Author’s response to reviews

Title: Lymphangioleiomyomatosis, multifocal micronodular pneumocyte hyperplasia, and sarcoidosis: more pathological findings in the same chest CT, or a single pathological pathway?

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To Sanjay Haresh Chotirmall, MD PhD

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Manuscript Title: Lymphangioleiomyomatosis, multifocal micronodular pneumocyte hyperplasia, and sarcoidosis: more pathological findings in the same chest CT, or a single pathological pathway?
Dear Editor,

We thank you for the opportunity to submit this revised version of our paper. We also thank the Reviewers for their helpful criticisms and suggestions, which helped us improve the manuscript. As you can appreciate in the “Manuscript” file, it has been significantly modified starting from comprehensive language editing.

We hope that you will consider this revised version suitable for publication in BMC Pulmonary Medicine.

Yours sincerely,

Prof. Fabiano Di Marco, MD, PhD

Reviewer 1: This case report adds to the limited and conflicting current knowledge on lymphadenopathy prevalence in TSC-LAM disease, whether link to sarcoidosis or not.

Major comments

The prevalence of lymphadenopathy in TSC-LAM and LAM varies from 0% to up to 50% (in a report back in 1989 by Sherrier et al). Although the authors innovatively proposed that the presence of multiple rare diseases challenge the concept of a potential common underlying mechanism via mTOR and MAPK pathway, the authors should stress that lymphadenopathy has been described (although not established) as a feature of LAM CT evaluation.

Authors: We agree with the reviewer. In a recent study, Tobino et al. found a prevalence of 9.4% for mediastinum and pulmonary hilum lymphatic lesions. Therefore, we added the following sentence in the text: “Lymphadenopathy, both thoracic and abdominal, has been described as another possible feature of LAM. For instance, a recent study on 138 patients with LAM, both sporadic and associated with TSC, found a prevalence of 9.4% for mediastinum and pulmonary hilum lymphatic lesions”. However, this evidence does not challenge our diagnosis of sarcoidosis, based on the result of the skin biopsy and the presence of bilateral mediastinal lymphadenopathy.

Reviewer 1: Minor comments: Line 34, Page 3 - Please indicate the timeline between initial diagnoses of LAM on chest CT scan versus recent clinical evaluation (Line 56)
Authors: The information was added in the text (Line58, Page 3).

Reviewer 1: Please pay attention to English usage and spelling ie Line 5, hystopathologic amongst many others.

Authors: The text has been extensively reviewed by a native English speaker.

Reviewer 2: The case report manuscript submitted by Di Marco et al. represents an interesting discussion of a rather unusual clinical case they encountered. Their manuscript describes a patient with reported prior history of autoimmune hepatitis, though no corroborating data are included to confirm that organ features consistent with the diagnosis of TSC, and with reported prior genetic testing revealing a TSC1 mutation (corroborating genetic test data on this not supplied in the manuscript). They also describe features of mediastinal and hilar adenopathy on chest CT radiograph, as well as patchy skin involvement with an apparent dermatitis. The skin process was by report biopsied, with some of the features of the histology described, but with no supportive histological images provided in the manuscript. The manuscript discussion of the patient's clinical circumstance and the test data raises a possible mechanistic link between sarcoidosis and TSC, the latter a disease for which there are substantial data directly linking mTORC1 dysfunction in disease pathogenesis. Di Marco et al. raise the possibility that sarcoidosis as well as TSC may be mediated in part by dysfunction or dysregulation of mTORC1, and reference a recent publication by Linke et al. in support of their pathogenetic speculation. The manuscript provides very little data to directly support the intriguing pathogenesis speculation offered by the authors. In addition, clinical features suggesting sarcoidosis are not typically encountered in TSC or LAM, nor are features suggestive of TSC or LAM typically encountered in sarcoidosis. So while their report offers some rather intriguing and interesting speculation about possible shared cellular dysregulation pathways playing pathogenic roles in both sarcoidosis and TSC, establishing a clear link between these two diseases is not possible from the material included in the manuscript. The manuscript does function as an interesting alert to both clinicians and clinician-scientists that there may in fact be a mechanistic link, but establishing that link would require much work, and is clearly beyond the scope of this manuscript.

Authors: We greatly appreciate the Reviewer’s comment on our manuscript. In the introduction section we added the results of the genetic analysis, which, together with the clinical data, confirms the diagnosis of TSC (page 3, line 24).

We agree that this paper should be considered an “alert” about a possible pathogenic link but that establishing this link would indeed need an extensive work, beyond the scope of a case report with limited length. This is why we have been very cautious in our conclusions, taking into
consideration also the possibility of the concurrent presence of the two conditions by chance, as follows: “Although at present it is not possible to demonstrate a common mechanism underlying LAM/TSC, sarcoidosis, primary biliary cirrhosis and autoimmune hepatitis, and their coexistence could well occur by chance, we might speculate that the dysregulation of the pathway involving mTOR and MAPK and their interaction may play a role in the alteration of the diseases. Further reports are needed to demonstrate our hypothesis.”

Reviewer 3: This is a well-written and interesting case report of a middle-aged female with TSC1 mutation with cystic lung disease and PBC/ autoimmune hepatitis presenting with granulomatous inflammation. The case presented had an extensive work up to tuberous sclerosis and had cortical tubers, facial angiofibroma, periungual fibroma and renal angiomyolipoma. Chest computerized tomography demonstrated cystic lesion/ nodular infiltrates and lymphadenopathy. Skin lesion showed granulomatous inflammation on biopsy.

Though the authors conclude the nodules are MMPH, these could represent nodular infiltrate due to sarcoidosis. The information available is not definitive for the conclusion made the writers.

Authors: Multiple diffuse pulmonary nodules/ground glass opacities in patients with TSC are more suggestive of MMPH (which was very common in patients with TSC, with a prevalence of 50% in our case series, Di Marco et al, Plos One 2016) than sarcoidosis. However, we agree with the reviewer that our diagnosis should be considered only “possible” without a lung biopsy. Of note, this aspect affects only the title we chose for our paper (intriguing for respiratory physicians), since the main message of our case report (i.e. the contemporary presence of PBC/autoimmune hepatitis, together with LAM/TSC and sarcoidosis) is not challenged by the presence or not of MMPH. If the reviewers think this aspect is important, we can change the title as follows: “A woman with lymphangioleiomyomatosis/tuberous sclerosis complex, sarcoidosis and autoimmune hepatitis/primary biliary cirrhosis overlap syndrome: the result of chance or a single pathological pathway?”

Reviewer 3: Sarcoidosis is a diagnosis of exclusion, and several sarcoid mimics need to be considered. Granulomatous inflammation occurs in cases of primary biliary cirrhosis / autoimmune hepatitis. The workup included in the manuscript is not complete to either establish the extent of sarcoidosis nor to exclude other causes of granulomatous inflammation…… What medications was the patient talking? Sirolimus-induced granulomatous inflammation has been described (PMCID: PMC3920426). Were other causes of granulomatous inflammation excluded such as fungal exposures, tuberculosis of GLILD associated with CVID? …. The discussion is all speculative and focuses on the association of mechanisms that link TSC-LAM to granulomatous inflammation while there is more literature on the association of autoimmune hepatitis and granulomatous inflammation (OR 6.7, PMID:19520873). Case reports also exist
that show a link between granulomatous hepatitis and PBC. ….. The reference list should include the association of autoimmune hepatitis/PBC with granulomatous inflammation to give the reader a more accurate reflection of the current status of literature.

Authors: We agree: a more accurate discussion of the differential diagnoses of skin granulomatous lesions is needed, but in the first version it was not included in order to respect length limits. The presence of GLILD associated with CVID has been ruled out, in presence of normal immunoglobulin levels, and so were HIV and the diagnosis of drug induced or infectious granulomatous lesions. We added this in the text.

Reviewer 3: Was the patient taking other medications for autoimmune hepatitis?

Authors: The patient was treated only with ursodeoxycholic acid (15 mg/kg/day) for autoimmune hepatitis

Reviewer 3: Was evaluation done for identifying dysregulation of Vitamin D metabolism (25 hydroxy and 1,25 dihydroxy vitamin D levels)?

Authors: We limited our evaluation to blood and urinary calcium levels

Reviewer 3: Was an evaluation done to determine for ocular or cardiac involvement?

Authors: There was no ocular or cardiac involvement. We added this in the text.