CASE REPORT

Hypercalcemia as a Rebound Phenomenon of LOXO-292 Efficacy in Medullary Thyroid Cancer

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Introduction

Medullary thyroid cancers (MTC) are neuroendocrine tumors of thyroid parafollicular C cells, which account for 5% to 10% of all thyroid cancers. The C cells secrete different types of peptides and hormones with calcitonin being the most common. Increased calcitonin levels confirm the diagnosis of MTC and are used in the follow-up of patients longitudinally for recurrence. Normal calcitonin values are less than 5 pg/mL in women and below 8.5 pg/mL in men. Calcitonin directly inhibits bone resorption and quickly promotes renal excretion of calcium, leading to a decrease in serum calcium 2 hours after administration.[1]

Calcitonin levels are increased in all MTC cases, of whom 70% to 80% harbor a sporadic *RET* gene mutation. The other 20% to 30% are caused by hereditary mutations. A wide range of cancers, including papillary thyroid cancer, melanoma, pancreatic cancer, lung adenocarcinomas, leukemia, and breast cancer, are associated with anomalies or overexpression of RET fusion proteins.[2-9] Although *RET* somatic mutations have been found in different codons, the most frequently reported changes are in 634 in exon 11 and 918 in exon 16.[10]

Tyrosine kinase inhibitors, such as vandetanib and cabozantinib, are approved for MTC by the Food and Drug Administration. These drugs have been found to have encouraging results in the treatment of MTC; however, they are not curative, and patients develop resistance to the therapy.[11,12] Selpercatinib (LOXO-292) is a highly selective, small–molecule RET tyrosine kinase inhibitor with nanomolar potency against diverse *RET* alterations, favorable pharmacokinetic properties, and considerable central nervous system penetration.[13] Recently, published data reported that LOXO-292 therapy produced an objective response rate of 68% in 105 patients who had received a median of three previous treatment regimens. In addition, 34 previously untreated patients achieved an objective response rate of 85%. Interestingly, these responses were achieved in different solid tumors of varied origins that had a *RET* gene alteration in the tumor or blood.[14]

Here, we report the case of a 57-year-old man with MTC who was treated with LOXO-292 in a clinical trial at a dosage of 160 mg orally twice daily. He presented an abrupt shrinkage of the lung masses with rapidly declining calcitonin levels during the first 2 weeks of treatment. Concurrently, he developed acute hypercalcemia, hypothetically owing to a secondary rebound mechanism.

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Drs. Kian and Levitas equally contributed to this work.

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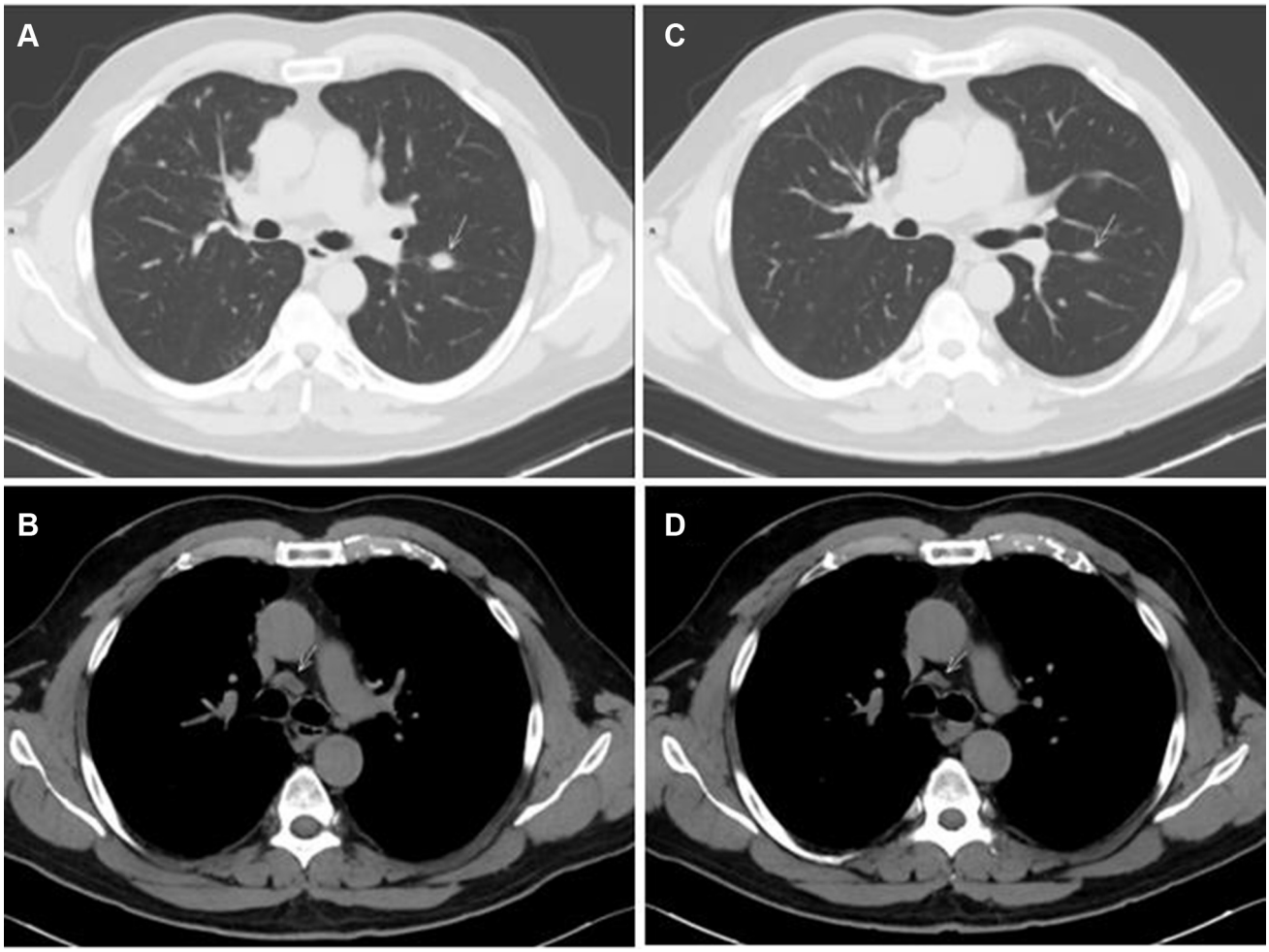

Figure 1. Pre- and posttreatment imaging by computed tomography. (*A*) Pretreatment dominant lung nodule located on the left lung fissure and (*B*) largest lymph node located in right parabronchial mediastinum. Consecutive computed tomography images posttreatment with decrease in size of lung nodule (*C*) and mediastinal lymph node (*D*).

Case Report

A 57-year-old Caucasian man was diagnosed with metastatic MTC in 2015. Previously, he had undergone subtotal thyroidectomy with cervical lymph node dissection and a debulking operation after local recurrence without adjuvant radiation therapy. He had iatrogenic hypocalcemia after thyroidectomy, which was treated with 4 g of replacement calcium once a day for 4 years. His comorbidities included chronic renal disease with a baseline serum creatinine level of around 1.5 mg/dL and a glomerular filtration rate of 60 mL/min. When he harbored a *RET* M918T mutation in 2018, he was further treated with vandetanib until disease progression and increasing calcitonin levels one year later (Fig. 1). On May 2, 2019, he began receiving LOXO-292 under a clinical trial. His baseline calcitonin levels, pre–LOXO-292 initiation, were 3300 pg/mL (Fig. 2*A*) with normal calcium and phosphorus levels (Fig. 2*B*). After LOXO-292 was initiated (160 mg orally twice daily), there was a marked decrease in calcitonin levels from 3300 pg/mL to 456 pg/mL within 6 days (Fig. 2*A*). Calcium, phosphorus, and creatinine levels unexpectedly increased during the first 2 weeks of the therapy (Fig. 2*B*). Consequently, calcium supplementation and LOXO-292 therapy were stopped, and fluid replacement therapy was initiated. After the fluid replacement therapy, calcium, phosphorus, and creatinine levels gradually returned to their normal values. LOXO-292 and calcium supplementation were resumed at lower dosages (80 mg orally twice daily and 1 g once a day, respectively). Since then, the patient has been in complete response with normal calcitonin levels.

Discussion

In this report we have described the case of a patient with metastatic MTC who harbored a *RET* M918T mutation with high levels of calcitonin and had a marked decrease in calcitonin levels accompanied by

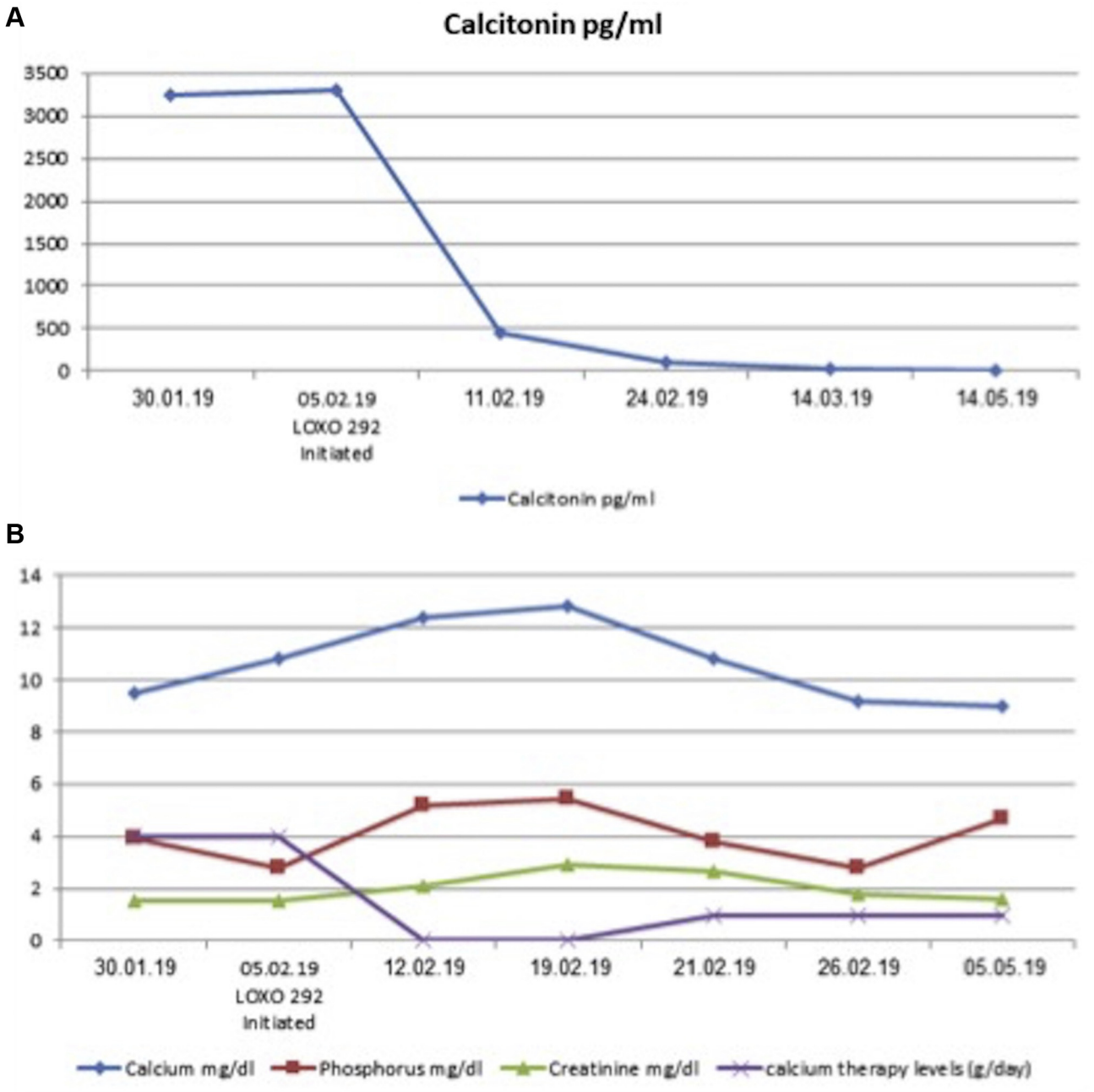

Figure 2. Calcitonin levels before and after initiation of LOXO-292 therapy (*A*). Calcium, phosphorus, and creatinine levels before and during initiation of LOXO-292 therapy. In addition, calcium replacement therapy dosage during this period (*B*).

hypercalcemia during the first 2 weeks of LOXO-292 therapy. His phosphorus and creatinine levels were also elevated during this period, conceivably owing to a secondary rebound mechanism. A study by Dellay et al. suggests that calcitonin carries a risk of immediate hypocalcemia, rebound hypercalcemia, and the propensity to develop tachyphylaxis after 2 days to 3 days of therapy.[1]

To our knowledge, this is the first reported case of rebound hypercalcemia within the first 2 weeks of LOXO-292 therapy. We believe that this phenomenon is related to a rapid decrease in calcitonin levels within the first 2 weeks of the therapy. Therefore, we recommend tight monitoring of calcium and phosphorus levels when treating MTC with drugs such as LOXO-292 that present high and selective efficacy.

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