Dear Editor of Acta Médica Portuguesa, Prof. Dr. Rui Marinho

Many thanks for the possibility to review our article, and also for all the suggestions and comments provided by the reviewers. Please find attached the amended version of our manuscript (a version with identification of the changes and a clean version). The detailed comments in reply to the referees are given below.

Reviewer A

The title is not totally in accordance with the paper. I think in this case the authors highlight the importance of the recognition this diagnosis but they do not write about the diagnostic and management challenges.

We understand the comments of the reviewer and indeed one relevant message of our manuscript is to provide awareness of this diagnosis. However, we do feel that we have illustrated diagnostic challenges in the description and discussion of this clinical case, which includes not only the caveats of diagnostic tools but also challenges in the diagnostic recognition/expertise by clinicians, perhaps the most important diagnostic challenge. Management has been briefly discussed, as we have approached controversial topics regarding not only hormonal replacement, but also issues such as high vs low dose of corticosteroids, and the appropriateness of stopping vs maintaining the ipilimumab. Thus, we feel that our title is appropriate and suitable with what has been discussed in the article, so we would like to keep our original title. However, we will leave the ultimate decision to the Editor.

1. What was the dose of levothyroxine? Do you have TSH and T4 before the ipilimumab? Do you have thyroid antibodies?

She was on 75mcg of levothyroxine. That information has now been added to the case report. Unfortunately, we do not know what was the thyroid status before surgery, nor the thyroid antibodies, as there was no reason the measure these before the treatment, and the patient was known to have post-thyroidectomy hypothyroidism and was on replacement therapy.

2. What was the value of ACTH ?

ACTH was not measured. Nevertheless, the ACTH deficiency is unquestionable as regarded by the basal serum morning cortisol and the Synacthen test, there was no pigmentation, and no reason to suspect primary adrenal failure..

3. The gonadotrophins were low for a menopausal women. I think it would be better to emphasize that.

We appreciate this point, and indeed now better emphasize this; the third paragraph now reads: "The involvement of the gonadotrophin axis was suggested by the low concentrations of gonadotrophins, contrary to what is expected for a menopausal women". Moreover, in the Table 2 the reference range for FSH was changed for the normal reference for menopausal women.

3. What is the importance for the diagnosis of the hypophysis antibodies?

Currently, there is no value of these antibodies for the diagnosis of ipilimumab-hypophysitis. Also, for the diagnosis of lymphocytic hypophysitis, the clinical value of these antibodies is very low as these assays have very low sensitivity and diagnostic specificity. (see Falorni A *et al* –reference 4). We decided to note this in the revised article, and write in the second paragraph of the Discussion: "There is no reliable serologic test available to aid/make the diagnosis of ipilimumab-induced AH, although it is presumed that pituitary antibodies may be involved[11]. Currently, this diagnosis is best made based on clinical suspicion (including the chronological relation with ipilimumab), laboratory evaluation of pituitary function and a consistent MRI[11]."

4. Do you have the ophthalmological study?

An ophthalmological study was not requested. Campimetry by confrontation was performed clinically, and visual fields were full.

5. The figue 1 is the same of the original article, it was not adapted. Do you have permission to do that?

The authors have requested permission to use the figure. The figure is an original figure from a paper of the second author, and the European Journal of Endocrinology, where it is published, have given permission subject to acknowledgement.

6. In this case there was any recovery of pituitary function?

In our case there was no recovery of pituitary function. We have added this information to the discussion: "In our case there was no recovery of the pituitary function, and therefore the patient remains on glucocorticoid replacement."

Reviewer B

O caso clínico é muito interessante, encontra-se bem redigido e numa linguagem simples e clara. A temática é atual, chamando a atenção para a necessidade de focar a atenção nos eventuais efeitos laterais das novas terapêuticas imunomoduladoras, no sentido do diagnóstico e tratamento precoces.

Sugeria a leitura do artigo – Tiu C, Pezaro C, Davis ID, Grossmann M, Parente P. Early recognition of ipilimumab-related autoimmune hypophysitis in patients with metastatic melanoma: Case studies and recommendations for management. Asia Pac J Clin Oncol. 2015 Jun; 11(2):190-4. doi: 10.1111/ajco.12348. Epub 2015 Apr 9.
We note the publication, and we have now included it in our reference list (article 15). Many thanks for the suggestion.

Breve discussão acerca do risco acrescido desta doente com hipocortisolismo e a fazer terapêutica de substituição com levotiroxina.
We thanks the comment. Indeed, in patients requiring hydrocortisone and levothyroxine, the replacement should include first hydrocortisone, and at later stage levothyroxine. The other way around may trigger an Addisonian crisis, as levothyroxine improves kidney function and glomerular filtration, which may accelerate the excretion of cortisol. That is truly important for patients with concomitant autoimmune thyroiditis and Addison disease. In our case, we feel that the discussion of this specific point should be omitted as the patient was on a normal and adequate dose of thyroxine prior to the secondary adrenal insufficiency.

O tratamento com ipilimumab está também associado a desenvolvimento de patologia tiroideia. A doente efectuou estudo da hemitiroide direita? Alguma alteração de novo? Auto-imunidade de novo (anticorpos anti-tiroideus)?
Histological analysis was of multinodular goitre. There was no reference to lymphocytic thyroiditis from the pathology report, and also she just started levothyroxine following surgery. Unfortunately, we also do not have available thyroid antibodies, so we cannot provide a solid and clear view regarding this issue. Nevertheless, as there was no need to change levothyroxine doses at/after the diagnosis of Ipilimumab-hypophysitis, assessed by the measurement of thyroid hormones (not TSH), we can speculate that eventually there was no autoimmune involvement of the thyroid. However, as mentioned that cannot be definitely affirmed.

Havia antecedentes familiares de patologia auto-imune / endocrinopatia?

There was no familial history of endocrinopathy or autoimmune diseases. A sentence has been added to the first paragraph of the case report: "She had no familial history of any endocrinopathy or autoimmune disease".

Uma vez que o melanoma metastiza frequentemente para o cérebro, seria também interessante discutir um pouco o diagnóstico diferencial com metástase hipofisária. Embora a biópsia seja o gold standard é difícil efectuá-la, pelo que as características da imagem RM são normalmente sugestivas, assim como a resposta ao tratamento.

A brief discussion on the differential diagnosis with metastatic disease has been added to the fourth paragraph: "A metastatic lesion must be considered in patients with malignant melanoma with evidence of pituitary enlargement (with or without hypopituitarism). The absence of diabetes insipidus and the improvement following glucocorticoids is suggestive of AH; continuous growth despite corticosteroids favours the hypothesis of metastatic lesion. Although a biopsy is the gold standard to differentiate these two entities, it is rarely needed as the clinical behaviour, MRI findings, response to therapy and follow-up reassessments allow an accurate diagnosis in the majority of the cases[2]."

Reviewer C

Quer dizer 4 administrações com intervalos de 3 semanas? Embora se compreenda como está descrito parece fazer de cada vez 4 admistrações.

Line 5, Resumo: This sentence has been changed as suggested by the reviewer "…(quatro administrações com intervalos de 3 semanas)…"

It wooul be usefull to describe the exact posology: 10+5+5?

Line 15, Case Report: Information regarding the exact posology was added. We now report: "(20mg/day in three divided doses: 10+5+5mg)".

Line 17, Discussion: The word secretion was added, as suggested by the reviewer: "… more vulnerable to ipilimumab because ACTH and TSH secretion seem to be invariably lost in most cases…"

The word "begun" was corrected.

In Table 2*: Sugestion to add ACTH baseline levels.*

ACTH was not measured, so we cannot add it. Nevertheless, the ACTH deficiency is unquestionable as regarded by the basal serum morning cortisol and the Synacthen test.

In Figure 2: *I would suggest to discuss this in the discussion as the suggestion of a microadenoma is not convincing.*

The images were again reviewed by a neuroradiologist. It was felt that we cannot assume unequivocally that there is a microadenoma (as also it cannot be visualized in the image A that we provided). The suggestion of a microadenoma is thus controversial (could be just kind of "pseudonodule" from the autoimmune process), so we felt that the mention of this eventual microadenoma should be excluded. Therefore, the legend of the figure has been changed accordingly.

All alterations that were made are noted by being outlined in yellow. We attach the manuscript with the changes identified and also a final 'clear version' for your convenience.

Once again thanks for the recommendations and suggestions, which we consider have enhanced the quality of our article.

Lisbon, 9th September 2015

Best wishes

Pedro Marques