Posterior Reversible Encephalopathy Syndrome due to Hypercalcemia Associated with Parathyroid Hormone-related Peptide: A Case Report and Review of the Literature

Nobuhito Nakajima 1, Masayuki Ueda 2, Hiroshi Nagayama 2, Mineo Yamazaki 2 and Yasuo Katayama 2

Abstract

We herein report the case of a 58-year-old man with advanced esophageal carcinoma who developed posterior reversible encephalopathy syndrome (PRES). He initially presented with a severe consciousness disturbance. A subsequent examination revealed hypercalcemia and an elevated serum parathyroid hormone-related peptide (PTHrP) level. Magnetic resonance imaging performed on admission and 24 days later showed reversible widespread white matter abnormalities, which confirmed a diagnosis of PRES. The patient’s clinical and radiological manifestations improved upon normalization of the serum calcium level. To the best of our knowledge, this is the first report describing hypercalcemia-induced PRES occurring in association with elevated PTHrP.

Key words: posterior reversible encephalopathy syndrome, hypercalcemic crisis, parathyroid hormone-related peptide

(Intern Med 52: 2465-2468, 2013)
(DOI: 10.2169/internalmedicine.52.0444)

Introduction

Posterior reversible encephalopathy syndrome (PRES) is characterized by headaches, altered consciousness, seizures and visual disturbance, as well as vasogenic edema occurring predominantly in the posterior occipital and parietal lobes of the brain (1-3). While the exact pathogenesis of PRES remains unclear, various risk factors, such as severe hypertension, eclampsia and exposure to immunosuppressants, have been implicated (1-3). We herein report the rare case of a patient with PRES caused by severe hypercalcemia that was associated with an increased parathyroid hormone-related peptide (PTHrP) level.

Case Report

A 58-year-old man was admitted to a previous hospital for appetite loss, where he was diagnosed as having advanced esophageal cancer (Fig. 1A, B) after an endoscopic biopsy revealed well-differentiated squamous cell carcinoma. He received no treatment for the esophageal cancer at that hospital. Five days later, he was transferred to our hospital in a comatose state. On admission, his weight and height were 63.6 kg and 166 cm, respectively. A physical examination revealed sinus tachycardia (136 bpm), pyrexia (38.6°C) and mild hypertension (152/60 mmHg). His blood pressure was reported to be normal at the previous hospital. A neurological examination revealed a severe consciousness disturbance (Glasgow Coma Scale 6: E1, V1, M4), sluggish pupillary response and flaccid limbs with normal reflexes. He had not taken any antihypertensive drugs, activated vitamin D products or calcium preparations.

Blood tests showed mild liver dysfunction, as indicated by the following data: aspartate aminotransferase, 53 IU/L; alanine transaminase, 68 IU/L; lactate dehydrogenase, 541 IU/L; γ-glutamyl transpeptidase, 578 IU/L; and alkaline phosphatase, 541 IU/L. Renal failure was also observed, as...
indicated by the following findings: blood urea nitrogen, 119.5 mg/dL; and serum creatinine, 4.71 mg/mL. The total calcium level corrected based on the serum albumin level was significantly increased (17.5 mg/dL). Endocrinological tests revealed decreased serum levels of intact parathyroid hormone (6 pg/mL) and 1,25(OH)2 vitamin D (<4 pg/mL), a normal serum calcitonin level and an elevated serum PTHrP level (4.8 pmol/L; normal, <1.1 pmol/L). No other endocrinological abnormalities were observed. A cerebrospinal fluid examination was unremarkable, except for a high opening pressure (205 mmH2O). Brain magnetic resonance imaging (MRI) revealed widespread hyperintense lesions predominantly located in the occipital cerebral white matter on fluid-attenuated inversion recovery (FLAIR) images (Fig. 2A). These lesions were slightly hyperintense on diffusion-weighted images (not shown). Whole-body bone scintigraphy demonstrated no obvious abnormalities.

Due to the patient’s general prostration and consciousness disturbance, he received neither chemotherapy nor radiotherapy for advanced esophageal cancer after being transferred to our hospital. Instead, he was treated with aggressive hydration in combination with pamidronate disodium, elcatonin and furosemide for the hypercalcemic crisis. An immediate improvement in the hepatic and renal functions was observed, and the serum calcium level normalized within two weeks of admission. The patient’s consciousness disturbance improved concurrently with normalization of the serum calcium level. Follow-up MRI performed 24 days after admission revealed no abnormalities (Fig. 2B). Based on these findings, a diagnosis of PRES due to hypercalcemia was made.

**Discussion**

PRES is an acute encephalopathy characterized by diverse neurologic symptoms, including headaches and visual disturbances. Typically, the clinical diagnosis is based on MRI changes in hyperintense lesions on T2 and FLAIR sequences, predominantly in the posterior occipital and parietal lobes of the brain. Various risk factors, such as severe hypertension, eclampsia and exposure to immunosuppressants, have been implicated; however, the occurrence of PRES associated with hypercalcemia is a rare phenomenon. In this study, we report the case of a 58-year-old man with hypercalcemia-induced PRES occurring in association with an increased level of PTHrP. Reversible widespread FLAIR abnormalities were found predominantly in the occipital white matter. Upon normalization of the serum calcium level, the patient’s consciousness disturbance and FLAIR...
abnormalities improved.

To date, only eight patients with hypercalcemia-induced PRES have been described in the literature (4-10). In these patients, hypercalcemia occurred as a result of the prolonged use of oral calcium preparations, primary hyperparathyroidism, mycobacterial infection, plasmacytoma, lymphoma, metastatic bone disease or transfusion during cancer surgery with hyperparathyroidism (Table). Several of these cases involved malignancy-related hypercalcemia; however, to the best of our knowledge, hypercalcemia-induced PRES occurring in association with an increased PTHrP level has not been previously reported.

The precise pathophysiology of vasogenic edema in patients with PRES remains controversial; however, the occurrence of hypertension-related cerebral autoregulation and subsequent endothelial injury is a popular theory (11). Although hypercalcemia is known to induce arterial hypertension (12), we do not believe that hypertension was the causative factor for the development of PRES in this case since the patient was not hypertensive before being transferred to our hospital and was only mildly hypertensive on admission. Andersson et al. previously reported that functional and vascular alterations can occur in the vascular wall in hypercalcemic patients due to hyperparathyroidism (13); thus, capillary leakage due to hypercalcemia in the absence of hypertension may have been involved in the development of PRES in our patient.

Hypercalcemia is the most frequent paraneoplastic disorder, estimated to affect approximately 20-30% of cancer patients (14). In addition, 50-90% of hypercalcemic patients with cancer reportedly exhibit elevated serum levels of PTHrP (15). PTHrP is a tumor-associated factor responsible for the development of cancer-induced hypercalcemia and localized osteolysis associated with bone metastasis (16). Of the PTHrP-producing tumors, squamous cell carcinomas are common and can potentially lead to hypercalcemia (17). However, a large case study comprised of 382 patients with esophageal carcinomas reported that hypercalcemia was apparent in only 1.3% of the patients at the time of diagnosis (18). Therefore, hypercalcemia may be relatively rare in patients with esophageal cancer.

In the present patient, the symptoms of PRES improved following normalization of the serum calcium level; thus, hypercalcemia was the inducing factor for the development of PRES rather than the increased PTHrP level. This hypothesis is corroborated by our finding that the serum PTHrP level increased from 4.8 pmol/L to 7.3 pmol/L despite the improvement in the patient’s radiological findings and clinical symptoms. However, the elevated serum PTHrP level, derived from the esophageal carcinoma, may have been the underlying cause of the hypercalcemic crisis in this patient, since other well-known causative conditions were ruled out during the diagnostic examinations.

In conclusion, the present observation highlights the fact that PTHrP can cause cancer-induced hypercalcemia, which may be a potential risk factor for the development of PRES. Clinicians should be aware that hypercalcemia-induced PRES is a possible phenomenon, since the disorder is associated with a severe consciousness disturbance and can be a life-threatening condition.

The authors state that they have no Conflict of Interest (COI).

References

6. Kawano H, Suga T, Terasaki T, Hashimoto Y, Baba K, Uchino M.

<table>
<thead>
<tr>
<th>Table. Previous Reports of Hypercalcemia-induced Posterior Reversible Encephalopathy Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
</tr>
<tr>
<td>(4)</td>
</tr>
<tr>
<td>(5)</td>
</tr>
<tr>
<td>(6)</td>
</tr>
<tr>
<td>(7)</td>
</tr>
<tr>
<td>(8)</td>
</tr>
<tr>
<td>(9)</td>
</tr>
<tr>
<td>(10)</td>
</tr>
<tr>
<td>Present case</td>
</tr>
</tbody>
</table>

© 2013 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html