Hypercalcemia in Glioblastoma Multiforme

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Abstract

Hypercalcemia is commonly associated with cancer, occurring in around 10–20% of cancer patients. Hypercalcemia is usually related to solid and non-solid malignancies specifically breast cancer, lung cancer and multiple myeloma. Hypercalcemia has been reported to occur in association with astrocytomas, and uncommonly in gliomas. We report a case of a previously healthy man presenting with glioblastoma multiforme. He was found to have persistently elevated serum calcium and calcitriol with normal parathyroid function. This is the first reported case of hypercalcemia associated with glioblastoma multiforme.

CASE STUDY

Case presentation

Mr. A.S. is a 40 year old man, hypertensive on bisoprolol, presenting with few days history of occipital headache, left arm paresthesias and left hemineglect. Neurological examination revealed normal alertness and orientation, normal speech, acalculia, word agnosia, normal motor power and deep tendon reflexes, left hemineglect asterognosis in the left hand. No evidence of palpable lymph nodes on exam. Normal cranial nerves and fundi. Normal gait, no cerebellar signs. MRI done revealed a large enhancing mass in the right parietal lobe with necrotic center, midline shift and obliteration of the ventricles. The patient was put on steroids and anti-epileptic therapy after the initial laboratory studies were taken. Steroid therapy was continued and tapered postoperatively. Wada test was performed followed by craniotomy. The tumor was resected surgically under microscopy guidance. Pathology revealed glioblastoma multiforme (GBM). Studies on admission were normal except for a persistently elevated serum calcium level of 11.3 mg/dl (8.5–10.5). Workup for hypercalcemia was done revealing a PTH of 20 pg/ml (8–76), TSP=Albumin/Globulin 80 g/l (60–83) = 50/30 (36–53/24–30), TSH 0.418 µu/ml (0.27–4.2), PTHrP<1.5 (<4 pg/ml), 25-Vitamin D 11.20 ng/ml (20–60) and 1, 25-Vitamin D 53.20 pg/nl (20–46.2), Phosphorus 3.8 mg/dl (2.9–6.2), Alkaline Phosphatase 82 IU/l (35–120), Angiotensin converting enzyme (ACE) levels was normal. Chest radiography was normal with no lymphadenopathy. Sistamibi parathyroid scan showed no focal area of abnormal uptake in the neck or chest to suggest a parathyroid adenoma. Follow up studies done one month post-op showed normalization of calcium, and vitamin D levels. Calcium of 9.1 mg/dl (8.5–10.5) with Phosphorus 3.2 mg/dl (2.9–6.2), PTH 34 pg/ml (8–76), 1, 25-Vitamin D 12.1 pg/nl (20–46.2).

Discussion

Hypercalcemia of malignancy is usually associated with breast cancer, lung cancer, and multiple myeloma [7], and usually denotes a poor prognosis [6]. There are three postulated mechanisms behind hypercalcemia of malignancy. The most common cause accounting for around 80% of cases is related

to the production of PTHrP, which is a protein secreted by the tumor [7]. Less commonly, hypercalcemia may be secondary to osteolytic lesions from metastatic involvement of bones[7]. The third etiology for hypercalcemia may be related to the tumor production of calcitriol [7], this being a rare occurrence. There are few reports in the literature of brain tumors associated with hypercalcemia. These were astrocytomas, meningiomas [4], and cerebellar medulloblastomas [2]. The postulated cause of hypercalcemia was attributed to the expression of CaR (calcium receptors) and PTHrP by these tumors [4]. Another case report showed that human cerebellar neurons expressed PTHrP receptors, thus PTHrP may function in an autocrine/paracrine manner in the CNS [4]. Other reported causes of hypercalcemia were related to the skeletal metastatic spread in medulloblastoma [5].Hypercalcemia after partial excision of the cererbellar medulloblastoma was attributed to increased bone resorption by metastatic tumor cells and renal tubular handling of calcium presumably mediated by tumor production of humoral factors [2]. Our case is the first report of GBM associated with persistently elevated serum calcium without elevated PTH or evidence of parathyroid adenoma on scan. In addition, the normal PTHrP levels failed to explain the elevated levels. There was no evidence of osteolytic metastatic lesions in our case. In our case, the drop in calcitriol level from 53.2pg/nl before surgery to 12.1pg/nl after surgery suggests that the hypercalcemia was secondary to tumor secretion of calcitriol, a known but rare mechanism behind hypercalcemia of malignancy. This mechanism was documented in hypercalcemia caused by granulomas: sarcoid [11], tuberculosis [1], histoplasmosis [8], and coccidiomycosis [3]. Calcitriol is also known to be the cause of almost all cases of hypercalcemia associated with Hodgkin's lymphoma and in around one third of hypercalcemia in the setting of non-Hodgkin lymphoma. In these cases, the association between hypercalcemia and calcitriol production by the tumor cells was further shown by the drop in 1, 25-Vitamin D observed after chemotherapy or tumor resection [10]. Cases were also reported in the literature of lymphomatoid granulomatosis and angiocentric lymphoma where hypercalcemia was linked to excess calcitriol production [9]. Recently the isolation of six novel genes termed glioma-amplified sequences (GASs) were isolated from glioblastoma cell lines TX3868 using microdissected mediated cDNA capture. This was the first report of gene amplification for 25-hydroxyvitamin D3, 1α-hydroxylase and the appearance of m-RNA splice variants in glioblastoma multiforme. The endogenous expression of the 25-hydroxyvitamin D3, 1α-hydroxylase gene and the appearance of alternative splice variants reveal a new feature of the molecular pathogenesis of glioblastoma and may represent a new target for glioma therapy [12]. Also, 16 splice variants of CYP27B1 were reported in glioblastoma multiforme. Preliminary evidence for enzymatic activity of endogenous CYP27B1 in glioblastoma multiforme cell cultures was reported, but not the functionality of the splice variants. The addition of calcitriol led to proliferative effect for some cell lines depending on the dose added. The addition led to elevated expression of CYP27B1 and CYP24.Thus, it was noted that glioblastoma multiforme cell lines metabolize calcidiol. A special vitamin D3 metabolism and mode of action in glioblastoma multiforme was found and can be taken into account in future vitamin D3 related therapies[13]. In our case, hypercalcemia was secondary to tumor secretion of calcitriol as documented by elevated blood levels of calcitriol pre-op with a significant drop after surgery.

Conclusion

We conclude that hypercalcemia secondary to elevated calcitriol levels can be also seen in malignant brain tumors. Whether this finding is a reflection of the degree of malignancy or not needs to be further assessed by a study of calcium and calcitriol levels in different types of CNS tumors.

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