A very long story

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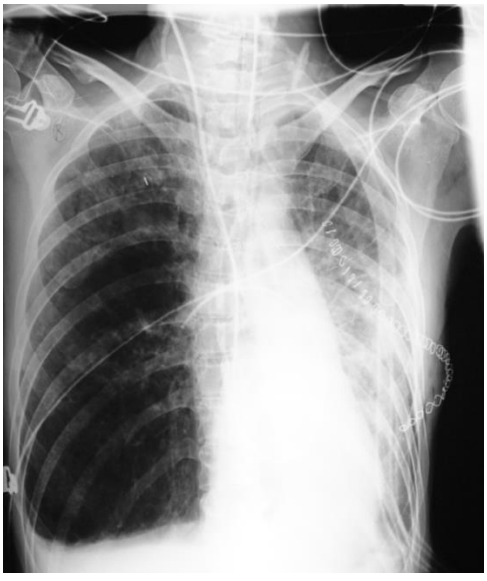
Case summary

Miss C, a 31-year-old secretary with unremarkable past health, was first presented with spontaneous bilateral pneumothoraces in 1991. While her left pneumothorax resolved on conservative treatment, intercostal drainage followed by chemical pleurodesis was performed on the right side. Ultimately surgical pleurodesis was done because of the unresolved right pneumothorax. In 1992, she had recurrent left pneumothorax so surgical pleurodesis was performed. In 1993, she complained of progressive decrease in exercise tolerance. Chest X-ray showed increase reticular shadowing over both lung fields. CT thorax showed hyperinflation with diffuse cystic changes over both lungs and heterogenous fat-containing lesions over both kidneys compatible with renal angiomyolipomas (AML). A clinico-radiological diagnosis of lymphangioleiomyomatosis (LAM) was made. It was subsequently confirmed by histological review of the lung tissues resected during previous surgical pleurodesis. Hormonal manipulation with monthly progestogen injection was tried but her condition continued to deteriorate and she required long term oxygen therapy (LTOT) since 1994. In 1996, she was referred for assessment for lung transplant. During that time, she was in a very poor general condition, being largely home bound and dependent on high flow oxygen supplementation. Her FEV was 0.4L (15% of predicted) and she had compensated type 2 respiratory failure. After work up, she was accepted for wait-listing for lung transplant despite the understanding of the unfavourable high risk factors for failure, including the previous surgical pleurodesis and the very very severe cachexic physical state making the

transplant surgery technically difficult and with high risk of prolonged respiratory failure after transplant.

She was admitted on 5th May 1998 in a state of severe decompensated type 2 respiratory failure which showed no improvement despite bi-level positive airway pressure (BiPAP) therapy. Both patient and her husband gave the advance directives of not for intubation and mechanical ventilation because of the irreversible nature of the disease. On 8th May 1998, at the verge of dying from respiratory failure, a donor lung was available from a victim died from traffic accident with right lung contusion but the left lung was assessed to be suitable for transplant. She underwent a single left lung transplant, which was the third lung transplant in Hong Kong. The surgery was uneventful, but on the immediate post-operative day, she developed hypoxaemia and hypotension. Chest-x-ray showed hyperinflation of her native right lung and consolidative changes in her transplanted left lung (Figure 1). The diagnosis was hyperinflation of native right lung due to air-trapping and severe primary graft dysfunction in her transplanted left lung. Her condition was critical with very severe hypoxaemia and very low blood pressure despite maximal ventilator and inotropic support. It was decided to change the patient from single lumen to a double lumen endotracheal tube and for differential lung ventilation strategies with the two lungs ventilated with two different ventilator settings. She survived the very critical post-operative course and the ventilation and haemodynamic condition gradually improved. She was extubated on Day 4 and out of ICU on Day 17 after transplant.

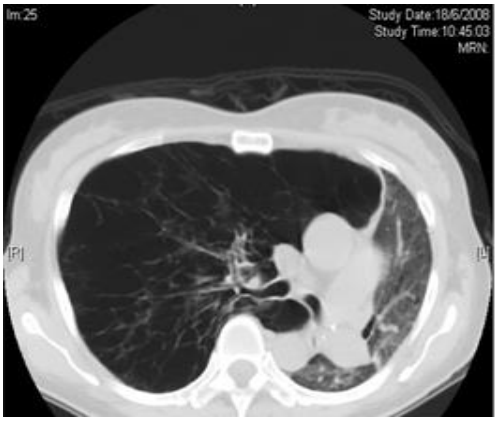
Figure 1

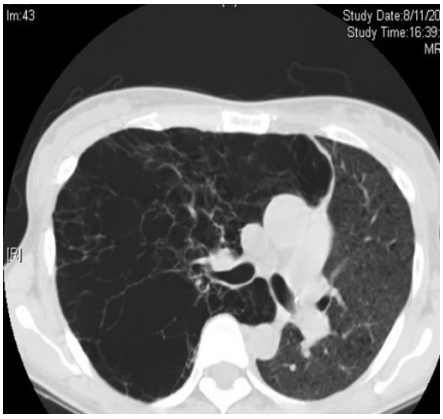


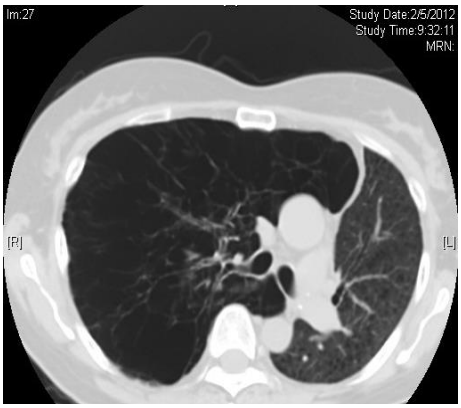
She was put on immunosuppression and had regular rehabilitation after transplant. There was

progressive improvement in her general condition and exercise tolerance. Her FEV1 peaked at 1.41L in Feb 1999 (9 months after transplant). She had an episode of acute rejection in August 1999 (15 months after transplant). Pulse steroid was given and her lung function recovered. Over the subsequent years, her condition was largely stable but there was a slow progressive decline in her FEV1 due to progression of the hyperinflation of her native right lung. Cystic changes in the left lung suggestive of recurrence of LAM in her transplanted left lung (Figure 2) were also noted. She also had mild renal impairment which was probably due to the long term use of Cyclosporin.

Figure 2

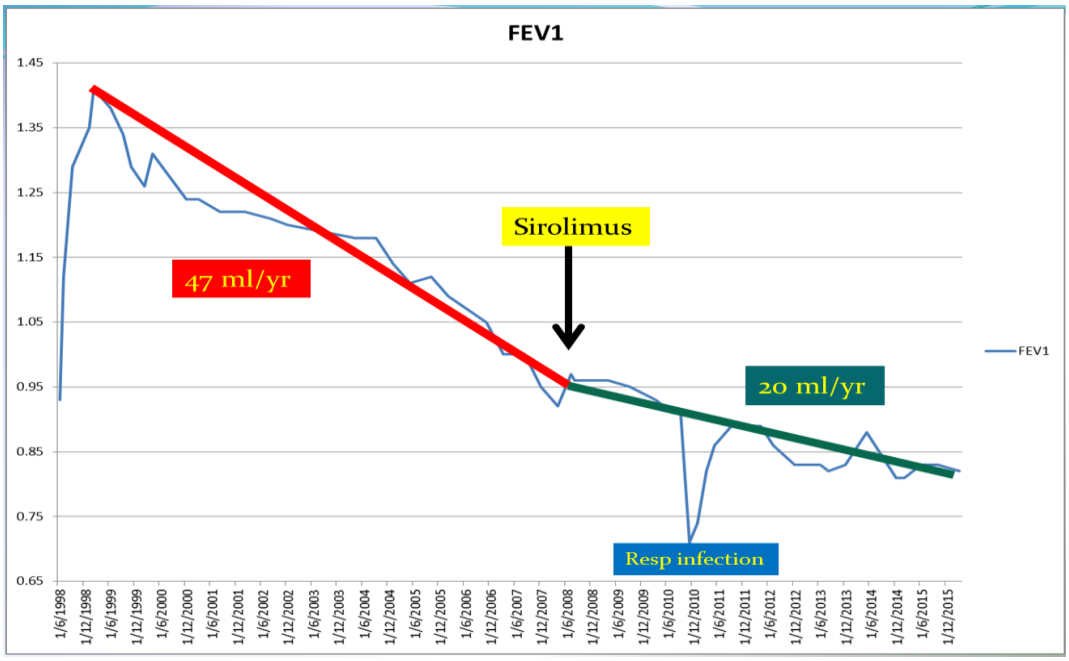






In 2008, there was an episode of severe AML bleeding in her right kidney. Bleeding was stopped with urgent embolization but there was acute on chronic renal impairment with serum creatinine up to 280mmol/L. Because of the worsened renal function, Cyclosporin was switched to Sirolimus, a mammalian target of rapamycin (m-TOR) inhibitor, which was not nephrotoxic. Her renal function recovered afterwards and the FEV1 decline appeared to slow down (Figure 3). The progression of the hyperinflation of her native right lung also appeared to slow down.

Figure 3



Azithromycin was added since early 2013 for possible bronchiolitis obliterans syndrome (the commonest form of chronic rejection).

Miss C is now 56-year-old and eighteen years post lung transplant. With the progressive decline in her lung function, she had now some difficulty in strenuous activities of daily living and her exercise tolerance was less than half flight-of-stairs. Her oxygen saturation was 95% with room air at rest. Her latest FEV1 was 0.77L. A lung perfusion scan done earlier showed that her native right lung only contributed about 7% of her lung function.

Possible factors accounting for her poor lung function included hyperinflation of the native right lung compressing onto her transplanted left lung, recurrence of LAM and chronic rejection in her transplanted left lung.

On what one can do to improve the patient's lung function and performance, apart from pulmonary rehabilitation and avoidance of infections, the followings are possible interventional options and the problems associated:

- Bronchoscopic lung volume reduction
    - Case reports of such intervention for same condition yielded poor outcome

- Lung volume reduction surgery
  - Hyperinflation due to LAM was not an established indication
- Right pneumonectomy or lobectomy
  - Inherent risk and complications especially with the patient on immunosuppression
- Re-transplant (bilateral or single right lung)
  - An acceptable and perhaps the only option when lung function deteriorates further with no other interventions being feasible

Discussion

LAM is a rare multisystem disorder affecting predominantly women of childbearing age. It is characterized by cysts formation in the lungs, pneumothorax, chylothorax, renal angiomyolipomas (AMLs) and mediastinal, retroperitoneal & pelvic lymphangioleiomyomas. In the respiratory community, LAM was usually classified as a form of interstitial lung disease. But World Health Organization classified LAM as a kind of mesenchymal tumor of the lung in 2004 (Ref 1). There are two forms of LAM. Sporadic LAM is caused by somatic mutations of the TSC2 gene. Tuberous Sclerosis Complex (TSC) associated LAM is associated with seizures, cognitive impairment, skin lesions and benign "hamartomatous" tumors of the brain, heart and kidney, and is an autosomal-dominant disorder caused by mutations in the TSC1 or TSC2 genes with high penetrance (ref 2). The histological hallmark is LAM cells, which have characteristics of both smooth muscle cells and melanocytes, diffusely infiltrate the lungs, lymphatics and AMLs. The TSC2 gene encodes tuberin, a GTPase-activating protein (a tumor suppressor protein). TSC1 encodes hamartin, which heterodimerizes with tuberin and is essential for its function. Hamartin and tuberin together inhibit the mTOR signaling pathway, a major regulator of cell size and proliferation. Absence of tuberin (or hamartin) leads to unchecked mTOR and consequent abnormal LAM cell proliferation. mTOR inhibitors by inhibition of the mTOR complex may stop the activation of downstream kinases and restores homeostasis in cells with defective TSC gene (ref 2).

The fact that LAM cells have a low proliferative index and little or no evidence of cellular atypia suggests LAM is a benign process. However, LAM has growth promoting DNA mutations, evidence of clonal origins & metastatic potential (for example, identical TSC2 mutations have been found in the lungs and kidneys of the same patient with sporadic LAM), and the fact that LAM recurs in transplanted lungs, & the cells that comprise the lesion within the allograft express the TSC mutations of the host. So most experts now consider LAM as a low-grade metastatic malignancy (ref 3). Sirolimus is the most extensively studied mTOR inhibitors for LAM. The landmark study was the MILES trial which was an international, multicenter randomized controlled trial where LAM patients with post-bronchodilator FEV1 <70% of predicted were randomized to Sirolimus (trough level 5-15ng/ml) and placebo. During the 12- month treatment period, the FEV1 slope was −12±2 ml per month in the placebo group and 1±2 ml per month in the sirolimus group (P<0.001).

However, after discontinuation of sirolimus, the decline in lung function resumed in the sirolimus group and paralleled that in the placebo group. The sirolimus group also had improvement from baseline to 12 months in measures of forced vital capacity, functional residual capacity, quality of life and functional performance. Although there were more adverse events in the sirolimus group, the number of serious adverse events was similar in both groups. The most common adverse events were mucositis, diarrhea, nausea, hypercholesterolaemia, acneiform rash and swelling in the lower extremities (Ref 4). In a single center observational study of 19 LAM patients with either progressive disease or chylous pleural effusions, treatment with sirolimus (trough level 5-15ng/ml) was associated with improvement or stabilization of lung function and decrease in the size of chylous effusions and lymphangioleiomyomas (Ref 5). In another retrospective, observational study in Japanese patients with LAM with all patients treated with Sirolimus trough level <5ng/mL (mean 2.16; range 0.8–4.3 ng/mL),

improvement in lung function and chylothorax was again observed (Ref 6). Everolimus is another mTOR inhibitor. In the International, multicenter EXIST-2 trial, Everolimus reduced the volume of AMLs in LAM patients (Ref 7).

According to international data, prior to the successful trial of sirolimus in LAM, about one third of patients with LAM progressed to require lung transplant (Ref 8). In Hong Kong, since the first lung transplant for a patient with LAM in 1995, 48 lung transplants have been performed so far. Among the lung transplant recipients in Hong Kong, six were LAM patients and most of them were done in the earlier years (in 1995, 1998, 1999, 1999, 2007 & 2012). The clinical course of the LAM patients referred to our lung transplant clinic before and after the Sirolimus era was quite different. Before 2011, 7 LAM patients were referred to our lung transplant clinic. All were wait-listed for lung transplant and 6 had lung transplant done. The other patient died before she was transplanted. After 2011, 8 LAM patients were referred to our lung transplant clinic. Sirolimus was started in 7 of them and none required wait-listing at the moment. In the 7 patients on Sirolimus, their lung function and exercise capacity were stabilized or even improved after Sirolimus treatment (Table 1)

Because of mTOR inhibitor's inhibitory effect on cell proliferation, delay wound healing is one of its serious side effect. The use of mTOR inhibitors in the immediate post-lung transplant period has been shown to be associated with a marked increased risk of bronchial dehiscence (Ref 9,10). Because of its very long half-life, stopping sirolimus before lung transplant surgery would still put the patient at risk of this serious complication. Currently, most Lung transplant programs request that women with LAM to stop using sirolimus while awaiting lung transplant. However, that may lead to a more rapid decline in their lung function and potentially compromising survival to lung transplant. This dilemma could be circumvented by the use of Everolimus which has a much shorter half-life than that of Sirolimus. In a randomized control trial of Everolimus for idiopathic pulmonary fibrosis patients, 5 patients took Everolimus up to and including

the morning of lung transplant and no patient developed bronchial dehiscence (Ref 11). From this observation, there was expert opinion suggesting that Everolimus, with dosage that keeping the trough levels at lower end of therapeutic range, was likely to be safe in patients awaiting lung transplant (Ref 12).

Summary

LAM is considered a low grade malignancy. It is caused by mutations of TSC1 or TSC2 genes that encode hamartin and tuberin, two proteins with a major role in control of the mTOR signaling pathway. Two mTOR inhibitors, Sirolimus and Everolimus, have been shown to be effective in stabilizing lung function, and reducing the size of chylothorax, lymphangioleiomyomas & AMLs.

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Table 1

Sex	age	Starting date of Sirolimus	Baseline assessment				Latest assessment				
			FEV1 (%)	FVC (%)	DLCO (%)	6MWT (m)	FEV1 (%)	FVC (%)	DLCO (%)	6MWT (m)	Months on tx
F	42	7/13	28		17		45		34		28
F	41	8/13	66			465	101			480	15
F	57	10/13	29	67		309	19	23		285	21
F	37	2/15	74	72	39	493		90	42	441	7
F	30	5/15	18	33	29	145	19	62	17	317	8
F	50	11/15	23	89	27	260	27	101		315	3
F	49	1/16	49	78	21	189	65	81	30	287	3

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