

肺部隱球菌症藉由分泌過多的活化態維他命D引致頑固性高血鈣：一意識障礙的罕見原因

Refractory hypercalcemia via 1,25-dihydroxyvitamin D excess secondary to pulmonary cryptococcosis: A rare cause of conscious disturbance

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Case Report:

A 71-year-old woman presented with two days of conscious disturbance and fever. She had a 6-year history of type 2 diabetes, and her most recent Hgb A1c was 9.5%. Three months before admission, she was diagnosed with pulmonary cryptococcosis, confirmed by the presence of noncaseating granulomas and histochemical staining of cryptococcal spores in lung biopsies. Treatment with fluconazole (450 mg per day) led to dramatic improvement in the chest radiograph after one month (Figure 1A). Physical examination indicated that she was normotensive, febrile (38.5°C), had drowsy consciousness, and had no focal neurologic deficit. Laboratory analysis was as follows: C-reactive protein 17.23 mg/dL (<0.5 mg/dL), sugar 263 mg/dL, blood urea nitrogen 26 mg/dL, creatinine 2.6 mg/dL, sodium 136 mmol/L, and normal liver function tests. Urinalysis indicated numerous white blood cells per hpf, protein 1+, and bacteria 4+. Brain computed tomography (CT) showed no evidence of stroke. Noncontrast chest and abdominal CT showed no abnormalities, except for infiltrations at lung bases. Chest radiography at admission (Figure 1B) showed no obvious changes compared with two months previously (Figure 1A). After treatment with meropenem, her fever subsided, C-reactive protein and serum creatinine declined to 9.21 and 2.2 mg/dL, respectively, and urinalysis returned to normal. However, she remained drowsy. The serum cryptococcal antigen titer was 1:258, higher than it was three months previously (1:128). Consolidations in the left lung became larger on day seven (Figure 2). A lumbar puncture indicated no evidence of cryptococcal meningitis. She had hypercalcemia (3.19 mmol/L), serum albumin of 1.6 g/dL, phosphate of 3.6 mg/dL, and intact parathyroid hormone (iPTH) of 32.3 pg/mL (normal range, 10-65 pg/mL). Thyroid and adrenal function were normal and immunofixation electrophoresis of serum and urine was negative. There was no evidence of malignancy and a CT scan of the thorax and abdomen was normal, except for infiltrations. She was treated with 0.9% saline infusion and calcitonin, and her daily urine reached more than 1000 mL. However, the ionized serum calcium (iCa) level only declined from 1.677 to 1.569 mmol/L and she remained drowsy. Hemodialysis was initiated on day-10. Her iCa level declined to 1.466 mmol/L and her consciousness became clear after two sessions. Hemodialysis was discontinued for two days, but her iCa level increased to 1.719 mmol/L and she was drowsy again. Her serum

25-hydroxyvitamin D level was 26.0 ng/mL (normal range, 5.3-30 ng/mL) and 1,25-dihydroxyvitamin D level was 36.1 ng/mL (normal range, 25.1-66.1 pg/mL). Thus, severe overproduction of 1,25-dihydroxyvitamin D secondary to pulmonary cryptococcosis was the cause of refractory hypercalcemia and conscious disturbance. She was hemodialysis-dependent for refractory hypercalcemia but eventually died of catheter-related infection after 38 days.

Discussion:

Granulomatous diseases often cause hypercalcemia, and sarcoidosis and tuberculosis are the most common underlying disorders. We are only aware of three patients reported to have cryptococcal infection-induced hypercalcemia. Extrarenal 1- α -hydroxylation of 25-hydroxyvitamin D may occur in granulomas and this may lead to extrarenal unregulated overproduction of 1,25-dihydroxyvitamin D. This is the likely cause of fungal hypercalcemia in our patient. Although our patient had normal iPTH, she had exceptionally elevated 1,25-dihydroxyvitamin D level that surpassed the bodily load of normal urinary calcium excretion and required hemodialysis for normalization.

Transplantation, immunosuppressive treatment, HIV infection, dialysis, and poorly-controlled diabetes increase the risk for relapse and dissemination of pulmonary cryptococcosis. High serum cryptococcal antigen titers correlate with more advanced radiographical lesions or extrapulmonary presentation, such as CNS infection or fungemia. However, the association between the degree of serum cryptococcal antigen titer and hypercalcemia remains elusive. This case shows that hypercalcemia can be mediated by excessive 1,25-dihydroxyvitamin D in patients who present with pulmonary cryptococcosis and unexplained conscious disturbance.