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18-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) in Patients with Non-tuberculous Mycobacterial Infections

Short title: "A case series on the use of Nuclear Medicine in NTM-PD"

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Dear editor,

Following a recent article in this journal [1], we would like to point out the importance of applying new tools in the management of non-tuberculous mycobacteria (NTM). These are widespread microorganism that can lead to significant morbidity and mortality in selected hosts [2]. Pulmonary localization is the commonest site for NTM infection characterizing NTM lung disease (NTM-LD); it has been identified in patients with cystic fibrosis (CF), bronchiectasis and in those with HIV/AIDS [2]. Furthermore, with the increase in primary or secondary immune-dysfunctions the susceptible pool of individuals is continuously increasing [2]. Despite specific guidelines based on clinical, radiological and microbiological criteria symptoms are poorly specific and late diagnosis common [3]. Specific features, markers and tools are lacking in increasing the diagnosis yield, in predicting clinical outcomes and response to therapy. These issues are of outmost importance since anti-NTM treatment is long, poorly tolerated and incompletely effective [2,4]. Additionally, the risk of relapse and/or reinfection is significant and this increases the challenge of deciding who should receive antibiotics for treating NTMs [2-4]. 18-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET), is a nuclear medicine technique assuring both good spatial definition and measuring of the functional activity of a radiological finding. It is increasingly available and routinely performed, both in the diagnostic and follow-up process of oncological, autoimmune and infectious diseases [5]. Different tracers exist, allowing specific analysis and further characterization of radiological findings. Additionally, FDG-PET performed for differential diagnosis has shown promising results in the assessment of patients with pulmonary tuberculosis (TB) [6]: a good sensitivity for diagnosis and a fair association with disease activity/severity and have been shown in patients TB [5,6]. Despite several differences, TB and NTMs share common features. These data could interestingly lead to a tailored use of FDG-PET in the patients with NTM-LD. This work aims to describe the features of patients with NTM-LD who underwent FDG-PET for any clinical indication at our center. We performed a secondary analysis of a prospective observational cohort study including adult (>= 18 years of age) patients with NTM-LD

followed at the Amedeo di Savoia Hospital (Turin, Italy) who underwent FDG-PET/CT between 2015 and 2021. All patients were part of the prospective study from the Italian Register of pulmonary Non-tuberculous mycobactEria (IRENE), that comprises more than 900 NTM patients [7]. Informed consent was obtained from all participants included in the study. We evaluated demographic, clinic, radiological and therapeutic characteristics of our population. Patients underwent F-FDG PET/CT using a whole-body scanner according to standard operating procedures. Images were acquired with 3 General Electric PET/CT scans (Discovery ST-E, Discovery IQ, Discovery MI) using a dose of 18F-fluorodeoxyglucose based on the patient's weight. CT scans without contrast were also performed. Images were interpreted qualitatively and semi quantitatively with the standardized uptake value (SUV) by an experienced radiologist in nuclear medicine. A total of 20 patients with NTM-LD were identified: features of the study population are reported in **Table 1.** All isolated NTM were sensitive to both macrolides and aminoglycosides, with *M. abscessus* showing inducible resistance to macrolides. Only one patient had a concomitant sputum culture for *Pseudomonas aeruginosa*. Twelve (60%) patients performed a base spirometry with FEV1 being above 80% predicted in eleven of them (11/12, 91.7%). The median (IQR) FEV1% prediction was 85% (IQR 81%-108%). Four patients performed 2 FDG-PET, two performed 3 FDG-PET and one patient 6 FDG-PET. The main reasons were differential diagnosis (particularly malignancies, in 15 patients, 75%). FDG-PET showed a median of 2 (2-3) positive pulmonary lesions with a diameter of 8 (5.8-10.3) mm. Median SUV max was 4.2 (IQR 3.6-5.3, with the minimum of 2.4 and the maximum of 8.6) We found no difference in SUV max according to demographic, radiological and clinical patients' variables nor to different NTM species (MAC vs. Non-MAC). At univariate regression model, only asthma (p=0.035) and HIV co-infection (p=0.023) were independently associated with a significantly increased number of FDG-PET positive pulmonary lesions. We collected data on FDG-PET scans in patients with NTM-LD and observed that patients had a median 2-3 FDG-PET positive lesions with a SUV max between 2.4 and 8.6, which is in line to what is reported in previous case series/reports where median SUV max was 4.8 (with 1 to multiple positive lesions) [8,9]. Features of our study population did not differ from what has been reported in other cohorts, except for the high number of HIV patients in our series. We could not identify FDG-PET specific differences between rapidly growing and slowly growing mycobacteria species nor between nodulary and cavitary disease. More frequently, FDG-PET exam was performed

either for differential diagnosis or as follow-up of other conditions. Therefore, NTM-LD was in most cases diagnosed accidentally because of FDG-PET leading to subsequent analysis. Time of FDG-PET execution was not homogenous among our population. As expected, immune-suppressed patients showed more FDG-PET positive lesions. On the other hand, we could not identify an explanation for the finding of more pulmonary lesions in patients with asthma compared to others, although the use of inhalatory steroids should be assessed. As highlited in a recent paper, radiomics may be useful for differentiating TB to NTM cavities and it may be applied to nuclear medicine imaging [10]. In view of the complexity of NTM-LD, especially for the decision on whether starting antimycobacterial treatment or in case of relapse/reinfection, PET imaging may have a prominent role in the future, evaluating the presence of active lesions, and their relation to disease severity, microbiology and quality of life. Based on these observations, we suggest three possible scenarios for FDG-PET use in NTM: differential diagnosis, disease activity and treatment evaluation. Ideally, FDG-PET and SUVMax measurement should possibly be part of the baseline assessment for patients newly diagnosed with NTM-LD; that would allow a prospective comparison, also between NTM species. In conclusion, we described the largest case series of patient with NTM-LD undergoing FDG-PET. Prospective studies, possibly using alternative radiotracers, are warranted in order to investigate the role of nuclear medicine in the management of complex patients with NTM-LD.

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Availability of data and material The data that support the findings of this study are available upon reasonable request.

List of abbreviations: TB Tuberculosis; NTM non-tuberculous mycobacteria; NTM-LD non-tuberculous mycobacteria lung disease PET/FDG; RGM rapidly growing mycobacteria; SGM slowly growing mycobacteria; SUV: standardized uptake value; CF: cystic fibrosis

Ethical approval and informed consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication: Consent was obtained from all individual participants included in the study

Author's contributions: All authors contributed to the study conception and design. Patients were assisted by A. G., G. S., A. C., T.L., C.B., P.P. and F.V. Material preparation, data collection and analysis were performed by G.S., A.G., A.C, D.P. PET/FDG analysis were performed by D.P. The first draft of the manuscript was written by G.S. and A.G., and all authors commented on previous versions of the manuscript. Tables and figures were prepared by A.G., G.S. and A.C. All authors read, reviewed and approved the final manuscript. All listed authors have approved the manuscript before submission, including the names and order of authors.

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Table 1 caption: Clinical, demographic, microbiological and radiological features of the study population

	Patients characteristics N=20	
	N or Median	**Percentage or Interquartile Range**
Male sex	3	15%
Age (years)	67.9	63.2-74.0
European ancestry	16	80%
Body mass index (Kg/m^2)	19.7	15.2-22.8
Risk factors & clinical features:		
Active smoking	3	15%
Previous smoking	6	30%
Alcohol abuse	2	10%
Previous tuberculosis	2	10%
HIV infection	8	40%
Malignancy	3	15%
Rheumatic disorders	3	15%
- Rheumatic arthritis	1	5%
- Psoriasis	1	5%
- Sjogren syndrome	1	5%
GERD	8	40%
DM	1	5%
Depression	6	30%
Anxiety	6	30%
Osteoporosis	2	10%
CVd & AHT	4	20%
Pre-existing thoracic diseases:	17	85%
COPD	4	20%
Asthma	3	15%
Bronchiectasis	10	50%
Chest wall deformity	6	30%

Symptoms		
Fever	5	25%
Productive/Dry cough	12	60%
Asthenia	5	25%
Dyspnoea	1	5%
Weight loss	8	40%
Haemoptysis	2	10%
Radiological patterns (CT)	**N**	**Percentage**
Nodules	13	65%
Cavitations	2	10%
Bronchiectasis	10	50%
"Tree-in-Bud"	7	35%
Consolidation	5	25%
Pleural effusion	1	5%
Radiological patterns (PET)	**Median**	**IQR; Min-MAX**
SUV MAX	4.2	3.6-5.3; 2.4-8.6
Number of lesions	2	2-3; 1-14
Diameter (mm)	8	5.8-10.3; 5-11
	N	**Percentage**
Slow growing NTM isolates:	18	90%
M. avium	10	50%
M. intracellulare	3	15%
Other species (*M. celatum, M. lentiflavum, M. fortuitum, M. chimera, M. xenopi)*	5	25%
Rapid growing NTM isolates:	2	10%
M. abscessus,	1	5%
M. fortuitum,	1	5%