

Case Report

First Case of Chylous Ascites after Laparoscopic Myomectomy: A Case Report with a Literature Review

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Abstract: Introduction: Chylous ascites is a rare form of ascites characterized by milk-like peritoneal fluid, rich in triglycerides. Clinical signs and symptoms include abdominal distention, pain, nausea, and vomiting. In gynecology, the most common cause for its occurrence is lymph dissection leading to impairment of major lymphatic vessels. There are only a few reported cases of chylous ascites arising after operations for benign diseases. Case report: We report a case of a 46-year-old female patient, who underwent laparoscopy for a myomatous node with chylous ascites occurring on post-surgery Day 2. The ascites was conservatively managed. The exact cause of the chyloperitonitis could not be determined. Conclusion: Although extremely rarely, chylous ascites may also occur in operative interventions for benign diseases in gynecological surgery.

Keywords: chylous ascites; myomectomy; benign disease; surgery

1. Introduction

Chylous ascites (CA) is a rare form of ascites, which represents milk-like peritoneal fluid, rich in triglycerides [1,2]. The incidence of chylous ascites is approximately 1 in 20,000 patients [3,4]. Chylous ascites after surgery appears due to injury to the thoracic duct, cistern chill, or its intestinal tributaries. Chyloperitonitis can be an early complication a few days after surgery or can occur several months later [5,6]. Clinical symptoms and signs are often nonspecific [3]. There is controversy regarding the cut-off value of triglyceride confirming the diagnosis. Many studies have reported elevated ascitic fluid triglyceride (TG) levels as the best parameter for detecting chylous ascites. Staat suggested a cut-off value of 110 mg/dL, whereas a recent study reported a single-point triglyceride cut-off of 187 mg/dL (2.13 mmol/L) or alternatively an equivocal range of 148-246 mg/dL (1.69-2.80 mmol/L) to establish CA and observed a sensitivity and specificity of up to 95%. Chi-Hang Hsiao reported a cut-off >2 for the ratio of ascites TG/serum TG. The current consensus utilizes levels of triglycerides from the milky fluid above 200 mg/dL as the criterium for diagnosis of CA [5,7–10]. It is an uncommon complication in oncogynecological surgery, which occurs when pelvic and paraaortic lymph dissections are performed, as a result of impairment of the major lymph vessels. Although exceptionally rare, chylous ascites may occur as a complication in gynecological operations for benign diseases [1,2].

We present a case in which chylous ascites occurred after performing a myomectomy. In our review of the literature, we did not find any similar cases described.

2. Case Report

We present a 46-year-old, gravida 0 para 0 Caucasian woman with heavy, painful menstrual bleeding and dyspareunia for three months. No previous diseases, surgeries, or comorbidities were reported. The general physical examination detected no abnormalities. The gynecological examination found a tumor mass located on the left posterior uterine wall, of 4×4 cm size. Transvaginal ultrasonography demonstrated an intramural/subserous myoma of 40×41 mm. It was classified as Type 6 according to the International Federation of Gynecology and Obstetrics (FIGO) [11]. Laparoscopic myomectomy was performed (Figure 1). There were no difficulties for the first trocar placement. We made a skin incision inferior to the umbilicus, and then used a Verres needle to create a pneumoperitoneum. This was followed by the blind insertion of an 11 mm sharp trocar.

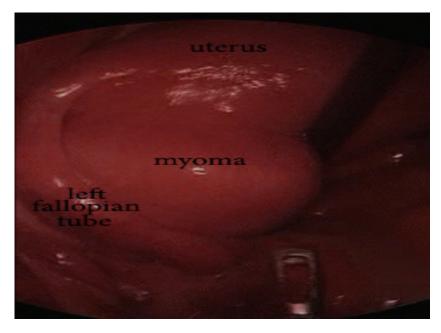


Figure 1. Intraoperative finding of the subserous myoma.

We closed the myometrium with interrupted sutures and extracorporeal knots. We decided to use a pelvic drain. Blood loss of 100 mL occurred. The pathology report of surgical specimens revealed fibroleiomyoma.

On post-surgery Day 1, the patient felt well and had normal peristalsis, diuresis, and hemoglobin levels. The patient was afebrile, and there was an output of 300 mL from the drain with a small amount of blood. On post-surgery Day 2, 400 mL of milky-white fluid was noticed in the drain. Vital signs of the patient were stable with no abdominal pain and normal peristalsis (Figure 2).

Suspecting chylous ascites, an analysis of the liquid was performed, which revealed high levels of triglyceride: 13.00 (high) mmol/L (1150 mg/dL). Laboratory characteristics of ascitic fluids revealed: glucose 3.57 (low) mmol/L; total protein 43.7 (low) g/L; albumin 24.4 (low) g/L; lactate dehydrogenase 668 (high) mmol/L; amylase 56 U/L; creatinine 84 mmol/L; and urea 4.9 mmol/L. We sent the fluid for cytological examination to determine the prevalence of erythrocytes, neutrophils, mature lymphocytes, and absence of tumor cells. No abnormalities of blood urea and creatinine of the patient were detected. A computed tomography (CT) was performed in her case. The purpose of the CT scan was to detect any unknown diseases, causing chylous ascites. There were no pathological findings. The patient initiated a low-fat oral diet with medium-chain triglycerides. During the next three days, 100 mL of milky white fluid was found in the drain. On Day 6, the drain fluid became serous (100 mL). On the

next day, the drain was removed, and the patient was discharged from the hospital. Ten months later, the patient was free of symptoms and in a good health condition. The patient signed an informed consent form for the publication of anonymous clinical data.



Figure 2. Ascites.

3. Discussion

Chylous ascites is a rare form of ascites. Clinical findings are nausea, vomiting, abdominal distention, and pain [3,12]. The diagnosis of chylous ascites is based on the levels of triglyceride from the milky fluid. They are supposed to be above 200 mg/dL [5].

The chylous ascites has a various etiology and may be either atraumatic or traumatic (Table 1) [3,4]. It may also be divided into congenital, acquired, malignant, inflammatory, postoperative, etc. [13].

Atraumatic		Traumatic	
(I) Neoplastic	Cardiac	(I) Iatrogenic	
Solid organ cancers	Constrictive pericarditis	(A) Surgical	
Lymphoma	Congestive heart failure	Abdominal aneurysm repair	
Sarcoma	Gastrointestinal	Retroperitoneal lymphadenectomy	
Carcinoid tumors	Celiac sprue	Placement of peritoneal dialysis catheter	
Lymphangioleiomyomatosis	Whipple's disease	Inferior vena cava resection	
Chronic lymphatic leukemia	Intestinal malrotation	Pancreaticduodenectomy	
(II) Diseases	Small bowel volvulus	Vagotomy	
(A) Congenital	Ménétrier disease	Radical and laparoscopic nephrectomy	
Primary lymphatic hypoplasia	Inflammatory	Nissen fundoplication	
Klippel-Trenaunay syndrome	Pancreatitis	Distal splenorenal shunts	
Yellow nail syndrome	Fibrosing mesenteritis	Laparoscopic adrenalectomy	
Primary lymphatic hyperplasia	Retroperitoneal fibrosis	Gynecological surgery	
Lymphangioma	Sarcoidosis	(B) Nonsurgical	
Familial visceral myopathy	Systemic lupus erythematosus	Radiotherapy	
(B) Acquired	Behçet's disease	(II) Noniatrogenic	
Cirrhosis	Peritoneal dialysis	Blunt abdominal trauma	
Infectious	Hyperthyroidism	Battered child syndrome	
Tuberculosis	Nephrotic syndrome	Penetrating abdominal trauma	
Filariasis	Drugs	Shear forces to the root of the mesenter	
Mycobacterium avium in AIDS	Calcium channel blockers	(III) Idiopathic	
Ascariasis	Sirolimus	Rule out lymphoma	

Table 1. Etiological classification of chylous ascites [4].

The basic causes of chylous ascites in developed countries are abdominal malignancies and cirrhosis [2], while in developing countries, infectious diseases and especially tuberculosis are common causes [14–16]. Press reported 24 adult cases of CA, and 21 of them were caused by malignancies [4]. There are three treatment options for iatrogenic chylous ascites: pharmacological, nonpharmacological, and surgery. Nonpharmacological treatment includes dietary measures: restriction of salt and water intake and the use of a high protein and low-fat diet with medium-chain triglycerides (MCTs). MCTs are absorbed by the enterocytes and then transported as free fatty acids and glycerol directly to the liver, reducing the production and flow of chyle. The intake level of long-chain triglycerides (LCTs) should be restricted, as they need conversion to monoglycerides and free fatty acids that are transported as chylomicrons to the intestinal lymph ducts. Coconut oil, palm kernel oil, whole milk, butter, and cheese are rich in MCTs, whereas fish, nuts, meat, and olive oil should be avoided because they contain LCTs. Dietary measures are effective in 50% of cases and should continue several months. If the above measures are ineffective, bowel rest and total parenteral nutrition (TPN) should be started. Bowel rest and TPN bypasses the bowel and may reduce lymph flow. TPN is effective in 60%–80% of cases and should be maintained for 2–6 weeks [10,13,17–23]. If first-line treatment is unsuccessful, pharmacological treatment should be started, either alone or in combination with TPN. The drugs used for pharmacological treatment (somatostatin and octreotide) inhibit lymph fluid excretion through specific receptors found in the normal intestinal wall of lymphatic vessels. Somatostatin has a half-life of 1–3 min, whereas octreotide, a synthetic version of somatostatin, has a longer half-life of \sim 2 h. Subcutaneous octreotide has a maximum effect in the first month, and treatment should continue six months. Resolution rates of CA from 60% to 100% after pharmacological therapy have been reported. Most authors suggested a trail of conservative management for at least 4-8 weeks before surgery [3,13,24–33]. Etilefrine is an adrenergic agonist with sympathomimetic effect. Etilefrine acts by contracting the smooth muscle of the main lymphatic duct. In one of the biggest studies, a combination of etilefrine and octreotide showed an effectiveness of 75% [19,34,35]. If conservative measures fail, surgery should be performed (laparotomy or laparoscopy suture or clips ligation of the damaged lymphatic vessel). Yao described three cases of chylous ascites after bilateral pelvic and para-aortic lymphadenectomy for gynecological malignancies. He concluded that laparoscopic ligation of broken lymphatic vessels is a next step of treatment if conservative management failed [14]. In a review by Browse, closure of a retroperitoneal fistula was the most successful operation, when conservative treatment failed [3,14]. According to different authors, surgical treatment is effective in 41%–95% of cases [14,22,36] (Table 2) [36].

Treatment	Mechanism	Effectiveness (%)	Treatment Duration
Nonpharmacological:			
Dietary modifications: high protein and			
low-fat diet with medium chain	Reduce the production and	50%	Several months
triglycerides (MCT)-coconut oil, palm	flow of chyle	0070	Several months
kernel oil, whole milk, butter, cheese			
Bowel rest and total parenteral nutrition	Reduce lymph flow by bypasses the bowel	60%-80%	2–6 weeks
Pharmacological:			
Octreotide/Somatostatin	Inhibit lymph fluid excretion.	60%-100%	6 months
Etilefrine/Octreotide	Contract the smooth muscle of the main lymphatic duct	75%	3–4 weeks
Surgery:			
Laparotomy or Laparoscopy	Suture or clips lymphatic ligation	41%-95%	Immediate termination of the leak

Table 2.	Treatment of	iatrogenic	chylo	us ascites.

Paracentesis or peritoneovenous shunting can be considered as options for patients who are poor candidates for surgery [9,37,38].

Iatrogenic surgical chyloperitonitis can be divided into two types after surgery: chylous ascites after oncogynecological operations or after operations for benign gynecologic pathology.

It is most common after retroperitoneal oncogynecological operations [39]. Ulas Solmaz et al. reported 36 cases of chylous ascites among 399 patients who underwent retroperitoneal lymph node dissection. They demonstrated that the frequency of postoperative chylous ascites is higher after para-aortic lymphadenectomy than after pelvic lymphadenectomy. They concluded that the number of removed paraaortic lymph nodes was greater in patients with chylous ascites [39].

Chylous ascites is an extremely rare complication in gynecological operations for benign pathology. There are very few cases that have been reported in the literature.

Miller reported a case of chylous ascites after modified radical hysterectomy for placenta accreta, and he concluded that it is a potential complication [1]. Zhang et al. described a case with chylous ascites after spontaneous vaginal delivery. According to them, idiopathic chylous ascites in pregnancy may be related to congenital lymphatic system dysplasia or pressure from an enlarged uterus during late pregnancy [2]. Vimee Bindra reported a case with idiopathic chylous ascites simulating rupture of a hemorrhagic cyst in the ovary. He concluded that chylous ascites should be a part of differential diagnosis in a female patient with acute abdomen [40]. Rodrigo Soto and colleagues reported a case with a 34-year-old woman with primary chylous ascites due to lymphangiectasias. In their conclusion, they said that chylous disorders are rare and complex conditions that represent a diagnostic and therapeutic challenge [6].

We did not find a report of chylous ascites after myomectomy. In our case, we had evidence of CA (triglycerides level of 1150 mg/dL), but we could not find a cause for it. Based on the examinations performed on this patient, nothing abnormal was detected. There were no data of tuberculosis or other infectious diseases. Because the ascites occurred immediately after the operative intervention and disappeared after conservative treatment of several days, we considered that the myomectomy was its cause. We cannot explain its mechanism of occurrence, but we consider that it is possible to occur after such types of surgery.

4. Conclusions

Although extremely rare, chylous ascites may also occur in operative interventions for benign diseases in gynecological surgery, and physicians must be ready to deal with such a complication.

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References

- Miller, H.; Anderson, M.L.; Smith, C.P.; Shamshirsaz, A.A.; Fox, K.A. Chylous Ascites Complicating Modified Radical Hysterectomy for Placenta Percreta. *Obstet. Gynecol.* 2016, 128, 973–975. [CrossRef] [PubMed]
- Zhang, B.; Zhang, X.; Wang, Y. Idiopathic Chylous Ascites in Pregnancy: A Case Report. *Iran. J. Public Health* 2018, 47, 1034–1036. [PubMed]
- Al-Busafi, S.A.; Ghali, P.; Deschênes, M.; Wong, P. Chylous ascites: Evaluation and management. *ISRN Hepatol.* 2014, 3, 240473. [CrossRef] [PubMed]
- Press, O.W.; Press, N.O.; Kaufman, S.D. Evaluation and management of chylous ascites. *Ann. Intern. Med.* 1982, 96, 358–364. [CrossRef] [PubMed]
- 5. Cárdenas, A.; Chopra, S. Chylous ascites. Am. J. Gastroenterol. 2002, 97, 1896–1900. [CrossRef]
- Soto, R.; García, I.; Hinojosa, C.; Torre, A. Refractory Chylous Ascites. *Gastroenterol. Res.* 2008, 1, 57–59. [CrossRef] [PubMed]
- 7. Thaler, M.A.; Bietenbeck, A.; Schulz, C.; Luppa, P.B. Establishment of triglyceride cut-off values to detect chylous ascites and pleural effusions. *Clin. Biochem.* **2017**, *50*, 134–138. [CrossRef]

- 8. Staats, B.A.; Ellefson, R.D.; Budahn, L.; Dines, D.E.; Prakash, U.B.; Offord, K. The lipoprotein profile of chylous and nonchylous pleural effusions. *Mayo Clin. Proc.* **1980**, *55*, 700–704.
- Almakdisi, T.; Massoud, S.; Makdisi, G. Lymphomas and chylous ascites: Review of the literature. *Oncologist* 2005, 10, 632–635. [CrossRef]
- 10. Hsiao, C.H.; Yu, C.C.; Hsieh, T.Y.; Kao, Y.L.; Wang, S.C.; Chen, W.J. Chen S.L. Chylous ascites as a complication of nephroureterectomy. *Urol. Sci.* 2015, *26*, 139–141. [CrossRef]
- 11. Munro, M.G.; Critchley, H.O.; Broder, M.S.; Fraser, I.S. The FIGO Classification System ("PALM-COEIN") for causes of abnormal uterine bleeding in non-gravid women in the reproductive years, including guidelines for clinical investigation. *Int. J. Gynaecol. Obstet.* **2011**, *113*, 3–13. [CrossRef]
- 12. Steinemann, D.C.; Dindo, D.; Clavien, P.A.; Nocito, A. Atraumatic chylous ascites: Systematic review on symptoms and causes. *J. Am. Coll. Surg.* 2011, 212, 899–905. [CrossRef]
- 13. Bhardwaj, R.; Vaziri, H.; Gautam, A.; Ballesteros, E.; Karimeddini, D.; Wu, G.Y. Chylous Ascites: A Review of Pathogenesis, Diagnosis and Treatment. *J. Clin. Transl. Hepatol.* **2017**, *6*, 105–113. [CrossRef]
- Browse, N.L.; Wilson, N.M.; Russo, F.; al-Hassan, H.; Allen, D.R. Aetiology and treatment of chylous ascites. Br. J. Surg. 1992, 79, 1145–1150. [CrossRef] [PubMed]
- 15. Khoury, T.; Schneider, R. Chylous ascites: A rare adverse effect of methimazole treatment for grave's disease-a case report and review of the literature. *Case Rep. Endocrinol.* **2015**, 2015, 1–4. [CrossRef]
- 16. Capristo, E.; Spuntarelli, V.; Treglia, G.; Arena, V.; Giordano, A.; Mingrone, G. A case report of chylous ascites after gastric bypass for morbid obesity. *Int. J. Surg. Case Rep.* **2016**, *29*, 133–136. [CrossRef]
- 17. Lizaola, B.; Bonder, A.; Trivedi, H.D.; Tapper, E.B.; Cardenas, A. Review article: The diagnostic approach and current management of chylous ascites. *Aliment. Pharmacol Ther.* **2017**, *46*, 816–824. [CrossRef]
- 18. Weinstein, L.D.; Scanlon, G.T.; Hersh, T. Chylous ascites. Management with medium-chain triglycerides and exacerbation by lymphangiography. *Am. J. Dig. Dis.* **1969**, *14*, 500–509.
- 19. Kumar, P.; Chandra, K. Chylous ascites due to tuberculosis: A Case Report and Review of Literature. *Indian J. Clin. Pract.* **2013**, *24*, 640.
- 20. Leibovitch, I.; Mor, Y.; Golomb, J.; Ramon, J. The diagnosis and management of postoperative chylous ascites. *J. Urol.* **2002**, *167 Pt* **1**, 449–457. [CrossRef]
- 21. Baniel, J.; Foster, R.S.; Rowland, R.G.; Bihrle, R.; Donohue, J.P. Management of chylous ascites after retroperitoneal lymph node dissection for testicular cancer. *J. Urol.* **1993**, *150*, 1422–1424. [CrossRef]
- 22. Aalami, O.O.; Allen, D.B.; Organ, C.H., Jr. Chylous ascites: A collective review. *Surgery* 2000, *128*, 761–778. [CrossRef]
- 23. Petrasek, A.J.; Ameli, F.M. Conservative management of chylous ascites complicating aortic surgery: A case report. Can. *J. Surg.* **1996**, *39*, 499–501.
- Aerts, J.; Matas, A.; Sutherland, D.; Kandaswamy, R. Chylous ascites requiring surgical intervention after donor nephrectomy: Case series and single center experience. *Am. J. Transplant.* 2010, 10, 124–128. [CrossRef]
- 25. Karagol, B.S.; Zenciroglu, A.; Gokce, S.; Kundak, A.A.; Ipek, M.S. Therapeutic management of neonatal chylous ascites: Report of a case and review of the literature. *Acta Paediatr.* **2010**, *99*, 1307–1310. [CrossRef]
- Yildirim, A.E.; Altun, R.; Can, S.; Ocal, S.; Akbaş, E.; Korkmaz, M.; Selçuk, H.; Yilmaz, U. Idiopathic chylous ascites treated with total parenteral nutrition and octreotide. A case report and review of the literature. *Eur. J. Gastroenterol. Hepatol.* 2011, 23, 961–963. [CrossRef]
- 27. Joanny, G.; Celia, A.; Zeccolini, G.; Del Biondo, D.; Breda, G. Chylous ascites following laparoscopic adrenalectomy: Case report and literature review. *Arch. Ital. Urol. Androl.* **2010**, *82*, 186–188.
- 28. Zhou, D.X.; Zhou, H.B.; Wang, Q.; Zou, S.S.; Wang, H.; Hu, H.P. The effectiveness of the treatment of octreotide on chylous ascites after liver cirrhosis. *Dig. Dis. Sci.* **2009**, *54*, 1783–1788. [CrossRef]
- 29. Widjaja, A.; Gratz, K.F.; Ockenga, J.; Wagner, S.; Manns, M.P. Octreotide for therapy of chylous ascites in yellow nail syndrome. *Gastroenterology* **1999**, *116*, 1017–1018. [CrossRef]
- 30. Talluri, S.K.; Nuthakki, H.; Tadakamalla, A.; Talluri, J.; Besur, S. Chylous ascites. *N. Am. J. Med. Sci.* **2011**, *3*, 438–440. [CrossRef]
- 31. Berzigotti, A.; Magalotti, D.; Cocci, C.; Angeloni, L.; Pironi, L.; Zoli, M. Octreotide in the outpatient therapy of cirrhotic chylous ascites: A case report. *Dig. Liver Dis.* **2006**, *38*, 138–142. [CrossRef]
- 32. Link, R.E.; Amin, N.; Kavoussi, L.R. Chylous ascites following retroperitoneal lymphadenectomy for testes cancer. *Nat. Clin. Pract. Urol.* **2006**, *3*, 226–232. [CrossRef]

- Mincher, L.; Evans, J.; Jenner, M.W.; Varney, V.A. The successful treatment of chylous effusions in malignant disease with octreotide. *Clin. Oncol.* 2005, 17, 118–121. [CrossRef]
- 34. Ohkura, Y.; Ueno, M.; Iizuka, T.; Udagawa, H. Effectiveness of etilefrine regimen for chylothorax after esophagectomy with thoracic duct resection. *Esophagus* **2018**, *15*, 33–38. [CrossRef]
- 35. Guillem, P.; Billeret, V.; Lecomte Houcke, M.L.; Triboulet, J.P. Successful management of post esophagectomy chylothorax/chyloperitoneum by etilefrine. *Dis. Esophagus* **1999**, *12*, 155–156. [CrossRef]
- Paul, S.; Altorki, N.; Port, J.; Stiles, B.; Lee, P. Surgical management of chylothorax. *Thorac. Cardiovasc. Surg.* 2009, 57, 226–228. [CrossRef]
- 37. Yao, S. Laparoscopic Ligation of Broken Lymphatic Vessels for the Treatment of Chylous Ascites after Pelvic or Para Aortic Lymphadectomy. *J Minim. Invasive Gynecol.* **2018**, 25, S171. [CrossRef]
- 38. Makino, Y.; Shimanuki, Y.; Fujiwara, N.; Morio, Y.; Sato, K.; Yoshimoto, J.; Gunji, Y.; Suzuki, T.; Sasaki, S.I.; Iwase, A.; et al. Peritoneovenous shunting for intractable chylous ascites complicated with lymphangioleiomyomatosis. *Intern. Med.* **2008**, *47*, 281–285. [CrossRef]
- Solmaz, U.; Turan, V.; Mat, E.; Dereli, M.L.; Ekin, A.; Peker, N.; Tosun, G.; Dogan, A.; Gokcu, M.; Sanci, M. Chylous ascites following retroperitoneal lymphadenectomy in gynecologic malignancies: Incidence, risk factors and management. *Int. J. Surg.* 2015, *16 Pt A*, 88–93. [CrossRef]
- 40. Bindra, V.; Sarada, P. A case of idiopathic chylous ascites simulating rupture of hemorrhagic cyst in the ovary. *J. Minim. Invasive Gynecol.* **2019**, *26*, 388–389. [CrossRef]



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