Neuroendocrine Carcinoma of the Endometrium with Ectopic Secretion of Parathyroid Hormone Presenting as Hypercalcemia-Related Posterior Reversible Encephalopathy syndrome: A Case Report

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Abstract

Purpose: Posterior reversible encephalopathy syndrome (PRES) displayed various acute neurological symptoms. PRES is a rare presentation of hypercalcemia. Here we present a case with ectopic secretion of parathyroid hormone from neuroendocrine carcinoma of the endometrium presenting as hypercalcemia-related PRES.

Case report: A 67-year-old woman presented with acute generalized tonic-clonic seizure followed by post-ictal confusion and neuropsychiatric behaviors. The diagnosis is PRES. Investigations showed uterine cervical region with multiple liver metastasis complicated with hypercalcemia, elevated intact parathyroid hormone. Further pathology concluded as a poorly differentiated adenocarcinoma of the endometrium with neuroendocrine differentiation and immunoreactive for PTH. The patient's neurologic manifestations had resolved. Serum free calcium level and intact-PTH had declined after first course of definitive chemoradiation.

Conclusion: Immunostaining of the tumor tissue can be used to estimate the ectopic PTH production within the tumor cells. Early detection and appropriate clinical treatment hold the potential to improve the prognosis of refractory hypercalcemia and hypercalcemia related PRES.

Keyword: Posterior reversible encephalopathy syndrome; hypercalcemia; intact-parathyroid hormone; parathyroid hormone-related peptide; neuroendocrine carcinoma of endometrium.

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INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) exhibits different kinds of neurological symptoms [(1)] and related to different kinds of etiologies [(2-8)]. PRES is a rare presentation of hypercalcemia. Hypercalcemia is a condition with potential ramifications for various systems, including the musculoskeletal, cardiovascular, gastrointestinal, and central nervous systems, requiring prompt evaluation and treatment [(9)]. Immunohistochemistry staining for parathyroid hormone (PTH) in tumor tissue is important in the clinical management of patients with severe hypercalcemia. This is particularly true for patients with malignancies who do not present with primary or ectopic parathyroid tissue, bone metastasis, or normal serum PTH-related protein levels [(10)]. Herein, we present what we believe to be the first case of hypercalcemia-related posterior reversible encephalopathy syndrome (PRES) due to PTH-secreting neuroendocrine carcinoma of the endometrium.

CASE REPORT

A 67-year-old woman, presented with a generalized tonic-clonic seizure followed by post-ictal confusion (Glasgow Coma Scale: E4V3M5) and neuropsychiatric behaviors. She denied any past underlying diseases. Upon physical examination by the emergency department, the following results were obtained: a temperature of 37.2 °C, blood pressure(BP) level of 178/102 mmHg, and heart rate of 79 bpm.

After admission, laboratory examinations revealed the presence of both hypercalcemia (free calcium: 8.10 mg/dL) and acute kidney injury (creatinine: 2.1 mg/dL; previous creatinine level: 1.0 mg/dL). Consciousness still existed confusion after seizure control and blood pressure stabilized (BP 142/91 mmHg). Neurological examinations showed disorientation to person, place or time, incoherent speech, diminished ability of recall, visuospatial construction and calculation, normal limb strength and muscle tension with no signs of meningeal irritation nor pathologic reflexes. Brain magnetic resonance imaging (MRI) showed hyperintense T2 signals in the bilateral posterior occipital and parietal lobes without water diffusion restriction, suggesting the presence of PRES (Figure.1A, 1B). Parenteral fluid, diuretic agents, calcitonin, bisphosphonate, and hemodialysis were administered for intractable hypercalcemia. Consequently, neuropsychiatric symptoms improved after serum hypercalcemia normalized though serum azotemia still remained. We investigated the patient's hypercalcemia in order to distinguish between primary and secondary hyperparathyroidism, identify any hematological malignancies, determine the presence of vitamin D intoxication, and investigate possible bone metastases. The results revealed a high level of intact parathyroid hormone (i-PTH; 624.0 pg/mL), low levels of serum vitamin D 25-OH (10 ng/mL), and serum phosphate (2.6 mg/dL), a normal level of serum immunoglobulin, and mildly elevated serum alkaline phosphatase (135 U/L). A Tc99m-methoxyisobutylisonitrile scintigraphy scan revealed no obvious uptake in the parathyroid glands,

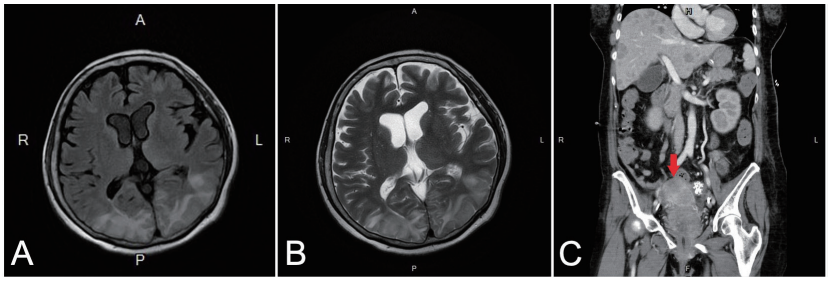

Figure 1. (A): hyperintense in the bilateral posterior occipital on T2 flair sequence
(B): hyperintense in the bilateral posterior occipital on T2 sequence
(C): mass-like soft tissue thickening (7.5x4.1cm in size) in the uterine cervical region, lobulated poor-enhancing lesion (sized about 6.8x6.1cm) in the uterus with involvement of endometrium and myometrium and there are multiple liver metastases

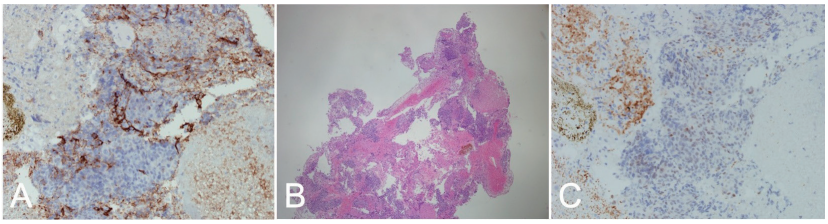

Figure 2. (A): The endometrioid adenocarcinoma is stained positive for CD56
(B): Pathology of uterine-cervical tissue revealed pleomorphic and hyperchromatic tumor cells with prominent tumor necrosis arranged in solid nested pattern infiltrating in stroma of the uterine cervical tissue (H&E, 40x)
(C): The endometrioid adenocarcinoma is stained positive for INSM-1

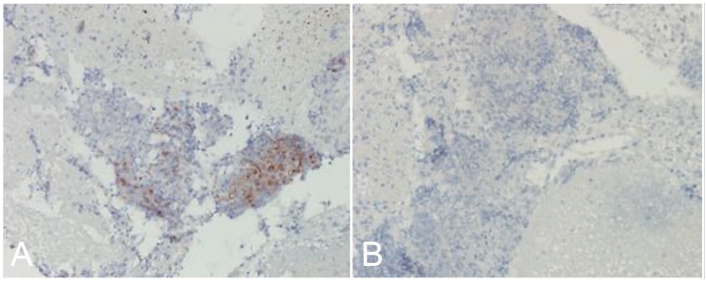

Figure 3. (A): Immunohistochemistry showed focally stained positive for parathyroid hormone
(B): Immunohistochemistry showed negative for parathyroid hormone-related protein

and no ectopic parathyroid glands were found. Moreover, a whole-body bone scan showed no widespread bone metastases. However, abdominal computed tomography (CT) revealed mass-like soft tissue thickening (7.5 × 4.1 cm in size) in the uterine cervical region, a lobulated lesion with poor enhancement on contrast-enhanced CT (approximately 6.8 × 6.1cm) in the uterus involving the endometrium and myometrium, and multiple liver metastases (Figure. 1C). The elevated i-PTH level could not be explained by the bone metastases or PTH-related protein (PTHrP). Hence, ectopic PTH production by the tumor was suspected. We arranged for repeated diagnostic dilation and curettage to be performed. A small piece of uterine-cervical tissue measuring 0.6 × 0.5 × 0.3 cm in size was collected. Pathological examination using hematoxylin and eosin staining revealed pleomorphic and hyperchromatic tumor cells with prominent tumor necrosis arranged in a solid nested pattern infiltrating the stroma of the uterine cervical tissue (Figure. 2B). Upon further immunochemical staining, positive results were obtained for two neuroendocrine markers, namely CD56 and INSM1 (Figure. 2A, 2C). These findings suggested neuroendocrine differentiation. The specimen was immunoreactive for PTH instead of PTHrP in a few tumor cells (Figure. 3A, 3B). The clinical stage was IVB, and a diagnosis of T3bN1M1 was given. We began definitive chemoradiation along with a regimen of paclitaxel and carboplatin.

A week after chemotherapy, the serum free calcium level had returned to normal (free calcium: 4.49 mg/dL) and the i-PTH had declined (i-PTH: 271.0 pg/mL). The patient experienced residual abdominal fullness due to malignant ascites. Neurological examination yielded clear consciousness, intact cognition, absence of focal weakness, sensory deficits, pathologic reflexes, headache, visual disturbance, or seizure attack.

DISCUSSION

PRES is a clinicoradiological entity that presents with various acute neurological symptoms, such as headaches, seizures, conscious impairment, and visual disturbances. T2/FLAIR hyperintensities were observed predominantly in the parietal-occipital regions via MRI. PRES is believed

to be precipitated by malignant hypertension, cytotoxic drugs, eclampsia, preeclampsia, renal failure, sepsis, or organ transplantation [1]. A prior review have shown that the clinical outcome of hypertension-related PRES is excellent after normalization of the blood pressure within a few days [11]. Removing trigger factors and intensive blood pressure controlling is necessary and brings good outcomes [11]. In our case, no clinical improvements was noticed after blood pressure stabilized urged us seeking etiologies of PRES. Eventually, neuropsychiatric symptoms improved after managements of hypercalcemia before kidney function recovery. To the best of our knowledge, this is the first case of hypercalcemia induced by intact PTH secreted by neuroendocrine carcinoma of the endometrium. A review of the previously reported cases of hypercalcemia related to PRES revealed that the etiology of hypercalcemia included malignancy [2], vitamin D or calcium overdose [3,4], primary hyperparathyroidism [5], tertiary hyperparathyroidism [6], parathyroid hormone-related peptide [7], acquired immunodeficiency syndrome, and Mycobacterium avium intracellulare infection [8]. Various mechanisms have been associated with hypercalcemia-induced PRES in the literature. Vasospasm in cerebral arteries, which is caused by changes in smooth muscle cell tone and increased vascular resistance, is one such explanation [12]. In addition, endothelial dysfunction has been found to develop due to inflammatory responses in endothelial cells triggered by hypercalcemia [13]. Hypomagnesemia, which can develop due to hypercalcemia, has been suggested to lead to cerebral autoregulation failure [2]. It is critical that the clinical and imaging characteristics of PRES be recognized and the precipitating factors be promptly eliminated.

The effects of hypercalcemia are varied and involve numerous systems, such as the nervous, musculoskeletal, cardiovascular, and gastrointestinal systems. Neurological manifestations of the condition include PRES, psychosis, deterioration of concentration, confusion, stupor, and coma [9]. The most common causes of hypercalcemia are primary hyperparathyroidism caused by parathyroid adenoma; malignancies or parathyroid glands in ectopic sites; granulomatous diseases; osteolytic lesions; iatrogenic causes; and PTHrP-related hypercalcemia induced by various malignancies, such as lung or breast cancer, hematological malignancies, or squamous cell carcinomas of the head and neck [10]. Hypercalcemia resulting from intact PTH secreted by gynecological malignancies is rare [14].

In our case, elevated intact serum PTH levels were noted in the absence of primary or ectopic parathyroid lesions identified by whole-body 99mTc-sestamibi scanning. This led us to suspect that the intact PTH was being synthesized by the neuroendocrine features of a poorly differentiated adenocarcinoma of the endometrium. Immunohistochemistry of biopsy specimens taken from the cervix and endometrium revealed focal areas within the poorly differentiated component that stained positive for neuroendocrine markers. Both the hypercalcemia and serum intact serum PTH level markedly improved once concurrent chemoradiotherapy for endometrial cancer was initiated. This suggests that instead of storing PTH, tumor cells secrete the hormone into circulation shortly after synthesis [15]. Hence, intact PTH may serve as a marker of tumor burden during disease follow-up.

CONCLUSION

In conclusion, we report what we believe to be the first case of hypercalcemia-related PRES due to PTH-secreting neuroendocrine carcinoma of the endometrium. It is both important and necessary to measure not only serum PTHrP levels but also serum PTH levels in patients with hypercalcemia related to endometrial cancer. In addition, immunostaining of the tumor tissue can be used to estimate the ectopic PTH production within the tumor cells. Early detection and appropriate clinical treatment hold the potential to improve the prognosis of refractory hypercalcemia and its neurological complications.

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