Reviewer's report

Title: Nivolumab-induced thyroid dysfunction lacking antithyroid antibody is frequently evoked in Japanese patients with malignant melanoma

Version: 0 Date: 26 Oct 2017

Reviewer: Davide Mauricio Costa Carvalho

Reviewer's report:

General comments

The paper "Nivolumab-induced thyroid dysfunction lacking antithyroid antibody is frequently evoked in Japanese patients with malignant melanoma" reviews a series of 34 metastatic melanoma patients treated with Nivolumab. After excluding 10 patients, they analyse the data from 24 patients. Some of the patients had change from thyrotoxicosis to hypothyroidism.

The paper is very interesting reporting a higher prevalence of the disorders in a Japanese background population. The paper is carefully written and with appropriate bibliography.

Specific comments

1 - The authors state that "autoimmune thyroid disease is common, but the mechanism of its development is not fully understood. I think that the authors should go a little bit more deeper in the evaluation of different thyroid antibodies.

Nowadays there are different laboratorial assays for TRAbs detection, each one with different diagnostic effectiveness, limitations and clinical utility. (Barbesino G, Tomer Y. Clinical review: Clinical utility of TSH receptor antibodies. J Clin Endocrinol Metab. 2013 Jun;98(6):2247-55;

TBI assays only permit to identify the presence of TRAbs, indicating its concentration in the serum of patient. With this type of assay, it is not possible to discriminate antibodies with a stimulatory action over the TSH-receptor from antibodies with an antagonist/weak agonists action or neutral action. (Gupta MK. Thyrotropin-receptor antibodies in thyroid diseases: advances in detection techniques and clinical applications. Clin Chim Acta. 2000 Mar;293(1-2):1-29.; Kahaly GJ. Bioassays for TSH Receptor Antibodies: Quo Vadis? Eur Thyroid J. 2015 Mar;4(1):3-5.)

Using a bioassay, it is possible to specifically detect the type of autoantibody present in patient serum. Historically, bioassays had been used mainly as research tools to study the pathophysiology of GD.( Kahaly GJ. Bioassays for TSH Receptor Antibodies: Quo Vadis? Eur
Thyroid J. 2015 Mar;4(1):3-5.) Its generalized use had also been limited by feasibility and cost issues. However, more recently, these assays are becoming more easy to perform and its clinical utility in management of GD have been demonstrated, favouring its practical implementation in some clinical situations. Kahaly GJ. Bioassays for TSH Receptor Antibodies: Quo Vadis? Eur Thyroid J. 2015 Mar;4(1):3-5.)

2 - Although the main objective is to evaluate the thyroid aspects, I think they should give an information if they observe any other immune endocrine adverse events / hypophysitis, adrenal insufficiency)

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

**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?**
If not, please explain in your comments to the authors.
Yes

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Not relevant to this manuscript

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