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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 45324

Title: Small cell lung cancer with panhypopituitarism due to ectopic ACTH syndrome: A case report and review of the literature

Reviewer's code: 03086186

Reviewer's country: Taiwan

Science editor: Fang-Fang Ji

Date sent for review: 2019-02-20

Date reviewed: 2019-02-21

Review time: 7 Hours, 1 Day

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

Dr. Ting Jin and the other authors described a man with complaints of hemoptysis, polyuria, polydipsia, increased appetite, weight loss, and pigmentation, and was diagnosed with small cell lung cancer, ectopic adrenocorticotropic hormone syndrome

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(EAS), hypogonadism, hypothyroidism, and central diabetes insipidus. After three rounds of chemotherapy, levels of ACTH, cortisol, thyroid hormone, gonadal hormone, and urine volume returned to normal levels. In addition, the pulmonary tumor was reduced in size. EAS is known to cause disturbance in glucose metabolism, hypokalemia, peripheral edema, proximal myopathy, hypertension, hyper-pigmentation, and severe systemic infection, results from dysfunction of adrenal hormones. However, it is uncommon to observe dysfunction in other hypothalamus-pituitary hormones. These authors hypothesized that EAS induced high levels of serum glucocorticoid and a negative feedback on the synthesis and secretion of ADH from the paraventricular nucleus, and trophic hormones from the anterior pituitary. They need more evidence from the literature to support the hypothesis. The authors wrote that it is also possible that inadequate secretion of ADH due to tumor metastasis to the posterior pituitary may have been involved. Further studies will be needed to distinguish these possibilities. I suggest the authors to complete these studies to rule out metastasis to hypothalamus-pituitary axis.

Answer

1.the evidence from the literature to support the hypothesis of the dysfunction of trophic hormones due to EAS

Thank you very much for your suggestion. We have carefully review the literature. Glucocorticoids are well known to influence the secretion of TSH from the anterior pituitary gland. Previous study have demonstrate that glucocorticoids influence the concentration of pro-TRH mRNA in a cell-specific manner and thereby result in changes in the biosynthesis and release of TRH (1). Meanwhile, glucocorticoids can inhibit the peripheral conversion (T_4 to T_3) through the effect on the activities of deiodinase (2). The low levels of T_4 are probably related to a glucocorticoid-mediated suppression of

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thyroxine-binding globulin (3). Clinically, the patients with Cushing's syndrome frequently complain of hypogonadism or oligomenorrhea. Glucocorticoids not only suppress the gonad, but also inhibit the secretion of gonadotropin of hypothalamic-pituitary level (4). The above mechanisms have be verified in cases of Cushing's syndrome secondary to adrenal adenoma, and all these patients have recovered normal gonadal function after successful adrenalectomy (5). These studies offer the pathophysiological evidence to support the hypothyroidism and hypogonadism due to EAS.

(1). Kakucska I, Qi Y, Lechan RM Changes in adrenal status affect hypothalamic thyrotropin-releasing hormone gene expression in parallel with corticotropin-releasing hormone. Endocrinology 1995 **136** 2795-2802

(2). Duick DS, Wahner HW Thyroid axis in patients with Cushing's syndrome. Arch Intern Med 1979 139 767-772

(3). Otsuki M, Dakoda M, Baba S Influence of glucocorticoids on TRF-induced TSH response in man. J Clin Endocrinol Metab 1973 36 95-102

(4). Stewart PM The aderenal cortex: Clinical features of Cushing's syndrome; in Kronenberg HM, Melmed S, Polonsky KS, Larsen PR (eds): Williams Textbook of Endocrinology, ed 11. Amsterdam, Saunders/Elsevier 2008 pp 461-464

(5). Marazuela M, Cuerda C, Lucas T, Vicente A, Blanco C, Estrada J Anterior pituitary function after adrenalectomy in patients with Cushing's syndrome. Postgraduate Medical Journal 1993 **69** 547-551

Duick DS, Warren DW, Nicoloff JT, Otis CL, Croxson MS Effect of single dose dexamethasone on the concentration of serum triiodothyronine in man. The Journal of Clinical Endocrinology & Metabolism 1974 **39** 1151-1154.

2.the studies to rule out metastasis to hypothalamus-pituitary axis

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The case report of EAS with central diabetes insipidus have been cited (see reference 9). The mechanisms of the case is metastasis in the posterior pituitary. The pituitary MRI of our patient revealed normal, but it was necessary to recheck the imaging exanimation of the pituitary. However, the follow-up survey of the patient was terminated because of the contact information change of the patient.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

[ ] The same title

[ ] Duplicate publication

[ ] Plagiarism

[ ] No

BPG Search:

[ ] The same title

[ ] Duplicate publication

[ ] Plagiarism

[ ] No

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Reviewer's code: 02445408

Reviewer's country: Cuba

Science editor: Fang-Fang Ji

Date sent for review: 2019-02-10

Date reviewed: 2019-02-22

Review time: 20 Hours, 11 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript described a rare case of a patient presenting panhypopituitarism associated to an EAS in a patient with small cell lung carcinoma. They confirmed metabolic disorders associated to this diagnose Is a high quality article that could serve

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as a reference for clinical oncologist. New findings: small cell lung carcinoma complicated with EAS, hypogonadism, hypothyroidism, and central diabetes insipidus. It was emphasized that metabolic disorders desapeared without specific treatment of all of these diseases, only got control with systemic specific treatment Authors hypothesis about a negative feedback by high levels of serum glucocorticoid affected the synthesis and secretion of ADH from the paraventricular nucleus and trophic hormones from the anterior pituitary and inadequate secretion of ADH due to tumor metastasis to the posterior pituitary has to be proved in further studies

Answer

Thank you very much for your helpful acceptance.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

[ ] The same title

[ ] Duplicate publication

[ ] Plagiarism

[ ] No

BPG Search:

[ ] The same title

[ ] Duplicate publication

[ ] Plagiarism

[ ] No