PARANEOPLASTIC HYPERCALCEMIA WITH METASTATIC CALCIFICATION – CLINICOPATHOLOGIC STUDIES

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Hypercalcemia is a common paraneoplastic syndrome that may result in metastatic calcification [1]. We report here on four autopsy cases with paraneoplastic hypercalcemia with metastatic calcification, to evaluate the clinicopathologic manifestations. All were males, aged 37–63 years old. Primary tumors included one transitional cell carcinoma of the urinary bladder, one multiple myeloma, and two squamous cell carcinomas of the esophagus. Calcium concentrations ranged from 3.3 to 5.9 mmol/L. Chronic hypercalcemia resulted in metastatic calcification. The kidney and stomach were the most vulnerable organs. Only case 1 presented with an increase in plasma calcium above 5 mmol/L (about twice the normal value); the metastatic calcification involved the capillary walls of his lungs, and he died of fulminant pulmonary edema. Our conclusion is that judicious treatment for paraneoplastic hypercalcemia is important with respect to the occurrence of pulmonary edema associated with metastatic calcification.

Key Words: paraneoplastic hypercalcemia, metastatic calcification, pulmonary edema

Received: August 26, 2005 Accepted: November 28, 2005
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PATIENTS AND METHODS

From July 1990 to July 2005, a total of 242 autopsies were performed in Hualien Tzu-Chi Hospital. The four cases in our database that presented with paraneoplastic hypercalcemia included one transitional cell carcinoma of the urinary bladder, one multiple myeloma, and two squamous cell carcinomas of the esophagus. No disseminated osteolytic metastatic lesions were found in the case with transitional cell carcinoma of the urinary bladder, or in the two cases with squamous cell carcinoma of the esophagus. Continuous laboratory calcium examination was performed. Renal function test results and chest radiograph series were collected. Moreover, all slides of the autopsied organs were reviewed by two pathologists.

RESULTS

All four cases studied were males aged 37–63 years old (mean, 49 yrs). Calcium concentrations ranged from 3.3 to 5.9 mmol/L. Metastatic calcification involved, primarily, the renal tubules with nephrocalcinosis (Figure 1) and the stomach mucosa (Table). Two cases with abnormal renal function (blood urea nitrogen 106–261 mg/dL; serum creatinine 3.4–5.0 mg/dL), including one multiple myeloma and one transitional cell carcinoma of the urinary bladder, were noted. Histopathologic examination revealed myeloma cast nephropathy accompanying nephrocalcinosis in the multiple myeloma case and chronic pyelonephritis due to obstructive uropathy accompanying nephrocalcinosis in a large transitional cell carcinoma of the urinary bladder.
The other two cases revealed nephrocalcinosis with normal renal function. In case 1, calcium deposition also occurred in the salivary and pancreatic ducts (Table). No evidence of acute or chronic pancreatitis was noted. Only case 1 died of acute respiratory failure. Bilateral pulmonary edema (right, 1100 g; left 890 g) was noted. Histopathology revealed prominent calcium deposited in the capillary wall accompanied by prominent pulmonary edema (Figure 2).

**DISCUSSION**

Hypercalcemia is a common paraneoplastic syndrome. In our series, two squamous cell carcinomas of the esophagus, one multiple myeloma, and one transitional cell carcinoma of the urinary bladder were included. The incidence of squamous cell carcinoma of the esophagus with hypercalcemia was about 27.6%, as reported by Geddes et al [2]. The incidence of multiple myeloma with hypercalcemia was reported at about 30% [3]. Urinary bladder transitional cell carcinoma with hypercalcemia is very rare, with only a few cases ever reported [4]. Tumors induce hypercalcemia by a local mechanism associated with the tumor’s production of various cytokines that increase bone osteolysis. In addition, many tumors release humoral factors, mainly parathyroid hormone (PTH)-related protein, which stimulates bone resorption and/or tubular calcium reabsorption, leading to hypercalcemia [1,4–6]. Classically, PTH-related protein-induced hypercalcemia was known as 'humoral hypercalcemia of malignancy', so-called paraneoplastic hypercalcemia, to distinguish it from...
hypercalcemia arising from osteolytic hypercalcemia. In our study, cases 1, 3, and 4 had no disseminated osteolytic hypercalcemia. Multiple myeloma has also presented with PTH-related protein causing hypercalcemia [6].

Chronic hypercalcemia results in metastatic calcification. The kidneys and stomach are the most vulnerable organs, as corroborated in our series. Virchow suggested that the reason for this selective vulnerability is that all of these organs excrete acids and are, therefore, slightly alkaline [7]. Usually, the mineral salts cause no clinical dysfunction. Occasionally, however, massive involvement of the lungs produces remarkable radiographic and respiratory deficits [8], as in our case 1. Histopathologically, prominent calcium deposition in the capillary walls accompanied prominent pulmonary edema, which was the cause of death. Pulmonary calcification may lead to slowly diminishing diffusion capacity, and hypoxemia may ensue [9]. Patients may die from progressive respiratory failure [10,11]. However, in some cases, respiratory failure is rapid and acute [12], such as our case 1. Probably, the calcium-phosphorus products lead to metastatic calcification [12]. In our four cases, only case 1 involved the lungs because of high calcium levels (> 5.0 mmol/L). The mechanism of pulmonary edema in metastatic calcification suggests that this calcification destroyed the alveolar/capillary barrier, causing pulmonary edema and death [12]. Massive calcium deposited in the kidneys (nephrocalcinosis) may, in time, cause renal damage. The earliest functional defect of nephrocalcinosis is an inability to produce a concentrated urine. Other tubular defects, such as tubular acidosis and salt-losing nephritis, may also occur. With further damage, a slowly progressive renal insufficiency develops. This also involves calcium stones and secondary pyelonephritis [8]. In our case 2, myeloma cast nephropathy caused acute renal failure. Case 1 was a victim of chronic pyelonephritis due to a large transitional cell carcinoma of the urinary bladder, resulting in chronic obstructive uropathy. Both cases 1 and 2 also showed calcium deposition in the renal tubules (nephrocalcinosis). Moreover, nephrocalcinosis can exacerbate impairment of renal function. Although hypercalcemia is associated with acute or chronic pancreatitis, no hypercalcemia-associated acute or chronic pancreatitis was proved in this series.

In conclusion, paraneoplastic hypercalcemia can induce metastatic calcification involving multiple organs, especially the lungs, resulting in pulmonary edema. Thus, careful treatment for malignancy-associated hypercalcemia is important to avoid the occurrence of metastatic calcification-associated pulmonary edema.

**References**

副腫瘤高鈣症合併轉移性鈣化
— 臨床病理研究

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高血鈣是常見副腫瘤症候群，高血鈣症可導致轉移性鈣化。我們報告 4 例副腫瘤
高血鈣合併轉移性鈣化以了解這種合併症之臨床病理表現。所有病患均是男性。
年齡 37 到 63 歲。原發腫瘤包括一例膀胱移形上皮癌，一例多發性骨髓瘤及二例
食道鱗狀上皮癌。鈣離子濃度從 3.3 到 5.9 mmol/L。慢性高血鈣導致轉移性
鈣化。腎臓和骨是最常發生的器官。只有第一例血鈣超過 5 mmol/L 而導致轉移性
鈣化侵犯肺臓微血管壁，導致肺水腫而往生。
結論：臨床上謹慎處理副腫瘤高血鈣症是重要的，因為這種併發症可導致轉移性鈣化
有關之肺水腫。

關鍵詞：副腫瘤高血鈣，轉移性鈣化，肺水腫
（高雄醫誌 2006;22:85–8）

收文日期：94 年 8 月 26 日
接受刊載：94 年 11 月 28 日
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