**Summary:** A man aged 65 years with metastatic renal cell carcinoma presented for evaluation after a recent fall. A thorough workup of the case was performed and secondary adrenal insufficiency induced by the administration of megestrol acetate was determined to be the cause. Adrenal insufficiency is a serious disorder that is a potential adverse event of megestrol acetate, a medication used to help patients with cancer cachexia increase their appetite and gain weight. This association is not well recognized in clinical practice, so this case highlights the importance of distinguishing possible endocrine complications induced by the long-term administration or sudden discontinuation of megestrol acetate.

**Introduction**

Adrenal insufficiency is a serious complication that is a potential adverse event of megestrol acetate, a medication used to help patients with cancer cachexia increase their appetite and gain weight.\(^1\) However, this association is not well recognized in clinical practice.\(^3\)

**Case Report**

A man aged 65 years with hypertension and stage 4 clear cell renal cell carcinoma (RCC) with metastases to the brain, lungs, bones, and pancreas was admitted for evaluation after a recent fall. His past surgical history was significant for left nephrectomy and adrenalectomy nearly 20 years ago. After his RCC did not respond to sunitinib and pazopanib treatment, his chemotherapy regimen was changed about 1 month ago to twice daily oral axitinib (5 mg). During his admission, he was hypotensive and his mental status was altered.

Vitals were blood pressure of 71/49 mm Hg, respiratory rate of 18 breaths/minute, heart rate of 101 beats/minute, temperature of 98.8 °F, and oxygen saturation of 96% on room air. Findings on physical examination were unremarkable, except for tenderness and swelling in his left lower extremities secondary to the recent fall. Findings on complete blood count with a differential and comprehensive metabolic panel were all within normal limits. Findings following a workup for sepsis and brain imaging were negative.

After ruling out potential causes, including infection, brain metastases, dehydration, electrolyte imbalances, and hypothyroidism, a workup for adrenal insufficiency was performed because hypotension persisted while his mental status improved. A morning serum cortisol level was below 1.0 µg/dL. A co-syntropin stimulation test revealed serum cortisol levels of 5.9 and 8.9 µg/dL at 30 and 60 minutes, respectively, with a pretest plasma adrenocorticotropic hormone (ACTH) level below 5 pg/mL, indicating secondary adrenal insufficiency.

A review of the patient’s medication list unveiled no agents commonly known to induce adrenal insufficiency with one exception. He had recently been treated with daily megestrol acetate (oral suspension 625 mg) for about 4 weeks prior to his current admission, and this dose had been continued for the initial portion of this hospitalization. We suspected that this agent might be the likely culprit, so it was discontinued.

Oral hydrocortisone 20 mg every morning/10 mg every evening was initiated for adrenal insufficiency, and his blood pressure significantly improved. Steroids were discontinued prior to a follow-up appointment 3 months following discharge. Repeat serum cortisol level and ACTH value were 20 µg/dL and 68 pg/mL, respectively; these results confirmed resolution of the adrenal insufficiency secondary to megestrol acetate.

**Discussion**

Adrenal insufficiency is a serious, potentially life-threatening condition that stems from primary adrenal failure or secondary adrenal disease owing to an impaired hypothalamic–pituitary–adrenal (HPA) axis.\(^1\) The disorder can chronically cause fatigue, anorexia, weakness, abdominal pain, and hypotension, whereas the acute syndrome may induce hypotensive crisis, fever, clouded sensorium, and myopathy.\(^1\) Those affected typically require stress-dose steroids for surgical pro-
cedures or severe illness and glucocorticoid replacement on a long-term basis.

Although management of the disorder is relatively straightforward, making an accurate and timely diagnosis often proves to be challenging in the oncology setting. Patients with cancer frequently experience these symptoms, sometimes as a result of disease progression, surgery, radiation, chemotherapy, or a combination of all of these. Oftentimes, cachexia seen over time with adrenal insufficiency can mimic wasting characteristic of metastatic disease. Paraneoplastic syndromes and malnutrition may cause severe electrolyte abnormalities, clouding, or covering up of the evidence of the role of adrenal insufficiency in such irregularities. In addition to causing adrenal insufficiency–associated symptoms, such as fatigue, weakness, myopathy, and pain, chemotherapy and immunotherapy agents can directly give rise to the disorder. The tyrosine kinase inhibitors sunitinib and imatinib and, more frequently, the checkpoint-blocking immunotherapies ipilimumab, nivolumab, and pembrolizumab have been reported to cause adrenal insufficiency. Given the limited data available, it will be interesting to see whether the effects of these agents on adrenal function extend to other members of their respective classes as their use continues to increase.

Medications commonly used as supportive care can also induce adrenal insufficiency. The detrimental impacts of the long-term administration and abrupt discontinuation of steroids on adrenal function are well known. Use of glucocorticoids is also common in patients with cancer, and these agents play a critical role in the treatment of various hematological malignancies, immune-related adverse events, the relief of symptoms secondary to brain metastases, and pain management.

Similarly, megestrol acetate, which is a synthetic progestin with antiestrogenic properties, is often used to help patients with cancer cachexia increase their appetite and gain weight. Secondary to its inherent glucocorticoid-like effect, the agent is thought to cause suppression of the HPA axis at the hypothalamus through negative feedback, thus resulting in low levels of serum cortisol and plasma ACTH.

Although stimulating the appetite through the use of megestrol acetate was useful in a patient like ours, megestrol acetate has been associated with thrombosis, hyperglycemia, hypertension, osteoporosis, hypogonadism, and adrenal insufficiency. Its clinical benefit is often outweighed by these potential adverse events, many of which are already at a heightened risk of occurring in this patient population (eg, thrombosis). Several questions regarding the length of time needed for megestrol acetate–induced adrenal suppression and subsequent restoration of HPA axis function after discontinuation of the drug are still unknown.

Leinung et al conducted a trial that initiated 80 mg megestrol acetate 3 times a day in study patients with normal cortisol and ACTH levels prior to therapy. After 1 month, both values significantly decreased, and study participants also displayed a significantly decreased response to cosyntropin stimulation. An interventional trial found that 6 of 7 study patients with adrenal suppression recovered normal function within 2 weeks, with the remaining patient doing so in 6 weeks (NCT00575029). However, general data are lacking, so definitive timeframes are uncertain. Nevertheless, our case describes a patient who developed treatment-related adrenal insufficiency after 1 month of therapy, but successfully recovered in 3 months after the medication was discontinued.

Although adrenal insufficiency is a reported potential adverse event of megestrol acetate, it is not well recognized in clinical practice. Adrenal suppression can stem from abrupt discontinuation of the agent. However, as in our case, megestrol acetate has been found to cause this effect in patients actively taking the agent, thus complicating the diagnosis. Postulated mechanisms for the latter scenario include a dual agonist–antagonist action (binding to the glucocorticoid receptor while simultaneously preventing endogenous glucocorticoids from doing so), a greater tendency to suppress the HPA axis rather than induce glucocorticoid-like effects, and concurrent acute stress or illness in a patient whose HPA axis is already suppressed. Retrospectively, the patient was not taking any other medication likely to cause such an effect.

The origin of our patient’s adrenal insufficiency was also clouded by numerous factors, including prior left adrenalectomy, tyrosine kinase inhibitor use, and metastatic RCC. This case of megestrol-induced adrenal insufficiency was only discovered after extensive workup and elimination of other possible causes.

Conclusions
Although obtaining and analyzing a patient’s medication history may be challenging, thorough and accurate assessment of previous and current medication use is a necessity that proved to be pivotal in this case. Given the potentially severe complications of adrenal insufficiency, this report underscores the importance of recognizing possible endocrine complications induced by the long-term administration or sudden discontinuation of megestrol acetate. However, further study is still needed to draw definitive conclusions on the effects of megestrol acetate on adrenal function.

Acknowledgment: We thank the patient for his cooperation throughout the duration of the case.
References