Case Report

Ulkem Colak, Gul Y. Mutlu*, Banu O. Sozmen, Esra B. Yucel, Hulya Kayserili and Sukru Hatun **Zoledronate-responsive calcitriol-mediated hypercalcemia in a 5-year-old case with squamous cell carcinoma on the background of xeroderma pigmentosum**

<https://doi.org/10.1515/jpem-2019-0158>

Received April 26, 2019; accepted October 1, 2019; previously published online November 29, 2019

Abstract: Malignancy-induced hypercalcemia is a very rare condition in children whereas it is more common among adult patients with malignancy. The mechanisms of malignancy-induced hypercalcemia include the over-secretion of parathyroid hormone-related protein (PTHrP), osteolytic metastases and the over-production of 1,25-dihydroxyvitamin D (calcitriol). Although hypercalcemia due to PTHrP secretion has been published before, overproduction of calcitriol has not been reported yet in pediatric squamous cell skin carcinoma cases. Herein, we report calcitriol-mediated severe hypercalcemia in a 5-year-old boy with squamous cell skin carcinoma arising in the background of xeroderma pigmentosum (XP) which responded well to zoledronate treatment. To the best of our knowledge, this is the first pediatric case of malignancy-induced hypercalcemia which is mediated by calcitriol in squamous cell skin carcinoma.

Keywords: hypercalcemia; xeroderma pigmentosum; zoledronic acid.

Background

Hypercalcemia in children is a rare condition, which is primarily associated with endocrine disorders like

hyperparathyroidism, inactivating mutations of calcium-sensing receptors and vitamin D intoxication [1]. Although it is more common among adults, hypercalcemia presents in less than 1% of children with malignancy [2].

Malignancy-induced hypercalcemia has been reported in leukemia, lymphoma, myeloma, neuroblastoma, hepatocellular carcinoma, ovarian carcinoma, hepatoblastoma, rhabdomyosarcoma, 2 brain cancer, squamous cell carcinoma and dysgerminomas [2, 3]. The underlying mechanisms are classified into two main groups. First, the osteolytic metastases of tumor cells and second, the humoral products of tumor [2]. The most common humoral product is parathyroid hormone-related protein (PTHrP) which mimics endocrine parathormone effects [4]. The other humoral products are 1,25-dihydroxyvitamin D (calcitriol), prostaglandins, interleukin 1 and interleukin 6, transforming growth factor β and tumor necrosis factor generation of tumor [2].

Herein we present a pediatric case of severe hypercalcemia mediated by calcitriol secondary to squamous cell skin carcinoma developed on the background of xeroderma pigmentosum (XP).

Case presentation

A 5-year-old boy from Somalia presented to the pediatric clinic due to growing masses on the scalp. He was reported to have dry skin and freckling over his entire body for 8 months. He showed symptoms of dehydration, malnutrition and growth retardation with a height of 90 cm (-4.62 standard deviation score [SDS]), weight of 10.9 kg (-4.5 SDS) and BMI of 13.46 (-1.56 SDS, <5 p). Skin overlying his neck and scalp was very dry, atrophic, freckled, scaly and rough. An ulcerated scalp mass was noted on the right parietal region of cranium accompanied with right peripheral facial palsy and right submandibular mass (Figure 1). A second polypoid mass had been growing into the left infraorbital region. Cranial magnetic resonance imaging (MRI) showed right frontoparietal mass infiltrating the extra-axial area with multiple metastatic lymph

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Figure 1: Ulcerated mass on the right parietal region.

nodes in the infra temporal fossa and parotid gland. The histopathological examination of the right parietal and left infraorbital masses revealed well-differentiated squamous cell carcinoma and squamous cell carcinoma with sarcomatous differentiation. Based on the clinical history and findings, he was diagnosed with XP with multifocal squamous cell carcinoma.

Clinical exome sequencing revealed the homozygous splicing c.2251-1G>C pathogenic mutation [5] in the *XPC* gene (NM_004628), associated with XP, group C (OMIM#: 278720). Thus, the patient's clinical diagnosis of XP was confirmed molecularly.

Serum calcium (Ca) was 12.8 mg/dL, 25 OH -vitamin D 9 mg/dL, phosphorus: 4.1 mg/dL and intact parathyroid hormone: <0.51 pmol/L. Urine ca/creatinine ratio was increased as 0.80 (normal <0.20). A dynamic triphasic bone scintigraphy showed a single lytic lesion on the right fronto-parietal region. Serum parathyroid hormone (PTH)-rP level was <0.5 pmol/L, serum 1,25 dihydroxyvitamin D level >210 ng/L (Table 1). The QuantiFERON®-TB Test for diagnosing latent tuberculosis infection yielded a negative result.

Table 1: Serum Ca, P, ALP, PTH (intact), 25-OH vitamin D, 1,25-OH vitamin D, ALP, PTH-rP levels and urine Ca/creatinine ratio.

	Serum level	Reference range
Ca, mg/dL	12.8	8.8–10.8
P, mg/dL	4.8	3–6
ALP, U/L	216	142–335
Parathyroid hormone (PTH), pg/mL	3.8	15–65
25-OH-D, ng/mL	9	20–50
1,25 vitamin D, ng/mL	>210	17.6–109
Urine Ca/creatinine ratio	0.8	<0.2
PTH-rP, pmol/L	<0.5	<1.3

In order to correct hypercalcemia, hydration with normal saline and intravenous (IV) furosemide was administered; however, calcium steadily increased, and hence pamidronate (PA) sodium 1 mg/kg was administered. After a slight decrease, the serum calcium level increased despite second and third doses of PA and methyl-prednisolone treatment at a dose of 2 mg/kg/day for 3 days. IV calcitonin was administered but was withdrawn after the 3rd day of treatment due to tachyphylaxis. As serum calcium increased after the discontinuation of calcitonin, zoledronate 0.0125 mg/kg single dose was administered intravenously. Finally, hypercalcemia was corrected and did not re-occur during the hospitalization period of 7 days. Figure 2 demonstrates serum calcium levels in response to different therapy regimens during hospitalization.

Discussion

We present a very young patient with squamous cell carcinoma of skin in the XP background, presenting with severe hypercalcemia. XP is a rare autosomal recessive disorder of DNA repair resulting in increased sensation to UV radiation [6]. Classical manifestation is freckling before the age of 2 years, severe burning following minimal sun exposure and skin cancer at an early age in childhood.

Inherited syndromes like Fanconi anemia, epidermolysis bullosa, XP and Bloom syndrome significantly increase the head and neck skin cancer risk in children. Indeed, patients with XP have a 10,000-fold increased risk for basal cell and squamous cell carcinomas [7].

Hypercalcemia was mostly driven by PTHrP secretion by malignant cells in the previously reported cases. It has been shown that approximately 80% of malignancy-related hypercalcemia is mediated by the production of PTHrP. The structure of PTHrP resembles that of PTH. PTHrP, acting on the same receptors with PTH, leads to enhanced synthesis of receptor activator of nuclear factor- κ B ligand (RANKL)

Figure 2: Response of serum calcium level to different medications.

and subsequent activation of osteoclast and bone resorption resulting in hypercalcemia [8]. Given that the most probable mechanism in similar cases is PTHrP secretion, the present case was investigated for PTHrP levels which unexpectedly were in a low range.

The second common mechanism of malignancy-induced hypercalcemia is osteolytic metastases and subsequent excessive calcium release from bones [8]. A dynamic triphasic bone scintigraphy performed showed no other lytic lesions other than the primary lesion. The third mechanism is ectopic activity of 1- α -hydroxylase and the formation of 1,25-dihydroxycholecalciferol (calcitriol) which is observed in lymphomas and in some ovarian germ cell tumors. The serum 1,25 dihydroxy-vitamin D level was extremely high in the case reported which confirmed the third mechanism as the etiology of severe hypercalcemia. 1- α -hydroxylase production by activated macrophages is claimed to be responsible for hypercalcemia. Elevated calcitriol level leads to hypercalcemia by several mechanisms including increase in the absorption of calcium in the gastrointestinal tract, decrease in the renal excretion of calcium and increase in the calcium release from the bone by induction of osteoclasts [9]. Calcitriol-mediated hypercalcemia related to squamous cell skin carcinoma in the pediatric age group has not yet been reported. To the best of our knowledge, this is the first report of a child with hypercalcemia mediated by 1,25 dihydroxy-vitamin D due to squamous cell carcinoma.

The treatment options for hypercalcemia include IV hydration, calcitonin, bisphosphonate (BP), denosumab, gallium nitrate, prednisone and hemodialysis. The most commonly used medications are BPs in cases with malignancy-induced hypercalcemia. Notwithstanding the extensive experience on adult cases, reports on pediatric

cases treated with BPs for malignancy-induced hypercalcemia are missing. PA, a second-generation BP is the most widely used intravenous BP, and has been successfully used for hypercalcemia due to vitamin D intoxication [10, 11]. Three sequential doses of PA was administered in the present case; however, a normal serum calcium level could not be achieved. More recently, several studies have demonstrated that zoledronic acid (ZA), a more potent third-generation BP, can be used safely and effectively in childhood osteoporosis. However, data with respect to its use in the treatment of malignancy-induced hypercalcemia in children is missing. ZA was demonstrated to be superior to PA in the treatment of malignancy-induced hypercalcemia in two randomized, controlled clinical trials among adults with normalization of serum calcium levels occurring by day 4 in approximately 50% of patients treated with ZA and in only 33.3% of the PA-treated patients [12]. It was shown that the response to medical treatment in hypercalcemia mediated by calcitriol is limited in the literature. For instance, in a case series, it was reported that most patients with calcitriol-mediated hypercalcemia received higher doses of glucocorticoid than usual, even greater than 50 mg prednisone equivalent per day; however, it did not appear to be of any benefit in terms of time for the serum calcium to normalize [13]. Several studies showed that the median time to normalization of serum calcium was 7–10 days [13–15]. In the present case, glucocorticoid treatment was ceased on day 4, as there was no improvement. Early discontinuation of glucocorticoid treatment may be discussed but taking the osteoclast-activating effect of high levels of vitamin D [9] into consideration, BP treatment was started immediately. However, no response to three doses of intravenous PA administration was observed, and hence calcitonin was

administered. Followed by a transient normocalcemic phase, hypercalcemia re-occurred. Finally, ZA was administered at a dose of 0.0125 mg/kg, which was well below the administration dose of previous reports. Twenty-four hours after the administration of ZA hypercalcemia resolved with no adverse effects and no further dose of ZA was needed.

Although a small number of cases of skin cancer-related hypercalcemia have been reported in the literature, almost all of these are associated with elevated PTHrP and BP has been used primarily in the treatment. Furthermore, the response to BP treatment was reported to be variable in these cases [16, 17]. To the best of our knowledge, hypercalcemia related to only calcitriol overproduction in skin cancer has not been reported yet.

In conclusion, the treatment of malignancy-induced hypercalcemia in children can be complicated. ZA was effective in the relief of hypercalcemia in the case which was irresponsive to PA. The reported observation is suggestive that ZA could be considered as a first line of treatment when BPs are required in the treatment of malignancy-induced hypercalcemia, although further reports are needed to support this observation.

What is new?

Calcitriol production related to squamous cell skin carcinoma in the pediatric age group has not yet been reported. This is the first report of a child with hypercalcemia mediated by 1,25 dihydroxy-vitamin D due to squamous cell carcinoma.

Malignancy-induced hypercalcemia was successfully treated with ZA in this case.

Acknowledgments: We cordially thank the patient and his parents for their cooperation.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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