

Diagnostic Problems in Crohn's Disease: A Case Report

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ABSTRACT

Crohn's disease is marked by transmural inflammation of the digestive tract and is categorized into inflammatory bowel disease (IBD). In Indonesia, Simadibrata et al, reported 20% from 107 patients who experienced non-infective chronic diarrhea, actually suffered from IBD.

A 33-year old male patient complained of watery stool since 3 months before hospital admission. He experienced stabbing stomachache and loss of body weight. Physical and laboratory examination results were within normal limits. Faecal analysis revealed intestinal infection caused by gram-negative bacteria and intestinal maldigestion. Colonoscopy examination exhibited the presence of hyperemic mucosa, edematous, and positive cobblestone appearance in the terminal ileum. Additionally, the histological evaluation showed the impression of chronic ileitis usually found in IBD. Meanwhile, moderate pangastritis was obtained in the esophagoduodenoscopy examination. Results of histological biopsy of the antrum showed absence of Helicobacter pylori infection. An active lesion in chronic ileitis was found in immunohistochemistry examination. Acid fast bacterial culture was also performed to the ileum tissue and revealed negative results in clinical microbiology examination. From the examinations conducted, patient was diagnosed as Crohn's disease and treated with budesonide capsule 3 mg and mesalazine tablet 1,000 mg twice daily. Later, he felt improvement of the complains.

This case illustrated Crohn's disease which is rarely found in Indonesia. This is because diagnosis requires supporting examinations which could only be done in tertiary health care facilities. However, possibility of other diagnosis should be considered, particularly intestinal tuberculosis and infective colitis. Early diagnosis and prompt treatment may improve patient's prognosis and quality of life.

Keywords: IBD, Crohn's disease, positive cobblestone

ABSTRAK

Penyakit Crohn ditandai oleh peradangan transmural saluran pencernaan, dan dikategorikan dalam kelompok penyakit peradangan usus. Di Indonesia, Simadibrata dkk, melaporkan 20% dari 107 pasien yang mengalami diare kronik non infeksi menderita penyakit peradangan usus.

Pasien laki-laki usia 33 tahun datang dengan keluhan buang air besar (BAB) cair sejak 3 bulan sebelum masuk rumah sakit. Pasien juga merasakan nyeri perut seperti ditusuk-tusuk dan penurunan berat badan. Dari pemeriksaan fisik dan laboratorium dalam batas normal. Pada analisa feses didapatkan infeksi usus karena bakteri gram negatif serta maldigesti usus. Pemeriksaan kolonoskopi menunjukkan pada ileum terminal ditemukan mukosa hiperemis, edematous dengan cobblestone positif serta dari pemeriksaan patologi anatomi (PA) didapatkan kesan ileitis kronik yang dapat ditemukan pada penyakit peradangan usus. Sementara pada esofagogastroduodenoskopi didapatkan pangastritis sedang. Hasil biopsi PA dari antrum menyatakan tidak ditemukan Helicobacter pylori. Pemeriksaan imunohistokimia menunjukkan suatu lesi aktif pada ileitis kronik. Pada pasien dilakukan pula pemeriksaan bakteri tahan asam kultur dari jaringan ileum di bagian mikrobiologi

klinik dan didapatkan hasil negatif. Dari hasil pemeriksaan tersebut, pasien diduga menderita penyakit Crohn. Pasien mendapat pengobatan budesonide kapsul 3 mg 2 kali sehari, serta mesalazine tablet 1000 mg 2 kali sehari. Pasien merasakan keluhan perbaikan.

Kasus ini menggambarkan penyakit Crohn yang jarang ditemukan di Indonesia, dikarenakan membutuhkan pemeriksaan penunjang yang hanya bisa dilakukan di sarana pelayanan tersier. Kemungkinan diagnosis lain harus dipertimbangkan terutama tuberkulosis usus dan kolitis infeksi. Diagnosis dini dan tatalaksana yang tepat dapat memperbaiki prognosis dan kualitas hidup pasien.

Kata kunci: IBD, penyakit Crohn, cobblestone positif

INTRODUCTION

Crohn's disease is a problem with uncertain etiology, which is marked by transmural inflammation of the digestive tract. This inflammation frequently causes fibrosis and intestinal obstruction not usually found in ulcerative colitis. Nonetheless, microperforation and fistulas could also be present.¹ It is predicted that 1.4 million people in the United States suffered from Crohn's disease or ulcerative colitis, collectively known as inflammatory bowel disease (IBD). IBD is rarely found in Indonesia, which is then become the reason why patients with IBD problems frequently late to be diagnosed and treated. Simadibrata et al, reported 20% from 107 patients who experienced non-infective chronic diarrhea, actually suffered from IBD.¹⁻³ This study also reported that the incidence of Crohn's disease in Indonesia was still lower compared to Western countries, though it tends to increase. Incidence of Crohn's disease in this study was higher compared to ulcerative colitis. This is in contrast with the findings in North Europe and North America which showed that the incidence of ulcerative colitis was higher compared to Crohn.⁴

Clinical manifestation of Crohn's disease varies from initial clinical presentation, including: fever, stomachache, diarrhea, loss of body weight, malnutrition, and gastrointestinal bleeding. Thus, adequate knowledge is needed to differentiate it with other diseases. In Indonesia, intestinal tuberculosis (TB) and infective colitis need to be considered as the differential diagnoses. Complaints in intestinal TB is usually unspecific. Establishment of diagnosis may be complicated with the absence of pulmonary tuberculosis.^{2,4} Negative tuberculin test cannot be used to exclude the diagnosis, also acid fast bacilli culture of the intestinal tissue does not always show positive results. In endoscopic examination of IBD, sometimes we found similarity with intestinal tuberculosis, including the presence of ulcerative mucosa and hyperemic and fragile pseudopolyps.^{5,6} This case report will discuss problems

in diagnosing and treating Crohn's disease in 33-years old male.

CASE ILLUSTRATION

A patient, 33-year old male complained of watery stool since 3 months before hospital admission. Patient experienced watery stool and sometimes soft stool five times/day, approximately 150 cc every time he defecated; no blood or mucous in the stool. He also complained of stabbing stomachache, no pain in the anus, no nausea or vomit, and no fever. He had consumed loperamide and amoxicillin and felt the frequency of diarrhea decreased, however stomachache was still present. He went to the Gastroenterology Clinic in Cipto Mangunkusumo Hospital to seek for treatment and received metronidazole tablet, rebamipide tablet 100 mg, and New Diatab[®] tablet three times daily. He felt that the frequency of diarrhea decreased to 1-2 times per day. However, stomachache was still present. History of blackish stool and nodule in the anus which came out during defecation were denied.

A month later, patient came for follow-up and to undergo several diagnostic examinations, such as fecal analysis, endoscopy and biopsy, mantoux test, and complete blood count. Result of complete blood count was hemoglobin (Hb) 14.9 g/dL, hematocrite (Ht) 41.7%, erythrocytes 5.25 million/mm³, mean corpuscular volume (MCV) 79.4 fL, mean corpuscular hemoglobin (MCH) 28.4 pg, mean corpuscular hemoglobin concentration (MCHC) 35.7 g/dL, leukocytes 6,500/mm³, and thrombocytes 220,000/mm³. In addition, result of differential count was basophils 0.2, eosinophils 0.9, neutrophils 70%, lymphocytes 21.1%, and monocytes 7.8%. From electrolyte examination, it was found that sodium 136 mEq/dL, potassium 3.77 mEq/L, and chloride 108 mEq/L. Other results were serum aspartate transaminase (AST) 18 u/L, alanine aminotransaminase (ALT) 28 u/L, ureum 19 mg/dL, creatinine 0.8 mg/dL, random blood glucose

83 mg/dL, normal urinalysis, HIV negative, mantoux negative. Faecal analysis revealed intestinal infection caused by gram negative bacteria and intestinal maldigestion. X-ray examination was within normal limits. Colonoscopy examination was performed to the patient and impression of grade 2 internal hemorrhoid with ileitis (differential diagnosis of Crohn's disease) was obtained. Esophagoduodenoscopy examination revealed the presence of moderate erosive pangastritis (Figure 1 and 2). Results of the histological biopsy of the antrum stated that no *Helicobacter pylori* (*H. pylori*) was found. From biopsy of antrum and duodenum, impression of reactive gastroduodenitis was obtained, while from biopsy of the ileum, presence of malignant lymphoma was suspected.

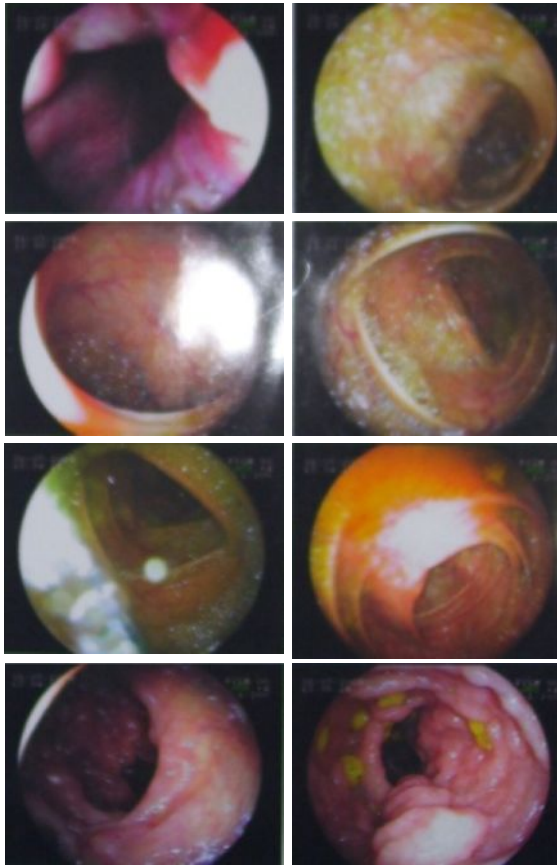


Figure 1. Initial colonoscopic result showed cobblestone appearance in Crohn's disease

Later, examination to the patient was continued with immunohistochemistry examination with an active lesion in chronic ileitis and acid fast bacilli culture from ileum tissue show negative result. From the results of performed examinations, patient was suspected to suffer from Crohn's disease. Patient received budesonide capsule 3 mg and mesalazine tablet 1,000 mg twice daily. Later, he felt improvement in complains.

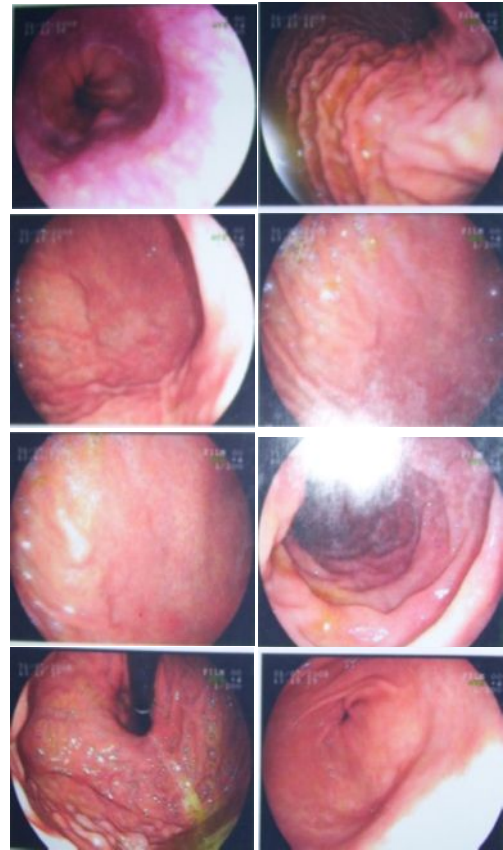


Figure 2. Initial EGD result showed moderate erosive pangastritis

Three days before hospital admission, patient complained of increasing watery stool became 3 times per day, no mucous or blood. Other complains were fatigue, decrease appetite, and nausea but no vomit. He was then hospitalized. He also felt that his body weight decrease from 80 kg to 57 kg in the last 2 months. He felt fever which is not too high at the early course of illness and no night sweat. History of cough for a long period and contact with tuberculosis patient was denied. He also had a habit of eating spicy food, soupy, and rarely consume vegetables or in big portion. He used to consume snacks between meals. He did not smoke or drink alcohol. There was no previous history of diabetes mellitus, hypertension, heart disease, and allergy. In family history, there was no family members who experienced similar complains.

From physical examination, it was found that patient was fully alert, blood pressure 120/80 mmHg, heart rate 80 beats/minute, afebris, and respiratory rate 20 times/minute. Body weight was 57 kg and height was 175 cm, with body mass index 18.6 kg/m². Skin turgor was adequate, conjunctiva not pale or icteric, wet lips mucosa, JVP 5-2 cmH₂O, lungs and heart were within normal limits. From the abdominal examination, following data was obtained: flat abdomen, supple, normal bowel sound, liver and spleen were not

palpable and no pain on deep palpation. There was no lymph node enlargement, either in cervical, axilla, or inguinal region and warm acral. Rectal touché revealed the presence of soft mass in the 3 o'clock region and no blood was found. Additionally, the results of laboratory examination were Hb 16.4 g/dL, Ht 47.2%, erythrocytes 5.5 million/mm³, MCV 85.8 fL, MCH 29.8 pg, MCHC 34.7 g/dL, leukocytes 6300/mm³, and thrombocytes 237,000 mm³. In the differential count, it was found that basophils 0.1, eosinophils 1.3, neutrophils 65%, lymphocytes 21.5%, and monocytes 12.1%. Results of electrolyte examination were sodium 143 mEq/L, potassium 3.54 mEq/L, and chloride 112 mEq/L.

Patient underwent repeated colonoscopy, which exhibited the presence of hyperemic mucosa, edematous with positive cobblestone in terminal ileum (Figure 3). Besides, histological examination of ileum tissue found specimen with pieces of ileum mucosal tissue with shortened and rounded villi. Lamina propria was full of immediate inflammatory cells and eosinophil cells. In addition, lymphoid follicle was also observed and impression of chronic ileitis could be found in IBD was obtained (Figure 4).

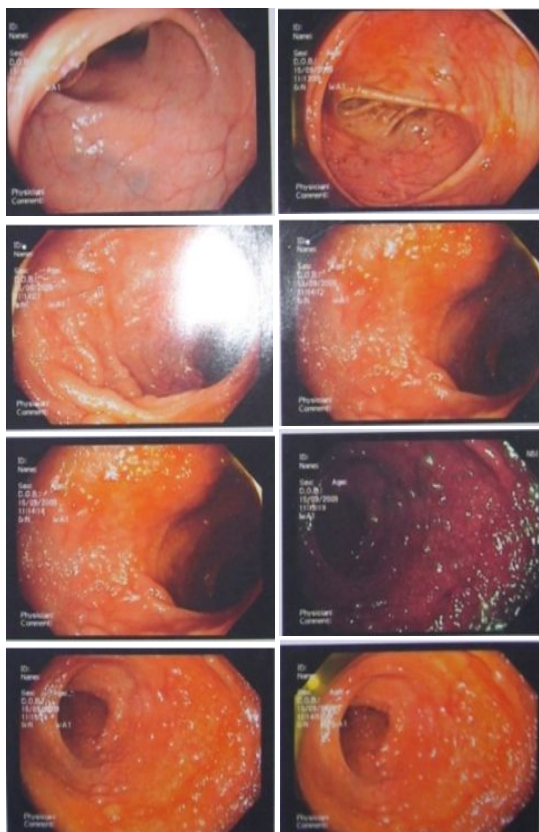


Figure 3. Repeated colonoscopy revealed presence of cobblestone appearance in Crohn's disease

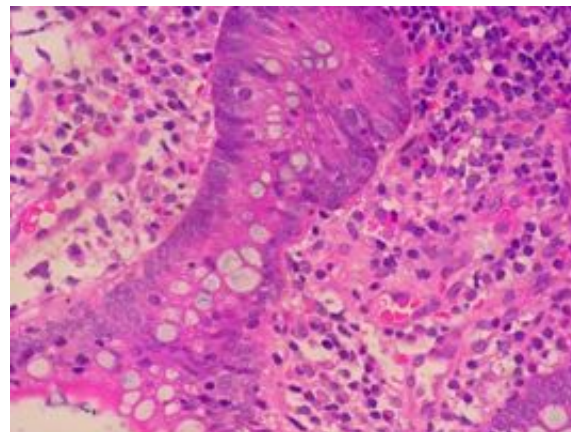


Figure 4. Anatomy pathology examination of ileum tissue showed impression of chronic ileitis in IBD

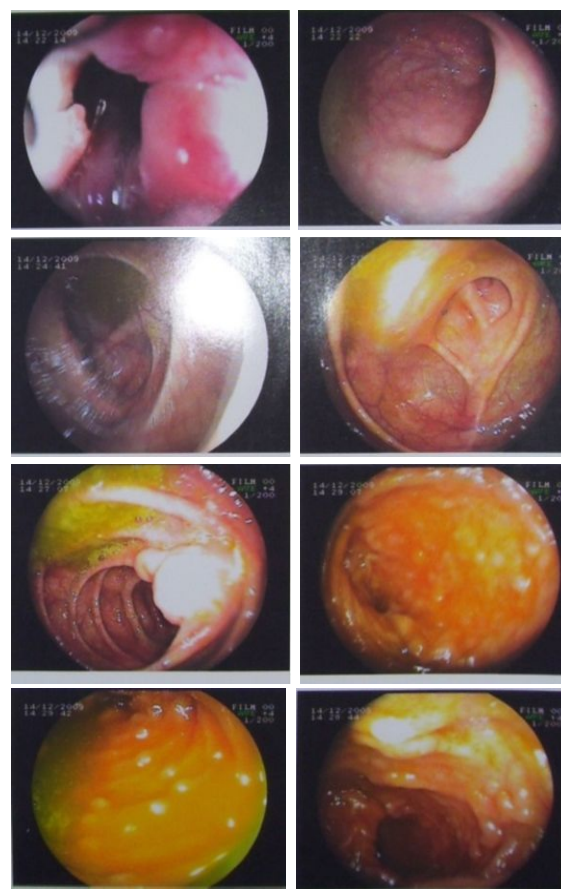


Figure 5. Final colonoscopic examination revealed improvement of cobblestone appearance

Patient was given parenteral nutrition intravenously 500 cc in 8 hours twice daily and intravenous lactated ringer IV in 8 hours once daily, rebamipide tablet three times daily, sucralfate 1 spoon once daily, ondansetron tablet 8 mg three times daily, budesonide capsule 3 mg and mesalazine tablet 1,000 mg twice daily, and 1,900 kkal diet without fiber. After treatment, patient experienced clinical improvement with decrease frequency of defecating and was planned to undergo outpatient treatment with therapy of budesonide

capsule 3 mg and mesalazine tablet 1,000 mg twice daily, and rebamipide tablet 100 mg three times daily.

Patient later undergo final colonoscopy examination and results exhibited positive multiple inflammatory polyp, and no mass, which was in accordance with impression of improvement of Crohn's disease (Figure 5). Currently, patient was still continuing therapy with the regimen of budesonide capsule 3 mg and mesalazine tablet 1,000 mg twice daily.

DISCUSSION

Clinical manifestation of Crohn's disease varies compared to ulcerative colitis due to transmural involvement and variable severity of the disease. Fatigue, prolonged diarrhea accompanied with stomachache, decrease of body weight, and fever, with or without bleeding are characteristics of Crohn's disease. However, 10% patients with Crohn's disease did not experience diarrhea. Growth problems commonly occur in children and can be seen before other clinical manifestation of this disease become apparent. In some patients, there could be a fistula or abdominal abscess which both has variable clinical manifestations depending on the location and severity.⁷

Patients may experience the same symptoms for years before diagnosed.⁷ This is described in series of studies with 66 IBD patients, which comprises of 45 patients with Crohn's disease and the other 21 patients with ulcerative colitis. Non-specific gastrointestinal symptoms mimicking inflammatory bowel disease could be found averagely for 7.7 years before diagnosis of Crohn's disease was established. This is significantly longer compared to the time needed to establish the diagnosis of ulcerative colitis (average 1.2 years).^{7,8} Clinical manifestations specific for most patients with Crohn ileitis, ileocolitis, or colitis are diarrhea, stomachache, decrease body weight, and fever.⁹ Diarrhea can be caused by (1) excess of fluid secretion which disrupt the absorption of fluid in inflamed intestine or bowel, (2) malabsorption of bile salt due to terminal ileum inflammation or resection, and (3) steatorrhea associated with ileum resection and loss of bile salt. Bacterial overgrowth from the strictured intestine, enterocolonic fistula, and extensive jejunal disease may also lead to steatorrhea. Furthermore, ileitis and Crohn colitis are difficult to be differentiated, except for colitis is limited to the left colon. In this patient, bloody stool similar to ulcerative colitis could be found.⁹

Systemic symptoms, such as fatigue, loss of body weight, and fever are main systemic symptoms in

Crohn's disease. Body weight is a general complain commonly associated with decrease intake, as patient felt well when they did not eat. Body weight may also be related to malabsorption. Fever found in patient with Crohn's disease is usually with unknown origin. However, it may be caused by inflammation process or resulted from perforation with complication of intestinal infection.^{3,10}

Variable clinical description sometimes complicate in differentiating it with other diseases commonly found in Indonesia, such as infective colitis and intestinal tuberculosis. It is also difficult to differentiate Crohn's disease from gastrointestinal tuberculosis through endoscopic, radiologic, and histological examinations, particularly due to the same anatomic predilection, the ileocaecal region.^{3,10}

In intestinal tuberculosis, symptoms found are anorexia, weakness, fever, night sweat, decrease body weight, diarrhea, constipation, or bloody stool. Palpated mass in the right lower quadrant is found in 25-50% patients; presence of intestinal obstruction and colon perforation have also been reported. Presence of ascites is useful to distinguish intestinal TB with Crohn's disease.⁶ In this patient, there was complain of diarrhea since the previous 3 months, accompanied with stabbing stomachache, fever on the initial period of illness, and no blood or mucous in stool. Nonetheless, patient complained of significant decrease of body weight which reached 23 kg with decrease of appetite.

Diagnosis is usually determined through endoscopy examination with appropriate clinical history in patient. Colonoscopy is the main examination used to ascertain the diagnosis of Crohn's disease. In endoscopy, we could find ulcerative focus located near the normal mucosal region and mucosa which had changed into polypoid and gave cobblestone and pseudopolyps appearance.^{2,7}

In intestinal TB, endoscopic findings which can be obtained varied from ulcer, stricture, nodule, pseudopolyp, fistula, and abnormality of ileocaecal valve. Ulcer in TB tends to be round in shape and is usually surrounded by inflamed mucosa. Conversely, ulcer in Crohn's disease is surrounded by normal mucosa and or the presence of cobblestone appearance.^{2,5}

Intestinal biopsy is usually performed to confirm endoscopic findings. Specimen obtained from surgery has higher diagnostic value compared to specimen obtained through endoscopy. This is because lesion in Crohn's disease usually has transmural character which

is difficult to be obtained by using biopsy technique through endoscopy. Main finding is the presence of tuberculoid granuloma (in 20-40% cases) accompanied with macrophage infiltration and lymphocytes in lamina propria with deep ulceration. Granuloma in TB tend to be bigger and confluent, frequently accompanied with caseous, and ulcer surrounded by histiocytes epithel aggregation and submucosal inflammation. Differently, granuloma found in Crohn's disease is usually small in size, not confluent, and no caseous is found. Granuloma can also be found in *Yersinia spp*, Bechet disease, and lymphoma.^{2,6}

Radiologic examination may also be useful in determining location and length of stricture in Crohn's disease if it affects digestive tract segment which cannot be accessed by colonoscopy. Double contrast barium may visualize the presence of stricture, fistulation, irregular mucosa, ulcer appearance, and polyp or even alteration on colon lumen distensibility in the form of intestinal wall thickening and haustre. Radiologic evaluation currently is being developed through the use of computed tomography (CT) and magnetic resonance imaging (MRI), particularly to detect the presence of abscess or fistula.^{7,11}

In this patient, colonoscopic examination has been conducted with the result of second degree internal hemorrhoid and ileitis. Erosive pangastritis was found in EGD examination. Anatomy pathology result of antrum biopsy revealed absence of *H. pylori*. From the biopsy of antrum and duodenum, impression of reactive gastroduodenitis was obtained; while from the biopsy of ileum, presence of malignant lymphoma was suspected. Immunohistochemistry examination exhibited an active lesion in chronic ileitis. Acid fast bacilli culture from ileum tissue showed negative result.

In the repeated endoscopy examination, there was hyperemic mucosa, edematous and positive cobblestone in the terminal ileum. Furthermore, anatomy pathology examination revealed impression of chronic ileitis usually found in IBD. Presence of abnormal laboratory parameter, including hemoglobin level, leukocytes, erythrocytes sedimentation rate (ESR), thrombocytes, C-reactive protein, serum iron level may occur in IBD cases, though these may also be present in infection cases. There was no significant difference in the laboratory results of ulcerative colitis and Crohn's disease, similarly with intestinal TB. However, tuberculin test could be done though with a limitation of not being able to determine active disease with previous immune sensitization.^{12,13}

Elevated CRP level has been observed in patients with IBD and found to be higher in Crohn's disease compared to ulcerative colitis. This finding showed that determination of CRP may have a role in differentiating between these diseases, and also to differentiate IBD patients from patients with symptoms caused by other diseases.¹²

Crohn's disease has several complications. Local complication associated with inflammatory activity includes intestinal obstruction, bleeding, acute perforation, development of fistula abscess, and megacolon toxic.¹ Similar to ulcerative colitis, there seem to be an increase risk of colorectal cancer in patients with Crohn colitis, which has occurred for a long time. In regard to the similar degree and duration of illness, risk in Crohn's disease may be similar with ulcerative colitis, knowing the incidence of adenocarcinoma in Crohn's disease is also higher compared to general population.¹³

Generally, with suspect of the presence of factor/pro-inflammatory agent in the form of intestinal intralumen bacteria and daily diet component which could provoke chronic inflammation process, elimination through antibiotic administration, intestinal lavage, binding bacterial products, resting the intestinal work, and diet changes was attempted.¹

Till date, glucocorticoid is the drug of choice in all degree of Crohn's disease. Usually, the chosen drugs are prednisone, methylprednisolone, and enema steroid. In severe condition, enteral steroid could be administered. Dose given to reach emission phase is similar to prednisone 40-60 mg, and usually 60-80% patients showed positive response after administration for 10-14 days. Further, tapering dose was given until remission was reached in 8-12 weeks. If good response has been achieved, maintenance dose of mesalazine tablet 3 g/day or budesonide capsul 6 mg/day was administered.^{1,14}

Therapy in Crohn's disease also used 5-aminosalicylic acid tablet with the dose of 2-4 g/day or sulfasalazin caplet 2 g/day. After monitoring for 3-4 weeks, if no positive response was achieved, therapy can be continued with antibiotic administration such as metronidazole tablet 10 mg/kg/day, combination of metronidazole and ciprofloxacin, rifamixin tablet 800 mg twice daily or clarythromycin tablet 50 mg twice daily. Corticosteroid is used in mild disease which does not response to administration of previous regimen explained above or in patients with severe initial symptoms.^{1,14} If refracter, administration of immunomodulator, such as azathiophrine, 6-mercaptopurine, methotrexate,

infliximab, adalimumab, and certolizumab can be considered.^{1,14} In certain cases or in cases with complication of perforation, massive bleeding, stenosis due to ileus, and megacolon toxic, surgical intervention is required.¹

Initially, patient received metronidazole tablet 500 mg three times daily. There was improvement in symptoms of diarrhea, though nausea was still present due to adverse reaction of drugs. After diagnosis of Crohn's disease has been confirmed, patient received budesonide capsule 3 mg and mesalazine tablet 1000 mg twice daily. Patient experienced clinical improvement and after final endoscopic evaluation, impression of improvement in Crohn's disease was obtained.

Prognosis in patients with Crohn's disease was 10-20% patient will experience prolonged remission after initial presentation.¹⁵ Predictor of bad prognosis in a study includes age < 40, presence of perianal disease, and earlier administration of corticosteroid.

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