

[CASE REPORT]

Effective Intractable Chylous Ascites Treatment by Lymphangiography with Lipiodol in a Patient with Follicular Lymphoma

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Abstract:

A 66-year-old woman was diagnosed with stage IV follicular lymphoma with a large tumor extending from the celiac artery to pelvis. Initial chemotherapy improved her lymphoma, but caused severe chylous ascites, requiring frequent paracentesis. Lymphoscintigraphy revealed radioisotope leakage into the abdominal cavity at the level of the renal hilum, indicating lymphatic vessel perforation. Lymphangiography with Lipiodol quickly resolved the chylous ascites. This case indicates that refractory chylous ascites with shrinking retroperitoneal lymphoma may require direct intervention in lymphatic vessels, and lymphangiography with Lipiodol may be effective not only as a tool for diagnosing lymphatic leakage sites but also as a treatment for lymphatic vessel damage.

Key words: chylous ascites, malignant lymphoma, lymphangiography, Lipiodol

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Introduction

Chylous ascites is derived from leakage from lymphatic vessels, resulting in whitish ascites containing triglycerides and lymphatic fluid. Chylous ascites can result from trauma, malignancy, inflammatory disease, and surgery, among other causes (1). It also develops in patients with liver cirrhosis who have undergone abdominal surgery. Malignant lymphoma-related chylous ascites is rare, occurring in 13 of 570,000 hospital admissions (2), and its treatment has not been established. We herein report a case of chylous ascites in a patient with malignant lymphoma that did not improve with systemic chemotherapy, but which improved with direct lymphangiographic intervention for the lymphatic vessels.

Case Report

A 66-year-old woman diagnosed with refractory pemphigus was referred to our hospital. The patient's medical history included hypertension and ovarian cysts. Her vital signs were normal, but multiple erosions were found in the oral cavity, the abdomen was distended, and a >10-cm mass was palpated. No abnormal cells were found in the peripheral blood, and the coagulation function and biochemical findings were normal. Her serum soluble interleukin-2 receptor level was elevated at 1,350 U/mL, and the presence of an anti-desmoglein 3 antibody supported the diagnosis of tumor-associated pemphigus (Table 1). A retroperitoneal tumor of 20 cm in diameter and swelling of the para-aortic lymph nodes was observed on computed tomography (CT),

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Table 1. Laboratory Findings.

Complete bloo	d count	Biochemis	try	Immunoserolog	y
WBC	4,900 /μL	T-Bil	0.6 mg/dL	CRP	0.19 mg/dL
Seg	47 %	AST	20 U/L	IgG	416 mg/dL
Eo	3 %	ALT	10 U/L	IgA	82 mg/dL
Baso	2 %	LDH	107 U/L	IgM	35 mg/dL
Mono	8 %	ALP (IF)	66 U/L	ANA	<1:40
Lymph	40 %	γGTP	10 U/L	HBsAg	(-)
Aty-lymph	0 %	TP	5.7 g/dL	HBsAb	(-)
Ab-lymph	0 %	Alb	4.0 g/dL	HCVAb	(-)
RBC	$3.91 \times 10^{6}/\mu L$	BUN	9 mg/dL	HTLV-1 Ab	(-)
Hb	12.6 g/dL	Cre	0.68 mg/dL	HIV Ag/Ab	(-)
Plt	$414 \times 10^{3}/\mu L$	Na	142 mmol/L	sIL-2R	1,350 U/mL
Coagulation fu	ınction	K	4.3 mmol/L	β 2MG	2.52 mg/L
PT	12.8 s	Cl	106 mmol/L	Anti-Dsg1 IgG	1.69 (Index)
APTT	34.1 s	TG	87 mg/dL	Anti-Dsg3 IgG	22.50 (Index)
Fibrinogen	407 mg/dL	LDL-C	104 mg/dL		
D-dimer	1.0 μg/mL	HDL-C	50 mg/dL		

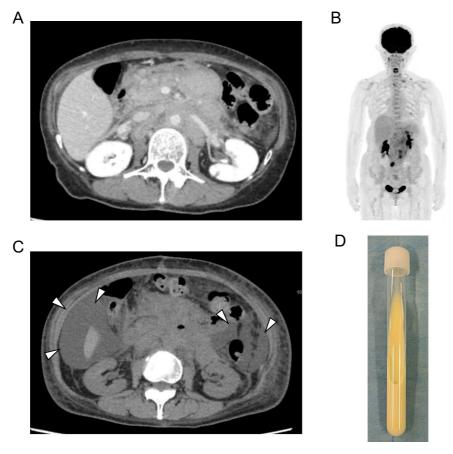


Figure 1. Patient presentation. (A) Computed tomography (CT) on admission. A large retroperitoneal tumor was seen in the abdomen. Ascites was not observed. (B) Positron emission tomography showed abnormal accumulation with SUV_{max} of 10.5 in the abdomen. (C) CT after the diagnosis of FL, showing an increase of ascites (arrowheads). (D) Paracentesis revealed yellowish ascites.

along with the formation of a retroperitoneal tumor (Fig. 1A). Positron emission tomography (PET)/CT imaging revealed abnormal accumulation with an maximum standard uptake value $_{max}$ of 10.5 in the retroperitoneal giant tumor; lymph nodes with ^{18}F -fluorodeoxyglucose accumulation were

also identified in the neck and clavicular regions (Fig. 1B). Laparoscopic lymph node biopsy was performed, and a small amount of chylous ascitic fluid was observed before specimen resection. Histopathological examination of the tumor revealed the proliferation of small- to medium-sized

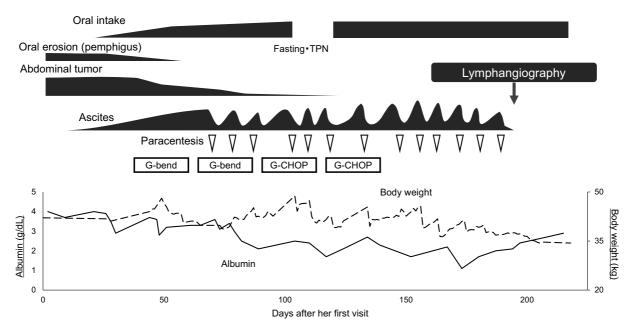


Figure 2. Clinical course. Ascites increased in contrast to tumor regression caused by systemic chemotherapy, and frequent abdominal paracentesis was required. Total parenteral nutrition and fasting were ineffective. Lymphangiography with Lipiodol was performed on the left inguinal lymphatic vessel on day 197. G-bend: obinutuzumab, and bendamustine, G-CHOP: obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, TPN: total parenteral nutrition

lymphoid cells, with some displaying follicular-like structures and expressing B-cell markers. Additionally, abnormal lymphoid cells were identified in the bone marrow, and fluorescence *in situ* hybridization (FISH) confirmed the presence of t(14;18) translocation, indicating bone marrow infiltration. Based on these findings, a diagnosis of stage IV follicular lymphoma (FL) with grade 1-2 follicular disease was made. Before the initiation of chemotherapy, a further increase in ascites was observed (Fig. 1C). The fluid obtained from the abdominal paracentesis had a milky white appearance and demonstrated increased triglyceride levels, suggesting chylous ascites (Fig. 1D). A cellular analysis and flow cytometry did not reveal the presence of a tumor, and bacterial cultures were negative.

Obinutuzumab in combination with bendamustine therapy resulted in tumor shrinkage and resolution of oral ulcers, allowing for the restoration of oral intake. However, the chylous ascites worsened, necessitating frequent paracentesis. Owing to the presence of residual tumors, the treatment regimen was changed to obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (G-CHOP) therapy, which was effective against residual tumors. Despite this, the chylous ascites was significantly exacerbated and required frequent paracentesis. Nutritional indicators, including serum albumin levels, gradually decreased with body weight after paracentesis. Fasting and central venous nutrition were attempted to reduce the lymph fluid volume within the lymphatic circulation; however, no alleviation was observed (Fig. 2).

After 3 courses of chemotherapy, lymphoscintigraphy was performed. We observed that the radioisotope administered

in the foot region leaked into the abdominal cavity near the height of the renal hilum as well as near the mammary glands, indicating that the leakage into the abdominal cavity originated from this area (Fig. 3A). At 197 days after her first visit, we performed lymphangiography with Lipiodol in an attempt to treat her persistent ascites. By injecting Lipiodol into the small lymph nodes of the inguinal region, the lymphatic vessels were visualized (Fig. 3B), and the contrast agent remained stationary. After this procedure, the ascites accumulation immediately improved. Scintigraphy performed 3 weeks after lymphangiography revealed no leakage, and the lymph flow was traceable up to the thoracic duct (Fig. 3C). Her abdominal distension also improved and there was no further increase in ascites due to food intake. The patient was able to walk unaided and was discharged. At 9 months after the initiation of chemotherapy, the patient was under outpatient follow-up, and PET/CT showed that the tumor remained in complete remission.

Discussion

We report the case of a patient with FL who developed chylous ascites, independent of lymphoma shrinkage. Lymphangiography with Lipiodol led to the recovery of chylous ascites without sequelae.

Chylous ascites develops due to trauma, malignancy, inflammatory diseases, and surgery. Portal hypertension is an etiology of chylous ascites, but cases with a neoplastic etiology are classified as nonportal hypertension (1). Malignant neoplasms may induce direct or indirect exudation of lymphatic material through the walls of dilated retroperitoneal

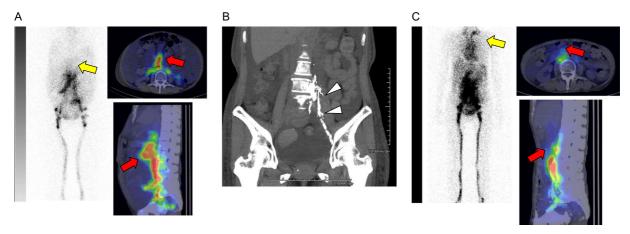


Figure 3. (A) Lymphatic scintigraphy after 3 courses of chemotherapy, before lymphangiography with Lipiodol. Before lymphangiography with Lipiodol, the lymphatic flow leaked into the abdominal cavity (red arrows) and was disrupted at the renal hilum level (yellow arrow). (B) Lymphangiography with Lipiodol. The dilated lymphatic vessels were contrasted by Lipiodol administered from the left inguinal lymphatic vessel (arrowheads). (C) Lymphatic scintigraphy after lymphangiography with Lipiodol. After 3 weeks of lymphangiography, leakage into the abdominal cavity was stopped (red arrows), and the lymphatic flow reached the left subclavian venous angle (yellow arrow).

vessels (megalymphatics) into the abdominal cavity through a fistula in the peritoneal cavity, which may also form secondary to acquired lymphatic duct obstruction, resulting in direct leakage of chyle through a lymphoperitoneal fistula (1). In addition, malignancy may cause fibrosis of the primary lymph node, which may eventually obstruct the flow of lymph from the gut to the cysterna chyli, resulting in leakage from the dilated subserosal lymphatic system into the peritoneal cavity (1). Treatment options for chylous ascites include dietary measures, the administration of pharmacological agents, such as somatostatin and octreotide, and surgical or percutaneous interventions, such as peritoneovenous shunting. Other treatments, such as low-dose radiation therapy, have been attempted (3); however, salvage treatment for resistant chylous ascites has not been established. In this case, chylous ascites was present at the time of the surgical procedure of tumor biopsy and the volume increased after chemotherapy, despite the tumor shrinking. This indicates that the lymphatic leakage worsened irrespective of the chemotherapy response, necessitating direct medical treatment for the lymphatic rupture.

Twenty-six patients with lymphoma and chylous ascites were previously reported (Table 2) (3-23); 10 cases had FL, and most cases had retroperitoneal and/or mesenteric lymphoma lesions. Chylous ascites resolved with systemic chemotherapy as the tumor decreased in 11 cases. However, in another 9 cases, chylous ascites did not improve after chemotherapy for lymphoma; 3 (33%) survived in the patients without improvement of ascites, while 9 (82%) survived in the patients with cured ascites. To treat residual ascites, diuretics, laparotomy, repeated paracentesis, radiotherapy, and somatostatin were attempted, and 2 out of 9 patients underwent lymphangiography. The 2 patients who underwent lymphangiography were FL patients (age: 42 years and 52

years, respectively) with retroperitoneal masses. In the 42-year-old patient, chylous ascites was identified at the time of the diagnosis of FL; in the 52-year-old patient, it developed after the biopsy of the FL lesion. In these patients, ascites persisted even after the completion of systemic chemotherapy. Lymphangiography was attempted; however, it was not effective for them. Finally, the chylous ascites resolved with low-dose radiotherapy (13). In our case, systemic chemotherapy did not ameliorate the chylous ascites despite the regression of the tumor. This phenomenon probably occurred because the lymph flow at the rupture site of the lymphatic vessels increased after the release of the obstruction at the lymphoma lesions. Conservative treatment was ineffective in these cases.

Lipiodol, also known as ethiodized oil, is an oily contrast medium consisting of a mixture of long-chain (C16 and C18) diiodinated ethyl esters of fatty acids derived from poppy seed (*Papaver somniferum* var. *nigrum*) oil, which contains 98% unsaturated fatty acids (24). In oncology, it is emulsified with cytotoxic drugs and administered to the hepatic artery for transcatheter arterial chemoembolization (TACE) in patients with hepatocellular carcinoma. In TACE, Lipiodol is used for drug delivery, transient and plastic embolization, and radiopacity, and plays an ancillary role in the treatment of hepatocellular carcinoma (24).

Lipiodol is also recognized as a diagnostic tool for lymphangiography (25). A small number of studies have reported that lymphatic leakage improves after the injection of Lipiodol into lymphatic vessels (26). Lymphangiography with Lipiodol improved lymphatic leakage in patients with refractory chylothorax, chylous ascites, lymphoceles, and lymphatic fistulas. Lymphatic leakage can be completely occluded in 70% of patients when the lymphatic drainage volume is <500 mL/day (27). Although the mechanisms for im-

Table 2. Case Series of Chylous Ascites Complicated with Lymphoma.

Reference	Age	Sex	Types of lymphoma	Retroperitoneal or mesenteric lesion	Chemotherapy	Disappearance of ascites by chemotherapy (additional treatment)	Out- come	Prognosis
(4)	49	F	Mixed large and small cleaved cell lymphoma	Yes	CVP×2 → CHOP×4	Yes	Alive	NA
(4)	67	M	Small cleaved cell lymphoma	Yes	$RT \rightarrow CVP \times 4$	No (diuretics)	Alive	NA
(4)	58	M	HL	Yes	MOPP×5	Yes	Alive	NA
(4)	60	M	Small cleaved cell lymphoma	Yes	CHOP+MTX+Bleomycin×1	Yes	Alive	NA
(5)	32	F	Primary effusion lymphoma	No (ascites)	THP- $COP \times 4 \rightarrow aPBSCT \rightarrow relapse$	Yes	Dead	22 months
(6)	53	M	HL	No (hepatic hilus)	ABVD	Yes	Alive	NA
(7)	43	M	Non-Hodgkin BCL	Yes	CHOP \times 5 \rightarrow aPBSCT \rightarrow relapse	No (laparotomy)	Dead	2 months
(8)	NA	F	FL	Yes	(Conducted but not described in detail)	Yes	Alive	NA
(9)	38	F	PTCL	Yes	CHOEP	No (repeated paracentesis)	Dead	18 months
(10)	18	F	BL	No (ovary)	CV+MTX	No	Dead	1 month
(11)	28	M	Non-Hodgkin BCL (relapse)	Yes	VMCP	No	Dead	<1 month
(12)	74	M	DLBCL	Yes	R-CHOP× 2	Yes	Alive	NA
(13)	42	F	FL	Yes	R -CHOP×6 \rightarrow R -DHAP \rightarrow Dexa-BEAM	No (lymphangiography, RT)	Alive	NA
(13)	52	M	FL	Yes	G-bendamustine×6	No (lymphangiography, somatostatin, RT)	Alive	NA
(14)	67	M	ENKL	No (nasal cavity)	CP×1	Yes	Dead	15 months
(15)	78	F	FL	Yes	BR×6	Yes	Alive	NA
(16)	76	M	AITL	Yes	NA	NA	Dead	<1 month
(17)	87	M	MCL	Yes	PEPC	No	Dead	<1 month
(18)	75	F	HGBCL	Yes	$R\text{-}CVP \rightarrow R\text{-}GCVP$	No	Dead	NA
(19)	71	F	FL	Yes	NA	NA	NA	NA
(3)	60	M	FL	Yes	$R\text{-}CHOP\times 1 \rightarrow RT \rightarrow R$	Yes	Alive	NA
(20)	74	M	Non-Hodgkin BCL	Yes	R-EPOCH×4	Yes	Alive	NA
(21)	62	F	FL	Yes	NA	NA	NA	NA
(22)	69	F	FL	Yes	R-CHOP×6	NA	NA	NA
(23)	53	M	FL	Yes	NA	NA	NA	NA
Present case	66	F	FL	Yes	G-bendamustine×2 → G-CHOP×2	No (lymphangiography)	Alive	>9 months

NA: not available, F: female, M: male, BCL: B-cell lymphoma, HL: Hodgkin lymphoma, DLBCL: diffuse large B-cell lymphoma, FL: follicular lymphoma, PTCL: peripheral T-cell lymphoma, BL: Burkitt lymphoma, ENKL: extranodal NK/T-cell lymphoma, nasal type, AITL: angioimmunoblastic T-cell lymphoma, MCL: mantle cell lymphoma, HGBCL: high-grade B-cell lymphoma, CVP: cyclophosphamide, vincristine, and prednisone/prednisolone, CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone/prednisolone, RT: radiotherapy, MOPP: mechlorethamine, vincristine, procarbazine, and prednisone/prednisolone, MTX: methotrexate, THP: tetrahydropyranyl doxorubicin, aPBSCT: auto peripheral blood stem cell transplantation, ABVD: doxorubicin, bleomycin, vinblastine and dacarbazine, CHOEP/EPOCH: cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone/prednisolone, CV: cyclophosphamide and vincristine, VMCP: vincristine, mitoxatrone, cyclophosphamide and prednisone/prednisolone, R-: combination with rituximab, DHAP: examethasone, high-dose cytarabine and cisplatin, Dexa-BEAM: dexamethasone, carmustine, cytarabine, etoposide and melpharan, G-: combination with obinutuzumab, CP: cyclophosphamide and prednisone/prednisolone, gcclophosphamide, etoposide and procarbazine, GCVP: gemcitabine, cyclophosphamide, vincristine and prednisone/prednisolone

proving lymphatic leakage have not been clarified, it is assumed that infused Lipiodol accumulates at the point of leakage, causing a local inflammatory reaction adjacent to the area of retention. Lipiodol retention in the lymphatic vessel on the distal side of the point of leakage has been shown to act as an embolic agent (28). Lymphangiography with Lipiodol may be effective in lymphoma patients with

lymphatic vessel leakage. Despite resistance to treatment approaches for the underlying disease or conservative treatment, lymphangiography with Lipiodol might be beneficial for both the diagnosis and treatment.

In conclusion, we report the case of a patient with FL who presented with a bulky retroperitoneal mass with chylous ascites that increased in size after chemotherapy and tu-

mor regression. Lymphangiography with Lipiodol improved lymphatic fluid leakage. Lymphangiography with Lipiodol may be effective not only as a tool for diagnosing sites of lymphatic leakage, but also as a treatment for lymphatic vessel damage.

Author's disclosure of potential Conflicts of Interest (COI).

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