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Leucovorin/5-Fluorouracil Induced Hypocalcemia

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Abstract:

Hypocalcemia is a relatively common metabolic abnormality that is observed in hospitalized patients. Drug related hypocalcemia is usually missed in such patients as a consequence of multiple contributing factors that lead to low calcium levels. We report a case of hypocalcemia in a 34 years old lady with metastatic gastric adenocarcinoma after initiation of palliative chemotherapy with combination of leucovorin and 5-fluorouracil. The mechanism beyond this side effect is explored in this case. Effective clinical management can be handled through awareness of this adverse effect induced by certain chemotherapeutic agents on serum calcium level.

Key words: Adenocarcinoma, Calcium, Dihydroxycholecalciferols, Hypocalcemia, Leucovorin.

Introduction

Hypocalcemia is a commonly encountered metabolic abnormality in hospitalized patients. Drug induced hypocalcemia may be masked by other adverse drug reactions or disease states, and the involvement of a specific agent in its pathogenesis may be overlooked. On the other hand, the degree of severity of drug related hypocalcemia is usually mild and often a symptomatic, though it can be severe sometimes. Among chemotherapeutic agents, cisplatin is a well-known cause of hypocalcemia. In contrast, combination of leucovorin/5-fluorouracil (LV/5-FU) is less commonly addressed cause. In this case we report a case of hypocalcemia developed after starting this chemotherapeutic agent.

Case Report

34 years old woman was referred to our oncology service for further management of metastatic gastric adenocarcinoma. She initially presented to the primary institution with three months history of fatigue, weakness, poor oral intake, dysphagia, vomiting, abdominal pain and 7 kg weight loss. Rest of systemic review was unremarkable. Physical examination showed pleasant young lady who was alert and oriented. She was afebrile and her blood pressure was 123/90 mmHg, heart rate 94 beats/minute with oxygen saturation of 98% in room air. Systemic examination was unremarkable except for diffuse mid-epigastric tenderness with mild to moderate ascites. No rebound and no palpable

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masses were elicited. There was no detectable lymphadenopathy in neck, axilla or groin.

Work up with esophagogastroduodenoscopy (EGD) revealed narrowing of the esophagus with ingurgitated gastric mucosal folds in the corpus and fundus of the stomach. Multiple biopsies were taken and were consistent with poorly cohesive carcinoma with signet cell features. Further staging with chest, abdomen and pelvis CT showed ascites and abnormal soft tissue density surrounding the celiac artery and superior mesenteric artery extending into the left adrenal fossa and associated with mild left hydronephrosis. Abdominal paracentesis was performed and consistent with a malignancy. In the context of advanced gastric adenocarcinoma with intra-abdominal metastasis and malignant ascites, she was not considered a surgical candidate and a decision was made to start systemic palliative chemotherapy with FOLFOX (combination regimen of leucovorin, 5-fluorouracil and oxaliplatin).

Prior to starting the chemotherapy, baseline investigations showed mild hypokalemia 3 mmol/L (3.6-5.1), bicarbonate 30 mmol/L (22-32) and estimated glomerular filtration rate (eGFR) 89 ml/min/1.73m^2. Bone profile was normal with corrected calcium 2.36 mmol/L (2.23-2.58), magnesium 0.77 mmol/L (0.74-1.03) and phosphorus 1.2 mmol/L (0.78-1.53). Six days after first cycle of chemotherapy, the patient was readmitted with 3 days history of weakness, poor oral intake, loss of appetite and severe mucositis, stomatitis, keratoconjunctivitis, mouth and genital ulceration as well as skin discoloration.

Initial investigation showed beside hypokalemia, mild hypocalcemia with corrected calcium level 2.13 mmol/L (2.23-2.58), hypophosphatemia with phosphorus level 0.38 mmol/L (0.78-1.53) and magnesium level 0.67 mmol/L (0.74-1.03). Corrected calcium continued to drop slowly and on the fifth day post admission, her corrected calcium was 1.86 mmol/L with phosphorus level 0.31 mmol/L, magnesium level 0.78 mmol/L and eGFR 95 ml/min/1.73m^2. At the same time, intact parathyroid hormone (iPTH) was 51.27 pmol/L (1.6-6.9) and 25- hydroxyvitamin D level was 95 nmol/L (50-150).

Total parenteral nutrition (TPN) was started on the next day and two days post TPN initiation, endocrinology consultation was obtained for hypocalcemia with secondary hyperparathyroidism. Labs were repeated (while on TPN) and showed the following results: corrected calcium 2.15 mmol/L, magnesium 0.91 mmol/L, phosphorus 0.53 mmol/L, iPTH 13.1 pmol/L, 25- hydroxyvitamin D 86 nmol/L, 1,25- dihydroxyvitamin D 24 ng/L (20-80) equivalent to 58 pmol/L (48-192).

Unfortunately, the patient developed pancytopenia with neutropenic fever ended up with septic shock and she passed away few days later.

Discussion

To our knowledge, few studies were published regarding hypocalcemia associated with chemotherapy, especially in the LV/5-FU regimen. Among chemotherapeutic drugs, cisplatin is commonly known to cause hypocalcemia through inducing hypomagnesemia [1]. This leads to functional hypoparathyroidism and parathyroid hormone (PTH) resistance [2]. FOLFOX is a chemotherapy regimen that contains beside oxaliplatin, a combination of LV/5-FU. Most of the studies on this combination report the hematological and other non-hematological toxicities including mucositis, stomatitis and other gastrointestinal side effects [3,4]. Hypocalcemia as a side effect of this combination is usually overlooked despite the fact that this combination has been reported to cause hypocalcemia in 65% of patients [5].

Hypocalcemia was observed with different number of chemotherapy courses in which some patients developed it even after one chemotherapy course. It had been found that combination of LV/5-FU was associated with significant reduction of $1,25(OH)_2D_3$ level on measurements obtained on the fifth day post-chemotherapy compared to pre-chemotherapy level [5]. Despite the fact that the mechanism for the decrease in $1,25(OH)_2D_3$ with this chemotherapy remains obscure, one possibility is inhibition of the renal 1α-hydroxylase activity [5].

In our case, 1,25 dihydroxyvitamin D was in the lower normal range despite normal 25 hydroxyvitamin D level, appropriate PTH response and normal magnesium level. In profound vitamin D deficiency, the level of $1,25(OH)_2D_3$ is usually low. In moderate vitamin D deficiency, the stimulation of the renal 1α-hydroxylase by PTH can result in a normal or even elevated $1,25(OH)_2D_3$ level. These high levels of $1,25(OH)_2D_3$ reflect the action of PTH on the renal 1α-hydroxylase [6].

Conclusion

It is assumed that this side effect (hypocalcemia) is transient with the chemotherapy courses and this case emphasizes the importance of monitoring hypocalcemia clinically and biochemically in patients receiving chemotherapy with leucovorin/ 5-fluorouracil regimen and replacing accordingly with calcium and active vitamin D analogue once needed.

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