

Clinical evaluation of chronic pulmonary aspergillosis in patients with nontuberculous mycobacterial lung disease

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Background

Nontuberculous mycobacterial lung disease (NTM-LD) is increasingly recognized as an important predisposing condition for the development of chronic pulmonary aspergillosis (CPA).

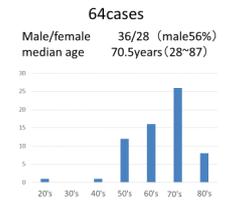
On the other hand, NTM-LD is also reported increasing globally. Especially in Japan, the incidence rate of NTM-LD was estimated to be 14.7 cases per 100,000 person-years in 2014, which is 2.6 times the incidence rate reported in 2007, its rapid increase is problem.

Purpose

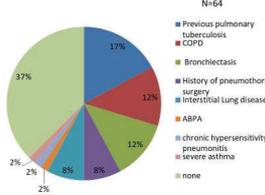
To clarify clinical features of chronic pulmonary aspergillosis (CPA) in patients with nontuberculous mycobacterial lung disease (NTM-LD).

Methods

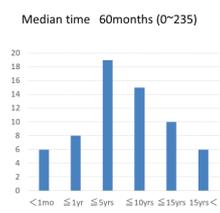
We retrospectively investigated the medical records of 64 patients with CPA treated with the antifungals at Tokyo National Hospital from October 2013 to September 2018, who had been previously or simultaneously diagnosed with NTM-LD.



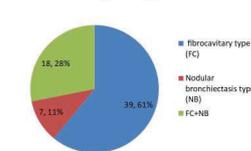
Underlying pulmonary diseases



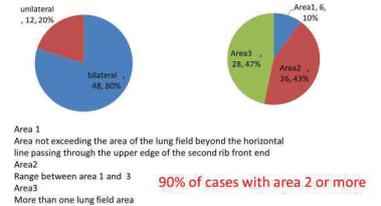
Period from NTM diagnosis to CPA diagnosis



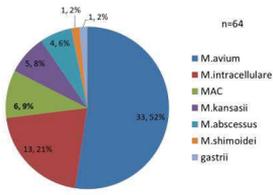
Radiological type of NTM



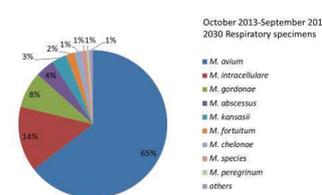
NTM imaging findings at diagnosis of pulmonary aspergillosis



Species identification of NTM-LD

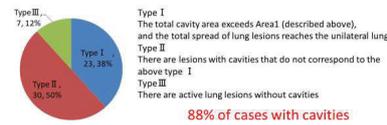


NTM isolates at Tokyo Hospital Bacteriology Laboratory

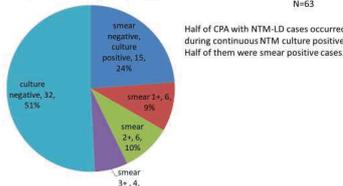


	NTM n=2030	NTM+CPA n=63	P value
M. intracellulare	290 (14.3%)	13 (20.6%)	0.1584
M. kansasii	66 (3.3%)	5 (7.9%)	0.0431

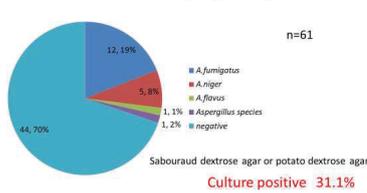
M. kansasii is significantly more common as etiologic organism of NTM-LD with CPA



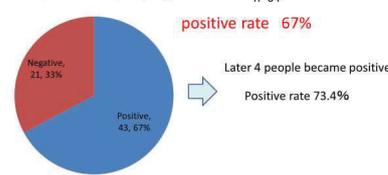
NTM smear and culture at diagnosis of pulmonary aspergillosis



Isolates of Aspergillus spp.



Aspergillus antibody test at diagnosis of pulmonary aspergillosis



Aspergillus precipitating antibody test

	Culture positive	Aspergillus antibody positive	
A. fumigatus	12 cases	10 cases	83%
A. niger	5 cases	2 cases	40%

Positive rate of aspergillus precipitating antibody test in CPA by *Aspergillus niger* is lower than by *Aspergillus fumigatus*

New symptoms at diagnosis of pulmonary aspergillosis

fever	27
blood sputum	20
increased cough	13
increased sputum	13
general malaise	4
appetite loss	2
hemoptysis	2
Exacerbation of respiratory failure	2
no change	2
no symptoms	2

n=64

Include duplicates

58 out of 64 cases showed new symptoms

New radiological findings at diagnosis of pulmonary aspergillosis

Cavity / cyst wall thickening	34
infiltration	31
niveau	15
enlargement of cavity	12
fungal ball formation	8
appearance of cavity lesion	6
centrilobular nodules	1

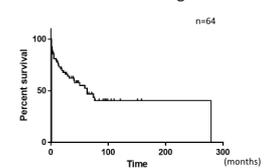
n=64

Include duplicates

Treatment

Stop RFP 21cases	culture negative persistence 13
	culture positive again 4
	culture positive persistence 2
	culture not done 2
Change to RFB 2cases	culture positive persistence 2

Survival curve from the diagnosis of CPA



Summary and discussion

The causative NTM species in NTM-LD with CPA included *Mycobacterium avium complex* (MAC;82%) and *Mycobacterium kansasii* (8%). *M. kansasii* was a significantly higher proportion in NTM-LD with CPA compared to the whole NTM.(7.9% vs 3.3%, respectively;P=0.0431)

Many of NTM-LD patients were severe cases, exhibiting cavitory lesions (90%) and both sides of the lung involved (90%) in the radiological findings, and presenting smear-positive in a quarter of cases at the time of diagnosis of NTM-LD combined with CPA. Considering that most CPA associated with tuberculosis develops after TB treatment, NTM and *Aspergillus* is likely to coexist in the lesion compared to *M. tuberculosis* and *Aspergillus*.

At the time of combined diagnosis of the diseases, fever and hemoptysis were common symptoms. The imaging demonstrated the thickened walls of cysts and cavities in half of the cases and infiltration also in half. Since many imaging findings are common, it is difficult to distinguish both diseases. If symptoms such as blood sputum and fever appear without deterioration of sputum mycobacterial findings during NTM treatment, it was considered necessary to examine the imaging findings in detail and to repeatedly confirm the serodiagnosis of *Aspergillus* antibodies.

Though regular checking of *Aspergillus* antibodies in NTM cases may make early diagnosis of CPA complications, we need attention because CPA by *Aspergillus niger* is often negative for *Aspergillus* antibodies.

Twenty-six cases have already died by April 2019; with median survival time of 12 months after the diagnosis of the combined diseases.

Conclusion

Since many of CPA patients in association with NTM-LD were severe with poor prognosis, comorbid pulmonary aspergillosis should be noted as early as possible in severe cases of NTM-LD.

prognosis

survival	32cases
follow-up continued	22
change hospital	7 (4 cases transferred due to exacerbation of lung lesions)
drop out	3

death	32cases
due to NTM-LD with CPA	26
due to other disease	6

Survival time

26 death cases due to NTM-LD with CPA
Median time 12mos
(8 days~23yrs3mos)

