



PALLIATIVE CARE CASE OF THE MONTH

“Assessing and Managing Adverse Immune-Related Events of Cancer Immunotherapy”

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Case: Mr. R is a 52-year-old man with metastatic gastric carcinoma, most recently treated with pembrolizumab who was admitted to the hospital with delirium, nausea, abdominal pain and acute kidney injury. Despite treatment with intravenous fluids which improved his renal function, he remained delirious. There was no evidence of decreased motility, constipation or obstruction to account for his nausea. With supportive symptom management, his nausea and pain improved, but his delirium persisted. An astute intern on the oncology service ordered a cortisol stimulation test which demonstrated adrenal insufficiency. This case demonstrates that an immune-related adverse effect may have played a role in the patient’s presentation and encourages a deeper understanding of immunotherapy side effects.

Discussion:

What is immunotherapy and how does it work?

Immunotherapy is a type of cancer treatment that activates the body’s immune system to fight malignancy. This therapy has been shown to prolong survival in a variety of cancer types including melanoma, urothelial, and non-small cell lung cancer. There are currently six immune check point inhibitors approved by the U.S. Food and Drug Administration. Ipilimumab (Yervoy) targets the cytotoxic T-lymphocyte antigen 4 (CTLA-4). The drugs nivolumab (Opdivo) and pembrolizumab (Keytruda) target programmed cell death 1 (PD-1). And atezolizumab (Tecentriq), avelumab (Bavencio), and durvalumab (Imfinzi) each target programmed cell death ligand 1 (PD-L1). These treatments are referred to as immune checkpoint blockade.

What are the potential adverse effects?

Inflammation can be a side effect of activating the immune system. While the exact mechanism is unknown, there is suspected involvement of T-cell antibodies and cytokine responses. While inflammation can occur anywhere, the most commonly reported immune-related adverse effects are seen in the gastrointestinal tract, including pancreatitis, autoimmune diabetes, colitis, and enteritis; endocrine glands, including adrenal insufficiency, thyroiditis, hypo/hyperthyroidism, and hypophysitis; skin, including rash and vitiligo; and liver, in the form of hepatitis.¹ The majority of immune-related adverse events are mild to moderate. However, serious events have been reported, and treatment-related deaths occur in up to 2% of patients, depending on the specific immune checkpoint inhibitor.

When do immune-related adverse events occur?

If immune-related events occur, they most commonly occur weeks-to-months after the start of treatment. However, patients can develop adverse events at any time, including months to years after treatment is stopped.

How do we treat immune-related adverse effects?

There are no prospective trials to guide management. The severity of the adverse effect guides treatment. Generally, immunosuppression with glucocorticoids is first line treatment. In more severe cases, such as colitis with severe pain or peritoneal signs, the addition of immunosuppressants such as infliximab, which is an antibody against tumor necrosis factor alpha, is recommended².

Do immune-related adverse effects impact cancer treatment efficacy?

At this point there is not enough data to answer this question definitively.

Back to the case:

This patient had developed adrenal insufficiency as a result of cancer treatment with pembrolizumab. After adrenal replacement therapy, the patient’s mental status improved to his baseline. He continued to have abdominal pain but required fewer opioids to remain comfortable. His nausea resolved, and his anti-emetics were weaned. This case highlights the importance of developing a thorough differential diagnosis for symptoms which includes immune-related adverse effects. Some of these side effects can mimic symptoms of the underlying disease and premature closure in developing the differential diagnosis could potentially lead to a life-threatening complication. As the prevalence of immunotherapy increases, we will see more patients with these side effects.

References:

1. Postow MA et al. Immune-Related Adverse Effects Associated with Immune Checkpoint Blockade. *NEJM*. 378 (2) 158-168, 2018
2. Puzanov et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *Journal for Immunotherapy of Cancer*. 5:95, 2017

Personal details in the case published have been altered to protect patient privacy.

For palliative care consultations please contact the Supportive and Palliative Care programs at PUH/MUH, 412-647-7243, pager # 8511, Shadyside, 412-647-7243, pager # 8513, Perioperative/ Trauma Pain, 412-647-7243, pager # 7246, UPCI Cancer Pain Service, pager 412-644-1724, Magee Women’s Hospital, pager 412-647-7243 pager # 8510, VA Palliative Care Program, 412-688-6178, pager # 296. Hillman Outpatient: 412-692-4724. For ethics consultations at UPMC Presbyterian-Montefiore and Children’s pager 412-456-1518

With comments about “Case of the Month” call Dr. Robert Arnold at (412) 692-4834.