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CORRESPONDENCE

Silence of the LAM

To the Editors:

We read with interest the article by WARTH *et al.* [1] on mediastinal angiomyolipoma and tuberous sclerosis. Apart from mediastinal angiomyolipoma, lymphangioleiomyomatosis (LAM) can occur as part of the genetic condition tuberous sclerosis [2]. Since the first report by CORNOG and ETERLINE [3], LAM has been increasingly studied for the pathological processes involved in atypical smooth muscle LAM cell proliferation. However, it has been difficult to gain complete understanding of the natural history of LAM due to its rarity. LAM tends to progress slowly and ultimately leads to respiratory failure. Nevertheless, the clinical course of patients with LAM can vary, with 10 yr survival between 10–60% [2]. Some patients survive for 20 yrs following presentation [2]. LAM may remain silent until spontaneous pneumothorax occurs, which is the most frequently presenting symptom [4]. The indications for pleurodesis in this condition are not well established. In our experience, surgical pleurodesis is usually recommended for patients with recurrent or spontaneous bilateral pneumothoraces, but higher rates of recurrence can be expected for this group of patients [4]. In addition, pleural symphysis following surgical pleurodesis may make future lung transplantation impossible. Multiple diffuse blebs may be seen intraoperatively (fig. 1), alerting the clinician towards this condition.

Classically, a computed tomography (CT) scan shows multiple thin-walled cysts distributed throughout both lungs, although unilateral lung involvement has been described [5]. A CT scan can also help to detect other unsuspecting pathology [6].

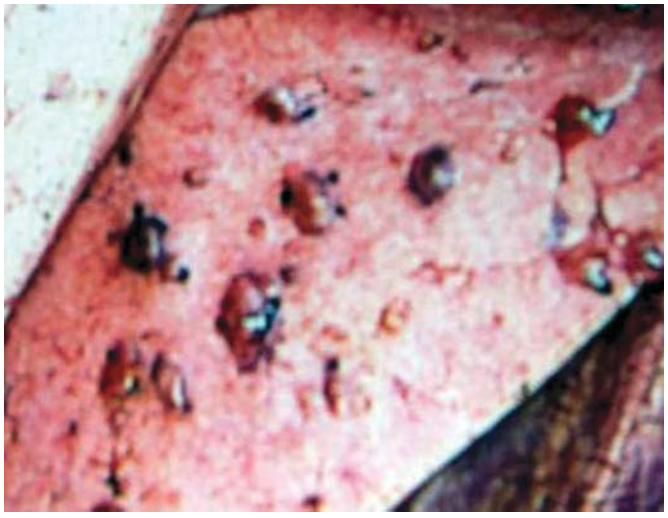

FIGURE 1. Intraoperative video-assisted thoracic surgery view of lymphangioleiomyomatosis on the surface of lung.

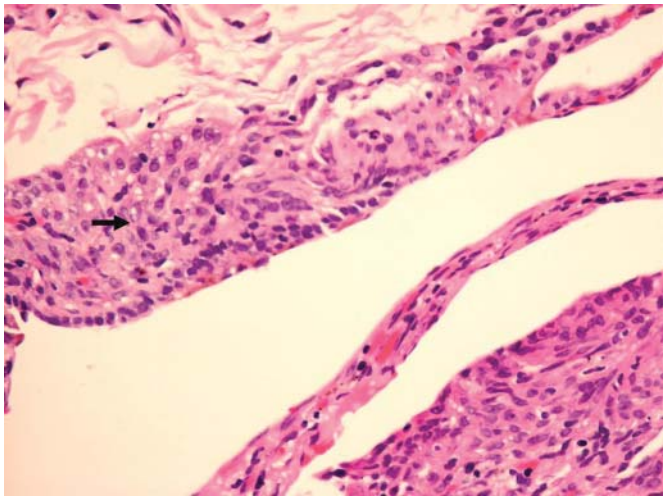

FIGURE 2. Histopathology section showing blood-filled cystic spaces with fascicular spindle cells (lymphangioleiomyomatosis cells) and vascular congestion. Interstitial proliferation (vascular and bronchial) and sub-pleural proliferation is also seen.

Pathological examination is required for confirmation of LAM, which can be obtained by transbronchial, percutaneous or surgical biopsy. We advocate video-assisted thoracic surgery biopsy with excision of any bleb and culprit lesion, particularly in the case of associated pneumothorax. The lung is characterised by cystic changes associated with proliferation of atypical smooth muscle cells (LAM cells), which can involve bronchioles, vessels and airspaces explaining, in part, the occurrence of pneumothorax, chylothorax and haemoptysis in these patients. (fig. 2) Positive HMB-45 immunostaining and the presence of oestrogen and progesterone receptors are also characteristics of LAM. Despite reports of various therapeutic regimens, none offer a consistently effective response. Corticosteroids and cytotoxic agents usually provide little benefit. Medical hormonal therapy (progesterone, tamoxifen, luteinising hormone-releasing hormone agonist) and surgical hormonal therapy (oophorectomy, ovarian radiofrequency ablation) have been used with variable responses [7].

For end-stage lymphangioleiomyomatosis, lung transplantation can be an effective treatment option, but recurrences in the transplanted lung may occur following lymphangioleiomyomatosis cell migration [7].

C.S.H. Ng, S. Wan, I.Y.P. Wan and M.J. Underwood
The Chinese University of Hong Kong, Dept of Surgery, Prince of Wales Hospital, Shatin, NT, Hong Kong, China.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Warth A, Herpel E, Schmähl A, *et al.* Mediastinal angiomyolipomas in a male patient affected by tuberous sclerosis. *Eur Respir J* 2008; 31: 678–680.
2 Johnson SR, Whale CI, Hubbard RB, Lewis SA, Tattersfield AE. Survival and disease progression in UK patients with lymphangioleiomyomatosis. *Thorax* 2004; 59; 800–803.
3 Cornog JL Jr, Enterline HT. Lymphangiomyoma, a benign lesion of chyliferous lymphatics synonymous with lymphangiopericytoma. *Cancer* 1966; 19: 1909–1930.
4 Taylor JR, Ryu J, Colby TV, Raffin TA. Lymphangioleiomyomatosis: clinical course in 32 patients. *N Engl J Med* 1990; 323: 1254–1260.
5 Avila NA, Chen CC, Chu SC, *et al.* Pulmonary lymphangioleiomyomatosis: correlation of ventilation-perfusion scintigraphy, chest radiography, and CT with pulmonary function tests. *Radiology* 2000; 214: 441–446.
6 Ng CS, Wan S, Lee TW, Yim AP. Cystic lesions of the lung: a forgotten menace. *Eur Respir J* 2005; 26: 748–749.
7 Taveira-Da Silva AM, Stylianou MP, Hedin CJ, Hathaway O, Moss J. Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. *Chest* 2004; 126: 1867–1874.

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Inhaled steroids and COPD

To the Editors:

We read with interest the paper by SUISSA *et al.* [1], in which he and his co-authors state that ''the effectiveness of inhaled corticosteroids in treating chronic obstructive pulmonary disease remains doubtful.'' They review the reported efficacy of inhaled corticosteroids (ICS), noting a lack of pulmonary function improvement but reduction in exacerbation frequency, and a meta-analysis showing reduced mortality [2]. However, they conclude that these findings could be biased by methodological problems. One form of bias that they highlight is failure to follow patients after premature withdrawal from randomised clinical trials. SUISSA *et al.* [1] opine that the TORCH (Towards a Revolution in COPD Health) [3] and OPTIMAL [4] studies have provided important evolution in understanding these issues. While both studies used intent-to-treat analysis, at least for the primary end-points, TORCH showed a nonsignificant trend towards improved survival and OPTIMAL did not show significant differences in the proportion of patients experiencing at least one exacerbation over a 12-month period.

Perhaps a more important form of bias highlighted by SUISSA *et al.* [1] is the effect of withdrawal of previously prescribed medications on entry into a randomised clinical trial. In the TORCH study, 48% of patients recruited were previously taking ICS (although SUISSA *et al.* [1] report 51%), whereas in OPTIMAL the proportion was 76% (although SUISSA *et al.* [1] report 77%). Because of the high frequency of patients already taking ICS on entry into these studies, they actually represent two comparisons: 1) continuation of ICS *versus* withdrawal of ICS, and 2) introduction of ICS *versus* no change in treatment. We agree that the results of this type of study are equally, if not more, likely to be influenced by the former comparison than the latter. Furthermore, as SUISSA *et al.* [1] point out, a difference due to the former comparison does not necessarily equate to efficacy in the conventional sense, as exemplified by the latter. In their analysis, SUISSA *et al.* [1] show a difference in exacerbation frequency due to withdrawal of ICS but no difference due to the introduction of ICS.

These issues are arguably just as pertinent in the interpretation of the INSPIRE (Investigating New Standards for Prophylaxis in Reducing Exacerbations) study, a recently reported comparison between an ICS/long-acting β-agonist combination and tiotropium [5]. The INSPIRE study was remarkable for its run-in phase, during which patients were given prednisolone 30 mg daily for 14 days to ''standardize their COPD management before randomization'' [5]. Rather than standardising chronic obstructive pulmonary disease management, this approach to study design surely represents a marked departure from recommended maintenance therapy for patients in clinically stable state and is, therefore, likely to amplify the phenomenon described by SUISSA *et al.* [1]. Furthermore, in the INSPIRE study the proportion of patients previously taking ICS was 50%. We consider, therefore, that the INSPIRE study also falls into the category of studies described by SUISSA *et al.* [1] as potentially biased by methodological problems and its conclusions should be viewed with caution.

In their paper, SUISSA *et al.* [1] suggest that trials of tiotropium might be subject to the same type of bias due to withdrawal of previously prescribed anticholinergic inhaler therapy prior to randomisation, although, to date, there is no scientific evidence to support such an implication. Access to the database of tiotropium clinical trials should enable a meta-analysis of exacerbations in subgroups that had anticholinergic therapy withdrawn at entry, compared with those that were naïve to anticholinergic therapy. Should such an analysis of tiotropium studies show a similar benefit in either group, then it will be reasonable to conclude that the benefits of long-acting anticholinergic therapy are genuinely due to introduction of the therapy rather than its withdrawal. Implications with regard to the efficacy of tiotropium should be reserved until such an analysis is published.

C.B. Cooper* and M. Decramer#
*David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA. #Katholieke Universiteit Leuven, Leuven, Belgium.

STATEMENT OF INTEREST

Statements of interest for all authors can be found at www.erj.ersjournals.com/misc/statements.shtml