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MULTIMODAL TREATMENT OF CHYLOUS FISTULA. A RETROSPECTIVE CASE-CONTROL STUDY

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ABSTRACT

Chylous fistulas (CF) are rare surgical complications and there is no standard treatment. This study presents the treatment modalities performed on patients who developed CF over a 10-year period. During the observation period, CF developed in 29 patients, 16 of whom were women. The mean age was 55.76± 13.48. Lymphatic duct injury was mostly seen in the abdomen (58.6%) and the most common reason was nephrectomy (20.7%). Extended lymphatic dissection due to malignancy was performed in 82.7% of all cases. Chylous leakage started postoperatively on 3.78±3.94 days (range: 1-19 days). Fasting, total parenteral nutrition (TPN), and somatostatin treatment were applied to all patients, and 75.8% of the fistulas were resolved completely with medical treatment. Surgical ligation of the lymphatic canal was performed in 7 patients. One was not successful and underwent percutaneous embolization of the thoracic lymphatic leakage cavity. All fistulas were resolved in 18.18±10.4 days. The resolution time and hospital stay were significantly higher in thoracic fistulas (p=0.017; p=0.003, respectively). In addition, malignant cases had longer resolution time (32.40±28.72 vs 16.27±11.25, p=0.036) and hospital stay (35.0±29.74 vs 16.25±14.05p= 0.002 respectively) than non-malignant. There was no chylothorax, chylous ascites, or recurrence at 20.55±22.88 months follow-up. Treatment of CF with fasting, TPN, and somatostatin analogs are effective. Other interventions such as surgical ligation with or without fibrin glue and interventional radiology treatments may be considered when conservative treatments fail.

Keywords: chylous fistula, chylous leakage, somatostatin, ductus ligation

The lymphatic system earliest discoveries and reports date to the 17th century with investigations ever since (1). The lymphatic system is involved in immunity and long-chain fatty acid digestion. It also is pathway for the spread of cancer cells (2). Therefore, lymphatic circulation and lymph node involvement are essential components in cancer surgery. Lymphatic dissection increases cancer patients' survival rates, but unfortunately, increases the risk of lymphatic leakage. These leakages often resolve spontaneously, however, if it turns to a chylous fistula (CF), it may need to be treated (2).

In the literature, mainly case reports and a few articles have been reported on CF and there are very limited randomized controlled studies. This is likely due to the fact that there is no optimal treatment method for CF due to lymphatic injury yet established. Some surgeons suggest that different treatments should be applied to each patient considering their characteristics (3).

This study aims to present an algorithmic perspective on the treatment of chylous

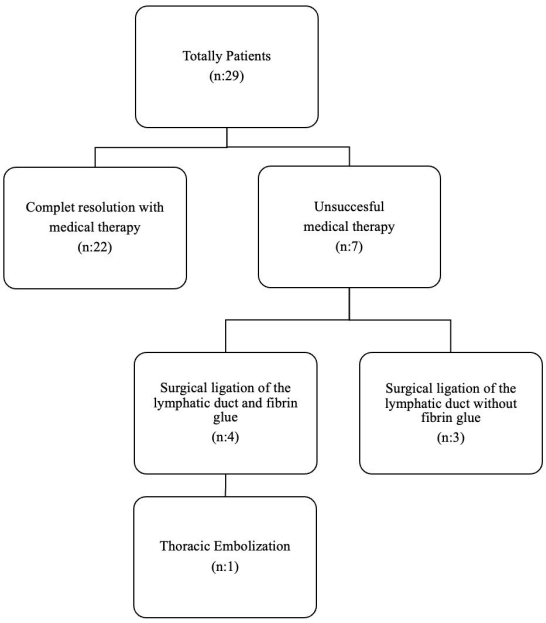

Fig. 1. The treatment algorithm of the study cohort.

fistula. The second aim is to investigate whether there is a difference between fistula closure times in patients with cervical, axillary, thoracic, and abdominal leaks. The third aim is to reveal whether the fistulas resolve later in patients who underwent lymphatic dissection for cancer.

PATIENTS AND METHODS

This study is a retrospective analysis of patients with CF from patients who developed postoperative CF in our hospital between 2010 and 2020. Demographic and clinic characteristics of patients were determined, and we reviewed the surgical procedures which caused the CF. The treatment modalities, resolution time of CF and the length of stay hospital were analyzed. *Figure 1* shows the treatment algorithm of case series. The study was approved by the Institutional Review Board of Cukurova University Faculty of Medicine (No. Jun 5, 2020/ 100-25) and written informed consent statement was obtained from every patient. It has been performed by the ethical standards laid down in the Declaration of Helsinki.

Medical Treatment

First, daily drainage output of the chylous liquid was measured and its biochemical properties were examined (*Fig. 2a*). CF that developed in the postoperative period was treated medically.

Fig. 2. Clinical images of the chylous fistula. a) Chylous leakage developed after laparoscopic nephrectomy. The patient was followed up by wearing a stoma bag. b) The appearance of chylous leakage during the surgery in the patient who did not resolve with medical treatment identifying the site for closure.

Fig. 3. Lymphangiography performed by injection of 10 ml Lipiodol by entering the lymph node from the right inguinal area (Cisterna chyli could not be demonstrated).

Fasting, somatostatin therapy (subcutaneous 0.1 mg/8h), and total parenteral nutrition (TPN) were utilized. Oral intake was started when the fistula flow rate fell below 50 ccs/ day. Medium-chain and short-chain fatty acid diets were then started and TPN was stopped. The somatostatin infusion was stopped when the fistula was resolved entirely.

Surgical Treatment

Surgery was performed in patients whose leakage volume was not reduced or was increased with medical treatment. Visualized lymphatic leakages were ligated with non-absorbable sutures or metal clips (*Fig. 2b)*. In cases where the lymphatic vessel could not be identified exactly, fibrin glue was used.

Interventional Radiology Management

Lymphangiography was first performed in patients who had a planned thoracic duct embolization. If the cisterna chylii could not be identified by imaging at 24 or 48 hours later, it was decided that embolization could not be performed by lymphatic route (*Fig. 3*). Sometimes computed tomography (CT) imaging identified a lymphatic collection limited within a cavity (*Fig. 4)*. In this case, a 21-gauge trocar needle was inserted using a Cone-beam CT and a 6F coaxial introducer sheath was inserted to aspirate the oily contrast agent (*Fig. 5a*). Vascular and pleural structures were checked by administering intravenous contrast material and it was determined whether there was a leak (*Fig. 5b*). 1.5 ml of n-butyl cyanoacrylate mixed with 10 ml of lipiodol from the introducer was injected into the cavity. The drain was removed due to the absence of chylous leak in the follow-up.

Fig. 4. Right paramediastinal lymphatic collection demonstrated on CT image.

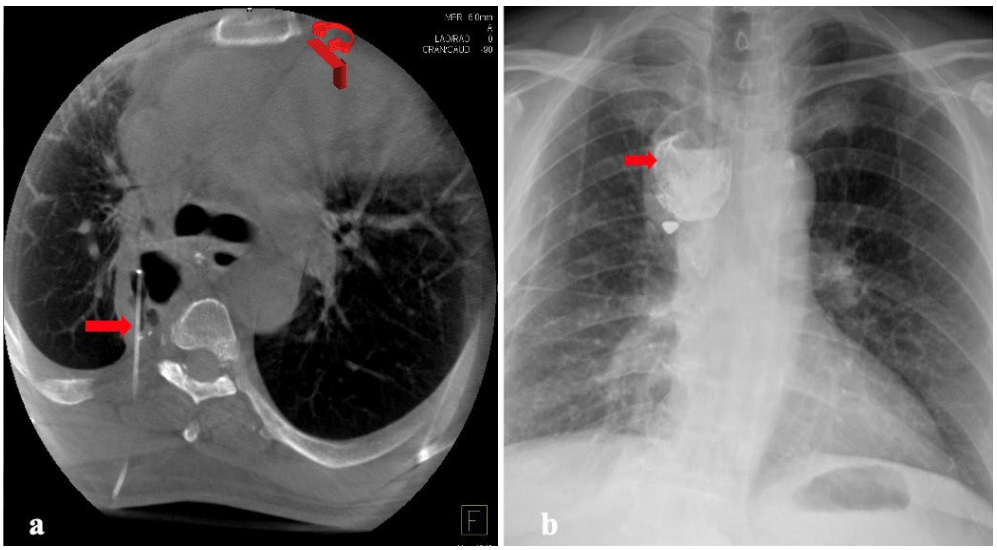

Fig. 5. Images of the application of interventional embolization to the thoracic fistula cavity that did not resolve with medical and surgical treatment. a) The lymphatic collection was localized in cone-beam CT (red arrow). A paravertebral safe access tract was determined. After insertion of the introducer sheath, the chylous contents were aspirated and 1.5 ml of n-butyl cyanoacrylate mixed with 10 ml of lipiodol from the introducer was injected into the cavity. b) Anterior-posterior X-ray after the embolization. The red arrows show the pouch formation at the CF leak site in the thorax.

Data Analysis

Data were analyzed using SPSS 23.0 package software. Categorical data were analyzed using numbers and percentages, and continuous data were analyzed using mean, standard deviation and minimum-maximum. The normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk Tests). Mann-Whitney U test was used in the binary variables. Statistical significance value was accepted as 0.05 in all tests.

RESULTS

Twenty-nine patients were identified with 16 women (55.2%) 13 men (44.8%). The mean age was 55.76 (± 13.48) years (range: 32-83 years).

Localization

Lymphatic duct injury was seen mainly in the abdominal region (58.6%), and the most common cause was nephrectomy (20.7%). Lymphatic dissection due to malignancy was performed on 24 patients (82.7%) *(Table 1*). There was also thyroid cancer (n:5), breast cancer (n:2), esophageal cancer (n:4), pancreas cancer (n:4), renal cell carcinoma (n:4), lymphoma (n:2), and colorectal cancer (n:3).

Clinical Findings

The interval between surgery to chylous leakage was 3.78±3.94 days (range:1-19 day). The chylous fluid's triglyceride level was between 358±112 mg/dL (range:120-2778 mg/dL).The fistula's mean volume on the first day of the leakage was 474.78±415.86 ml (range: 100-2000 ml). There was no correlation between daily fistula volume and resolution time.

Treatment

First, medical treatment with fasting, TPN, and somatostatin was used for all patients. During medical treatment, bradycardia was observed in 1 patient after somatostatin was started. In this patient, somatostatin treatment was continued after heart rhythm improved in the intensive care unit. In 22 of 29 patients (75.8%), the fistula was closed with conservative treatment.

Surgery was performed in 7 patients whose fistula did not heal with medical treatment. This included 4 abdominal fistulas, 2 thoracic fistulas, and 1 cervical fistula. Surgical lymphatic duct ligation was performed with a non-absorbable suture in these patients. Fibrin glue used 4 of these procedures. Six fistulae resolved after surgical ligation with one patient unchanged. Percutaneous embolization of lymphatic leakage of thoracic ductus was performed in this patient after the failure of surgical treatment.

Follow-Up

All fistulas were resolved at 18.18±10.4 days, and the length of stay hospital was 19.56±11.54 days. The mean follow-up period was 20.55±22.88 months, and seven patients died due to primary disease. No recurrent chylothorax, chylous ascites, or chylous leakage developed during the follow-up.

Comparative Analysis of Patients

The fistula's resolution time and length of stay hospital were significantly higher in thoracic fistulas than in other regions (p= 0.017; p=0.003; respectively) (*Table 2*). The hospital stay and resolution time were statistically significantly longer in patients who underwent lymphatic dissection due to malignancy (p=0.036, p=0.002 respectively) (*Table 3*).

DISCUSSION

Lymphatic fluid is usually clear, however, is named chylous fluid if it contains chylomicron and has a milk-like color. The chylous liquid is odorless and sterile. Leibovitch et al mentioned that chylous liquid should be alkaline with a high triglyceride content (4). According to Weniger et al, the triglyceride level should be >110 mg/dL (5).

TABLE 1
Clinic Features of the Patients

Variables			n	%
Gender	Women		16	(55.2%)
	Men		13	(44.8%)
Localizations	Cervical		6	(20.7%)
	Axillar		2	(6.9%)
	Thoracic		4	(13.8%)
	Abdominal		17	(58.6%)
Surgical Procedures	Head and Neck Surgery		1	(3.5%)
	Thyroidectomy		5	(17.2%)
	Axillary dissection		2	(6.9%)
	Esophagectomy		4	(13.8%)
	Distal Pancreatectomy		3	(10.3%)
	Hepatectomy		1	(3.5%)
	Whipple Procedure		1	(3.5%)
	Nephrectomy		6	(20.7%)
	Splenectomy		3	(10.3%)
	Colorectal resection		3	(10.3%)
Lymphatic dissection due to malignancy	Yes		24	(82.7%)
	No		5	(17.3%)
Additional procedures after medical treatment	Surgical ligation	Abdominal (n:2) Cervical (n:1)	3	(10.3%)
	Surgical ligation and fibrin glue	Abdominal (n:2) Thoracic (n:2)	4	(13.7%)
	Thoracic imbolization	Thoracic (n:1)	1	(3.4%)

	Mean±sd	
Age	55.76±13.48	(32-83)
Triglyceride level of the drain (mg/dl)	358±112	(120-2778)
The interval between surgery to leakage (day)	3.78±3.94	(1-19)
Volume on the first day of the leakage (ml)	474.78±415.86	(100-2000)
Resolution time (day)	18.18±10.4	(1-75)
Length of stay hospital (day)	19.56±11.54	(4-78)
Follow up (month)	20.55±22.88	(1-96)

TABLE 2
Comparison of Resolution Time and Length of Stay Hospital with Clinic Localization and Lymphatic Dissection

	Localizations				p
	Cervical	Axillar	Thoracic	Abdominal	
Resolution time Mean ± sd, (min-max)	8.40±1.81 (6-10)	4.50±0.70 (4-5)	39.25±26.84 (10-75)	20.58±12.26 (10-49,0)	0.017
Length of stay hospital Mean ± sd, (min-max)	8.50±2.73 (4-11)	4.50±0.70 (4-5)	46.50±29.58 (11-78)	18.76±13.17 (6-54)	0.003

TABLE 3
Comparison of Resolution Time and Length of Stay Hospital with Malignancy

	Lymphatic dissection due to malignancy				p
	Yes		No		
Resolution time Mean ± sd, (min-max)	32.40±28.72	(10-75)	16.27±11.25	(4-41)	0.002
Length of stay hospital Mean ± sd, (min-max)	35.0±29.74	(11-78)	16.25±14.05	(4-62)	0.036

However, some authors suggest it should be >200 mg/dL (3). In our study, drains of all patients had a milk-like white discharge (chylous) and the triglyceride level of the chylous fluid in our series was over 120 mg/dL.

Some investigators have reported the incidence of CF as 1-11.7% in head and neck surgery, chest, abdominal, and pelvic surgery (6-15). The most common cause of leakage in our study was abdominal surgery (nephrectomy). In addition, in our series, we reported two axillar CF developed after axillary dissection due to breast cancer. The axillary CF is very rare in the literature, its frequency is uncertain, and its mechanism is not fully understood (16).

The increased incidence of CF is related to the extent of lymphatic dissection (17) and it is common to see more frequently in patients who undergo wide lymphatic dissection due to cancer. A series published by Pan et al reported that 95% of chylous leaks developed after cancer surgery (18). Most of the patients in our series were cancer patients, as in the literature.

There is no guideline for treatment yet. Most surgeons first prefer medical treatment, including fasting, TPN, somatostatin analog drugs, and diet control with medium-chain fatty acids (3).The mechanism of the somatostatin analog drug is not fully understood. Most hypotheses are based on several mechanisms including the reduction of gastroenteropancreatic secretion. It also can inhibit serotonin and other gastrointestinal peptides which can reduce intestinal absorption and decreases hepatic venous pressure gradient and splanchnic blood flow. This influence on the hemodynamics of splanchnic circulation and intestinal motility may be reflected in reducing chyli output (19). In our clinical practice, 0.1 mg/8-hour subcutaneous somatostatin was applied to all patients.

Nevertheless, somatostatin is not a harmless drug. The most common side effect of somatostatin analogs is dyspeptic disorders, and it may have several endocrine or cardiac side effects such as hypo/hyperglycemia or cardiac arrhythmia (20). In this series, one of the pa-

tients developed severe bradycardia due to somatostatin; however, the side effects disappeared upon the drug's interruption. In the following days, somatostatin treatment was continued more carefully.

The medium-chain fatty acid diet is highly water-soluble and absorbed via the enterohepatic circulation rather than the lymphatics, so it bypasses the lymphatic system. Accordingly, the lymphatic circulation decelerates, and the lymphatic duct injury heals faster. Unfortunately, diet control does not stop chyli production entirely (21).

Total parenteral nutrition is critical for non-operative treatment. If fasting is combined with TPN, it may decrease the production and flow of chyli. Leibovitch et al emphasized the success rate of two to six-week parenteral nutrition therapy with a medium-chain fatty acids diet to be 60% to 100% (4). In our series, CF was started at a mean 3.78±3.94 postoperative day, and medical treatment was successful in 22 of 29 (75.8%) of our patients. Finally, after surgical treatment and duct embolization, all fistulas resolved at a mean of 18.18±10.4 days.

Some surgeons believe that fistula should primarily be treated with surgery and suggest early ligation of the lymphatic ducts to prevent metabolic complications (22). However, no studies are comparing early surgical ligation and conservative therapy. In our series, conservative treatment was applied primarily to all patients. Surgical decision was made only after unsuccessful medical treatment. While making the surgical timing decisions, the patients' general condition and the daily output of the fistula were often taken into consideration.

The localization of the leakage may not always identify during the operation. Some researchers recommend using fibrin glue in this situation (3). In our series, intraoperative fibrin glue was used in 4 of the patients when the duct could not be identified. However, although we used fibrin glue, leakage continued in one of our patients. In this patient, thoracic duct embolization successfully closed the leak.

Therapeutic lymphangiography and, if necessary, embolization of the percutaneous thoracic duct or leak (with microcoil, ml n-butyl cyanoacrylate or onyx) can be performed as an alternative to surgical treatment in patients whose conservative treatment is unsuccessful (23). This is a new treatment modality. In recent studies, 64-86% of the thoracic leakages can identify with lymphangiography and can close with embolization with a success rate of >90% (24).In one series, lymphangiography was performed in one patient, but since the cisterna chylii could not be demonstrated, embolization was performed by percutaneous administration of n-butyl cyanoacrylate to the leak cavity (25).

Our study has some limitations. The main limitations are its retrospective nature and a low number of patients. Other limitations are the surgical treatment timing decision is made entirely according to the subjective criteria (surgeon's decision), and the study does not compare different treatment methods.

CONCLUSION

Conservative treatment with fasting, TPN, and somatostatin analogs are the traditional treatments for CF. In the failure of conservative treatment, surgical ligation with or without fibrin glue or even lymphatic cavity embolization applications can be performed. According to the results of this study, the resolution time of CF is longer in thoracic leaks and in patients who underwent lymphatic dissection due to malignancy.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

AUTHORS' CONTRIBUTIONS

Conceptualization: KD, AGS, SG; Formal Analysis: All authors; Investigation: All authors; Methodology: KD, AGS, SG; Project Administration: All authors; Writing - Original Draft: SG; Writing - Review & Editing: KD, AGS, HBO, ATA, AU, GS

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