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 Bilroth, 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. Ipilumumab 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.

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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 I diabetes. Like with any other hyperglycemic complications of diabetes, initiation of insulin therapy with careful monitoring in addition to attaining euvolemia 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