Singapore Med J 1999; Vol 40(7):477-479

# A Breathless Lady with Lumpy Kidneys

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## ABSTRACT

**Tuberous sclerosis complex (TSC) is now known to be associated with pulmonary lymphangiomyomatosis (PLAM). Patients with either isolated PLAM or pulmonary involvement in TSC suffer from progressive respiratory failure and death within ten years of diagnosis. We report a case of TSC with PLAM, and a short review of recent literature regarding the conditions.**


**Keywords: respiratory failure**

## INTRODUCTION

Tuberous sclerosis is not a rare disease, with an incidence ranging from 1/9,000 to 1/170,000, and an associated spontaneous mutation rate of up to 60%[1].

We know the disease to be mainly of an autosomal dominant inheritance, of variable expression but high penetrance. There are few reported cases of asymptomatic obligatory carriers of the tuberous sclerosis complex (TSC) gene (which has yet to be definitively identified)[1].

The disease is now accepted as a complex syndrome with multiple organ involvement and the patient's clinical symptoms/signs may lead us to investigate a certain system. Mortality and morbidity in patients with TSC depend on the organ involved and the extent of the involvement. Though there are no specific measures for the prevention of deterioration of the different organs, it is mandatory to keep a close watch on the progression of the disease so that necessary interventions may be made.

One of the most common causes of death in a patient with TSC is progressive respiratory failure from the associated pulmonary lymphangiomyomatosis (PLAM)[2].

We report here, the first case of TSC associated with PLAM and a short review of the recent literature on the subject.

## CASE REPORT

Miss NBG is a 33-year-old lady who works at a factory in the production line. Her highest educational level achieved was primary school.

Until aged 22 in 1986, Miss N was perfectly healthy, and the only sign of her disease was her dermatological features, (ie. adenoma sebaceum and subungual fibromas) which she shared with her father and her brother. In the same year, she presented to a private hospital with generalised fits and a CT scan of her brain was done. It revealed calcified cortical tubers. Her symptoms have been controlled by *Tegretol* since then.

And again in the same year, she underwent an emergency laparotomy for abdominal pain in another hospital. The surgeons found a lobulated mass which occupied the space of her left kidney, bleeding into the retroperitoneal space. The mass was subsequently removed and the right kidney was spared because, though lobulated, it was not bleeding.

Histology of the left kidney, and CT scan of the abdomen (Fig 1) confirmed that our patient was suffering from angiomyolipomas of her kidneys, which is well known to be associated with TSC. CT scans of the abdomen during the next few years also revealed multiple haemangiomas in the liver.

In 1990, Miss N presented to a third hospital with severe shortness of breath. Chest X-ray revealed bilateral pneumothoraces and chest tubes were

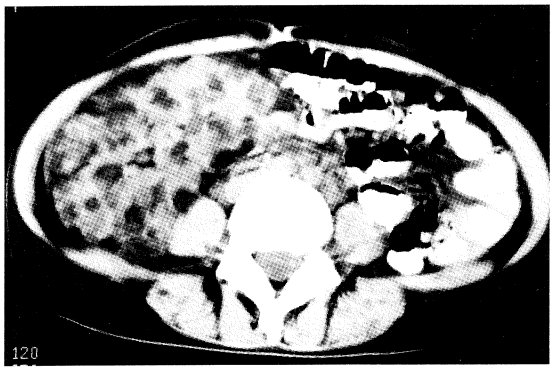


Fig 1a


Fig 1b

**Fig 1a & b** – Computed tomogram of the abdomen showing cystic changes in the liver and kidney.

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inserted. The right lung expanded very well but the left lung remained collapsed. Our patient then underwent a median sternotomy, and had two bullae stapled at the right apex. Tetracycline was infused into the chest cavity bilaterally.

Since then she had been under regular follow-up with a urologist, nephrologist and a cardiothoracic surgeon. Subsequent chest X-rays revealed recurrence of pneumothoraces on the left side (Fig 2). However, Miss N remained completely asymptomatic. She denied any cough, haemoptysis or shortness of breath.

In July 1997, a chest X-ray at our hospital showed bilateral pneumothoraces amounting to more than 50% on each side. She revealed that she was then more breathless for three days. Chest tubes were again inserted in both sides of the thoracic cavity. Again the left lung failed to re-expand adequately.

On review of Miss N's clinical history, the possibility of PLAM associated with TSC in her case was suggested. A high resolution CT scan of the thorax showed classical features of PLAM (Fig 3).

She underwent thoracotomy and an open lung biopsy was performed. Intraoperatively, multiple cysts were seen in the left lung and dense adhesions with thickening of the pleura were seen in the left thoracic cavity. The pleural adhesions were lysed and the left thoracic cavity was pleurodesed with talc aerosol. Histology of the lung tissue was highly suggestive of PLAMS, and oestrogen and progesterone receptors were mildly positive.

Currently, Miss N's clinical condition is stable and the chest tubes have been removed. We plan to initiate medroxyprogesterone once a baseline full pulmonary test has been obtained.

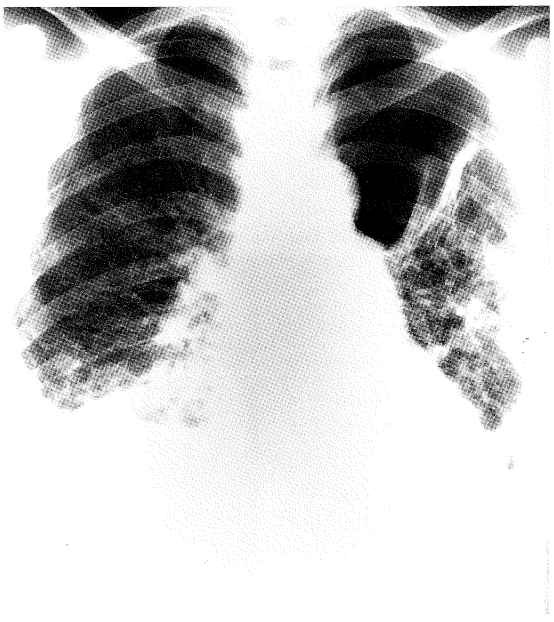

**Fig 2** – Chest X-ray of the patient.

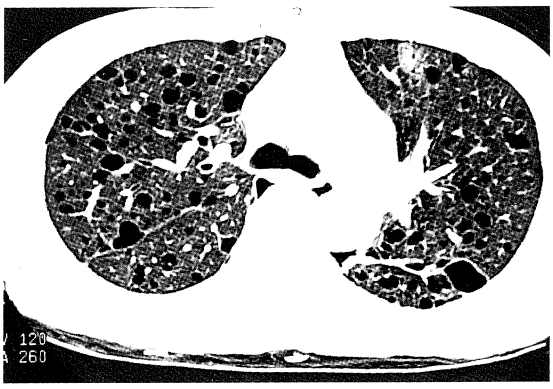


**Fig 3** – Computed tomogram of patient depicting classic 'Swiss cheese' appearance of the lungs.

## DISCUSSION

The first case report of a patient with TSC and cystic lung was in 1918 by Lutembacher, but he interpreted the bilateral pneumothoraces to be the result of metastases from fibrosarcoma of the kidneys.

In the years after Lutembacher, many studies have been done about PLAM as an isolated syndrome which strikes women of childbearing ages, and who die of progressive respiratory failure within ten years of diagnosis[3].

At the same time, the medical profession found out more about the involvement of lungs in patients with TSC. Numerous studies have come up with the conclusion that it is almost identical to that of isolated PLAM, whether in histology, clinical signs and symptoms, radiological features and clinical progression. Both are characterised by numerous parenchymal cysts whose walls contain abnormal proliferating smooth muscle fibers. They both cause pneumothoraces from air trapping, chylothorax from blockage of lymphatic drainage and haemoptysis from venular blockage. HRCT of both diseases reveal multiple cysts ranging from 1 mm to 5 cm scattered all over the lung fields, with no predilection for airways or vessels. Eventually, patients suffering from both conditions may die from progressive respiratory failure within ten years[3].

Recent review articles have suggested that TSC is a syndrome with incomplete penetrance, ie., there is a possibility of isolated expression of individual organ defect. This is especially true of PLAM, where patients are treated as if they are suffering from isolated PLAM and the diagnosis of TSC delayed for up to 16 years when the patients present with generalised fits. In other patients, their lung condition is wrongly diagnosed as asthma or emphysema. The condition of isolated PLAM is now thought to be a *forme fruste* of TSC. This is in keeping with the finding of PLAM in males. The predominance of females reported to have PLAM in the literature would reflect the hormonally influenced process and hence the successes with hormonal therapy[6].

In the past, the association of PLAMS was thought to be 1%, but a review by Mayo clinic revealed it to be as high as 2.3%[7].

In the presentation of pulmonary involvement in TSC, dyspnoea and pneumothorax are the most common. In asymptomatic individuals with TSC, the first sign of deterioration in pulmonary function may be spirometry showing an obstructive picture. In fact, there have been suggestions of using spirometry as a screening test for patients with TSC[4].

But what is the value of finding pulmonary involvement in TSC when eventually, the patients will perish from respiratory failure within ten years of diagnosis?

Although much is still unknown about TSC and its pulmonary involvement, previous experiences in treating PLAM may serve as a guide in treating patients who have pulmonary involvement in TSC.

The mainstay of treatment of PLAM has been that of hormonal manipulation since it occurs almost exclusively in pre-menopausal women[5]. Oophorectomy, tamoxifen, and progesterone have all been tried but the combination of oophorectomy and progesterone has been hailed as the most tested treatment. Tamoxifen has been rejected because of its possible agonistic effect on oestrogenic receptors[6]. In terminal stages, isolated case reports named lung transplant the only solution. However, there have been suggestions that PLAM may recur in the transplanted lung. Furthermore, patients with multiple organ involvement are deemed unsuitable for lung transplant.

In the last ten years, there have been reports of successes in the treatment of pulmonary involvement in TSC. In both isolated PLAM and PLAM associated with TSC, treatment only showed stabilisation of condition or resolution of symptoms and radiological features if the treatment was started early in the condition. If all the above is true, then an early diagnosis of PLAM must be made in patients with TSC. Past reports except for one, suggest that tissue diagnosis is needed in the diagnosis of PLAM, either by open lung biopsy or bronchoscopic lung biopsy[8].

At the moment, there are no reports on the justification of invasive techniques in obtaining a diagnosis of asymptomatic pulmonary involvement in TSC. Chest X-rays tend to be obvious only when there are pneumothoraces or pleural effusions and at later stages, appearances of cystic lesions. High resolution CT scan of the chest, being more sensitive and specific, may have a role in screening for asymptomatic pulmonary involvement in TSC[9]. This is definitely more diagnostic than a simple spirometry, but the financial implications may mean that spirometry may be the best first line option.

At the same time, actively looking out for features of TSC in patients with PLAM and vice versa may be a method of discovering and learning about the disease processes. By keeping a keen eye, we may be able to reduce mortality and morbidity.

Currently for Miss N, we are considering offering her hormonal treatment even though she is otherwise completely asymptomatic. We may also screen her family for organ involvement although they only reported minor skin involvement.

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