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Non-tuberculous mycobacterial infections during cancer therapy with immune checkpoint inhibitors: a systematic review

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Keywords: immune checkpoint inhibitors; non-tuberculous mycobacteria; immune-related adverse events; MAC; NTM-LD.

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Summary: NTM infections occurring during ICIs therapy are mainly caused by MAC, involve primarily the lungs, on average one year after the start of treatment and are not associated with immunosuppressive treatments.

Abstract

Immune checkpoint inhibitors (ICIs) are drugs growingly employed in the treatment of cancers but there are still uncertainties about their possible role in the risk of developing non-tuberculous mycobacteria (NTM) infections.

To understand this, we performed a systematic review of the literature including studies published between 20/06/2012-20/06/2022 which described the occurrence of NTM infections among patients treated with ICIs.

Overall, we included 7 studies describing 9 patients with NTM infection occurring during ICIs therapy.

NTM infections occurring during ICIs therapy are mainly caused by germs belonging to the *Mycobacterium avium complex*, involve primarily the lungs, on average one year after the start of treatment and are not associated with immunosuppressive treatments.

Introduction

Immune checkpoint inhibitors (ICIs) bind to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1). ICIs can re-establish an "exhausted" immune response against a specific antigen and a growing number of tumours are being treated with them. Since ICIs introduction in the therapeutic armamentarium, there were concerns about the possible association with infections. Early reports mainly associated the use of immunosuppressive drugs, employed to manage immune-related adverse events (IRAEs) caused by ICIs, with the development of infectious events.[1] A direct role of ICIs, secondary to the exacerbation of the immune response against a certain pathogen was instead postulated for mycobacterial disease.[2] Currently, infections occurring under ICIs therapy are classified as those related to immunosuppression and those induced by dysregulated immunity.[3]

Still unclear is the role of ICIs therapy on the risk of developing non-tuberculous mycobacteria (NTM) infection. The presence of a dysfunctional immune response against NTM, showing several features of immune exhaustion, has been clearly described, thus providing the theoretical explanation for the appearance of immunopathology among patients treated with ICIs while infected by NTM.[4] Moreover, ICIs have been even postulated as a possible adjuvant in the treatment of NTM-lung disease (NTM-LD).[5] A case series from Japan in 2020 was the first one reporting three cases of NTM-LD among patients receiving ICIs immunotherapy.[6] A subsequent retrospective review performed on the US Food and Drug Administration Adverse Events Reporting System (FAERS), including cases reported until 31 March 2020, identified 13 cases of NTM infection resulting from treatment with PD-(L)1 inhibitors. The reporting odds ratio (ROR) was measured to compare the risk of infection between PD-(L)1 inhibitors and other drugs, and it corresponded to 5.49 (95% CI: 3.15–9.55, $p < 0.0001$), highlighting an increased risk of NTM infection associated with ICIs treatment.[7]

Considering the growing number of patients receiving ICIs and the difficulties associated with diagnosis and treatment of NTM infection, especially among patients with tissues already altered by the cancerous process, is of paramount importance to understand the relevance of NTM infections potentially associated with ICIs therapy. To fill this gap of knowledge we performed a systematic review of the literature aiming at assessing the clinical and therapeutic characteristics of the individuals displaying this complication.

Methods

We performed a systematic review of the literature employing the search query *("non-tuberculous" OR "NTM" OR "avium" OR "MAC") AND ("immune checkpoint" OR "pembrolizumab" OR "nivolumab")* including studies published between 20/06/2012-20/06/2022 which described the occurrence of NTM infections among patients treated with ICIs. We included any kind of study, including case reports, published in English. Overall, we identified 180 articles through the PubMed, Scopus and Embase databases and 5 were retrieved through an additional literature search. We excluded study not providing information about the ICI administered or the NTM isolated. Overall, 9 studies were included for the full-paper evaluation and 7 were included in this review (Supplementary Figure 1).[6, 8–13] Two authors evaluated independently the selected articles. For each study we extracted demographic data, cancer type and standard neoplastic treatment received, ICI treatment administered, NTM isolated, tissue involved, NTM-specific treatment administered and management of immunotherapy after NTM infection diagnosis. Response to NTM treatment was classified as good (NTM treatment tolerated with NTM disease improvement), fair (NTM treatment tolerated without NTM disease progression) and poor (NTM treatment discontinued due to intolerance, death).

Results

Overall, we included 7 studies describing 9 patients with NTM infection occurring during ICIs therapy. Male were the majority (7/9, 77.7%), lung the organ most frequently involved by neoplasia

(6/9, 66.6%) and nivolumab the ICI most employed (4/9, 44.4%), followed by pembrolizumab (3/9, 33.3%). NTM infections involved the lung (7/9, 77.7%), were mainly due to NTM belonging to *Mycobacterium avium* complex (MAC) and occurred on average 12 months/15 cycles after treatment start. Specific treatment for NTM was started in 7/9 (77.7%) patients and the response to therapy was considered good in three cases, fair in two cases and poor in two cases, with one reported dead among the latter two. Of note, most cases occurred among Japanese patients (8/9, 88.8%) and none received a concomitant immunosuppressive treatment (TNF-α inhibitors, steroids) for the management of IRAEs. A global overview of the characteristics of the patients included is provided in table 1.

Discussion

NTM infections occurring during immunotherapy with ICIs appear to be an acknowledged condition, with several cases identified in the literature. They are mainly due to MAC, involve primarily the lungs in patients with concomitant pulmonary neoplasia, occur on average one year after the start of ICIs treatment and are not associated with immunosuppressive treatment for the management of IRAEs. Apparently, this condition is more prevalent among patients from Eastern Asia, particularly Japan.

To the best of our knowledge, this is the first study depicting all the cases of NTM infection occurring during ICIs immunotherapy described in the literature. Based on the elaboration of data collected by the VAERS, the ROR for NTM infection is 5.49 among patients receiving PD-1/PD-L1 inhibitors, much higher than the ROR of 1.79 estimated for Tb among the same population.[7] Therefore, the case reports we included are probably only the tip of the iceberg of NTM infections occurring during immunotherapy with ICIs, which probably are unrecognized or underreported. Overall, we did not identify any case of NTM infection among patients treated with inhibitors of CTLA-4 (ipilimumab), but only among those treated with anti-PD1 (nivolumab, pembrolizumab) or anti-PD-L1 (atezolizumab, durvalumab). Similarly to what has been reported for Tb cases among

patients receiving ICIs, NTM infections involved mainly the lung and were reported chiefly among patients with concomitant lung cancer, as expected considering both the therapeutic indications of ICIs and the lung as the main entry door of mycobacteria in the host.[14]

The predominance of patients from Eastern Asia, and Japan, in particular, is not surprising, considering that prevalence rates of NTM-LD are among the highest worldwide in this area.[15, 16] Moreover, Japan has an economic status able to provide the global access to ICI for patients with tumours, thus allowing the occurrence in the same patient of two infrequent events: ICI immunotherapy and NTM infection. It is highly probable that reduced frequencies of NTM-LD during ICI therapy can be observed in other region of the world characterized by a lower incidence of NTM infection. Moreover, considering the differences existing in terms of NTM species epidemiology, different microorganisms other than MAC can be found as predominant in other geographical settings.

Interesting is also the predominance of male patients, which is unusual considering that normally female are more frequently affected by NTM-LD.[17] It should be considered how lung cancer, the reason justifying the employment of ICI, instead is much more common among male individuals in the Western-Pacific WHO Region (Estimated age-standardized incidence rates in 2020 46.5/100,000 for male vs 21/100,000 for female), probably explaining this result.[18]

It is finally worth to note that, according to the classification proposed by Morelli et al., the NTM infections described in our review should be classified as immunotherapy infections due to dysregulated immunity.[3] Indeed, none of the individuals included received a concomitant immunosuppressive treatment for an IRAE and the clinical manifestations observed should be probably viewed as a “reactivated” immune system exerting an excessive and dysregulated immune response against the NTM encountered by the patient. This is a very relevant observation, considering that also in a case series of Tb infections under ICIs only a few cases received

concomitant corticosteroid administration.[14] Instead, infections with other agents were associated, even though not universally, with concomitant immunosuppressive therapy for IRAEs.[1, 19]

Our study has some intrinsic limitations, being a collection of case reports with all the biases associated with this kind of study. Nonetheless, it is the first one collecting organically all the cases reported of NTM infections during ICIs immunotherapy. Considering the nature of the data collected it is not possible to calculate the odd/risk ratio but only to describe the general clinical features of those developing the infection. Moreover, the patients identified are all from Eastern Asia, and therefore it is challenging to speculate on the transferability of these observations outside this specific geographic area.

As stated in the introduction, the possibility of having enhanced manifestations of mycobacterial infection during ICIs treatment was postulated early after the introduction of ICIs in therapy, based on the identification of mycobacteria-specific T cells with a dysfunctional profile like that identified in neoplastic conditions. Therefore, in the cases we identified, it is possible to assume that the treatment with ICIs enhanced the immune response of NTM-specific T lymphocytes against the mycobacteria encountered by the host during the immunochemotherapy, leading to more severe clinical manifestations and thus increasing the diagnostic rates. At least for two studies, we have the certainty of *de novo* infections, Baba et al. described negative sputum culture before ICIs start whereas Yamaba et al. did not highlight alterations compatible with NTM-LD at baseline CT scan.[8, 10]

Acknowledging the increased risk of Tb among patients receiving ICIs, evaluation of previous Tb exposure, through tuberculin skin test or interferon-γ release assay, is a practice recommended by oncologic societies before treatment start to identify those subjects who may have a latent tuberculosis infection.[20] Moreover, a recent study has validated the usefulness of this test among patients receiving ICI as a tool to monitor for the development of active tuberculosis.[21] No similar tests are available for NTM and these mycobacteria are not associated with the development

of latent infection, making it hard to identify *a priori* those patients at higher risk of NTM infection. Therefore, particular care should be reserved for those patients developing infectious events under ICIs therapy, especially when involving the lung and when without microbiologic results at commonly performed diagnostic tests or not responding to first line antimicrobic agents, because an NTM infection can be an overlooked cause of the infection. An infectious disease specialist or a pneumologist can be of support in these cases and should be involved in the clinical management of these patients.

Overall, the amount of data regarding the occurrence of NTM infection during ICIs immunotherapy is quite limited and based mainly on case reports. Further studies, such as cohort studies, are needed to understand organically the real incidence of NTM infections under ICIs, the risk factors associated and the relevance of this condition also in areas with a lower endemicity of NTM such as Western Europe or Northern America. This is of paramount importance considering both the increasing prevalence of NTM-LD in Western Countries and the growing number of patients who are going to receive ICIs immunotherapy in the near future.

Conflict of interest

AL reports personal fees from Gilead Sciences Inc. and Isnmed Italy. AGr reports personal fees from Grifols, Chiesi, GSK, Vertex and Insmed Italy. MO reports personal fees from Grifols. FB reports grants and personal fees from AstraZeneca, grants and personal fees from Chiesi, personal fees from Grifols, grants and personal fees from GSK, personal fees from Guidotti, personal fees from Insmed, grants and personal fees from Menarini, personal fees from Novartis, personal fee from OM pharma, personal fees from Pfizer personal fees, personal fees from Janssen, personal fees from Vertex, personal fees from Viatris, personal fees from Zambon, in the last 3 years outside the submitted work All the other authors have nothing to declare.

Author contribution

AL, AGo, and FB conceived the study. AL, AGr, MO, and CA reviewed the literature and extracted the data. AL analysed the data and wrote the first draft of the manuscript. All the authors reviewed the final version of the manuscript.

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Ethical approval

Not required.

Table 1. A global overview of the included studies with patient characteristics and NTM-infection description.

Study	**Fujita 2020 (a[§])**	**Fujita 2020 (b[§])**	**Fujita 2020 (c[§])**	**Baba 2021**	**Okamoto 2021**	**Koyama 2021**	**Chi 2022**	**Omori 2022**	**Yamaba 2022**
Age (years)	66	80	66	80	69	44	58	74	82
Gender	Female	Male	Male	Male	Male	Female	Male	Male	Male
Neoplasia	Lung adenocarcinoma	NSCLC	Lung squamous cell carcinoma	Lung squamous cell carcinoma	Lung squamous cell carcinoma	Breast cancer	Renal cell carcinoma	Lung cancer	Gastric cancer
Country	Japan	Japan	Japan	Japan	Japan	Japan	Taiwan	Japan	Japan
Chemotherapy*	(i) Carboplatin + pemetrexed (ii) Gemcitabine	(i) Carboplatin + nabPTX	(i) Carboplatin + nabPTX (ii) Nivolumab (iii) Docetaxel	(i) Carboplatin	Carboplatin + nabPTX (concomitant to ICI)	(i) Doxorubicin + tamoxifen (ii) Leuprorelin acetate (iii) Bevacizumab + paclitaxel (concomitant to ICI)	Axitinib (concomitant to ICI)	Unknown	(i) Tegafur/gimeracil/oteracil
Previous radiotherapy	60-Gy stereotactic	66-Gy stereotactic	37.5-Gy palliative	60-Gy	-	-	-	-	45-Gy
ICIs administered (cycles†)	Nivolumab (38)	Atezolizumab (24)	Nivolumab (6) Atezolizumab (4)	Durvalumab (unknown)	Pembrolizumab (6)	Nivolumab (6)	Pembrolizumab (8)	Pembrolizumab (unknown)	Nivolumab (22)
Time since ICI started (months)	17	17	19	8	6	5	6	8	22
NTM isolated	*M. intracellulare*	*M. intracellulare + M. avium*	*M. intracellulare*	*M. avium*	*M. abscessus*	*M. mageritense*	*M. avium complex*	*M. abscessus* subsp *abscessus*	*M. intracellulare*
Organ/tissue	Lung	Lung	Lung	Lung	Lung	(i) CRBSI (ii) ABSSI	Lung	Vertebral osteomyelitis +	Lung

involved								epidural abscess	
NTM treatment	Yes	Yes	No	Unknown	Yes (IMP + AMK + CLR)	Yes (AMK + MEM + CIP)	Yes	Yes (IMP + AMK + CLR)	Yes (RIF + ETB + CLR)
Management of immunotherapy	Maintained	Maintained	Discontinued	Unknown	Suspended and restarted after lobectomy	(i) Maintained; (ii) Discontinued	Unknown	Already suspended at time of diagnosis	Discontinued
Response to NTM therapy	Good	Fair	No treatment	Unknown	Good	Fair	Poor, discontinued after 4 months	Poor, patient died at day 43 after admission	Good

NSCLC: non-small cell lung cancer; ICI: immune checkpoint inhibitor; nabPTX: nanoparticle albumin-bound paclitaxel; ICI: immune checkpoint inhibitor; IMP: imipenem; AMK: amikacin; CLR: clarithromycin; RIF: rifampicin; ETB: ethambutol; MEM: meropenem; CIP: ciprofloxacin; CRBSI: catheter-related bloodstream infection; ABSSI: acute bacterial skin and skin structure infection.

[§]Case series

*Preceded ICI if not otherwise specified.

†At time of NTM infection diagnosis.

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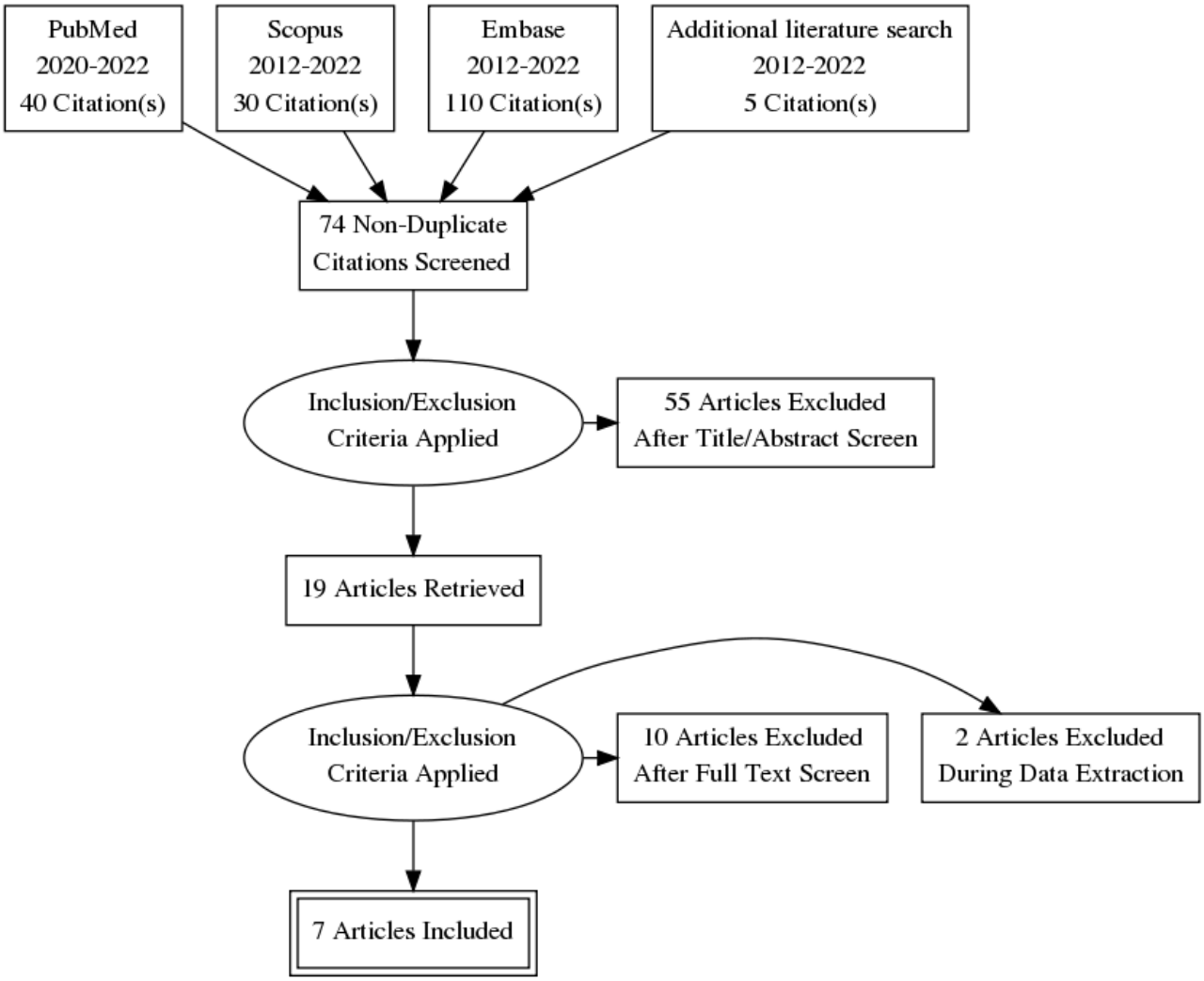

Supplementary Figure 1