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# Chylothorax as Part of Lymphatic Cystic Malformations Developing in Adulthood

## Yetişkinlikte Ortaya Çıkan Lenfatik Kistik Malformasyonların Bir Parçası Olarak Şilotoraks

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### Abstract

Lymphatic cystic malformations (LCMs) are rare, benign anomalies that, despite being congenital, may not be diagnosed until adulthood. LCMs that affect the skin, mucous membranes or underlying soft tissues are referred to as superficial LCMs, while those involving deeper organs are termed deep LCMs. Genetically, LCMs result from the activation of a somatic postzygotic mutation in the PIK3CA gene that disrupts and activates the PI3K/ATK/mTOR cell-signaling pathway involved in lymphangiogenesis, which predicts a good response to mTOR inhibitors. We report here on the case of a 23-year-old patient who presented in 2010 with both superficial and deep LCMs, and whose symptoms regress following treatment with mTOR inhibitors.


**Keywords:** *Lymphatic malformations, chylothorax, MTOR inhibitor.*


### Öz

Lenfatik kistik malformasyonlar (LCM'ler) nadir görülen, iyi huylu malformasyonlardır ve konjenital olmalarına rağmen tanı yetişkinlikte konulabilir. LCM'ler cildi, mukoz membranları veya cilt altı yumuşak dokuları tutabilir ve bu durumda yüzeysel LCM'ler olarak adlandırılır veya altta yatan organları tutabilir ve bu durumda derin LCM'ler olarak adlandırılır. Genetik açıdan bakıldığında, LCM'ler lenfanjiyogenezde rol oynayan PI3K/ATK/MTOR hücre sinyal yolağını bozan ve aktive eden PIK3CA geninin aktive edici somatik postzinotik mutasyonu ile ilişkilidir ve bu da mTOR inhibitörüne iyi bir yanıt alınmasını öngörmektedir. Bu makalede, 2010 yılından beri yüzeysel ve derin LCM'leri olduğu bildirilen ve mTOR inhibitörü ile tedavi edilerek semptomları gerileyen 23 yaşında bir hasta sunulmuştur.


**Anahtar Kelimeler:** *Lenfatik malformasyonlar, şilotoraks, MTOR inhibitörü.*

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Lymphatic cystic malformations (LCMs) are rare, benign malformations that can be life-threatening due to their local invasiveness. Males and females, as well as people of different ethnic origins, are affected equally. Although congenital, they are not always apparent at birth, and while diagnosis can be delayed until adulthood, around 90 percent of cases are diagnosed before the age of 5 years. Genetically, LCMs are linked to the activation of a somatic post-zygotic mutation in the PIK3CA gene that disrupts and activates the PI3K/AKT/mTOR cell-signaling pathway that plays a role in lymphangiogenesis, suggesting a favorable response to mTOR inhibitors (1-3). In the absence of consensus on the optimum treatment, we present a case who presented with both superficial and deep MCLs and who responded well to treatment with mTOR inhibitors.

## CASE

We present the case of a 23-year-old patient with a subcutaneous lesion in the right inguinal fold that had been developing since 2010. This lesion exhibited a rapid increase in both size and depth, extending to the scrotum and contralateral inguinal fold, and accompanied by signs of superinfection. This prompted the patient to consult a urologist in May 2018, when a pelvic CT scan revealed a tumoral process involving the superficial soft tissues of the anteromedial aspect of the right thigh, along with osteolytic bone lesions in the pelvis. Neoplastic origin was initially suspected, but a bone scan conducted in June 2018 revealed no bone fixation.

The patient was lost to follow-up between 2018 and 2020, but was reassessed on September 2020, when a pelvic MRI (Figure 1) revealed an infiltrative process characterized by poorly defined microcystic structures, situated supraponeuratically and with subaponeurotic extension affecting the bilateral inguinal regions. The infiltrate extended superiorly through the obturator region to the pelvic floor, posteriorly infiltrating the presacral space and retroperitoneum, and inferiorly to the right adductor fossa and the base of the scrotum, and ultimately infiltrating the perineal region. A distinct mass measuring 60 x 83 mm was identified on the medial aspect of the right thigh. Imaging revealed hyperintensity on the T2 and STIR sequences and isointensity on T1 with discreet and heterogeneous enhancement following contrast administration. This infiltration involved the external iliac and inferior mesenteric vessels, both of which remained patent. Additionally, multiple osteolytic lesions were identified in the sacrum and bilaterally in the iliac wings that were not enhanced by contrast. The findings suggested a lymphatic malformation, while the observed enhancements pointed to superinfection.

*Figure 1: MRI: Infiltrate made up of microcystic structures, involving the bilateral inguinal regions, and infiltrating the perineal region, creating a true mass on the medial aspect of the right thigh measuring 60 x 83 mm. The whole is described as hypersignal T2 and STIR, iso-signal T1, discreetly and heterogeneously enhanced after contrast; the infiltration encompassed the external iliac and inferior mesenteric vessels, which are permeable. Multiple osteolytic lesions involving the sacrum and iliac wings bilaterally, not enhanced with contrast*

*Figure 2: Swelling at the root of the right thigh*

A diagnosis of inguinoscrotal lymphangioma was established that was treated with sclerotherapy and bleomycin, leading to a slight regression of the condition. Treatment involving an mTOR inhibitor was indicated, but the patient declined to initiate this treatment and was again lost to follow-up.

The patient presented to the emergency department 1 year later with symptoms that had persisted for 1 month, including pelvic swelling and severe bone pain in the left hip radiating down the left leg that had become bilateral and debilitating. The pain rendered sitting impossible and the patient could stand only with assistance, while there were no accompanying sensory or motor deficits. The patient's condition had worsened 5 days before the consultation with the acute onset of dyspnea, dry cough with chest pain, a fever of 40°C and asthenia.

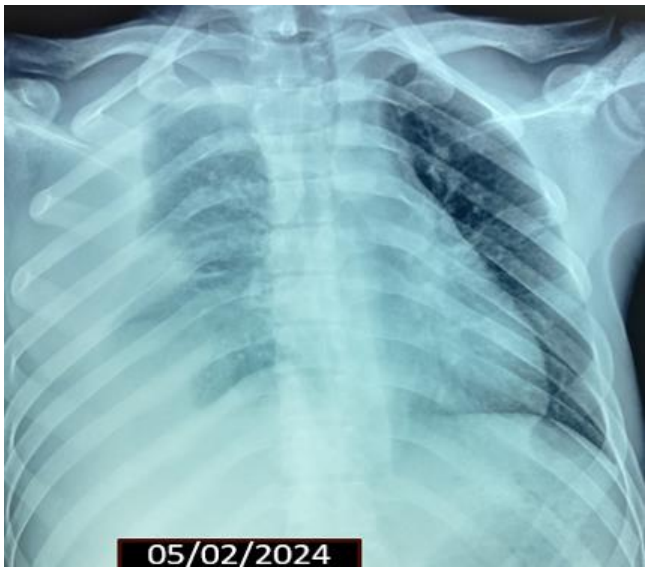


*Figure 3: Front chest X-ray showing encysted pleurisy*

A clinical examination revealed polypnea and 94% oxygen saturation, while a pleuropulmonary assessment indicated the presence of liquid effusion syndrome in the right thoracic hemithorax. A soft, non-tender swelling was identified upon palpation that was characterized by multiple flesh-colored cysts located in the right inguinal region (5 cm), at the root of the right thigh (7 cm), and on the underside of the right scrotum (6 cm) and perineum (Figure 2).

A frontal thoracic X-ray revealed an appearance consistent with encysted pleurisy (Figure 3).

In a thoraco-abdomino-pelvic CT scan performed in February 2024 (Figure 4), the supra- and subaponeurotic tissue infiltration was found to have increased in size and to have extended intra- and sub-peritoneally, associated to an appearance of a pleural localization, and the bone involvement identified during previous imaging was noted to have worsened. The combined findings pointed to multifocal lymphangiomatosis with a malformed appearance.

A thoracic MRI was performed to further investigate the thoracic duct revealing ectasia of the axillary and right intercostal lymphatic ducts characterized by hyperintensity on T2-weighted images, consistent with dilated lymphatic vessels. Additionally, a tubular structure was noted in the posterior mediastinum along the lateral border of the aorta, indicating an abnormal dilation of the thoracic duct. Furthermore, a significant pleural effusion was noted on the left and a moderate effusion on the right with heterogeneous hyperintensity on T2-weighted images, suggestive of chylothorax (Figure 5).

Pleural puncture revealed a milky fluid (Figure 6) that was identified as lymphocytic exudate by biochemical and cytobacteriological analyses with a triglyceride level of 8.47 g/L and a positive chylomicron assay. No microbial growth was detected in the culture, confirming the diagnosis of chylothorax.

The patient underwent drainage and was placed on a low-fat diet. The drain produced an average of 1200 cc of lactescent fluid per day. A multidisciplinary consultation deemed surgery to be inappropriate due to the high risk of recurrence, and the decision was made to initiate medical treatment with the Everolimus mTOR inhibitor at a dosage of 10 mg/day (off-label indication), with the possibility of subsequent surgery depending on clinical progress.

An assessment following 6 months of treatment revealed bilateral regression of pleurisy, leading to the cessation of drainage after first 3 months of treatment, as well as a reduction in the size of the inguinal swelling and resolution of pain.

## DISCUSSION

Lymphatic Cystic Malformations (LCMs) are benign, slow-flowing anomalies characterized by abnormal cystic dilatations, the etiology of which remains poorly understood. LCMs that affect the skin, mucous membranes or underlying soft tissues are classified as superficial LCMs, while those that involve deeper organs are referred to as deep LCMs. Superficial LCMs are more prevalent than deep LCMs. LCMs were first described by Rodenber back in 1828, however, there have been few studies since then contributing to epidemiological knowledge of the condition (1,4).

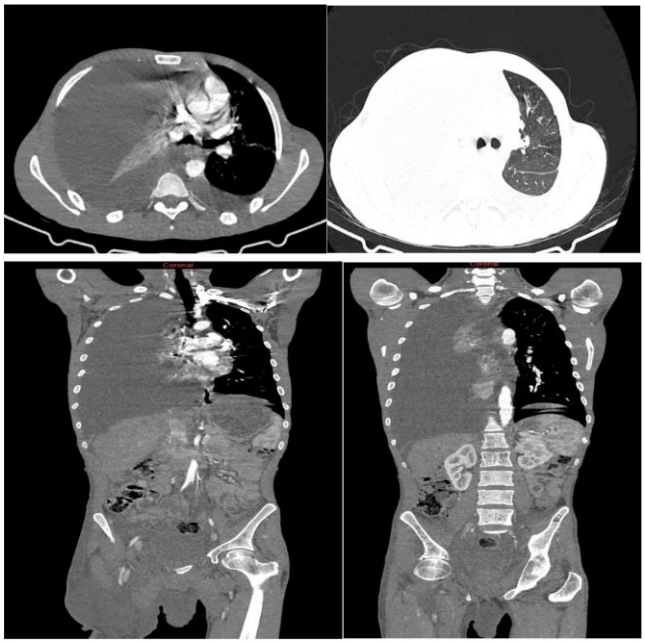

*Figure 4: CT scan showing supra- and subaponeurotic tissue infiltration with intra- and subperitoneal extension, pleural localization and worsening bone involvement*

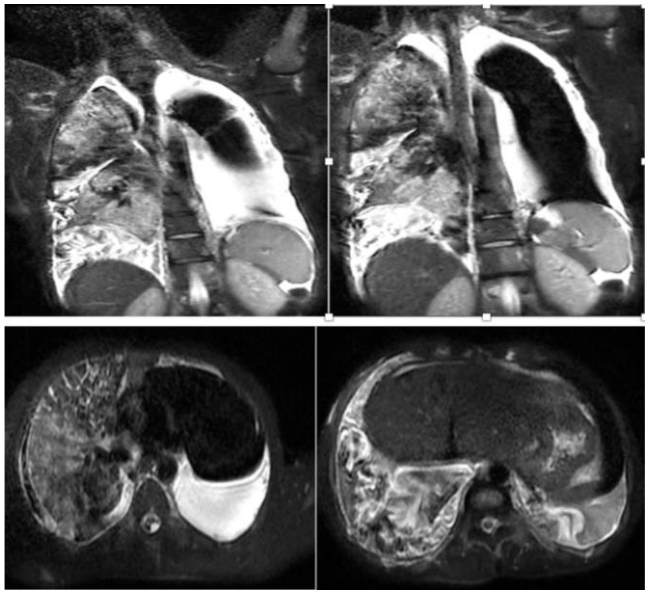

*Figure 5: Ectasia of the intrapulmonary lymphatic sector and lymph node areas, associated with thoracic duct dilatation and chylothorax in the context of lymphangiomatosis*

Clinically, superficial LCMs may present as round or lobulated subcutaneous masses several centimeters in diameter, exhibiting normal skin coloration and a soft or firm, elastic consistency. The most common anatomical locations include the neck, proximal limbs, axilla and inguinal regions, and approximately 90 percent of cases are diagnosed before the age of 5 years. In the case presented here, no diagnosis was made until adulthood.

Deep LCMs can affect all lymphatic territories and can involve single or, more commonly, multiple organs, with thoracic involvement being the most prevalent. The affected structures can include the lungs, mediastinum, heart, pleura, thoracic duct and chest wall. The prognosis of deep LCMs varies depending on the organ involved, with hepatic, splenic and thoracic involvement being associated with poorer prognoses due to their diffuse nature and limited surgical accessibility. A review of 53 cases of thoracic involvement in LCMs conducted by Alvarez et al. reported a worse prognosis in those under the age of 16 years when compared to older patients, with respective mortality rates of 39% and 0% (5-7). Thoracic involvement in particular is linked to a poor prognosis (4).

Bone involvement in LCMs is exceptionally rare, with only 16 cases documented in the literature reporting an association between chylothorax and bone involvement. Chylothorax and bone lesions were identified concurrently in 13 of these recorded cases, while in the remaining cases the bone involvement manifested as pain and preceded the development of chylothorax, with delays ranging from 6 months to 5 years (9).

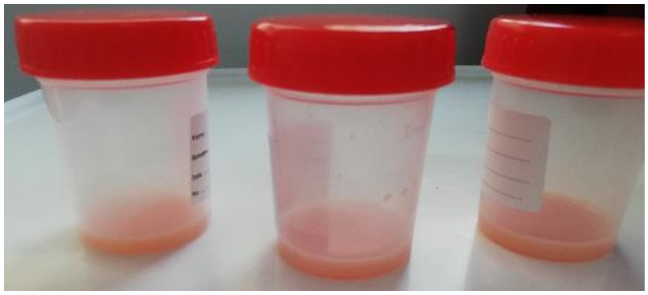

*Figure 6: Pleural fluid with a milky macroscopic appearance*

Our patient exhibited infiltrations of the microcystic structures affecting the bilateral inguinal regions, along with infiltration of the perineal region and multiple osteolytic lesions involving the sacrum and bilateral iliac wings, accompanied by chylothorax. This presentation encompasses both superficial and deep lymphatic malformations (LCMs) and is a notably rare manifestation of the disease.

Diagnosis LCMs is typically delayed due to the rarity of the pathology, and the varied clinical presentations based on the specific organs affected (1,8).

The disease may occasionally present with such nonspecific symptoms as tracheal wheezing, dry cough, chest pain, dyspnea, tightness and wheezing, often leading to misdiagnosis as asthma or other respiratory pathologies. Significant pleural effusion, frequently chylous in nature, may be associated with chylopericardium and progressive pulmonary infiltration, with the potential to result in respiratory failure (8).

Chest X-rays may reveal interstitial involvement along with pleural effusion, although such findings are not specific to LCMs (1).

CT imaging exposes patients to radiation and falls short of the diagnostic value of magnetic resonance imaging (MRI). Lymphography can assess the extent of lesions, although this technique carries the risk of pulmonary complications – a concern also applicable to isotopic lymphoscintigraphy – and so both methods are of limited utility in the evaluation of LCMs (1,8).

MRI is thus the preferred modality for assessing anatomical extent and for the effective characterization of lesions. Magnetic resonance lymphography employs highly T2-weighted sequences to provide a detailed anatomical representation of structures containing stationary or slow-moving fluids. The primary objectives of magnetic resonance lymphography are to localize the source of the leak, to identify any aneurysmal dilatation of the thoracic duct or its afferent vessels, and to evaluate the permeability of the thoracic duct. The technique can also visualize lymphangiectasias relevant to the peribronchovascular lymphatics, the lymphatics of the interlobular septa and even the extravasation of lymph within the alveoli (10).

There is no specific biological test for LCMs, but biopsy is seldom required as diagnoses are primarily based on clinical and radiological findings (1).

The progression of LCMs is characterized by asymptomatic intervals interspersed with episodes of painful inflammation, superinfection or intracystic hemorrhage, and is particularly accelerated in puberty, although the influence of hormones has not been definitively established (1).

There remains a lack of consensus on the optimum the treatment of LCMs with pleural effusion, given the rarity and relative obscurity of the condition (8).

The initial management of chylothorax typically involves dietary modifications and thoracentesis (2). Various treatments have been explored for the treatment of lymphatic malformations, including glucocorticoids, bisphosphonates, imatinib, thalidomide, interferon, cyclophosphamide, tamoxifen and sildenafil, as well as sclerotherapy and radiotherapy. While these therapies have shown benefits in certain patients, they may also be associated with significant adverse effects (7). Propranolol and bevacizumab have also been tried as treatments for LCM, but there is insufficient evidence to recommend their use (1,7).

Genetically, LCMs have been associated with an activating somatic post-zygotic mutation in the PIK3CA gene that disrupts and activates the PI3K/AKT/mTOR cell signaling pathway involved in lymphangiogenesis. This alteration is been shown to respond well to mTOR inhibitors. mTOR inhibitors have been used to treat complicated LCMs since 2011, and have produced promising results (2,3,8,11,12).

Several authors have reported significant improvements in patients treated with mTOR inhibitors:

In 2016, Nadal et al. (13) reported on 83 cases with vascular anomalies who were managed with mTOR inhibitors, noting the efficacy of 2 weeks to 6 months treatment.

Nasser et al. (6) reported a case of a 32-year-old woman who presented with cardiac tamponade, mediastinal infiltration and pleural effusion, and whose treatment with an mTOR inhibitor resulted in clinical improvement after 10 months, and the resolution of both the mediastinal infiltration and pleural and pericardial effusions.

In a 2011 study by El Zein et al. (3), a 25-year-old patient with a giant unresectable mesenteric cystic lymphangioma associated with a mutation in the PIK3CA gene was treated with an mTOR inhibitor, resulting in a favorable response, allowing a complete resection of the lesions after 9 months of treatment and subsequent cure.

In 2024, Chang et al. (2) published the case of a 12-year-old patient who presented with both superficial and deep LCMs involving the mucocutaneous region and parotid gland. A genetic analysis revealed a somatic PIK3CA mutation, and the patient was subsequently treated with an mTOR inhibitor, resulting in the resolution of the lesions after 4 months.

mTOR inhibitor treatments can lead to significant, although incomplete, improvements in most cases with LCMs, but are reserved primarily for the more complex and severe cases. The treatment period is typically long, and there are currently no established criteria for discontinuation other than the presence of adverse effects (1).

Adverse effects may be clinical, including gastrointestinal disorders, asthenia, headaches, hypersensitivity pneumonitis and venous thrombosis; or biological, such as thrombocytopenia, anemia, lymphopenia and neutropenia. Consequently, regular clinical and biological monitoring is necessary, starting 1 month after the initiation of treatment and every 2 to 3 months thereafter (1)

Targeted therapies, particularly anti-PI3K agents, are currently under clinical evaluation (1).

Surgical interventions are typically reserved for cases with advanced stages of the disease that are resistant to the pharmacological treatments, and typically involve thoracotomy with pleurectomy. More favorable outcomes reported with pleurectomy, either with or without thoracic duct ligation, however, thoracic duct ligation alone is not effective, indicating that the source of lymphatic fluid does not originate solely from the thoracic duct, but rather from aberrant lymphatic vessels within the chest wall. The application of fibrin glue (Tisseel) can support the control of lymphatic leakage and prevent postoperative recurrence (8,9,14).

Patients with LCMs and their caregivers require regular psychological support (1).

## CONCLUSION

Lymphatic malformations (LCMs) are a significant and potentially disabling condition. In the present study, mTOR inhibitors were found to be effective in alleviating the patient's symptoms, similar to numerous cases reported in the literature. The duration of treatment is prolonged, and there are currently no established criteria for discontinuation. Other targeted therapies are currently under evaluation, while surgical interventions continue to be reserved for severe cases that are resistant to alternative treatment options.

## CONFLICTS OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

Concept - M.K.A., L.S., B.A., M.S.; Planning and Design - M.K.A., L.S., B.A., M.S.; Supervision - M.K.A., L.S., B.A., M.S.; Funding - M.K.A., M.S.; Materials - M.K.A., M.S.; Data Collection and/or Processing - M.K.A.; Analysis and/or Interpretation - M.K.A., M.S.; Literature Review -

M.K.A.; Writing - M.K.A.; Critical Review - M.K.A., L.S., B.A., M.S.

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