Description of Colonoscopy and Histopathology of Chronic Diarrhea Causes in Non-Neoplasm: Literature Review

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ABSTRACT

Chronic diarrhea is a diarrhea symptom which persists for ≥ 4 weeks as a symptom of a disease. Chronic diarrhea is a symptom that often becomes the patient's main reason for referral to gastroenterologist. In general, the prevalence of chronic diarrhea is estimated to be 5% in each population, but there are obstacles in diagnosing the cause of chronic diarrhea. This is due to many differential diagnoses as the cause of chronic diarrhea. The aetiology of chronic diarrhea could be neoplasm and non-neoplasm. In several studies, through results of colonoscopy and histopathology, it was found that the most common cause of chronic diarrhea was non-neoplasm, including inflammatory bowel disease (IBD), microscopic colitis as a risk factor, and infectious colitis as a differential diagnosis. Each of those diseases has similar symptoms, but different pathological description.

Through descriptions of colonoscopy and histopathology of chronic diarrhea causes, it is possible to differentiate each non-neoplasm causes of chronic diarrhea. It could facilitate in differentiating the causes of chronic diarrhea especially in non-neoplasm cases, therefore possibly establishing a definite diagnosis.

Keywords: *chronic diarrhea, colonoscopy, histopathology, inflammatory bowel disease (IBD), microscopic colitis, infectious colitis.*

ABSTRACT

Diare kronik adalah gejala diare yang berlangsung ≥ 4 minggu yang merupakan suatu gejala dari penyakit. Diare kronik menjadi suatu gejala yang sering menjadi alasan pasien ke gastroenterologi. Secara umum prevalensi diare kronik sekitar 5% pada setiap populasi, namun memiliki kendala dalam mendiagnosis penyebab diare kronik. Hal ini disebabkan banyaknya diagnosis banding penyebab diare kronik. Penyebab diare kronik dapat berupa neoplasma dan non-neoplasma. Dalam beberapa penelitian, melalui hasil gambaran kolonoskopi dan histopatologi didapatkan penyebab diare kronik terbanyak adalah non neoplasma, yaitu inflammatory bowel disease (IBD), Microscopic colitis sebagai salah satu factor risiko IBD dan infectious colitis sebagai diagnosis banding IBD. Masing-masing penyakit tersebut memiliki gejala yang mirip, namun gambaran patologi yang berbeda.

Melalui gambaran kolonoskopi dan histopatologi penyebab diare kronik dapat membedakan setiap penyebab diare kronik pada non neoplasm. Hal tersebut memudahkan dalam melihat perbedaan antara penyebab diare kronik terutama pada non neoplasm, sehingga dapat menegakkan diagnosis pasti.

Kata kunci: *chronic diarrhea, colonoscopy, histopatology, inflammatory bowel disease (IBD), microscopic colitis, infectious colitis*

INTRODUCTION

Chronic diarrhea is the condition of faeces with watery consistency and frequency of ≥ 3 times within 24 hours with weight of faeces >200 g/24 hours, which could persist up to ≥ 4 weeks.[1,2,3] Chronic diarrhea is a general symptom that may occur in several diseases and becomes one of the most common causes of referral to the gastroenterology clinic. Chronic diarrhea affects approximately 5% of each population in a certain span of time and around 7-14% in elderly populations.[1,2,4]

The causes of chronic diarrhea are quite diverse and are not always caused by intestinal disorders. The causes could be neoplasm or non-neoplasm. The most common cause of chronic diarrhea is inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease (CD). Moreover, it could be caused by microscopic colitis, colorectal cancer, maldigestion, influence of certain drugs, and infectious colitis.[1,2,5,6] Those causes are difficult to differentiate as they exhibited similar symptoms. Therefore it becomes an obstacle in diagnosing the cause of chronic diarrhea.

Procedures of colonoscopy and biopsy are needed to assist in providing a definitive diagnosis as the cause of chronic diarrhea. In a study, procedures of colonoscopy and biopsy could lead to a definitive diagnosis of chronic diarrhea in approximately 15-31% of cases. The most common diagnoses are non-neoplasms such as IBD, microscopic colitis as a risk factor for IBD, and infectious colitis as a differential diagnosis of IBD.[1,2] Since non-neoplasm causes of chronic diarrhea are affected by several diseases with similar symptoms, this review discusses the description of colonoscopy and histopathology of non-neoplasm causes of chronic diarrhea.

INFLAMMATORY BOWEL DISEASE (IBD)

Inflammatory bowel disease (IBD) is a disease with mucosal immune activation, resulting in continuous chronic intestinal inflammation.[7] IBD is a global disease and health problem throughout the world since the beginning of the 21st century.[7,8,9]

The type of IBD can be seen from the difference in colonoscopy and histopathological features. Using colonoscopy, we can identify the involved segment, from the terminal ileum to the rectum. In histopathology examination, it is possible to compare the normal and the abnormal tissue, to help determining the degree of histological changes in the patient.[9] In such examination, there are 2 main types of IBD, namely ulcerative colitis and Crohn's disease, with histopathologic results as follows: architectural abnormalities including crypt branching/shortening, decreased crypt density, and irregular mucosal surface and inflammatory feature including transmucosal increase of lamina propria mononuclear cells, and the presence of epithelioid granulomas.[10]

Ulcerative Colitis

Ulcerative colitis is a chronic inflammatory disease of the intestines which could involve the rectum and continuous to spread proximally. The main symptoms are bloody diarrhea, abdominal pains, faecal urgency, and tenesmus.[11,12]

Based on the Montreal classification, lesion locations in ulcerative colitis are classified into proctitis (lesion limited to the rectum), left-sided (lesion limited to the distal colonic mucosa to the splenic flexure), and extensive (limited proximal to the splenic flexure).[13] According to several studies, based on lesion locations according to the Montreal classifications, proctitis (lesion limited to the rectum) was dominantly found.[9,11,14,15,16] However, in some cases it can spread proximal colon, sometimes involving the entire colon (pancolitis).[9,17]

Lesion which could be identified in colonoscopy descriptions of ulcerative colitis can be identified based on the severity of the disease.[18] In the acute phase, the lesions were identified due to the signs of inflammation, such as erythema of the mucosa, irregular vascular pattern, oedema, and erosion or even ulceration of the mucosa with irregular size.[9,13,14,19] In addition, there are reddish bumps called pseudopolypes with small and variation shapes.[19] In the advanced stage, the colon become narrowed and shortened, and stenosis occurs. In the recovery stage, there are usually no ulcers, mucosal atrophy, and in some cases the mucosa is normal.[13,18]

Furthermore, in the appearance of abnormal lesions, tissues were taken for biopsy with the aim to identify the histopathology of the lesions. In the acute phase, there is an increase in inflammatory cells, such as infiltration of neutrophil and eosinophils in the lamina propria, basal plasmocytosis and basal lymphoid aggregates, as well as the accumulation of neutrophils in the crypt which forms crypt abscess.[19,20] The progressive damage to the crypt causes changes in crypt form, such as crypt atrophy, crypt branching, crypt shortening, and crypt distortion.[9,11,14,19,21] There could be diffused damages to the mucosa, such as abnormal epithelial cells, mucin depletion, and Paneth cell metaplasia, which is an indication of chronic colitis. In the recovery stage, usually there is the presence of normal mucosa with increased mucin. However, there is still an abnormal

gland with irregular shape, gap between the crypt and the muscularis mucosa, Paneth cell metaplasia.[15,18]

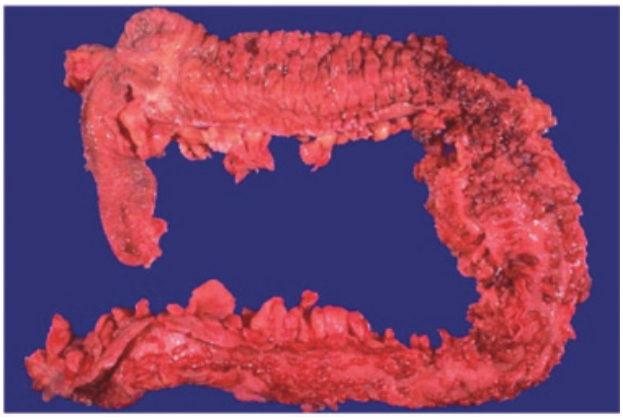

Figure 1. Macroscopic features of ulcerative colitis. Diffuse erythema, edema, and many inflammatory polyps are noted in the rectum, left colon, transverse colon, and hepatic flexure.[22]

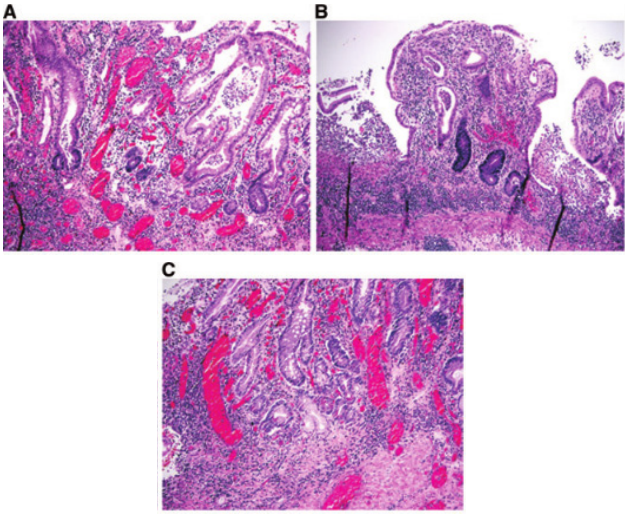

Figure 2. Microscopic featues of ulcerative colitis. A and B: architectural distortion, including shortening of crypts, variation in the sizes and shapes of crypts, and basal lymphoplasmacytosis. C: paneth cell metaplasia and pyloric gland metaplasia in the left colon[22]

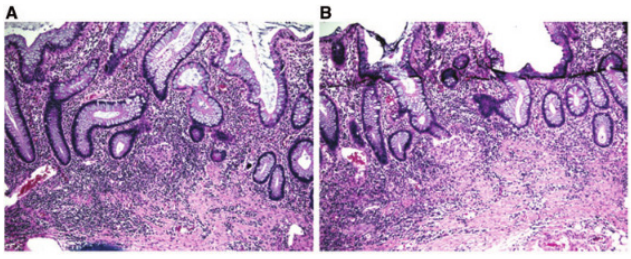

Figure 3. A. proximity of histiocytes near a crypt. B: association of histiocytes with damaged crypts on deeper levels[22]

Crohn's Disease

Crohn's disease is a chronic inflammation of the digestive tract, from the mouth to the anus, most commonly found in the ileum and colon.[7,9,23] The main symptoms in Crohn's disease are abdominal pain, watery diarrhea, and weight loss.[9]

Based on the Montreal classification, lesions in Crohn's disease are divided into L1 (ileal), L2 (colonic), L3 (ileocolonic), and L4 (upper GI).[13] According to several studies, based on the Montreal classification, lesions were dominantly found in the ileocolonic segment.[9,15,24,25,26,27] Additionally, Crohn's disease lesions are often found on the right side of the colon and is extremely rare in the rectum. The distribution of the lesion is spread to certain segments only, rarely completely.[26,28]

Lesions which could be identified in colonoscopy descriptions of Crohn's disease were signs of inflammation and distributions per segments, rarely found thoroughly. The forms of the lesion that can be found as signs inflammation include irregular vascular pattern, erythema, erosion or even ulceration, called aphthous ulcer, which then enlarges and deepens, then forming edema.[15,21,25] In the healing stage, there is the formation of scars which causes strictures, friability, and presence of cobblestoning.[9,28,29] Lesions which are characteristics of Crohn's disease are aphthous ulcer and cobblestoning (an area a like to a round stone due to presence of longitudinal and circular gap along with ulcer which separates mucosal surface).[9,24]

Furthermore, histopathological examination in Crohn's disease showed crypt abnormalities such as focal crypt atrophy and distortion, and villous atrophy.[15,21] Additionally, there were also inflammatory cells infiltration such as epithelial cell non caseating granuloma, focal inflammation in lamina propria, focal cryptitis, focal crypt abscess, eosinophil infiltrate in mucosal layer, lymphoplasmocytic infiltrate in submucosal layer, and lymphoplasmocytic infiltrate in

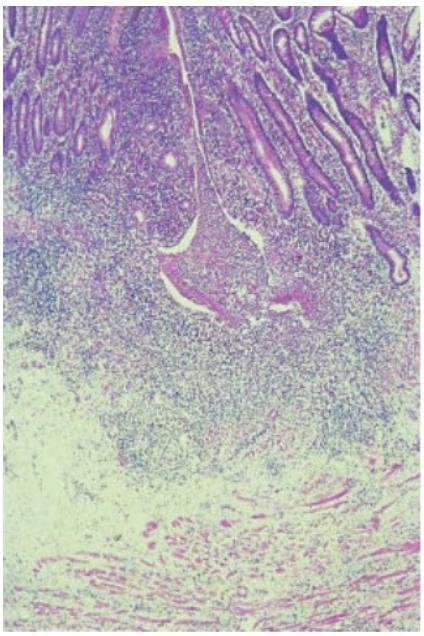

Figure 4. Crohn's disease. Aphthoid ulcer In the ileum: early mucosal ulcer, centrally located and appearing as a mountain top ulcer[31]

muscular layer.[25,30] Complications in Crohn's disease can include carcinoma of the colon, but the incidence is lower than that of ulcerative colitis. Characteristics found are mucosal changes, such as Paneth cell metaplasia and neural cell hyperplasia.[9,26]

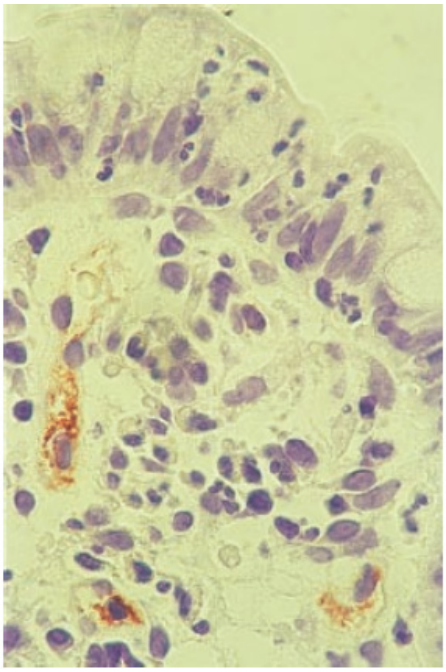

Figure 5. Early mucosal lesion in Crohn's disease (CD) be associated with damage of small capillaries[31]

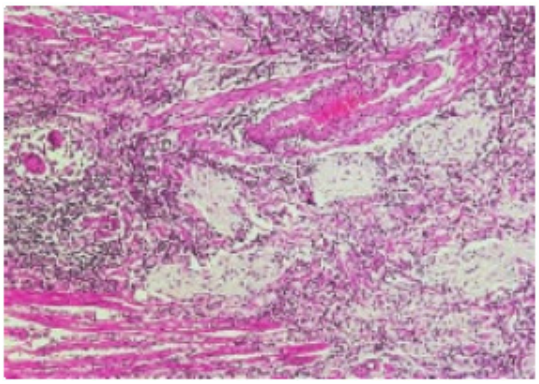

Figure 6. Crohn's disease is characterized by the presence of granulomas and by hyperplasia of the submucosal nerves, sometimes called neuromatous lesion.[31]

MICROSCOPIC COLITIS

Microscopic colitis is an idiopathic disease with chronic diarrhea, not bloody nor watery, without weight loss, despite the presence of abnormality on endosocopy.[32,33,34,35] Microscopic colitis is divided into 2 types: collagenous colitis (CC) and lymphocytic colitis (LC) with the same clinical symptoms, but differences in the histopathology descriptions. Histopathological descriptions are required to determine the diagnosis by procedures of endoscopy.[32,33] In several studies, it was found that the occurrence of Lymphocytic Colitis is more common than Collagenous Colitis.[32,34,36]

Colonoscopic descriptions in microscopic colitis could be found in the terminal ileum, right side colon, left side colon, and some in the rectum.[32,37,38] Lesion in the right colon is mostly found in collagenous colitis, while lesion in the left colon, mostly found in lymphocytic colitis.[34,33] In those areas, there were several lesions identified such as normal mucosa and abnormal mucosa. In the abnormal mucosa, there could be found inflammation signs such as erythema, irregular vascular pattern, presence of oedema, formation of linear ulceration, a bit of mucosal laceration and mucosal nodularity.[34,32,39,40]

Furthermore, histopathology identification was conducted on microscopic colitis to differentiate each types of microscopic colitis. In lymphocytic colitis, the following were found: increased surface intraepithelial lymphocytes >20 per 100 epithelial cell, increased inflammation in lamina propria, and flat surface epithelial damage, mucin depletion, and vacuolization, and absence of collagen thickening in the subepithelial or slightly thickened subepithelial collagen.[33,37,38,39,40] Meanwhile, in collagenous colitis, the following were found: thickened subepithelial collagen band >10 µm, increased inflammation in lamina propria, subepithelial surface, and epithelial surface damage nearly the same as lymphocytic colitis.[33,34,38,39]

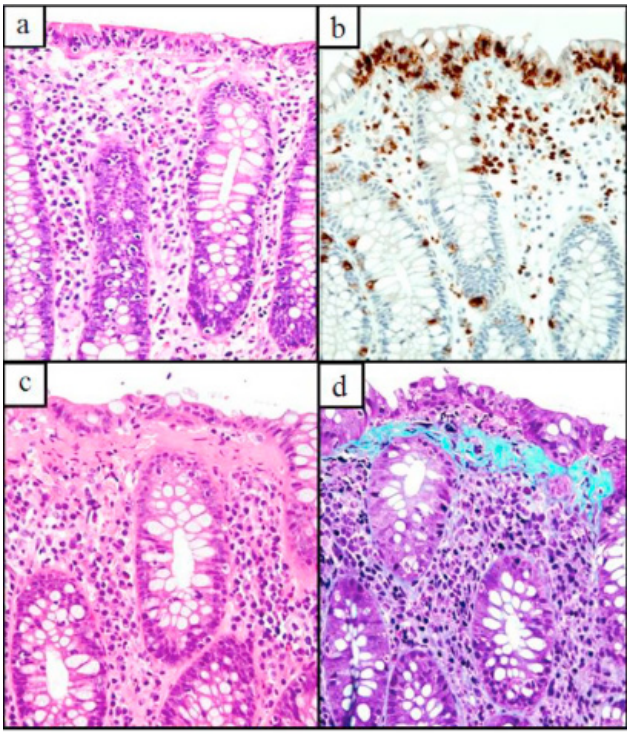

Figure 7. Histology of lymphocytic colitis and collagenous colitis. A: lymphocytic colitis; haematoxylin and eosin. B: lymphocytic colitis; CD3. C: collagenous colitis; haematoxylin and eosin. D: collagenous colitis, Masson's trichrome[38]

Another type of microscopic colitis is incomplete microscopic colitis. Incomplete microscopic colitis has similar clinical symptoms to microscopic colitis but does not meet the criteria of CC nor LC based on histopathology descriptions. Histopathology found in incomplete lymphocytic colitis were increased intraepithelial surface lymphocytes with > 10 to ≤ 20 per 100 epithelial cells. Furthermore, histopathology in incomplete collagenous colitis were thickened subepithelial collagenous band > 5 to ≤ 10 µm.[34,38,39,40]

INFECTIOUS COLITIS

Infectious colitis is a diarrhea symptom found with inflammation in the colon seen by visualization, by history taking, colonoscopy, with bloody diarrhea or presence of mucus in diarrhea, and examinations of lactoferrin and culture.[41]

Possible causes of infectious colitis include bacterial, viral, or parasite infections. Bacterial causes include *Salmonella, Campylobacter jejuni, E.coli, Clostridium difficile, Mycobacterium tuberculosis infections*, and so on. Viral causes include Rotavirus, Cytomegalovirus, Adenovirus, and Norovirus. Parasite infection by *Entamoeba histolytica*.[6,41,42]

In general, lesions of infectious colitis could be found in the terminal ileum, cecum, colon, ileocecal, sigmoid, and rectum. Furthermore, histopathology descriptions in infectious colitis could include focal abnormal architecture, predominantly acute mucosal inflammation, abnormal focal mucosal inflammation, basal plasmacytosis, predominant neutrophil, and pseudomembrane.[5,43] However, in each causes of infectious colitis, there is a specific pathology.

In *Mycobacterium tuberculosis*, lesions were often found in the cecum and ileocecal regions. Forms of lesion include transverse ulceration, surrounded by inflammation cells and damaged ileocecal valve.[6,44] Furthermore, histopathology in *Mycobacterium tuberculosis* is similar to Crohn's disease, mimicking Crohn's disease, in the form of multiple submucosal inflammation granulomas in the submucosa, consisting of epithelioid histocytes and multinucleated giant cell with central caseation necrosis.[5,6,43]

Clostridium difficile has a characteristic histopathology of pseudomembrane. Pseudomembrane is formed due to increased growth in *C. difficile*, resulting in an increase of inflammation cells which causes bacterial death and accumulation of damaged mucosal tissue.[5,43,45] Pseudomembrane is found mostly on the left sided colon and few cases can be found on the right sided colon.[46,47]

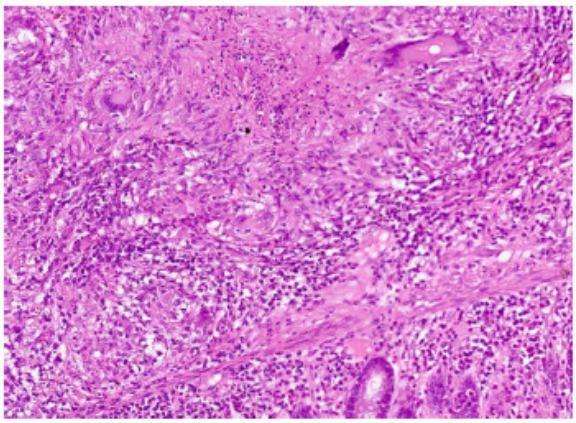

Figure 8. Histology of *Mycobacterium tuberculosis* showed granulomatous colitis characterised by histiocytes and giant cells with caseous necrosis[43]

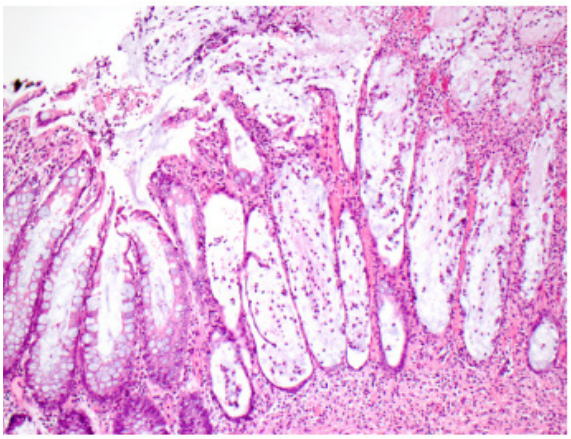

Figure 9. Histology of pesudomembranous *(Clostridium difficile)* colitis showed a spray of nuclear debris, neutrophils, fibrin and mucin erupting out of the crypts, forming an inflammatory membrane[43]

Yersinia enterocolitica has lesions like oedematous, ulcers with an irregular shape, and with exudates. Lesion is usually found in the terminal ileum and proximal colon.[6,44] Histopathology examination may reveal the presence of granulomatous inflammation, which contains lots of histiocytes, as well as the presence of hyperplastic Payer's patches.[43,47]

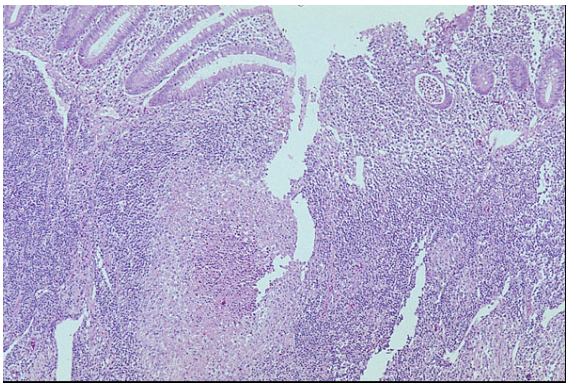

Figure 10. Histology of *Yersinia enterocolitica* showed granulomas formed in the thickened mucosa showing lymphoid hyperplasia. Courtesy of Pathology outlines

Cytomegalovirus are single or multiple round lesions that can be found in the caecum and sigmoid.[44,48] Besides, it can be in the form of erosions, erythema, and inflammatory polyps with predominance of granulation tissue and necrosis.[47,48] Histopathologic examination of cytomegalovirus is an enlarged intranuclear inclusion body in the host cell nucleus which is noisy like a halo, thus it is shaped like an owl's eye and smaller cytoplasmic inclusions.[43]

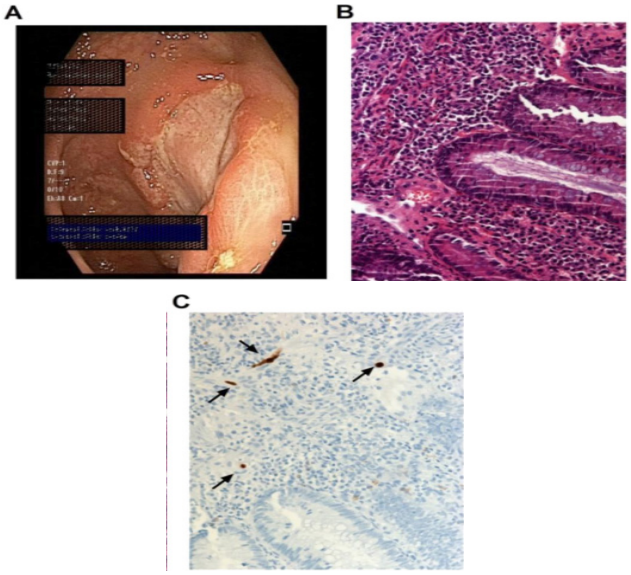

Figure 11. Representive CMV-related findings in a patient with refractory irColitis. A: deeply excavated, large ulceration in the sigmoid observed during colonoscopy. B: histology showed plasma cell-rich inflammation with reactive changes of crypt epithelium[48]

In *Entamoeba histolytica* infection, there are round or irregularly shaped lesions with exudate and ulceration. Lessions are commonly found in the cecum, right sided colon, sigmoid, and rectum.[44] Furthermore, histopathology of *E. histolytica* includes an increase of eosinophil and neutrophils in the lamina propria, and phagocytic red blood cell in the cytoplasm.[6,44] Later, an inflammatory process occurs and forms exudates and nuclear debris.[47]

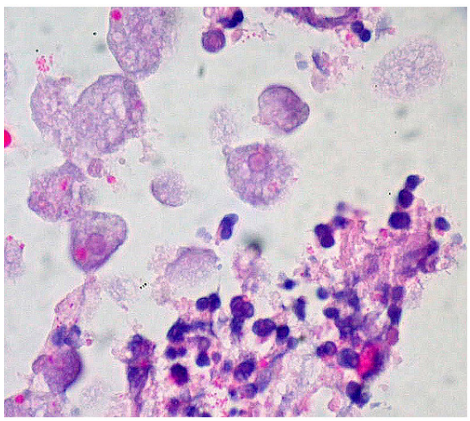

Figure 12. Histology of *Entamoeba histolytica*. Courtesy of Pathology outlines (http://www.pathologyoutlines.com)

CONCLUSION

In chronic diarrhea patients, it is necessary to accurately distinguish the cause, because there are many causes of chronic diarrhea with similar symptoms. Differences in chronic diarrhea causes could be identified by descriptions of colonoscopy and histopathology. This is expected to be an accurate tool to differentiate the pathology of each causes of chronic diarrhea.

IBD has symptoms of chronic, bloody diarrhea, characteristic changes of inflammation in the lesion, and presence of architectural changes in the mucosa, lamina propria, and crypts, and increase of inflammation cells in histopathology. Degree of severity, lesion distribution, and description of histopathology are an important frame for differential diagnoses against other diseases, such as erythema, ulceration, erosion, changes of vascularization pattern, damage in mucosal layer, Paneth cell metaplasia, damage in crypt and ileum, colon, and rectal involvement. Those descriptions could differentiate ulcerative colitis and Crohn's disease with each of its characteristic histopathology. Differential diagnoses similar to IBD include prolonged infectious colitis. Colonoscopy descriptions between IBD and infectious colitis, often found such as ulceration, erythema, changes of vascularization pattern, oedema, and similar distributions of lesion, but with differing histopathology between IBD and infectious colitis.

Microscopic colitis is a cause of watery chronic diarrhea without bleeding. There are 2 types of MC: collagenous colitis and lymphocytic colitis. Collagenous colitis and lymphocytic colitis have colonoscopy descriptions with similar lesions and the same distributions, but there are differences in histopathology. Furthermore, there is another variant of microscopic colitis: incomplete microscopic colitis. Symptoms of incomplete microscopic colitis are the same with MC, which includes incomplete collagenous colitis and incomplete lymphocytic colitis. In MC and IMC, there are the same colonoscopic descriptions, but differences in histopathology. Currently, description of colonoscopy and histopathology is a mean to determine a specific diagnosis of the cause of chronic diarrhea.

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