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Case Report

A Complicated Case of Diffuse Large B-Cell Lymphoma in an Elderly Presenting with Massive Gastrointestinal Bleeding Successfully Treated with R-mini CHOP

Agus Jati Sunggoro[a, b] Ery Kus Dwianingsih[c]
Bambang Purwanto Utomo[d] Ibnu Purwanto[a]

[a]Hematology and Medical Oncology Division, Internal Medicine Department, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University/Dr. Sardjito Hospital, Yogyakarta, Indonesia; [b]Hematology and Medical Oncology Division, Internal Medicine Department, Faculty of Medicine, Sebelas Maret University/Dr. Moewardi Hospital, Surakarta, Indonesia; [c]Anatomical Pathology Department, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University/Dr. Sardjito Hospital, Yogyakarta, Indonesia; [d]Radiology Department, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University/Dr. Sardjito Hospital, Yogyakarta, Indonesia

Keywords
Non-Hodgkin lymphoma · Intestinal lymphoma · Chemotherapy · Gastrointestinal bleeding

Abstract
Gastrointestinal lymphoma accounts for up to 20% of all extranodal lymphoma cases. Among them, the ileum is the second most commonly affected site after the stomach. The majority of gastrointestinal lymphoma originates from the B cell lineage. We report the case of 60-year-old male with persistent anemia, hematochezia, and poor performance status (PS). After thorough workup, imaging, and pathological study, the patient was diagnosed with diffuse large B-cell lymphoma of the terminal ileum. He was treated with R-CHOP based chemotherapy with dose tailoring to accommodate his poor PS. His symptoms promptly subsided after the first chemotherapy cycle. After eight cycles of chemotherapy, terminal ileum wall thickening was gone and the patient was disease-free for 6 months. This case report shows that chemotherapy can be beneficial in patients with gastrointestinal lymphoma despite poor PS. Therefore, it should be given when possible with proper dose tailoring.

Ibnu Purwanto
Hematology and Medical Oncology Division
Internal Medicine Department, Gadjah Mada University
Jalan Farmako, Sekip Utara, Yogyakarta 55281 (Indonesia)
ibnupurwanto@ugm.ac.id

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Introduction

Gastrointestinal lymphoma, often a manifestation of extranodal non-Hodgkin lymphoma (NHL), is difficult to diagnose due to its nonspecific signs and symptoms. Previous studies reported a gastrointestinal lymphoma prevalence ranging from 5 to 45% [1, 2]. The most commonly affected site for gastrointestinal lymphoma is the stomach, followed by the small intestine with ileum predominance (60–65%) [3]. The majority of gastrointestinal lymphomas are of B-cell origin while T-cell lymphoma only accounts for 8–10% of cases [2, 3]. Advances in cancer treatment have resulted in significantly improved survival of NHL patients. Unfortunately, some patients might present with unfavorable characteristics, such as older age at presentation and poor performance status (PS), which might discourage medical practitioners from aggressive and curative treatment. However, curative intent can still be achieved in these high-risk patients with a careful and tailored approach. We report a case of diffuse large B-cell lymphoma (DLBCL) of the terminal ileum in a 60-year-old male with poor PS successfully treated with R-mini CHOP.

Case Report

A 60-year-old male presented to the emergency room with acute nonspecific abdominal pain and recurrent bloody stool for the last 30 days. The patient had been feeling weak for the last month with changes in bowel habit. He initially experienced loose dark stool (melena) which turned into fresh blood (hematochezia) during the last few weeks. He had been admitted four times in 30 days and had received multiple transfusions. On general examination, the patient had grade 4 ECOG PS. He was pale and weak with mild hypotension (90/60 mm Hg), tachycardia (110/min), and tachypnea (24/min). Multiple lymphadenopathies were found on the right axilla, right neck, and both inguinal regions. Blood work showed low hemoglobin (4.4 g/dL), with normal leukocyte (14.4 × 10^3/μL), thrombocyte (78 × 10^3/μL), and hemostasis parameters. Liver and renal function were also normal. Electrolyte panel showed hypokalemia (2.16 mmol/L) and severe hypoalbuminemia (1.95 g/dL). The patient immediately received fluid resuscitation and transfusion.

No abnormality was observed on upper gastrointestinal endoscopy and chest X-ray. On abdominal CT scan, terminal ileum wall thickening with aneurysm was found, referring to small intestine lymphoma (Fig. 1). Laparotomic biopsy of the ileum was not performed due

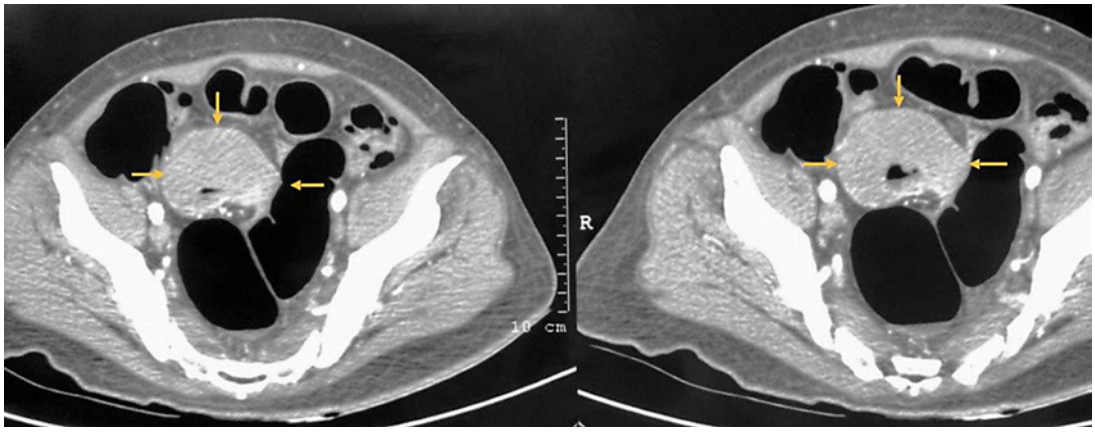

Fig. 1. Abdominal CT showed terminal ileum wall thickening (arrows).

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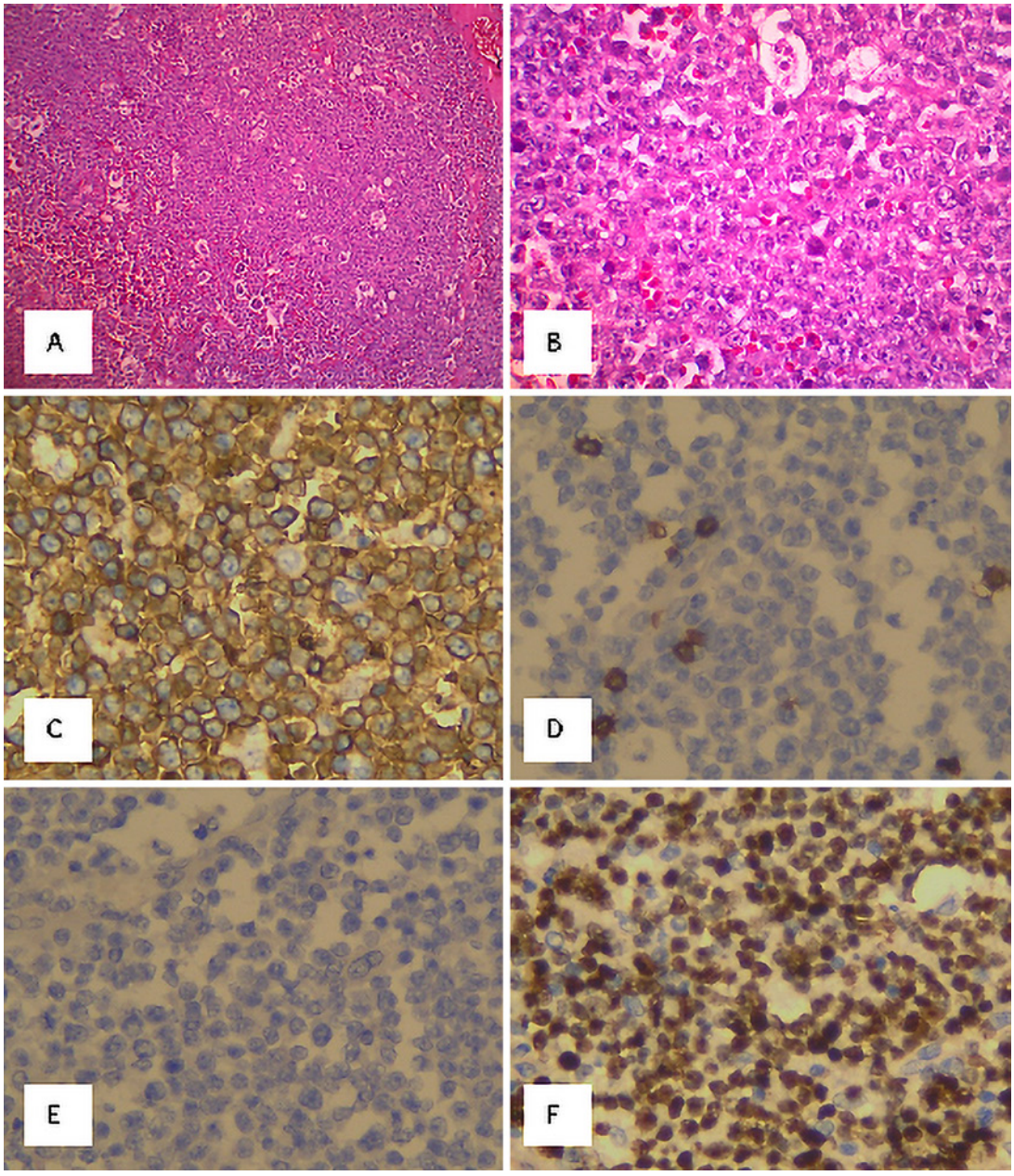

Fig. 2. Hematoxylin and eosin staining analysis. **A** The tumor is in diffuse growth pattern with large cells consisting of immunoblasts and centroblasts (×100). **B** Higher-magnification feature (×400) showing nuclear feature of large round cell with scanty cytoplasm, eccentric nuclei with one central nucleolus or central nuclei with two to three nucleoli, and mitosis. Macrophage tingible bodies are also observed. Immunohistochemistry analysis showed strong membranous expression of CD20 (×400) (**C**), negative expression of CD3 (×400) (**D**), negative expression of CD30 (**E**), and high proliferation index of Ki-67 (80%) immunostaining (**F**).

to the patient's poor PS and an incision biopsy of the submandibular lymph node was done instead. Pathology results showed NHL large cell type (Fig. 2). Immunohistochemistry showed negative CD3, positive CD20, negative CD30, and 80% Ki-67 (Fig. 2). The patient was then diagnosed with DLBCL. At this point, he was experiencing multiple episodes of hematochezia. His hemoglobin increased to 8 g/dL after packed red cells transfusion but went back to 6 g/

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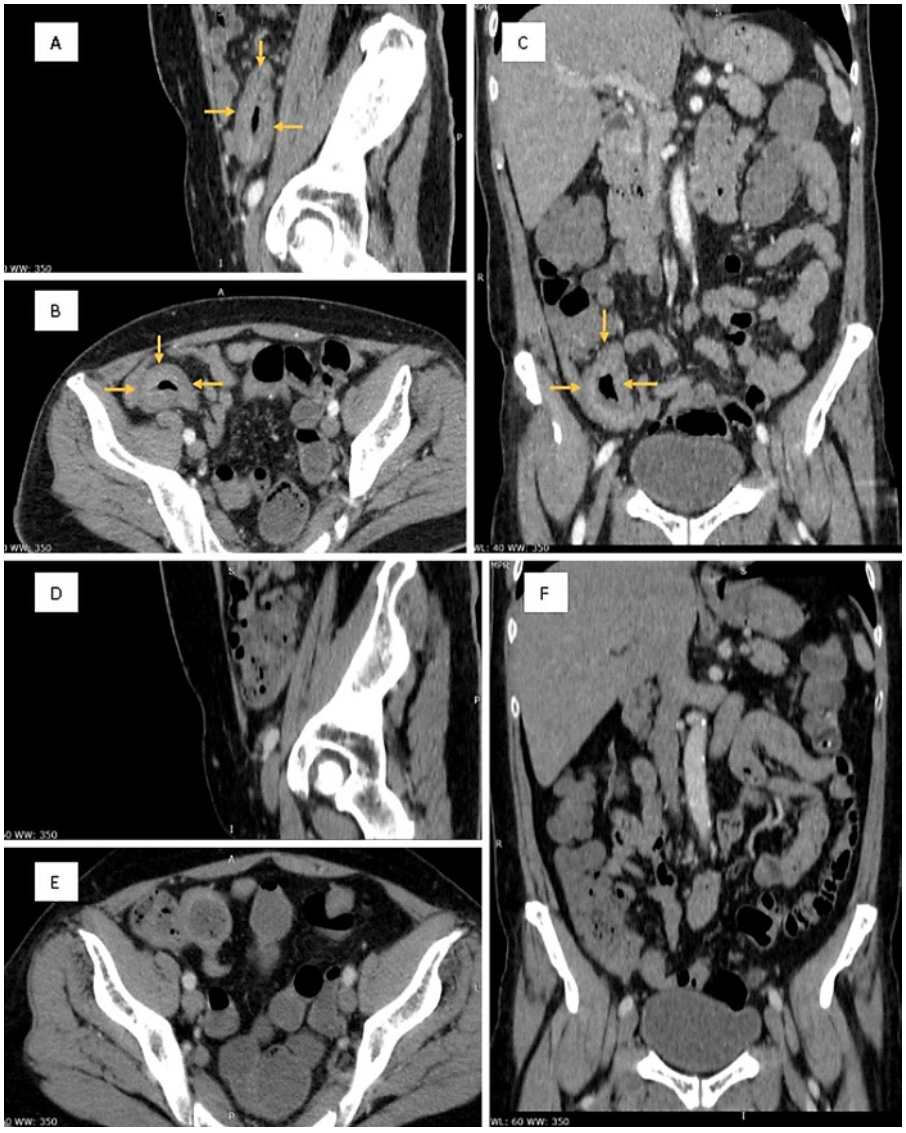

Fig. 3. Abdominal CT after the sixth cycle of CHOP chemotherapy in sagittal (**A**), axial (**B**), and coronal view (**C**). Terminal ileum thickening was still present with marked shrinkage (arrows). After chemotherapy abdominal CT scan showed absence of terminal ileum thickening in sagittal (**D**), axial (**E**), and coronal view (**F**).

dL. Echocardiography showed a left ventricular ejection fraction of 61% with a segmental kinetic disturbance on the basal and mid-anteroseptal region.

After thorough examination and tests, the patient was diagnosed with DLBCL of the terminal ileum. Despite his poor PS, he agreed to receive chemotherapy. A mini-COP regimen (cyclophosphamide 400 mg/m^2 on day 1, vincristine 1 mg on day 1, and prednisone 40 mg/m^2 on days 1–5) was given for the first cycle of chemotherapy. After the first cycle hematochezia stopped, with a progressive increase in hemoglobin (10.4 g/dL) and thrombocyte level (190 × 10^3/μL). Chemotherapy was continued with an R-mini CHOP regimen (rituximab 375 mg/m^2 on day 1, cyclophosphamide 400 mg/m^2 on day 1, doxorubicin 25 mg/m^2 on day 1, vincristine 1 mg on day 1, and prednisone 40 mg/m^2 on days 1–5) for the second to fourth cycle. The patient's general condition was gradually improving, and after a few days he was

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discharged. He was planned to receive the remaining chemotherapy cycles (fifth to eighth with full R-CHOP dose) as an outpatient. Upon evaluation after the sixth cycle, an abdominal CT scan showed marked shrinkage of terminal ileum wall thickening. A CT scan of the neck also showed a single lymph node enlargement with a diameter of 1.1 cm. The patient was offered surgical resection of the terminal ileum but refused. Therefore, chemotherapy alone was continued for a total of eight cycles. After the last chemotherapy, CT scan showed no residual thickening of the ileum and the patient was disease-free for 6 months (Fig. 3).

Discussion

Extranodal lymphomas originating from solid organs account for one-third of NHL cases. These extranodal involvements are usually found in the gastrointestinal tract, Waldeyer's ring, skin, and bone [4]. The histological subtypes of lymphoma in the gastrointestinal tract are mostly from B cell origin. A multicenter prospective study in Germany reported that the distribution of localized primary gastric lymphoma was dominated by DLBCL (59.5%), followed by marginal-zone B-cell lymphoma (37.9%), mantle cell lymphoma, and follicular lymphoma (1.3%), and lastly T-cell lymphoma (1.3%) [5].

The ileum is the predominant small intestinal lymphoma which accounts for 60–65% of cases, followed by the jejunum (20–25%) and duodenum (6–8%) [3]. A previous study reported a highly variable diagnostic age for small intestinal lymphoma ranging from 13 to 65 years, with a male tendency [6]. The most common histology types were mucosa-associated lymphoid tissue and DLBCL [2, 3, 6]. The symptoms and signs of small intestinal lymphoma are nonspecific, including abdominal pain, ileus, diarrhea, weight loss, gastrointestinal bleeding, palpable mass, and nausea [7]. The main symptoms of our patient were anemia and hematochezia preceded by melena. The anemia was most likely caused by recurrent intestinal bleeding since no abnormalities were found on upper gastrointestinal endoscopy.

Since the signs and symptoms of small intestinal lymphoma are highly unspecific, the diagnosis of DLBCL should be based on pathological assessment of an adequate tissue sample [8]. In our case, obtaining samples from the affected organ through surgical biopsy of the terminal ileum was not possible due to the patient's poor PS. Alternatively, an incisional biopsy of the affected lymph node was performed and a DLBCL diagnosis was established.

Aggressive B-cell lymphoma is a potentially curable disease. Different chemotherapy approaches are based on the pathological diagnosis of the lymphoma. In B-cell extranodal lymphoma, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) remains the first-line treatment regimen. The introduction of immunochemotherapy using rituximab in combination with chemotherapy significantly improved the prognosis of DLBCL patients. The addition of rituximab improved complete response, event-free survival, as well as progression-free survival [9]. After the rituximab era, the role of surgery became somewhat redundant. However, a study from the Korean Lymphoma Study Group reported a better 3-year overall survival and a lower relapse rate in intestinal DLBCL patients receiving surgery and chemotherapy than chemotherapy alone (overall survival 91 vs. 62%, relapse rate 15.3 vs. 36.8%, $p < 0.001$). Surgical resection with chemotherapy is especially beneficial in localized intestinal DLBCL, with an acceptable quality of life tradeoff [10].

Our patient showed poor PS, which might have been caused by persistent symptoms. Among the many factors affecting patients' prognosis, PS remains one of the most important variables to consider. A previous study reported poor PS as one of the most important unfavorable variables to predict survival [11]. Surgery was not a viable option for our patient due to his poor PS. However, chemotherapy was well tolerated and resulted in satisfactory outcome. The absence of anemia and hematochezia followed by normalization of terminal

ileum wall thickening showed the benefit of chemotherapy without notable side effects. A previous study showed similar benefits of intensive chemotherapy even in elderly patients with very poor PS. Patients who were treated with intensive chemotherapy regimens such as CHOP, R-CHOP, or CODOX-M/IVAC (cyclophosphamide, doxorubicin, vincristine-methotrexate alternating cycles with ifosfamide, VP16, and cytarabine) showed a markedly better 3-year overall survival (64%) compared with untreated patients (0%) and those who received modified regimens (14%) [12]. It was also mentioned that patients with worse PS might be better off starting with steroid pre-phase or dose reduction. Our patient was also started with a lower dose and showed good tolerance. If the patient has better PS, surgical resection in addition to chemotherapy should be considered [10].

Although our patient received a total of eight cycles of R-CHOP chemotherapy, a previous study suggested that CHOP chemotherapy with or without rituximab in the elderly beyond six cycles is not recommended if the patient has already achieved partial response after four cycles of chemotherapy [13]. It should be noted that our patient received a reduced dose initially and after the sixth cycle, the abdominal CT scan showed persistent terminal ileum wall thickening. Our patient was also relatively young and did not show any chemotherapy-related side effects. This justified the continuation of chemotherapy up to eight cycles in our case. In elderly patients, multiple regimens have been suggested such as R-CHOP14, R-CHO21, R-mini CHOP, R-CVP, R-split CHOP, O-mini CHOP, and R-CEOP, with varying results [8, 14]. Therefore, the decision to tailor the chemotherapy dose cannot be generalized and should be based on individual patients. Comprehensive geriatric assessment can also be used to assess elderly DLBCL patients as candidates for aggressive therapy. A study reported that elderly patients who were deemed "unfit" actually benefited from treatments with curative intent. The treatment group showed better 1-year overall survival than those who received palliative measures (66.1 vs. 19.0%, $p < 0.001$) [15].

Conclusions

DLBCL is the most common type of primary extranodal lymphoma of the gastrointestinal tract. Patients with primary small intestinal lymphoma usually have unspecific presentations which hinder diagnosis and prompt treatment. The delay in diagnosis might contribute to patients' poor PS. Available diagnostic modalities should be utilized to diagnose DLBCL early in order to treat this potentially curable disease. Immunochemotherapy using the R-CHOP regimen remains the first-line treatment for extranodal lymphoma in general owing to its effectiveness despite poor patient PS. Dose tailoring might also be considered in order to help the patient tolerate the side effects of chemotherapy. In patients with localized intestinal DLBCL, surgical resection with chemotherapy might be more beneficial compared to chemotherapy alone.

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Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report including accompanying images.

Conflict of Interest Statement

All authors were involved in the publication of this case report and declare no conflicts of interest.

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Author Contributions

A.J. Sunggoro and I. Purwanto were involved in work conception, data acquisition, and manuscript drafting. E.K. Dwianingsih and B.P. Utomo were involved in data acquisition and manuscript drafting.

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