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Case Report

Pulmonary Nocardiosis in a Non-Small Cell Lung Cancer Patient Being Treated for Pembrolizumab-Associated Pneumonitis

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Keywords

Pulmonary nocardiosis · Pembrolizumab · Immune-checkpoint-inhibitor · Immune-related adverse events · Non-small cell lung cancer

Abstract

Introduction: Immune-check-point inhibitors (ICIs) are established in the treatment of many malignancies. Many immune-related adverse events (irAEs) are well described; however, there is less information about opportunistic infections in cancer patients receiving ICIs. ***Case Presentation:*** We describe the case of a 62-year-old woman with non-small cell lung cancer, who relapsed after surgical resection and chemotherapy. She received 13 months of pembrolizumab, achieving stable disease, before presenting with suspected pneumonitis 2 weeks prior to departure for an international vacation. She was treated with high-dose corticosteroids and, shortly thereafter, developed severe nocardiosis, requiring venovenous extracorporeal membrane oxygenation and lengthy hospitalization. ***Conclusion:*** To our knowledge, this represents the second known case of pulmonary nocardiosis in a patient on pembrolizumab. Moreover, this is a rarely reported instance of opportunistic bacterial infection following steroid treatment for ICI pneumonitis. This case report emphasizes the risk of bacterial infection associated with ICI pneumonitis, both due to the difficulty of excluding underlying infection at presentation, and the immunosuppression caused by irAE treatment. As such, we suggest that clinicians maintain a high suspicion for potential infection in ICI pneumonitis, and strongly consider initiating infectious workup with regular follow-ups for monitoring. Prophylactic antibiotics could be considered when such monitoring is not possible.

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Introduction

Immune-check-point inhibitors (ICIs) have become an integral tool in medical oncology [1]. Although ICIs are remarkably effective against a multitude of cancers, immune system over-activation also leads to a unique array of toxicities, collectively termed immune-related adverse events (irAEs) [1]. Skin manifestations such as rash are most common, yet irAEs can occur in numerous organ systems, such as pneumonitis, hepatitis, and colitis. Immunosuppression with corticosteroids is the primary treatment for significant irAEs [2], with emerging reports of heightened infection risk during such immunosuppression, including fatal opportunistic infections [3, 4]. In this report, we describe a case of pulmonary nocardiosis in a patient on pembrolizumab who was receiving oral corticosteroids for ICI pneumonitis, a seldom-reported case of opportunistic bacterial infection during ICI pneumonitis treatment. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000541694).

Case Presentation

A 62-year-old female with a history of type 1 diabetes, cardiovascular disease, and 30 pack-years of cigarette smoking presented to her family doctor in August 2020 with several months of fatigue. Subsequent CXR showed a new right lower lobe mass and after comprehensive staging investigations, she underwent surgical resection for a pT2bN1 squamous cell carcinoma. Two cycles of adjuvant cisplatin and vinorelbine were started in January 2021 and discontinued early due to emesis.

In December 2021, the patient relapsed with stage 4 disease after presenting with worsening pleuritic chest pain. A CT chest revealed a pleural effusion with pleural thickening, and a diagnostic tap confirmed malignancy. PD-L1 expression was >90%; thus, pembrolizumab was started in February 2022. This therapy was well tolerated, with occasional grade 1 diarrhea and pruritus.

After 13 months of therapy with stable trace effusion and pleural thickening (shown in Fig. 1a), the patient planned a Caribbean cruise that had been deferred from the prior year. Routine CT scans 3 weeks prior to departure reported new bilateral lower lobe peripheral reticulation and ground-glass opacities, consistent with organizing pneumonia (shown in Fig. 1b, c), but due to the history of pembrolizumab use, the radiology report noted a concern for drug-induced pneumonitis. The patient presented to the clinic the following week (March 2023) with new mild shortness of breath on exertion; however, she was non-febrile with no cough and an unremarkable white blood cell (WBC) count. A 5-week taper of 50 mg prednisone (10 mg reduction per week) was initiated for pneumonitis with follow-up in 1 week. Immunotherapy was held. No infectious workup was performed due to low clinical suspicion of infection. After 1 week her symptoms had resolved, and she was deemed medically fit to travel.

Two weeks into the taper and while on the cruise, the patient developed significant shortness of breath and subsequently presented to a hospital in Cozumel, Mexico. She was profoundly hypoxemic (pO_2 40 mm Hg) requiring intubation. She was started on broad-spectrum antibiotics and antifungals. A CT scan demonstrated new bilateral diffuse centrilobular ground-glass nodules, tree-in-bud opacities, a new necrotic left upper lobe consolidation mass and left lower lobe consolidation (shown in Fig. 1d). Due to the inability to maintain target oxygen saturations while intubated, she was placed on venovenous extracorporeal membrane oxygenation. A medevac transfer to Canada happened after 5 days. She

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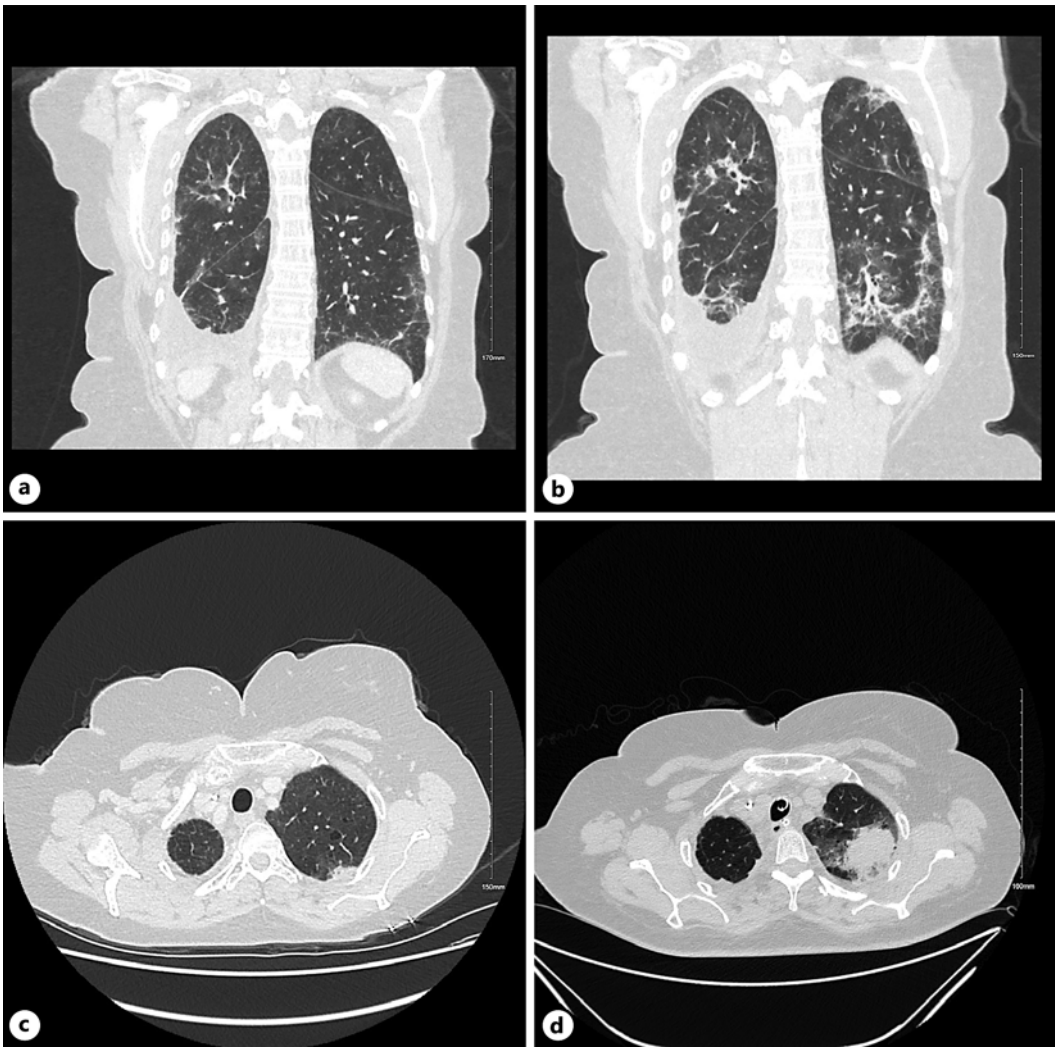

Fig. 1. a January 2023: coronal CT with good cancer control on pembrolizumab. March 2023: evidence of pneumonitis on coronal scan (**b**), but no mass in the left upper lobe on axial imaging (**c**). **d** April 2023: new left upper lobe mass reflecting *Nocardia* infection.

was de-cannulated 2 days later. Sputum cultures in Mexico reported unspeciated *Nocardia*, confirmed as *Nocardia cyriageorgica* via repeat culture performed upon repatriation. Blood cultures were negative. The patient remained afebrile throughout admission. On repatriation, she was started on combination antibiotic therapy consisting of meropenem and trimethoprim/sulfamethoxazole (TMP-SMX) until susceptibility results were available and clear radiographic improvement was demonstrated (~1 month). Antibiotics were then tailored to TMP-SMX for an additional 5 months. An expedited prednisone taper was also completed during admission as underlying pneumonitis could not be ruled out. In total, the patient was admitted to a hospital for 53 days, including 10 days in the intensive care unit, and further required hemodialysis due to AKI (presumed from sepsis) for 51 days.

The cancer remained stable throughout the admission. Due to uncertainty about whether underlying pneumonitis had contributed to the patient's pulmonary insult, and the anticipated inability to distinguish pneumonitis from infection relapse, the pembrolizumab has

been held indefinitely. At the latest radiological and clinical follow-up in summer 2024, the patient is well with ongoing cancer control and no infection recurrence, now >12 months since discharge.

Discussion

Nocardiosis refers to the infection caused by *Nocardia* spp., which are gram-positive aerobic bacilli prevalent throughout the world in both terrestrial and aquatic environments. Such infections are exceedingly rare and are widely considered opportunistic in nature [5]. Infections with *Nocardia* predominantly occur in immunocompromised hosts, although infection can infrequently occur among immunocompetent patients, usually when underlying comorbidities are present including diabetes and smoking [6]. However, these comorbidities can hardly raise suspicion of nocardiosis (in the absence of immunocompromise) as the prevalence of such comorbidities far exceeds that of nocardiosis (only 500–1,000 nocardiosis cases are reported in the USA annually) [5]. While *Nocardia* can cause disease at any route of entry, pulmonary infection represents 80% of cases (usually from inhaling contaminated aerosols) [5, 7]. Invasive pulmonary infection is overwhelmingly associated with an immunocompromised state and carries an especially poor prognosis given that ~50% of cases progress to disseminated infection [5, 8].

There is increasing consensus that ICI use is not a priori associated with heightened infection risk [9]. Of interest are two cases of nocardiosis in patients on pembrolizumab monotherapy, one cerebral and one pulmonary, and each without concurrent immunosuppression [10, 11]. Both presented 3–4 months after initiating pembrolizumab as such the authors hypothesize that pembrolizumab induced immune dysregulation akin to immune reconstitution inflammatory syndrome (IRIS) observed in HIV treatment. Although IRIS is poorly understood, it generally presents within 6 months of HIV treatments [12]. IRIS is therefore unlikely to explain this case, where nocardiosis occurred 13 months after pembrolizumab initiation. In the cerebral case, the authors also suggest latent infection could have developed prior to initiating pembrolizumab. While cerebral nocardiosis is known to be latent for up to 3 years, the latency of pulmonary nocardiosis is not characterized (many individuals have asymptomatic colonization) [7] and, therefore, would be difficult to evaluate in this case.

In contrast to infection risk, irAEs represent a far more pressing concern of ICI treatment. The frequency and symptoms of irAEs are highly variable across organ systems; however, they are consistent in that the moderate-to-severe forms can be life-threatening [2]. Such is the case with pneumonitis, for which the American Society of Clinical Oncology (ASCO) reports an overall incidence of 2.7% on PD-1/PD-L1 inhibitors [2]. While this case highlights a pulmonary complication in an NSCLC patient, where imaging can sometimes be difficult in distinguishing the disease from complications, these pulmonary complications can occur with ICI use across a broad range of malignancies.

Troublingly, it is difficult to rule out infection in suspected ICI pneumonitis. Clinical presentation is similar (dyspnea, cough, and fever), and no radiographic features are pathognomonic for pneumonitis [2, 3]. Further, even if no underlying infection exists at diagnosis, pneumonitis treatments will leave patients more vulnerable to infection. As per ASCO guidelines, the treatment for most moderate-to-severe irAEs (pneumonitis included) is a high-dose steroid taper, with infliximab as an alternative or if refractory [2]. Such treatments are clearly understood to increase the risk of severe and opportunistic infections; emerging evidence shows this risk remains present in the treatment of irAEs [1, 3, 4, 9]. However, there are no clear guidelines for infectious workup or antibiotic use in ICI pneumonitis. ASCO

guidelines only note that such investigations or empiric antibiotics may be considered if grade 2 severity or higher.

This case highlights the diagnostic uncertainty and risk of infection associated with ICI pneumonitis. Even after extensive review of this case, it remains unclear whether nocardiosis infection was already developing at the patient's initial March 2023 presentation, or only developed following immunosuppression from high-dose steroids. Although it seems unlikely that an otherwise immunocompetent patient (only on pembrolizumab monotherapy) would contract nocardiosis, such a case has been documented in the literature [10], and infection was not definitively ruled out in our patient. Given that suspicion for infection was low at her March 2023 presentation (she was afebrile with no leukocytosis, and the CT report specifically noted a concern for pneumonitis), a trial of steroid therapy seemed a reasonable option (rather than pursuing further infectious workup, especially invasive bronchoscopy). Pneumonitis was an entirely reasonable diagnosis supported by radiographic data and an excellent response to steroids, yet it remains possible that the nocardiosis was temporarily masked by steroids until she decompensated on vacation. Without clinical monitoring or infectious workup, one cannot be certain that underlying infection is absent when diagnosing ICI pneumonitis. Given the known risk of opportunistic infection in patients on high-dose steroids; however, this case may also represent opportunistic infection secondary to steroid-induced immunocompromise. Naturally, in hindsight, should the patient have been cleared for travel after just 7 days of corticosteroids? This was a long-planned (and delayed) trip with children and grandchildren and highlights the challenge of balancing clinical goals with personal goals.

There are few reports of opportunistic bacterial infection during irAE treatment. Most reports of opportunistic infection are of *Pneumocystis jirovecii*, Aspergillosis, tuberculosis reactivation, and various viral infections [1, 3, 4, 9]. For ICI pneumonitis treatment specifically, there are virtually no reported cases of opportunistic bacterial infection beyond one instance of each of *Pseudomonas* and *Corynebacterium striatum* [13, 14].

In summary, this case represents a rare instance of nocardiosis in a patient on pembrolizumab. Moreover, it represents one of the few reported cases of opportunistic bacterial infection during steroid treatment for ICI pneumonitis. This case highlights the dually elevated risk of infection in ICI pneumonitis, both due to the difficulty of identifying infection based on clinical presentation and the subsequent immunocompromise associated with treatment. As such, we suggest that in the absence of clear guidelines for infectious workup and antibiotic use in ICI pneumonitis, physicians should remain vigilant for potential infection in suspected ICI pneumonitis. This sentiment applies across the breadth of malignancies wherein ICIs are used. Even if clinical suspicion for infection is low at first presentation, clinicians should strongly consider initial infectious workup (such as viral swabs and sputum cultures), with regular follow-up and patient education to monitor for signs of developing infection. Physicians could further consider prophylactic antibiotics when monitoring is not possible due to time or geographic constraints, as in this case. TMP-SMX would be reasonable prophylaxis against bacterial infection when high-dose steroid regimens are used as ASCO guidelines already recommend adding this for *P. jirovecii* prophylaxis in the context of chemotherapy [15].

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Verbal consent from the patient discussed in the case report has been received. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.Q. was responsible for conceptualization of the project, data curation, writing of the original draft, and review and editing. P.W.-P. was responsible for conceptualization of the project, methodology, project administration, supervision, and review and editing. C.A.B. and E.K. were involved in the clinical care in this case and responsible for review and editing.

Data Availability Statement

Data will be made available upon request to the corresponding author (pwheatleyprice@toh.ca). These data are only available upon request, given the inclusion of sensitive patient data and data transfer agreements may be required.

References

1 Morelli T, Fujita K, Redelman-Sidi G, Elkington PT. Infections due to dysregulated immunity: an emerging complication of cancer immunotherapy. Thorax. 2022;77(3):304–11. https://doi.org/10.1136/thoraxjnl-2021-217260
2 Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol. 2021;39(36):4073–126. https://doi.org/10.1200/JCO.21.01440
3 Ocaña-Guzmán R, Osorio-Pérez D, Chavez-Galan L. Opportunistic infections and immune-related adverse events associated with administering immune checkpoint inhibitors: a narrative review. Pharmaceuticals. 2023;16(8):1119. https://doi.org/10.3390/ph16081119
4 Ross JA, Komoda K, Pal S, Dickter J, Salgia R, Dadwal S. Infectious complications of immune checkpoint inhibitors in solid organ malignancies. Cancer Med. 2022;11(1):21–7. https://doi.org/10.1002/cam4.4393
5 Rawat D, Rajasurya V, Chakraborty RK, Sharma S. Nocardiosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. [Cited 2024 Aug 4]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526075/
6 Steinbrink J, Leavens J, Kauffman CA, Miceli MH. Manifestations and outcomes of nocardia infections: comparison of immunocompromised and nonimmunocompromised adult patients. Medicine. 2018;97(40):e12436. https://doi.org/10.1097/MD.0000000000012436
7 McNeil MM, Brown JM. The medically important aerobic actinomycetes: epidemiology and microbiology. Clin Microbiol Rev. 1994;7(3):357–417. https://doi.org/10.1128/CMR.7.3.357
8 Spelman D, Saullo J, Sexton D, Hall K. Nocardia infections: epidemiology, clinical manifestations, and diagnosis [Internet]. [cited 2024 Jun 24]. Available from: https://www.uptodate.com/contents/nocardia-infections-epidemiology-clinical-manifestations-and-diagnosis?search=pulmonary%20nocardiosis&source=search_result&selectedTitle=2%7E8&usage_type=default&display_rank=2#H4
9 Redelman-Sidi G, Michielin O, Cervera C, Ribi C, Aguado JM, Fernández-Ruiz M, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors). Clin Microbiol Infect. 2018;24(Suppl 2):S95–107. https://doi.org/10.1016/j.cmi.2018.01.030

Case Rep Oncol 2024;17:1222–1228
DOI: 10.1159/000541694

10 Lasagna A, Arlunno B, Imarisio I. A case report of pulmonary nocardiosis during pembrolizumab: the emerging challenge of the infections on immunotherapy. Immunotherapy. 2022;14(17):1369–75. https://doi.org/10.2217/imt-2022-0152
11 Petitgas P, Lesouhaitier M, Boukthir S, Cattoir V, Tattevin P, Bénézit F. Cerebral nocardiosis in a patient treated with pembrolizumab: a first case report. BMC Infect Dis. 2022;22(1):306. https://doi.org/10.1186/s12879-022-07288-4
12 Thapa S, Shrestha U. Immune reconstitution inflammatory syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. [Cited 2024 June 24]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567803/#:~:text=Immune%20reconstitution%20inflammatory%20syndrome%20(IRIS,of%20IRIS%20is%20still%20unknown
13 Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in patients treated with anti–programmed death-1/programmed death ligand 1 therapy. J Clin Oncol. 2017;35(7):709–17. https://doi.org/10.1200/JCO.2016.68.2005
14 Liu Z, Liu T, Zhang X, Si X, Wang H, Zhang J, et al. Opportunistic infections complicating immunotherapy for non-small cell lung cancer. Thorac Cancer. 2020;11(6):1689–94. https://doi.org/10.1111/1759-7714.13422
15 Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. J Clin Oncol. 2018;36(30):3043–54. https://doi.org/10.1200/JCO.18.00374