Case Report/Series

Systemic amyloidosis following inflammatory bowel disease, follicular lymphoma, and diffuse large B-cell lymphoma: a case report

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pISSN: 0853-1773 • eISSN: 2252-8083
https://doi.org/10.13181/mji.cr.247428
Med J Indones. 2024;33:198–202

Received: January 31, 2024
Accepted: August 26, 2024
Published online: October 09, 2024

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ABSTRACT

Systemic amyloidosis is a rare disorder characterized by the widespread deposition of misfolded amyloid proteins in several organs, leading to organ failure and potentially death if not promptly recognized. The occurrence of inflammatory bowel disease (IBD), follicular lymphoma, and diffuse large B-cell lymphoma (DLBCL) developing into systemic amyloidosis is uncommon. Here is a case of a 55-year-old Asian woman with a history of IBD, follicular lymphoma, and abdominal DLBCL who developed systemic amyloidosis affecting her gastrointestinal, cardiac, and renal organs. Gastrointestinal symptoms (abdominal pain and melena) initially manifested in this patient with systemic amyloidosis. She underwent treatment with three cycles of rituximab and bendamustine. However, she passed away after 2 months of hospitalization due to multiple organ failure. Hence, physicians must be vigilant in recognizing amyloidosis as a potential complication of lymphoma or other inflammatory diseases, as early recognition can contribute to improved clinical outcomes.

KEYWORDS amyloidosis, diffuse large B-cell lymphoma, follicular lymphoma, gastrointestinal tract, inflammatory bowel disease

Amyloidosis is a rare condition characterized by the deposition of misfolded proteins in the form of amyloid fibrils in tissues, leading to organ dysfunction and damage. Amyloid light chain (AL) amyloidosis involves the deposition of monoclonal light chains produced by clonal non-proliferative plasma cells.[1,2] These light chains can be deposited in various organs, including the kidneys, heart, liver, gastrointestinal tract, and peripheral nervous system, affecting multiple organs locally or systemically.[3] AL amyloidosis is the most prevalent form of systemic amyloidosis.[4]

Amyloidosis can occur alongside chronic inflammatory diseases such as inflammatory bowel disease (IBD), plasma cell disorders like plasma cell dyscrasia, and lymphoproliferative disorders such as non-Hodgkin lymphoma (NHL).[1,2,5] However, amyloidosis as a complication of NHL is uncommon. The prevalence of AL-associated lymphoma is approximately 2–6% of all AL cases, often observed in indolent lymphomas.[2,5] In contrast, diffuse large B-cell lymphoma (DLBCL) is an aggressive subtype. According to data from a single center, AL association with DLBCL was observed in two of 21 AL-associated lymphoma cases, localized or peritumoral AL.[2] Cases of systemic amyloidosis associated with DLBCL are rare, and no reports have described systemic amyloidosis in patients with a history of IBD, follicular lymphoma, or DLBCL.

Here, we present an unusual case of systemic amyloidosis involving the gastrointestinal, cardiac, and renal organs in a patient with a history of IBD, follicular lymphoma, and DLBCL. This is the first case report on systemic amyloidosis as an unexpected complication in IBD, follicular lymphoma, and DLBCL in Indonesia.

CASE REPORT

In October 2015, a 55-year-old Asian woman with a medical history of dyspepsia, IBD, and scoliosis presented with an enlarged neck lymph node. She was diagnosed with two types of NHL: follicular lymphoma stage 3B and DLBCL. She underwent six cycles of immunochemotherapy with the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen. Positron emission tomography-computed tomography (PET-CT) scans confirmed a complete response (CR) to the treatment.

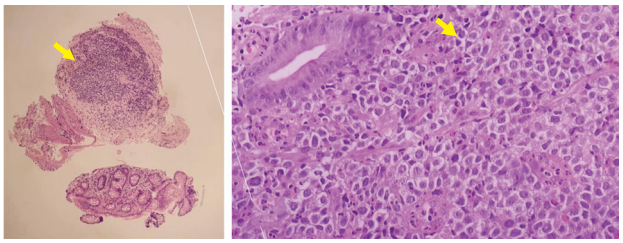

Figure 1. Histopathological findings of colon biopsy. Colonic tissue was infiltrated by diffuse atypical lymphoid cells with prominent nucleoli and elevated mitotic activity (yellow arrows) (hematoxylin and eosin [H&E], 40× [left] and 400× [right] magnification)

In May 2018, she presented with chronic diarrhea and fever. A colon mucosal biopsy revealed diffuse atypical lymphoid cells with prominent nucleoli and elevated mitotic activity infiltrating the colonic tissue (Figure 1). Most of her lymphoid cells were also positive for CD10, CD20, and multiple myeloma oncogene 1 (MUM1) (Figure 2). These findings indicated that the disease had relapsed as DLBCL in the abdominal region. After six cycles of rituximab, cyclophosphamide, etoposide, vincristine, and prednisolone (R-CEOP) chemotherapy, CR was confirmed on PET-CT.

In April 2019, she experienced recurrent fever and weight loss as the disease relapsed a second time, along with an acute cytomegalovirus (CMV) infection indicated by positive CMV IgM. She was initially scheduled to receive a rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) regimen; however, due to her frail condition despite an ECOG performance status of 1, the regimen was modified to rituximab, gemcitabine, and oxaliplatin

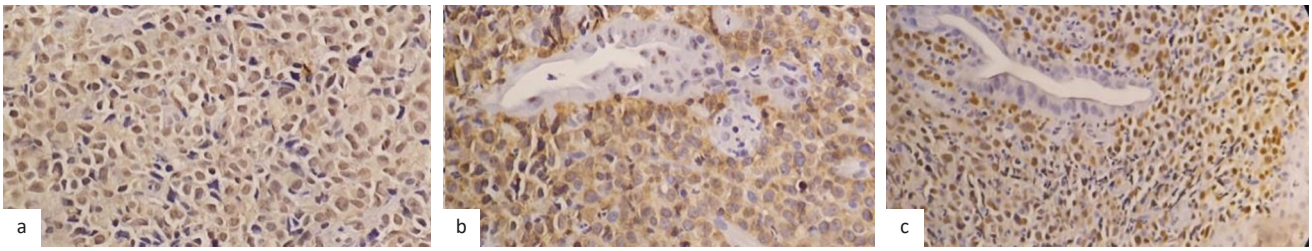

Figure 2. The immunohistochemical findings of colonic tissue. The lymphoid infiltrate stained positive (depicted in brown color) for CD10 (a), CD20 (b), and multiple myeloma oncogene 1 (MUM1) (c) (immunoperoxidase, 400× magnification)

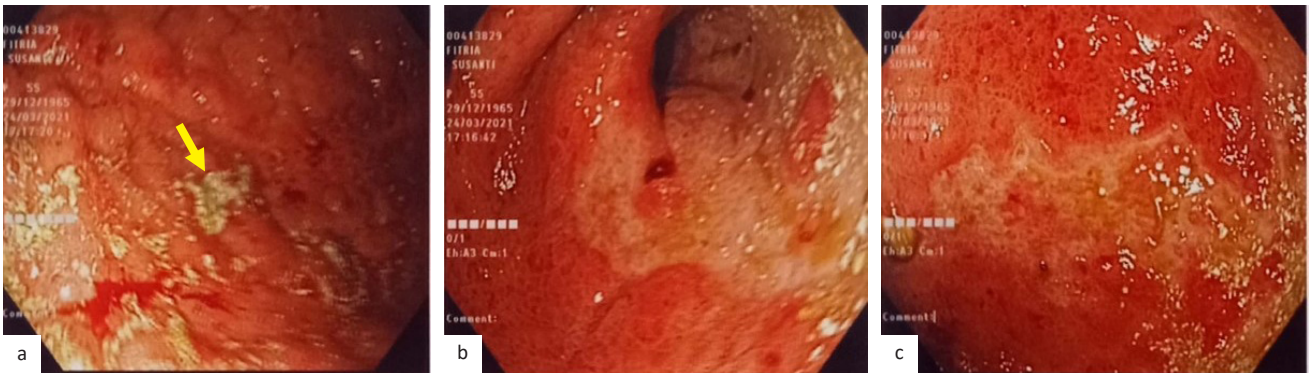

Figure 3. Endoscopic findings of gastric lesions revealed a diffuse erythema with friable and granular mucosa (a–c) and a large gastric ulcer covered with fibrin plaque in the antrum (yellow arrow)

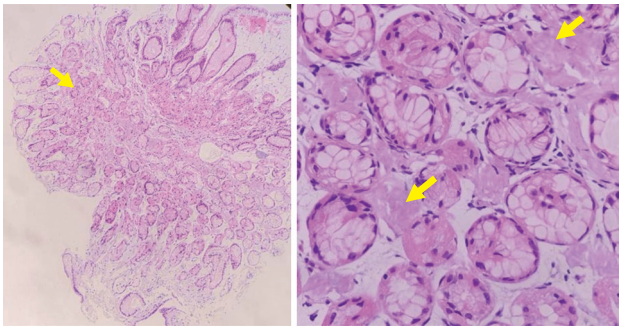

Figure 4. Histologic features of antral gastric mucosa biopsy revealed erosive and ulcerative mucosa, along with infiltration of acute and chronic inflammatory cells and amyloid materials (yellow arrows) in the lamina propria (Congo red and periodic acid-Schiff [PAS] stain, 40× [left] and 400× [right] magnification)

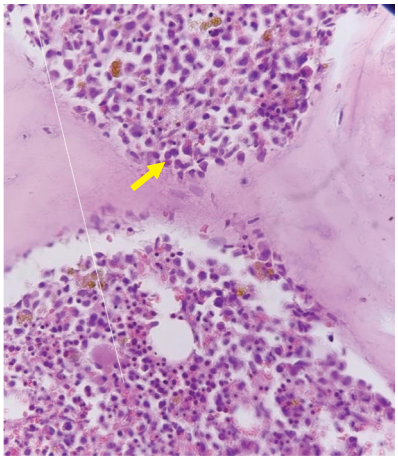

Figure 5. The histological examination revealed the bone marrow involvement of DLBCL. The bone marrow showed hypercellularity and was infiltrated by lymphoma cells, characterized by large atypical cells with prominent nucleoli (yellow arrow), primarily in the interstitial and para trabecular regions of the bone marrow (H&E, 400× magnification). DLBCL=diffuse large B-cell lymphoma; H&E=hematoxylin and eosin

(R-GemOx) starting in May 2019. Throughout the two chemotherapy courses of R-GemOx, she developed severe neutropenia and recurrent fever. Despite these complications, chemotherapy was continued after a CT scan revealed a partial response.

In December 2020, she reported melena, severe abdominal pain, and a persistent fever. Laboratory tests indicated anemia (hemoglobin [Hb], 9.7 mg/dl), severe neutropenia, and normal plasma urea/creatinine levels. Esophagogastroduodenoscopy revealed bleeding of the gastric mucosa (Figure 3), and a gastric biopsy, with Congo red and periodic acid-Schiff staining, confirmed the presence of amyloid materials in the lamina propria, diagnosing gastric amyloidosis (Figure 4). A PET-CT scan in December 2020 revealed lymph node enlargement in the lower-right, mid-, and upper-left abdominal areas. However, the specific type of amyloidosis could not be definitively determined due to limitations at our facility.

One month later, the patient was admitted to the emergency department (ED) with shortness of breath. She was diagnosed with acute heart failure, acute coronary syndrome with anteroseptal ischemia, and acute kidney injury. Blood tests revealed elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP, 7,664 ng/l), high-sensitivity cardiac troponin T (hs-cTnT, 22.4 pg/ml), urea (164 mg/dl), creatinine (3.67 mg/dl), immature platelet fraction (9%), and lactate dehydrogenase (546 IU/l), alongside anemia (Hb 8.9 mg/dl), thrombocytopenia (120,000 cells/µl), and a normal leukocyte count (6,480 cells/µl). No proteins were detected in the urine. Echocardiography revealed a normal heart structure and left ventricular ejection fraction of 72%.

The patient's blood urea and creatinine levels gradually normalized within a few days. However, she developed pancytopenia (Hb 8.9 mg/dl, leukocyte count 2,200 cells/µl, and thrombocyte count 27,000 cells/µl). Bone marrow puncture results indicated hypercellular bone marrow infiltration by lymphoma and malignant large lymphoid cells, consistent with metastasis of DLBCL to the bone marrow (Figure 5).

In March 2021, 2 months after receiving three cycles of rituximab and bendamustine chemotherapy, she was admitted to the ED with abdominal pain, diarrhea, and fever. A biopsy of the gastric and rectosigmoid mucosa was performed to assess disease progression. Unfortunately, the biopsy results confirmed the presence of amyloidosis in both the gastric and rectosigmoid mucosa. Serum free light chain (FLC) examination revealed low kappa FLC (κ 1.99 mg/l) and lambda FLC (λ 1.66 mg/l), with a normal κ/λ ratio (1.2). Protein electrophoresis revealed hypoproteinemia, hypoalbuminemia, and decreased levels of gamma globulin without the typical pattern of monoclonal gammopathy. However, IgM levels were normal.

Owing to the progressing amyloidosis and abdominal DLBCL, her condition continued to deteriorate. She was scheduled to undergo bortezomib chemotherapy; however, her deteriorating condition,

marked by severe pancytopenia and worsening kidney function, made the therapy unfeasible. After spending 2 months in the intensive care unit, she died due to multiple organ failure. The patient's next of kin provided written informed consent for the publication of this case report and the accompanying images. Institutional approval was not required for this study.

DISCUSSION

We report a rare case of systemic amyloidosis involving the gastrointestinal, cardiac, and renal organs in a patient with a history of IBD, follicular lymphoma, and DLBCL in Indonesia. The UK National Amyloidosis Centre reports that AL amyloidosis accounts for 68% of amyloidosis cases, followed by amyloid A (AA) (12%), hereditary (6.6%), and acquired wild-type transthyretin (3.2%) types, making AL amyloidosis the most prevalent form of systemic amyloidosis.[6] Clinical features of systemic amyloidosis are often non-specific, contributing to challenges and delays in diagnosis. Before diagnosing systemic amyloidosis, monoclonal paraproteins must be detected through examinations such as protein electrophoresis with serum and urine immunofixation, and serum FLC assay. In this case, despite the presence of cardiac and renal complications, laboratory data supporting monoclonal components were negative. The gold standard for confirming amyloidosis is a biopsy with Congo red staining, while methods such as immunohistochemistry, electron microscopy, and mass spectrometry are used to ascertain the specific amyloid type.[6–8] In this case, although amyloid materials were identified in the tissue biopsy, the specific amyloid subtype could not be determined.

Sanchorawala et al[5] found that only 2% of AL amyloidosis cases are associated with B-cell lymphoproliferative disorders, with the majority (81%) being systemic. In contrast, la Torre et al[2] identified 6.2% of AL amyloidosis cases linked with B-cell lymphoma, including two cases of AL amyloidosis in DLBCL, one of which had transformed from follicular lymphoma. Approximately 60% of the cases involve localized or peritumoral AL. Telio et al[9] previously documented two cases of B-cell lymphoma with plasmacytic differentiation associated with systemic AL amyloidosis. Another type of amyloidosis potentially associated with NHL is the rare AA-type amyloidosis, with only six reports in the literature.[10]

Most cases of amyloidosis are associated with indolent NHL, such as lymphoplasmacytic lymphoma and Waldenström's macroglobulinemia. In contrast, the aggressive lymphoma subtype DLBCL is infrequently linked to amyloidosis.[2,10] Additionally, secondary systemic amyloidosis or AA amyloidosis can arise as a complication of chronic inflammatory diseases or chronic infections, including IBD, rheumatoid arthritis, systemic lupus erythematosus, and tuberculosis. In the context of AA amyloidosis, amyloid proteins stem from serum AA protein, an acute-phase reactant produced in response to various inflammatory cytokines.[7,11]

In our case, the patient presented with abdominal pain and additional symptoms, such as vomiting, nausea, and weight loss. The initial diagnosis leaned towards abdominal DLBCL metastasis to the stomach or possibly arising from a gastric ulcer. Gastric bleeding and stenosis are common complications in DLBCL cases following chemotherapy.[12] The stomach is the most common site of extranodal NHLs, accounting for 30–40% of extranodal lymphomas and 55–65% of gastrointestinal lymphomas.[13]

Goteri et al[14] reported 82 cases of follicular lymphoma, of which 10 exhibited both follicular and large B-cell lymphoma. Typically, B cell germinal centers undergo differentiation into plasma cells during their development, expressing the B-cell markers CD10 and BCL6, followed by CD38, CD138, and MUM1 in plasma cells.[14,15] In this study, lymphoid cells in the colon tissue displayed positive CD10, CD20, and MUM1 staining.

Cardiac involvement is the primary cause of morbidity and mortality in amyloidosis, particularly AL amyloidosis, affecting survival outcomes in 50–75% of cases. Cardiac involvement is often indicated through echocardiography, showing pan-cardiac thickening (affecting the ventricular free walls, septa, and valves) and atrial enlargement, manifesting as diastolic heart failure, heart failure with preserved ejection fraction, and infiltrative cardiomyopathy. Other commonly affected organs include the kidneys and liver. Cardiac involvement in AA amyloidosis is rare. AA amyloidosis frequently affects the kidneys, presenting as non-diabetic proteinuria or associated with NHL, such as kidney dysfunction and nephrotic syndrome cases.[3,6,8,10,16]

The prognosis of AL amyloidosis varies according to the stage. NT-proBNP and hs-cTnT levels are used for staging and prognostic assessment. Stages I and II

generally yield favorable outcomes, with a 57% 10-year survival rate for stage I and a median survival of 67 months for stage II. Meanwhile, stage IIIa and IIIb are associated with worse outcomes, with median survival rates of 15 and 4 months, respectively.[3,8]

Furthermore, DLBCL with concurrent bone marrow involvement is associated with an exceptionally poor prognosis, with only a 10.3% 5-year survival rate.[17] Supportive therapy tailored to the affected organ systems can improve the patient's quality of life.[18] The patient was well-informed about the disease and expected the best available treatment. However, her deteriorating condition prevented the planned bortezomib treatment. Bortezomib is recognized as a standard treatment for AL amyloidosis, aiming to achieve early hematologic response and long-term organ improvements.[16,19] The progressive amyloidosis (stage III) and concurrent bone marrow involvement in DLBCL worsened the prognosis, leading to multiple organ failure and eventual death.

The limitations of this case report include our inability to determine the specific subtype of amyloidosis due to inadequate facilities and the lack of diagnostic confirmation through tissue biopsies of affected organs, such as the heart and kidneys. Additionally, the progressive systemic amyloidosis contributed to the development of multiple organ failure and an unfavorable prognosis.

This case highlights systemic amyloidosis involving the gastrointestinal, cardiac, and renal organs following a history of IBD, follicular lymphoma, and DLBCL. Systemic amyloidosis initially presents with gastrointestinal symptoms, with other symptoms emerging as the disease progresses. Therefore, timely recognition and diagnosis of amyloidosis are crucial, as they can significantly affect the prognosis and overall outcome of patients.

Conflict of Interest

The authors affirm no conflict of interest in this study.

Acknowledgment

The authors would like to thank Renata Tamara, MD for assisting in writing the manuscript.

Funding Sources

None.

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