PALLIATIVE CARE CASE OF THE MONTH

"Pain in the Ads! Adrenal Insufficiency in Palliative Care"

by

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Case: Mr. W. is a 58 year-old man with melanoma metastatic to the pancreas and lung. He was treated with ipilimumab plus nivolumab for three months. He had progression of disease, so he enrolled in a clinical trial with combined nivolumab and a novel agent. Since receiving cycle 1 of his clinical trial drugs, he developed 2 weeks of worsening abdominal pain and nausea as well as new confusion. Palliative care was consulted for pain management. The patient's wife had been administering oxycodone 5 or 10mg for his pain every 3 to 4 hours, but his pain was not controlled, and his delirium persisted. He was diagnosed with secondary adrenal insufficiency thought to be an adverse effect of one of the trial drugs.

Mr. M is a 65 year-old man with metastatic melanoma who was being treated with nivolumab for eight months. He was transferred from an outside hospital with intractable nausea and vomiting despite Reglan and Zofran. He developed fevers, tachycardia, hypotension, and started to become somnolent despite medical management prior to transfer. Palliative care was consulted for pain and symptom management. He was diagnosed with secondary adrenal insufficiency from hypophysitis caused by nivolumab.

Discussion: Adrenal insufficiency (AI) is a less common cause of otherwise common symptoms. However, delayed diagnosis can be associated with prolonged symptoms not well-managed by analgesics or antiemetics alone. Therefore, prompt recognition of risk factors and workup where appropriate is key to achieving relief. AI mimics the nausea, vomiting, and abdominal pain that could otherwise be caused by such etiologies as progression of metastatic disease, chemotherapeutic adverse effect, gastric or small bowel obstruction, or pancreatitis. Here, we describe the clinical presentation of adrenal insufficiency and review the prevalence of adrenal insufficiency as it relates to cancer and immunotherapy.

The most common symptoms in adrenal insufficiency are anorexia and fatigue, followed by GI symptoms (nausea, vomiting, abdominal pain, or changes in bowel habits). These, along with hypotension (systolic blood pressure <110mmHg) are prevalent in 90% or greater of patients with AI. Symptoms can be insidious in the case of Addison's disease (autoimmune AI).1 In contrast, adrenal crisis causes dehydration, tachycardia, hypotension, and fever. Confusion or lethargy, severe abdominal pain, nausea, vomiting, unexplained hypoglycemia, and electrolyte disturbances (hyponatremia, hyperkalemia, hypercalcemia) may occur. Prompt treatment prevents worsening shock. Hyperpigmentation may be present in cases of primary adrenal insufficiency related to increased production of ACTH.2

Adrenal insufficiency can arise from primary dysfunction of the adrenal glands, or AI can occur secondary to a deficiency of ACTH to stimulate the adrenal glands. Primary AI may result from Addison's disease in the general population and may be associated with other autoimmune disorders. Withdrawal of long-term glucocorticoid treatment can induce AI as well. In patients with cancer, bilateral adrenal metastases rarely cause primary AI.3 But in the era of immunotherapy, primary adrenal insufficiency can also occur in 0.3%-1.5% of patients treated with nivolumab.4 Ipilimumab has only been implicated in case report.4

Secondary AI may result from hypophysitis (inflammation of the pituitary gland), caused by ipilimumab more often than nivolumab or pembrolizumab. In patients on ipilimumab, the prevalence of hypophysitis has been reported in the range of 1.5% to 25%,4 suggesting that many palliative care providers may encounter it in their clinical practice. It can be differentiated from primary AI by low serum ACTH levels in addition to low AM cortisol levels. MRI of the pituitary shows inflammation. Other endocrinopathies can result from concomitant low levels of TSH or gonadotropins.5 Recent ASCO guidelines for treatment recommend endocrinology consult and replacement corticosteroids.6

Palliative care providers have developed experience and expertise in treating the adverse effects of conventional chemotherapeutic agents including nausea and neuropathy. Now that immunotherapy has become more common, we are confronted with managing symptoms that may arise from side effects and endocrinopathies in the population of patients whose risk is increased due to treatment with ipilimumab, pembrolizumab, or nivolumab. Clinical suspicion based on risk factors increases our ability to detect AI as one cause, and effectively treat its symptoms.

Resolution of the case: Mr. W. was given IV fluids and started on hydrocortisone IV as recommended by the endocrinology team. Over three days, his abdominal pain and nausea resolved, requiring no prn medications. His mental status improved from intermittently asking who the woman in his room was (his wife) to normal cognition. Mr. M was also started on glucocorticoid replacement therapy. His pain resolved, and his nausea was managed with prn ondansetron. Both patients were discharged home. These cases demonstrate the importance of broadening our differential diagnoses for the causes of common symptoms like abdominal pain, nausea, and vomiting in order to avoid missing an opportunity to provide effective treatment.

References:

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