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Management of refractory chylothorax in pulmonary lymphangioleiomyomatosis

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Abstract

This case reports the successful management of chylothorax in a non-transplanted patient with pulmonary lymphangioleiomyomatosis (pLAM). Prolonged initial therapy failed, including total parenteral nutrition, pleural drainage, surgical pleurodesis, and pleurectomy. Commencement of sirolimus 2 mg daily (2 mg alternating days had failed) led to resolution of chylothorax after 20 days. Discontinuation of sirolimus for abdominal surgery led to recurrence of the chylothorax. Reinstitution of sirolimus led to rapid resolution of the effusion, stabilization of lung function, and there has been no recurrence in the ensuing 4 years. We conclude that sirolimus should be considered in the management of pLAM-related chylothorax, perhaps before surgical intervention.

Introduction

Pulmonary lymphangioleiomyomatosis (pLAM) is a rare condition characterized by the presence of pathological smooth muscle-like "LAM" cells. Chylothorax can be encountered in three clinical scenarios in pLAM: (i) spontaneous chylothorax, thought secondary to lymphatic obstruction by LAM cells; (ii) early post lung transplantation as a surgical complication; and (iii) late post-transplant as disease recurs [1, 2]. The management of chylothorax is challenging. Traditional management with surgical pleurodesis or pleurectomy is often unsuccessful. Sirolimus (or rapamycin), an oral inhibitor of the mammalian target of rapamycin (mTOR) cell proliferation pathway, has been shown to prevent deterioration of lung function in patients with pLAM [3]. This case highlights the apparent successful use of sirolimus in a spontaneous pLAM-related chylothorax that was refractory to stepwise medical and surgical management.

Case Report

In August 2009 a previously well, non-smoking, 31-year-old woman with no significant past medical history presented with 3 months of progressive dyspnea. Bilateral pleural effusions were seen on chest X-ray and a subsequent chest computerized tomography showed cystic lung disease with large pleural effusions bilaterally. She was admitted to her local hospital and an intercostal catheter (ICC) drained 2 L of fluid from the right effusion. Biochemistry showed a pleural triglyceride level of 18.1 mmol/L (1601 mg/dL), cholesterol >2 mmol/L confirming a chylothorax. She had no clinical features of tuberous sclerosis complex and was given a diagnosis of sporadic LAM. Lung function was performed post drainage and showed Forced expiratory volume in 1 sec (FEV_1) 1.85 (57% predicted) and Forced vital capacity (FVC) 2.6 (68% predicted).

One month later, dyspnea and bilateral effusions recurred. She was transferred to our institution for consideration of surgical management and evaluation for lung transplantation. Initial medical management included insertion of an ICC, nil by mouth, and commencement of total parenteral nutrition (TPN; using standard protein 20% lipid) at target rate of 70 mL/h over 24 h. Two attempts at therapeutic lymphangiogram and non-invasive blockage of the thoracic duct were made. The first was with 2.0 × 5.2 m embolization coils + 5 mL alcohol and second

with 14 mL lipiodol under fluoroscopic guidance. After an initial improvement, recurrence of her bilateral effusions led to an octreotide infusion trial, but this was also unsuccessful. Anti-estrogen therapy was considered but not utilized due to limited evidence and concerns about adverse effects on bone health.

After a further 2 months of failed conservative therapy, a left parietal pleurectomy and chemical pleurodesis (iodine/alcohol) was performed using video-assisted thoracoscopy (VAT), targeting the larger left-sided effusion. Immediately post pleurodesis 2 mg of sirolimus every second day was started. The postoperative recovery period was complicated by pleural space infection with a *Staphylococcus aureus* and thus sirolimus was ceased due to infection concerns. The left-sided effusion improved over a 1-month period allowing the commencement of TPN and a very low fat oral diet. During this time, the right-sided effusion increased in size and was associated with worsening symptoms and hypoxic respiratory failure. After further 1 month of conservative management, a right VAT talc pleurodesis was performed. There was ongoing high ICC output of greater than 500 mL daily persisting 10 days postop; thus, sirolimus 2 mg daily was commenced. Over the next month ICC outputs reduced, even with the re-introduction of very low fat oral intake. Sirolimus 2 mg daily was continued with monitoring of serum levels and serum lipids. The patient was discharged on a low fat diet after a 5-month admission. Her lung function stabilized over the next 6 months to FEV_1 2.60 (80%), FVC 2.9 (80%), and diffusing capacity of the lung for carbon monoxide (DLCO) 13.7 53%.

Chylothorax did not recur over the next 1 year until the patient required elective surgery for an enlarging and symptomatic ovarian cyst. Sirolimus was ceased 1 week period prior to surgery due to concerns regarding wound healing. In the 5 days following surgery, she had recurrence of bilateral pleural effusion and hypoxia, which did not improve with antibiotics, optimization of fluid balance, and diuretic therapy. Sirolimus was recommenced and 3 days later there was improvement in saturations, symptoms, and effusions.

In the 4 years following diagnosis, our patient remains well on sirolimus with no recurrence of pleural effusions and no adverse effects. She is able to work, exercise regularly at the gym, and has an FEV_1 of 2.39 (75%), FVC 3.35 (86%), and DLCO 13.4 (54%). Her sirolimus levels have been consistently between 3 and 6 mcg/L (average level 3.11 mcg/L).

Discussion

Lymphangioleiomyomatosis is a systemic disease of young women with pulmonary and extrapulmonary involvement. Pulmonary manifestations are the most common presenting complaint – progressive dyspnea from cystic lung disease, pneumothorax, or chylothorax [4]. Extrapulmonary manifestations are abdominal tumor such as angiomyolipoma of kidneys, spleen, or liver and adenopathy, which can cause obstruction of lymphatic ducts, thus causing chylous ascites or chylothorax. The cystic lung disease seen in pulmonary LAM occurs from destruction of normal lung architecture by abnormal smooth muscle-like LAM cells, which have excessive proliferation via activation mutations in the mTOR cell signaling pathway [3].

Chylothorax is seen in ~10% of patients with LAM [2]. In the early post-transplantation context, chylothorax is a commonly encountered management issue in patients with or without pLAM due to surgical trauma to the lymphatics. However, cases reported in the literature describe recurrent chylothorax months to years post lung transplantation [5]; it is likely that the mechanism of late post-transplantation reflects recurrence of the disease causing obstruction of lymphatics with LAM cells.

Sirolimus is a potent immunosuppressant that inhibits T-lymphocyte activation and proliferation. Sirolimus has been shown to prevent decline in lung function, improve quality of life, and reduce symptoms compared with placebo in patients with pulmonary LAM [3, 6]. The largest series to date (by Taveira-DaSilva) describes 11 patients, eight with LAM-related chylothorax, treated with sirolimus (average dose 2.6 mg/day) resulting in improved symptoms and/or total resolution of effusions in six (assessed at 411 days) [6]. These patients had also previously been treated with recurrent pleural drainage procedures and attempts at chemical pleurodesis prior to the commencement of sirolimus. The other studies describing the use of sirolimus to control LAM-related chylothorax are in the context of refractory chylothorax post lung transplant for pLAM. There are three case reports showing control of refractory chylothorax post transplant with sirolimus after traditional methods failed [1, 5, 7, 8].

This case provides some additional information regarding the use of sirolimus in pLAM-related chylothorax. Dose dependence is apparent with 2 mg on alternating days failing to control the effusions. A 2 mg daily dose with levels of 3–6 mcg/L ultimately controlled the chylothorax, which is lower than the range previously described in the MILES trial [3]. Second, discontinuation of sirolimus led to recurrence of chylothorax and with reintroduction of sirolimus there was rapid resolution of chylothorax. Further, the effects seem to be durable, with no recurrences of the chylothoraces in the subsequent 4-year period on therapy. No serious adverse effects of sirolimus were encountered, no sepsis, stable lipid profile, and normal blood pressure on regular screening.

In summary, this patient's response therapy was very instructive; her chylothoraces did not respond to standard

therapies including surgery. Sirolimus therapy was successful in a dose-dependent manner. Further evidence of efficacy is the recurrence of effusions on cessation of sirolimus and return of efficacy (resolution of chylothorax) on reintroduction of sirolimus. Perhaps in the future with earlier use of sirolimus invasive surgical interventions could be avoided, while still controlling the distressing symptoms from chylous effusions.

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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