

Growth hormone therapy in non-islet cell tumor mediated hypoglycemia associated with metastatic lung adenocarcinoma

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Abstract

Severe hypoglycemia is a rare but serious sequela of malignancy. It may be seen with either islet or non-islet cell tumors. Treatment of non-islet cell tumor mediated hypoglycemia (NICTH) is often challenging, especially when rapid tumor debulking is not feasible. Medical therapies with glucocorticoids and enteral feeds have been utilized in the past, but with limited success. The use of recombinant human growth hormone (rhGH) in cases of NICTH, although seemingly effective, has been limited to end-stage cancers, due to its potential for accelerating tumor growth. Here, we report the successful use of rhGH in severe and refractory NICTH, in a patient with non-operable metastatic lung adenocarcinoma, without altering the patient's oncological outcome.

Introduction

Severe hypoglycemia is a rare but serious sequela of malignancy [1]. It can be seen with both islet and non-islet cell tumors. In regards to non-islet cell tumor hypoglycemia (NICTH), no single pathogenic mechanism explains all cases of this paraneoplastic phenomenon. It is thought, however, that the majority of cases occur as a result of tumor production of molecules with insulin-like activity which in turn stimulate insulin receptors. An incompletely processed insulin-like growth factor 2 (IGF-2), known as "big" IGF-2, has been implicated in the majority of the reports found in the medical literature [1].

Tumor debulking, through surgical and/or medical oncologic treatments, is the mainstay therapy for NICTH [2]. When rapid debulking is not feasible, medical therapies such as glucocorticoids and recombinant human growth hormone (rhGH) have been utilized to ameliorate the hypoglycemic episodes [3]. Unlike glucocorticoids, experts recommend limiting the use of rhGH within the realm of palliation, in end-stage cancers, due to its potential for accelerating tumor growth. Few case reports have been published on the use of rhGH in NICTH, the majority of which have been reported in palliative care settings [4,5]. Herein, we report the successful use of rhGH, outside of the conventional palliation window, in treating severe and refractory NICTH, without altering the patient's oncological outcome.

Case presentation

A previously healthy 78-year-old man with no previous chronic conditions was diagnosed with non-operable lung adenocarcinoma with metastases to the brain and spine. Factoring in his pre-treatment ECOG (Eastern Cooperative Oncology Group) performance status of 1, he had a projected life expectancy of approximately 3 years. Shortly after his cancer diagnosis, and prior to starting therapy with Afatinib (Gilotrif), he reported several episodes of diaphoresis and blurry vision, particularly after prolonged fasting states. During these episodes, he

was documented to have blood glucose (BG) measurements in the range of 25-30 mg/dL (normal range: 65-100 mg/dL).

After documenting the presence of Whipple's triad in the outpatient setting, the patient underwent an inpatient fast-study. His laboratory evaluation at the onset of hypoglycemia with a BG value of 35 mg/dL were significant for suppressed levels of C-peptide at 0.2 ng/mL (normal range: 0.8-3.2 ng/mL), low free insulin at 4.5 mU/L (normal range: 1.0-24.0 mU/L), low proinsulin at 2.3 pmol/L (normal range: <8.0 pmol/L), suppressed beta-hydroxybutyrate at < 0.10 mmol/L (normal range: <0.28 mmol/L). On further evaluation he was found to have an IGF-1 level at 158 ng/mL (normal range: 22-216 ng/mL) and an IGF-2 level at 297 ng/mL (normal range: 333-967 ng/mL). His insulin antibody assay and sulfonylurea drug screens were both negative. Adrenal and thyroid evaluations were unremarkable. Although his IGF-1 level was not suppressed, the rest of his laboratory studies fitted the typical pattern of NICTH. It was concluded at that point that his hypoglycemia was likely mediated by the presence of a tumoral molecule with the capacity of stimulating insulin receptors.

To counteract his hypoglycemia, the patient was scheduled to have frequent high protein and complex carbohydrate containing meals throughout the day. Continuous intravenous dextrose infusions and enteral tube feeds were also added to his regimen. He was also started on prednisone 40 mg daily, which was subsequently increased to 60 mg daily in split doses. Despite these interventions, he continued to

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experience frequent recurrences of severe hypoglycemia with BG documented as low as 24 mg/dL (Figure 1). Given the severity of the hypoglycemic episodes and their detrimental effects on the patient's overall quality of life, it was felt at that point that his case warranted a trial of rhGH therapy, despite the patient being in a "non-palliative" timeframe with regards to his life-expectancy.

Following an informed discussion regarding the risks and benefits of the use of rhGH, the patient elected to start the therapy. Given the high severity and life-threatening nature of his hypoglycemic episodes, he was started on rhGH 3.0 mg once daily. To achieve a better effect the rhGH was increased to 2.0 mg twice daily then to 4.0 mg twice daily, a dose previously reported in the literature [4]. The patient's hypoglycemia significantly improved after initiation of rhGH (Figure 1). The enteral tube feeds and the continuous intravenous dextrose infusions were all discontinued shortly after initiation of rhGH. The prednisone was tapered off within 1 week, and patient was safely discharged home on rhGH only. Thereafter, the patient was able to maintain all BG values above 70 mg/dL.

At a follow up visit, 6 weeks post-rhGH initiation, the patient continued to maintain his BG between 81 and 118 mg/dL. At that time, his tumor staging imaging showed regression of tumor size at primary and distant metastatic sites, as expected with his current oncology regimen. The patient experienced no side effects related to rhGH therapy, even at the high dosages. He continued to do well and has remained on Afatinib therapy with favorable oncological response up-to-date.

Discussion

NICTH is a rare paraneoplastic phenomenon encountered in the setting of a wide variety of benign and malignant tumors. The majority of cases have been described with mesenchymal tumors and hepatocellular carcinoma, but other reported tumor types include sarcomas, adenocarcinomas, gastrointestinal stromal tumors and renal cell carcinoma [7]. To our knowledge, no other cases of NICTH have been previously described in association with adenocarcinoma of the lung.

In most of the cases, the pathogenesis of NICTH has been related to presence of "big" IGF-2 molecules. These molecules are formed due to abnormal processing of an IGF-2 precursor in tumors with aberrant IGF-2 gene transcription and gene expression [8,9]. This disrupts the normal creation of ternary complexes of IGF-2, IGF-binding protein 3 (IGFBP-3), and acid labile subunit (ALS). Consequently, big IGF-2 molecules are mainly found within smaller binary complexes and a greater fraction stays in the free form. Both the binary complexes and the unbound big IGF-2 can cross the capillary membranes and can act on insulin and IGF-1 receptors, ultimately leading to hypoglycemia and suppression of the pituitary GH-IGF-1 axis [10-12].

The typical pattern for NICTH includes low serum glucose level with simultaneous low insulin/proinsulin/C-peptide/beta-hydroxybutyrate levels, and negative results on an oral hypoglycemic agent screen [7]. The IGF-2 levels may or may not be elevated [13], though have been consistently reported to be higher than the IGF-1 levels. And thus, reported IGF-2:IGF-1 ratios in cases of NICTH have been elevated, in some cases as high as 10:1 [11,14].

Treatment of NICTH should be focused on treating the malignancy itself. If removal is not possible, palliative tumor debulking is likely to decrease the severity of hypoglycemic events [2]. Treatment with chemotherapy and radiation has also proven to be of benefit [7]. When the tumor cannot be excised, other alternative therapies have an integral role in the management of this condition.

As with any episode of hypoglycemia, the immediate goal is to achieve euglycemia. Initially, an increase in enteral intake (whether in amount of food, caloric density, and/or frequency) should be tried in addition to intravenous glucose or dextrose [7]. If nutritional interventions do not suffice, injected glucagon may also be used as a transient measure when hypoglycemic episodes arise. For a more prolonged effect, continuous glucagon infusion has been tried with success in some cases [15,16], but it does not provide a realistic long-term solution for non-palliative patients.

Glucocorticoids are the most extensively described medical therapy for NICTH. They can be useful in treating hypoglycemia via reduction

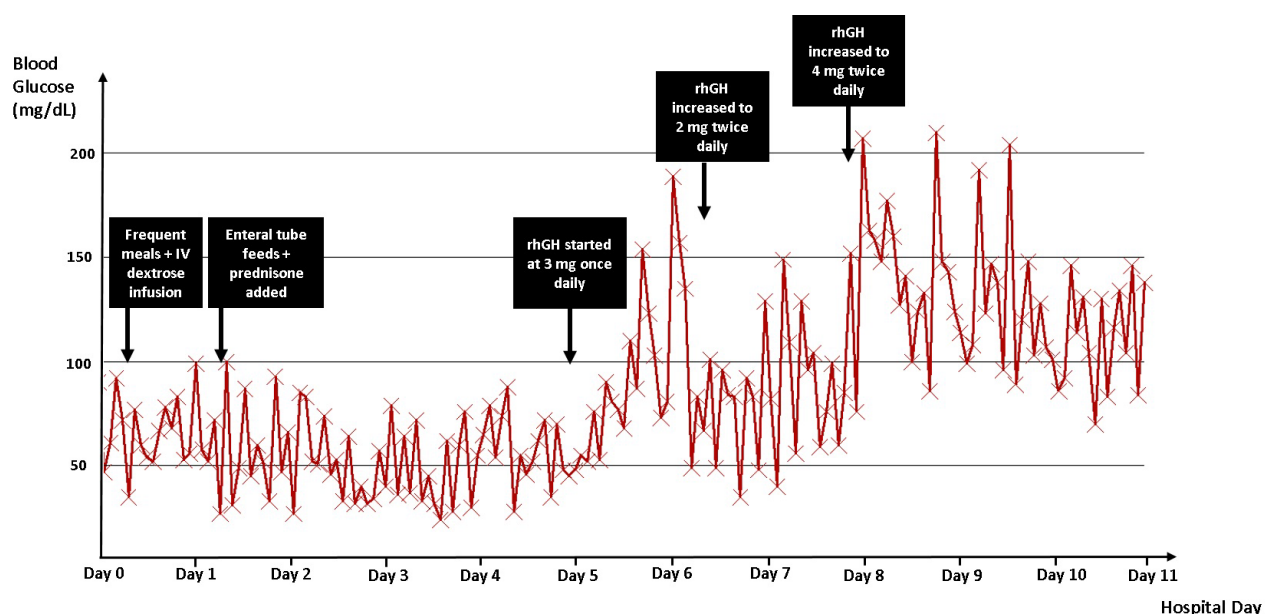


Figure 1. Blood glucose trend throughout patient's hospital stay. rhGH: recombinant human growth hormone.

in IGF-2 levels [17]. However, several cases have been reported where glucocorticoids failed to treat NICTH, even with extremely high doses [18,19]. In a refractory setting, as was shown in this case, rhGH can be considered as well. GH suppresses peripheral glucose uptake [3] and leads to increased levels of IGF-1, IGFBP-3, and ALS, with resultant promotion of the normal ternary-complexed IGF-2 [13,17,20]. Drake et. al. reported the use of rhGH in two patients with pleural masses who both continued to experience hypoglycemia despite several attempted treatments. Both patients improved when treatment with rhGH was initiated [4]. The glucose levels stabilized on 6 and 8 mg daily of rhGH daily [4]. Others reported the use of up to 12 mg of rhGH daily for treatment of malignancy-induced hypoglycemia [5]. It should be noted that use of rhGH should reduce the need for other therapies, such glucocorticoid therapy, the latter of which puts patients at a high risk for pathologic fractures, especially in the setting of concomitant bone metastases.

The current literature and experts' recommendations for the use of rhGH implicate the use of the latter for palliation purposes in NICTH. The case presented here raises questions regarding the definition of "palliation" in this context. We believe it ought to be based on a measure of quality of life rather than the conventional "6 months or less" outlook. More importantly, such treatment should always be discussed with patients, in the context of shared medical decision-making, for the therapy to be aligned with their wishes and values.

Conclusion

We demonstrated the successful use of rhGH as a therapy outside of the conventional palliative care setting, in treating a case of severe, refractory NICTH.

Disclosure statement

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