

Case Report

Fulminant necrotizing amoebic colitis presenting as acute appendicitis: a case report and comprehensive literature review

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Abstract

Intestinal amoebiasis is a parasitic infection caused by *Entamoeba histolytica*. It is commonly found in developing countries with poor hygiene. A rare, life-threatening complication of amoebiasis is fulminant necrotizing amoebic colitis (FulNAC). We report a 59-year-old male with acute lower right abdominal pain. Before coming to our institution, he was diagnosed with acute appendicitis. Extensive necrosis near the caecum involving the appendix and colon was observed intraoperatively. The patient underwent a right hemicolectomy, followed by an ileostomy and colostomy. Histopathologic examination confirmed the diagnosis of FulNAC. After the surgery, the patient was transferred to the high care unit and treated with metronidazole after histopathologic findings confirmed the etiology. The patient showed excellent response to the antibiotic prescribed, and the symptoms subsided. He was discharged from the hospital on day nine. Additionally, we reviewed fifty-one existing case reports on invasive intestinal amoebiasis worldwide, confirmed by histopathological examination following their preoperative diagnosis, surgery, pharmacology treatment, and outcomes. The learning point of this case is that intestinal amoebiasis should be considered a differential diagnosis for patients around fifty years old with bowel symptoms and travel history or living in tight quarters. Blood tests, radiological examinations, and serological evaluations are valuable diagnostic modalities. Metronidazole should be given as early as possible, and health promotion is recommended to prevent this disease in the population.

Key words: amoebiasis, intestinal, necrosis, metronidazole, Indonesia.

J Infect Dev Ctries 2022; 16(4):717-725. doi:10.3855/jidc.15419

(Received 05 June 2021 – Accepted 03 November 2021)

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Introduction

Intestinal amoebiasis is typically caused by the protozoan parasite, *Entamoeba histolytica*, which lives in two forms — invasive trophozoites and indolent cysts. Humans are the main reservoir of infection [1]. The prevalence is disproportionately more common in developing countries than in developed countries, with poor sanitation and low socioeconomic status [1,2]. Globally, it is estimated that this infection causes 40-50 million cases of amoebic colitis and has become the second leading cause of death by a parasitic disease, with a mortality rate of approximately 100,000 deaths annually due to amoebic liver abscess [2]. Amoebiasis spreads through ingestion of contaminated food or water or fecal-oral contact of cysts. Sexual contact is a rare way to spread the disease [1,3]. The clinical spectrum of intestinal amoebiasis ranges from asymptomatic carrier to severe fulminant necrotizing

colitis with bleeding and perforation. In many reports, amoebic colitis is found as ulcers in the colon and manifests as abdominal pain, dysentery with watery mucus, bloody diarrhea, and weight loss due to invasive infection of *E. histolytica* [4,5].

Fulminant necrotizing amoebic colitis (FulNAC) is an uncommon presentation of invasive amoebic colitis (less than 0.5–3% cases), which is more aggressive, life threatening, complicated and is associated with high mortality and morbidity [6,7]. FulNAC may cause large bowel gangrenous necrosis, perforation, and peritonitis [8,9], observed in the endoscopic examination as mucosal and/or submucosal ulcers [4]. Due to their low incidence and similar clinical and endoscopic findings with inflammatory bowel disease (IBD), intestinal amoebiasis is easily misdiagnosed. This misdiagnosis may cause fallacious steroid therapy, resulting in an increased possibility of devastating complications [10].

Difficult diagnosis, fulminant complications, and late treatment will aggravate the outcomes. Currently, colectomy with an ileostomy has been advocated for patients with extensive lesions, considering the poor results reported for conservative treatment [11]. However, the outcome of FulNAC is still poor after surgical treatment over the decades, ranging from 55–100% in recent years [12,13], most commonly due to septicemia as a complication of perforation and peritonitis [14,15].

FulNAC cases in Indonesia are rarely discussed. Therefore, this case report attempted to emphasize a rare case of intestinal amoebiasis, presenting as appendicitis with a large area of multiple ulcers in the colon due to a fulminant course. A comprehensive review of intestinal amoebiasis worldwide will also be discussed, which contains the lessons to be learned on diagnosing the disease, prescribing the proper treatment, and analyzing the case outcomes of survival or death.

Case presentation

A 59-year-old male presented with an acute lower right abdominal pain five days before admission. The pain was dull, colicky, and worsened each day. The

patient also had fever, nausea, vomitus, dyspnea, and a history of upper tract infection. Two days before admission, the patient had dark-red and watery stool. He has had recurring constipation for the last six months. The patient denied taking steroids or other medications. He had no alcohol consumption or smoking history. There was no history of traveling to other countries or rural areas in Indonesia. He lives in an urban, densely populated residential area. He denied any prior history of medical illness. The patient was previously diagnosed with suspected acute appendicitis in the primary health center and was referred to our hospital for further treatment.

Investigation

On admission, his blood pressure and heart rates were 140/80 mmHg and 100 beats/minute, respectively. There was shortness of breath (respiratory rate: 32 times/min) with a venous oxygen saturation of 95% and body temperature of 38.9 °C. A palpable mass with dimensions 10×10×7 cm was observed on abdominal examination in the lower right abdominal region. The mass was firm and tender with indefinite borders. The patient's abdomen was mildly distended and tender, with a positive McBurney sign. Psoas, Rovsig, or obturator sign were negative. On direct rectal examination, the rectum was empty, and the examining finger was tinged with brown stool without any mucous. The patient weighed 65 kg and was 165 cm tall. He was classified as overweight according to the Asia-Pacific BMI classification.

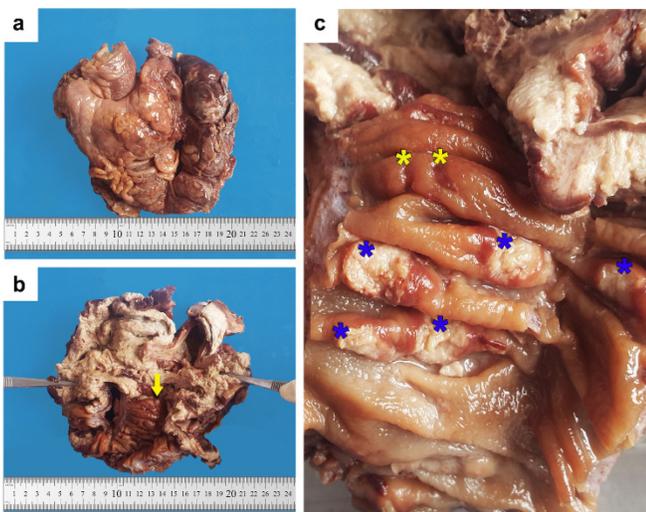
Remarkable laboratory results are leukocytosis (28,700/μL), slightly decreased Na⁺ level (130 mEq/L), increased lactate acid level (5.5 mmol/L), and slightly increased procalcitonin level (1.09 ng/mL). Hemoglobin, platelet count, and erythrocyte count were within normal limits. The panel for liver and kidney function was unremarkable. The patient tested negative for HIV, hepatitis B, and hepatitis C.

The patient's chest X-ray indicated no visible pneumoperitoneum below the diaphragm. A lung infiltrate was found, suspected to be due to pneumonia. The abdominal X-ray and CT scan were not performed due to the patient's difficulty in completing the examination maneuvers.

Preoperative diagnosis

The presumptive diagnosis for the patient was appendicular infiltrate with abscess and prior community-acquired pneumonia (CAP). A differential diagnosis of colon tumor was possible due to the

Figure 1. Findings in the gross examination of the resected specimen. (a) A surgical specimen of fulminant necrotic colitis (15.5×14.5×5 cm) shows ischemia as a complication of extensive adhesions due to near-perforation and severe acute serositis, as shown by the dark-colored segments. (b) Colon revealing extensive full-thickness necrosis, a large area of sloughing, and yellowish fibrin plaque on the surface, leaving the only little normal mucosal area (note yellow arrow pointing to a sharply demarcated ulcer). (c) Cut surface area of resected colon revealed multiple small to medium active ulcers (irregular white-colored area marked by a blue asterisk) and two healing ulcers (showed by a yellow asterisk).



patient's advanced age and complaints of changed bowel habits.

Treatment

The patient's condition was progressively worsening, and therefore he was brought to the operating room for exploratory laparotomy. Intraoperatively, infiltrative appendicitis was found, with a wide area of necrosis nearly perforating the caecum, involving the inflamed ascending colon. The patient underwent a right hemicolectomy by removing the caecum and ascending colon up to the proximal part of the transverse colon. A side-to-side anastomosis between the terminal ileum and transverse colon was performed, continued by an ileostomy and colostomy.

The resected bowel specimen of the terminal ileum to the proximal transversal colon was sent to the Anatomical Pathology laboratory for further histopathological examination. Figure 1 shows the gross appearance of the resection specimen.

Definitive diagnosis

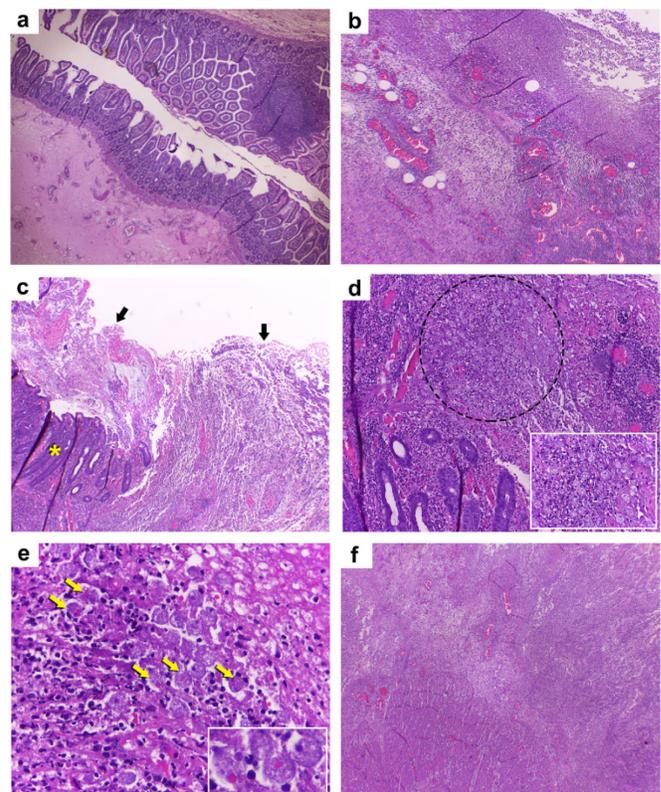
Histopathological examination confirmed the diagnosis of FulNAC due to invasive amoebiasis. Gross investigation revealed extensive necrosis in the appendix and colon with multiple ulcers and perforation. The mucosa of the appendix and colon were severely ulcerated, extending into the muscular and serosal layers. Abundant acute and chronic inflammatory cells were found along with necrosis areas. Amoebic trophozoites were easily found between necrotic areas in the appendix and colonic walls. The resection margins of the ileum were clear but showed an area of ulceration in the colonic margin. Figure 2 shows the microscopic view of the specimen.

Prognosis, follow up, and outcome

After surgery, the patient was admitted to the high care unit (HCU) ward and treated with intravenous antimicrobials (meropenem (three grams per day) and amikacin (one gram per day), analgesics, antiemetics, vitamins, and minerals for four days due to his infectious colitis and CAP. The next day, meropenem was replaced by metronidazole 500 mg every 8 hours intravenously since histopathologic findings confirmed the etiology. Metronidazole oral doses were reintiated five days after surgery and continued until ten days. Seven days after admission to HCU, the patient showed a good treatment response to the antibiotic prescribed. The symptoms subsided, and pneumonia also was resolved. The patient was then transferred to the surgical ward, and treatment was continued for two

days. On day nine, he was discharged from the hospital and prescribed cefixime 2 × 100 mg, taken orally for six days, and oral metronidazole with the same dose for the remaining days to complete the treatment course for amoebiasis. Family members were also given a short educational talk regarding disease prevention. Two weeks after being discharged, the patient visited the outpatient clinic. No sequelae to the symptoms were reported. The incision wound was perfectly closed with no sign of inflammation.

Figure 2. Histopathologic finding of fulminant necrotizing amoebiasis colitis stained by hematoxylin and eosin (H&E). (a) Ileum with unremarkable mucosa showing vast areas of submucosal and deeper edema (M40X). (b) Section of appendix showing extensive necrosis with superficial debris, M40X. (c) The colon section shows a large necrosis area with accumulated debris materials (black arrow) located side by side with unaffected mucosa (yellow asterisk), M40X. (d) Groups of amoeba invasively penetrate the submucosal layer of colon tissue with surrounding dirty basophilic debris containing neutrophils as a sign of acute inflammation (the inserted picture showed multiple amoebae in colony form), M100X. (e) Higher magnification of scant amoebic trophozoites between necrotic tissues (yellow arrow) in the colon wall. The trophozoites are unicellular, pale, round to oval with abundant cytoplasm, and have central round small nuclei with the prominent nuclear membrane and some containing ingested red blood cells (close-up of amoeba in the inserted picture), pathognomonic in the appearance of *Entamoeba histolytica*, M400X. (f) Necrosis reaches the muscular layer leading to near-perforation of the colon, M40X.



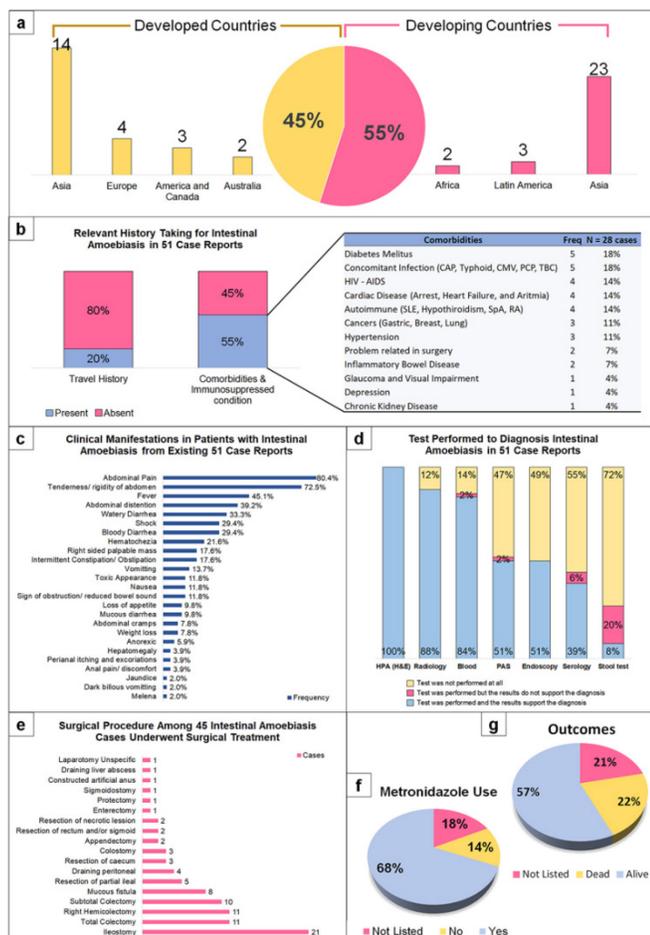
Discussion

FulNAC, as one of the disease entities in intestinal amoebiasis's disease spectrum, is a very uncommon occurrence since only 1% of intestinal amoebiasis develops into fulminant amoebic colitis [1]. Supplementary Table 1 and Figure 3a showed that intestinal amoebiasis among the fifty-one existing case reports [4,5,7,11,13–59] tends to occur mainly in developing countries; Asia remains the region with the highest incidence of amoebiasis. Most incidences in developed countries occur among travelers or visitors

from developing countries. Two studies reported the incidence of amoebiasis in Indonesia as around 10-18% [60,61], and only one case report from Indonesia was published [59].

In the cases reviewed, the highest incidence of intestinal amoebiasis was in men, possibly due to a male-related increased susceptibility to invasive disease [62]. Our patient was a 59-year-old male, similar to the median age of 54.5 years old (age range: 4–80 years) among the fifty case reports reviewed. One case of a 10-day old baby was excluded from the age calculation due to skew. Clinicians should pay more attention to males around fifty years old who are more susceptible to invasive amoebiasis and naturally will be at greater risk for complicating bowel perforation as in our patient. Fortunately, in this case, there was only near-perforation with moderate peritonitis in this patient. Perforation and peritonitis cause absorption of toxins, destruction of tissue, and passage of bacteria, consequently increasing the mortality rate towards 75–100%. It also potentially causes septicemia, shock, and multi-organ failure, which considerably worsens the prognosis [11]. In addition, the physician should also be alerted that, although it rarely occurs in the pediatric population, in this review, four cases were found to occur in children aged 4–9 years old [54].

Figure 3. Findings related to diagnosis of the spectrum of intestinal amoebiasis based on a review of 51 case reports around the world. (a) the incidences of intestinal amoebiasis across countries based on research reports. (b) specific medical history related to amoebiasis. (c) clinical manifestations presented. (d) test performed to diagnose amoebiasis. (e) surgical procedures. (f) metronidazole use. (g) outcomes of patients reported. Notes: HIV-AIDS (Human Immunodeficiency Virus infection - Acquired Immunodeficiency Syndrome); SLE (Systemic Lupus Erythematosus); SpA (Spondyloarthritis); RA (Rheumatoid Arthritis); CAP (Community-Acquired Pneumonia); CMV (Cytomegalovirus); PCP (Pneumocystis Carinii Pneumonia); H&E (Haematoxyllin and Eosin); HPA (Histopathological examination by H&E stain); PAS (Periodic acid–Schiff stain).



Medical history

While reviewing the medical history of a patient with acute abdominal complaints, several points needed to be considered: traveling history to endemic and rural areas, immunosuppressive conditions such as steroid consumption, susceptible populations (pediatric, pregnant, and geriatric) [32], malnutrition, and HIV-AIDS status [63]. In the fifty-one cases presented in Figure 3b, it turns out that ten patients reported travel history to endemic/rural areas. In addition, 27 patients had comorbidities and immunosuppressive conditions, which correlates to intrusive amoebiasis. These conditions included diabetes mellitus [13,15,20,36,47], HIV-AIDS [22,23,42,54], acute or chronic heart disease [33,38], autoimmune disease [37,44,56], hypothyroidism [50], cancers [5,14,21], hypertension [5,29,47], pregnancy [32], chronic kidney disease [27], and concomitant infection [40,42,53], as also presented in our reported patient with CAP.

Concurrent infection with CAP was also found in the case report by Arvind *et al.* [33]. In this case, the etiology of the pneumonia was not definitively worked up, although pulmonary amoebiasis can also present due to hematogenous dissemination in several studies [64,65]. The patient's condition improved after

treatment with empiric antibiotics. Amoebiasis is a usual opportunistic infection among patients with HIV infection associated with immunosuppressive conditions [63]. In our scenario, the patient did not have other risk factors except possibly poor hygiene related to living in a dense living space and concomitant infection as a worsening contributor.

Clinical manifestations

The symptoms of intestinal amoebiasis are not specific. Around 80–90% of infected individuals remain asymptomatic and appear to be misdiagnosed [9,34,66]. Due to the low incidence of intestinal amoebiasis in the developed world, signs and symptoms of this disease entity are not familiar, resulting in common misdiagnosis as IBD [4,17,27,32]. The summary in Figure 3c demonstrates that the five most common symptoms are abdominal pain, abdominal tenderness, fever, abdominal distention, and diarrhea, either watery or bloody. In addition, patients often present with shock or rectal bleeding, and when examined, a right-sided palpable mass is found. Nevertheless, the most important question still unsettled is how only around 10% of patients with intestinal amoebiasis present with symptoms [67]. The susceptibility to worse prognosis related to host or parasite genomics is still unknown [68].

In this case, the patient had acute lower right abdominal pain, fever, nausea, vomiting, and bloody stool, similar to the literature. The abdomen was distended and tender. There was also a firm and tender mass in the lower right region with a positive McBurney sign-on palpation. Our patient was suspected of having an abscess of the appendix. A preoperative working diagnosis of amoebic appendicitis, specifically FulNAC, is almost impossible to work up due to the symptoms being indistinct. Appendicitis of amoebic origin is relatively rare, and the incidence reported is 0.5–2.3% in endemic areas [35,69,70]. However, around a third of cases of amoebic appendicitis are complex and have high mortality rates compared to other causes of appendicitis [7,71,72].

Diagnostic test modalities

Patients with suspicion of an acute abdomen should be investigated through blood checks and radiology to establish a preoperative diagnosis. According to the review in Figure 3d, these two tests were valuable to support a presumptive diagnosis. In blood tests, valuable parameters are leukocytosis, neutrophilia, anemia, increased markers of liver injury, and elevated inflammation marker such as C-reactive protein (CRP),

procalcitonin, and erythrocyte sedimentation rate (ESR) [32,42,45,46,73]. Various radiological modalities can include X-rays, ultrasonography (USG), or computed tomography (CT) scans. Both abdominal and chest X-rays will support the diagnosis if findings include: pneumatosis of the intestinal wall, distention, gas under the diaphragm, and multiple air-fluid levels [20,25]. USG will reveal dilated bowel loops [36]. At the same time, a CT scan can show edematous and diffuse wall thickening of the colon, dilated terminal ileum and colonic loops, bowel ischemia and necrosis, gangrenous changes, perforating intestines, pneumoperitoneum, liver cyst, and liver abscess with or without rupture [5,33,42,45,46,73]. In this case, the patient had leukocytosis and increased procalcitonin level indicating local infection. Furthermore, a chest X-ray was performed to exclude signs of peritonitis and found no free air under the diaphragm, along with lung infiltration findings, suggesting pneumonia.

Various studies attempted to diagnose amoebiasis using fecal analysis to find acute bleeding, stool culture, parasitic cysts, and trophozoites. A fecal examination is unfavorable due to low detection rate (up to only 50%) [7]. Of the cases reviewed, only 8% of cases were reported with positive fecal findings, 20% had non-specific results, and in the remaining 72%, a fecal examination was not performed. Serology of antigen and antibody, detection of stool antigen, and isoenzyme/zymodeme analysis are helpful and remain effective while waiting for the definitive diagnostic tool of histopathology to identify *E. histolytica* as a pathogenic etiology of the acute abdomen [4,74]. Endoscopically, the physician can find a discrete and random distribution of ulcers resembling IBD. The literature review found four reports presenting patients with prior IBD suspicion before a definitive diagnosis of amoebiasis [4,17,27,32]. However, we did not perform an endoscopy for this patient due to his acute condition.

Surgical treatment

Amoebiasis primarily affects the colon and liver, with the caecum and ascending colon being involved in 70% of the cases [10,36]. In this case, FulNAC made an extensive necrotic area consisting of the caecum, appendix, ascending colon, and transverse colon, similar to a previous study [75]. As presented in this patient, any part of the colon can be involved, predominantly on the right side [31,75]. The non-invasive cysts transform into highly motile trophozoites in the terminal ileum and proximal colon to establish tremendous tissue injury. They attack and burrow

within the colonic mucosa and more extensively into submucosal layers resulting in submucosal flask-shaped ulcers as a pathognomonic sign of amoebic colitis [1,4].

The patient underwent a right hemicolectomy followed by construction of ileostomy and colostomy. Eleven case reports showed that right hemicolectomy is the typical procedure in treating several cases of amoebic colitis, although the option of the course is highly dependent on individual characteristics and disease presentation [15,18,51,23,28–30,34,37,40,47]. The other more common surgical procedures, as presented in Figure 3e, are total and subtotal colectomy accompanied by ileostomy.

Postoperative histopathologic examination

In the gross examination, the colon specimen, in this case, showed ischemia as a complication of extensive adhesions due to perforation and severe acute serositis, demonstrated by dark-colored segments. Extensive full-thickness necrosis, large sloughing, and yellowish fibrin plaques on the surface, leaving only little normal mucosal patches, were observed. Additionally, multiple ulcers also presented on the surface of the colonic mucosa. In our case, the colonic margin of the specimen had an ulcerative area. This condition indicates extensive involvement of the entire colon of the patient.

Microscopically, necrosis was found as deep as the muscular layer, which leads to near-perforation of the colon. Bowel perforation is a rare complication of amoebiasis with a 1–6% frequency, leading to mortality [52]. Histopathological examination has a vital role in revealing the definitive diagnosis of intestinal amoebiasis. However, it is quite challenging to detect trophozoites in usual practice due to the rarity of trophozoites or cysts within the debris of necrotic ulcers, and it needs excellent suspicion and logical thinking. PAS stains are recommended to confirm the histopathological findings if the appearance is unremarkable [35]. In hematoxylin and eosin-stained slides, the blue 'ghost-like appearance' and ingested red blood cells (RBCs) are highly associated with *Entamoeba* and are a direction to its identification within ulcers [34]. In our cases, colonies with ingested red blood cells were noted in the resected specimen, as presented in Figure 2e.

Differentiating amoebic colitis cases from IBD is essential to eliminate fallacious treatment and poor disease outcomes. Corticosteroids, a first-choice drug in IBD, are contraindicated for amoebic colitis and may result in progressive disease and possible development

of FulNAC and intestinal perforations [10]. However, patients previously diagnosed with IBD should also be ruled out for the presence of amoebic colitis since reports show a relatively high prevalence of amoebiasis in patients with IBD [76].

Pharmacological treatment

The patient showed an excellent response to treatment after the definitive antibiotic metronidazole was given in the HCU. Thus, identifying an etiologic pathogen through histopathologic findings is warranted to achieve the best outcomes. As noted in Figure 3f, metronidazole was often used in cases of amoebiasis and gave satisfactory improvement. Thirty-five cases (69%) used it individually or combined with other antimicrobials; seven patients did not use it; however, nine other cases did not list the medication data. Metronidazole empirically in the perioperative phase can be beneficial for patients with acute abdomen. Cysts of *E. histolytica* rapidly spread throughout the digestive tract, and around 10% of them will develop into highly motile trophozoites with worse manifestations if treatment is delayed [4].

Treatment of amoebiasis is emphasized to eradicate highly motile trophozoites and eliminate cysts in the intestinal tissue. For the invasive spectrum of amoebiasis, the primary therapy options are metronidazole 500–750 mg three times a day for ten days or tinidazole 2 g once daily for three days [22,77]. Several studies used metronidazole for 7–14 days [17,22,23,26,28,30–32,35,38,39,43,46,47,49,55]. In a systematic review, tinidazole had decreased clinical failure rate and lower frequency of adverse events than metronidazole [77]. Although metronidazole or tinidazole alone are successful in eliminating intestinal cysts, adding a second luminal agent is still the best option for effectively treating amoebiasis, such as diloxanide furoate (500 mg three times a day for ten days) or paromomycin (25–30 mg/kg BW per day for seven days) [77].

Outcomes

The outcome of this patient was good, and no sequelae were followed up in two weeks. Severe intestinal amoebiasis can heal with proper surgery, adequate pharmacological therapy, and sufficient nutritional intake. As presented in Figure 3g, 29 studies stated that their patients with intestinal amoebiasis were alive (57%) with an average length of time for discharge and recovery of 5–30 days; 11 cases were reported to end in death (mortality rate: 22%); either before surgery (30 minutes after admission), or four days to two

months after surgery. The remaining reports did not specify the outcome (22%). In Japan, the overall mortality rate of amoebic appendicitis reported from 12 summarized articles was 25% [40]. It is considerably higher than in a systematic review conducted by Otan *et al.* (5.5%) [72]. This high mortality rate is due to delayed treatment with metronidazole [35]. Even though surgery had been performed, considerable intestinal wall inflammation still required metronidazole treatment.

The researchers are aware of some limitations present in the presented case. No preoperative imaging data were taken due to the patient's worsening condition. In addition, the presence of amoeba was not confirmed from fecal specimens. However, the histopathological examination confirmed the presence of amoeba in the tissue in large numbers. Despite those limitations, FulNAC studies presenting appendicitis are rarely presented, and cases from Indonesia have not been published comprehensively, and this case study is important since it contains critical clinical data. This article also presents comprehensive literature on the data regarding amoebic colitis in various regions.

Conclusions

FulNAC is a part of the amoebic colitis disease spectrum with high mortality rate and is a great imitator of several etiology of acute abdominal pain. Clinicians should pay more attention to any bowel symptoms, and care must be taken to exclude this disease entity, including in prior or newly suspected IBD patients. It is recommended to be more cautious of this disease in male patients around fifty years of age, especially those with immunosuppressive conditions. Moreover, it is beneficial to consider travel history. It is highly recommended to perform preoperative blood examination, imaging modalities, and serological testing to check for amoebiasis colitis in treating patients. Several works of literature favor early presumptive anti-amoebic therapy in severe colitis diagnosis in endemic areas to improve survival and outcomes. Further research to evaluate FulNAC cases is needed to understand susceptibility factors, the majority of asymptomatic incidences, risk factors, and prevention of complicating effects of FulNAC.

Consent

The patient has given his consent and permission for publication with de-identified details. The consent form can be retrieved on request from Editors. The CARE guidelines were followed for this case report writing.

Authors' Contribution

NR conceptualized the case report, provided histopathological data, and wrote the manuscript. MH collected clinical data, searched and reviewed the literature, and made contribution to the manuscript's writing. ASP performed the clinical examination, surgical treatment, and follow-up of the patient. DRH released the histopathological data of the patient and reviewed the manuscript. MS and EK performed the final review and editing of the manuscript. All authors have read and approved the final version of the manuscript.

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Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

Supplementary Table 1. Summary of findings of existing intestinal amoebiasis case reports worldwide among patients who underwent histopathological examination.

No	Author, year	Country	Sex	Age	Number of signs and symptoms identified*	Onset (days)	Travel	Comorbidities (de novo or prior medical illness)	Preoperative Test					Presumptive/ Preliminary diagnosis	Operative Procedure	HPA/ PAS	Final Highlighted Definitive Diagnosis	Metronidazole Use (Duration)	Outcome (Time of death/ discharge/ recovery)
									Blood	Scrology	Stool test	Radiology	Endoscopy						
1.	Present case	Indonesia	M	59	10	5	No	CAP	+	—	—	+	—	Appendicitis or colon tumor	Right hemicolectomy, ileostomy, colostomy	+ / —	FulNAC presenting as appendicitis	Yes (10 days)	Alive (day 9)
2.	Tomino [5], 2021	Japan	M	64	6	N/A	No	Depression, HT, Lung carcinoma	+	—	—	+	+	Intussusception, perforation	Colectomy and enterectomy	+ / +	FAC	No	Dead (day 10)
3.	Beg [13], 2020	India	M	50	7	5	No	DM	+	—	—	+	—	Non-specific acute abdomen Paralytic ileus (due to electrolyte imbalance)	Subtotal colectomy and ileostomy	+ / +	FulNAC of the whole large bowel	Yes (20 days)	Alive (day 8)
4.	Kiriwathuduwa [57], 2020	Sri Lanka	M	9	7	7	No	Bilateral glaucoma and VI	+	—	—	+	+	Total colectomy, ileostomy; creating a mucous fistula	Resection of necrotic ileum, caecum, and ileocaecal junction	+ / +	Acute FulNAC	Yes (30 days)	Alive (month 1)
5.	Verma [58], 2020	India	M	45	5	3	No	Chronic alcoholism	—	—	—	+	—	Intestinal obstruction	Resection of necrotic ileum, caecum, and ileocaecal junction	+ / +	Amoebic colitis presents as an intestinal obstruction; perforation	Not listed	Not listed
6.	Kamarlis [59], 2020	Indonesia	M	4	2	N/A	No	Congenital anal fistula	—	—	—	—	+	Enterocolitis	No surgery treatment	+ / —	Invasive Amoebiasis	Not listed	Not listed
7.	Maryam [16], 2020	US	M	63	6	6 mo	No	No	—	+	—	+	+	Infectious colitis or UC	No surgery performed	+ / —	FAC	Yes (N/A)	Not listed
8.	Cheng [17], 2020	Malaysia	M	54	2	1 year	Yes	No	—	—	—	—	+	IBD	No surgery treatment	+ / +	Caecal amoebiasis mimicking IBD	Yes (10 days)	Alive (year 1)
9.	Kaushik [18], 2020	India	M	72	5	10	No	No	—	—	—	+	—	Non-specific acute abdomen	Right hemicolectomy, end ileostomy.	+ / +	Acute FulNAC	Not listed	Alive (day 9)
10.	Morris [19], 2019	Australia	M	73	3	14	Yes	No	+	—	—	+	—	Non-specific acute abdomen	Total colectomy	+ / —	FAC causing shock	No	Alive (N/A)
11.	Wang [4], 2019	Canada	M	49	4	N/A	No	No	NS	—	—	+	+	IBD	Total colectomy, ileal resection	+ / NS	Intestinal amoebiasis, multiple colonic and ileal perforation	No	Dead (month 2)
12.	Rodriguez-Wong [20], 2018	Mexico	M	67	7	7	No	DM	+	+	—	+	—	Non-specific acute abdomen	Subtotal colectomy	+ / —	FAC with caecal pneumatosis	Not listed	Not listed
13.	Umamoto [21], 2018	Japan	M	71	4	7	No	Right breast cancer	+	—	NS	+	—	Non-specific acute abdomen	Total colectomy, partial removal of ileum, ileostomy	+ / +	Acute FulNAC	Yes (15 days)	Dead (day 23)
14.	Wingfield [22], 2018	UK	M	56	2	14	Yes	HIV	+	+	NS	+	—	Infective gastroenteritis	Subtotal colectomy	+ / —	Invasive intestinal amoebiasis	Yes (14 days)	Alive (week 5)
15.	Ciftci [23], 2018	Turkey	F	74	6	14	Yes	HIV	+	+	NS	+	+	Acute abdomen with peritonitis and perforation	Right hemicolectomy, ileostomy, and ileo-transverse anastomosis	+ / —	FAC	Yes (10 days)	Alive (day 26)
16.	Kinoo [24], 2018	South Africa	M	59	7	7	No	No	+	—	—	+	+	Non-specific acute abdomen	Diverting loop ileostomy	+ / —	FAC	Not listed	Not listed
17.	Raviraj [25], 2017	Sri Lanka	M	65	3	N/A	No	No	+	+	+	+	+	Intestinal obstruction	Subtotal colectomy and colostomy	+ / +	FulNAC	Not listed	Not listed
18.	Ueno [26], 2017	Japan	M	80	3	N/A	No	No	+	+	—	+	+	Non-specific acute abdomen with peritonitis	Total colectomy, mucous fistula, ileostomy, drainage of intraperitoneal	+ / —	FAC	Yes (14 days)	Alive (day 20)
19.	Jhavar [27], 2016	India	F	63	2	N/A	No	CKD	+	NS	NS	+	+	IBD	No surgery treatment	+ / +	Acute FulNAC in atypical presentation	Yes (N/A)	Alive (N/A)
20.	Ichikawa [7], 2016	Japan	M	47	2	N/A	No	No	+	—	NS	+	+	Acute appendicitis	Appendectomy	+ / +	Amoebic appendicitis	No	Alive (day 5)
21.	Mitra [28], 2016	India	M	5	7	5	No	No	+	+	—	+	+	Non-specific acute abdomen	Right hemicolectomy, ileostomy, mucous fistula of the ileum	+ / +	FAC	Yes (10 days)	Alive (day 10)
22.	Al-Rehily [29], 2016	Saudi Arabia	M	54	8	N/A	Yes	HT	+	+	—	+	—	Obstructing colonic carcinoma with liver metastases	Right hemicolectomy, resection of partial ileum, ileostomy, drainage of liver abscess	+ / +	Amoeboma	Yes (8 days)	Dead (day 16)
23.	Gardiner [30], 2015	Australia	M	74	5	14	No	No	+	+	—	+	—	Non-specific acute abdomen	Right hemicolectomy and peritoneal lavage	+ / —	Amoebic colitis	Yes (10 days)	Alive (week 2)
24.	Raj [31], 2015	India	M	4	2	14	No	No	+	—	—	+	+	Peritonitis	Ileocecal resection, ileostomy, colostomy	+ / +	Acute FulNAC with perforation, peritonitis	Yes (11 days)	Alive (day 11)
25.	Goto [32], 2015	Japan	F	30	5	9	No	Post e-section (P3A3)	+	+	—	—	—	IBD, peritonitis, ascites; necrosis of intestine	Necrotomy, draining of ascites, construction of artificial anus	+ / +	Fulminant amoebic enteritis on post-partum female	Yes (10 days)	Alive (day 45)
26.	Arvind [33], 2015	Malaysia	M	41	4	10	Yes	ADHF, AF, CAP	+	—	—	+	+	Non-specific acute abdomen	Subtotal colectomy and end ileostomy	+ / —	FAC	No	Alive (day 18)
27.	Moorchung [34], 2014	India	M	57	7	5	No	No	+	+	—	+	—	Non-specific acute abdomen	Right hemicolectomy, ileostomy	+ / —	Caecal amoebic colitis mimicking obstructing colonic carcinoma with liver metastases	Yes (N/A)	Alive (N/A)
28.	Ito [35], 2014	Japan	F	31	2	2	No	No	+	+	+	+	+	Acute appendicitis and enterocolitis	Appendectomy	+ / +	Amoebic appendicitis	Yes (12 days)	Alive (day 12)
29.	Saha [36], 2014	India	M	65	9	6	No	DM	+	—	—	+	—	Non-specific acute abdomen with the sign of ileus	Resection of perforated caecum; ileostomy; and mucous fistula	+ / —	Invasive amoebiasis with colonic amoeboma	Yes (N/A)	Not listed
30.	Restrepo [37], 2014	Brazil	F	46	5	14	No	SpA on anti TNF therapy	+	—	—	—	—	Acute peritonitis	Right hemicolectomy, mucous fistula, peritoneal drainage	+ / —	Colonic perforation due to amoebic colitis during anti-TNF therapy	Yes (30 days)	Alive (month 2)
31.	Hugelshofer [38], 2013	Switzerland	F	45	7	14	No	Cardiac arrest + VF	+	—	NS	+	—	Non-specific acute abdomen	Total colectomy	+ / —	Toxic megacolon due to FAC	Yes (10 days)	Alive (week 3)
32.	Lin [39], 2013	Taiwan	M	45	3	4	No	No	+	—	—	+	+	Colon carcinoma	No surgery performed	+ / +	Amoeboma, a colon carcinoma-like lesion	Yes (14 days)	Alive (day 3)
33.	Shilpa [40], 2013	India	M	55	8	N/A	No	Typhoid 15 days back	—	—	—	+	—	Non-specific acute abdomen	Right hemicolectomy	+ / +	Acute FulNAC	Not listed	Not listed
34.	Phadke [41], 2013	India	M	22	2	10	No	No	—	—	—	—	—	Ruptured liver abscess	No surgery performed	+ / +	Ruptured liver abscess; amoebic colitis	Not listed	Dead (minute30)
35.	Torigoe [42], 2012	Japan	M	29	2	N/A	No	AIDS, CMV, PCP	+	+	—	+	—	Perianal abscess	End-sigmoidectomy, necrotomy of the perianal skin, and proctectomy	+ / —	Acute FAC developing perianal ulcer and necrosis of the skin	Yes (N/A)	Alive (month 11)
36.	Pirti [43], 2012	Turkey	M	62	8	2	No	No	+	—	—	+	+	Inflammation of caecal mass and appendicitis.	PCNL, right hemicolectomy, removal of the middle part of the ureter	+ / +	Colonic amoebiasis with complicating hydronephrosis	Yes (7 days)	Alive (day 7)
37.	Lee [44], 2012	South Korea	F	47	3	1	No	SLE, AIHA	+	NS	—	+	+	Intestinal vasculitis	Total colectomy and end-ileostomy	+ / +	FAC	Yes (30 days)	Alive (month 1)

37.	Arora [45], 2012	India	M	54	3	14	No	No	+	+	—	+	—	Non-specific acute abdomen	Non-specific laparotomy	+ / —	FulNAC	Yes (N/A)	Not listed
38.	Kawazoe [46], 2012	Japan	M	63	3	7	No	No	+	+	+	+	+	Non-specific acute abdomen	No surgery performed	+ / —	Amoebic colitis with atypical symptoms	Yes (14 days)	Alive (N/A)
39.	Ishioaka [15], 2011	Japan	M	39	8	2	Yes	DM	+	+	NS	+	+	Peritonitis and obstructing colonic carcinoma	Right hemicolectomy, ileostomy, and resection of perforated caecal	+ / +	Amoeboma of the colon mimicking colonic carcinoma	Yes (N/A)	Not listed
40.	Lizcano [47], 2011	Colombia	F	53	4	5	No	DM and HT	+	—	—	+	—	Appendicitis complicated by appendical mass adhesions	Right radical hemicolectomy, terminal lateral ileoileostomy	+ / +	Caecal amoeboma as a complication of intestinal amoebiasis	Yes (7 days)	Alive (day 7)
41.	Koh [48], 2010	Malaysia	M	58	7	30	No	No	+	—	—	—	+	Amoebic colitis	Total colectomy; and end-ileostomy	+ / +	Amoebic and fungal colitis (<i>H. capsulatum</i>)	Yes (5 days)	Not listed
42.	Hanaoka [14], 2009	Japan	M	52	7	6	No	Gastric cancer	+	—	—	+	+	Peritonitis	Colostomy; peritoneal lavage	+ / —	FAC	Yes (N/A)	Dead (day 50)
43.	Gupta [49], 2009	India	M	68	5	1	No	IBD	+	NS	—	+	—	Non-specific acute abdomen	Total colectomy, ileostomy, creation of a mucous fistula	+ / —	Acute FulNAC	Yes (12 days)	Dead (day 12)
44.	McGregor [50], 2007	UK	F	58	8	12	Yes	Hypo-thyroidism	+	+	NS	+	—	Non-specific acute abdomen	Subtotal colectomy, ileostomy	+ / +	FAC after loperamide use prior to the hospital	Yes (N/A)	Alive (N/A)
45.	Ng [51], 2006	Hong-kong	M	57	5	10	Yes	No	+	+	—	+	—	Obstructing colonic carcinoma with liver metastases	Right hemicolectomy	+ / —	Colonic amoebic abscess mimicking carcinoma of the colon	Yes (N/A)	Alive (week 6)
46.	Ishida [52], 2003	Japan	M	48	2	7	No	IBD (UC)	+	+	—	+	+	Non-specific acute abdomen	Total colectomy, rectosigmoid mucous fistula, drainage of peritoneal, ileostomy.	+ / +	FAC	Yes (30 days)	Alive (month 1)
47.	Shimada [11], 2002	Japan	M	62	6	1	No	No	+	+	+	+	+	Acute appendicitis	Total colectomy, ileostomy	+ / —	Acute FulNAC	Yes (22 days)	Dead (day 22)
48.	Park [53], 2000	South Korea	M	49	6	7	No	Intestinal TBC	+	—	—	+	—	Diverticular perforation	Subtotal colectomy; resection of partial ileum, ileostomy	+ / +	Toxic AC coexisting with Intestinal TBC	Not listed	Dead (day 6)
49.	Rennert [54], 2000	South Africa	M	<1	6	7	No	Probable HIV from Mother (+)	+	—	NS	+	+	Necrotizing enterocolitis	Rectosigmoid resection and placement of diversion colostomy	+ / —	FAC	No	Dead (day 10)
50.	Babb [55], 1985	US	F	55	5	7	Yes	No	+	—	NS	+	—	Sepsis and acute abdomen	Total colectomy; ileostomy; removal of the rectum	+ / —	Acute FAC	Yes (14 days)	Alive (week 6)
51.	Essenhigh [56], 1966	UK	M	56	7	20	No	RA	+	—	—	+	—	Perforated diverticulitis; mesenteric vascular occlusion	Subtotal colectomy; ileostomy; sigmoid colon exteriorization	+ / —	Massive necrosis of the colon due to amoebiasis	No	Dead (day 4)

*Signs and symptom identified is presented in Figure 3. M: male; F: female; N/A: no data mentioned in the article; "+": Test was performed, and the results support the diagnosis, NS: Test was performed, but the results were not specific or did not support the diagnosis; "—": Test was not performed at all; ADHF: Acute Decompensated Heart Failure; AF: Atrial Fibrillation; AIDS: Acquired Immunodeficiency Syndrome; AIHA: Autoimmune Hemolytic Anemia; CAP: Community-Acquired Pneumonia; CKD: Chronic Kidney Disease; CMV: Cytomegalovirus; DM: Diabetes Mellitus; C-section: Caesarean section; FAC: Fulminant Amoebic Colitis; FulNAC: Fulminant Necrotizing Amoebic Colitis; *H. capsulatum*: *Histoplasma capsulatum*; HIV: Human Immunodeficiency Virus infection; HPA: Histopathological examination by H&E stain; HT: Hypertension; IBD: Inflammatory Bowel Disease; P3A3: Para 3, Abortus 3; PAS: Periodic Acid Schiff stain; PCNL: Percutaneous Nephrolithotomy; PCP: Pneumocystis Carinii Pneumonia; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematosus; SpA: Spondyloarthritis; TBC: Tuberculosis; TNF: Tumor Necrosis Factor; UC: Ulcerative Colitis; UK: United Kingdom; US: United States; VF: Ventricular Fibrillation; VI: Visual Impairment.