Clinical Presentations and Outcomes of Patients Receiving Immune Checkpoint Inhibitors Presenting to the Emergency Department

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Abstract

Immune checkpoint inhibitors (ICIs) are increasingly used in the treatment of cancer. Immune checkpoint inhibitors may cause a wide-range of autoimmune toxicities referred to as immune-related adverse events (irAEs). There is a paucity of data regarding the presentations and outcomes of patients receiving ICIs who seek care in an emergency department (ED). We performed a retrospective review of patients receiving an ICI who presented to a tertiary care ED between May 1, 2017, and April 30, 2018. Data including ED chief complaint, diagnosis, treatment, and disposition were collected along with baseline characteristics and diagnosis at the time of outpatient oncology follow-up. We report descriptive statistics summarizing the characteristics of the cohort. There were 98 ED visits identified among 67 unique patients. Immune-related adverse events were diagnosed in 16 (16.3%) cases. The most common chief complaints within the irAE group were gastrointestinal symptoms 10 (62.5%). Among the 16 confirmed irAE cases, the most common irAE diagnosed was colitis 9 (56.3%). Two (12.5%) patients with irAEs received corticosteroids during their stay in the ED, and 10 (62.5%) patients with irAEs required hospital admission. Emergency medicine providers documented consideration of an irAE in the differential diagnosis in 14.3% of all ED visits and in 43.8% of visits in which an irAE was ultimately diagnosed. Emergency providers should be familiar with ICIs given their expanding use and potential adverse effects to improve early recognition and patient outcomes in ED settings.

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The use of immune checkpoint inhibitors (ICIs) has expanded rapidly in recent years. Immune checkpoint inhibitors are cancer treatment strategies directed at improving the host immune response to cancer by blocking immune checkpoint molecules. Immune checkpoints are inhibitory receptors and ligands which, when activated, transmit signals preventing excessive cellular responses, helping maintain self-tolerance and limiting tissue damage during inflammatory responses. Immune checkpoint inhibitors have been used in the treatment of many cancers, most commonly melanoma and non–small-cell lung cancer. The US Food and Drug Administration recently granted approval for use in a broad range of malignancies.

By targeting and blocking immune checkpoints, the “brakes” are taken off, allowing for T cell activation, proliferation, and antitumor responses; however, by this same mechanism, autoimmune attack can result in any organ system — the so-called immune-related adverse events (irAEs) which vary in spectrum and severity. The most common irAEs involve the skin and gastrointestinal tract. Several societies have published guidelines for the management of irAEs, including the Society for Immunotherapy of Cancer, detailing the most recent clinical practice guidelines to date. In general, treatment is driven by toxicity grade, with grade 2 or higher toxicity...
requiring at least temporary withholding of ICI therapy and introduction of corticosteroids as a first-line treatment.

With expanding use of ICIs, associated irAEs should be a diagnostic consideration for emergency providers, as they are a source of morbidity and mortality. There is sparse literature describing the presentations and initial care of patients on ICIs who present to the emergency department (ED). The objective of this study is to describe the presentations, management, and disposition of patients receiving ICIs who present for emergency evaluation and describe the frequency and types of irAEs among this cohort.

PATIENTS AND METHODS
We obtained institutional review board approval before initiating the study. All patients receiving ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, or any combination thereof at Mayo Clinic in Rochester, MN, were catalogued by the central pharmacy. From this database, we identified those patients receiving ICI therapy who had a contemporary evaluation in the Mayo Clinic Hospital ED between May 1, 2017, and April 30, 2018. The Mayo Clinic Hospital ED is a tertiary-care ED in Rochester, MN, with 77,000 patient visits annually. The sample size of our cohort was determined by the study period.

We reviewed the available ED, inpatient care, and subsequent outpatient follow-up care documentation in the electronic medical record (EMR), which were temporally related to the index presentation. All patients at Mayo Clinic are consented for retrospective observational research purposes; we excluded those who declined consent. Data were abstracted by a single investigator (RMC) into a standardized data abstraction tool. Demographic data and data regarding the ED encounter including chief complaint, diagnosis, treatment, and disposition were recorded.

Thorough review by a single investigator (RMC) of all ED documentation was performed to capture consideration of irAEs within the differential diagnosis. This included mention of an irAE or complication from ICI in the provider documentation with the use of key words such as “immunotherapy-induced” or “side effect” or “adverse effect” as well as line-by-line review of all provider documentation. Patients were excluded if they had not received an ICI within the 6 weeks before ED presentation. Data regarding subsequent inpatient admission and/or outpatient follow-up was collected to confirm the presence of an irAE as diagnosed by an oncology provider.

We summarized the characteristics of the cohort using descriptive statistics. Continuous and categorical variables were presented as percentages and medians. Analyses were performed using Microsoft Excel 2013. We used the equator network Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies.

RESULTS
There were 164 ED visits among patients who received ICIs during the study period. Among these, 98 patient visits had received ICI within 6 weeks before ED presentation. There were 67 unique patients identified that comprised these 98 ED visits (Table 1). The median age was 65 years and 31 (46.3%) patients were female. The most common cancer types were lung 23 (34.3%) and melanoma 19 (28.4%). Other cancer types included hematologic 9 (13.4%), gastrointestinal 6 (9.0%),

| Table 1. Patient Demographics and Clinical Characteristics |
|----------------------------------------------------------|
| Characteristic                                           | No. of Patients (%) |
| Total                                                    | 67               |
| Age, median (range), y                                   | 65 (24-88)       |
| Women                                                    | 31 (46.3)        |
| Race                                                     |                  |
| White                                                    | 63 (94.0)        |
| African-American                                         | 1 (1.5)          |
| All others                                               | 3 (4.5)          |
| Cancer type                                              |                  |
| Lung cancer                                              | 23 (34.3)        |
| Melanoma                                                 | 19 (28.4)        |
| Hematologic malignancies                                 | 9 (13.4)         |
| Gastrointestinal cancer                                  | 6 (9.0)          |
| Genitourinary cancer                                     | 4 (6.0)          |
| Head and neck cancer                                     | 2 (3.0)          |
| Other solid cancer                                       | 4 (6.0)          |
Among 98 ED visits, 14 (14.3%) had documentation in the EMR describing emergency medicine (EM) provider consideration of irAE in the differential diagnosis (Table 2). Sixty-six (67.3%) visits led to inpatient admission. Among those admitted, 65 (98.5%) were admitted to a general care floor and 1 (1.5%) was admitted to the intensive care unit. The remaining 32 (32.7%) cases were discharged from the ED.

Among the unique 98 ED visits, the most common presenting chief complaints were gastrointestinal (abdominal pain, diarrhea, or nausea and vomiting), accounting for 31 (31.6%) cases. Other chief complaints included respiratory symptoms 16 (16.3%), musculoskeletal symptoms 10 (10.2%), nonspecific symptoms such as weakness and confusion 10 (10.2%), cardiac symptoms 7 (7.1%), neurologic symptoms 7 (7.1%), fever 5 (5.1%), trauma 4 (4.1%), genitourinary symptoms 3 (3.1%), psychiatric symptoms 3 (3.1%), and endocrine-related symptoms 2 (2.0%).

Among 98 unique ED visits, an irAE was ultimately diagnosed in 16 (16.3%) patients (Table 3). Emergency medicine providers documented consideration of irAEs in 7 (43.8%) of these cases, and the provider’s diagnosis was congruent with ultimate diagnosis by an oncologist in 6 of 7 (85.7%) cases where irAE was considered. The one exception was a case of type 1 diabetes mellitus diagnosed at outpatient follow-up; the ED diagnosis was hyperglycemia without attributed etiology. In 9 (56.3%) of the 16 cases ultimately diagnosed with irAE, the irAE diagnosis was not considered in the ED setting.

Among patients with confirmed irAEs, all had melanoma or lung cancer, and pembrolizumab was the most frequently used ICI 14 (87.5%). The most common ED chief complaints among this group were gastrointestinal in nature (abdominal pain, diarrhea, or nausea and vomiting), accounting for 10 (62.5%) cases. Other complaints included dyspnea 2 (12.5%), hyperglycemia 2 (12.5%), chest discomfort 1 (6.25%), and dizziness 1 (6.25%). The most common irAE diagnosed was colitis 9 (56.3%). Additionally, there were 2 (12.5%) cases of type 1 diabetes mellitus, 2 (12.5%) cases of pancreatitis, 1 (6.25%) case of pneumonitis, 1 (6.25%) case of myasthenia gravis, and 1 (6.25%) case of adrenal insufficiency. Two (12.5%) patients were treated with corticosteroids in the ED. Among the 16 patients ultimately diagnosed with irAE, 10 (62.5%) were admitted to a general medical unit after the index ED visit, none were admitted to the intensive care unit, and the remainder were discharged from the ED.

**DISCUSSION**

Immune checkpoint inhibitors are a relatively new class of medication, and their adverse effects may be unfamiliar to emergency providers, despite increasing use in patients with malignancies. The literature describing the emergency care of patients taking ICIs is sparse. The largest studies to date come from specialty oncologic EDs, which may not be generalizable to other tertiary-care or community-ED settings, and focuses on the clinical spectrum of irAE in the ED and patient survival after ED encounter.10,11 Our study uniquely tries to capture the diagnostic considerations of EM providers confronted with these patients and tracks the immediate clinical course of patients with irAEs within the health care system.

We found that EM providers practicing at a large tertiary-care ED infrequently considered irAEs in the differential diagnosis for patients on ICIs, although when they did so, it
was with reasonable accuracy. Among 98 discrete ED visits by patients on ICI therapy, the possibility of an irAE was documented as being considered in only 14 (14.3%) cases. Emergency medicine providers are required to consider a wide differential diagnosis, focused upon ruling out life-threatening conditions that can commonly occur in patients with malignancies, such as infection, fever with neutropenia, and hemorrhage. Although the risk of life-threatening irAEs has been estimated to be less than 2%, under-recognition of irAEs could result in progression to more serious toxicity and morbidity. For example, a missed diagnosis of type 1 diabetes mellitus could lead to the development of diabetic ketoacidosis and an underappreciated mild transaminitis could progress to life-threatening hepatotoxicity. Emergency medicine providers should be cognizant of the risk of irAE in patients taking ICIs, while taking care to avoid premature closure on a diagnosis irAE. Additionally, providers should be aware that patients receiving combination ICI therapies, typically nivolumab with ipilimumab, the one combination ICI approach that is US Food and Drug Administration—approved, are at increased risk for toxicity. A higher incidence of all grade toxicities and fatal toxicity (particularly from colitis and myocarditis) has been reported in this group.5

We observed that, of the 16 (16.3%) ED visits in which an irAE was confirmed, the EM provider initially considered an irAE in 7 (43.8%) cases. In 6 of these 7 cases, the diagnosis of ICI assigned by the EM provider was congruent with the subsequent oncology provider’s assessment. This suggests that when irAEs are considered by EM providers in the differential diagnosis, the diagnostic accuracy is in line with that of the subject-area experts. Increasing EM provider awareness of ICIs and related irAEs will reasonably lead to increasingly accurate and timely recognition and treatment.

Of the patients with confirmed irAEs, colitis was the most common manifestation, which is consistent with prior ED-based studies.10,11 Colitis and diarrhea secondary to irAE are estimated to occur in up to 21% of patients on pembrolizumab and 62% of patients on dual ICI therapy (ie, ipilimumab/nivolumab).14 Thus, it is important for EM providers to consider ICI-induced diarrhea and/or colitis for all patients on ICIs who present with gastrointestinal symptoms. The less common irAEs pose a unique challenge to EM providers.10,11

We identified one case each of the following conditions: pneumonitis, myasthenia gravis, and adrenal insufficiency. Each of these cases was diagnosed upon subsequent outpatient oncology follow-up and were not considered or diagnosed in the ED setting. These conditions are difficult to diagnose given nonspecific presentations and overall rarity; however, they require prompt recognition and treatment to prevent morbidity and possible mortality.10,11 The ED “worst first” cognitive approach must include irAEs, as higher-grade irAEs may benefit from early administration of corticosteroids in the ED, in consultation with the primary oncology team.10,15

In instances of diagnostic uncertainty in patients receiving ICIs, conferring with the patient’s oncology team at the time of ED care can be invaluable. As the use of ICI therapy continues to expand, it is likely that tertiary-care facilities will develop care-team based approaches to facilitate early recognition and management of irAEs, in close partnership with the ED. Such a practice has recently been developed at our institution, initiated following the conclusion of this study. All patients on ICIs at our institution now have an EMR “flag” to alert all care providers to their use, and an institutional ICI pager is now staffed continuously to allow for prompt specialty consultation. To further increase awareness for front-line providers, the American Society of Clinical Oncology recently published a top-10 innovative institutional solutions manuscript highlighting the importance of early recognition and detailing possible interventions directed at patients, providers, and institutions.16

Challenges regarding treatment face EM providers even after irAEs are recognized. In general, irAE treatment is guided by the severity and organ system affected. Corticosteroids are the first line of treatment for grade 2 or higher irAEs.17 We identified only 2 (12.5%) cases in which corticosteroids were
initiated in the ED setting. This implies there is presently undertreatment with corticosteroids even when the EM provider suspects irAE. However, there are instances in which a conservative approach is indicated, for example, when concern for infection remains. Consideration of a steroid-sparing approach in a patient with progressive malignancy may also be considered when there is concern for a potentially negative effect of corticosteroids on cancer response. When faced with therapeutic uncertainty even in the setting of a confirmed irAE, conferring with the patient’s treating oncology team is imperative.

TABLE 3. ED Visits With Confirmed Outpatient irAE Diagnosis

| ED visit | Cancer type | ICI | EM provider considered irAE | ED irAE-specific treatment | ED chief complaint | ED diagnosis | Hospital discharge diagnosis | irAE |
|----------|-------------|-----|---------------------------|---------------------------|-------------------|-------------|------------------------------|------|
| 1        | Melanoma    | Pembrolizumab | No | — | Abdominal pain | Abdominal pain | Acute pain in setting of anal melanoma status postsurgical resection, chemoradiation therapy | colitis |
| 2        | Melanoma    | Pembrolizumab | No | — | Hyperglycemia | Diabetic ketoacidosis | Diabetic ketoacidosis type 1 diabetes | |
| 3        | Melanoma    | Pembrolizumab | Yes | Dexamethasone 10 mg | Diarrhea | Colitis | — | colitis |
| 4        | Melanoma    | Pembrolizumab | Yes | Prednisone 60 mg | Diarrhea | Diarrhea | — | colitis |
| 5        | Lung cancer | Pembrolizumab | Yes | Shortness of breath | Pneumonitis | Community acquired pneumonia | Adrenal insufficiency likely secondary to nivolumab | pneumonia |
| 6        | Lung cancer | Nivolumab | No | — | Abdominal pain | Pneumonia | — | Adrenal insufficiency |
| 7        | Melanoma    | Pembrolizumab | No | — | Dizziness | Altered mental status | Probable autoimmune colitis related to pembrolizumab | colitis |
| 8        | Lung cancer | Nivolumab | No | — | Chest pressure/tightness | Abdominal pain | Acute pancreatitis | pancreatitis |
| 9        | Lung cancer | Pembrolizumab | No | — | Abdominal pain | Small bowel obstruction | — | colitis |
| 10       | Melanoma    | Pembrolizumab | No | — | Shortness of breath | Shortness of breath | Multifactorial acute on chronic hypoxic and hypercapnic respiratory failure | myasthenia gravis |
| 11       | Lung cancer | Pembrolizumab | Yes | — | Abdominal pain | Immunotherapy-mediated colitis | Grade 3 postimmunotherapy colitis | colitis |
| 12       | Lung cancer | Pembrolizumab | Yes | — | Nausea and vomiting | Nausea and vomiting | — | colitis |
| 13       | Melanoma    | Pembrolizumab | Yes | — | Hyperglycemia | Hyperglycemia | Newly diagnosed diabetes mellitus | type 1 diabetes |
| 14       | Lung cancer | Pembrolizumab | No | — | Abdominal pain | Pancreatitis | — | pancreatitis |
| 15       | Lung cancer | Pembrolizumab | Yes | — | Nausea and vomiting | Acute colitis | — | colitis |
| 16       | Lung cancer | Pembrolizumab | No | — | Abdominal pain | Hypokalemia | — | colitis |

*aED, emergency department; EM, emergency medicine; ICU, intensive care unit; irAE, immune-related adverse event. bED irAE-specific treatments only include steroids administration. If blank, patient did not receive steroids. cHospital Discharge Diagnosis: If blank, patient was discharged directly from the ED.
Our study has several limitations. We conducted our study at a single tertiary-care ED, thus, generalizability to other settings is not clear. Further, most patients were white, limiting generalizability to more diverse populations. The retrospective nature yields inherent limitations, as all data is obtained from the EMR. It is possible that EM provider consideration for the possibility of an irAE is underestimated, as we relied on documentation in the ED medical record, which may not be exhaustive. We sought to mitigate this limitation by creating and using a standardized data abstraction tool and creating rules for each data point to minimize inconsistency. We excluded ED visits for patients who had been off ICIs for greater than 6 weeks, in large part because the vast majority of irAEs present while patients are actively receiving ICI. However, some irAEs, specifically rheumatic, may present weeks to months after ICI discontinuation. It is possible such cases were missed. Further, to confirm the accuracy of the irAE diagnosis, we relied on confirmation in the outpatient follow-up. This could result in underestimation of irAE as the cause for the ED visit. Finally, in our institution, the oncology clinical practice has care mechanisms aimed at identifying patients developing irAEs in the outpatient setting, and initiating management to prevent ED visits and hospitalization. Additionally, our institution has various mechanisms to admit patients, including oncologists having the ability to directly admit patients. As such, a portion of irAEs at our institution are identified and managed outside the ED setting.

CONCLUSION
In this study, emergency providers infrequently considered irAE in patients on ICIs who presented to the ED for care. Patients were uncommonly diagnosed with an irAE, and among those who were, colitis was the most frequent manifestation. It is imperative that emergency providers become familiar with the side-effects of immunotherapy given their expanding use in order to improve early recognition of irAEs in the ED setting. Increasing collaboration of emergency physicians and oncologists is needed to develop systems and standardized care approaches for patients on ICI therapy who present to the ED.

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Abbreviations and Acronyms. ED, emergency department; EM, emergency medicine; EMR, electronic medical record; ICI, immune checkpoint inhibitor; irAE, immune-related adverse effect

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