Title: Transient hypercortisolism and symptomatic hyperthyroidism associated to primary hyperparathyroidism in an elderly patient: case report and literature review

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

The paper entitled: “TRANSIENT HYpercORTISOLISM AND SYMPTOMATIC HYPERTHYROIDISM ASSOCIATED TO PRIMARY HYPERparathyroidISM IN AN ELDERLY PATIENT: CASE REPORT AND LITERATURE REVIEW” has been revised and corrected according to the Editor’s and reviewers’ observations.

Editor’s additional request:
(1) Please provide an abstract formatted according to the guidelines for authors <http://www.biomedcentral.com/info/ifora/abstracts>. Potential referees will be asked to review the manuscript having seen only the title and abstract, so it is important that these are both informative and concise.
Abstract revision has been made.

(2) Please do not upload cover letters as additional files. They form attachments to the main manuscript.
Ok, I am sorry.

Reviewer’s report:
Reviewer #1:
This case report provides details of an elderly man presenting with marked hypercalcaemia and pulmonary emboli. The elevated calcium was found to be due to hyperparathyroidism and dehydration. Scans suggested a left lower parathyroid thyroid adenoma, but ultimate histology is stated to have shown hyperplasia. He underwent 3-gland parathyroidectomy, and had transient post-operative thyrotoxicosis due either to the Yod Basedow phenomenon or surgical trauma to the thyroid (these possibilities are not able to be distinguished from the data provided). The patient also had a period of hypercortisolism with elevated ACTH probably due to stress, although the authors also propose temporary parathyroid/calcium-driven hypercortisolism.
My feeling is that this is a case report of primary hyperparathyroidism, generally well managed (although with renal impairment I would have favored use of Pamidronate rather than Zoledronate in initial treatment). The thyroid and adrenal aspects, although interesting, are readily explained. The main point of general interest is the persistence of activation of the HPA axis beyond the immediate stress of the acute illness and surgery, but with his age and comorbidities, it is likely the prolonged hypercortisolism was related to ongoing illness and stress.

If the report is to be published there are a number of errors of spelling or expression that require revision and the discussion could readily be shortened.

Thank you for your annotations. We reviewed the Discussion section. One of the purposes of this clinical case was to report the possible derangement of cortisol secretion in PHPT, especially in elderly patients, and to suggest its involvement in cardiovascular, metabolic and psychiatric complications associated.

Rehydration was the first measure to take in this patient, not only to correct dehydration and improve renal failure, but also to dilute calcium excretion. Bisphosphonate administration was effective in reducing calcium levels and bone resorption, in particular recent controlled trials demonstrated the superiority of zoledronate compared with previous treatments (Smith MR at al., Cancer Treat Rev 2005).

In Discussion section (lines 125-129), we added this sentence to explain our therapeutic choice. Patient’s slight renal failure was well resolved after adequate hydration and did not prevent zoledronate administration.

Language and wide Discussion revision have been made.

**Reviewer #2:**

The authors present a case of various endocrine diseases which concomitantly occurred: severe primary hyperparathyroidism followed by hyperthyroidism and hypercortisolism. It is a truly remarkable case of apparent separate endocrine disease which may be more related to each other than would been estimated in advance.

Major compulsory revisions:
1. the diagnosis of hypercortisolism is only pursued in case of hypercortisolistic stigmata. This is not properly described in the case report. (lines 71-73)
This is a general rule because otherwise intermittent stress-related disorders are confused with Cushing syndrome. May be the authors would comment on this. I would not have considered measuring cortisol in this case, to avoid this pitfall.

Thanks for your comments.
We reviewed the Discussion section related to HPA axis and the suspicion of Cushing’s syndrome. In particular, lines 178-184:

In our case, HPA axis was evaluated because of multiple co-morbidities of the patient.
The data suggestive of Cushing’s syndrome were the incidental pulmonary thromboembolism, the uncontrolled hypertension and diabetes and the evidence of a pituitary microadenoma; however, the absence of typical stigmata and the presence of many confounding factors made the diagnosis uncertain. After discharge, further investigations excluded a Cushing’s syndrome, but the slow normalization of HPA axis only after four months seems to be related to the resolution not only of the acute stressful condition but also of PHPT.

2. Iodine induced hyperthyroidism is more frequent on patients with underlying thyroid disorders. Please provide a description of the thyroid gland at presentation. (size, nodules, pathological neck lymphoma)
Thyroid ultrasound description has been added (lines 84-85)

3. The level of PTH is very as is the presenting calcium concentration. In the differential diagnosis parathyroid carcinoma must be considered. Can you comment on the histological examinations. Considering the amount of radiological and nuclear examinations, did you find brown tumors?
The biochemical/clinical presentation could also raise the suspicion of parathyroid carcinoma, which was excluded by the histological examinations.
This sentence has been added in Discussion section (lines 124-125)
Patient did not suffer for bone pain (as added in line 72), skeletal deformities and/or pathological fractures, which could be considered a bone disease. All the radiological exams did not find brown tumors (line 89) and for these reasons we did not perform other investigations.

Minor Essential Revisions

1. the language needs some adjustments at several places.
   Done

2. The addition of ultrasonography and 131-I scan are of little added value. Please consider only a description in the test.
   Done

3. The paper is a rather bulky. Please consider shortening the discussion.
   Done

All authors have read and approved the submission of the manuscript; the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.

The authors have nothing to disclose.

Best regards,

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