Reviewer's report

Title: Safe and effective use of nivolumab for treating lung adenocarcinoma associated with sporadic lymphangioleiomyomatosis: a rare case report

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Reviewer: Carles Escriu

Reviewer's report:

This case report describes the case of a young female smoker with a history of LAM resistant to oestrogen therapy and on Sirolimus before developing a synchronous lung cancer. There is a 2 year period of a stable, SUV high, apical lung mass where the patient was off Sirolimus treatment, before obtaining a diagnosis of lung adenocarcinoma. This was treated with stereotactic radiotherapy, then two lines of cytotoxic chemotherapy on progression and eventually Nivolumab, to which an excellent response was finally obtained. 18 months after starting Nivolumab, her LAM symptoms progressed and concurrent Sirolimus treatment was given with apparent clinical response.

In spite of the fact that the "highly immunogenic" (line 153) LAM had been stable while untreated for five years until Nivolumab therapy started, the authors conclude that "this case highlights the safe and effective use of nivolumab for managing metastatic lung adenocarcinoma that occurred in a patient with sporadic LAM".

This was a successful case that meets the high need to contextualize lung immune therapy in real-life practice, especially when confronted with rare co-morbidities, but fails to do it in a way that describes the many uncertainties inherent to a case report. Instead, it transmits a sense of causality, for example when hypothesising about the pathophysiological similarities of LAM with melanoma, and chooses to omit the possibility that Nivolumab could have triggered a LAM exacerbation.

Suggested corrections:

Line 102 - the SUVmax of the apical mass is described could only be obtained through a PETCT, and not with a CT as stated

Line 107 - please state that Sirolimus was not re-started

Line 106 - Biopsy of the apical mass revealed fibroelastotic scarring in 2013. It is not clear the reason why a second biopsy on a high SUV mass in a young smoker was not performed. There is
no indication of how often imaging was repeated before radiological growth in 2015, and it is not clear if it grew slowly or it was a sudden pattern of growth two years later (if it had grown earlier, it would have met the criteria for stereotactic radiotherapy before it was administered).

Line 121- Persistence of pneumothorax at 48 hours justifies surgical pleurodesis, not a 2-month hospitalization.

Line 130- Please state the patient's deterioration was attributed to LAM

Line 132- How often was the patient followed up and what investigations were done? Did the patient have regular lung function tests? Was there any evidence on toxicity of Nivolumab and Sirolimus combination? How was the ethical challenge of lack of evidence confronted?

Line 141 - The phrasing suggests risks and benefits were discussed amongst the medical team and not with the patient

Line 166 - The conclusion should state the possibility to administer Nivolumab in patients with LAM, the need for close LAM follow up while on Nivolumab treatment and the possibility of concomitant treatment of both afflictions.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Unable to assess

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
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No

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