

Tyrosine Kinase Inhibitors' Newly Reported Endocrine Side Effect: Pazopanib-Induced Primary Adrenal Insufficiency in a Patient With Metastatic Renal Cell Cancer

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Abstract

Tyrosine kinase inhibitors (TKIs) have been used in the treatment of multiple types of cancer. Pazopanib is one of the TKIs and is considered a first-line treatment for adult patients with metastatic renal cell carcinoma. Many endocrine-related adverse effects have been noted with the use of TKIs including hypothyroidism, vitamin D deficiency, altered bone density, secondary hyperparathyroidism, abnormal glucose metabolism, gynecomastia, and hypogonadism. Subclinical glucocorticoid deficiency and adrenal insufficiency have been reported with the use of TKIs in only a few cases so far; thus, its true prevalence and clinical significance have yet to be fully elucidated. The mechanism is still not fully understood; however, adrenal toxicity with hemorrhage and/or necrosis of the adrenal glands has been observed in studies. In this article, we describe the first reported case of pazopanib inducing primary adrenal insufficiency in a patient with metastatic renal cell carcinoma diagnosed after the exclusion of all other causes of primary adrenal insufficiency.

Keywords

tyrosine kinase inhibitors, pazopanib, primary adrenal insufficiency, renal cell carcinoma

Introduction

Pazopanib is a multi-kinase inhibitor medication indicated as a first-line treatment for adult patients with metastatic renal cell carcinoma (RCC).¹ It targets the vascular endothelial growth factor receptor, c-kit protein, and the platelet-derived growth factor receptor. Additionally, it strongly inhibits angiogenesis.^{2–4} Given the increase in the use of tyrosine kinase inhibitors (TKIs) in the treatment of multiple types of cancer, more endocrine-related side effects have been reported in the literature. TKIs have been linked to adrenal insufficiency given their role in the hypothalamic-pituitary-adrenal (HPA) axis and in glucocorticoid secretion. Adrenal toxicity represented in the form of hemorrhage and necrosis is due to the reduced density of capillary networks in the adrenals on the administration of anti-VEGF compounds. Other histological changes such as inflammation and hypertrophy of the adrenals have been also noted. To our knowledge, only a few cases of TKI-induced adrenal insufficiency have been reported in the literature.^{5–7} It has not been reported yet with the use of pazopanib. We describe the first reported case of pazopanib-induced primary adrenal insufficiency

(PAI) in a patient with metastatic RCC diagnosed after the exclusion of all other causes of PAI.

Case Description

A 64-year-old male with a past medical history of metastatic RCC to the thyroid and the lung presented to the emergency department in February 2020 with a 5-month history of nonbloody diarrhea (2–3 bowel movements daily), decreased appetite, 25-lb weight loss, and memory loss. The patient had left nephrectomy and left adrenalectomy in 2004, total thyroidectomy with neck dissection,

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Table 1. Summary of the Laboratory Workup Done on Admission Day.

Laboratory blood test	Results	Reference levels
Serum sodium	122 mmol/L	134-147 mmol/L
Serum potassium	5.7 mmol/L	3.6-5.3 mmol/L
Serum chloride	88 mmol/L	95-108 mmol/L
Blood urea nitrogen	27 mg/dL	8-25 mg/dL
Serum creatinine	1.79 mg/dL (baseline was 1.1 mg/dL)	0.6-1.5 mg/dL
Serum bicarbonate	21 mmol/L	19-31 mmol/L
Serum glucose	95 mg/dL	70-115 mg/dL
Serum osmolality	276 mOsm/kg	280-301 mOsm/kg

and parathyroid re-implantation in 2017. Pathology of the latter was clear cell carcinoma with a small focus of follicular variant papillary thyroid carcinoma measuring 0.4 cm, negative lymph nodes. No metastatic lesions were documented in the left adrenal gland pathology. Furthermore, he had radiation therapy to the lung in 2017 followed by chemotherapy with pazopanib since March 2017. The starting dose was 800 mg orally daily and then it was decreased to 400 mg daily afterward.

There was no prior history of steroids, opiate, appetite stimulants like Megace, or new medications use since 2017. There was no history of trauma to the abdomen nor any history of autoimmune disease (personal or in the family). Interestingly, the patient had a prior history of type 2 diabetes diagnosed at age 54, requiring more than 50 units of insulin as a total daily dose. However, there was a significant improvement in his blood glucose levels in the past 6 months; hence, insulin was discontinued. Vital signs on admission showed a blood pressure of 115/55 mm Hg, a heart rate of 71 beats per minute, a temperature of 36.5 °C, and a respiratory rate of 18 breaths per minute with an oxygen saturation of 98% on room air. Orthostatic vital signs were positive. Physical examination revealed diffuse skin hyperpigmentation with no significant abnormalities on the abdominal examination. Initial laboratory tests revealed hyponatremia, hyperkalemia, elevated creatinine, and normal blood glucose (Table 1).

Originally, hypovolemic hyponatremia was suspected; hence, volume resuscitation with normal saline 0.9% was started. Workup for other causes of hyponatremia including endocrine causes such as thyroid function tests and morning cortisol were ordered. The morning cortisol was 5 µg/dL, thyroid stimulating hormone level was 0.23 uIU/mL with normal free thyroxine and total triiodothyronine levels. The patient was on a stable dose of levothyroxine replacement therapy 125 µg for the past year. Adrenocorticotropic hormone (ACTH) stimulation testing was subsequently ordered. Abnormal test results were noticed with baseline cortisol level of 4.9 µg/dL and 60 minutes cortisol level of 6.1 µg/dL, thus confirming the diagnosis of adrenal insufficiency. Notably, albumin was normal at 4.1 g/dL, with ACTH level

at baseline at 309 pg/mL and suppressed dehydroepiandrosterone sulfate level. Other workups for pituitary hormones did not show significant abnormalities except for low insulin-like growth factor 1 level (Table 2). Notably, magnetic resonance imaging of the head performed 5 days prior to admission did not show any intracranial abnormalities, specifically no pituitary lesions. A recent computed tomography scan of the abdomen showed normal right adrenal and status post left adrenalectomy. Additionally, 21-α hydroxylase antibodies were negative.

The patient was treated empirically with high-dose steroids intravenously every 8 hours. Two days later, repeat ACTH level continued to be elevated at 324 pg/mL, confirming the diagnosis of PAI. The steroid dose was subsequently tapered to maintenance physiological daily dose of oral hydrocortisone (10 mg in the morning/5 mg in the afternoon orally). The patient demonstrated significant symptomatic improvement including mental status and appetite with a reduction in nausea, vomiting, and malaise as well as normalization of electrolyte levels. He was provided with education regarding adrenal insufficiency and a follow-up with the endocrine division upon discharge.

Discussion

Tyrosine kinase inhibitors have been effective in treating a variety of malignancies since their appearance some decades ago. Tyrosine kinase enzymes are responsible for the phosphorylation and thereby activation of many proteins involved in signaling cascades for proliferation, cell-cycle control, mitogenesis, cellular growth, and reproduction.⁸ As such, TKIs have been widely studied and developed to impede these processes in malignant cells. TKIs act by a wide variety of mechanisms. They compete with ATP on the active site of tyrosine kinase enzymes locking the tyrosine kinases in a closed or self-inhibited conformation, which prevents enzyme activity of the protein semi-competitively. For example, in chronic myelogenous leukemia, imatinib has been developed to inhibit the tyrosine kinase BCR-ABL by acting selectively as a competitive inhibitor to its ATP binding site.⁹

Table 2. Summary of the Endocrine Hormonal Workup Done During Hospitalization.

Laboratory blood test	Results	Reference levels
Serum ACTH level	309 pg/mL	6-50 pg/mL
Morning cortisol at 8 AM	5 µg/dL	4.8-19.5 µg/dL
Baseline serum cortisol prior to cosyntropin injection	4.9 µg/dL	4.8-19.5 µg/dL
30 minutes serum cortisol after cosyntropin injection	5.5 µg/dL	4.8-19.5 µg/dL
60 minutes serum cortisol after cosyntropin injection	6.1 µg/dL	4.8-19.5 µg/dL
TSH level	0.23 uIU/mL	0.45-4.5 uIU/mL
Free T4 level	1.2 ng/dL	0.8-1.7 ng/dL
Total T3 level	90 ng/dL	80-200 ng/dL
Prolactin level	20.0 ng/mL	2.5-22.5 ng/mL
DHEAS level	8 µg/dL	12-227 µg/dL
Follicle-stimulating hormone level	9.8 mIU/mL	1.5-12.4 mIU/mL
Luteinizing hormone level	20.4 mIU/mL	1.7-8.6 mIU/mL
Total testosterone level	382 ng/dL	250-840 ng/dL
IGF1 level	33 ng/mL (Z score -2.4)	41-279 ng/mL (Z score -2.0 to +2.0)
Hemoglobin A1C	6.9%	≥5.6%

Abbreviations: ACTH, adrenocorticotropic hormone; TSH, thyroid stimulating hormone; T4, thyroxine; T3, triiodothyronine; DHEAS, dehydroepiandrosterone sulfate; IGF1, insulin-like growth factor 1.

While certainly beneficial in the treatment of malignancies, TKIs have been shown to cause a variety of side effects including endocrine problems such as hypothyroidism, hypophosphatemia, vitamin D deficiency, altered bone density, secondary hyperparathyroidism, gynecomastia, and hypogonadism.^{5,10-13} Additionally, alteration of glucose metabolism, hyperkalemia, hyponatremia, and hemorrhage have been reported in patients using TKIs. Adrenal insufficiency as a side effect of TKIs have been described in only a select few studies so far, but its true prevalence and clinical significance have yet to be fully elucidated.^{5,12,13}

Hutson et al in 2010 studied the efficacy and safety of pazopanib in patients with metastatic RCC.⁴ They reported that there is a similarity in the majority of adverse events of pazopanib in comparison to sorafenib and sunitinib; however, there is variation in incidence and severity from agent to agent. The most common side effects of pazopanib were diarrhea and fatigue. Additionally, hypertension, liver toxicity, nausea, hyponatremia, and hyperkalemia have been reported. There were no reports of any type of adrenal insufficiency. Moreover, fatigue and nausea may be misleading as the side effects of the medication rather than symptoms of adrenal insufficiency.^{4,14}

Goodman et al in 2007 reviewed sunitinib as a treatment for metastatic RCC and gastrointestinal stromal tumors in patients who have failed treatment with imatinib. Studies demonstrating clinical toxicities of this medication in the endocrine organs including the adrenal gland. Abnormalities in adrenal histology including hemorrhage and necrosis were observed in nonclinical repeat-dose studies in rats and monkeys at plasma exposures as low as 0.7 times the area under the curve observed in clinical studies.^{15,16} In human studies

with the same TKI, imaging obtained from 336 patients showed no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials with sunitinib. Only one patient among this group demonstrated consistently abnormal test results after a normal baseline test. This particular patient though did not exhibit any clinical symptoms of adrenal insufficiency.¹⁵ The Food and Drug Administration summary on sunitinib as a treatment for metastatic RCC and gastrointestinal stromal tumors in patients who have failed treatment with imatinib suggests that medical practitioners should be aware of the subclinical toxicity that sunitinib may have on the adrenal gland and overall HPA axis. Thus, monitoring for adrenal insufficiency in the setting of any stressor while using these medications is essential.^{5,15}

Bilgic et al in 2009 demonstrated a potential causal relationship between imatinib and dysregulation of the HPA axis in patients undergoing treatment for chronic myelogenous leukemia.¹⁷ Twenty-five patients were evaluated in the study. Glucagon stimulation test and low-dose (1µg) ACTH stimulation test were used to assess the HPA gland axis. Twelve subjects failed to show response to low-dose ACTH stimulation test (peak cortisol was <18 µg/dL) and thus those patients were identified as “HPA deficient” in the study. Only 2 patients of the total 25 had low morning cortisol (<7.22 µg/dL) and failed the glucagon stimulation test and/or low-dose ACTH stimulation test. This suggested a possible increased prevalence of subclinical glucocorticoid deficiency in patients receiving imatinib.¹⁷

Our patient has been on pazopanib for ~2 years prior to admission. Given the elevated ACTH level in the setting of low cortisol and failing to stimulate with the ACTH stimulation test, the diagnosis of PAI was confirmed. Imaging

studies including computed tomography scan of abdomen did not reveal any masses, hemorrhage, or necrosis of the right adrenal gland; however, microscopic tissue damage could not be ruled out as TKI-related histologic abnormalities in the adrenal including hemorrhage and necrosis have been reported in animal studies in rats and monkeys.^{15,16} It is unlikely that adrenal insufficiency is related to the remote history of left adrenalectomy in 2004 given the long duration and no metastatic lesions were found on pathology at that time. Workup for PAI including antibodies did not reveal any other causes so it was attributed to the use of pazopanib as it has been reported in the literature with other TKIs.

Conclusion

Tyrosine kinase inhibitor–induced adrenal insufficiency has been described in only a few studies so far. We report a case of pazopanib inducing PAI in a patient with metastatic RCC. Physicians should be aware of endocrine-related side effects of TKIs and the need of endocrinology follow-up in these patients. Further studies to elaborate on the relationship between TKIs and adrenal insufficiency are needed.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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