# Pulmonary non-tuberculous mycobacteria disease and anti-neutrophil cytoplasmic antibody positivity: a retrospective analysis of long-term clinical outcomes including vasculitis onset

N. Oda[1], H. Matsui[2,3], N. Oya[1], T. Suzuki[4,5], R. Hazue[1], R. Rokutanda[1]

*[1]Department of Rheumatology, Kameda Medical Center, Chiba; [2]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo; [3]Clinical Research Support Division, Kameda Medical Center, Chiba; [4]Department of Nephrology, Kameda Medical Center, Chiba; [5]Department of Clinical Epidemiology, Graduate School of Medicine, Fukushima Medical University, Japan.*

## Abstract

### Objective

*To investigate the positivity rate of anti-neutrophil cytoplasmic antibody (ANCA) and the incidence of ANCA-associated vasculitis (AAV) in pulmonary non-tuberculous mycobacterial (NTM) disease.*

### Methods

*We conducted a retrospective observational study using electronic medical records of patients diagnosed with pulmonary NTM disease who subsequently underwent testing for myeloperoxidase (MPO) or proteinase 3 (PR3) ANCA. We identified cases of vasculitis among these patients and documented those who developed AAV. Additionally, we reviewed the literature for previously reported cases of AAV following pulmonary NTM disease.*

### Results

*We identified 63 patients with pulmonary NTM disease who subsequently underwent ANCA testing. Seven cases (11.1%) tested positive, predominantly for MPO-ANCA. Among them, five patients (71.4%) developed AAV, with three demonstrating concurrent NTM culture positivity at the time of AAV diagnosis. Three patients were diagnosed with microscopic polyangiitis, while the remaining two were diagnosed with granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis, respectively. In our case series of AAV,* most *patients developed glomerulonephritis. Additionally, a review of the existing literature revealed eight previously reported cases of AAV associated with pulmonary NTM disease.*

### Conclusion

*This study is one of the largest to investigate the proportion of patients positive for ANCA with pulmonary NTM infection. Our findings suggest an association between NTM infection and AAV and highlight the importance of measuring ANCA in patients with NTM. Further studies are needed to clarify the underlying mechanisms and identify risk factors.*

**Key words**

ANCA-associated vasculitis, pulmonary *nontuberculous mycobacterial* disease, MPO-ANCA, PR3-ANCA, retrospective study

*Nobuhiro Oda, MD*
*Hiroki Matsui, MPH*
*Naoki Oya, MD*
*Tomo Suzuki,MD, PhD*
*Ryo Hazue, MD*
*Ryo Rokutanda, MD*

*Please address correspondence to:*
*Nobuhiro Oda*
*Department of Rheumatology,*
*Kameda Medical Center,*
*929 Higashi-cho,*
*Kamogawa,*
*Chiba 296-8602, Japan.*
*E-mail: oda.nobuhiro.2021@gmail.com*

*Received on March 29, 2025; accepted in revised form on June 9, 2025.*



*Competing interests: N. Oda has received personal fees from Eli Lilly and AbbVie. T. Suzuki has received payment for speaking and educational events from Kissei Pharmaceutical CO., Ltd. The other authors have declared no competing interests.*

## Introduction

Anti-neutrophil cytoplasmic antibody (ANCA) is commonly detected in ANCA-associated vasculitis (AAV) and plays a key role in its pathogenesis (1). However, it has been reported that ANCA can be present even in the absence of vasculitis (2). Among the factors inducing ANCA production, infections have been identified as a potential trigger (3). Notably, tuberculosis (TB) has been associated with a high ANCA positivity rate and is clinically regarded as a 'great mimicker' of AAV, requiring careful differentiation (4). Moreover, there have been reports of cases where TB was associated with myeloperoxidase (MPO)-ANCA positivity and AAV development, and a history of TB has been suggested as a risk factor for systemic vasculitis (5, 6). However, there is limited data on ANCA positivity or AAV development in patients with non-tuberculous mycobacteria (NTM), a condition closely related to TB. Previous studies have reported only false-positive ANCA results in NTM disease and a few cases of AAV complicating NTM disease (7, 8).

Therefore, in this study, we conducted a single-centre retrospective analysis to investigate the ANCA positivity rate and the development of AAV in patients with NTM disease.

## Materials and methods

We conducted a retrospective observational study of patients diagnosed with pulmonary NTM disease who subsequently underwent MPO or proteinase 3 (PR3) ANCA testing at the Kameda Medical Center and Kameda Kyobashi Clinic from January 1, 2000, to January 24, 2024. Kameda Medical Center is a tertiary care centre with approximately 2,000 daily patient visits, while Kyobashi Clinic serves as a satellite centre. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. This study has been approved by the research ethics committee of Kameda Medical Center (approval number: 23-107-250307). All participants provided informed consent through an opt-out process.

### *Outcome*

This study had two primary objectives: firstly, to assess the positivity rates of MPO-ANCA and PR3-ANCA in patients with pulmonary NTM disease, and secondly, to determine the incidence of AAV among those who tested positive for ANCA in this cohort.

### *Exposure*

Patients with respiratory specimens (sputum, bronchoalveolar lavage (BAL) specimens, and other respiratory specimens) positive for mycobacteria and tested for MPO or PR3 ANCA were screened. Subsequently, patients with pulmonary NTM disease were identified, and those with ANCA measured after diagnosis were analysed. Pulmonary NTM disease was diagnosed based on the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) diagnostic criteria, and AAV was diagnosed clinically based on the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (9, 10). Clinical diagnoses of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) were made according to 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria (11-13).

### *Data collection*

Clinical and laboratory data were obtained from the medical records at the time of ANCA measurement. Clinical data included date of birth, sex, clinical course, autoimmune comorbidities, imaging findings, and laboratory data, MPO-ANCA, PR3-ANCA, and Mycobacterium species identified in respiratory cultures. Smoking status at the time of ANCA measurement and the reason for ANCA measurement were not included in this retrospective study because it was difficult to collect accurate data. Additionally, differentiating interstitial pneumonia or bronchiectasis from NTM-related lung lesions was challenging; therefore, these data were not reported for the overall study population (14).

The ANCA testing method at our institution changed over the study period.

The details of how ANCA levels were measured between 2000 and 2012 are unknown. The upper limit of normal in the electronic medical records was 20, so that was adopted. From 2012 to 2018, ANCA was measured using commercial Enzyme-Linked Immunosorbent Assay (ELISA) kits (Premmune, EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany). From 2018 onward, ANCA was measured using commercial Chemiluminescent Enzyme Immunoassay (CLEIA) kits (STACIA® MEBLux™ test, Medical and Biological Laboratories, Aichi, Japan). Due to a median diagnostic delay of approximately 3 months in Japan, we defined ANCA measured within 1 month before NTM diagnosis as 'simultaneous' to account for real-world conditions (15). This cut-off ensures that ANCA measurements performed shortly before an official NTM diagnosis were included in the analysis. In patients with multiple ANCA measurements, only the first measurement was used. The diagnosis date of pulmonary NTM disease was defined as the date of submission of the first culture test confirming NTM. If NTM diagnosis was made at another hospital and the exact date was unknown, the 15th day of the following month was assigned. The follow-up period was defined as the date of NTM diagnosis to the date of the last recorded hospital visit. For patients still attending the hospital, the follow-up period ended on 24 January 2024.

*Statistical analysis*

Descriptive statistics were obtained for ANCA positive and ANCA negative groups. Continuous variables were summarised as means and standard deviations, while categorical variables were presented as the number of cases and proportions (%). The frequency of missing data for each variable was also presented. For AAV incidence, the number of cases and proportion (%) in each group were reported. A survival analysis evaluating the period from NTM diagnosis to AAV onset was conducted using the Kaplan–Meier curve with a calculated 95% confidential interval. Statistical analyses were performed using R version 4.1.0.

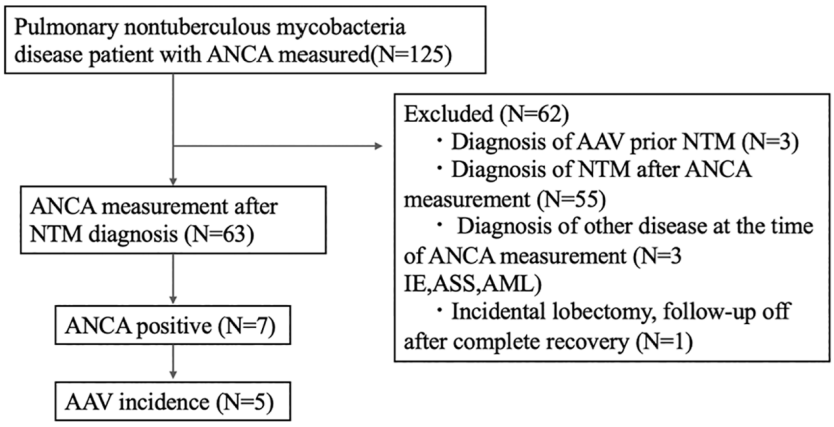


**Fig. 1.** Patient flow of this study.
NTM: non-tuberculous mycobacteria, ANCA: anti-neutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; IE: infectious endocarditis; ASS: anti-synthetase syndrome; AML: acute myeloid leukaemia

*Case presentation and review*

We conducted a detailed chart review to describe the clinical characteristics of each AAV case. To integrate and describe previously reported AAV cases complicated by NTM with the cases confirmed in this study, we performed a PubMed literature review for reports of AAV complicated by NTM, covering publications up to February 20, 2025 (search terms are listed in the online Supplementary file). We collected data on age, sex, period from NTM diagnosis to AAV onset, NTM species, ANCA serotype, ANCA titre, AAV subtype, biopsy site (results), and NTM treatment status before AAV onset.

## Results

Patients with respiratory specimens (sputum, BAL or other respiratory samples) positive for mycobacteria who underwent MPO or PR3 ANCA testing were screened (n=165). A chart review was conducted, and patients meeting the ATS/IDSA diagnostic criteria for NTM disease were extracted (n=125) (Fig. 1). To investigate the ANCA positivity rate after NTM onset, patients who had ANCA tested before NTM diagnosis were excluded (n=55). Additionally, patients who underwent lobectomy were excluded due to potential surgical influence (n=1). Cases where NTM developed after AAV onset were also excluded (n=3). Patients whose ANCA tests were performed during the diagnosis of other diseases were also excluded (n=3). Ultimately, 63 patients were included in our analysis.

Of the 63 patients with pulmonary NTM disease who underwent ANCA testing, seven (11.1%) were positive for ANCA, with five positives for MPO-ANCA and two positives for PR3-ANCA. The mean age was 71.21±10.76 years in the ANCA-negative group and 68.92±19.14 years in the ANCA-positive group. The proportion of male patients was 32.1% (18/56) in the ANCA-negative group and 57.1% (4/7) in the ANCA-positive group. The average duration from NTM diagnosis to ANCA testing was 562.32±979.01 days in the ANCA-negative group and 1699.00±1724.31 days in the ANCA-positive group. In two patients with ANCA-positive, testing was performed at the time of NTM diagnosis. Five of seven (71.4%) patients had AAV at the time of ANCA measurement, and two did not develop AAV during the observation period (Table I). Among the seven patients, *M. avium* was identified in two, *M. intracellulare* in four, and *M. kansasii* in one.

Two patients did not develop AAV. In both cases, ANCA levels were measured at the time of NTM diagnosis, and neither patient was receiving treatment for NTM. One patient with M. kansasii tested slightly above the upper limit of normal for PR3-ANCA (3.5 U/mL by CLEIA; normal range: <3.5 U/mL), and another with M. intracellulare had elevated MPO-ANCA (102, unknown method), which turned negative on follow-up examination and no vascu-

**Table. I.** Characteristics of patients with pulmonary NTM with and without ANCA positivity.

| | ANCA-negative (mean (SD)) | ANCA-positive (mean (SD)) |
|---|---|---|
| n | 56 | 7 |
| Age (years old) | 71.21 (10.76) | 68.92 (19.14) |
| Male (%) | 18 (32.1) | 4 (57.1) |
| Comorbidities | | |
| Autoimmune disease | 15 (26.8) | 0 (0.00) |
| Mycobacterium species (%) | | |
| *M.avium* | 26 (46.4) | 2 (28.6) |
| *M.intracellulare* | 27 (48.2) | 4 (57.1) |
| *M.gordonae* | 1 (1.8) | 0 |
| *M.kansassii* | 2 (3.6) | 1 (14.3) |
| ANCA | | |
| ANCA positive | 0 | 7 |
| MPO-ANCA positive | 0 | 5 |
| ~2012 (unknown) | 6 | 1 |
| 2012~2018(ELISA) | 13 | 1 |
| 2018~(CLEIA) | 37 | 3 |
| PR3-ANCA positive | 0 | 2 |
| ~2012 (unknown) | 6 | 1 |
| 2012~2018(ELISA) | 11 | 0 |
| 2018~(CLEIA) | 37 | 1 |
| The period from NTM diagnosis to ANCA measurement (days) | 562.32 (979.01) | 1699.00 (1724.31) |
| AAV | | |
| AAV onset | 0 | 5 |
| Co-occurrence of AAV at diagnosis of NTM | - | 0 |

SD: standard deviation; WBC: white blood cell; RBC: red blood cell; Cre: creatinine; CRP: C-reactive protein; ANCA: anti-neutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; MPO: myeroperoxidase; PR3: proteinase3; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis.

litis developed during the observation period (104 days in the former and 322 days in the latter).

Five patients developed AAV (Table II, III). Of these, four tested positive for MPO-ANCA and one for PR3-ANCA. The subtypes of AAV were MPA in three patients (Cases 1~3), EGPA in one (Case 4) and GPA in one (Case 5). Of the five patients, all had Mycobacterium avium complex (MAC), with M. avium identified in two cases and M. intracellulare in three cases. In three patients (Cases 1, 2, and 5), NTM culture positivity was confirmed at the time of AAV diagnosis. Two patients developed AAV while undergoing treatment for NTM. Only one patient developed AAV without having received any treatment for NTM. The remaining patients developed AAV after completing treatment. In total, four patients were either receiving treatment or were in the post-treatment phase when AAV was diagnosed. Notably, all patients demonstrated lung lesions on chest CT at the time of AAV diagnosis, which resembled those observed at the time of NTM diagnosis. The median duration from NTM diagnosis to AAV onset was 1,176 days (interquartile range, 510-2,352 days) and Kaplan–Meier analysis demonstrated that the AAV-free survival rate among patients with NTM gradually decreased over time. None of the patients with a negative initial ANCA had chart-confirmed AAV onset during the observation period.

**Table II.** Fulfillment of the 2022 ACR/EULAR classification criteria for MPA, GPA, and EGPA in patients from this study.

| | Case 1 MPA | Case 2 MPA | Case 3 MPA | | Case 4 EGPA | | Case 5 GPA |
|---|---|---|---|---|---|---|---|
| p-ANCA/MPO-ANCA (+6) | 1 | 1 | 1 | obstructive airway disease (+3) | 0 | bloody nasal discharge, nasal crusting or sino-nasal congestion (+3) | 0 |
| lung fibrosis or interstitial lung disease (+3) | 1 | 0 | 0 | nasal polyps (+3) | 0 | cartilaginous involvement | 0 |
| pauci-immune glomerulonephritis (+3) | 1 | 0 | 1 | mononeuritis multiplex/motor neuropathy not due to radiculopathy (+1) | 1 | conductive or sensorineural hearing loss (+1) | 0 |
| sino-nasal symptoms or signs (–3) | 0 | 0 | 0 | eosinophilia (+5) | 1 | c-ANCA/PR3-ANCA (+5) | 1 |
| c-ANCA/PR3-ANCA (-1) | 0 | 0 | 0 | extravascular eosinophilic predominant inflammation (+2) | 1 | pulmonary nodules, mass or cavitation on chest imaging (+2) | 1 |
| eosinophilia (-4) | 0 | 0 | 0 | cANCA/PR3-ANCA (-3) | 0 | granuloma or giant cells on biopsy (+2) | 0 |
| | | | | haematuria (-1) | 0 | inflammation or consolidation of the nasal/paranasal sinuses on imaging (+1) | 0 |
| | | | | | | pauci-immune glomerulonephritis (+1) | 0 |
| | | | | | | p-ANCA/MPO-ANCA (-1) | 0 |
| | | | | | | eosinophilia (-4) | 0 |
| Points ≥5 | 12 | 6 | 9 | Points ≥6 | 8 | Points ≥5 | 7 |

MPO: myeroperoxidase; NTM: non-tuberculous mycobacteria; PR3: proteinase3; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; ANCA: anti-neutrophil cytoplasmic antibody; ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology.

**Table III.** Details of patients with AAV diagnosed after NTM disease in our study and previously reported cases.

| Case/Reference | age/sex | The period rom NTM diagnosis to AAV onset | Species of NTM | ANCA serotype | Titre | AAV subtype | Biopsy site (findings) | NTM treatment status before AAV onset | Mycobacterial culture status at the time of AAV diagnosis | CT findings from the initial presentation of NTM lung disease at the time of AAV diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|
| **Our cases** | | | | | | | | | | |
| Case 1 | 80M | 9 months (278 days) | *M.avium* | MPO | ≥300U/mL (CLEIA) | MPA | Kidney (Crescentic glomerulonephritis) | Under treatment (CAM,EB) | Positive | Unresolved |
| Case 2 | 76F | 6 years (2,386 days) | *M.intracellulare* | MPO | ≥200.0RU/mL (ELISA) | MPA | No | Untreated | Positive | Unresolved |
| Case 3 | 74F | 10 years (3,894 days) | *M.intracellulare* | MPO | ≥300U/mL (CLEIA) | MPA | Kidney (Necrotising crescentic glomerulonephritis, Medullary angiitis),skin (Perivascular neutrophilic infiltration) | 6 months after completion of treatment (CAM, RFP, EB) | Negative | Unresolved |
| Case 4 | 74M | 10 years (3,878 days) | *M.avium* | MPO | 163U/mL (CLEIA) | EGPA | Skin (Epidermal intracellular oedema and intradermal and eosinophilic perivascular dermatitis) | 3 years after completion of treatment (CAM, RFP, KM) | Negative | Unresolved |
| Case 5 | 67F | 3 years (1,450 days) | *M.intracellulare* | PR3 | 34(unknown) | GPA | Kidney (mild vasculitis, interstitial nephritis) | Under treatment (CAM, RFP) | Positive | Unresolved |
| **Previous reports** | | | | | | | | | | |
| Chaiamnuay, *et al*. (16) | 75F | 20 months | M.Avium Intracellae | MPO | 29(unknown) | GPA | Lung, skin | 2months after completion of treatment (CPFX, AZM, EB) | Unknown | - |
| Aneet, *et al*. (17) | 59F | 12 months | MAC | c-ANCA | 1;40 | GPA | No | Completion of treatment (AZM, RFP, EB) | Unknown | - |
| Asano, *et al*. (18) | 73F | 1 year | MAC | MPO | 7.9 U/mL | MPA | Kidney (crescentic glomerulonephritis, interstitial nephritis with immuno deposition) | Treatment (CAM, REF, EB) preceded but stopped after 2 days | Unknown | - |
| Addy, *et al*. (19) | 70F | 3 months | *M.abscessus* | MPO | 8 AI | MPA | No | Simultaneous treatment (IV Cefoxitin/Amikacin/ CAM/ Minocycline) started | Positive | - |
| Alnaser, *et al*. (20) | 27M | Simultaneous | *M.kansasii* | MPO | 150U/mL | MPA | Kidney (Necrotising crescentic glomerulonephritis) | Simultaneous treatment (NTM treatment RFP, EB, INH, PZA) | Positive | - |
| Kato, *et al*. (21) | 65F | 2 years | MAC | MPO, GBM | 14.1U/mL | MPA | Kidney (crescentic glomerulonephritis, Medullary angiitis, interstitial nephritis) | Untreated | Unknown | - |
| Tomoshima, *et al*. (8) | 81F | Simultaneous | *M.avium* | MPO | 107IU/mL | OMAAV | No | Simultaneous treatment (CAM, RFP, EB) | Positive | - |
| Yoshii, *et al*. (22) | 72M | 7years | *M.intracellulae* | MPO | 611U/mL | MPA | Kidney (Necrotising crescentic glomerulonephritis) | Under treatment (CAM, RFP, EB) | Unknown | - |

M: male; F: female; MPO: myeroperoxidase; NTM: non-tuberculous mycobacteria; ANCA: anti-neutrophil cytoplasmic antibody; PR3: proteinase3; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; OMAAV: otitis media with anti-neutrophil cytoplasmic antibody-associated vasculitis; PSL: prednisolone; RTX: rituximab; AZA: azathioprine; PE: plasma exchange; CYC: cyclophosphamide; MAC: Mycobacterium avium complex; CAM: clarithromycin; RFP: rifampicin; INH: isoniazid; EB: ethambutol; AZM: azithromycin; KM: kanamycin.

*Case presentation*

Case 1: An 80-year-old man with a history of diabetes mellitus presented with worsening kidney function and haematuria 9 months after diagnosis and 6 months after treatment for pulmonary NTM disease with *M. avium*. Blood tests revealed positive MPO-ANCA, CT showed infiltrating shadows with cavities, and kidney biopsy showed crescentic glomerulonephritis, leading to a diagnosis of MPA.

Case 2: A 76-year-old woman with a history of pulmonary NTM disease due to M. intracellulare presented with fatigue, anorexia, and low-grade fever for 2 months. She had worsening kidney function with an elevated inflammatory response, proteinuria, haematuria, and MPO-ANCA positivity, leading to a diagnosis of MPA. She did not undergo biopsy.

Case 3: A 74-year-old woman with a history of pulmonary NTM disease of M. intracellulare had pain in her extremities for 6 months, purpura on her lower legs for 2 months, anorexia, and low-grade fever. Further examination revealed kidney impairment with haematuria and proteinuria, and positive MPO-ANCA. Kidney biopsy revealed necrotising crescentic glomerulonephritis and medullary angiitis, leading to a diagnosis of MPA.

Case 4: A 74-year-old man with pulmonary NTM disease by M. avium, previously treated but currently untreated, developed new lung consolidations and elevated inflammatory markers 1 month before AAV diagnosis. He was treated for bacterial pneumonia but remained refractory. Simultaneously, he began to notice purpura, an abnormal sensation in both lower extremities, and muscle weakness. Further examination revealed MPO-ANCA positivity and increased eosinophilia. A skin biopsy of the purpura revealed intradermal and eosinophilic perivascular dermatitis, leading to a diagnosis of EGPA.

Case 5: A 67-year-old woman with pulmonary NTM of M. intracellulare treated with antibiotics was diagnosed with AAV after a 3-month history of fever of unknown origin, proteinuria, and positive PR3-ANCA. Kidney biopsy showed mild vasculitis and interstitial nephritis. Despite the absence of granulomatous lesions in the biopsy, the patient was diagnosed with GPA based on 2022 diagnostic criteria retrospectively.

*Literature review*

We screened 97 articles in PubMed and identified 8 case reports of AAV complicated by pulmonary NTM disease (8, 16-22) (Table II). The mean patient age was 65.3 years, and 75% were female. Seven patients were positive for MPO-ANCA, while one was positive for c-ANCA. AAV subtypes included 2 cases of GPA, 5 of MPA, and one of otitis media with AAV (OMAAV). Vasculitis developed concurrently with NTM culture positivity in 38% (3/8) of cases, while the remaining patients developed vasculitis between 3 months and 7 years after NTM diagnosis. 75% of patients had pulmonary NTM disease with MAC. 50% (4/8) patients who developed AAV was either undertreated or had completed treatment for NTM.

## Discussion

This study is one of the largest to examine the proportion of ANCA-positivity with pulmonary NTM disease. We found that ANCA was positive in 11.1% of patients, predominantly MPO-ANCA. Two patients who tested positive for ANCA but did not develop vasculitis were weakly positive or measured using previous assays and improved spontaneously. 71.4% of patients demonstrating ANCA positivity developed AAV, predominantly MPA. Most patients had MAC infections. In three patients, NTM culture positivity persisted at the time of AAV diagnosis, and all patients had lung lesions consistent with prior NTM infection. Finally, we identified 8 previous reported cases of AAV complicated by pulmonary NTM disease. The prevalence of ANCA positivity in NTM has been rarely reported in the literature. Only one case of false-positive ANCA results has been reported in a patient with NTM (23). In contrast, there have been eight reported cases of AAV occurring in association with NTM. (8, 16-22). This skewed report supports our observation that most patients with ANCA positivity developed systemic vasculitis. This study found that two patients who were positive for ANCA did not develop vasculitis. In the general Japanese population, ANCA positivity has been reported in approximately 0.9% of individuals (24). In comparison, our study found that even among NTM patients without AAV, 3.2% were ANCA-positive, suggesting a potential association between NTM infection and increased ANCA production.

In our study, we identified 5 cases of AAV in patients with pulmonary NTM disease. Furthermore, according to our PubMed search, eight cases of AAV in patients with pulmonary NTM have been reported to date (Table II). In previous reports, six of eight cases of NTM with AAV involved female patients, consistent with our findings where three out of five patients were female, demonstrating a female preponderance. Furthermore, most patients in our study were MPO-ANCA positive. Similarly, most previously reported cases were MPO-ANCA positive, suggesting a potential association between NTM and MPO-ANCA. Reflecting this antibody trend, the majority of AAV subtypes in our study and previous reports were MPA with glomerulonephritis. On the other hand, we diagnosed one case each of EGPA and GPA, and previous reports included one case each of GPA and OMAAV. This suggests that, while MPA is the most common subtype, other forms of AAV can also occur in association with NTM. The time from NTM disease onset to AAV onset varied widely from 9 months to 10 years in our study, and a similar trend was observed in previous reports ranging from several months to 7 years (Fig. 2). Some cases of NTM disease and AAV were diagnosed simultaneously in previous reports. As for the bacterial strains, in our study, M. avium was identified in two cases and M. intracellular in three. Similarly, four previously reported cases involved M. avium, which may reflect the predominance of MAC among NTM infections (25). It is also noteworthy that all cases in this study involved pathogenic NTM species. The most commonly affected

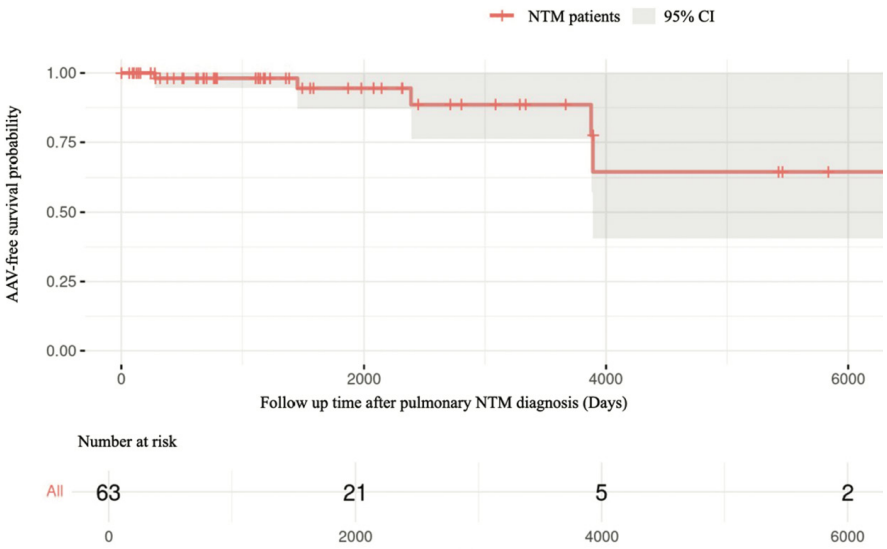


**Fig. 2.** Kaplan-Meier curve showing AAV-free survival in patients with NTM, with 95% confidence intervals
NTM: non-tuberculous mycobacteria; AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; CI: confidence interval.

organ in vasculitis was the kidney, and many cases were accompanied by fever. Therefore, when an unexplained fever or glomerulonephritis/acute kidney injury occurs during an NTM infection, the possibility of concurrent AAV should be considered.

While the role of infections in autoantibody induction in connective tissue diseases is known, our research proposes a potential link between NTM infection and AAV development, potentially through ANCA production, especially MPO-ANCA, through three proposed mechanisms (26). First, ANCA production may arise from pulmonary NTM infection. MPO-ANCA is known to be pathogenic in inducing nephritis, with its generation linked to MPO exposure via NETosis and impaired NET clearance (27-29). Necrotising granulomas and NETosis are documented in NTM-infected lungs, mirroring potential pathways in TB where NETosis in caseous necrosis has been implicated in ANCA production (30-32). The established association between infections and AAV, particularly the increased incidence of MPO-ANCA-positive AAV with infections (3, 33) and the correlation between pneumonia and MPO-ANCA-associated AAV, further supports this hypothesis. Animal models demonstrating MPA-like disease with co-induced influenza infection in MPO-ANCA injected mice also highlight this relation (34). Our observation of NTM excretion in over half the patients at the time of ANCA positivity or AAV diagnosis, along with the tendency for longer NTM disease duration in ANCA-positive patients, suggests a role for NTM lung infection and chronic inflammation in MPO-ANCA production and AAV onset. Second, ANCA production and AAV onset may be secondary to NTM-associated interstitial pneumonia or bronchiectasis. ANCA has been reported in patients with interstitial pneumonia, some of whom later develop AAV. Given that interstitial pneumonia can be a complication of NTM infection, its impact cannot be excluded (14, 35). Bronchiectasis, another complication of NTM, is also a recognised risk factor for MPO-ANCA-positive AAV (36, 37). In our study, AAV was observed many years after NTM diagnosis in several patients, including two with persistent pulmonary infiltrates despite the absence of ongoing bacterial excretion. Taken together with previous reports linking tuberculosis to systemic vasculitis, these findings suggest that NTM infection itself, particularly when persisting for more than 10 years may induce structural pulmonary changes that contribute to vasculitis development (6). Third, drug-induced ANCA is a possibility. Although ANCA production has been associated with anti-tuberculosis drugs, and most AAV patients in our study were exposed to such treatments, at least one AAV case occurred without any prior anti-TB therapy (38). Based on these findings, we propose the potential existence of a distinct clinical entity, "NTM-AAV", representing a subgroup of patients in whom chronic NTM infection may play a role in the pathogenesis of AAV. However, further research is warranted to definitively establish the causal relationship and elucidate underlying mechanisms.

Our study has some limitations. Firstly, although it represents the largest study of its kind to date, it was conducted at a single-centre and involved a small number of cases. Therefore, generalisability of the findings may be limited, and due to insufficient statistical power, we were unable to perform statistical analyses to identify risk factors for ANCA positivity. Furthermore, since ANCA measurement was left at the discretion of the treating physician, the possibility of selection bias cannot be denied. Secondly, in many of the patients who developed AAV, a period of time had elapsed since their NTM diagnosis, and questions remain regarding the correlation. Whether the presence of NTM causes AAV requires studies including appropriate healthy control groups. Thirdly, the mechanisms underlying ANCA induction are not well understood, raising the possibility of confounding factors. Notably, our study did not examine the presence of interstitial pneumonia or bronchiectasis; therefore, the possibility that these factors preceded the development of NTM and AAV cannot be ruled out. Lastly, there was a period during which the ANCA testing method was unknown, and the results from this period may not be generalisable. In Japan, PR3-ANCA testing by ELISA became available in 1993, followed by MPO-ANCA testing in 1998. Since 2012, CLEIA has been widely used (39). Although ANCA measurement methods have evolved over time in Japan, a study comparing ELISA (commonly used before 2012) and CLEIA (widely adopted thereafter)

found that both methods had comparable diagnostic accuracies for AAV (40). Since only a small number of cases in this study were tested before 2012, and the accuracy of the test method at that time was likely comparable to the current one, we did not consider the impact to be significant. Finally, as this was a single-centre retrospective study, the prevalence of asymptomatic ANCA positivity among NTM patients remains unclear. These limitations can be resolved in prospective studies.

## Conclusion

This study is one of the largest to show the proportion of patients demonstrating ANCA positivity in pulmonary NTM disease. ANCA was positive in 11.1% of patients, predominantly MPO-ANCA. Additionally, 71.4% of cases with positive ANCA developed AAV, predominantly MPA. These findings suggest a potential link between NTM infection and AAV. Based on our results and the consideration of possible underlying mechanisms, we propose the existence of a distinct subgroup of patients with NTM-AAV. Since NTM-AAV frequently involves glomerulonephritis, monitoring ANCA should be considered in patients under NTM follow-up, particularly in patients presenting with haematuria or unexplained inflammatory responses. Further large-scale studies are needed to elucidate the association between NTM infection, ANCA production and the development of AAV.

## References


1. KITCHING AR, ANDERS HJ, BASU N *et al*.: ANCA-associated vasculitis. *Nat Rev Dis Primers* 2020; 6(1): 71. https://doi.org/10.1038/s41572-020-0204-y
2. BORNSTEIN G, BEN-ZVI I, FURIE N, GROSSMAN C: Clinical significance of positive anti-neutrophil cytoplasmic antibodies without evidence of anti-neutrophil cytoplasmic antibodies-associated vasculitis. *Int J Rheum Dis* 2019; 22(5): 940-45. https://doi.org/10.1111/1756-185x.13483
3. GEETHA D, JEFFERSON JA: ANCA-associated vasculitis: core curriculum 2020. *Am J Kidney Dis* 2020; 75(1): 124-37. https://doi.org/10.1053/j.ajkd.2019.04.031
4. MARTINS JD, SOARES C, BARREIROS C, TEIXEIRA F, FERREIRA M: Granulomatosis with polyangiitis misdiagnosed as tuberculosis: a case report. *Cureus* 2024; 16(10): e71834. https://doi.org/10.7759/cureus.71834
5. HUAN G, YANG G, XIAO-YU Q, JIANCHENG X, YAN-QING S: Antineutrophil cytoplasmic antibodies in Chinese patients with tuberculosis. *Rev Soc Bras Med Trop* 2018; 51(4): 475-8. https://doi.org/10.1590/0037-8682-0400-2017
6. HAN M, HA JW, JUNG I, KIM CY, AHN SS: Incidence of systemic vasculitides after Mycobacterium tuberculosis infection: a population-based cohort study in Korea. *Rheumatology* (Oxford) 2025; 64(3): 1400-8. https://doi.org/10.1093/rheumatology/keae185
7. FARUQI S, KASTELIK JA, McGIVERN DV: Diagnostic pitfall: mycobacterium avium complex pulmonary infection and positive ANCA. *Eur J Intern Med* 2008; 19(3): 216-18. https://doi.org/10.1016/j.ejim.2007.03.019
8. TOMISHIMA Y, SUDA M, TAMAKI H: Antimicrobial therapy for nontuberculous mycobacterial pulmonary disease improved hearing loss and normalized myeloperoxidase-antineutrophil cytoplasmic antibody level: a case report. *Mod Rheumatol Case Rep*. 2023; 7(1): 283-87. https://doi.org/10.1093/mrcr/rxac047
9. GRIFIFTH DE, AKSAMIT T, BROWN-ELLIOTT BA *et al*.: An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175(4): 367-416. https://doi.org/10.1164/rccm.200604-571ST
10. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum* 2013; 65(1): 1-11. https://doi.org/10.1002/art.37715
11. SUPPIAH R, ROBSON JC, GRAYSON PC *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. *Ann Rheum Dis* 2022; 81(3): 321-26. https://doi.org/10.1136/annrheumdis-2021-221796
12. ROBSON JC, GRAYSON PC, PONTE C *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Ann Rheum Dis* 2022; 81(3): 315-20. https://doi.org/10.1136/annrheumdis-2021-221795
13. GRAYSON PC, PONTE C, SUPPIAH R *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. *Ann Rheum Dis* 2022; 81(3): 309-14. https://doi.org/10.1136/annrheumdis-2021-221794
14. WATANABE M, HAGIWARA E, SHINTANI R *et al*.: Clinical characteristics of pulmonary mycobacterium avium complex disease in patients with interstitial lung disease. *J Infect Chemother* 2025; 31(1): 102515. https://doi.org/10.1016/j.jiac.2024.09.004
15. HAYASHI M, TAKISHIMA H, KISHINO S *et al*.: Time to diagnosis of nontuberculous mycobacterial pulmonary disease and longitudinal changes on CT before diagnosis. *Heliyon* 2024; 10(9): e30060. https://doi.org/10.1016/j.heliyon.2024.e30060
16. CHAIAMNUAYH S, HECK LW: Antineutrophil cytoplasmic antibody vasculitis associated with mycobacterium avium intracellulare infection. *J Rheumatol* 2005; 32(8): 1610-12.
17. KAUR A, KLAIR JS, ROCHLANI YM, KURIAKOSE K, KHAN NA: A rare case of multiple digital infarcts in a patient with mycobacterium avium-intracellulare (MAI) infection. *BMJ Case Rep* 2015; 2015: bcr2015209582. https://doi.org/10.1136/bcr-2015-209582
18. ASANO S, MIZUNO S, OKACHI S *et al*.: Antineutrophil cytoplasmic antibody-associated vasculitis superimposed on infection-related glomerulonephritis secondary to pulmonary mycobacterium avium complex infection. *Intern Med* 2016; 55(17): 2439-45. https://doi.org/10.2169/internalmedicine.55.6588
19. ADDY C, DORAN G, JONES AL, WRIGHT G, CASKEY S, DOWNEY DG: Microscopic polyangiitis secondary to Mycobacterium abscessus in a patient with bronchiectasis: a case report. *BMC Pulm Med* 2018; 18(1): 170. https://doi.org/10.1186/s12890-018-0732-3
20. ALNASER A, PARERIS K: Mycobacterium kansasii infection and microscopic polyangiitis: an unexpected association. *Cureus* 2018; 10(6): e2831. https://doi.org/10.7759/cureus.2831
21. KATO M, WAKIYA R, KAMEDA T *et al*.: The development of rapidly progressive glomerulonephritis associated with both antineutrophil cytoplasmic antibody-associated vasculitis and anti-glomerular basement membrane nephritis in the course of nontuberculous mycobacterium infection: a case report. *BMC Rheumatol* 2020; 4(1): 68. https://doi.org/10.1186/s41927-020-00167-y
22. YOSHII R, KAJIWARA K, UEMURA N *et al*.: The successful treatment of microscopic polyangiitis associated with non-tuberculous mycobacterial-pulmonary disease. *CEN Case Rep* 2024; 13(4): 271-76. https://doi.org/10.1007/s13730-023-00839-x
23. FARUQI S, KASTELIK JA, McGIVERN DV: Diagnostic pitfall: mycobacterium avium complex pulmonary infection and positive ANCA. *Eur J Intern Med* 2008; 19(3): 216-18. https://doi.org/10.1016/j.ejim.2007.03.019
24. TAMAKI H, FUKUI S, NAKAI T *et al*.: AB0533 anti-neutrophil cytoplasmic antibody (anca) in general population without anca associated vasculitis. *Ann Rheum Dis* 2020; 79: 1563.
25. MORIMOTO K, HASEGAWA N, IZUMI K *et al*.: A laboratory-based analysis of nontuberculous mycobacterial lung disease in japan from 2012 to 2013. *Ann Am Thorac Soc* 2017; 14(1): 49-56. https://doi.org/10.1513/annalsats.201607-573oc
26. CONTICINI E, DOURADO E, BOTTAZZI F *et al*.: Idiopathic inflammatory myopathies: one year in review 2023. *Clin Exp Rheumatol* 2024; 42(2): 213-24. https://doi.org/10.55563/clinexprheumatol/dh5o6c
27. XIAO H, HEERINGA P, HU P *et al*.: Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest* 2002; 110(7): 955-63. https://doi.org/10.1172/jci15918
28. HU P, XIAN H, ALBA MA *et al*.: Myeloperoxidase-ANCA IgG induces different forms

of small vessel vasculitis based on type of synergistic immune stimuli. *Kidney Int* 2024; 106(5): 870-86. https://doi.org/10.1016/j.kint.2024.08.022

29. KAGIYAMA N, TAKYANAGI N, KANAUCHI T, ISHIGURO T, YANAGISAWA T, SUGITA Y: Antineutrophil cytoplasmic antibody-positive conversion and microscopic polyangiitis development in patients with idiopathic pulmonary fibrosis. *BMJ Open Respir Res* 2015; 2(1): e000058. https://doi.org/10.1136/bmjresp-2014-000058
30. LHOTE R, CHILLES M, GROH M *et al*.: Spectrum and prognosis of antineutrophil cytoplasmic antibody-associated vasculitis-related bronchiectasis: data from 61 patients. *J Rheumatol* 2020; 47(10): 1522-31. https://doi.org/10.3899/jrheum.190313
31. NAKAMURA K, NAKAYAMA H, SASAKI S, TAKAHASHI K, IWABUCHI K: Mycobacterium avium-intracellulare complex promote release of pro-inflammatory enzymes matrix metalloproteinases by inducing neutrophil extracellular trap formation. *Sci Rep* 2022; 12(1): 5181. https://doi.org/10.1038/s41598-022-09017-y
32. ZLATAR L, KNOPF J, SINGH J *et al*.: Neutrophil extracellular traps characterize caseating granulomas. *Cell Death Dis* 2024; 15(7): 548. https://doi.org/10.1038/s41419-024-06892-3
33. RATHMANN J, STAMATIS P, JÖNSSON G *et al*.: Infection is associated with increased risk of MPO- but not PR3-ANCA-associated vasculitis. *Rheumatology* (Oxford) 2022; 61(12): 4817-26. https://doi.org/10.1093/rheumatology/keac163
34. SANGALETTI S, TRIPODO C, CHIODONI C *et al*.: Neutrophil extracellular traps mediate transfer of cytoplasmic neutrophil antigens to myeloid dendritic cells toward ANCA induction and associated autoimmunity. *Blood* 2012; 120(15): 3007-18. https://doi.org/10.1182/blood-2012-03-416156
35. NAKAZAWA D, SHIDA H, TOMARU U *et al*.: Enhanced formation and disordered regulation of NETs in myeloperoxidase-ANCA-associated microscopic polyangiitis. *J Am Soc Nephrol* 2014; 25(5): 990-97. https://doi.org/10.1681/asn.2013060606
36. MARCHEVSKY A, DAMSKER B, GRIBETZ A, TEPPER S, GELLER SA: The spectrum of pathology of nontuberculous mycobacterial infections in open-lung biopsy specimens. *Am J Clin Pathol* 1982; 78(5): 695-700. https://doi.org/10.1093/ajcp/78.5.695
37. YOON SH, KIM HJ, KIM J, KIM J, LEE JH: Nontuberculous mycobacterial pulmonary disease presenting as bronchiolitis pattern on CT without cavity or bronchiectasis. *BMC Pulm Med* 2024; 24(1): 432. https://doi.org/10.1186/s12890-024-03223-2
38. ELKAYAM O, BENDAYAN D, SEGAL R *et al*.: The effect of anti-tuberculosis treatment on levels of anti-phospholipid and anti-neutrophil cytoplasmatic antibodies in patients with active tuberculosis. *Rheumatol Int* 2013; 33(4): 949-53. https://doi.org/10.1007/s00296-012-2487-0
39. NARITA K (Ed.): Evidence-Based Guidelines for Rapidly Progressive Glomerulonephritis (RPGN). Tokyo, Tokyo Igakusha, 2020: 12-13.
40. HIROSE O, ITABASHI M, TAKEI T, NITTA K: Comparison of a novel chemiluminescence enzyme immunoassay (CLEIA) with enzyme-linked immunosorbent assay (ELISA) for the determination of MPO-ANCA in patients with ANCA-associated vasculitis. *Mod Rheumatol* 2015; 25(2): 230-34. https://doi.org/10.3109/14397595.2014.9511