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(Citation)

Internal Medicine, 65(16):2274-2279

(Issue Date)

2026-08-15

(Resource Type)

journal article

(Version)

Version of Record

(Rights)

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(URL)

<https://hdl.handle.net/20.500.14094/0100505485>



[CASE REPORT]

Diffuse Large B-cell Lymphoma Presenting with Protein-losing Enteropathy during Treatment for Systemic Lupus Erythematosus

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Abstract:

Protein-losing enteropathy (PLE) is a rare complication of systemic lupus erythematosus (SLE). A 38-year-old woman with well-controlled SLE developed abdominal pain, lower-extremity edema, anemia, and hypoalbuminemia. The patient was then diagnosed with PLE. Despite treatment with glucocorticoids and cyclophosphamide, persistent hypoalbuminemia was observed. A biopsy was performed using double-balloon enteroscopy due to small bowel lesions, which confirmed the diagnosis of diffuse large B-cell lymphoma. To the best of our knowledge, this is the first reported case of diffuse large B-cell lymphoma mimicking PLE associated with SLE. The possibility of malignant lymphoma should be considered in cases of treatment-resistant PLEs associated with SLE.

Key words: protein-losing enteropathy, systemic lupus erythematosus, diffuse large B-cell lymphoma

(Intern Med 65: 2274-2279, 2026)

(DOI: 10.2169/internalmedicine.5934-25)

Introduction

Protein-losing enteropathy (PLE) is a disease that causes a variety of symptoms, including hypoalbuminemia, edema, diarrhea, abdominal pain, and vomiting, owing to the loss of protein from the intestinal tract. PLE is diagnosed by demonstrating protein loss from the intestinal tract, either by an increase in fecal alpha-1-antitrypsin or by protein loss scintigraphy, in addition to hypoalbuminemia. PLE can be caused by various diseases including systemic lupus erythematosus (SLE), malignant lymphoma, inflammatory bowel disease, and congestive heart failure. Treatment of the underlying disease is important for improvement (1). Therefore, it is important to determine the cause by performing medical history tests, blood tests, and imaging tests. PLE

develops in 2-3% of patients with SLE and is often observed at the onset of SLE. It has also been reported to be relatively common in Asians (2-5).

Localized malignant lymphoma of the gastrointestinal tract is also a cause of PLE, regardless of the type of disease; however, the development of PLE is extremely rare. In this case, we encountered a patient with SLE who developed PLE that was resistant to immunosuppressive treatment. Accordingly, we performed a tissue biopsy and diagnosed diffuse large B-cell lymphoma (DLBCL). SLE can complicate PLE. We report the case of a patient with SLE who developed PLE, for whom diagnosing DLBCL as the underlying cause was difficult.

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Received: May 6, 2025; Accepted: November 20, 2025; Advance Publication by J-STAGE: January 15, 2026

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Table. Clinical Data at the Time of Diagnosis of PLE Due to SLE.

RBC	264×10 ⁴ /μL	Total protein	4.9 g/dL	Na	138 mmol/L
Hemoglobin	5.7 g/dL	Albumin	1.9 g/dL	K	4 mmol/L
MCV	79.2 %	AST	12 U/L	Cl	109 mmol/L
WBC	5,000 /μL	ALT	9 U/L	Ca	7.2 mg/dL
Neutrophil	56 %	Total bilirubin	0.2 mg/dL	Fe	6 μg/dL
Eosinophil	2 %	LDH	169 U/L	IgG	1,424 mg/dL
Basophil	1 %	Creatinine	0.83 mg/dL	IgA	111 mg/dL
Monocyte	15 %	BUN	11.8 mg/dL	IgM	31 mg/dL
Lymphocyte	26 %	CRP	1.15 mg/dL	C3	114 mg/dL
					(reference range 73-138)
Platelet	38.1×10 ⁴ /μL	Ferritin	<7 ng/dL	C4	43.4 mg/dL
					(reference range 11-31)
				Anti-dsDNA antibody	2.2 IU/mL
					(reference range ≤12)
				sIL-2R	2,014 U/mL
					(reference range 122-496)

RBC: Red Blood Cell, MCV: Mean Corpuscular Volume, WBC: White blood Cell, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, LDH: Lactate dehydrogenase, BUN: Blood Urea Nitrogen, CRP: C-reactive Protein, Na: Sodium, K: Potassium, Cl: Chloride, Ca: Calcium, Fe: Iron, Anti-dsDNA antibody: anti-double stranded DNA antibody (radioimmunoassay), sIL-2R: Soluble Interleukin-2 Receptor

Case Report

A 38-year-old woman underwent maintenance therapy for SLE. She was diagnosed with SLE at 18 years of age due to persistent proteinuria, butterfly erythema, Raynaud's phenomenon, positive anti-ds-DNA antibodies, and hypocomplementemia. A renal biopsy confirmed class IV and V lupus nephritis. She was positive for anti-SS-A antibodies and negative for anti-SS-B antibodies; however, as she had no symptoms of dry mouth or dry eyes, Sjögren's disease was not suspected and she did not meet the classification criteria. A lip biopsy and ophthalmological evaluation were not performed. At 19 years of age, she developed a renal infarction and was diagnosed with antiphospholipid antibody syndrome based on positivity for anti-cardiolipin-β2 glycoprotein I complex antibodies. The patient remained in remission with mycophenolate mofetil (500 mg), tacrolimus (3 mg), hydroxychloroquine (200/400 mg, every other day), and prednisolone (5 mg).

She had experienced abdominal pain for six months before admission and had developed anemia and hypoalbuminemia. Five months after the onset of symptoms, the patient experienced postprandial discomfort and mild lower-extremity edema. The anemia progressed rapidly. The laboratory examination findings were hemoglobin 5.7 g/dL, albumin 1.7 g/dL, C-reactive protein 1.16 mg/dL, ferritin <7 ng/mL, and iron 7 μg/dL. The anti-dsDNA antibody levels were normal, and hypocomplementemia was not observed. The soluble interleukin-2 receptor level was 2,014 U/mL. A urinalysis revealed no proteinuria, occult blood, or granular casts (Table). Contrast-enhanced computed tomography (CT) revealed diffuse thickening of the small-intestinal wall (Fig. 1A) and no extravasation was observed. Upper gastro-

intestinal endoscopy was unremarkable, whereas lower gastrointestinal endoscopy revealed mild edema and redness in the terminal ileum. A biopsy of the same area showed inflammatory changes, but no malignancy. A urinalysis ruled out a recurrence of lupus nephritis. PLE was suspected because of the persistent hypoalbuminemia. Protein-losing scintigraphy six hours after injection showed no accumulation of ^{99m}Tc-DTPA-human serum albumin (HSA-D) in the intestines (Fig. 1B). After 24 h, accumulation was observed in the descending colon and rectum (Fig. 1C), suggesting the leakage of protein from the small intestine. Capsule endoscopy revealed erosions and white villi in the small intestine (Fig. 1D). Consequently, the patient was diagnosed with SLE-associated PLE. The patient did not present with fever, night sweats, or weight loss. As there were no organ lesions other than PLE, the British Isles Lupus Assessment Group score was Category B (gastrointestinal). Anemia observed at the time of admission was due to bleeding from small intestinal erosions and malabsorption caused by small intestinal edema.

She was treated with prednisolone (60 mg/day) and cyclophosphamide pulse (500 mg/m², every two weeks). Despite the initiation of treatment, there was no improvement in her hypoalbuminemia, and the lower leg edema worsened. She exhibited hypocalcemia (corrected calcium, 7.0 mg/dL) and developed tetany due to malabsorption associated with PLE.

A CT scan two months after treatment showed persistent small intestinal wall thickening (Fig. 2A), and abdominal ultrasonography revealed thickened intestinal walls with significant blood flow (Fig. 2B). The persistent elevation of soluble interleukin-2 receptor (3,268 U/mL) and ultrasound findings raised the suspicion of malignant lymphoma. Double-balloon endoscopy was performed to investigate the cause of PLE. Biopsy specimens were obtained from villi

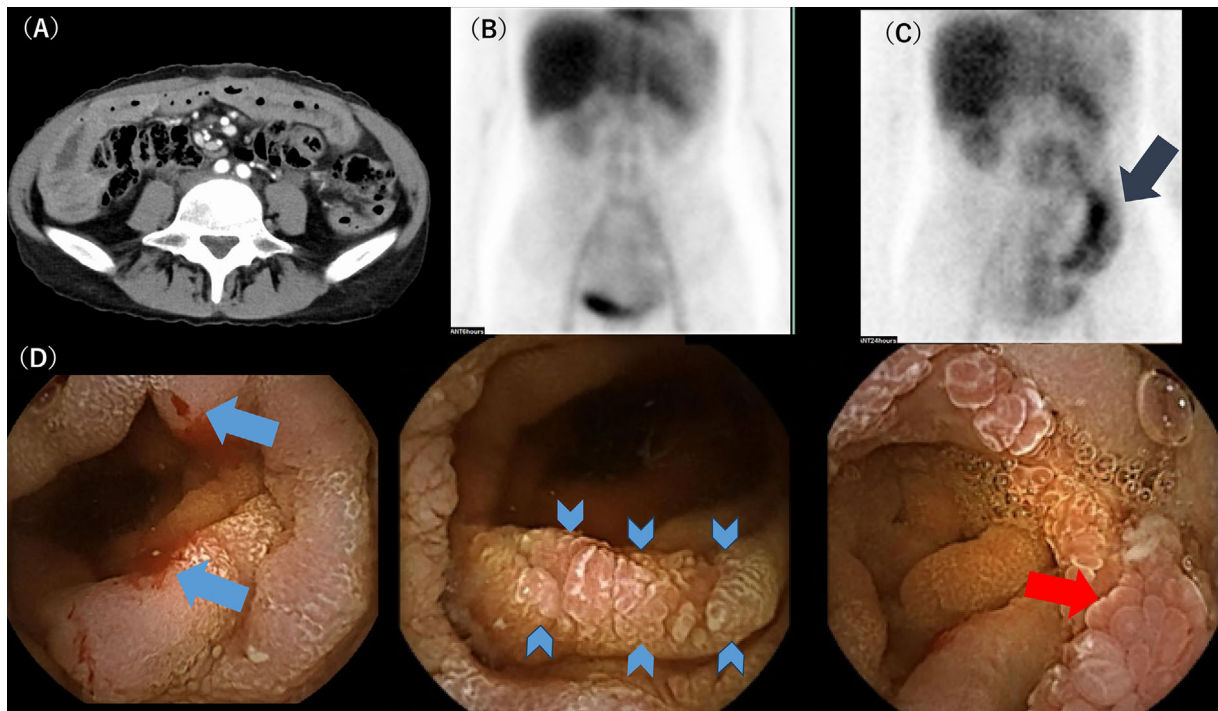


Figure 1. (A) Contrast-enhanced CT showing diffuse thickening of the small intestinal wall. (B) ^{99m}Tc -HAS-D scintigraphy performed at 6 h showing no tracer accumulation. (C) ^{99m}Tc -HAS-D scintigraphy performed at 24 h showing tracer accumulation (arrow) from the descending colon to the rectum. (D) Capsule endoscopy findings: mucosal erosion (blue arrows), white villi (blue arrowheads), and edematous villi (red arrow) in the small intestine. ^{99m}Tc -HAS-D: ^{99m}Tc -DTPA-human serum albumin

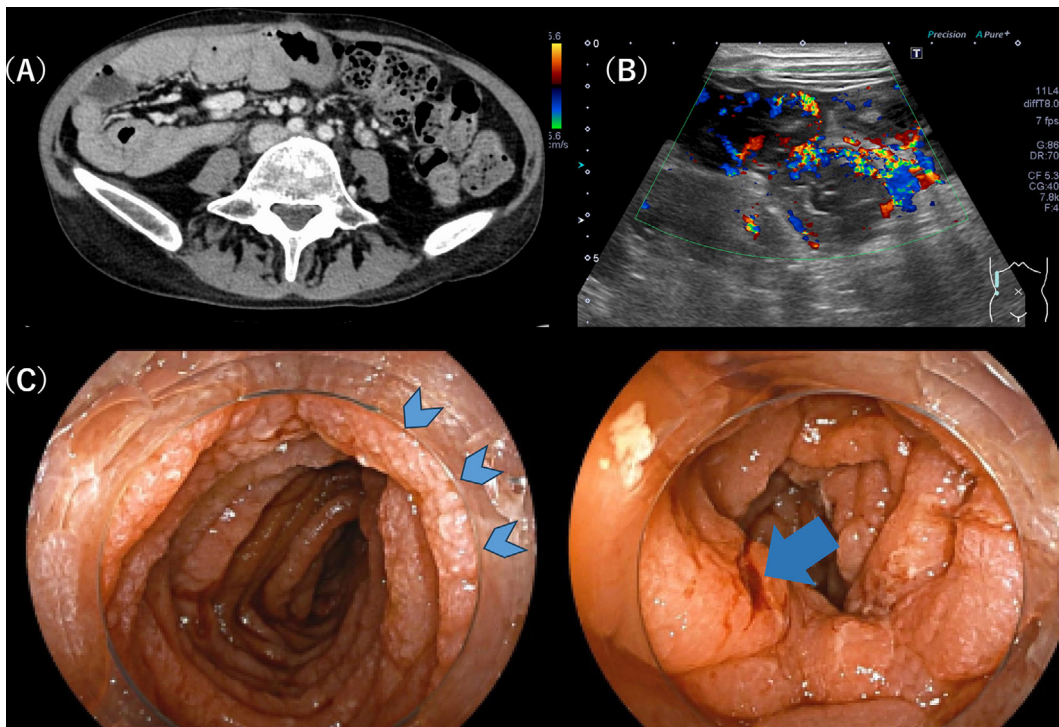


Figure 2. (A) Contrast-enhanced CT performed 11 weeks after the initiation of treatment showing persistent small intestinal wall thickening. (B) Abdominal ultrasound image showing a thickened ileal wall with abundant blood flow. (C) Double-balloon endoscopy findings: white villi (arrowheads) and mucosal erosion (arrow).

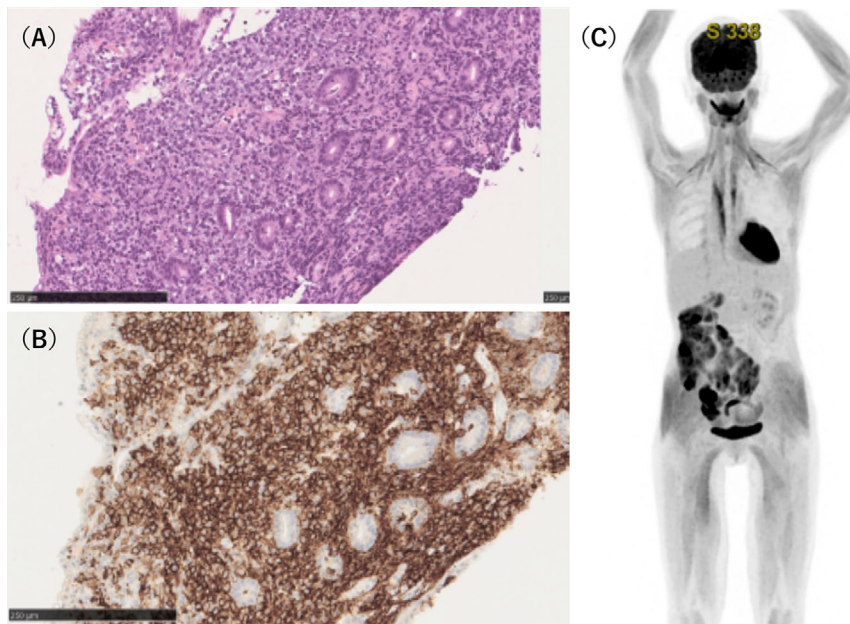


Figure 3. (A) The histopathological examination of the small intestinal mucosa. Hematoxylin and Eosin staining reveals large atypical cells. (B) Immunohistochemical staining for CD20 shows diffuse positivity of infiltrating lymphocytes in the small intestinal mucosa (magnification 200×). (C) An FDG-PET/CT image showing the increased uptake of FDG in the lower right abdomen. No lymphoma lesions were observed outside the small intestine. FDG-PET/CT: ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography

and eroded areas of the small intestine (Fig. 2C). A pathological examination revealed the presence of large cells with nuclei infiltrating the small intestine, as observed by hematoxylin-eosin staining. Furthermore, immunohistochemical staining showed diffuse positivity for CD20 in the small intestinal wall, leading to the diagnosis of DLBCL (Fig. 3A, B). In addition, the tumor cells expressed MUM1, whereas staining of CD10 and Bcl6 was negative. Taken together, these findings led to a diagnosis of DLBCL of the non-germinal center B-cell-like subtype. To investigate the distribution of malignant lymphoma lesions, ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography-CT revealed the uptake of FDG in locations corresponding to areas of intestinal thickening (Fig. 3C). The disease severity, according to the Lugano classification, was stage I. In addition, the International Prognostic Index, which serves as a prognostic indicator, was 1 point due to elevated lactate dehydrogenase levels alone, corresponding to the low-risk group.

The patient's performance status, according to the Eastern Cooperative Oncology Group scale, was 1 at the time of the diagnosis of DLBCL. Following the initiation of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) chemotherapy, her serum albumin levels increased to 3.2 g/dL within 43 days, accompanied by symptomatic improvement (Fig. 4).

Six months after the initiation of treatment for DLBCL, ^{18}F -FDG positron emission tomography-CT demonstrated an improvement in the FDG uptake in the small intestine. Consequently, the patient achieved complete remission.

Discussion

We encountered a patient with DLBCL who developed PLE during systemic lupus erythematosus treatment. PLE in SLE is typically treated using glucocorticoids. Azathioprine and cyclophosphamide are often used for patients demonstrating resistance to treatment (6). Treatment response with improvement in hypoalbuminemia has been observed in many cases within two months (2, 4). However, in this case, hypocalcemia progressed and lower extremity edema worsened. Furthermore, in patients with SLE who develop PLE, many cases show hypocomplementemia and elevated anti-DNA antibodies (3), and this point was also inconsistent with this case. Therefore, the diagnosis should be reconsidered.

Considering the differential diagnosis, persistently elevated soluble interleukin-2 receptor levels raised suspicion of malignant lymphoma. In addition, thickening of the small intestinal wall with increased blood flow on abdominal ultrasonography supported the diagnosis of malignant lymphoma. Ultrasound findings for intestinal primary malignant lymphoma include thickening of the intestinal wall without obstruction, characterized by low brightness and abundant blood flow (7). Conversely, intestinal wall thickening has been documented in 9% of SLE patients with PLE (8), and intestinal wall thickening and increased blood flow have also been observed in cases of intestinal inflammation (7). Consequently, patients with SLE may also present with intestinal wall thickening with abundant blood flow, and abdominal

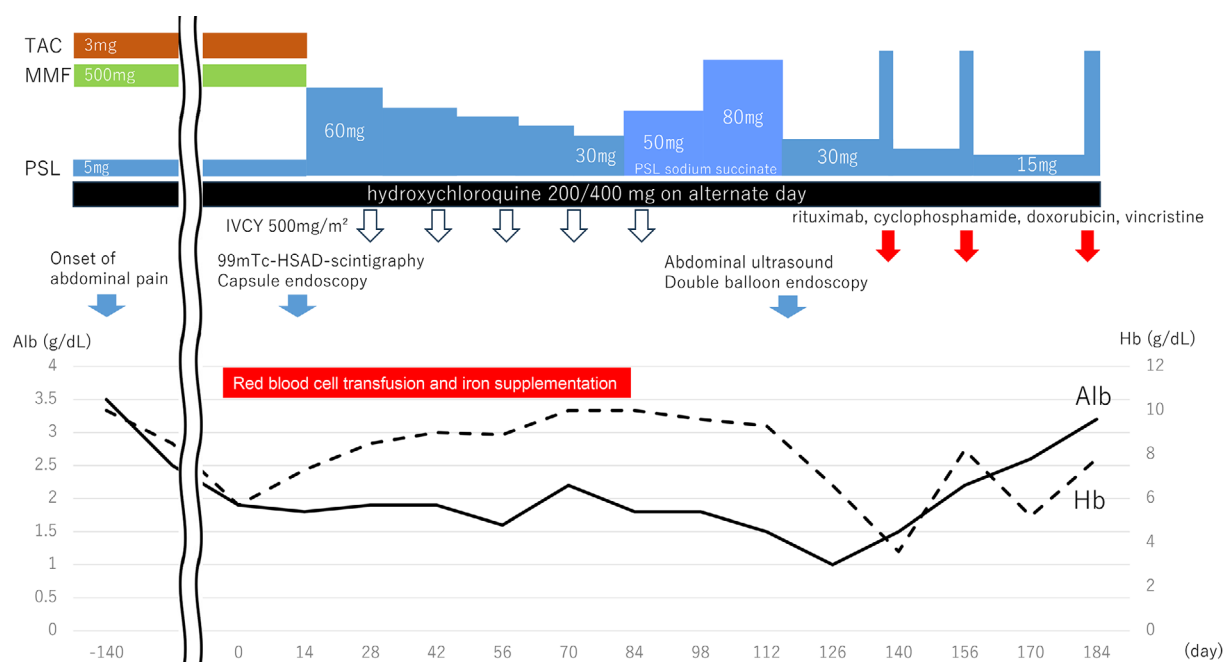


Figure 4. Treatment and clinical course from the onset of symptom. Prednisolone was administered orally (100 mg/day) for 5 days during R-CHOP treatment. TAC: tacrolimus, MMF: mycophenolate mofetil, IVCY: intravenous cyclophosphamide, PSL: prednisolone, ^{99m}Tc -HAS-D: ^{99m}Tc -DTPA-human serum albumin, Alb: albumin, Hb: hemoglobin

ultrasonography may not distinguish malignant lymphoma from SLE.

The risk of developing non-Hodgkin's lymphoma is higher in patients with SLE than in those without SLE, with a reported hazard ratio of 4.39 (95% confidence interval, 3.46-5.49). DLBCL is the most common type of malignant lymphoma in SLE patients (9). The patient was previously found to be positive for anti-SS-A antibodies. Sjögren's disease has been associated with an increased risk of developing malignant lymphoma, with a hazard ratio of 13.76 (95% confidence interval, 8.53-18.99) reported in the relevant literature (10). However, anti-SS-A antibodies are not considered independent risk factors for the development of malignant lymphoma, and their involvement in the present case remains unclear.

Therefore, malignant lymphoma was ruled out in this patient. Primary gastrointestinal lymphoma accounts for 30-45% of extranodal lymphomas (11). The stomach is the most common site for gastrointestinal lymphoma, followed by the small intestine. A similar trend was observed in the DLBCL cases. DLBCL is the most common form of malignant intestinal lymphoma. Localized malignant lymphoma of the gastrointestinal tract is often accompanied by abdominal pain in addition to B symptoms (12). However, the frequency of PLE due to malignant lymphoma remains unknown. To the best of our knowledge, only a few cases of PLE caused by malignant lymphoma have been reported, making it an extremely rare condition (13-15). Endoscopic findings in small-intestinal DLBCL frequently demonstrate ulcerative lesions and polyp formation (16). In this case, endoscopic findings revealed only white villi and mild erosion,

making it challenging to diagnose malignant lymphoma based on endoscopic findings. White villi were suggestive of intestinal lymphangiectasia, indicating lymphatic reflux. The etiology of lymphangiectasia includes SLE, malignant lymphoma, infection, and congestive heart failure, and it is not a disease-specific finding. Differentiation requires a histological examination, especially in patients with SLE-associated PLE (1). It is difficult to differentiate between these diseases based on endoscopic findings alone, and an additional histological examination is required. In particular, when PLE develops in a patient with SLE, a histological diagnosis is essential to differentiate it from a malignant lymphoma. For lesions where biopsy access is difficult, such as those in the small intestine, consultation with a hematologist is required, and a surgical biopsy should be considered.

To the best of our knowledge, this is the first reported case of DLBCL that mimicked SLE-associated PLE. In conclusion, when immunosuppressive therapy is ineffective in patients with SLE complicated by PLE, a thorough examination including tissue biopsy is recommended to consider the possibility of malignant lymphoma.

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

The authors state that they have no Conflict of Interest (COI).

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