



Case report

Paraneoplastic PRES from lymphoma induced hypercalcemia: Case report and review of the literature

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ABSTRACT

Hypercalcemia from tumors has been associated with Posterior Reversible Encephalopathy Syndrome (PRES) but the mechanism remains unclear. In this article, we describe a case of PRES caused by hypercalcemia from lymphoma. We summarize the available scientific evidence linking hypercalcemia to failure of cerebral autoregulation and potentially PRES. A major link is the hypomagnesemia induced by hypercalcemia. While this concept requires further clinical testing and validation, it is clinically significant for the management of PRES, even when not directly caused by hypercalcemia.

1. Case report

A 68-year-old woman with intermittent hypercalcemia for two months presented with altered mental status. On initial evaluation blood pressure was 178/78 mmHg but was rapidly controlled to 100–140 s systolic. She was alert but inattentive. Although her vision was profoundly impaired, she denied the deficit and confabulated responses.

Initial laboratory data revealed elevated serum calcium (18 mg/dl) and reduced magnesium (1.4 mg/dl). The hypercalcemia was rapidly corrected with IV hydration and calcitonin, and magnesium was repleted. Extensive biochemical workup showed hypercalcemia with an appropriately low PTH, normal PTHrP, and an inappropriately elevated 1,25(OH)₂-vitamin D, a pattern suggestive of lymphoproliferative disease.

Head CT showed bilateral occipital hypodensities and MRI showed corresponding FLAIR hyperintensities without restricted diffusion or pathologic enhancement. The occipital cortex was hypometabolic on PET imaging. EEG revealed frequent independent bilateral occipital sharp waves. She was treated with leviteracetam. CSF analysis was unremarkable (protein 43 mg/dl, cell count 1/mm³) with negative cytology, flow cytometry, and IgH rearrangement.

Body PET disclosed bulky FDG-avid retroperitoneal lymphadenopathy. Core biopsy of a left iliac lymph node demonstrated large B cell lymphoma. She gradually recovered her vision with continued

magnesium replacement. She was subsequently treated with high dose steroids and R-CHOP. At the time of discharge, three weeks after her presentation, her vision and mental status improved but she never returned to her baseline.

2. Discussion

The clinical presentation of encephalopathy, vision loss, occipital cortex edema and epileptiform activity was most consistent with PRES, in this case, a paraneoplastic manifestation of lymphoma from the associated hypercalcemia.

The pathophysiology of PRES involves endothelial dysfunction from elevated blood pressure or direct cytotoxins, which impair autoregulation and disrupt the blood brain barrier (BBB), subsequently causing cerebral edema [1]. Hypercalcemia, whether due to excessive intake, hyperparathyroidism, or malignancy, is an additional risk factor associated with PRES, although the exact mechanism underlying this association remains uncertain [2,3].

Vasospasm in the posterior cerebral arteries has been observed in cases of hypercalcemia-induced PRES [4,5]. Hypercalcemia directly alters contractile tone of the endothelium and underlying smooth muscle cells, leading to increased vascular resistance and potentially vasospasm. In both animal models and human experiments, hypercalcemia increases vascular tone by inhibiting basal nitric oxide release from endothelial cells [6,7]. In addition, hypercalcemia induces

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inflammatory responses in endothelial cells and leukocytes [8], possibly contributing to endothelial dysfunction.

Hypercalcemia also causes hypomagnesemia, leading to further endothelial and smooth muscle dysfunction, and failure of autoregulation. Low magnesium is an independent risk factor for PRES, associated with increased basal vascular tone and cerebral vasospasm [1].

Hypercalcemia causes absolute hypomagnesemia. High calcium levels induce renal wasting of magnesium by activating calcium-sensing receptors in the renal thick ascending tubules and suppressing paracellular magnesium transport.

Hypercalcemia also causes functional hypomagnesemia. Magnesium and calcium act as mutual antagonists at different receptors and channels [9,10]. For example, magnesium blocks inward calcium currents and competes with calcium for membrane binding sites. It modulates calcium binding and release from the sarcoplasmic reticulum in smooth muscle cells to maintain a highly regulated internal calcium concentration. In effect, hypomagnesemia leads to increased intracellular calcium and higher vascular resistance, which are reversed by magnesium infusions [9–11].

Magnesium exerts a similar but distinct effect on the endothelium. It directly increases endothelial nitric-oxide and prostacyclin production to reduce vascular smooth muscle tone [12,13]. Endothelial magnesium also antagonizes calcium at the cytoskeleton actin level, and therefore prevents endothelial contraction and maintains the integrity of blood brain barrier (BBB) tight junctions. Consequently, magnesium reduces BBB permeability and cerebral edema [11].

Hypercalcemia may also lead to PRES through neuronal excitotoxicity. This effect is likely mediated through the calcium permeable NMDA receptors. Magnesium normally blocks these receptors when the membrane is hyperpolarized (voltage-dependent block). In hypercalcemia, calcium competes with magnesium at its binding site, disinhibiting the NMDA receptors, which results in calcium influx into the neurons and causes excitotoxicity and seizures [14]. This mechanism might partially explain why magnesium is an effective treatment of eclampsia, which shares many features of PRES [11].

Despite the paucity of human clinical studies, basic science evidence supports the role of hypercalcemia and hypomagnesemia in the failure of cerebral autoregulation, as seen in PRES. In fact, subarachnoid hemorrhage-induced vasospasm, reversible cerebral vasoconstriction syndrome (RCVS), and eclampsia are all characterized by endothelial dysregulation and are often treated with calcium channel blockers and magnesium. However, this is not the current standard of care for PRES management. This report highlights the significance of the interplay between calcium and magnesium in cerebral autoregulation and its potential in understanding the pathophysiology and optimal

management of PRES.

Authors disclosures

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