

Critical Care Medicine Section

Immunotherapy Complications in the Emergency Department: Be on the Lookout for the Checkpoints!

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Cancer remains one of the largest health care burdens within the United States. According to the National Cancer Institute, approximately 1.7 million new cases of cancer will be diagnosed within the United States and approximately 600,000 people will die from the disease. The most common cancers are breast, lung/bronchus, prostate, colon/rectal, and melanoma.¹ Not only is cancer ever present in our society, it remains a force to be reckoned with, both in terms of mortality and financial aspects. Cancer is among the leading causes of death worldwide with 8.2 million cancer related deaths worldwide in 2012.¹ The Agency for Healthcare Research and Quality (AHRQ) estimates that the direct medical costs of cancer in the U.S. in 2015 were \$80.2 billion.² The National Cancer Institute estimated that national expenditures for cancer care in the United States in 2017 were \$147.3 billion dollars.¹

A major burden of costs for cancer is directed at cancer targeted therapies, whether it be curative or palliative. In the earliest history of cancer therapy, many saw surgical removal as the only hope. In the 19th century, Surgeons Biloath, Handley, and Halsted were performing and leading the surgical management of cancers.³ In the 20th century, radiation and chemotherapy became two more pillars of treatment for cancer as our understanding of cancer growth and science advanced with the utilization of radiation therapy as well as developing new drugs to halt or terminate cell growth (chemotherapy).

As time has progressed, many physicians and scientists continue to embark on finding new therapies to help ease or possibly eradicate the burden that cancer has placed on society today. More recently, immunotherapy has made a remarkable presence in the treatment of cancers. This is predicated that the body can possess natural defenses, the immune system, to combat cancer. The immune system can be tightly regulated with many checkpoints. Without checkpoints or “brakes,” the immune system would run rampant causing an array of dysfunctions. This can be seen with non-skeletal manifestations of rheumatological disorders. It is also known that cancer cells can escape the surveillance of the immune system. Dr. Allison of the MD Anderson Cancer Institute was able to identify a certain brake on the immune system that could target cancer cells. By turning off the brake of the immune system, the immune system is allowed to attack cancer cells. This led to the development of ipilimumab. Ipilimumab was found to extend the survival of patients afflicted with late stage melanoma.⁴ This has led to the development of other immunotherapy medications aimed at targeting late stage lung, kidney, bladder, head and neck cancers, melanoma, and Hodgkin’s Lymphoma. In addition to ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab have been developed.

As with any other cancer therapies, the emergency physician must be able to identify and treat the toxicities and/or adverse events associated with cancer therapies. It can be assumed that most emergency providers assume patients undergoing oncological treatments are considered

immunocompromised. However, with immunotherapy, patients can have an active immune system that can cause inflammatory side effects as well as organ dysfunction. Therefore, it is paramount that the emergency physician must be aware of the adverse events associated with immunotherapy as well as its workup and treatment modalities.

The most common organ system that is involved with immunotherapy medications is the dermis. Approximately 34% of the patients have some form of dermatological manifestations.⁵ Severity can range from mild to severe. Mild forms of dermatological complications from immunotherapy include an itchy macular or maculopapular rash. These mild forms are treated with topical corticosteroids. However, there have been cases where patients have progressed to meet the diagnostic criterion for Stevens-Johnson syndrome and Toxic Epidermal Necrolysis.^{6,7,8} In these patients, prompt consultation with ICU as well as dermatologist and oncologist is warranted. Given that patient’s immune system is hyperactive, administration of corticosteroids may be warranted to help suppress the immune system in addition to cessation of offending agent as well as aggressive supportive care.

Another organ system that can be affected by immunotherapy is the endocrine system; particularly the pancreas, thyroid, and adrenal glands can be affected. With respect to the pancreas, there have been case reports where immunotherapy drugs have caused autoimmune type 1 diabetes.⁹ These patients can present with a similar picture to those afflicted with congenital type 1 diabetes complicated by diabetic ketoacidosis. It is prudent to know that patients who have no prior history of diabetes can develop complications associated with autoimmune type 1 diabetes. Like with any other hyperglycemic complications of diabetes, initiation of insulin therapy with careful monitoring in addition to attaining euolemia and pain control are the basic foundations to treatment. Unlike with dermis complications, administration of steroids has no role in the treatment of autoimmune Type 1 diabetes.⁹ In addition to the pancreas, the thyroid can be disrupted as well. Cases of hyper- and hypothyroidism have been seen and present with vague symptoms such as fatigue or agitation. Hypothyroidism was reported in up to 10% of patients receiving monotherapy but could be more frequent (up to 25%) in sequential or combined ipilimumab, nivolumab, and pembrolizumab therapy. Hyperthyroidism is less frequent but was reported in up to 5%, and in up to 9.9% of cases receiving combined ipilimumab and nivolumab therapy.¹⁰ Destructive thyroiditis has been well documented in the literature as a complication of immunotherapy. Patients may develop symptoms of thyrotoxicosis as early as 4 days after treatment followed by a quick progression into hypothyroidism.¹² Therefore, it has been

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recommended that patients have thyroid function tests be monitored routinely when undergoing immunotherapy. Finally, adrenal insufficiency is a rare endocrine complication of immunotherapy that can present with vague symptoms. Immunotherapy can lend itself to causing inflammation of the pituitary gland causing inability for the pituitary gland to secrete its hormones. This can lend itself to causing primary adrenal insufficiency. Even worse, adrenal crisis can occur. Therefore, it is important that the emergency physician be aware of such complications as adrenal crisis as it can mimic sepsis. Furthermore, those undergoing immunotherapy can have unrelated acute problems such as sepsis or trauma that may require stress dose corticosteroid supplementation.⁵ Therefore, Dexamethasone administration is warranted if one is dealing with potential fatal adrenal complications of immunotherapy.

The most common gastrointestinal complaint is diarrhea. Most studies report at least 30% of diarrheic events, which commonly present after five weeks of treatment and are mild in nature. Diarrhea results from infiltration of the intestinal mucosa by immune cells following immune activation by the checkpoint inhibitor. Colitis is the severe consequence of diarrhea and there have been reports of bowel perforation and deaths.¹¹ When dealing with the abdominal complaint in those patients undergoing immunotherapy, the emergency physician must be aware that other complications such as *Clostridium Difficile* colitis, bacterial/viral gastroenteritis, as well as ischemic colitis can occur.

In addition to the gastrointestinal system, the hepatic system can be affected as well. Albeit rare, it can lend itself to major complications if not diagnosed and treated appropriately. There have been case reports of autoimmune hepatitis that have been successfully treated with corticosteroids. Fulminant hepatic failure is extremely rare.¹³

Approximately 5% of cancer patients treated with immunotherapy will be afflicted with pneumonitis.¹³ The patient may present him or herself with respiratory complaints such as cough, and fever. Typical evaluation for cough and fever in an oncological patient would warrant chest X-ray. Chest X-ray may reveal consolidative processes occurring in the lung fields that one may assume would be pneumonia and not consider the diagnosis of autoimmune pneumonitis. It is imperative that the differential diagnosis include autoimmune pneumonitis as this can lead to severe acute respiratory failure and possible acute respiratory distress syndrome (ARDS). If chest X-ray is negative for any lung field processes and there is still concern for a pulmonary process, a CT chest should be strongly considered in oncological patients undergoing immunotherapy as this can delineate more information regarding the lung parenchyma. Not only should pneumonia warrant attention but one should also consider the diagnosis of autoimmune pneumonitis and treat with steroids.

Fulminant myocarditis has also been reported to be an adverse reaction to immunotherapy. Johnson et al., at Vanderbilt University found that 101 patients developed myocarditis when treated with dual agent immunotherapy. The rates of myocarditis was low in patients who received single agent immunotherapy.¹⁴ It is not clear which patients are most at risk, although the authors of a separate analysis, published in the *Journal of the American College of Cardiology*, found a significant association between diabetes and risk of myocarditis following immune checkpoint inhibition therapy for cancer.¹⁵ Patients may present with chest pain, dyspnea at

rest and/or on exertion as well as signs and symptoms consistent with the clinical diagnosis of heart failure. Therefore, diagnostic testing should include electrocardiogram, chest X-ray, as well as troponin levels and continuous telemetry. Given that point of care ultrasound has gained momentum within the emergency medicine settings, one could perform a bedside transthoracic echocardiography to determine degree of cardiac suppression. In these settings, discontinuation of the immunotherapy and steroid administration are the first steps in treatment as well as aggressive supportive care.

Neurological side effects of immunotherapy may present itself such as blurred vision. Patients who complain of blurred vision may warrant concern for uveitis. There is thought that uveitis may be a surrogate marker for response in melanoma as there has been case reports with pembrolizumab induced uveitis associated with complete or partial tumor response.¹⁶ Kao and colleagues reported results of a single institution retrospective data analysis describing the frequency of neurological complications in patients with metastatic melanoma or solid tumors treated with one of the two immune checkpoint inhibitors, nivolumab and pembrolizumab. In their cohort of 347 patients, only 10 had treatment associated neurological conditions that had a diverse range of severity. The most common neuromuscular syndrome was neuropathy followed by myopathy.¹⁷ Kelly Wu et al., reported a patient who was diagnosed with Guillain Barre syndrome by electromyography. This patient recovered after treatment with intravenous immunoglobulin and aggressive supportive care.¹⁸

In conclusion, the emergency physician must be aware that immunotherapy is an evolving and growing field of hematology and oncology. Newer drugs will be developed with broader indications. Given that immunotherapy is flourishing, the provider must be aware of the subtle complaints that the patient undergoing immunotherapy may present to the emergency department. These subtle complaints can lead to catastrophic events if not treated early. Therefore, patients undergoing immunotherapy must undergo a thorough history and physical along with laboratory and radiological examination pertinent to the patient's symptoms. ●

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Continued on next page

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