Author’s response to reviews

Title: Spontaneous adrenocorticotropic hormone (ACTH) normalisation due to tumour regression induced by metyrapone in a patient with ectopic ACTH syndrome: Case report and literature review

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Author’s response to reviews:

Response to the reviewer 1

‘This paper describes a case of ectopic ACTH syndrome (EAS) in which the tumor reduced in size and ACTH reduced during therapy with metyrapone. These results are extremely surprising, and go against common expectation that ACTH level would either increase or not change upon reduction of cortisol burden by a steroidogenesis inhibitor. The authors describe other similar reports where similar event was described.’

As shown in Table 1, we reviewed 10 reported cases, including our case, of ectopic ACTH production that was suppressed by steroidogenesis inhibitors. All patients included in Table 1 showed a decrease in ACTH and cortisol/UFC levels to normal ranges after administration of metyrapone or ketoconazole. To specify that not only cortisol/UFC levels but also ACTH levels in all the patients were suppressed, we added the values of actual ACTH and cortisol/UFC levels before and after the initiation of metyrapone or ketoconazole to Table 1.

‘One has to wonder if this event was just coincidental, and that tumor infarcted independently. The authors do address this possibility.’
We discussed the possibility that tumour haemorrhage or infarction can be the cause of spontaneous remission of ectopic ACTH-producing tumour on page 11, line 14. We also added the following sentences:

‘High or low intensity, indicating haemorrhage or infarction, respectively, had not been found in the lung tumour by consecutive CT. The lung tumour gradually shrunk without a mixed pattern suspected to have haemorrhage or infarction.’ on page 11, line 17.

Minor points:

1. Case presentation line 16 ‘after stimulation with 8 mg of dexamethasone’ should read ‘after suppression...’

   We have revised the queried instance to ‘after suppression with 8-mg dexamethasone,’ on page 7, line 5, as suggested by the reviewer.

2. Just below, the 8 mg test is done to differentiate Cushing disease from EAS. As such it does not necessarily suppress to below 1.8. I would just write that lack of suppression by 8 mg of dex is consistent with EAS.

   We revised this instance as follows:

   ‘To differentiate between Cushing disease and EAS, an overnight 8-mg dexamethasone suppression test was performed. ACTH and cortisol levels were 184.8 pg/mL and 76.5 μg/dL, respectively, before the administration of dexamethasone. ACTH and cortisol levels 12 h after suppression with 8-mg dexamethasone were 176.7 pg/mL and 67.2 μg/dL, respectively. Lack of suppression of ACTH and cortisol by 8-mg dexamethasone is consistent with that with EAS.’ on page 7, line 2.

3. Following page, line 22. ‘its content’ maybe ‘its level’

   We revised this instance to ‘the level.’ on page 8, line 6.

Response to the reviewer 2

‘Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.’
We have included all comments in the text box of the Editorial Manager.

‘The main problem is the nature of the lung nodule whose biopsy, according to the authors did not reveal cancer cells: but which was the response of the pathologist? Which other cells/tissue was found?’

On page 8, line 9, we have added the following sentences:

‘Brush cytology using bronchoscopy showed only few neutrophils, dust cells, ciliated columnar cells, and squamous cells, and no malignant findings were found. Second, CT-guide biopsy was performed. Histological examination showed organising pneumonia-like reaction, thickening alveolar wall due to fibrosis, and accumulating histiocytes in the alveoli. Malignant findings were not found even at this time. Fungus were not found by Periodic acid-Schiff and Grocott staining. Subsequently, we tried CT-guided lung biopsy. However, the specimen did not include the lung tissue and only included pleura and muscles of the chest wall.’

Please let us know if this section needs to be concise.

‘In the response of the CRF stimulation test, ACTH levels are reported as basal and the lowest level. This is contradictory: being a stimulation test, the response is evaluated on the highest level.’

We have revised this instance to report basal and the highest level as follows: ‘highest ACTH level during the 120-min stimulation test, 214.0 pg/mL.’ on page 3, line 16 and page 7, line 9.

‘Why, among the tumor markers, chromogranin A was not considered?’

Chromogranin A is useful as an indicator for pheochromocytomas; however, chromogranine A cannot be commercially tested in Japan.

Minor points: ‘Page. 8, line 16: dexamethasone is used for a suppression, not for a stimulation test.’

We have revised this instance to ‘after suppression with 8-mg dexamethasone’’, on page 7, line 5, as suggested.
Page. 9, lines 7-10: what does it mean the enlargement of the lung tumor? How was it detected? The association of the tumor enlargement with the increase in ACTH is not diagnostic, as reported, for an ACTH secreting tumor.

The lung tumour enlarged to 5-cm-diameter mass that was detected by CT, as shown in Fig.S1. Along with enlargement of the lung tumour, the ACTH level was increased to 358.5 pg/mL. We added the following sentence: ‘CT detected enlargement of the lung tumour as a 5-cm-diameter mass.’ on page 8, line 1. We have also revised the timeline, adding ‘day 14’ in the time course and ‘tumour enlargement’ in the box.

Please let us know if Fig.S1 needs to be included in the body.

Pag 9, line 19-22: what does content mean? Concentration? Level?’

We revised this instance to ‘the level.’ on page 8, line 6.

Pag. 9, line 26: Gallium scintigraphy: please specify the somatostatine analogue molecule’.

We added information about gallium scintigraphy (67Ga-citrate) on page 8, line 7 and somatostatin scintigraphy (111In-Pentetreotide) on page 9, line 5. At the beginning, only gallium scintigraphy was performed. Somatostatin scintigraphy could not be performed during hospitalisation because it was not available at our hospital. After her discharge, somatostatin scintigraphy was available. We have also added this information in the figure legend.

Pag. 4 line 42 and pag. 7 line 45: Left lung

We have revised both of these to ‘left lung’ on page 3, line 13 and page 6, line 14.