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Case Report

Inflammatory bowel disease in Indonesian children

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Inflammatory bowel disease (IBD) is a term used to describe two disorders associated with gastrointestinal inflammation: Crohn's disease (CD) and ulcerative colitis (UC). The incidence of IBD is higher in developed countries, while there is unpublished data of pediatric IBD in Indonesia. Clinical manifestations of IBD vary, consist of gastrointestinal (such as diarrhea and abdominal pain) and extraintestinal manifestations. Definite diagnosis of IBD is based on endoscopy and histopathology. The management includes pharmacotherapy, nutrition, surgery, and psychotherapy. This disorder has a high recurrence rate, where CD's recurrence rate is higher than UC.[1,2]

Report of the case

A three-year-old girl was admitted to the Pediatric Gastroenterology Division, Cipto Mangunkusumo Hospital (CMH) because of diarrhea for 8 months. The characteristic of diarrhea was porridge-like to liquid, 2-8 times a day, yellowish, with mucus, but no blood. There was no fever, abdominal pain, nausea, or vomiting. She still had good appetite. Body weight was 15 kg. She was consulted to several pediatricians and diagnosed with gastroenteritis. She was then given antibiotics and anti-diarrhea but there was no improvement.

One month before admission, she had recurrent fever and abdominal pain particularly just before and during defecation with blackish stool. Two weeks later, she suffered from pain and swelling on her knee and ankle joints. She was not able to strectch her legs nor stand. There was no purpura or other skin lesions. Then, she was brought to a pediatrician and given antibiotics and non-steroid anti-inlamatory drugs. Because of no improvement, she was referred to Cipto Mangunuusmo Hospital (CMH). There was no family history of similar disorder, atopy, parental history of transfusion, drug abuse, or promiscuity.

At first admission in CMH, the patient looked well-nourished with normal vital signs. Bowel sound was normal. There was no anal fissure or any skin lesion. Her right knee and both her left and right ankles joints looked swollen and erythematous, warm, with pain on movement. Other physical signs were unremarkable.

The working diagnosis at that time was persistent diarrhea due to suspected infected colitis, anemia, and arthritis with differential diagnosis of IBD. Laboratory tests revealed Hb 8.8 g/dL, Ht 28 vol%, WBC 12,800/uL, platelets 562,000/uL, with normal differential count. *C-reactive protein* (CRP) was positive, ESR 94 mm/hour, bleeding time 4', clotting time 6'30", PT

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13.2" (12.3"), PTT 37.7" (30.3"), C3 173 (90-180), C4 47 (10-40), ASTO <200 (N), rheumatoid factor was negative. Stool analysis revealed signs of gastrointestinal tract infection with positive benzidin test. Knee and ankles X-ray showed consistent with arthritis of bilateral knees and ankles. Colonoscopy showed erosion and ulcers in most mucosal parts of sigmoid to ascending colon, and bleeding spots in several places, with conclusion of suggestive ulcerative colitis. Colon biopsy was performed in several parts, and while waiting for the result, the patient was given oral metronidazole 3x200 mg and cefixime 2x40 mg. She was also consulted to Allergy-Immunology Division and received oral naproxen 2x100 mg.

One week post colonoscopy, the patient came with the same pattern of defecation, decreased joint pain although she still could not stretch her legs. Stool culture for bacteria and parasites were negative. Histopathologic examination from the biopsy specimen showed some atrophic superficial epithelium, hyperemic lamina propria, with chronic and acute inflammatory cells and various size of crypts without signs of destruction, which disclosed an infectious colitis. Metronidazole and naproxen were continued, and probiotics were added. Within the next 3 months, the patient was only brought once to Allergy-Immunology Division due to difficulty in getting parental leave. The parents only continued administering naproxen.

As no significant improvement was seen, on December 2006 the patient was brought back to Gastrohepatology Clinic CMH for reevaluation. There was no change in defecation pattern. Body weight decreased to 12.7 kg. Laboratorium examination revealed Hb 9.2 g/dL, Ht 33 vol%, WBC 13,700/uL, platelets 597.000/uL, MCV 79 fl (↓), MCH 22 pg (↓), MCHC 28% (↓), differential count (%): basophil 0, eosinophil 3, band neutrophil 0, segment neutrophil 60, limphocyte 33, monocyte 4, ESR 100 mm/hour, blood film showed microcytic hypochromic anemia; AST 26 mg/dL, ALT 12 mg/dL, albumin 3.4 g/dL, gamma-GT 18 U/L (N), ureum 28 mg/dL, creatinine 0.2 mg/dL, serum iron (SI) 42 ug/dL (↓), total iron binding capacity (TIBC) 350 ug/dL (N), and ferritin 28.3 ng/dL (N). Second colonoscopy showed ulcerative colitis, similar to previous findings; but the histopathological findings showed some irregular superficial epithelium, some distorted crypts, transmucosal and diffuse acute and chronic inflammatory cells on lamina propria, with the conclusion of active chronic colitis with crypt destruction. This can be found in IBD.

Based on the data above, definitive diagnosis of IBD is ulcerative colitis with extraintestinal manifestation of arthritis, iron deficiency anemia, and undernourished. She was then given oral methylprednisolone 3x8 mg for 2 weeks and tapered off for 1 week, ferrous sulfate 2x150 mg, and vitamin C 1x25 mg. Naproxen was discontinued. Diet of 1500 calorie was given. Both parents were given education and information about the patient's condition and natural history of the disease. After one week of methylprednisolone, significant clinical improvement was seen. Defecation pattern was return to normal that is 1-2 times a day, solid, no mucus or blood. Joints pain also decreased significantly, and with physiotherapy, she started to be able to stretch her legs and to stand without assistant. Corticosteroid was tapered off and started maintenance therapy with oral mesalamine 3x200 mg. At three-month follow-up, body weight was 15.5 kg. Reevaluation of colonoscopy and therapy was planned to be performed in three months.

Discussion

Inflamatory bowel disease is classifified into ulcerative colitis (UC) and Crohn's disease (CD), depending on the location and inflammatory characteristics. Ulcerative colitis is a condition in which the inflammatory response and morphological changes remain confined to the colon,[1,2] while Crohn's disease can involve any part of the gastrointestinal tract from oropharynx to perianal area. Diseased segments are frequently separated by intervening normal bowel called 'skip area'.[3,4]

Inflammatory bowel disease occurs equally in male and female with no race predominance. It is more often found in developed countries, urban, and in cooler climate.[5] In the United States, the incidence is estimated to be 0.45-10/100,000 population.[3] Pediatric incidence in the United Kingdom is estimated to be 5.3/100,000 children (700 new cases/year) with Crohn's disease is found twice more often than UC. Mean age at diagnosis was 11.8 year (13% younger than 10 year of age).[6] However, published

data on IBD in Asian children is limited, and so is in Indonesia.

The etiology of IBD is still unclear. It is believed that the pathogenesis involves inappropriate and ongoing activation of the mucosal immune system, and the presence of normal luminal flora. It is also facilitated by defects in both barrier function of the intestinal epithelium and mucosal immune system.[7] Genetic susceptibility is the most important risk factor. First-degree family of IBD has an increased risk of 30-100 times compared to the general population. Defect in chromosome[6,16] and congenital disorders (Turner, inborn errors) were also associated with IBD.[2,4] Environemental factors such as the use of non steroid anti inflammatory drugs is also associated with intestinal barrier and may trigger IBD. Intestinal flora is also proven to play role in IBD.[7]

In this case, there were no family history or other condition that may increase the risk of IBD. Early age of onset of IBD is still possible in 13% of cases. Delayed diagnosis in this patient was due to unfamiliarity of the disease by Indonesian paediatricians as the incidence is low. Even in the developed countries with higher incidence, delayed diagnosis is common with median of 5 months after onset, and furthermore 25% cases have suffered for more than a year before the diagnosis of IBD was established.[6]

Pathogenesis of IBD is still unclear. Abnormality of gastrointestinal tract immunoregulation plays an important role in IBD. It is believed that uncontrolled physiological inflammation occurs in IBD is as a result of pathological inflammation with increased immune cells and inflammatory mediators. The consequences are tissue damage and electrolyte secretion that lead to diarrhea.[2,4] Animal studies showed that innate immunity may also play a significant role in pathogenesis of IBD.[8]

Clinical manifestations of IBD consist of gastrointestinal and extraintestinal symptoms. Gastrointestinal manifestations vary and may consist of diarrhea, abdominal pain, nausea, and vomiting. Bloody diarrhea is occured in most UC patients and in 50% CD patients. Abdominal pain is usually associated with defecation in UC but may occur anytime and more severe in CD. In CD patients, perirectal inflammation with fissures and fistulas occur in 25% cases and may be the first sign of disease. Apthae may also be found in CD. In some cases, fever is present without any obvious gastrointestinal symptoms and this may be diagnosed as fever of unknown origin.[2,4] In this patient, chronic diarrhea with abdominal pain and recurrent fever were present. No symptoms of nausea, vomiting, and no signs of inflammation in the mouth or perirectal area supported the diagnosis of UC rather than CD.

Extraintestinal manifestations may occur in 25-35% cases. Arthritis is the most common extra-intestinal manifestation found in IBD.[9] There are two types of arthritis in IBD: (1) peripheral type (10% cases) that occurs in large joints (knee, ankle, wrist, elbow) and associated with active colon disease; (2) axial type (ankylosing spondylitis, sacroiliitis), that is rarely found in children.1 Failure to thrive occurs in 10-30% IBD cases. The pathogenesis of IBD is multifactorial, including chronic malnutrition, corticosteroid, and release of proinflammatory cytokines. Failure to thrive is almost always found in long term corticosteroid therapy.[2,4] In this patient, extraintestinal manifestations were found, that are arthritis, microcytic anemia, and thrombocytosis. This patient suffered from peripheral arthritis. It is in accordance with the literature that arthritis is associated with active disease phase and showed a good response to UC therapy. There was also weight loss in this patient and the body weight increased with time as a response to therapy.

Based on the history, clinical manifestations and colonoscopy, IBD was already in the differential diagnosis since the patient first came to CMH. Unfortunately the histopathological results did not support it. The patient's noncompliance for re-evaluation visit also contributed to the delayed diagnosis. Some experts suggested treatment in clinically and colonoscopy proven with non-characteristics histopathology IBD cases. However this option is usually done by experienced experts. Complete data to support IBD diagnosis is still needed in this case. Diagnosis of IBD was established after reevaluation of histopathological findings and also was supported by the good response to IBD management.

Stool examination, including culture may exclude pathogen bacterial infection. In this case, initial data of stool analysis showed signs of gastro-intestinal infection. Inflammatory bowel disease may be present with infection on onset, but the symptoms

are not diminished with antimicrobial therapy or recured within days or weeks.[2,4] Stool culture of aerobic bacteria and parasites showed negative results. However, gastrointestinal infection by anaerobic microorganism could not be ruled out in this patient, therefore metronidazole was administered for 2 weeks.

Complete blood count demonstrated microcytic anemia, leukocytosis with shift to the left, and thrombocytosis. Erythrocyte sedimentation rate and CRP increased in 40 to 80% cases. Hypoalbuminemia may occur due to protein loss. In IBD cases with liver involvement, AST, ALT and GGT may also increased.[2,4] In this case, the patient showed microcytic anemia, leukocytosis, thrombocytosis and increased ESR and CRP. Currently there are available serological examination to differentiate between CD and UC, i.e. Perinuclear Anti-Neutrophilic Cytoplasmic Antibody (P-ANCA) and Anti-Saccharomyces Cerevisiae-Antibodies (ASCA). Positive P-ANCA is usually found in UC while ASCA is specific for CD.[1,10] However, some experts consider these examinations unnecessary.[4] These serologic tests were not performed in this case because according to the most current literature, these tests are not useful to establish IBD diagnosis but only beneficial to differentiate between CD and UC. Sabery *et al*11 even found that increased ESR and anemia are more specific and sensitive as screening tools of IBD than serological tests.

Colonoscopy in UC cases may show erythema, ulcer, loss of vascular pattern, and bleeding. These features are usually only limited to colon in UC cases, but may extend to upper GI tract in CD, with normal parts in between.[12] Granuloma is a pathognomonic sign of CD, although it is only found in 28% cases.[13] In most cases, histological examination may differentiate between CD and UC. However in some cases, it is difficult to be classified, and therefore called indeterminate colitis. In this case, initial colonoscopy suggested ulcerative colitis, but histopathologically is more likely to be infective colitis. This may be due to coexisting infection during first admission. Besides, the histopathological picture of infective colitis may mimic ulcerative colitis, particularly in the early stages as there was no distorted crypt could be found.[14,15] Upper tract endoscopy was not performed in this patient because all available data have supported diagnosis of UC.

Diagnosis of IBD is established through anamnesis, physical examination, and confirmed by supporting examinations. IBD working group from European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) set up Porto Criteria to help diagnose IBD. Diagnosis of IBD should be suspected if there is a history of persistent (=4 weeks) or recurrent (=2 if there is episodes in 6 months) symptoms such as abdominal pain, diarrhea, rectal bleeding and weight loss; with 3 most common laboratory parameters, i.e, anemia, thrombocytosis, increased ESR. Colonoscopy & histological examination are needed to confirm the diagnosis of IBD.[12] Diagnosis of IBD in this patient was suspected when the patient came with persistent diarrhea, abdominal pain, weight loss, arthritis and supported with findings of anemia, thrombocytosis and increased ESR. Diagnosis of IBD was established with colonoscopy and histopathological results. Chronic diarrhea may also occur in immunodeficiency state caused by HIV infection.[3]

Management of IBD consisted of pharmacotherapy, nutrition, surgery, and psychosocial therapy. Pharmacotherapy is divided into 6 categories: aminosalicylates, corticosteroids, immunomodulators, antibiotics, probiotics, and biologic therapy. The administration of these drugs depends on the severity of the disease. Patient with mild colitis may be initially treated with 5-aminosalicylates ***(level of evidence: 1a)***.[16] Patient with severe colitis (more than 5x bloody diarrhea, fever, hypoalbuminemia) should be hospitalized to received parenteral nutrition and intravenous corticosteroid ***(level of evidence: 4)***.[2] While patients with moderate disorder, such as in this case, may be given oral corticosteroid. Corticosteroid, both oral and intravenously, should be given as brief as possible followed by maintenance therapy. Maintenance therapies may be a choice of aminosalicylates, immunomodulators, or even infliximab in refractory CD cases ***(level of evidence: 1a)***.[2,17,18] Probiotics in both CD and UC cases has shown promising results in adults, although there were only few studies performed with placebo-controlled ***(level of evidence: 1b)***.[19]

Nutritional therapy may be a primary or adjunctive in CD, but is only adjunctive in UC cases. One pediatric clinical trial showed that enteral nutrition may be as effective as corticocteroid in

inducing CD remission (***level of evidence: 1b***).[20] Elemental or polymeric diet may help remission in 80% cases by reducing inflammation.[2,21,22] Polymeric formula is found equally effective as elemental formula.[23,24] In UC patients, diet is only adjunctive and is aimed to give adequate nutrition as replacement of decreased intake and increased colon loss. Omega-3 fatty acid supplement (fish oil) was reported to be able to reduce inflammation and reduce corticosteroid dose in adult IBD patients (***level of evidence: 2b***). Nonetheless, this issue is still controversial.[25]

Surgery has different objectives in UC and CD cases, although the indications are often similar. Surgery is indicated when there is uncontrolled gastrointestinal bleeding, perforation, obstruction, drugs side effect, and unresponsiveness to other therapies. In CD cases, surgery is not a definitive tool because of the high recurrence rate. In some UC cses, surgery may be definitive, and is inidicated in acute UC with severe anemia due to severe bleeding, or in severe colitis unresponsive to intensive conservative therapy for weeks.[2,3]

Psychosocial factor plays an important role in IBD. Beside psychological effect due to chronic disease, depressive disorder may also occur. Suggestion to any psychological disorder should lead to appropriate psychological therapy. Family education, emotional support to the patient and family, particulary on the diagnosis and early treatment phase are essential.[26]

In this case, pharmacotherapy with oral corticosteroid showed a good response, that soon followed by maintenance therapy with asetilsalicylates. Adequate nutrition according to her ideal needs has also been given as adjunctive therapy. Surgery was not indicated in this case. Education to the patient and family is important, considering the chronicity of this disease that may cause worriedness, exhaustion, and stress, which may impact social life of the patient and her family.[26]

Inflammatory bowel disease natural history is demonstrated by periods of exacerbation and remission. Seventy percents of UC cases will have remission in 3 months, and around half of these are still in remission in the next 1 year. Colectomy is needed in 26% severe cases and 10% of mild cases in 5 years after diagnosis. Around 70% CD cases need surgery in 10-20 years after diagnosis.[2] There was only 1% of CD cases that stay relapse-free.

Prognosis of this patient was ad vitam dubia ad bonam, ad functionam dubia, ad sanationam dubia ad malam. Remission occurred in short periods, but relapse and risk of cancer are still possible, in which a long term follow up is needed. Generally a colonoscopy to detect dysplasia is recommended 8 years after diagnosis and every 1-2 years afterwards.2 A study in Swedia found that the risk of colon cancer in pediatric IBD cases is 1% after 15 years, 6.5% after 20 years, and 15% after 25 years.[27] Follow up should include compliance to long term maintencance therapy, drugs' side effects, relapse, extraintestinal manifestations, and cancer risk.

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