Drug-induced Myelotoxicity in Patients with Crohn's Disease

Kaka Renaldi, Fransiscus Nikodemus Hosea***

* Division of Gastroenterology, Pancreatobiliary, and Gastrointestinal Endoscopy, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia Dr. Cipto Mangunkusumo Hospital
**Department of Internal Medicine, Cipto Mangunkusumo Hospital

Corresponding Author:
Kaka Renaldi, MD. Division of Gastroenterology, Pancreatobiliary, and Gastrointestinal Endoscopy, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia Dr. Cipto Mangunkusumo Hospital. Jl Diponegoro 71, Jakarta 10430, Indonesia.
email:kakarenaldi@gmail.com

ABSTRACT

As a chronic granulomatous disease, Crohn's disease (CD) poses a significant insinuation on morbidity and low quality of life. Long-term treatment is needed to control the disease activity. Observation and evaluation of disease activity are principal practices in treating CD, and sometimes clinicians tend to overlook the adverse effects of therapy that may occur and resemble disease progression.Hereby, we presented a 76-year-old female with a 10-year history of Crohn's disease who came to our emergency room with general weakness one week before admission. She complained of hematochezia and abdominal pain in the last month. She had been taking mesalazine 2x500 mg PO and azathioprine 2x50 mg PO in the previous three years. She was diagnosed with lung cancer six months before admission and had been prescribed erlotinib 1x150 mg PO in the last six weeks. Upon admission, pancytopenia was found in the blood study. Hematochezia, along with anemia and abdominal pain, might occur due to either disease activity or the adverse effects of the medication.Thorough observation and clinical evaluation regarding disease activity and side effects are required to manage Crohn's disease comprehensively.

Keywords: adverse effects, Crohn's disease, Inflammatory Bowel Disease, management, treatment

ABSTRAK

Penyakit Crohn menyebabkan morbiditas yang tinggi dan kualitas hidup yang rendah pada pasien. Perlu tata laksana jangka panjang untuk mengendalikan aktivitas penyakit. Penting untuk memantau aktivitas penyakit karena klinisi terkadang luput mendeteksi efek samping terapi yang gejalanya bisa mirip dengan progresi penyakit. Pada laporan kasus ini, kami melaporkan kasus seorang perempuan berusia 76 tahun dengan riwayat penyakit Crohn selama 10 tahun. Pasien tersebut datang dengan keluhan lemas sejak 10 minggu lalu. Satu bulan terakhir, pasien mengalami buang air besar merah segar dan nyeri perut. Pasien rutin mengonsumsi mesalazine 2 x 500 mg dan azathioprine 2 x 50 mg per oral selama tiga tahun terakhir. Selain itu, pasien juga didiagnosis kanker paru enam bulan terakhir dan mengonsumsi erlotinib 1 x 150 mg per oral selama 6 minggu. Disimpulkan bahwa gejala hematoschezia, anemia, dan nyeri perut pasien bisa disebabkan oleh aktivitas penyakit atau efek samping terapi. Oleh karena itu, pemantauan ketat dan evaluasi klinis terkait aktivitas penyakit dan efek samping terapi merupakan bagian penting dalam tata laksana komprehensif penyakit Crohn.

Kata kunci: efek samping, penyakit Crohn, Inflammatory Bowel Disease, terapi, tata laksana

INTRODUCTION

Inflammatory Bowel Disease (IBD), particularly Crohn's disease (CD), is a chronic granulomatous disease of which etiology has not yet been elucidated. Due to the nature of the disease, IBD poses a heavy burden, implying both morbidity and low quality of life.[1,2] While the inflammation occurs mainly in the gut system, 25% of patients with CD may present with extraintestinal manifestations, such as uveitis, conjunctivitis, arthritis, erythema nodosum, pyoderma gangrenosum, and primary sclerosing cholangitis.[1,3,4] Although the data is still limited, several studies showed that the lung might be involved in the extraintestinal manifestation of CD.[5] Liu J et al. also reported that CD might be associated with lung cancer, though the causality remained questionable.[6]

Because of the "lifelong" inflammation, CD necessitated long-term treatment, focusing on remission. Using an individualized approach, several pharmacological agents are available to opt for, among which are mesalazine (5-ASA), locally active steroid (budesonide), systemic steroids, thiopurines (azathioprine and mercaptopurine), methotrexate, and biological therapies.[1,3] In order to achieve remission, clinicians tend to be swept away to only focus on the evaluation of disease activity. At the same time, therapy-related adverse effects may occur. The challenge arises when the presentation of the adverse effects of the medications sometimes mimics the symptoms of the disease, and if neglected, they can aggravate disease progression.

This report was written to raise clinicians' awareness of the treatment of CD, especially those with comorbidities, to achieve remission while paying attention to possible adverse effects.

CASE PRESENTATION

A 76-year-old female came to our emergency room with general weakness one week before admission. The patient also complained of hematochezia and abdominal pain in the last month—no history of hematemesis or melena. The patient had a history of chronic diarrhea, recurring abdominal pain, and several episodes of hematochezia and had been diagnosed with Crohn's disease in the last ten years. She had been taking azathioprine and mesalazine for three years. The dose of azathioprine was increased to 2x50 mg PO and mesalazine 2x500 mg PO in the last year due to worsening symptoms. A colonoscopy was performed three years ago and showed terminal ileum ulceration. The histopathological study reported active chronic ileocolitis with ulceration and crypt distortion. An abdominal CT scan was performed about five months before admission. It showed mass projection in the ascending colon and thickening of the terminal ileum, ileocecal valve, and anorectal area, consistent with active Crohn's disease.

About 13 months before admission, the patient complained of cervical pain, which was difficult to control by medication. The patient then underwent anterior cervical corpectomy fusion (ACCF) of the cervical vertebrae (C5) and a neck biopsy six months later. The histopathological examination showed metastatic adenocarcinoma, which was confirmed by immunohistochemistry and originated from lung parenchymal tissue. Thoracal CT scan reported lung nodules. The patient then underwent palliative radiation four months before admission. Mutation of eGFR from cervical vertebrae tissue was examined and came out positive; thus, in the last six weeks, erlotinib was given to the patient as a treatment for lung cancer.

On admission, the patient was anemic (Hb 6.0 g/dl) and leukopenia (1.52x10³/µl). Thrombocyte count was normal on admission (171x10³/µl) but decreased upon evaluation on the third day of admission (53x10³/µl).

A colonoscopy three years ago (Figure 1) showed terminal ileum ulceration (C), ileocecal valve ulceration (B), and diverticula in the sigmoid (D). Histopathological study of colonic tissue reported active chronic ileocolitis with ulceration and crypt distortion.

On the colonoscopy evaluation in this admission (Figure 2), we found internal hemorrhoid (A), proctosigmoiditis (B), multiple ulceration in the rectum (B) and sigmoid (C), diverticula in the sigmoid (E), and ulceration found in the terminal ileum and ileocecal valve (G).

Abdominal CT scan showed a mass projecting in the ascending colon, thickening in the terminal ileum, ileocecal valve, and anorectal areas. A thoracal CT scan showed a solid nodule with malignant characteristics in segments 1 and 2 of the left lung. Bone scan study showed metastatic in vertebrae body of C2, C5, L2-L3, sacrum, right acetabulum, right symphysis, and right pubic bone. Histopathological analysis of cervical vertebrae showed metastatic adenocarcinoma, with an immunohistochemistry profile consistent with lung origin and positive mutation of EGFR (exon 21 L858R). Upon admission, 5-ASA, azathioprine, and erlotinib were discontinued. Packed red cell and thrombocyte transfusions were given as the

patient underwent gastrointestinal bleeding. After the gastrointestinal bleeding was resolved along with switching from azathioprine and 5-ASA to sulfasazaline and budesonide, periodic evaluation of blood smear showed blood cell count improvement.

DISCUSSION

Though data regarding IBD prevalence in Indonesia is still limited, a multinational epidemiology study reported that CD's annual incidence in Indonesia was 0.33 per 100,000 persons in 2012.[7] This number is projected to increase by 2035.[8] Kaplan GG reported that the prevalence of IBD in the Western world was increasing at the rate of 0.5% of the general population. Along with this increasing number of IBD cases, challenges to mitigate symptoms also evolved, bearing several choices of medications, with a considerable amount of cost. Therefore, clinicians should pay more attention to the rise of this "modern" disease.[9]

We presented a case where we treated a 76-year-old female who had been diagnosed with CD in the last ten years. She had a history of chronic diarrhea, recurring abdominal pain, and several episodes of hematochezia. The earliest colonoscopy documented at our center was three years ago, showing ileocecal ulceration and ulceration in the terminal ileum. This finding was confirmed by histopathological examination, which showed active chronic ileocolitis and crypt distortion. In the last three years, the patient was prescribed azathioprine 2x50 mg PO and mesalazine (5-ASA) 2x500 mg PO. Oral mesalazine is not recommended to be prescribed as a maintenance therapy for CD. Several randomized controlled trials failed to prove its efficacy in treating CD compared to placebo.[10–13] There was one RCT by Singleton et al. which reported that

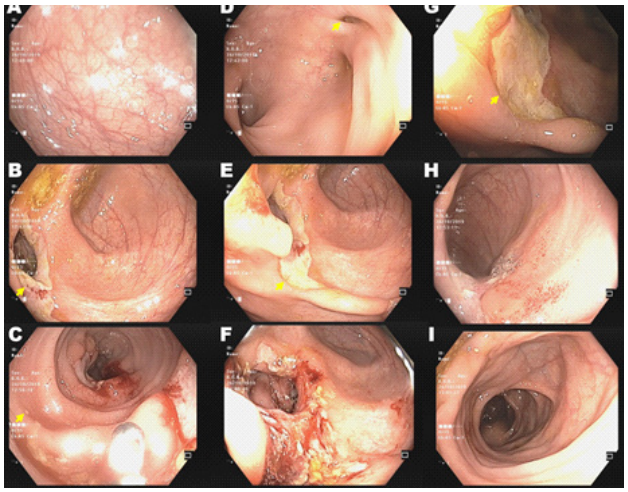

Figure 1. Colonoscopy 3 Years Before Admission
(Ileocecal ulceration is shown in panels B, E, and G (yellow arrow); diverticula in the sigmoid colon is shown in panel D (yellow arrow); ulceration in the terminal ileum shown in panel C (yellow arrow)

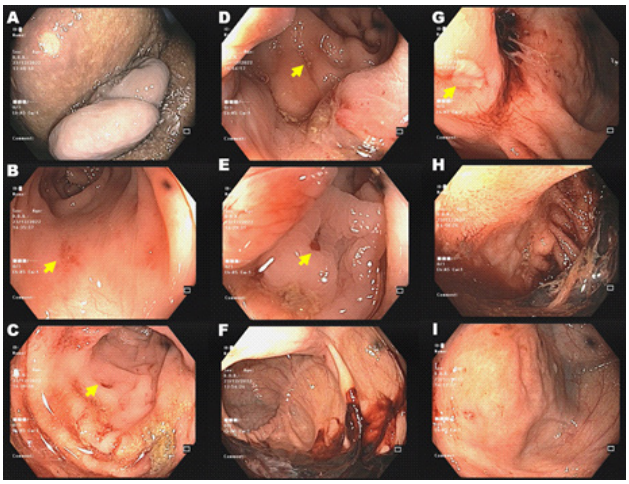

Figure 2. Recent Colonoscopy Evaluation
Proctosigmoiditis with multiple ulcerations is shown in panels B, C, and D (yellow arrow); diverticula in sigmoid colon is shown in panel E (yellow arrow); ulceration in ileocecal valve in panel G (yellow arrow)

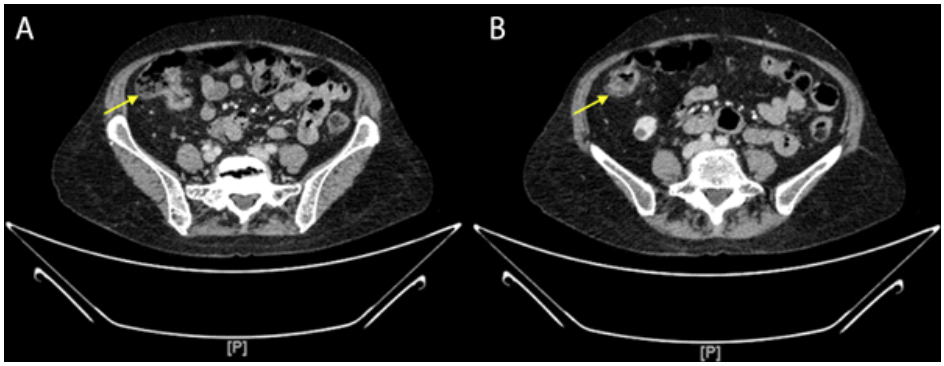

Figure 3. Abdominal CT scan
Ileocecal wall thickening is shown in panel A (yellow arrow); Mass projecting in the ascending colon is shown in panel B (yellow arrow)

mesalazine might be effective in treating active CD, but at the higher dosage needed (4 g/day) compared to ulcerative colitis.[14] Regarding maintenance, 5-ASA also showed no benefit compared to placebo in maintaining remission (ARR 5%; 95%CI -9.6 to 2.8%).[15] Conversely, azathioprine, a corticosteroid-sparing agent, is recommended as a maintenance therapy in CD through its immunomodulatory effects. However, 15-28% of those taking azathioprine might experience nausea, fever, fatigue, arthralgia, myalgia, and bone marrow suppression. Myelotoxicity was reported to be related to decreased thiopurine S-methyltransferase (TPMT) activity.[16] Bone marrow suppression was dose-dependent and might develop at any time during treatment (2 weeks – 11 years after initial dose). Infection and bleeding caused by leukopenia and thrombocytopenia were the most frequent cytopenia to be reported. Connell et al. reported that myelotoxicity would resolve one month after azathioprine discontinuation. Therefore, it is acceptable to evaluate blood count more frequently than three months to evaluate the possibility of myelotoxicity in those treated with azathioprine.[17]

Colonoscopy evaluation and abdominal CT scan revealed proof of active CD. Colonoscopy evaluation showed proctosigmoiditis and multiple ulceration in the rectum, sigmoid, terminal ileum, and ileocecal valve. These data were supported by imaging findings from an abdominal CT scan showing mass projecting in the ascending colon and thickening in the terminal ileum, ileocecal valve, and anorectal areas. Regarding these findings, hematochezia experienced by our patient might be caused either by the activity of Crohn's disease itself or by thrombocytopenia due to the myelosuppressive action of azathioprine. On the other hand, those two conditions might occur simultaneously and cause hematochezia.

In this case, discontinuing both 5-ASA and azathioprine was considered because of the objective finding of active CD and pancytopenia. This was in line with Rahim et al., who recommended reducing azathioprine dosage by 50 percent or discontinuing therapy should leukopenia (WBC $<4x10^3/\mu l$) or thrombocytopenia ($<150x10^3/\mu l$) develop.[18] The patient was then given budesonide 1x9 mg PO combined with sulfasalazine 2x1000 mg PO to induce CD's remission and blood products as supportive management due to myelosuppression. Budesonide was reported to be effective in induction therapy of CD, especially ileal or right-sided colonic Crohn's disease.[19]

Biologic agents, such as infliximab, adalimumab, certolizumab (anti-TNF agents), ustekinumab (anti-IL 12/23 antibody), and vedolizumab (anti-α-4-β-7 integrin monoclonal antibody) might become alternatives in our case. Still, these options were not selected due to cost considerations.

It is worth mentioning that our patient also had lung cancer treated with erlotinib 1x150 mg PO. Adverse effects of erlotinib that might be found include gastrointestinal symptoms (diarrhea, abdominal pain, nausea, and vomiting), which may mimic CD's manifestation.[20] There are also reports of erlotinib-associated gastrointestinal perforation.[21,22] Erlotinib, a tyrosine kinase inhibitor, is also reported to be associated with pancytopenia.[23]

CONCLUSION

Inflammatory Bowel Disease (IBD), especially Crohn's disease (CD), necessitates long-term treatment, focusing on remission. An individual approach is recommended in the management of this chronic condition. However, sometimes, to achieve remission, clinicians tend to be swept away to only focus on the evaluation of disease activity and are apt to neglect the adverse effects that may occur. Thorough observation and clinical evaluation are needed to treat those with IBD comprehensively.

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