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Posterior reversible encephalopathy syndrome due to malignant hypercalcemia: physiopathologic considerations

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Context: Posterior reversible encephalopathy syndrome (PRES) is a neurological entity characterized by seizures, headache and reversible subcortical vasogenic edema. It is associated with many etiologies, most often hypertension, chronic renal failure and chemotherapy. Hypercalcemia is rarely associated with PRES.

Objective: The aim of this study is to describe and discuss a case of PRES that developed in a patient with malignant hypercalcemia, with emphasis on the possible pathophysiologic mechanisms involved.

Patients and Methods: A 38-year-old woman presented with altered mental status. She had a 2-month history of lumbar pain of moderate intensity, weight loss and gastrointestinal complaints, in addition to a mass in her left breast. Her corrected serum calcium was 14.5 mg/dL. She was normotensive, had no focalizing signs and her cerebrospinal fluid was normal. Despite treatment, her neurologic state did not resolve, and she developed severe headaches at day 4 of her admission. Brain magnetic resonance imaging showed a bilateral and symmetric hyperintensity in the occipital and parietal lobes on T2-weighted and fluid attenuated inversion recovery imaging, a characteristic highly suggestive of PRES. After correction of hypercalcemia her symptoms and imaging abnormalities resolved.

Conclusions: The development of PRES in the setting of severe hypercalcemia is extremely rare. Hypercalcemia could lead to PRES in the absence of hypertension by various mechanisms, including vasospasm, endothelial dysfunction and an inflammatory state. A high index of suspicion is needed in this setting, as hypercalcemia can lead to neurological symptomatology, and prompt diagnosis is essential for adequate treatment.

In 1996, Hinchey et al described magnetic resonance imaging (MRI) findings of reversible subcortical vasogenic edema that mainly affected the posterior cerebral lobes in patients with hypertensive crises due to multiple etiologies (1). The term posterior reversible encephalopathy syndrome (PRES) was proposed. Although there are no established diagnostic criteria, PRES is a clinico-radiological entity characterized by neurological clinical fea-

tures, such as headache, visual disturbances and seizures, and focal reversible vasogenic edema that predominantly involves the parietal and occipital lobes. The list of conditions associated with PRES has since increased, and now includes hypertension, eclampsia, end-stage renal disease (ESRD), immunosuppressive drug use, and rheumatologic diseases among others (2). Hypercalcemia is an extremely rare cause of PRES. Here we report the case of a patient

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Abbreviations:

with hypercalcemia-induced PRES and discuss possible pathophysiological mechanisms.

Case Reports

A 38-year-old woman presented with a 2-month history of lumbar pain of moderate intensity with neither irradiation nor paresthesia. One month later she developed fatigue, anorexia, polyuria, abdominal pain and constipation. The day before she was admitted she developed an altered mental status, characterized by agitation alternated with somnolence, but she did not have any focalizing signs or symptoms. She also had a progressive and unintentional 15 kg body weight loss in the previous 3 months. On admission she was awake but in a confused state. On physical examination, her heart rate was 90 beats per minute, temperature was 37°C, and blood pressure (BP) was 120/80 mmHg in both arms. She remained normotensive during hospitalization. A 3/5 muscle weakness was noted in her four limbs and a 2-cm mass was palpable in her left breast.

Routine laboratory tests showed a normocytic normochromic anemia with a hemoglobin of 10.4 g/dL, and normal leukocyte and platelet counts; serum creatinine was 4.5 mg/dL with a FENa of 2.07% and a calculated glomerular filtration rate (GFR) of 15 mL/min. Serum calcium level was 13.1 mg/dL, corrected with an albumin of 2.3 g/dL to 14.5 mg/dL, and phosphorus was 7.5 mg/dL. Cerebrospinal fluid analysis was normal. Her neurological symptoms were attributed to hypercalcemia. Other electrolytes were normal. An intact parathyroid hormone (iPTH) level was 13.8 pg/mL (reference value: 15 to 65 pg/mL). Radiological examination showed osteolytic bone metastases in ribs, lumbar spine, and pelvis. Liver and kidneys were morphologically normal. A breast ultrasound showed a hypoechoic irregular nodule with lobulated borders and abnormal lymph nodes, suggestive of malignancy. Intensive IV fluids were initiated to reduce calcium levels and a biopsy of the breast mass was ordered. The histopathologic examination reported a triple negative invasive ductal carcinoma of the left breast.

Renal function improved but calcium levels remained elevated even with adequate diuresis (>2,500 mL/24 hours). Her confusion and agitation improved mildly. On day 4 the patient referred acute onset of headache. A brain MRI showed bilateral and symmetric hyperintensities in the occipital and parietal lobes on T2-weighted and fluid attenuated inversion recovery (FLAIR) imaging with an apparent diffusion coefficient map showing slightly increased signals (Figure 1). The cerebral vasculature was normal. These images were highly suggestive of posterior reversible leukoencephalopathy. Zolendronic acid was

added to the therapy with the dose adjusted to renal function (calculated GFR: 37 mL/min). Over the next days there was an improvement in symptoms and by day 15 the calcium serum level was 8.7 mg/dL with normal renal function. On clinical examination, her neurologic symptoms had resolved. A new MRI showed that the brain lesions had disappeared (Figure 1).

The patient and her family refused palliative chemotherapy. She was referred to the outpatient palliative care clinic, with indications to increase oral fluid intake to 2 L per day and 4 mg of zolendronic acid infusions as needed. Serum electrolytes were assessed serially.

Discussion

The global incidence of PRES is unknown and although there appears to be no predominance for any age group (3–6), women are more often affected. There are a wide variety of conditions known to cause PRES, but isolated hypercalcemia as a cause is extremely rare. Only 8 cases of hypercalcemia-associated PRES have been previously reported (Table 1); in three of these (7, 8, 13) the patients were also severely hypertensive, and isolated hypercalcemia alone could not account for the development of PRES. Seizures (66%–87%), headache (28%–53%), visual abnormalities (20%–42%) and nausea/vomiting/dizziness (42%) are the most common clinical manifestations of PRES (3–6). MRI is the imaging method of choice, with T2 FLAIR images showing hyperintensities that are not usually visible in diffusion-weighted imaging. It is recognized that anterior cerebral regions can be affected, that the alteration may be irreversible, and that it may also involve cortical areas (14, 15). Our patient was normotensive at presentation with an altered mental status and disoriented, later developing headache and characteristic bioccipital white matter alterations on MRI.

While mild hypercalcemia may be asymptomatic, moderate to severe hypercalcemia can be associated with a variety of symptoms (16). About 40% of patients with hypercalcemia show neurological abnormalities (17), with the most common alterations being weakness, fatigue, confusion, and coma. Seizures are very rare. Focal neurological deficits and even brain infarction have been reported in patients with severe hypercalcemia (18, 19). Therefore, the diagnosis of PRES in the setting of hypercalcemia requires a high index of suspicion. The cardiovascular system can also be affected, with manifestations that include a shortened QTc interval, and enhancement of digitalis effects. More pronounced hypercalcemia gives rise to ST segment elevation, hypotension, various bradyarrhythmias, increasing degrees of heart block, and in ex-

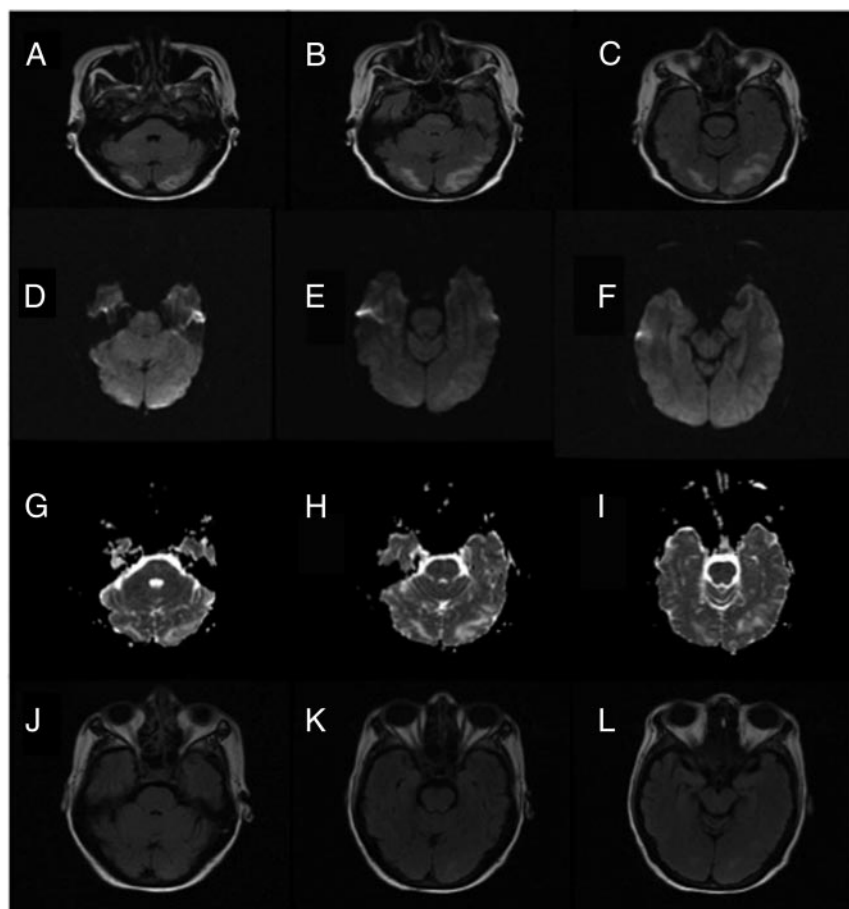


Figure 1. Brain MRI findings. Bilateral subcortical and cortical hyperintensities (FLAIR) are visible in the parieto-occipital regions (A–C). These lesions were almost not visible in diffusion-weighted imaging (D–F). Apparent diffusion coefficient map shows slightly increased signals (G–I). An MRI 15 days later revealed that the lesions had almost completely resolved (J–L).

treme cases, cardiac arrest. Other signs and symptoms such as abdominal pain, nausea, vomiting, and nephrocalcinosis are also common (20).

Several potential causes of hypercalcemia exist, including genetic, infectious, environmental, iatrogenic, and neoplastic etiologies. These can be broadly classified as those mediated by the effects of parathyroid hormone (PTH), and those that are not. By far, primary hyperparathyroidism (approximately 50%) and malignancy (30%–40%) are the most common causes of hypercalcemia, with the latter being more common in hospitalized patients (21, 22). The diagnosis of malignant hypercalcemia should be considered in any cancer patient presenting with altered mental status, and it is usually a manifestation of advanced disease, but other neurologic complications of malignancy must also be ruled out. Malignancy can lead to hypercalcemia through various mechanisms, such as osteolytic hypercalcemia, ectopic production of PTH or PTH-related protein (a test which is widely available and could be performed when PTH concentrations are below 20 pg/mL), inappropriate production of 1,25-dihydroxyvitamin D3

(always low when hypercalcemia is PTHrP-related), and immobility (22–24). Parathyroid hormone is usually low, as in our case, except in the rare cases of a PTH-secreting tumor.

The physiopathology of PRES remains poorly understood, and an excellent review is provided by Feske (2). Most commonly there are two essential conditions in the development of PRES: hypertension leading to increased capillary filtration and endothelial dysfunction leading to the development of cerebral edema. Hypertension induces a loss of cerebral autoregulation, leading to hypoperfusion due to vasospasm, vasoconstriction or both, but some studies have also found evidence of cerebral hyperperfusion (3). However, in many cases, PRES can occur in normotensive patients, which suggests that endothelial damage may play an important role. An inflammatory or circulating toxin mediating endothelial damage could explain the development of PRES in conditions such as sepsis, immunosuppressive therapy and vasculitides (5, 25). In the setting of acute renal failure, uremic toxins could play an

important pathophysiological role (26). Therefore, a “two-hit” hypothesis seems best to account for the development of PRES: hypertension and cerebral vascular alterations associated to endothelial injury and an inflammatory condition (2, 5). Our patient presented with acute renal failure, but at the time of her headache and MRI, renal function had improved markedly following rehydration.

Vasospasm of the cerebral vasculature has been proposed as the mechanism responsible for hypercalcemia-induced PRES (7, 8, 13), but MRI evidence of both vasogenic and cytotoxic edema has been found (9, 11). In at least one case there was angiographic evidence of transient posterior cerebral artery narrowing, which was highly suggestive of vasospasm (10). Some authors suggest that hypercalcemia-induced actin-myosin coupling with activation of vascular smooth-muscle contraction in the arteriolar circulation could be responsible (8), and there is independent evidence of hypercalcemia-associated vascular dysfunction. Our patient showed no signs of vascular

Table 1. Characteristics of patients with hypercalcemia-associated PRES described in the literature.

Reference	Age/sex	Neurological manifestations	Hypertension yes/no (mm Hg)	Calcium (mg/dL)	Etiology	Treatment	Neurologic Outcome
Frank <i>et al.</i> 1998	12 F	Desorientation, seizures	Yes (144/94)	15	MAI and HIV-AIDS	NA	Good
Kaplan. 1998	66 F	Hallucinations, seizures	Yes (NA)	13.6	Multiple myeloma	Hydration Pamidronate	Good
Kastrup <i>et al.</i> 2002	49 F	Stupor, seizures	No (NA)	17.2	Calcium overdose (oral)	Fluid loading and forced diuresis	Fair
	69 F	Stupor, desorientation	No (NA)	16.8	Plasmocytoma	Fluid loading and forced diuresis	Fair
Chen <i>et al.</i> 2004	43 F	Seizures	No (NA)	15.5	Metastatic breast cancer	Fluid loading Magnesium	Good
Kim <i>et al.</i> 2005	51 F	Headache, vomiting, desorientation, stupor	No (125/80)	15.5	Primary hyperparathyroidism	Hydration Calcitonin Pamidronate	Excellent
Choudary <i>et al.</i> 2005	39 M	Headache, desorientation, seizures	No (100/70)	13	MAI and HIV-AIDS	Corticosteroids	Fair
Au <i>et al.</i> 2012	58 M	Altered mental status, seizures	Yes (226 systolic)	21.2	Primary hyperparathyroidism	Hydration	Fair
					Calcitonin CVVH Present Case	38 F	Altered mental status, desorientation
Zolendronate							No (120/80) 14.5 Metastatic breast cancer Hydration Excellent

PRES: posterior reversible encephalopathy syndrome; NA: not available; SAH: subarachnoid haemorrhage; MRI: magnetic resonance imaging; CPM: cyclophosphamide; PP: plasmapheresis; PRL: posterior reversible leukoencephalopathy; MAI: *mycobacterium avium intracellulare*; CVVH: continuous venovenous hemofiltration. Prognosis: excellent: mental status returned to baseline; good: minor neurological sequelae; fair: major neurological sequelae.

alterations, although these cannot be conclusively ruled out without arteriography.

Patients with hypercalcemia due to primary hyperparathyroidism were shown to have impaired endothelium-independent vasodilation that may predominantly involve the arterial media (27). Using healthy volunteers who received calcium infusions, acute hypercalcemia has been shown to result in a dose-related impairment in endothelial vasodilatory function and increased systolic BP (28). In addition to vascular wall dysfunction, hypercalcemia could also lead to endothelial cell inflammatory injury. Rats with diet-induced hypercalcemia show a transformation of their endothelial cells to a predominantly proinflammatory phenotype (29). In experimental studies, hypercalcemia led to increased production of renal endothelin-1 (30) and to alterations in lung vascular permeability associated to increased expression of inducible nitric-oxide and proinflammatory cytokines (31).

Although this evidence is circumstantial, it suggests that two different conditions could lead to hypercalcemia-induced PRES: perfusion changes due to alterations in vascular reactivity leading to vasospasm, and an inflammatory state leading to endothelial cell injury. This would be in accord with what is known of the physiopathology of PRES concerning a “two-hit” phenomenon. The frequency and variety of neurological symptoms associated with hypercalcemia suggests that PRES could be under-

diagnosed in this setting. However, further studies are required to elucidate the precise mechanisms involved.

The mainstay of treatment of PRES is removing the triggering factor if it is identified (2, 4). There are many options in the management of malignant hypercalcemia (22–24). Volume resuscitation with physiologic saline is a critical early treatment to restore renal perfusion and calciuresis. Once euvolemia is established, either oral or maintenance intravenous (IV) fluids are continued to maintain a reasonable urine output. There is little evidence in favor of using furosemide to promote calciuresis. Calcitonin inhibits osteoclastic bone resorption and renal calcium reabsorption. Bisphosphonates are currently the treatment of choice due to their inhibitory action on bone resorption, but their effects are evident after 24–48 hours (22–24). Glucocorticoids can reduce extrarenal vitamin D 1 α -hydroxylase activity, inhibit osteoclastic bone resorption by decreasing tumor production of locally active cytokines and may be used in conjunction with other standard therapies in patients with other forms of malignant hypercalcemia. In severe cases of hypercalcemia or where rapid normalization of calcium is required, hemodialysis using a calcium-free dialysate could be effective. Early parathyroidectomy in hyperparathyroid crises can be required, especially in patients exhibiting poor medical response. The anti-RANKL monoclonal antibody denosumab and gallium nitrate are other options under

investigation. Prompt reversal of PRES symptomatology and of MRI abnormalities can be seen after treatment of hypercalcemia (11). Antiepileptic medications are useful in controlling seizures, if present. The prognosis is good, but stroke, persistent neurological deficit, and chronic seizures have been described occasionally as sequelae (2). Our patient responded well to aggressive hydration and bisphosphonate therapy.

In conclusion, PRES should be considered in patients with hypercalcemia and neurologic symptoms such as headaches, visual abnormalities, and seizures. Prompt reversal of hypercalcemia and correction of the underlying cause are essential, and associated with an excellent prognosis.

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