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Humoral Hypercalcemia in a Patient with Cholangiocellular Carcinoma – Effective Therapy with Denosumab

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 65
Final Diagnosis: Humoral hypercalcemia
Symptoms: Syncope
Medication: —
Clinical Procedure: Establishing diagnosis • lowering hypercalcemia with denosumab
Specialty: Endocrinology and Metabolic

Objective: Educational purpose (only if useful for a systematic review or synthesis)
Background: Hypercalcemia in cholangiocellular carcinoma is a highly uncommon event, mainly reported in Asian patients. In the absence of bone metastases, humoral hypercalcemia of malignancy (HHM) can be assumed. This is mostly the consequence of an elevated parathormone-related peptide (PTHrP) level. The standard therapeutic options in HHM are sometimes limited by the underlying disease or concomitant diseases.
Case Report: We report the case of a 65-year-old Caucasian male. A syncope due to a hypercalcemia of 4.16 mmol/L (normal range, 2.19–2.54 mmol/L) was the initial symptom that eventually led to the diagnosis of cholangiocellular carcinoma. He had no metastatic bone disease; HHM was suspected. PTHrP was moderately elevated. Since there were contraindications for the standard therapeutic options, a therapy with 120 mg denosumab was initiated and proved effective, safe, and restored the patient's quality of life for 11 months.
Conclusions: The moderate elevation of parathyroid hormone-related peptide (PTHrP) in this case is addressed in context with the recent insights of a substantial underestimation of this parameter by many commercial assays which can explain our observation. Denosumab, a human monoclonal antibody which acts as a RANKL-inhibitor (receptor activator of nuclear factor kappaB ligand) was recently suggested as a therapeutic alternative. In this case, the therapy of the hypercalcemia with denosumab due to contraindications for other therapies led to an effective and long-standing remission of hypercalcemia. Its effectivity should be studied in larger case samples.

MeSH Keywords: Cholangiocarcinoma • Hypercalcemia • Parathyroid Hormone

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Background

In primary tumors of the liver, hypercalcemia is a highly uncommon event [1]. It is discussed in 4.5% to 8% of the literature for hepatocellular carcinoma (HCC) [1]. Cholangiocellular carcinoma (CCC) is even more rarely reported to be associated with a paraneoplastic syndrome with hypercalcemia and only a few case reports have been published so far [2–12], mainly in Asian patients [3–8,10,11] (Table 1). Especially rare is the occurrence of CCC in children in general and even more in context of hypercalcemia of malignancy. Recently, the case of an 11-year-old Thai male patient was reported [13].

Apart from local osteolysis as one of the underlying mechanisms, humoral hypercalcemia of malignancy (HHM) is the most common cause [14]. It is defined by elevated serum calcium, low serum phosphorus, low parathormone (PTH), and low 1.25 (OH)₂ vitamin D levels [14]. The production and activity of parathyroid hormone-related protein (PTHrP) seems to be the most common mechanism [14]. Due to the close homology of the N-terminal sequence of PTHrP with PTH, both

hormones bind to the same receptors. This is why PTHrP has effects similar to those of PTH. Furthermore, PTHrP activates pathways that enable tumor cells to form bone metastases [1]. Ectopic calcitriol production is a further mechanism of hypercalcemia [12,15,16], sometimes occurring in other tumors as a coexisting mechanism that has to be considered. Further mechanisms include ectopic PTH secretion or cytokine-induced hypercalcemia. The latter mechanism is sometimes reported in lymphoma and myeloma [17].

As can be seen from the low number of case reports, the phenomenon of HHM is rare in CCC. The phenomenon of HHM also seems to be even rarer in Caucasian patients with CCC. Therefore, we report the case of such a patient, and describe possible diagnostic pitfalls in clarifying the etiology of hypercalcemia and the therapeutic approach that was used due to contraindications for established therapies.

Table 1. Case reports on adult patients with CCC and hypercalcemia of malignancy.

Author, year of publication	Patient sex, age	Serum PTHrP	G-CSF	1,25 OH Vit D	Leukocytosis	Immunostaining for PTHrP in tumor tissue	Therapy of hypercalcemia
Davis et al. 1994 [2]	Male, 54	Elevated	n.d.	“Normal”	n.r.	Positive	Hydration
Aizawa et al. 1997 [3]	Male, 69	Elevated	elevated	n.r.	13700	Positive	Pamidronate
Yamada et al. 2000 [4]	Male, 66	Elevated	n.d.	n.r.	12100	Positive	“Bisphosphonates”, calcitonin
Yen et al. 2004 [5]	Female, 50	Elevated	n.d.	n.r.	„normal“	n.d.	Hydration, pamidronate
Sohda et al. 2006 [6]	Male, 56	Elevated	elevated	n.r.	74300	Positive	Elcatonin, pamidronate
Yamada et al. 2009 [7]	Male, 43	Elevated	“normal”	n.r.	12530	Positive	Zoledronate
Lim et al. 2013 [8]	Male, 63; Male, 68	Elevated (both)	n.d.	n.r.	n.r.	n.d.	Hydration, Pamidronate (both)
Battal et al. 2014 [9]	Male, 53	n.d.	n.r.	n.r.	9430	n.d.	Hydration, calcitonin
Ashihara et al. 2016 [10]	Male, 63	Elevated	n.d.	Elevated	n.r.	Positive	Hydration, furosemide, betamethasone, zoledronate, denosumab
Takeda et al. 2017 [11]	Male, 74	Elevated	n.d.	n.r.	8900	Positive	Saline, furosemide, elcatonin, zoledronate
Yu 2018 [12]	Female, 79	Elevated	n.d.	Elevated	12250	n.d.	Hydration, pamidronate

G-CSF – granulocyte-colony stimulating factor; n.d. – means not done; n.r. – means not reported.

Case Report

A 65-year-old male patient with a long-standing history of nicotine and alcohol abuse was admitted to the hospital because of a syncope in June 2017. He had suddenly become unconscious. The patient reported a weight loss of several kg in the last months. He reported that he was significantly worse in terms of physical and mental performance for about 2 weeks. In the extended anamnesis survey, the patient himself reported a reduction in physical performance and self-motivation which had been increasing for about 3 to 4 months. He suffered from arterial occlusive disease stage 4 and had received a femoropopliteal bypass on the right side in November 2011 and on the left in February 2012. Diabetes mellitus type 2 was diagnosed approximately 3 years ago, the glycemic control was good under sitagliptin therapy. Moreover, he was treated with simvastatin, acetylsalicylic acid, and ramipril. Due to the alcoholism, in 2011, he completed a successful withdrawal therapy in the local psychiatry clinic. Nicotine consumption was about 12 cigarettes per day, in the past about 1 package per day.

At physical examination, the liver was enlarged, but not painful. No jaundice was observed. The patient was afebrile and alert. There were no pathological cardiopulmonary findings. The dental status was very poor.

Initial laboratory findings

Initial laboratory findings were: calcium of 4.16 mmol/L (normal range, 2.19–2.54 mmol/L); albumin of 38.3 g/L (normal range, 35–52 g/L) accounting for an albumin-corrected calcium level of 4.194 mmol/L; phosphorus of 0.75 mmol/L (normal range, 0.81–1.45 mmol/L); intact PTH of 0.19 pmol/L (normal range, 1.6–6.9 pmol/L); PTHrP of 1.5 pmol/L (normal range, <1.3 pmol/L, measurement methods included parathyroid hormone-related peptide RUO, Active® IRMA Beckman Coulter Life Sciences); vitamin D3 (25-OH) of 28.1 nmol/L (normal range, >50 nmol/L); vitamin D3 (1,25-OH) of 69.8 ng/L (normal range, 22–111 ng/L). Blood count was 11 000 leucocytes, otherwise inconspicuous blood count. Creatinine was 103 µmol/L (normal range, 62–106 µmol/L); glomerular filtration rate was 67.54 mL/min/1.7 m² (normal range, >70 mL/min/1.7 m²); uric acid was 538 µmol/L (normal range, 214–416 µmol/L); ALAT/GPT was 0.27 µkat/L (normal range, 0.17–0.83 µkat/L); gamma-GT was 6.20 µkat/L (normal range, 0.17–1.19 µkat/L); alkaline phosphatase was 3.27 µkat/L (normal range, 0.67–2.15 µkat/L); bilirubin total was 6.40 µmol/L (normal range, <17 µmol/L).

Magnetic resonance imaging demonstrated a hypodense tumor in the right liver lobe with a maximum extension about 13.6 cm. Because of the irregular form, several confluent lesions were likely (Figure 1).

Figure 1. Cholangiocellular carcinoma in the right liver lobe with a maximum extension of about 13.6 cm.

A computed tomography (CT)-guided puncture of the liver was performed. This showed infiltrates of a poorly differentiated glandular tumor. Additional immunohistochemical investigations of the liver biopsies were carried out and the tumor cells proved strongly positive for cytokeratin (CK) 19 and weakly membranous positive for CK 7. Alpha fetoprotein (AFP), CK 20, estrogen and progesterone receptor, hepar-1, napsin A, and thyroid transcription factor 1 (TTF-1) were negative. The immunohistochemical examination results corresponded with a bile duct carcinoma with pronounced sclerosis. Unfortunately, an additional staining for PTHrP was not possible.

Further imaging revealed no detectable metastases in other organs such as the lung or the bones, the latter was also confirmed by skeletal scintigraphy.

We initially treated the patient's hypercalcemia with a forced diuresis regimen. This was terminated on June 26, 2017, after the patient had shown a decrease in calcium levels below the normal range (patient level was 2.11 mmol/L). As to be expected, again, an increase in the calcium value occurred in the following days; therefore, on May 5, 2017 120 mg of denosumab was administered to the patient (Xgeva™). We chose this therapy on the basis of the patient's comorbidities and the poor dental condition, although there is potentially also the risk of jaw osteonecrosis, but presumably lower than with the use of bisphosphonates. In the time interval after the denosumab application, the patient had no more hypercalcemia until April 2018 (Figure 2).

Under the assumption of a curative option by surgery, a laparotomy was performed. Unfortunately, it revealed a clearly enlarged lymph node of about 2 cm in diameter on the liver

Figure 2. Course of the serum calcium levels in the patient with cholangiocellular carcinoma. Note the rise of serum calcium in April 2018, the patient deceased in May 2018.

hilus, and tumorous deposits in the left hepatic lobe. Thus, a resection did not appear to be sensible. For the histological confirmation of this situation, the excision of tumor with approximately 1.5 cm in diameter in the left hepatic lobe was performed in form of a wedge excision. The histological examination confirmed the diagnosis of CCC as already established in the initial liver biopsy.

The patient was treated with a chemotherapy with cisplatin and gemcitabine. In March 2018, imaging by means of CT-thorax and abdomen showed the known tumorous mass in the right liver lobe with a now newly appearing mass in the left lobe of the liver hilus, thus, proving progressive underlying disease. This caused the initiation of a second-line chemotherapy with capecitabine. In the same month, the patient had suffered from a confirmed influenza A infection and received oseltamivir, due to suspected bacterial superinfection; he was additionally treated with ampicillin/sulbactam.

The last available calcium serum calcium level measurement was from April 2018 and was slightly elevated with 2.83 mmol/L. In March 2018, the serum calcium level was in the normal range (Figure 2). The patient deceased in May 2018, presumably due to disease progression; he had no clinical signs of liver failure.

Discussion

Hypercalcemia that occurs in hepatic carcinoma is typically associated with a poor prognosis [2,8]. In unresectable cases in trials with systemic chemotherapy and with neoadjuvant chemoradiation, median survival times ranging from 2 to 15 months are reported [18].

Interestingly, in this very case, a syncope due to the severe hypercalcemia led to hospitalization and the diagnosis of CCC. In other case reports, in context to the initial hypercalcemia, fatigue, weakness, and anorexia were frequently reported. Sohda et al. [6] reported “consciousness disturbances” and, in some cases, hypercalcemia developed over the course of the disease and not as an initial finding.

There are different strategies of treating hypercalcemia of malignancy such as saline hydration to promote calcinuresis, or bisphosphonates to reduce pathologic osteoclastic bone resorption; calcitonin and glucocorticoids also exert calcium-lowering effects [19]. However, these therapies are sometimes limited by the underlying disease or the burden of comorbidities (impaired renal function, diabetes mellitus, hypertension) in this patient group. Due to the different mode of action, their onset of action varies, and an etiological clarification of the hypercalcemia is mandatory, too.

In the absence of bone metastases, HHM is the most frequent cause [14]: Since the identification of PTHrP, all case reports on the issue of humoral hypercalcemia of malignancy described serum PTHrP as elevated and, if applied, positive immunostaining for PTHrP in tumor tissue (Table 1).

However, the measurement of PTHrP has its pitfalls. In the case reported here, PTHrP was not dramatically raised, but moderately raised. A problem in the measurement of PTHrP is that the substance is very unstable. Another problem is that by establishing a liquid chromatography/mass-spectrometry method (LC-MS/MS), Kushnir et al. [20] demonstrated that commercial RIAs substantially underestimate the PTHrP concentration, which causes underdiagnosis of PTHrP as a cause of hypercalcemia in many patients. Given the suppression of PTH in our case, that can be expected as a result of PTHrP action, thus we regard it reasonable to assume the aforementioned problems were an explanation for the insignificantly elevated PTHrP levels. That said, and given the at least moderate elevation of serum PTHrP, a positive immunostaining of the tumor tissue was assumed, however, it was highly unfortunate that due to flaws in the workup of this case, staining was not possible. However, the second focus of this discussion lies on the therapeutic options in hypercalcemia:

According to previous reports, the serum calcium levels are problematic to control in patients with HHM in CCC, when a significant volume reduction of the tumor is unattainable [10]. As has already been discussed in this paper, the standard therapies to lower serum calcium in HHM have limitations and contraindications in some patients. This is why Ashihara et al. [10] recently reported the case of a 63-year-old male with CCC in whom a combined approach with hydration, furosemide, elcatonin, and zoledronic acid did only transiently reduce the

serum calcium levels. Eventually, a single dose of 120 mg denosumab proved to be effective. Denosumab is a human monoclonal antibody that acts as a RANKL-inhibitor (receptor activator of nuclear factor kappaB ligand). This mode of action is different from the standard therapies: Due to binding to the common PTH/PTHrP receptors located on osteoblast precursor cells, factors stimulating the activity of osteoclasts and their production (macrophage colony-stimulating factor and RANKL) are released, whereas osteoprotegerin (OPG), which blocks the interaction between the RANK receptor and RANKL, is decreased. In 2 models of hypercalcemia of malignancy (hypercalcemia was induced either by subcutaneous inoculation of syngeneic colon adenocarcinoma cells or by subcutaneous injection of high-dose recombinant PTHrP), Morony et al. [21] demonstrated that OPG caused a rapid reversal of hypercalcemia, and the speed and duration of hypercalcemia suppression were significantly greater than with high-dose bisphosphonates (pamidronate or zoledronic acid). OPG also caused greater reductions in biochemical markers of bone resorption compared to the bisphosphonates.

Our approach of treating the patient with denosumab to maintain a long-standing reduction of serum calcium levels was more likely determined by the concerns about the other approaches (e.g., bisphosphonates and his poor dental status, steroids, manifest diabetes mellitus, hypertension). The therapy proved to be very effective and the patient maintained normal serum calcium levels during the further course of his disease, for 11 months. It is also important to mention that the persistent normalization of the calcium levels (without other therapies being necessary) achieved a good quality of life, as reported by the patient. It is noteworthy that the serum calcium levels rose again 12 months after the injection; before a further injection could be performed, the patient deceased (Figure 2).

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The effectivity of the approach used in the case reported by Ashihara et al. [10] and in our patient case, underline the therapeutic potential of denosumab in hypercalcemia, even if not determined by osteolysis.

Conclusions

The prognosis of CCC and especially CCC with humoral hypercalcemia of malignancy is still limited. Despite the poor prognosis, an effective control of hypercalcemia and its symptoms restores life quality. Given contraindications to the standard therapies, a RANKL-antagonistic approach, even in cases with PTHrP-mediated hypercalcemia and not only in case of bone metastases, may be a reasonable approach that warrants further investigation.

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Conflict of interest

None.

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