Author's response to reviews

Title: Isolated adrenocorticotropic hormone deficiency developed during chemotherapy for gastric cancer: a case report.

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Version: 2
Date: 1 January 2014

Author's response to reviews: see over
Referee 1

Reviewer's report

Title: A patient with gastric cancer presenting with isolated adrenocorticotropic hormone deficiency during chemotherapy: a case report

Version: 1 Date: 10 December 2013

Reviewer: Hiroyuki Tamiya

Which of the following following best describes what type of case report this is?: Other

If other, please specify:

Educational case

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: Yes

Does the case report have diagnostic value?: Yes

Will the case report make a difference to clinical practice?: Yes

Is the anonymity
This case is gastric cancer patients coexisted with IAD. It will very educational to medical practitioners who are non-endocrinologists. However, I have a little bit doubt about diagnosis "IAD" is correct.

Please clearly write the important points about IAD and other endocrinological explanations in the manuscripts.

1. Diagnosis of IAD is really correct? Many missing informations remains. How about eosinophil counts on first blood tests?

   Eosinophil was normal limits in this patient. Although the presence of eosinophilia aids diagnosis of IAD as referee indicates, it is not the essential finding for definite diagnosis of IAD. Further, it is difficult to evaluate eosinophilia accurately because of chemotherapy.

   How about other 3 anterior pituitary hormonal test? You cannot say that spare ability of other 3 pituitary hormones are maintained without TRH, GRH, LHRH tests.

   Although the defined criteria for the diagnosis of IAD do not exist so far, we agree that what the referee says is correct. We did not perform TRH, GRH, LHRF tests in this case, because we consider the possibility of
pituitary apoplexy which has been reported as the side effects of TRH, LHRF tests. This case was a high-risk patient with poor prognosis due to metastatic gastric cancer. For these reasons, we avoided these stress tests. The plasma levels of all anterior pituitary hormones except for ACTH were slightly elevated. We think it is possible to diagnose IAD in this case combined with the result of CRH test. Actually, several reports about IAD in the past did not perform TRH, GRH, LHRF tests.

How about patient physical examination? No written important negative findings (eg. pigmentation) in this manuscripts. Is he pale?

We have added the following sentence in Page 5.

“No pigmentation was noted in the skin or oral mucosa. The pubic and axillary hair was normal. No abnormal findings were elicited by the chest and abdominal physical examination. “

Is the pituitary size normal? or a little bit atrophic? Why do you think TSH and PRL are slightly elevated? How about pituitary antibody or other autoimmune diseases.

The pituitary size was normal as the result of CT and MRI. We added the text: “no atrophic change” in Page 7.
The precise mechanism about the elevation of TSH and PRL is unclear. However, the other case reports of IAD often indicated that the other anterior pituitary hormones were slightly elevated along with our case. Further studies are needed to clarify this issue.

Pituitary and antipituitary and antithyroid peroxidase antibodies were negative as described case presentation. We have added the other results of immunological examination in Page 7.

[In addition, anti-skeletal muscle antibody (ASMA), anti-neutrophilic cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), anti-extractable nuclear antigen antibodies (anti-ENA), antimitochondrial antibody (AMA), antiparietal cell antibody (APCA), and anti-glutamic acid decarboxylase (anti-GAD) antibodies, were negative].

2. How about differential diagnosis of IAD? What is the candidate of differential diagnosis of IAD and why did you denied?

The most important differential diagnosis is primary adrenal insufficiency. The plasma ACTH level was very low in this case. In addition, the CRH test showed that the plasma ACTH and cortisol levels did not respond to CRH stimulation. According to these findings, we denied the primary adrenal insufficiency. The other differential diagnoses are the secondary IAD such as
pituitary tumor, lymphocytic hypophysitis, or head trauma. We denied these disorders on the basis of CT and MRI findings.

3. Why do you think this very acute course of this patient even though you diagnose this patient as autoimmune disease like IAD. When do you assume the starting point of IAD.

Because this patient had neither structural lesion in the pituitary gland nor autoantibody-associated disorders such as antipituitary and antithyroid peroxidase antibodies, I assume that IAD might develop in response to febrile neutropenia in this case. For these reasons, I speculated the stress of febrile neutropenia might trigger the onset of IAD. Similarly, it has been reported that the surgical stress after cardiotomy triggered the onset of IAD.

4. What is the condition of this patient when Cortisol test performed. Because plasma cortisol level 4.6 ug/ml is not low during night time supine position.

Also, all endocrinological data should be written with blood test condition (Standing? supine?, rest?). We performed the cortisol test in physiological rest position in the morning. We have added “in the rest
position” and “early morning” in Page 6 and 7 as the referee indicates.

5. Sodium chloride infusion is not the treatment of SIADH. (SIADH is water balance disease. Sodium infusion is sodium balance treatment, not water balance treatment. Please see the textbook of Electrolite or Nephrology.) Why did you choose this treatment?

We performed sodium chloride infusion not for SIADH but for hyponatremia. Anyway, we have deleted sodium chloride infusion from this article and Figure 2 to prevent the misunderstanding.

6. Do you think IAD and gastric cancer have relationship or only co-exist?

It can’t be denied that gastric cancer has relationship of the onset of IAD. In addition, as described in Question 3, the side effect of chemotherapy may also affect the onset of IAD. We can’t answer this question clearly in this article.

Quality of written English: Needs some language corrections before being published

Referee 2
Reviewer's report

Title: A patient with gastric cancer presenting with isolated adrenocorticotropic hormone deficiency during chemotherapy: a case report

Version: 1
Date: 13 December 2013
Reviewer: Katsuhiko Higuchi

Which of the following best describes what type of case report this is?: An unexpected event in the course of observing or treating a patient

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: Yes

Does the case report have diagnostic value?: Yes

Will the case report make a difference to clinical practice?: Yes

Is the anonymity of the patient protected?: Yes

Comments to authors:
Reviewer’s comment

In general, this manuscript is clearly written and discussion is well described. I have some minor comments for the authors that would improve the clarification of some points in the manuscript.

4. 1) The title had better be revised a little bit: for example, ‘Isolated adrenocorticotropic hormone deficiency developed during chemotherapy for gastric cancer: a case report’.

5. We revised the title as above described.

6. 2) In page 5, line 1, 'Six months after surgery' is an error in writing? Judging from context, I think that 'Six months after the completion of adjuvant chemotherapy' is correct.

   The reviewer is correct on this issue. We revised the sentence as he pointed out.

Quality of written English: Acceptable

Declaration of competing interests: I declare that I have no competing interests.

Referee 3
Reviewer's report

Title: A patient with gastric cancer presenting with isolated adrenocorticotropic hormone deficiency during chemotherapy: a case report

Version: 1

Date: 18 December 2013

Reviewer: Yasuo Hirono

Which of the following best describes what type of case report this is?: An unexpected association between diseases or symptoms

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: No

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: Yes

Does the case report have diagnostic value?: Yes

Will the case report make a difference to clinical practice?: Yes

Is the anonymity of the patient protected?: Yes

Comments to authors:
The author has written the contents of both discussion and conclusions in conclusions. It seems that the author had better write these separately.

We rewrote discussion and conclusions separately as the referee pointed out.

There is a careless mistake in Author's contributions.

We changed from “K Oyama” to “KO” in Author's contributions.

I think the number of co-authors is too much.

We decreased the number of co-authors from 22 persons to 12 persons.

Quality of written English: Acceptable

Declaration of competing interests: I declare that I have no competing interests.