The Eyes Cannot See What the Mind Does Not Know: Endocrinological Side Effects of Ibrutinib

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ABSTRACT

Introduction: Over the last 7 years, ibrutinib has been given US Food and Drug Administration approval for a rising number of indications ranging from chronic lymphocytic leukemia (CLL) and marginal zone lymphoma to Waldenstrom macroglobulinemia.

Case Presentation: An 85-year-old man with a history of CLL who had been treated with ibrutinib over 6 weeks developed a rash and progressive weakness, and he was ultimately admitted to the hospital for obtundation. He was hypotensive, hyponatremic, and hypothyroid. Despite extensive testing and treatment for syndrome of inappropriate antidiuretic hormone (SIADH), he remained unimproved. Results of an adrenocorticotropic hormone stimulation test indicated secondary adrenal insufficiency. He was treated with hydrocortisone, and his symptoms subsequently resolved.

Discussion: Previous studies have demonstrated the presence of endocrine dysfunction, such as adrenal insufficiency, thyroid dysfunction, hyperparathyroidism, and gonadal failure in some tyrosine kinase inhibitors (TKI). To our knowledge, no previous literature has reported this association specifically with the TKI ibrutinib. The case highlights the importance of spreading awareness amongst clinicians of potential side effects that can occur with targeted therapy such as ibrutinib. This, in turn, will facilitate prompt recognition and early management when such cases arise in a hospital setting.

INTRODUCTION

Tyrosine kinase inhibitors (TKI) are key regulators of signaling pathways involving cellular proliferation, differentiation, and apoptosis and affect TK-dependent oncogenic pathways.[1] Ibrutinib is the first drug approved by the US Food and Drug Administration (FDA) that is designed to target Bruton tyrosine kinase (BTK)—a key protein in the B cell.[2,3] Ibrutinib first received FDA approval for treatment of mantle cell lymphoma and since that time has been approved for numerous other indications. In 2016, it was approved as a frontline chronic lymphocytic leukemia (CLL) treatment, in 2017 for marginal zone lymphoma (MZL), in 2018 for Waldenstrom macroglobulinemia, and most recently—in 2019—for small lymphocytic lymphoma (SLL) along with obinutuzumab.[4] TKIs potentially provide a relatively low toxicity in comparison with conventional cytotoxic chemotherapy. However, with their increasing use, we are becoming aware of important side effects.

CASE PRESENTATION

An 85-year-old man with a history of CLL (diagnosed in 2013 and under observation until 2019) had been started on ibrutinib after development of an enlarged mass in the parotid and submental lymph nodes. He had an excellent response to therapy, with a reduction in the size of his lymph nodes and splenomegaly. After 2 weeks of therapy, he developed mucocutaneous bleeding; a purpuric rash over his scalp, neck, upper lip; and diffuse petechiae along his bilateral lower extremities. He also experienced arthralgias in the right knee and hip. Concern for worsening bleeding prompted discontinuation of ibrutinib, but it was later restarted at a lower dose. A week later, he developed symptomatic sinus bradycardia and weakness, and ibrutinib was again discontinued. Ten days later, he was admitted to the hospital for multiple syncopal episodes with increasing fatigue and obtundation. His only other medications were allopurinol, gabapentin, tamsulosin, omeprazole, and furosemide. Laboratory evaluation was significant for hypokalemia (potassium,

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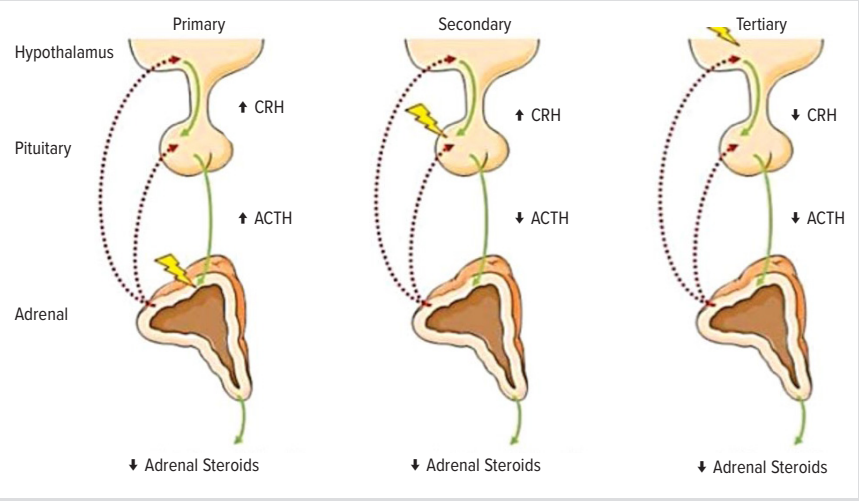
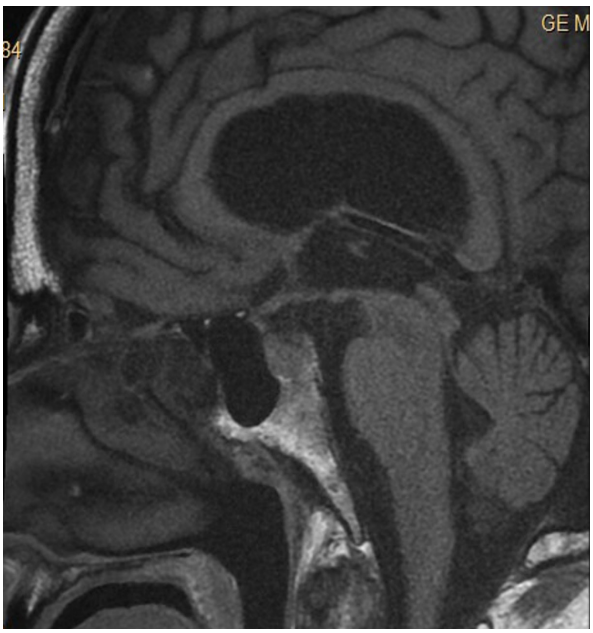
Figure 1. Types of Adrenal Insufficiency



Abbreviations: RH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone.

Figure 2. Normal Magnetic Resonance Imaging of Pituitary Sella



+3.4 mmol/L), hyponatremia (sodium, 123 mmol/L), and thyroid-stimulating hormone (TSH) (0.48 uU/mL, normal range 0.40-5.50 uU/mL). Workup for hyponatremia showed a low serum osmolarity 268 mosm/kg, urine osmolality of 240 mosm/kg, and a high urine sodium of 73 mmol/L (26 mmol/L after recheck post discontinuation of diuretic). Given the patient's recent ibrutinib use, chronic diuretic use, and laboratory values, there was a strong suspicion for syndrome of inappropriate antidiuretic hormone (SIADH). However, with fluid restriction, there was only a marginal improvement of his sodium levels. He was treated empirically for urosepsis with intravenous cefepime, but urine and blood cultures ultimately returned negative for growth and antibiotics were discontinued.

On hospital day 5, the patient experienced a near syncopal episode with systolic blood pressure of 60 mm Hg. An adrenocorticotropic hormone (ACTH) stimulation test resulted in a baseline cortisol of 10.04 µg/dL and levels at 30 and 60 minutes of 14.01 µg/dL and 14.89 µg/dL, respectively, after 250 mcg of cosyntropin was administered. A baseline ACTH was not obtained; however, the 21-hydroxylase antibody returned normal. Given the serum cortisol concentration <18 mcg/dL to 20 mcg/dL before and after corticotropin (ACTH), the patient was diagnosed with secondary adrenal insufficiency.[5] (See Figure 1.) At this time, a free thyroxine (T4) concentration also was measured and returned low (0.45 ng/dL). This, along with a low-normal TSH, was in line with a diagnosis of central hypothyroidism. Oral hydrocortisone was started immediately, but levothyroxine was not administered until 7 days later to avoid potential adrenal crisis. After initiation of hydrocortisone, the serum sodium concentration rose from 129 mmol/L to 134 mmol/L, with marked improvement in mentation to near baseline. Magnetic resonance imaging (MRI) of pituitary sella was performed 3 days after discharge and showed a normal pituitary gland with no evidence of pituitary masses, infiltrates, or lesions, thus confirming that there was no preexisting pituitary disease attributing to the patient's low cortisol levels (see Figure 2). On outpatient follow-up, he was noted to have maintained normal electrolyte levels, and his overall functioning continued to improve.

DISCUSSION

Previous studies have demonstrated the presence of endocrine dysfunction, such as adrenal insufficiency, thyroid dysfunction, hyperparathyroidism, and gonadal failure in some TKIs like sunitinib, imatinib, sorafenib, pazopanib, and axitinib.[6-12] However, to our knowledge there are no prior case reports or studies that have demonstrated this relationship specifically with the TKI ibrutinib. According to Kust et al, no papers have been published linking the ibrutinib to hypothyroidism as a side effect of therapy, even as an individual case report.[13]

In order to stipulate that hypopituitarism in this patient was related to ibrutinib therapy, other causes of potential pituitary insufficiency were assessed. The presence of underlying structural pituitary lesions was rebuked given that the outpatient MRI of the pituitary sella showed a normal-appearing pituitary gland with no

discrete masses. Functional hypogonadotropic hypogonadism also was ruled out as the serum testosterone (2.8 ng/dL) and luteinizing hormone (4.9 IU/L) were normal. Prolactin levels (18 ng/mL) were elevated.

A limitation of this study is that no ACTH level was obtained prior to the cosyntropin stimulation test, which would have given us more certainty in making the determination about whether this was a primary or secondary adrenal insufficiency. Additionally, renin and aldosterone levels were not obtained, therefore limiting our ability to definitively rule out a primary destructive adrenal etiology. That being said, the patient's 21 hydroxylase antibodies were normal and would have been elevated in the case of an underlying autoimmune process involving the adrenal glands. Therefore, we ruled out autoimmune adrenalitis, which is the most common cause of primary adrenal insufficiency in the United States. Another piece of evidence that goes against a primary adrenal process is that computed tomography (CT) of abdomen and pelvis performed 3 weeks after discharge showed the presence of normal adrenal glands. One also would expect to see much lower cortisol values in a primary process. Our patient's symptoms were likely a direct side effect of ibrutinib, as they developed after roughly two-and-a-half weeks of use and he was on no other concurrent or prior medications that might have caused these endocrine side effects.

We can refute the possibility that the initial thyroid dysfunction noted on admission was illness related (euthyroid sick syndrome), as the patient continued to require levothyroxine after discharge to maintain normal T4 and TSH levels. A repeat cosyntropin test (after holding the evening dose of hydrocortisone) was not performed in an outpatient setting to demonstrate persistent cortisol deficit. The patient has been continued on both levothyroxine and hydrocortisone since discharge with no dose adjustments and has been doing well.

This case illustrates endocrine-related side effects of ibrutinib, namely secondary adrenal insufficiency and central hypothyroidism. Although an association between TKIs and TSH and parathyroid hormone elevation has been established, the etiology behind these associations has not been elucidated. Multiple mechanisms for thyroid dysfunction have been postulated, including direct toxicity of TKI on follicular cells, induction of destructive thyroiditis, increased hormone clearance, thyroid capillary regression by vascular endothelial growth factor receptor (VEGFR) inhibition, and impaired iodide uptake.[14] Interestingly, a study by Lechner et al showed that new hypothyroidism in cancer patients treated with TKIs is associated with improved overall survival and, therefore, should not necessitate TKI dose reduction or discontinuation.[15] Understanding the clinical significance of thyroid dysfunction and with TKI therapy is important because it may alter decisions regarding discontinuation or dose reduction.

CONCLUSION

A paucity of literature reports the correlation of endocrinological adverse outcomes specifically with ibrutinib. As the use of ibrutinib continues to rise, early recognition of such potential side effects is important to prevent delays in prompt treatment and will help reduce morbidity and mortality in these patients. This report underscores the need for a retrospective study to determine the prevalence of endocrinological side effects of ibrutinib. Adverse effects like adrenal insufficiency can be potentially fatal if left untreated. Cases like these bring awareness about dangerous side effects of TKIs and help clinicians understand the association between the two, thereby reducing unnecessary testing and facilitating prompt management when such cases arise.

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