Nosocomial *Clostridium difficile* Diarrhea in Patient with Malignancy

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ABSTRACT

Clostridium difficile (C. difficile) is the main pathogen causing antibiotics associated diarrhea and colitis. This bacterium increases with hospitalization with incidence of 20-60 cases per 100,000 patients/day. C. difficile is gram positive bacilli which produce toxins in 2,700 cases in every 100,000 exposures to particular antibiotics, such as clindamycin, cephalosporin, and ampicillin. These antibiotics disrupt the intestinal normal flora and predispose to colonization of C. difficile.

This case described a 53-year old male patient with squamous cell carcinoma in his left ear who came to Department of Internal Medicine, Cipto Mangunkusumo Hospital, with the complain of diarrhea since two weeks after one month hospitalization in Department of Ear, Nose, and Throat. The characteristics of the diarrhea were 10 times per day ± 100 mL, watery consistency, green yellowish in color, and no blood in the feces. Additionally, the patient also complained of pain in all parts of his stomach, especially in the epigastric area. Earlier, patient was given ceftazidime for 30 days of hospitalization. The serology examination of C. difficile in the feces showed positive result (titer = 0.790 and control = 0.190). During the colonoscopy examination, pancolitis was found and the pathologic anatomy result was found appropriate for infective colitis. Thereafter, antibiotic administration was ceased and metronidazole was administered intravenously three times a day. The diarrhea stopped after seven days and the patient was discharged.

Keywords: *Clostridium difficile, nosocomial diarrhea, malignancy*

ABSTRAK

Clostridium difficile (C. difficile) adalah patogen utama yang menyebabkan diare dan kolitis akibat antibiotika. Bakteri ini meningkat dalam perawatan di rumah sakit dengan insiden 20-60 kasus per 100,000 pasien/hari. C. difficile adalah basil gram positif yang menghasilkan toksin pada 2,700 kasus dalam 100,000 paparan antibiotika seperti klindamisin, sefalosporin dan ampisilin. Antibiotika tersebut menggangu flora normal di usus dan merupakan predisposisi kolonisasi C. difficile.

Pada kasus ini dilaporkan seorang laki-laki, 53 tahun dengan karsinoma sel skuamosa di telinga kirinya yang datang ke ruang perawatan Departemen Ilmu Penyakit Dalam Rumah Sakit Cipto Mangunkusumo dengan keluhan diare sejak 2 minggu setelah perawatan selama satu bulan di Departemen Telinga, Hidung, Tenggorokan. Karakteristik diare sekitar 10 kali per hari ± 100 mL dengan konsistensi cair, warna hijau kekuningan, tidak terdapat darah. Selain itu pasien juga mengeluh nyeri di seluruh perutnya khususnya di daerah epigastrium. Sebelumnya pasien mendapat ceftazidim selama 30 hari selama perawatan. Pemeriksaan serologi toksin C. difficile pada feses memperlihatkan hasil positif (titer = 0,790; kontrol = 0,190). Dari hasil pemeriksaan

kolonoskopi ditemukan pankolitis dan pemeriksaan patologi anatomi ditemukan kolitis infektif. Pemberian antibiotika dihentikan kemudian diberikan metronidazole 500 mg intra vena tiga kali sehari. Diare berhenti setelah tujuh hari kemudian dan pasien dapat dipulangkan.

Kata kunci*: *Clostridium difficille, diare nosokomial, keganasan

INTRODUCTION

The term *Clostridium difficile (C. difficile)* diarrhea is used in diarrhea caused by infection of its own organism. This nosocomial infection has been noted to cause outbreak of *C. difficile* diarrhea in the hospitals, with incidence rate of 20-60 cases in every 100.000 patients/day and this number tends to increase. Similarly, 3 million cases of *C. difficile* diarrhea and colitis is reported every year in the United States.[1] In the hospital, infected and colonized patients and the contaminated environment are associated with the source of *C. difficile* infection.[2,3]

C. difficile is gram positive bacillus which is a colony in human intestine found in 1-3% healthy adult, approximately 20% of patients who received antibiotic, and 50% of neonates. Subsequently, a part of this colony will cause symptoms after the intestinal normal flora is changed and dominated by the pathogen.[4,5] The prevalence of toxin producing *C. difficile* is around 2,700 cases per 100,000 antibiotic exposures. Antibiotics often cause *C. difficile* diarrhea are clindamycin, cephalosporin, and penicillin. The use of these antibiotics will disrupt intestinal normal flora and will also lead to the predisposition of *C. difficile* colonization, commonly found in the health care centers.[1]

Currently, *C. difficile* has been an important nosocomial pathogen associated with morbidity and mortality. Upon exposure to *C. difficile* some patients become asymptomatic carrier, while others experienced diarrhea with a wide range of severity, from mild watery diarrhea to pseudomembranous colitis, which may eventually cause death.[5] Some diagnostic modalities in *C. difficile* infection are intended to find the presence of toxin A or toxin B. These modalities include rapid enzymatic examination or polymerase chain reaction (PCR) method, to find the presence of toxin B of *C. difficile* in fecal specimen, fecal culture, latex agglutination test to find the presence of clostridium glutamate dehydrogenase protein, and endoscopy.[5] In this case report would be reported a 53-year old male patient with squamous cell carcinoma in the left ear who experience nosocomial *C. difficile* diarrhea at the time further diagnostic examination and further treatment were to be performed.

CASE ILLUSTRATION

A 53-year-old male was hospitalized in Cipto Mangunkusumo Hospital with chief complain of watery stool for 15 days, after 30 days hospitalization in Ear, Nose, Throat (ENT) Department. Patient was diagnosed with stage IV squamous cell carcinoma in his left ear with intracranial infiltration and was intended to undergo chemoradiation therapy. During hospitalization, patient received ceftazidime 3 x 1 g administered intravenously for treatment of lung and connective tissue infection. On day-15 of hospitalization, he had watery stool with frequency of more than 10 times per day ± 100 mL, yellow greenish in color, but with no mucus or blood. There was also complaining of aching all over his stomach, especially in the epigastric area. Patient was still able to pass gas (flatulence). Nausea was present, but no vomiting or fever. History of hypertension was present since the previous few years, however the medicine name could not be recalled.

During visit to Department of Internal Medicine, patient was looking severely ill, fully alert, blood pressure 150/90 mmHg, heart rate 88 beats/minutes, respiratory rate 20 beats/minutes, and temperature of 36.8°C. Upon inspection, it was found that the patient had asymmetric face with no facies cholerica. Conjunctiva was not pale, sclera was not icteric, lagophtalmus, and esotrophia were present in the left eye. In the left ear, there was mass with solid consistency, immobile, with pus, but no blood. The right ear was within normal limits. Into his nose, nasogastric tube had been inserted, there was no septum deviation, mass, blood, or pus. There was no increase in the jugular venous pressure or enlargement of lymph nodes in the neck. Spider nevi were not found. The skin turgor was within normal limit. In the heart examination, impression of enlargement of the heart was conduded. No abnormality was found in lung examination. Abdominal examination revealed not distended abdomen, symmetric, supple, liver and spleen were not palpable, tymphani, positive shifting dullness, no pain on percussion of the costovertebrae angle, and normal bowel sound. Upon extremities examination, the acral was warm with pretibial and dorsum pedis edema. However, no cyanotic or palmar

erythema was found. Patient weighted 59 kg and measured height 166 cm.

In the laboratory examination during transfer to the Internal Medicine Department, it was found that hemoglobin 11.6 mg/dL, hematocryte 35.5%, leukocytes 8,800/µL, thrombocytes 256,000/µL, erythrocyte sedimentation rate 5 mm, differential count showed following results: eosinophil 0.1, basophil 0.2, neutrophil 12.1%, and monocytes 6.3%, aspartate aminotransferase (AST) 18 u/L, alanine aminotransferase (ALT) 24 u/L, albumin 2.1 g/dL, globulin 4.7 g/dL, cholinesterase 1654 u/L, ureum 23 mg/dL, creatinine 0.6 mg/dL, random blood glucose 139 mg/dL, sodium 135 mEq/L, potassium 2.04 mEq/L, and chloride 104 mEq/L. Fecal analysis revealed that the feces was yellow in color, watery consistency, full of leukocytes, erythrocytes 1-2, fat was present, and positive serological examination of *C. difficile* (titer = 0.790 and control = 0.190). Electrocardiography examination showed sinus rhythm, left axis deviation, QRS rate 98 bpm, P wave within normal limit, poor r-wave in V1 and V2, enlargement of the right and left ventricle. Posterior and anterior chest X-ray exhibit rough bronchovascular appearance and cardio-thoracic ratio > 50%.

Upon transfer to Department of Internal Medicine, patient's problems were listed: *C. difficile* diarrhea, stage IV squamous cell carcinoma in the left ear with anemia, grade I hypertension, chronic liver disease, hypokalemia, hypoalbuminemia with ascites, and old myocardial infarct in the septum. The treatment given was Calbamin® infusion: Triofusin E® 1000 = 1:1/12 hour and infusion of NaCl 0.9% 500 ml + KCL 25 mEq/8 hours, liquid diet through nasogastric tube (NGT) 4 x 250 mL/day, Lacidofil® 3 x 1 tablet/day, metronidazole 3 x 500 mg ingtravenously, Plasbumin® 50 mg 20% infusion 2 times, captopril 2 x 12.5 mg/day orally dan ascardia 80 mg/day orally. On day-38 of hospitalization, colonoscopy was performed and impression of pancolitis was established (Figure 1). Biopsy of the lesion in the colon concluded the presence of infective colitis (Figure 2).

On day-40 of hospitalization, there was improvement in the frequency of diarrhea and the amount in every defecation. Besides, blood pressure began to be under control and hypokalemia and hypoalbuminemia were improved. On day-42 of hospitalization, patient was advised to undergo radiotherapy. Results of gastroenterology consultation recommended to stop the administration of metronidazole and substitute it with oral ofloxacine 400 mg/day for 7 days. On day-46 of hospitalization, patient refused to undergo chemoradiation and decided to continue his treatment in the outpatient ward. At that moment, diarrhea had stopped, no complain of nausea, stomachache, vomiting, and edema in the stomach and feet.

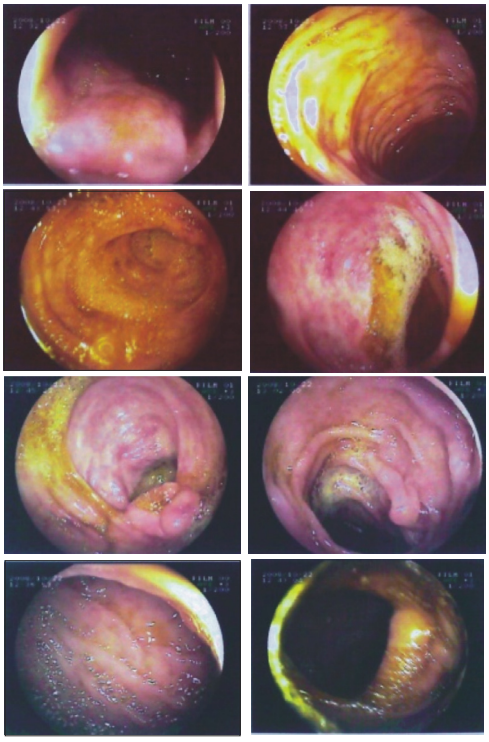

Figure 1. Colonoscopy examination showed the presence of inflammation in almost all part of sigmoid colon, pars descenden, transversum, and pars ascenden with the conclusion of pancolitis

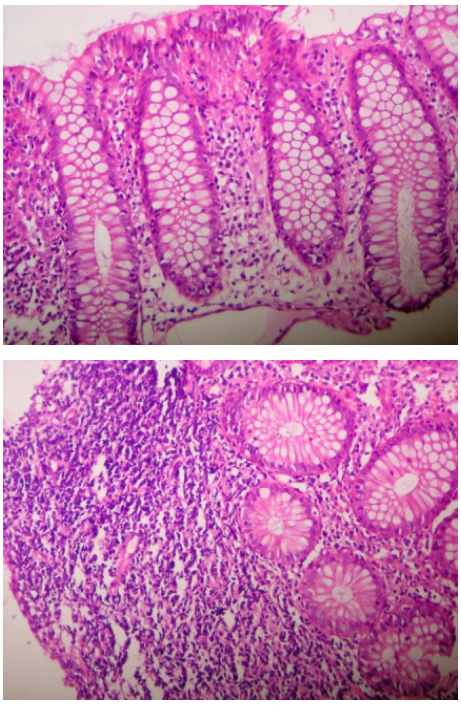

Figure 2. Specimen consisted of mucosal part of the colon tissue with conclusion no malignant cells were found in this specimen and impression of infective colitis

The prognosis of this patient was dubia ad malam for ad vitam, ad fungtionam, and sanactionam.

DISCUSSION

A 53-year-old male patient came due to advanced stage of malignant tumor in his left ear with intracranial infiltration. Initially, patient was hospitalized in ENT Department in Cipto Mangunkusumo Hospital for diagnosis and treatment of the tumor in the left ear. During hospitalization, particularly on day-15 of hospitalization, he started to experience diarrhea.

Patient had watery stool with frequency of 10 times ± 100 mL, feces was yellow greenish in color. Additionally, he also complained of nausea and stomachache. Upon transfer to the Internal Medicine Department, diarrhea had occurred for 15 days, specifically 8 days before the transfer of hospitalization to the Internal Medicine ward and thus, was still considered as acute diarrhea.[6] Patient experienced diarrhea with watery stool with no mucus or blood. He also complained of fever and stomachache. Fecal examination revealed the presence of a lot of leukocytes. These findings suggested the presence of inflammatory diarrhea, while in non-inflammatory diarrhea, there would be no fever and leukocytes in the feces. One of the inflammatory diarrhea etiologies is *C. difficile* apart from *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, invasive *Escheria coli (E. coli)*, *E. coli* O157:H7, *Staphylococcus aureus*, and *Vibrio parahemolyticus*.[7] If the diarrhea occurred during hospitalization and accompanied with stomachache, possibly this diarrhea was a nosocomial infection with *C. difficile* as the etiology.[6-8]

In the patient, there were 3 main risk factors which were associated with *C. difficile*, which included: exposure to antibiotic intravenous ceftazidime for 15 days, more than 3 days of hospitalization, and patient had background of malignant tumor in the left ear in which there had been host immunity distruption.[9,10] Additionally, in this patient, there was administration of proton pump inhibitor (PPI). In accordance with the study performed by Dial et al, *C. difficile* diarrhea was significantly associated with the use of PPI with odds ratio 2.1 (CI = 1.2-3.5). Therefore, it could be summarized that in hospitalized patients who received PPI, the risk of *C. difficile* diarrhea was elevated.[9-12]

Cytotoxic examination of tissue culture to detect the presence of cytotoxin *C. difficile*, particularly toxin B in the fecal specimen was thought to be the gold standard diagnostic due to its high specificity (99-100%). The sensitivity of this examination is 80-90%.[10,11] Rapid enzymatic immune examination has been developed to detect toxin A or both toxin A and B from fecal specimen. Test kit is more sensitive to detect both toxins because this test could identify the disease caused by *C. difficile* strain. However, this test has low sensitivity (65-85%) and specificity (95-100%) compared to cytotoxic examination.[12,13] Lately, PCR method to detect toxin A or B *C. difficile* or both has been developed with better sensitivity (92-97%) and specificity (100%) compared with the cytotoxin examination of tissue culture.[12-16]

In this patient, immunologic Elisa examination to detect the presence of toxin A or B of *C. difficile* from fecal specimen was performed. Results of this examination was obtained in few hours. Though this test has low sensitivity (65-85%), it has quite high specificity (95-100%).[10-14] The result of serologic examination in this patient was positive (titer = 0.790 and control = 0.190). Due to the high specificity of this serologic examination, the value of positive results from this examination will have diagnostic value for *C. difficile* diarrhea.

According to the guidelines published by American College of Gastroenterology, the diagnosis of *C. difficile* diarrhea and colitis actually involves the presence of associated symptoms, such as diarrhea and at least one positive results from these examinations: endoscopy reveals the presence of pseudomembrane, fecal cytotoxic test shows the presence of toxin B, enzymatic immunologic examination from fecal specimen exhibits the presence of toxin A or toxin B or fecal culture of *C. difficile*.[12,13,17] In this patient, there were symptoms associated with *C. difficile* diarrhea, particularly: watery and profuse diarrhea accompanied with pain in the stomach, nausea, and no appetite which appeared in more than 3 days of hospitalization. Furthermore, the patient had other few risk factors, such as frequent exposure of antibiotics specifically third generation cephalosporin, the use of PPI, and the underlying disease, malignant tumor in the ear. In the fecal serological Elisa examination to check the presence of *C. difficile* toxin, positive result was attained.

Initial step in the treatment of *C. difficile* diarrhea was to stop the administration of provoking agent, the most common is antibiotic if this action could be considered as appropriate medically. For mild illness, this action is usually adequate for total cure. For more severe illness, antibiotic therapy for *C. difficile* is usually required. Oral metronidazole therapy 250 mg four times a day or 500 mg twice a day for 10-14

days is recommended as choice of first line therapy. As a second line therapy, oral vancomycin 125 mg four times a day for 10-14 days is recommended.[17,18,19]

However, it needs to be bear in mind that recently resistance case towards metronidazole in treatment of *C. difficile* colitis has been reported. In a study performed by Mushe et al, failure of metronidazole in treating patients with *C. difficile* colitis was found. Earlier study stated that nitazoxanide was as effective as metronidazole as an initial therapy for *C. difficile* colitis. Similarly, in the study carried out by Mushe et al, it was concluded that nitazoxanide appear as an effective therapy for *C. difficile* colitis patient who has failed to be treated with metronidazole.[19,20,21]

A meta-analysis suggested that probiotic could be used in preventing antibiotic associated diarrhea and *Saccharomyces boulardii* dan *lactobacillus* probably could be used in this kind of situation. However, the efficacy of probiotic in the treatment of antibiotic associated diarrhea need to be investigated further.[22] *Lactobacillus* has few mechanisms of actions: *Lactobacillus GG* has shown beneficial effect in the intestinal immunity, increase the number of cells which produce immunoglobulin G and other immunoglobulin in the intestinal mucosa, and stimulate the release of local interferon. This also facilitates the migration of antigen in the underlying lymphoid cells and exhibits the increase of intake in Peyer patches.[21,22]

As a conclusion, *C. difficile* diarrhea is a nosocomial diarrhea which occurs in more than 3 days of hospitalization with previous exposure to antibiotics. The definite diagnosis of *C. difficile* diarrhea is cell culture which shows the cytopathic effect of *C. difficile* toxin. However, with regard to the limitation of facilities to perform it, this is difficult to do. The diagnosis of *C. difficile* diarrhea could be made base on the supporting symptoms with one of the examinations showing the presence of *C. difficile* toxin or supporting endoscopic lesion. The treatment of *C. difficile* diarrhea included rehydration, cease the administration of antibiotics, symptomatic, and treatment of the complications. Metronidazole could still be used as the first line treatment of *C. difficile* diarrhea. From this case, lesson on the rational use of antibiotics was obtained, including always consider the indication, contraindication, and adverse effects. In addition, policy of antibiotics administration in hospital needs to be made to prevent the occurrence of nosocomial infection.[23-25]

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