Author's response to reviews

Title: Ectopic ACTH secretion associated to a well-differentiated peritoneal mesothelioma. Case report.

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Author's response to reviews: see over
Dear Dr. Timothy Shipley. Executive editor of BMC Endocrine Disorders.

Author’s response to reviews

Title: Ectopic ACTH secretion associated to a well-differentiated peritoneal mesothelioma. Case report.

Version: 1 Date: 20 March 2015
Reviewer: Tatsuya Kondo

As suggested by one of the reviewers, we added the following points:

Major Compulsory Revisions

1. Midnight cortisol levels have to be evaluated. The loss of cortisol diurnal variation is important information for the diagnosis
   - Response: (Line 92-93) diagnostic tests showed the following data: urinary free cortisol: 186.5 µg/day, AM serum cortisol 21.83 µg/dL and midnight serum cortisol 16.09 µg/dL

2. Identification of ACTH producing tumor can be achieved by PET-CT scan. Therefore, CT and/or PET-CT images can be shown.
   - Response: (Line 332-336) FIGURE 1. Abdominal computed tomography (CT) showed a bilobed image with protrusion through the umbilicus, with attenuation coefficients of 3, 7 and 45 HU; after administration of contrast enhancement they reached 6, 16 and 88 HU. Multiplanar reconstructions showed that its origin was intra-abdominal, adjacent to a loop of small intestine, and the possibility of a mesothelioma was considered.

3. Although serum cortisol levels are not that high to be a life threatening, the use of metyrapon could be considered.
   - Response: (Line 119) As mentioned in the case presentation, the patient’s hypercortisolism has been controlled with ketoconazole, as in our country metyrapone is unavailable.

4. The author particularly discussed the differential diagnosis of EAS from Cushing’s disease of ACTH producing pituitary adenoma. Identification of EAS can be done by combination methods not only depending on high dose dexamethasone test. Discussion about PET scan or OctreoScan may be included.
   - Response: (Line 154-193) If the diagnosis of Cushing’s disease is excluded after BIPSS, the next step is to perform a CT scan or MRI of the neck, thorax, abdomen and pelvis to identify the non-pituitary ACTH-producing tumor [14, 17]; however, it has been described that in up
to 20% of patients the site of ectopic ACTH secretion cannot be identified. Because most neuroendocrine tumors express receptors for somatostatin, some case reports have mentioned the use of somatostatin receptor scintigraphy (SRS) in order to identify the origin of the ectopic ACTH secretion; nonetheless, Tabarin et al, reviewed 20 cases of ectopic ACTH secretion published in the literature finding that in 18 of the 20 cases, the tumor was visible using more conventional methods (CT scans and MRI), as well as SRS. The same authors present a series of 12 patients with ectopic ACTH secretion who underwent serial CT or MRI scanning and SRS, with the latter resulting in findings in only four of the patients, but in two of them the tumor detected both by SRS as by conventional imaging, was not the origin of the ectopic ACTH secretion, with the primary tumor remaining unknown. Another patient dies before the tumor, identified using SRS, could be resected and, in the last case, the image seen as abnormal in SRS turned out to be a carcinoid metastasis from an unknown primary site, unidentified by conventional imaging [18]. In the series by Doi, et al, 50% of tumors causing ectopic ACTH secretion were identified through CT or MRI, and 11 of the 16 cases presented underwent somatostatin receptor scintigraphy (SRS), four of which were positive (36%), with only one (11.1%) positive to [18F] fluorodeoxyglucose-positron emission tomography (FDG-PET) [4]. On the other hand, in the series of patients published by Ejaz, et al, CT or MRI identified the origin of the ectopic ACTH secretion in 67.5%, failing to find it in four patients in spite of performing CT, MRI, octreoscan and FDG-PET [13]. In another series of 19 patients, the usefulness of SRS with In 111 octreotide and Ga 68 DOTATATE PET-CT was evaluated, being positive in only 7 of these patients, 4 of which had undergone a previous CT that had shown the sites of abnormal uptake, and another in which the MRI had also shown an abdominal tumor; one more who had already undergone resection of a mediastinal mass and lymph nodes without showing clinical improvement underwent SRS which showed lymph node and bone metastasis. The last one had a pulmonary tumor, diagnosed with Ga 68 DOTATATE and had previously undergone a CT that failed to reveal the tumor. The authors suggest that performing SPECT or SPECT/TC imaging would improve the sensitivity of diagnosis with the planar images of SRS and propose that the images with Ga 68 peptide may offer better results in localizing ectopic ACTH-producing tumors than those performed with In 111 octreotide [19]. There are, to date, several case reports in which imaging with Ga 68 DOTATATE have identified the tumor secreting ectopic ACTH [20, 21, 22] but it must be remembered that case reports involve a selection bias per se in evaluating
the sensitivity of a diagnostic tool. Most authors currently coincide that once the ectopic secretion of ACTH is confirmed through BIPSS, imaging techniques such as CT or MRI should be preferentially employed in an initial stage as most tumors will be shown by their use. In the case here presented, abdominal CT evidenced an intra-abdominal tumor and the possibility of a mesothelioma was considered as the most likely, leading to an exploratory laparotomy in the patient, without performing other imaging tests, as SRS or PET/CT are difficult to access in most of our country.

5. The authors could discuss why this EAS case was no so aggressive compared to the EAS usually seen as progressively active to produce high amount of ACTH/cortisol. Histological evaluation could be included in Discussion.

- Response: (Line 194-201) Finally, the histological diagnosis of peritoneal mesothelioma was performed on the basis of a positive staining for keratin markers such as calretinin and thrombomodulin, as well as negative staining using markers for adenocarcinoma such as carcinoembrionic antigen (CEA), CA-125 and CK 5/6. Calretinin is expressed in normal and neoplastic mesothelial cells, with some authors reporting positive staining for this protein in 80% of mesotheliomas with a specificity close to 100% while, for thrombomodulin, some studies have reported a positivity of 80% in mesotheliomas and only 15% in adenocarcinomas. The sensitivity also depends on whether mono or polyclonal antibodies are employed, as well as the tissue fixation in large specimens [25, 26].

6. Minor Page 6, line 183, “testis” should be test is.

This line was corrected

Review #2 has no suggested changes for the manuscript.

The present manuscript has not been published or submitted to any other journal.

Yours sincerely, the Authors