic antibiotic associated diarrhea, but Cheng VC *et al*<sup>31</sup> claimed that patients with *K. oxytoca* present only antibiotic-associated diarrhea and nothemorrhagic colitis. Given the prevalence of AAHC symptoms, the missed diagnosis or misdiagnosis rate of *K. oxytoca* infection is high<sup>19</sup>. However, the pathogenic mechanism of *K. oxytoca* remains unknown, speculating that the overgrowth of bacteria was caused by the drug treatment<sup>32, 33</sup>. Flora-produced matter is closely related to the occurrence of disease<sup>29</sup>. *K. oxytoca*-produced cytotoxicities that damage the intestinal epithelial cells<sup>34</sup>, include nonribosomal peptides tilivalline and tilimycin<sup>35</sup>, as well as tilivalline-induced apoptosis and epithelial barrier disorder, which are consistent with intestinal mucosal injury in patients with AAHC<sup>29</sup>. Tse H *et al*<sup>36</sup> regarded that *K. oxytoca* causes diseases through kleboxymycin. Hogenauer C *et al*<sup>22</sup> showed that antibiotics inoculated with *K. oxytoca* to unexposed rats is not pathogenic. After infection with *K. oxytoca*, colon antibiotic hemorrhagic colitis (AHC) occurred on the right side of the rat's body, whereas none occurred on the uninfected rats, indicating that *K. oxytoca* is one of the AHC pathogenic bacteria.

The principal virulence factors of *Clostridium difficile* (*C. difficile*), toxins A, B and ADP-ribosyltransferase (CDT)<sup>37</sup>, are the main causes of pseudomembranous colitis<sup>24</sup>, accounting for 15–25% of the antibiotic-associated bloody diarrhea (AABD) inpatients<sup>38</sup>, especially in the aging population<sup>22</sup>. However, only 14% *C. difficile* infection presents bloody stools<sup>39</sup>. The morbidity rate of AAC increased because most patients developed secondary infection with *C. difficile*<sup>3</sup>. Hoffmann K Met *et al*<sup>40</sup> considered that *C. difficile* infection is not the true cause of AAHC; instead, the principal pathogen is *K. oxytoca*. In the French prospective study<sup>41</sup>, 50%(2/4) *C. difficile*-negative AAHC patients were distinguished from *K. oxytoca*-infected patients. A prospective study from Turkey<sup>33</sup> claimed that 50% AABD morbidity is relevant to *K. oxytoca*, for part of the patients with both *K. oxytoca* and *C. difficile*.

AAC might be caused by other pathogens in addition to *K. oxytoca* or *C. difficile*<sup>39</sup>. Stampfe L *et al*<sup>39</sup> reported 12 confirmed AAC cases, in which two were caused by *K. oxytoca*, two were caused by *C. difficile*, whereas no existing pathogens were observed for the remaining 8 cases. *E. coli* is a foodborne pathogen<sup>42</sup> that can cause watery diarrhea and hemorrhagic colitis<sup>43, 44</sup>. In addition, AAHC may also be associated with *Clostridium perfringens* infection<sup>45</sup>.

AAHC is self-limiting, and its treatment should be discontinued first, with supportive treatment as the main method, focusing on fluid rehydration and electrolyte correction<sup>46</sup>. In severe cases, short course intravenous hormone therapy is available. Moreover, the use of probiotics may be a beneficial treatment<sup>47</sup>, in which most of the patients recovered quickly with complete remission in a short time, and without complications.

## Abbreviations

AAC:antibiotic associated colitis; AAHC:antibiotic associated hemorrhagic colitis; CNKI:Chinese national knowledge infrastructure; WBC:white blood cell count; HGB:The laboratory tests for hemoglobin; RBC: red blood cell count; ESR:erythrocyte sedimentation rate; CRP:C-reactive protein; CT:computed tomography; K. oxytoca:*Klebsiella oxytoca*; OB:occult blood; CDT:ADP-ribosyltransferase; AABD:antibiotic-associated bloody diarrhea.

## Declarations

### Ethics approval and consent to participate

This article does not contain any studies with human or animalsubjects.

### Consent for publication

Written informed consent for publication was obtained from all participants.

### Availability of data and materials

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

### Competing interest

The authors declare that they have no competing interests.

### Funding

Not applicable.

### Authors' contributions

JS and LXB conceived, and designed this study; LXB, XW and GZY searched, and collected the data; SCT, YF and LDP performed the statistical analysis and interpretation of data; LXB, XW and LSB wrote the manuscript. All authors read, and approved the final manuscript.

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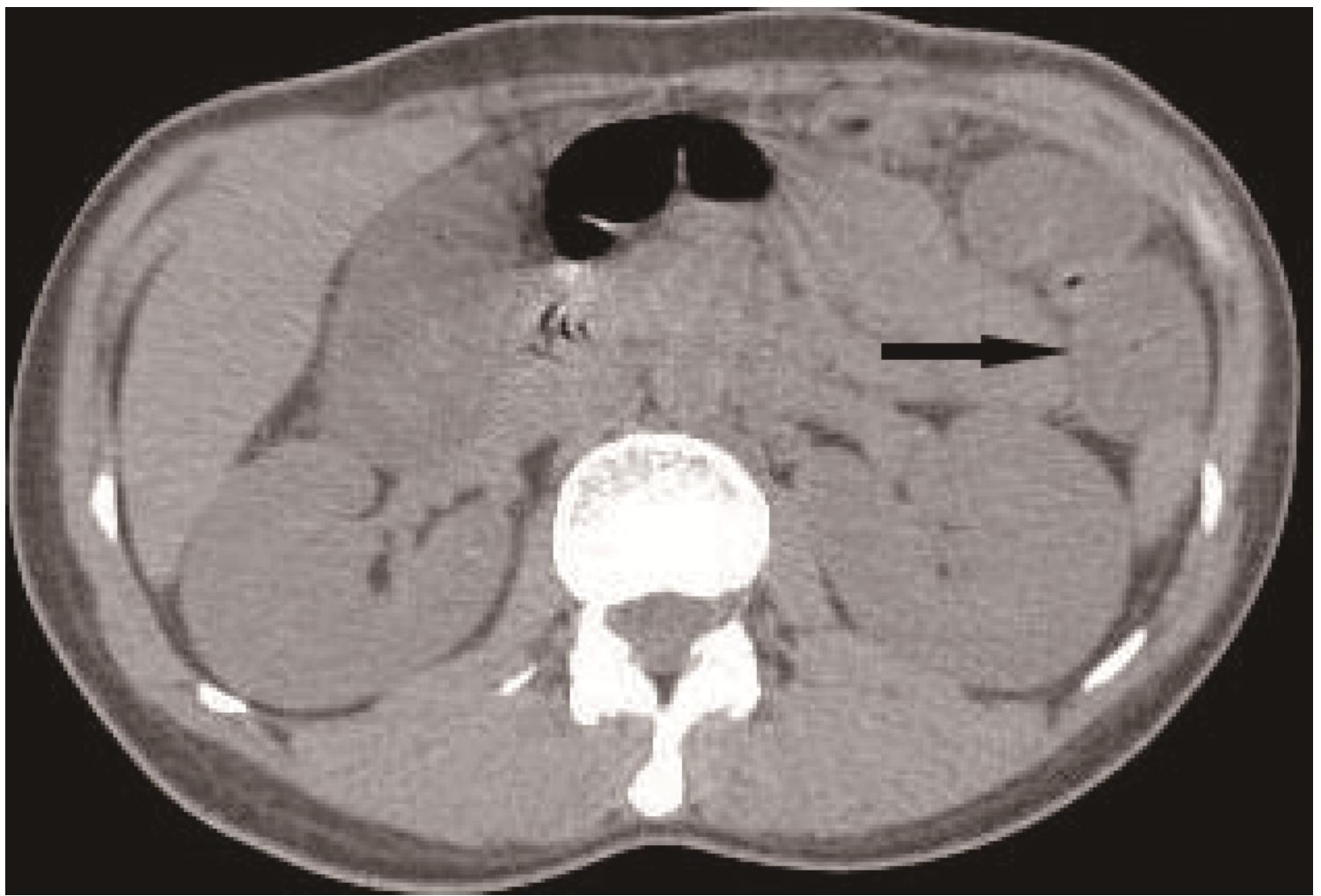
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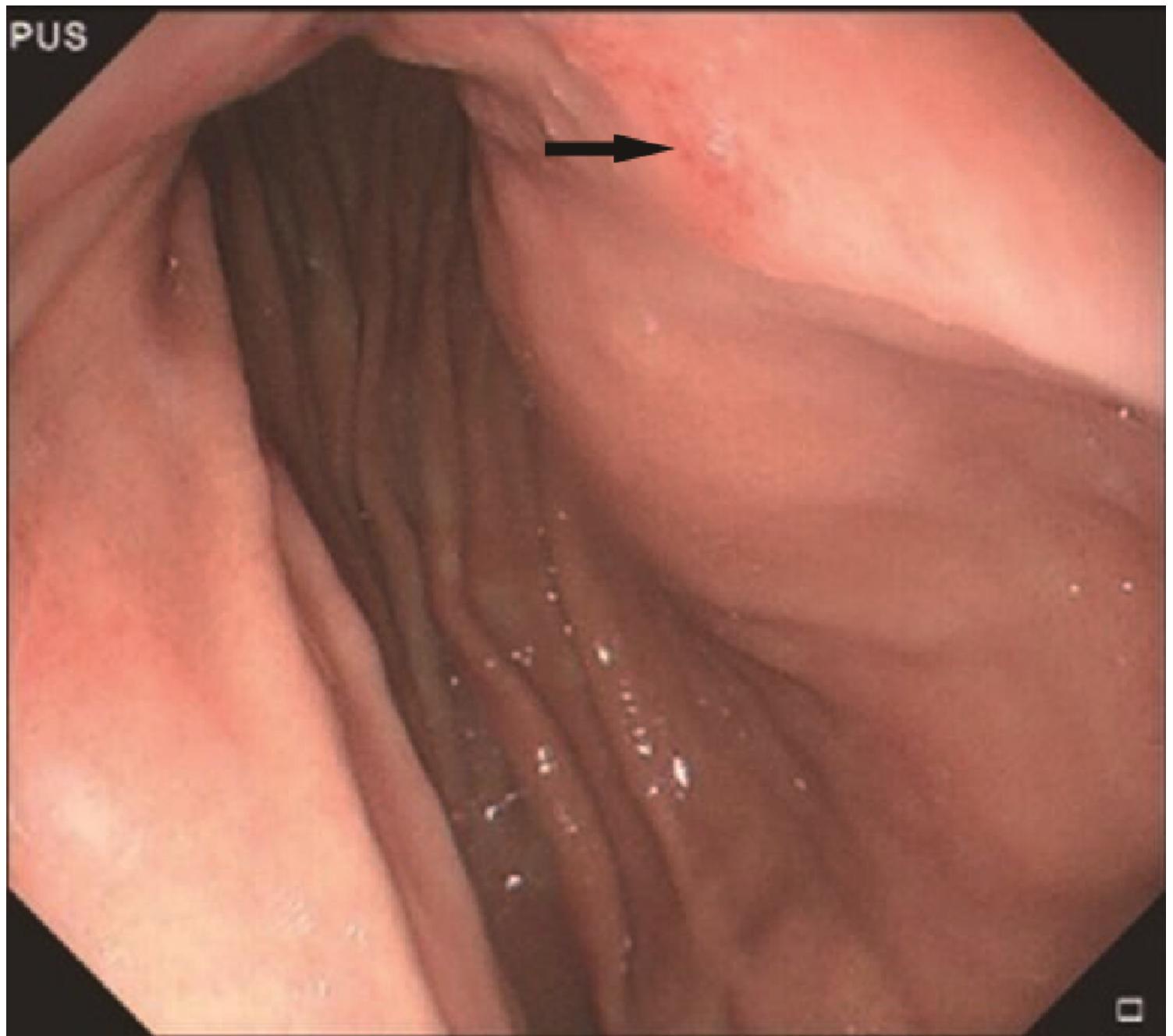
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## Figures



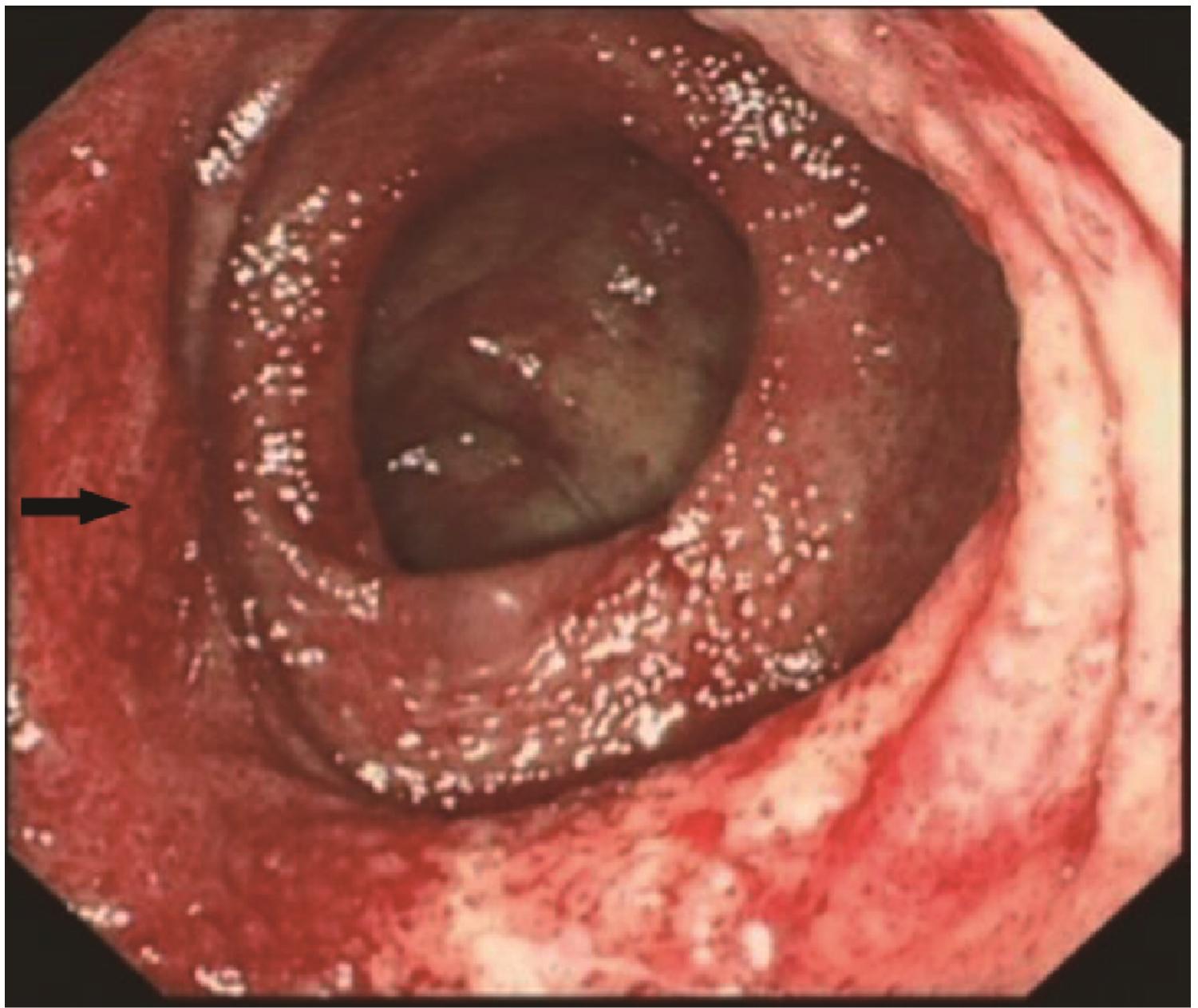
**Figure 1**

Total abdominal CT showed extensive and uniform thickening of the colon wall, possible inflammatory lesions, a small amount of peritoneal effusion, multiple calcifications in the right posterior lobe of the liver and splenomegaly (Figure1).



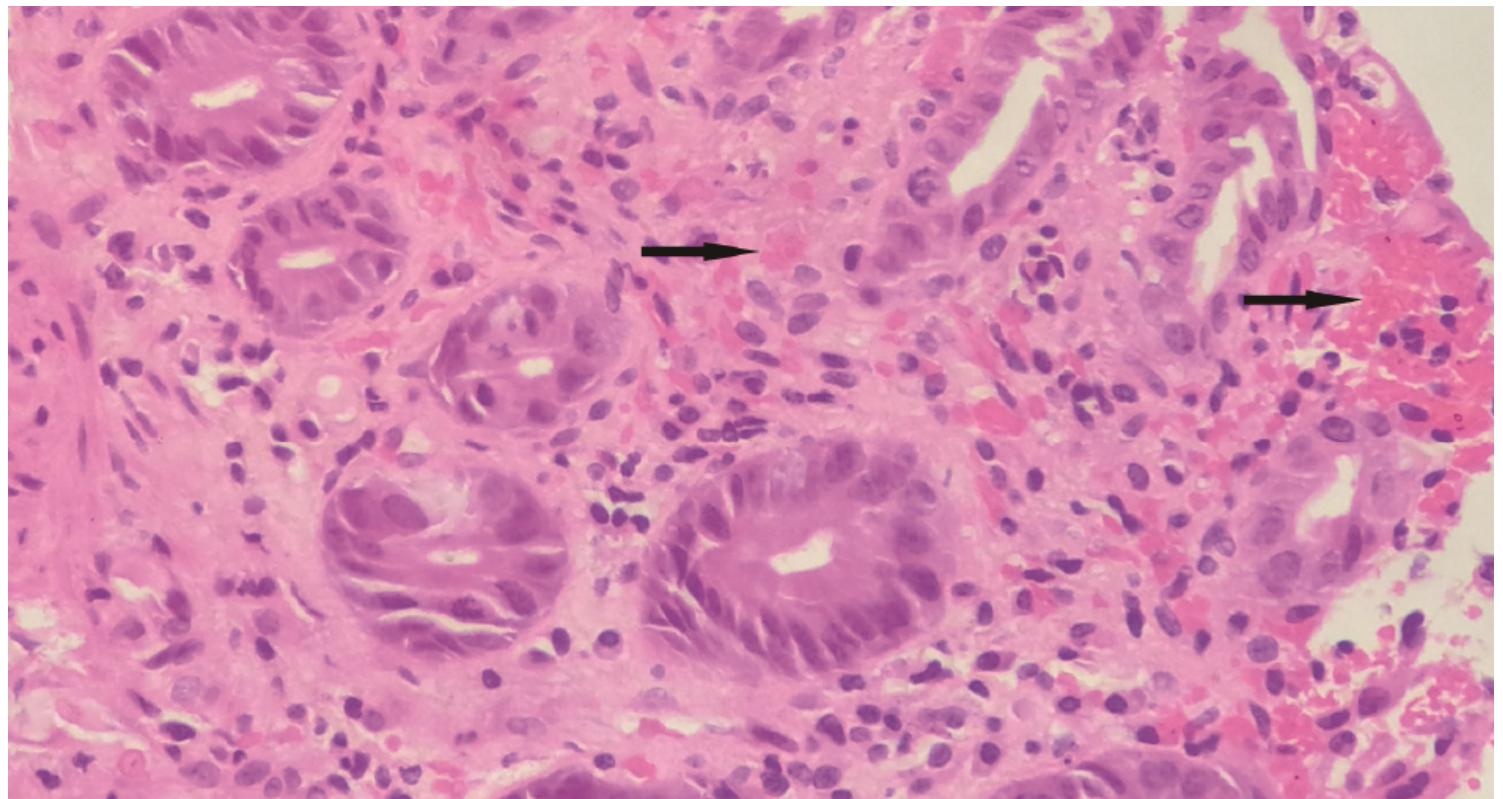
**Figure 2**

Gastroscopy revealed chronic superficial gastritis with erosion and duodenitis (Figure2).



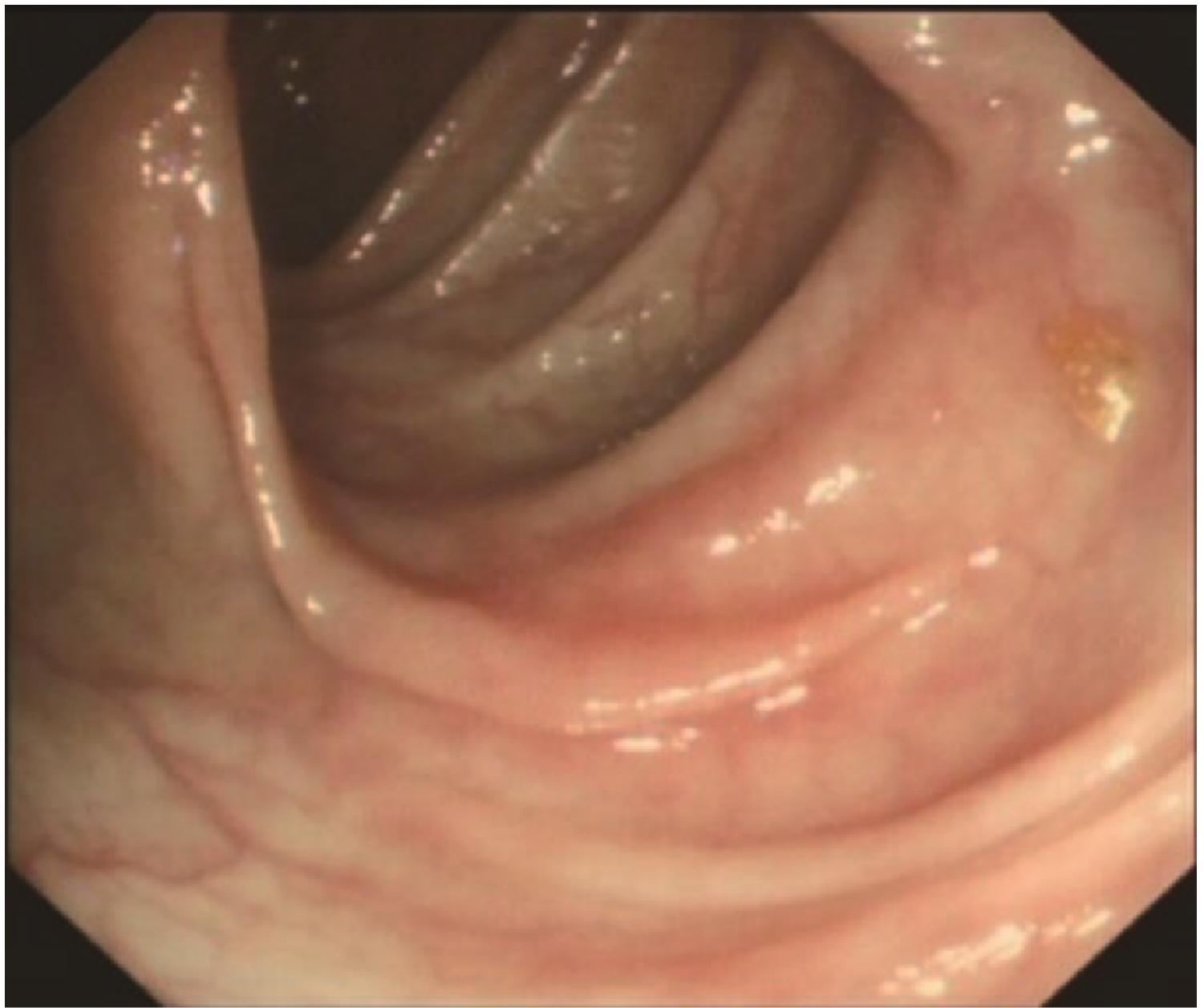
**Figure 3**

Enteroscopy was diagnosed as hemorrhagic colitis (Figure3).



**Figure 4**

Pathological results showed chronic inflammation of ascending colon mucosa with hemorrhage in the interstitium (Figure 4).



**Figure 5**

The colonoscopy results showed restoration to normal mucosal image (Figure5).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [tableS1.docx](#)
- [tableS2.docx](#)
- [PRISMA2009checklist.doc](#)