

## Acute Adrenal Insufficiency in a Patient with Metastatic Infiltrating Ductal Carcinoma

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Received May 28, 2020; Accepted for publication August 19, 2020; Published online Nov. 24, 2020  
<https://doi.org/10.17161/kjmvoll3.13754>

### INTRODUCTION

Oncologic patients often present to the hospital with nonspecific symptoms such as nausea, vomiting, and fatigue. These symptoms could be secondary to a life-threatening condition such as adrenal insufficiency. Tumor burden,<sup>1-4</sup> radiation therapy,<sup>5-8</sup> and intracranial metastases<sup>9-12</sup> represent potential etiologies in the oncologic patient presenting with adrenal insufficiency. Therefore, it is important to consider both primary and secondary adrenal insufficiency in the initial differential diagnosis.

Given that over 90% of the adrenal glands must be compromised to manifest as primary insufficiency,<sup>4</sup> tumor burden represents a rare<sup>2</sup> but clinically relevant manifestation that has been well-documented in case reports.<sup>1</sup> This phenomenon has a reported incidence ranging between 1.1% and 33%.<sup>2-4</sup> Stereotactic body radiation therapy (SBRT) is an emerging field that allows for more finely targeted and less toxic treatment than has been previously available for adrenal metastases.<sup>5-7,13-16</sup> However, particularly in patients that receive bilateral treatment, primary adrenal insufficiency is a documented toxicity<sup>6-8</sup> of which one retrospective review<sup>5</sup> estimated an incidence as high as 16%.

Finally, intracranial metastases affecting pituitary function must be considered in oncologic patients presenting with signs and symptoms of adrenal insufficiency. Anterior pituitary insufficiency was the third most common manifestation of symptomatic pituitary manifestations in one review, accounting for 23.6% of total cases.<sup>11</sup>

We report a female patient with past medical history significant for metastatic breast cancer status-post bilateral SBRT to the adrenal glands who presented with symptoms of adrenal insufficiency. Although there was a primary concern for primary adrenal insufficiency at time of initial presentation, she was found to have anterior pituitary insufficiency which led to a new diagnosis of intracranial metastases.

### CASE REPORT

The patient was a 65-year-old woman with a history of infiltrating ductal carcinoma (IDC) of the left breast initially diagnosed in 2012. At that time, she was treated with modified radical mastectomy (4/25 axillary lymph nodes), prophylactic right mastectomy, and adjuvant chemo-radiation which was completed in 2013. She was taking adjuvant anastrozole and was being followed with surveillance imaging when a computed tomography (CT) scan in late 2019 indicated that she had a new suspicious pulmonary nodule. A follow-up positron emission tomography scan showed bilateral adrenal hyperactivity. She had a biopsy of her right adrenal gland which showed adenocarcinoma consistent with metastatic recurrence of her primary breast cancer. She underwent therapeutic SBRT to the left lung (50 Gy in 5 fractions), right adrenal (45 Gy in 5 fractions), and left adrenal (40

Gy in 5 fractions) which were completed during the summer of 2019.

In the fall of 2019, the patient presented to the emergency department for intractable nausea and vomiting that she related to the start of her adrenal radiation treatments during the summer. Her admission labs were significant for hyponatremia (130, ref 137-147 mmol/l), hypokalemia 3.1 (3.5-5.1 mmol/l), hyperglycemia 235 (70-100 mg/dl), and low random cortisol 0.9 (ref: 5-20 mcg/dl).

Given her history, the major consideration at time of presentation was primary adrenal insufficiency secondary to recent bilateral adrenal SBRT. However, her adrenocorticotropic hormone (ACTH), drawn in the emergency department prior to initiation of systemic steroids, later came back low at 2 (7-63 pg/dl), suggestive instead of a secondary etiology. Her thyroid stimulating hormone was low normal 0.85 (0.35-5.00 mcu/ml) in the setting of low free thyroxine (FT4) 0.3 (0.6-1.6 ng/dl). A follicle-stimulating hormone level of 0.9 (27-153 mu/ml) and luteinizing hormone of less than 0.2 (11-64 mu/ml) also were low, indicating pituitary insufficiency.

A brain magnetic resonance image with contrast showed numerous (> 10) parenchymal intracranial metastases, as well as a 1.4 x 1.1 x 0.9 cm irregular enhancing mass involving the hypothalamus, pituitary, and infundibulum. She was treated initially with stress dose steroids which were transitioned to dexamethasone after the discovery of vasogenic edema due to brain metastases. Her presenting symptoms rapidly resolved with adrenal replacement therapy and thyroid replacement. She was started on whole brain radiation prior to discharge.

### DISCUSSION

Given our patient's history of bilateral radiation treatments, radiation-induced primary adrenal insufficiency was high on the initial differential. Surgery remains the standard of care for adrenal metastases.<sup>5</sup> More recently, stereotactic external-beam radiation therapy (SBRT) has emerged as an alternative option for local control in patients with limiting comorbidities.<sup>5-7,13</sup> SBRT typically is well tolerated with few significant toxicities, likely due to its ability to precisely target areas of interest.<sup>14-16</sup> Toxicities in these patients include nausea, vomiting, diarrhea, and fatigue.<sup>17,18</sup> Few studies specifically examined SBRT-related adrenal toxicity, though it has been reported in several case series.<sup>6-8</sup> The incidence of adrenal insufficiency in patients with bilateral treatment was reported to be 16% (n = 30).<sup>5</sup> Due to the lack of available data, it is difficult to establish a dose threshold or time course. There is, however, a well-described connection between primary insufficiency and tumor burden itself.<sup>1</sup> There potentially could be a mechanistic role for radiation treatments serving to exacerbate already reduced functional reserve in patients such as ours.<sup>7</sup>

The final diagnosis in our patient was anterior pituitary insufficiency presenting with adrenal insufficiency secondary to metastatic IDC. Breast and lung cancer are the most common primary tumors to metastasize to the pituitary, of which the majority are clinically silent.<sup>9</sup> Diabetes insipidus and panhypopituitarism are the most common

presentations of symptomatic pituitary metastasis.<sup>10</sup> There is a predilection of metastases to the posterior pituitary; this is thought to be due to its rich blood supply from the systemic circulation (as opposed to the more limited hypophyseal circulation supplying the anterior pituitary).<sup>10,12</sup> When discovered, treatment is focused on targeted therapy of the primary cancer, surgical resection, radiation therapy, and/or intrathecal chemotherapy.<sup>10</sup> While prognosis is dependent upon the nature of the primary malignancy and extent of metastasis, cases by this point are generally systemic and aggressive; prognosis is poor.<sup>11</sup>

In this case, the importance of both ACTH and cortisol levels being drawn prior to the empiric initiation of corticosteroid treatment for adrenal insufficiency could not be understated. It is possible that, in the absence of an available ACTH level or other localizing symptoms, radiation-induced insufficiency would have been presumed given only a low cortisol with our patient's history. As it is difficult to draw any conclusions about an ACTH level drawn after steroid treatment, it could have delayed true diagnosis significantly and subsequent treatment for our patient. This case illustrated the importance of keeping a broad differential diagnosis when evaluating complex oncologic patients who are found to have adrenal insufficiency.

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*Keywords:* primary adrenal insufficiency, adrenal insufficiency, ductal carcinoma, pituitary insufficiency, radiosurgery