Immunotherapy Adverse Events: An Emergency Nursing Perspective

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Contribution to Emergency Nursing Practice

- The current literature on management of immunotherapy adverse events (irAEs) indicates a gap in health-provider knowledge outside of oncology, including emergency nurses.
- This article contributes highlights of the mechanism of action of immunotherapy agents and delineates the etiology of adverse events.
- Key implications for emergency nursing practice found in this article are that rapid recognition and treatment of immune-related events have significant implications for the emergency care, treatment, and prognosis of oncology patients receiving immunotherapy alone or in combination with chemotherapy.

Illustrative Case Study

A 70-year-old man presented to the emergency department on a Saturday with complaints of shortness of breath, especially with activity; increased dry cough; and generalized weakness. He denied chest pain or hemoptysis. The patient reported a history of coronary artery disease; coronary artery bypass surgery; and lung cancer treated with surgery, chemotherapy, and radiation therapy. Most recently, he received treatment in his oncologist's office approximately 5 days before. His resting vital signs were as follows: blood pressure 150/54 mm Hg, heart rate 86 beats per minute, temperature 37°C (98.6°F), respiratory rate of 22, and an oxygen saturation of 91% on room air. On auscultation, he had bilateral decreased breath sounds at the bases and some scattered crackles in the lower right lung. He denied fever or chills and had not recently traveled outside the United States. The ED physician ordered a complete blood count (CBC), basic metabolic panel (BMP), and a computed tomography scan of the chest. Findings revealed new focal ground glass opacities and interstitial thickening along the fissure on the right upper and middle lobes, suggestive of inflammation. In addition, some infiltrates were noted bilaterally, increased on the left side, and some bronchiectasis also on the left side. The electrocardiogram was within normal limits, displaying a sinus rhythm. The CBC was remarkable with an absolute neutrophil count of 1,000 cells/mm^3 and white blood count (WBC) of 5.0 mm^3. His hemoglobin/hematocrit was 9.2 g/dL and 28.0%, and he had a platelet count of 100,000/mm^3. His BMP was within normal limits. The patient received 1000 mL of 0.45 normal saline intravenous fluid and a dose of ceftriaxone 2 gm intravenously. Following a conversation with the on-call oncologist, the patient was discharged home on oral antibiotics to cover a potential upper respiratory infection and was told to follow up with his medical team within 2 to 4 days or sooner, if symptoms did not improve. What are the differential diagnoses? Is this an infectious process due to his cancer treatment? Or could this be something else?

Background

Cancer and its treatment have long posed challenges for the oncology community. That is, how do providers best treat patients while minimizing the collateral damage of anticancer agents? The last 3 years have seen a revolution in the targeted treatment of malignancies with the addition of immunotherapy agents such as checkpoint inhibitors into treatment regimens. This new class of agents includes subclasses such as programmed death-ligand 1 (PD-L1), programmed cell death protein-1 (PD-1), and anticytotoxic T lymphocyte-associated antigen 4 (CTLA-4), among others. All agents offer different pathways to destroying cancer cells than previous therapies (eg, chemotherapy or

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radiation therapy) by stimulating the activation of a dormant immune system and, as a result, have new and complex adverse effect profiles.[1-3]

The concept of using the immune system to combat cancer goes back almost 200 years.[4] It is unfortunate that these results were not widely recognized. The use of immunotherapy in oncology was almost forgotten until experiments in the 1940s established the idea of tumor-associated antigen in lymphocytes for recognition of malignant cells for destruction by the immune system.[4] This theory led to discovery of antitumor cytokines such as interferon alpha-2 (IFN-2) and interleukin-2 (IL-2) for treatment of melanoma and kidney cancer.[5]

Monoclonal antibodies, such as herceptin and rituximab, were developed in the 1980s to attack a specific antigen on a tumor cell, a more targeted approach to immunotherapy. Checkpoints are proteins (CTLA-4, PD-1, PDL-1) on the surface of T cells and other body cells; they form ligands or bonds with T cells.[6] When these ligands form, they either stimulate T cells to mount an immune response against foreign or damaged cells or inhibit the T cells from damaging healthy cells.[4,6] As a result, checkpoint inhibitors block the interaction of these ligands, removing the brakes on the immune system and stimulating T cells to attack the tumor cell.[4,6]

Some of the new immunotherapy agents (eg, PD-1, CTLA-4) use checkpoint receptors within the immune system to support activation of suppressed or dormant T cells.[6] Thus, the adverse events or toxicities that occur may be a consequence of the upregulation or stimulation of various immune effector cells such as T cells, natural killer cells, and macrophages.[2] As a result, the stimulated immune system not only attacks malignant cells effectively but may also cause an autoimmune-like response, whereby healthy, normal tissues are also attacked.[2,6] Thus, fundamental knowledge of this class of medications and the possible presentation of these adverse events in emergency departments is critical.

In the United States, there are, at present, 7 checkpoint inhibitors approved by the Food and Drug Administration.[7,8] Every day the effectiveness of checkpoint inhibitors against additional malignancies, such as breast cancer and mesothelioma, are studied. In addition, the combination of checkpoint inhibitors with traditional treatments, such as chemotherapy and radiation therapy, is now expanding. Initially, they were restricted for use only in advanced stages of disease; now they are often being prescribed in earlier stages of cancer.[3,9] Table 1 provides a list of these medications and some of the indications.

Overview of Organ-Specific Toxicity Grades

A standardized organ level grading of immune-related adverse events (irAEs) is important and can guide appropriate diagnosis and treatment. The severity of an irAE is quantified using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, developed by the National Cancer Institute.[2,7,8,10] This uniform grading system was created as a standardized way of reporting AEs for patients undergoing clinical trials, and has expanded in the last decade into clinical practice.[7] For example, grade 1 events are considered mild and usually asymptomatic; grade 2 are moderate, usually requiring local or minimal management; grade 3 are severe and medically significant; and grade 4 are life threatening and requiring immediate medical care.[7]

These new agents present challenges for all health care providers involved in the care of oncology patients because the AEs have different etiologies from those historically seen

TABLE 1
FDA-approved checkpoint inhibitors with their indications

Checkpoint molecule targeted	Generic name	Trade name	Example indications
CTLA-4	Ipilimumab	Yervoy	Melanoma; NSCLC
	Tremelimumab	—	Mesothelioma
PD-1	Nivolumab	Opdivo	NSCLC; uurothelial carcinoma; melanoma
	Pembrolizumab	Keytruda	NSCLC; head and neck cancer
PDL-1	Atezolizumab	Tecentriq	NSCLC; urothelial cancer
	Durvalumab	Imfinzi	NSCLC; renal cell carcinoma; HNSCC
	Avelumab	Bavencio	Classical Hodgkin disease; HNSCC

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HNSCC, head and neck squamous cell carcinoma; PD-1, programmed death receptor-1; PDL-1, programmed death-ligand 1; NSCLC, non–small-cell lung cancer.

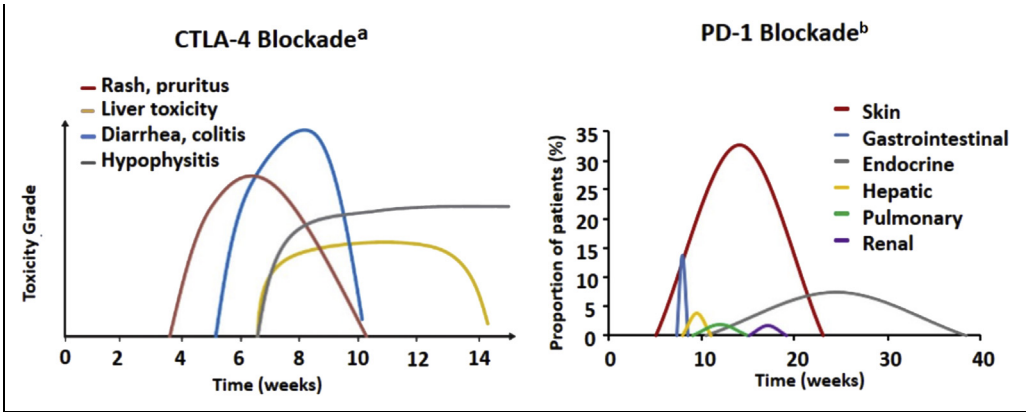

FIGURE 1

Timeline and incidence for most common immune-mediated adverse events by checkpoint inhibitor class. Reprinted with permission from Dr. Jeffrey Weber, *Journal of Clinical Oncology*. [a]Weber JS, Kahler KC, Hauschild A. Management of immune-realted adverse events and Kinetics of response with ipilimumab. *J Clin Oncol* 2012;30:2691-2697. [b]Weber JS, Antonia SJ, Topalian SL, et al. Safety profile of nivolumab (NIVO) in patients (pts) with advanced melanoma (MEL): A pooled analysis. *J Clin Oncol* 33(15 suppl), 2015;9018-9018. https://doi.org/10.1200/jco.2015.33.15_suppl.9018.

with more traditional treatments such as chemotherapy and radiation therapy. Some AEs may be confused with other medical conditions or infectious disorders and erroneously treated with antibiotics; this delays optimal treatment, contributes to decline in organ function, and possibly causes such results as increase in morbidity.[11,12] Rapid identification and management of irAEs in the emergency department is therefore essential. Figure 1 provides a list of the class of checkpoint inhibitors and a timeline of the most common irAEs.

Signs and Symptoms

The patient's medication history is invaluable. Once it is known with which checkpoint inhibitor the patient has been treated, it clarifies the possible type of irAE and the timeline for presentation of the AE. For example, cutaneous side effects—in the form of dermatitis, pruritus, and erythema—are among the most common, occurring in approximately 50% of patients receiving CTLA-4 checkpoint inhibitors and 30% to 40% in patients treated with PD-1/PDL-1 agents;[1,13] these typically present early after initiation of treatment. Similarly, immune-related colitis in the form of diarrhea, abdominal pain, cramping, or mucous stools is frequently seen. Immune-related colitis also occurs with a CTLA-4 agent such as ipilimumab, with which it is experienced by approximately one third of patients when CTLA-4 is used alone[14] and in approximately 45% of patients with combination therapy with another checkpoint inhibitor.[3] Colitis has a typical onset of 6 to 7 weeks after initiation of treatment.[1] The differential diagnoses in these patients include infectious processes, diverticulitis, or inflammatory bowel disease. It is also important to note that enterocolitis or colitis in this patient population can lead to perforation caused by the inflammatory damage to the tissues of the bowel.[11] Figure 2 provides a list of possible symptoms associated with irAEs.

Immune-mediated pneumonitis is rare, occurring in less than 10% of patients on immunotherapy. However, it can be fatal if not recognized and managed properly.[3,8] Pneumonitis is observed more commonly with use of a PD-1/PD-L1 checkpoint inhibitor than a CTLA-4; however, with combination therapy, the incidence is as high as 5% to 10%.[8,11] Patients with pneumonitis experience cough, shortness of breath, fever, and possibly chest pain and crackles. In severe cases, they can present to emergency departments with hypoxia, pulse oximetry of less than 90%, and respiratory distress.[8,11] Immune-mediated pneumonitis is seen most frequently in patients with lung cancer who had previously been treated with surgery, radiation therapy, and chemotherapy. These treatments seem to predispose the lung parenchyma to more inflammatory changes and damage.[15]

Case Study (Continued)

The patient received supportive care and treatment for a potential respiratory infectious process in his lungs as a result of the initial workup. After ruling out all other differential diagnoses—such as progression of disease, cardiac etiology, chronic pulmonary infections such as tuberculosis, or other structural problems such as pneumothorax or

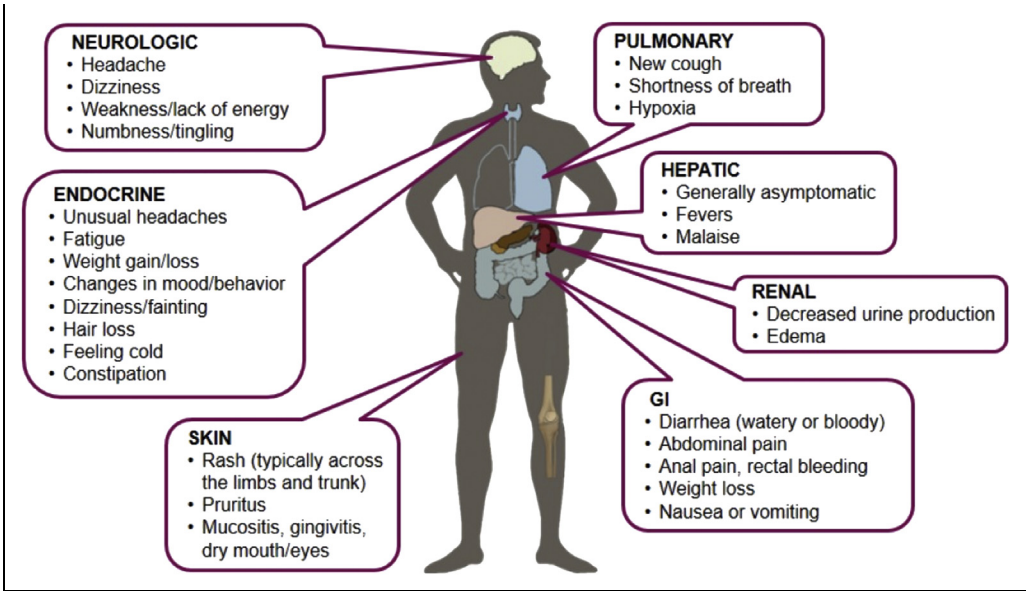

FIGURE 2

List of common symptoms associated with immune-mediated adverse events by organ system. Reprinted with permission from AstraZeneca.

atelectasis—the health care team should investigate the possibility that the patient is on immunotherapy and consider the likelihood of an immune-mediated pneumonitis.

Because many patients and caretakers are poor historians, and treatment with immunotherapy is often confused with chemotherapy, many facilities have created an immunotherapy wallet card, similar to the ones issued to patients with pacemakers. These wallet or alert cards serve to identify the patient promptly as someone at risk of irAEs and list possible AEs, the necessary workup, and contact information for the oncology team.[16,17] Figure 3 is an example of an immunotherapy wallet card. Patients should be issued this card at the beginning of therapy and be advised to present this card at any urgent care or emergency department when they present for care. Further, many facilities have worked with their clinical informatics department and information technology to flag patients in the electronic health record as receiving immunotherapy, making their identification easier. This, however, may not be easily accomplished when different electronic platforms are used by outpatient clinics.

Nursing Considerations in the Emergency Department

All health care providers involved in the care of oncology patients undergoing treatment with checkpoint inhibitors need to be aware of these new agents, as the AEs differ from those historically seen with chemotherapy and radiation therapy. Some patient presentations may be confused with infectious conditions and treated with antibiotics, delaying optimal treatment, contributing to decline in organ function, and possibly causing negative outcomes.[11,12] Such has been the case with immune-mediated myositis and myocarditis, which frequently co-occur. These cases are few, occurring ≤1% of the time; however, they have one of the highest mortalities—close to 40%—if not properly managed.[10,17]

ASSESSMENT

Any patient who presents to the emergency department with current or history of treatment with a checkpoint inhibitor should prompt a high level of suspicion for developing an irAE. IrAEs have been reported in the literature after only 1 dose and up to 6 to 12 months after discontinuation of treatment.[1,16] Understanding these complex treatments and their AE profile is important to the ED team. Figures 1 and 2 help to illustrate general guidelines for a timeline of presentation of irAEs and increase familiarity with the most common signs and symptoms. These patients will increase in presentation to the emergency department because indications and combinations for checkpoint inhibitors are increasing. Clinical studies for checkpoint inhibitors for the treatment of various malignancies are expanding, as are their indications for other

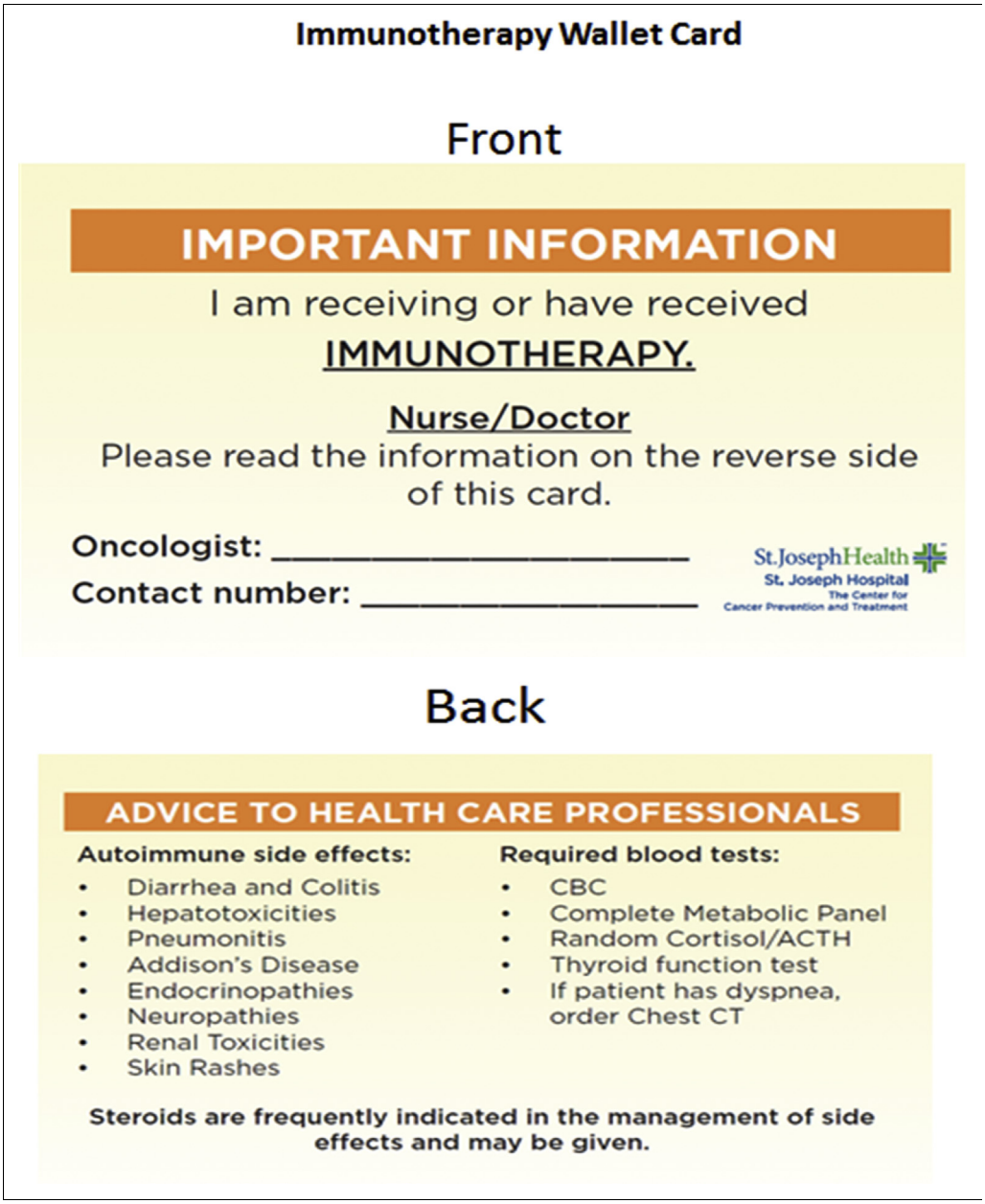

FIGURE 3

Immunotherapy identification card for patients. Reprinted with permission St Joseph Hospital, Orange, CA.

diseases such as infections with human immunodeficiency virus.[18]

Routine nursing assessment and a detailed medication history are imperative with these patients to gather essential information that will guide the working diagnoses in the emergency department. Having a fundamental knowledge of the AE-grading criteria is essential during the initial assessment of these patients. It is important to mention that many of these patients will be reluctant or afraid to report these adverse events for fear of having their treatments discontinued, especially when checkpoint inhibitors may be the last opportunity to control a fatal malignancy.[19,20] Communication with the rest of the medical team will be fundamental in working up and managing suspected irAEs.

TABLE 2
Important facts for emergency nurses about irAEs.

- Any patient with a history of cancer: inquire about treatment with immunotherapy (checkpoint inhibitor).
- Detail medication history is important.
- Patients suspected of having irAEs can receive antibiotics for suspected infections in conjunction with steroids for suspected irAEs.
- Patients may be neutropenic and at the same time suffer an irAE; treat both.
- irAEs can happen after 1 dose or months of therapy; irAEs can also happen weeks or months after discontinuation of treatment.
- Contact oncology team ASAP.
- Hospital pharmacist can be a great resource for questions about oncology medications.
- www.NCCN.org has an algorithm for management of irAEs.

irAEs, immune-related adverse events.

NURSING MANAGEMENT

Rapid recognition of patients with checkpoint inhibitor irAEs assists in the appropriate treatment being initiated in the emergency department. When an irAE is suspected, the desired treatment is withholding checkpoint inhibitor therapy and the administration of corticoid steroids orally or intravenously at 1 to 2 mg/kg/d; hospitalization is often considered.[1,18] It is important to note that treatment of an irAE with immunosuppressant therapy (ie, high doses of steroids) does not seem to hinder the efficacy of checkpoint inhibitor therapy;[18] unfortunately, this is often a concern for patients, especially with new AEs. Patients often require treatment with high doses of steroids for many weeks.[1,3] The literature supports concurrent administration with empirical antibiotics for a possible infectious process such as immune-mediated pneumonitis, colitis, or neurological complications. These patients do not require isolation unless they are neutropenic as a result of chemotherapeutic agents. Table 2 lists important facts to remember for emergency nurses. It is important that, in addition to starting therapy with high doses of steroids for suspected irAEs, ED personnel inform the patient's oncology team as well as organ specialists as soon as possible for additional support and guidance.

Conclusion

Traditionally, oncology patients present themselves to emergency departments with familiar and somewhat predictable oncologic emergencies—such as febrile neutropenia, sepsis, superior vena cava syndrome, and others—as a result of treatment with radiation therapy and chemotherapy for their malignancies. In recent years, the growing use of immunotherapy—specifically, checkpoint inhibitors—has signaled the era of new oncologic AEs with complex clinical scenarios and presentations in the emergency department. As a result, providers outside of oncology—including emergency physicians/nurses, intensivists, and endocrinologists—must become familiar with the mechanism of action of these agents to better understand and manage their AEs.[3,10,16]

The challenge with checkpoint inhibitor AEs is their lack of predictability of presentation. Figure 1 presents some general guidelines for presentation; however, these are wide-ranging patterns, in contrast to the more predicable AE profile of chemotherapy (eg, neutropenia 10 to 14 days after treatment). In addition, with the recent combination of checkpoint inhibitors with chemotherapy and radiation therapy, the incidence and complexities of these AEs will increase. Patients could present with neutropenia related to chemotherapy and concurrent immune-mediated AEs. Published data support the immediate use of high doses of steroids to initiate reversal of these irAEs.[1,3,8]

CASE STUDY CLOSURE

Because the history of immunotherapy was unknown and the on-call oncologist was not familiar with the patient's treatment history, steroids were not started until Monday, when the patient was followed in his oncologist's office. Based on his symptoms, his pneumonitis was classified as a grade 2 per CTCAE, v5 (cancer.gov).[7] Table 3 presents grading of most common irAEs. Therefore, in the emergency department, the patient should have been started on 1 to 2 mg/kg/d of an immunosuppressant, such as methylPREDNISolone, for suspected immune-mediated

TABLE 3
Most common immune-mediated adverse events

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Rash	Covering <10% BSA with or without symptoms; topical intervention indicated	Covering 10% to 30% of BSA with or without symptoms; oral treatment indicated	Covering >30% of BSA with or without associated symptoms, IV treatment indicated	—
Pneumonitis	Asymptomatic; clinical or diagnostic observations only	Symptomatic, medical intervention indicated; limited instrumental ADLs	Severe symptoms, limited self-care ADLs, oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (tracheostomy, intubation)
Diarrhea	Increase of <4 stools per day	4 to 6 stools per day	>7 stools per day, severely limited ADLs	Life-threatening consequences; urgent intervention indicated
Colitis	Asymptomatic, intervention not needed	Some abdominal pain or cramping; mucus or blood in stool	Stools may be bloody or with mucus; may have peritoneal signs; needs immediate hospitalization	Life-threatening consequences; urgent intervention indicated

ADL, activity of daily living; BSA, body surface area; IV, intravenous.
Common Terminology Criteria for Adverse Events (CTCAE) V 5.0[8].

pneumonitis, along with empirical treatment for a possible bacterial infection. Ideally, the oncology team should be informed of a patient's presentation in the emergency department so that a multidisciplinary approach could be used to ensure optimal treatment. However, because of the timing of the presentation with an on-call physician who was not familiar with the patient's treatment, critical information was not available.[10,16] Many centers have established ways to identify these patients through the electronic health record or with the use of a wallet card to make it easier for the medical team to identify them.

This case highlights the importance of patient education to provide the immunotherapy card when arriving in a nononcology setting. In addition, the ability to integrate electronic health records is important to have access to outpatient records by ED and hospital staff, ensuring pertinent information is available to the frontline staff when assessing and managing these patients.

Author Disclosures

Conflict of interest: None. Case study based on fictitious patient for illustrative purposes, and does not represent an actual, individual patient's care.

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