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BRIEF REPORT

Infections Simulating Immune Checkpoint Inhibitor Toxicities: Uncommon and Deceptive

Carlota Gudiol,[1,2,3] Rachel S. Hicklen,[4] Pablo C. Okhyusen,[5] Alexandre E. Malek,[5] and Dimitrios P. Kontoyiannis[6]

[1]Infectious Diseases Department, Bellvitge University Hospital, IDIBELL, University of Barcelona, Barcelona, Spain, [2]Institut Català d'Oncologia, Barcelona, Spain, [3]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), (CB21/13/00009), Instituto de Salud Carlos III, Madrid, Spain, [4]Research Medical Library, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, [5]Division of Infectious Diseases, LSU Health Shreveport, Shreveport, Louisiana, USA, and [6]Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Use of immune checkpoint inhibitors (ICIs), a revolutionary treatment in modern oncology, is frequently complicated by immune-related adverse events (irAEs), which can be confused with infections, and vice versa, thus complicating management decisions. In this study, we review the published cases of infections as simulators of irAEs in cancer patients.

Keywords. immune checkpoint inhibitors; infection; toxicity.

The discovery that malignant cells can prevent recognition and destruction by the immune system through the expression of immunoregulatory molecules, such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and the PD-1 ligand (PD-L1), has dramatically changed the landscape of medical oncology. Thus, the development of immune checkpoint inhibitors (ICIs), which are monoclonal antibodies that inhibit the aforementioned molecules, has revolutionized cancer care [1]. Unlike conventional chemotherapy that kills malignant cells, ICIs work by inhibiting the pathways cancer cells use to evade host immune recognition.

After the implementation of ICIs in cancer treatment, a plethora of autoimmune phenomena known as immune-related adverse events (irAEs) presented as a consequence of the immune checkpoint (ICP) blockade, with reported incidences ranging from 54% to 76% [2]. Immune-related adverse events may affect any system of the body and, occasionally, can simulate a variety of infections such as colitis, encephalitis, or pneumonitis [2]. Management of moderate to severe irAEs often involves therapy with glucocorticoids and other immunosuppressants, such as antitumor necrosis factor agents, in case of corticosteroid refractoriness. More importantly, this immunosuppressive therapy can be complicated by opportunistic infections [3]. In contrast, little is known regarding infections as simulators of irAEs, in the absence of immunosuppressive therapy. These infections may appear coincidentally or be unmasked by a dysregulated inflammatory immune response due to ICIs. In this sense, they have been recently cataloged as "infections due to dysregulated immunity (ITI-ID)" [4]. This hypothesis is based on several reports of infections during ICI treatment without additional immunosuppression and builds on the fact that patients with hereditary CTLA-4 dysfunction or mutations are more prone to present with recurrent infections, particularly respiratory infections, including tuberculosis [5].

Identifying infections that simulate irAEs is extremely important because the management is completely different. Misdiagnosing infections can lead to delayed diagnosis and treatment and a deterioration of the infectious condition due to the treatment with corticosteroids and other immunosuppressants used for the management of the suspected irAEs. Finally, diagnosis of irAEs requires the exclusion of other infectious or inflammatory causes.

In this study, we sought to review infections simulating irAEs. We do not discuss the unmasking of indolent or latent infections by ICIs that simulate progression of underlying cancer (eg, exacerbation of preexisting mycobacterial or fungal lung infection simulating lung cancer progression) (Supplementary Material References 1–11).

METHODS

Search Strategy and Selection Criteria

A comprehensive search of the literature was constructed and performed by a qualified medical librarian (R.S.H.). Medline (Ovid), Embase (Ovid), Scopus, Cochrane, and Google Scholar were queried, from database inception until January 2022, using both controlled vocabulary and natural language terms for ICIs and viral, bacterial, or fungal infections (see Supplementary Materials). A total of 291 articles and abstracts were retrieved with the search strategy, and 22 were finally included in the manuscript.

RESULTS

Infections Simulating Toxicities

A variety of viral, bacterial and fungal infections have been sporadically described as simulators of irAEs in cancer patients

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Correspondence: Dimitrios P. Kontoyiannis, MD, PhD (Hon), Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1460, Houston, TX 77030 (dkontoyi@mdanderson.org).

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treated with various ICIs with no additional immunosuppression (Table 1, Supplementary Table 1).

Viral Infections

Several case reports document reactivation of viruses from the herpesvirus family in patients on ICIs as irAEs [6–15]. Cytomegalovirus (CMV) was shown to simulate refractory gastrointestinal autoimmune colitis or gastritis in patients without previous immunosuppressants, and only biopsy was able to differentiate these entities [6–8]. These infections fully resolved with ganciclovir. Likewise, varicella-zoster virus (VZV) reactivation involving the central nervous system (CNS), causing encephalitis, cerebral vasculopathy and atypical Ramsay-Hunt syndrome followed with ataxic sensory neuropathy [9–11], and also granulomatous dermatitis simulating ICI-autoimmune effects have also been anecdotally reported [12]. In all cases, the subsequent appearance of a typical vesicular painful rash was the clue, and diagnosis was made with the detection of VZV deoxyribonucleic acid (DNA) in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) for the CNS manifestations, and by skin biopsy in VZV dermatitis. All patients were cured with acyclovir therapy. One case of Epstein-Barr (EBV)-induced acute cerebellar ataxia (confirmed with positive EBV DNA in the blood and CSF), and a case of fatal encephalitis, possibly in combination with concomitant pembrolizumab neurotoxicity have been reported [13, 14]. Finally, a single case of biopsy-proven human herpes virus 6 pneumonitis [15] and 2 cases of pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strictly simulating ICI-induced pneumonitis have been reported [16–18].

Patients with hematological malignancies are at heightened risk of prolonged SARS-CoV-2 shedding and sustained pulmonary inflammation [19]. Some of the coronavirus disease 2019 (COVID-19) symptoms may simulate ICI-related pneumonitis. Distinguishing between both conditions is crucial, albeit challenging, and may require additional invasive diagnostic procedures such as bronchoscopy. Although testing and nasal screening of SARS-CoV-2 virus before anticancer therapies initiation is largely standard in many oncologic centers, there is a relatively high rate (15%) of false-negative reverse-transcription PCR results [20]. Therefore, it is possible that patients with COVID-19 are erroneously thought to have ICI-related pneumonitis.

Hepatitis B (HBV) and hepatitis C virus (HCV) infection/reactivation in patients on ICIs, although rare (<1.5%), have been reported and can simulate ICI-autoimmune hepatitis [21]. However, the risk of HBV or HBV reactivation during treatment with ICIs is still unclear, because patients with chronic hepatitis infections are excluded from randomized clinical trials with ICIs. Therefore, the natural history of preexisting HBV and HCV is variable. In some patients, the viral load regresses, suggesting that ICIs may play a role in viral clearance. In this regard, it has been observed that patients with chronic HBV infection recover the function of HBV-specific $CD8^+$ T cells after ICI treatment [22]. Few cases of HBV reactivation have been reported in patients treated with immunotherapy and no additional immunosuppressants [21, 23–26]. Zhang et al [21] reported that among 114 patients with hepatitis B surface antigen-positive who were receiving anti-PD1/PD-L1 agents, 6 (5.3%) developed HBV reactivation, at a median of 18 weeks from ICI initiation, and 5 developed hepatitis. The risk of HBV reactivation was 17 times higher in patients without HBV prophylaxis (17.2% vs 1.2%; odds ratio = 17.50; $P = .004$). Four additional cases have been reported with the use of different ICIs, mainly due to lack of HBV diagnosis at baseline [23–26]. Two patients reactivated the infection after a single dose of immunotherapy, and one of them presented with fatal multiorgan failure [25, 26].

Bacterial Infections

Babacan et al [27] described 4 cases of superimposed *Clostridioides difficile*-associated diarrhea (CDAD) in patients with ICI-related colitis, and an additional CDAD case that developed without previous or concurrent treatment with steroids and antibiotics. In this case, CDAD preceded ICI-colitis by 2 months. Other cases of bacterial colitis simulating ICI colitis include 2 cases of *Aeromonas hydrophila* infection [28] and 1 case of *Campylobacter* spp and CMV coinfection [3].

A case of bilateral granulomatous anterior uveitis attributable to anti-PD-1 immunotherapy in a human immunodeficiency virus-positive patient with neurosyphilis has been reported [29]. The patient developed confusion with hallucinations before the fifth infusion of nivolumab. The *Treponema pallidum* hemagglutination assay became positive, and the lumbar puncture showed lymphocytic meningitis with no tumor cells. The clinical course was favorable with intravenous penicillin G. It was unclear whether granulomatous reaction was triggered by nivolumab in the setting of indolent syphilis.

Finally, a case of pneumonia due to *Corynebacterium striatum* was diagnosed in a patient receiving pembrolizumab who was unresponsive to therapy with corticosteroids due to suspected pulmonary toxicity. Bronchoscopy was crucial for diagnosis, and the patient improved with antibiotics [3].

Fungal Infections

Although exacerbation of preexisting Aspergillosis simulating cancer progression in the setting of ICI treatment has been reported (Supplementary Material References 9–11), fungi have been simulators of ICI immunotoxicity in only few instances. Specifically, *Pneumocystis jirovecii* pneumonia simulating ICI pneumonitis and *Blastomyces dermatitidis* and *Malassezia* spp (pityriasis versicolor) simulating ICP's dermatitis [3, 30–32].

DISCUSSION

We found that a variety of herpesviruses, and to a lesser degree hepatitis B and C viruses, SARS-CoV-2, gastrointestinal bacteria,

Table 1. Infections Mimicking Immune-Related Adverse Events by Immune Checkpoint Inhibitors

Organ/System Involved	Pathogen	Syndrome	Implicated ICI (Time From ICI Start)	Underlying Tumor	Reference
CNS	VZV	Encephalitis	Nivolumab (12 cycles)	Metastatic lung adenocarcinoma	Watanabe et al [9]
	VZV	Vasculopathy	Nivolumab (NA)	Lung	Ursu et al [10]
	VZV	Ramsay-Hunt syndrome + ataxic neuropathy	Nivolumab (13 cycles)	NSCLC	Sakoh et al [11]
	EBV	Cerebellar ataxia	Pembrolizumab (3 cycles)	Lung adenocarcinoma	Saikawa et al [13]
Lung	CMV	…	…	…	…
	Pneumocystis jirovecci	Pneumonitis	Nivolumab (3 cycles)	NSCLC	Liu et al [3]
	Aspergillus fumigatus	…	…	…	…
	HHV6	Pneumonitis	Nivolumab (3 months)	NSCLC	Foukas et al [15]
	SARS-CoV-2	Pneumonitis	Nivolumab (4 months)	Metastatic renal cell carcinoma	Artigas et al [16]
	SARS-CoV-2	Pneumonitis	Pembrolizumab (13 cycles)	Metastatic Merkel cell carcinoma	da Costa et al [17]
	Corynebacterium striatum	Pneumonitis	Pembrolizumab (3 cycles)	Lung adenocarcinoma	Liu et al [3]
	P jirovecci	Pneumonitis	Pembrolizumab (11 cycles)	Refractory PMBCL	Si et al [30]
Gastrointestinal tract	CMV	Gastritis	Atezolizumab (8 cycles), pembrolizumab (5 cycles)	Metastatic colon and bladder cancer	Lu et al [6]
	CMV	Colitis	Pembrolizumab (9 cycles)	Metastatic melanoma	Kim et al [7]
	CMV + *Campylobacter* spp	Colitis	Ipilimumab (anti-CD4)	Metastatic melanoma	Bossa et al [8]
	Clostridioides difficile	Colitis	Durvalumab + tremelimumab (3 months)	Metastatic lung adenocarcinoma	Babacan and Tanvetyanon [27]
	HBV	Hepatitis	Camrelizumab (3 weeks)	NPC	Zhang et al [21]
	HBV	Hepatitis	Camrelizumab (16 weeks)	NPC	…
	HBV	Hepatitis	Nivolumab (12 weeks)	HHC	…
	HBV	Hepatitis	Toripalimab (35 weeks)	HNSCC	…
Liver	HBV	Hepatitis	Nivolumab (20 weeks)	Soft tissue carcinoma	…
	HBV	Hepatitis	Ipilimumab, nivolumab (4 cycles)	Melanoma	Koksal et al [23]
	HBV	Hepatitis	Nivolumab (1 months)	Lung cancer	Lake [24]
	HBV	Hepatitis	Pembrolizumab (1 cycle)	Metastatic lung adenocarcinoma	Pandey et al [25]
	HBV	Hepatitis	Durvalumab (1 cycle)	Lung adenocarcinoma	Godbert et al [26]
Skin	VZV	Dermatitis	Nivolumab (6 months)	Lung adenocarcinoma	Gozzi et al [12]
	Blastomyces dermatitidis	Dermatitis (systemic infection)	Pembrolizumab (4 cycles)	Metastatic melanoma	Ferguson et al [31]
	Malassezia spp	Dermatitis	Pembolizumab followed by ipilimumab (30 weeks)	Metastatic melanoma	Li et al [32]
Eye	*Treponema pallidum*	Anterior uveitis	Nivolumab (5 cycles)	NSCLC	Ferreira et al [29]

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HHV6, human herpes virus 6; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; NA, not available; NPC, nasopharyngeal carcinoma; NSCLC, nonsmall cell lung cancer; PMBCL, primary mediastinal B-cell lymphoma; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VZV, varicella zoster virus.

and few fungi, can occasionally simulate irAEs, so a high index of suspicion is needed. Our review was limited by the fact that reported infections simulating ICI toxicity were case reports, subject to publication biases. Because there was no population-based assessment nor a case control design of such reports, the frequency and the spectrum of the infections simulating ICI autoimmune effects is unknown. Specifically, it is unclear whether these reported infections are merely coincidental or whether their reactivation is the bystander effect of an immunoregulatory change caused by ICI. This is an area for future prospective registries and a fertile area for future clinical research in the field of infection, immunity, and ICI treatment in modern oncology.

Furthermore, the evaluation (type and cost effectiveness) to rule out an occult infection in patients presenting with irAEs has not been validated. At present, such evaluation needs to be performed following a syndromic approach, based on atypical features of presumed irAEs and suspicion of infection. Table 2 depicts a suggested approach.

Table 2. Suggested Organ-Specific Work up to Evaluate for Infection in Patients With Presumed irAEs

Organ-Specific Consideration	Work up
Meningoencephalitis	Assess for immunosuppression Brain MRI w/wo contrast + pituitary protocol CSF examination indicated including opening pressure CSF studies for cell count, protein, glucose, NAAT meningoencephalitis panel (including PCR for HSV and other viral PCRs), Gram stain and culture, AFB smear and culture, fungi smear and culture, cryptococcal antigen
Pneumonitis	Assess for immunosuppression Obtain nasal respiratory viral NAAT panel (that includes SARS-CoV-2) Sputum Gram stain and culture Blood culture TB spot Serologic testing for endemic fungi Imaging studies Bronchoscopy plus bronchoalveolar lavage +/− transbronchial biopsy
Hepatitis	Viral hepatitis (HBV, HCV, HAV, and HEV if risk factors) Liver ultrasound Consider testing for CMV, HSV, HHV6, adenoviruses, enteroviruses and Leptospirosis if clinically suspected
Colitis	NAAT for enteropathogens including *Clostridioides difficile* with reflex EIA for toxin A & B Stool O&P CMV PCR from biopsy (extrapolating from IBD) Calprotectin, lactoferrin CT scan of abdomen and pelvis Consider GI endoscopy with biopsy
Dermatitis	Assess for cellulitis Screen for HSV and *Mycoplasma pneumoniae* in case of erythema multiforme Skin HSV and VZV DNA in case of bullous lesions +/− Skin biopsy plus culture with specific stains (AFB, H&E, and GMS) in severe cases
Endocrine toxicity (adrenal insufficiency)	Assess for immunosuppression Evaluate for infectious adrenalitis TB spot Serologic testing for endemic mycoses CMV testing Biopsy if clinically indicated
Hematologic toxicity (hemolytic anemia or aplastic anemia)	Assess for immunosuppression Testing for viral and bacterial causes (*Mycoplasma pneumoniae*; Parvovirus B19; CMV; HHV6; EBV and HIV) Cryoglobulin analysis Screen for Shiga toxin and *Escherichia coli 0157* if diarrhea and HUS Screen for HCV, HBV, HIV, and *Helicobacter pylori* if ITP

Abbreviation, AFB, acid-fast bacillus; CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; EIA, enzyme immunoassay; GI, gastrointestinal; GMS, Grocott methenamine silver; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; H&E, hematoxylin and eosin; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HHV6, human herpesvirus 6; HSV, herpes simplex virus; HUS, hemolytic uremic syndrome; IBD, inflammatory bowel disease; irAE, immune-related adverse event; ITP, immune thrombocytopenia; MRI, magnetic resonance imaging; MRSA, methicillin-resistant *Staphylococcus aureus*; NAAT, nucleic acid amplification test; O&P, ova and parasites; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TB, tuberculosis; VZV, varicella zoster virus.

NOTE: Consider infectious diseases consultation.

Some other future questions are whether these are pathogen-, host-, cell-, organ, and context-specific characteristics and whether these infections predispose to subsequent irAEs and/or influence their severity and frequency. Finally, future studies are needed to examine the questions of when to start ICIs after an infection simulating irAEs and whether specific oncological treatments predispose to develop atypical infections simulating irAEs. Because ICI use is rapidly increasing, we hope that our review will stimulate further activity in this area for future clinical research in the field of infection, immunity, and ICI treatment in modern oncology.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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