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CASE REPORT

Twin Pregnancy Following Sirolimus Therapy in Lymphangioleiomyomatosis

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ABSTRAK

Lymphangioleiomyomatosis (LAM) adalah penyakit sista paru-paru di mana ianya terjadi secara sporadik atau berkaitan dengan penyakit "tuberous sclerosis complex". Kami melaporkan satu kes "tuberous sclerosis complex" pada wanita berusia 26 tahun yang mengalami pneumothoraces serentak pada kedua-dua paru-paru dan memerlukan "pleurodesis" secara perubatan dan juga pembedahan. Pemeriksaan klinikal dan hasil siasatan mendapati beliau mempunyai angiomyolipoma pada hati dan ginjal, hamartoma pada retina kiri dan "subcortical tubers" dan "subependymal nodules" di otak berserta sista paru-paru berdinding nipis yang berlainan saiz pada dua-dua bahagian paru-paru. Hasil ujian histopatologi menunjukkan penyakit LAM. Beliau telah diberikan ubat sirolimus selama 12 bulan di mana tiada kemerosotan pada fungsi paru-paru atau peningkatan saiz sista paru-paru. Beliau mengandung 8 bulan selepas pemberhentian ubatan sirolimus dan melahirkan anak kembar pada minggu ke-30 kehamilan. Dalam kes ini, kami menekankan bahawa penggunaan ubat sirolimus berserta pleurodesis secara perubatan dan pembedahan berjaya mengelakkan kemerosotan fungsi paru-paru.

Kata kunci: anak kembar, kehamilan, limfangioleiomyomatosis, sirolimus

ABSTRACT

Lymphangioleiomyomatosis (LAM) is an orphan cystic lung disease which can occur sporadically or in association with tuberous sclerosis complex (TSC). We report a 26-year-old woman diagnosed with forme fruste of LAM, who presented with bilateral pneumothoraces requiring both surgical and medical pleurodesis. Clinical examination and investigations revealed hepatic and renal angiomyolipomas, a

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left retinal hamartoma, subcortical tubers and subependymal nodules in the brain as well as diffuse bilateral thin-walled lung cysts of varying sizes bilaterally. The histopathological examination (HPE) of the lung biopsy confirmed LAM. She was treated with 12 months of sirolimus with sustained effects on lung function and cystic lung lesions. Eight months post cessation of sirolimus, she conceived and delivered twins at 30 weeks. We describe the efficacy and safety of sirolimus and the successful twin pregnancy in a patient with LAM. This case highlights that treatment with sirolimus and surgical and medical pleurodesis was successful in preventing any further worsening of lung function.

Keywords: lymphangioleiomyomatosis, pregnancy, sirolimus, twin

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare systemic disease affecting mainly young women. It can occur sporadically or in association with tuberous sclerosis complex (TSC) (Franz et al. 2001). It is associated with cystic destruction of the lung, chylothorax, spontaneous pneumothoraces and angiomyolipomas of the kidneys (Mccormack 2008). The diagnosis is made by a combination of clinical characteristics, computed tomography revealing lung cysts and when there is doubt, a lung biopsy (Mccormack et al. 2016). The current treatment is with sirolimus which is a mammalian target of rapamycin (mTOR) inhibitor that has been shown to slow down the decline of forced vital capacity (FVC) (Mccormack et al. 2011). Newer studies have shown that sirolimus treatment improved lung texture and stabilises the lung cysts (Gopalakrishnan et al. 2019).

The LAM can be exacerbated by oestrogen. Pregnancy may also worsen the disease and has also been reported to unmask the diagnosis of LAM (Khaddour et al. 2019). Due to the concern of the negative impact of pregnancy, women with LAM are frequently advised against pregnancy. This case report describes the relative stability of LAM throughout pregnancy with no further episodes of pneumothorax. We also describe the safe outcome of twin pregnancy following discontinuation of sirolimus.

CASE REPORT

A 26-year-old previously well woman presented with bilateral pneumothoraces requiring bilateral chest tube insertion. A high resolution computed tomography (HRCT) of the thorax demonstrated diffuse, bilateral multiple thin-walled cysts suspicious of LAM (Figure 1). A magnetic resonance imaging (MRI) of the brain showed subcortical tubers with subependymal nodules. Further investigations revealed a left retinal hamartoma while an abdominal ultrasound revealed hepatic and renal angiomyolipoma. Echocardiogram was normal. There

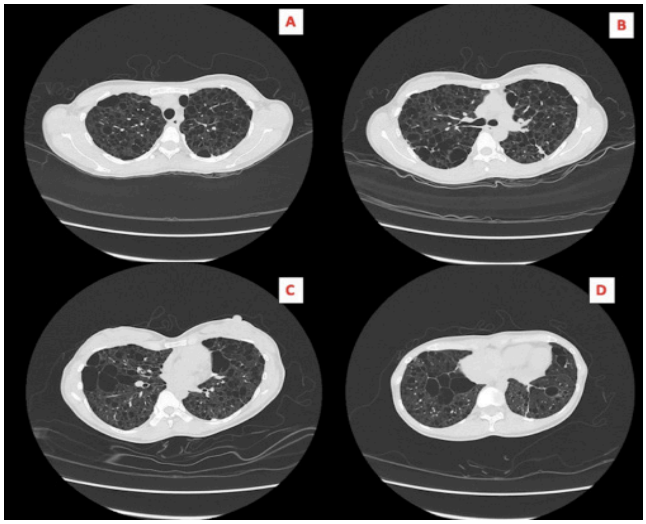

Figure 1: HRCT Thorax (A-D) showed bilateral diffuse cytic lesions of varying sizes

was no history of seizure. The patient was a non-smoker and had a history of taking oral contraceptive drugs for 6 months. Based on the findings a diagnosis of forme frustre of TSC was made.

Clinical examination revealed a moderately built woman, afebrile, pulse rate 72/minute, respiratory rate 26/minute, blood pressure 127/72 mmHg and oxygen saturation of 98% on 3 litres of oxygen. There were no skin changes seen. Cardiovascular and abdominal examinations were normal. Chest radiograph showed a left pneumothorax with a resolved right pneumothorax with chest tube in-situ. She underwent a right medical pleurodesis via pleuroscopy and a left video assisted thoracoscopy (VATS) bullectomy as well as surgical pleurodesis. The histologic examination of the lung tissue stained positive for human melanoma black-45 (HMB-45) and desmin.

Despite monthly injections of medroxyprogesterone she developed a recurrent right pneumothorax which required chest tube insertion. We initiated sirolimus at a dose of 2 mg daily for 12 months with blood levels maintained between 6.15 to 12.0 ng/mL and there was sustained effects on lung function and cystic lung lesions. The patient was a newly wed and was keen to conceive. She and her husband made an informed decision to proceed with pregnancy. She conceived spontaneously at 8 months post cessation of sirolimus. Her antennal course was uneventful with no exacerbation of respiratory status and she went on to deliver fraternal twins at the 30th week gestation. Her babies were delivered at 1.23 kg and 1.4 kg, respectively. Both required a longer period of stay in hospital. One was diagnosed with congenital pneumonia and stayed in hospital for weight gain while the other had extended spectrum beta-lactamase (ESBL) meningitis. Both were discharged well and reached their

developmental milestones. Baseline lung function before pregnancy; forced expiratory volume in one second (FEV_1) 1.39L (55%) FVC 2.14L (75%) FEV_1/FVC ratio 65%. Six-minute walk test (6MWT) was 420 metres. A repeat spirometry was performed 5 months post-delivery; FEV_1 1.23L, FVC 1.92L ratio 64% and the 6MWT was 396 metres. Despite the changes in FVC she had no significant deterioration of symptoms.

DISCUSSION

Pulmonary LAM is a rare disease of which occurs primarily in women of childbearing age. The median prevalence of LAM was reported at 4.9 cases/million female population (Harknett et al. 2011). Lymphangioleiomyomatosis is characterised by abnormal smooth muscle cells infiltrating the lungs and airways causing progressive cystic lesions in the lung and airflow obstruction. As the disease progresses, it can lead to respiratory failure and cor pulmonale. The most common presentation is pneumothorax occurring in childbearing women. Lymphangioleiomyomatosis can occur sporadically or in association with TSC.

Tuberous sclerosis is an autosomal dominant disorder usually associated with learning difficulties, behavioural problems, epilepsy, skin lesions, renal angiomyolipomas and encephalic lesions. Lymphangioleiomyomatosis as a pulmonary complication occurs infrequently with reported prevalence of clinically significance at 0.6 to 2.3% (Moss et al. 2001)

Pneumothorax is common in LAM. Up to 73% of patients with LAM will experience a pneumothorax in their lifetime (Oprescu et al. 2013). The pneumothorax recurrence rate following video assisted thoracoscopy (VATS) mechanical pleurodesis for primary spontaneous pneumothorax is around 5%; but in patients with LAM higher rates of recurrence can be expected (Maurer et al. 2007).

The current guidelines advocate treatment with sirolimus based on the MILES (Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus) trial which showed an improvement from baseline to 12 months of the forced vital capacity, functional residual capacity, serum vascular endothelial growth factor D (VEGF-D), and quality of life and functional performance with sirolimus (Mccormack et al. 2011).

There is a possible hormonal link evidenced by the presence of both oestrogen and progesterone receptors on the LAM cells (Mccormack 2008). Pregnancy has been shown to exacerbate LAM (Khaddour et al. 2019). Guidelines for LAM advices patients who are keen for pregnancy be informed of the increased incidence of pneumothorax, chylothorax and bleeding into the angiomyolipoma during pregnancy (Johnson et al. 2010). Pregnancy has been known to aggravate pre-existing LAM. Patients with LAM have also been reported to be at risk of worse pregnancy outcomes like premature births and miscarriages.

Sirolimus has been used safely in pregnancy with pregnant LAM patients reporting a more stable pregnancy

with its usage (Faehling et al. 2015). There have been reports of declining sirolimus level during pregnancy with levels 40% lower during pregnancy (Faehling et al. 2015). Further analysis of the MILES study showed sirolimus to be beneficial regardless of menopausal state, race baseline FEV_1 or TSC association (Gupta et al. 2019). Our patient discontinued the sirolimus prior to getting pregnant. Her blood levels on sirolimus was stable and well within the therapeutic treatment goal of 5-15 ug/L (Mccormack et al. 2011). Despite the typical course of expected decline of FVC, our patient went through an uneventful pregnancy despite discontinuation of sirolimus.

CONCLUSION

Lymphangioleiomyomatosis may not be a total contraindication to pregnancy. Sirolimus has sustained effects despite discontinuation of treatment. We describe a severe LAM patient with a history of recurrent pneumothoraces who successfully went through a twin pregnancy without any new pneumothoraces after cessation of sirolimus therapy.

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