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ORIGINAL RESEARCH

Metagenomic Next-Generation Sequencing Reveals *Tannerella forsythia* in Lung Abscesses: A Retrospective Case Series Linking Smoking, Oral Health, and Diagnostic Challenges

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Purpose: *Tannerella forsythia (T. forsythia)* is a Gram-negative anaerobic bacterium commonly found in the oral cavity of patients with periodontitis, but lung abscesses caused by this pathogen are extremely rare in the literature. This study aimed to characterize the clinical features, diagnostic challenges, and treatment outcomes of *T. forsythia-associated* lung abscesses through four case analyses.

Patients and Methods: We retrospectively reviewed four patients treated between April 2023 and May 2024 with lung abscesses confirmed by chest computed tomography (CT) and *T. forsythia* detection via metagenomic next-generation sequencing (mNGS) of bronchoalveolar lavage fluid (BALF). Conventional cultures were performed but yielded negative results. Clinical data, including demographics, symptoms, imaging findings, and treatment regimens, were analyzed.

Results: All patients had oral diseases, and 75% were long-term smokers. The primary clinical manifestations were nonspecific respiratory symptoms, including cough, fever, chest pain, and hemoptysis. Chest CT revealed consolidation and cavitation in the upper lobes of the lungs. *T. forsythia* was successfully detected by mNGS of BALF, while conventional cultures failed to identify pathogens in all cases. All patients received combination antibiotic therapy based on metronidazole and piperacillin-tazobactam, with some cases requiring additional antibiotics. Following treatment, significant clinical improvement was observed, and follow-up imaging demonstrated gradual resolution of the lesions.

Conclusion: This study is limited by its small sample size and the lack of confirmatory tests, which warrant validation in larger prospective cohorts. Our findings highlight the advantages of mNGS in detecting fastidious pathogens (such as the anaerobic bacterium *T. forsythia*), providing new insights for the diagnosis of similar infections in the future. Additionally, the results identify smoking and poor oral health as common features that may be associated with the development of *T. forsythia-associated* lung abscesses.

Keywords: lung abscess, *Tannerella forsythia*, metagenomic next-generation sequencing, mNGS, oral diseases

Introduction

Tannerella forsythia (T. forsythia) is a Gram-negative anaerobic bacterium first isolated by Tanner et al in 1986 from the oral cavity of patients with periodontitis.[1] It is recognized as one of the primary pathogens responsible for periodontitis. Along with *Porphyromonas gingivalis* and *Treponema denticola, T. forsythia* forms part of the "red complex", a group of bacteria that colonize dental plaque biofilms.[2] Anaerobic bacteria are common pathogens in pulmonary infections, often due to aspiration.[2] They are also a leading cause of community-acquired lung abscesses. Critically, conventional culture methods frequently fail to identify these fastidious organisms - a diagnostic gap now addressed by metagenomic next-generation sequencing (mNGS).

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This advanced approach offers an unbiased, highly sensitive means of pathogen detection, with recent evidence confirming its superior performance over conventional methods in identifying anaerobic/facultative anaerobic bacteria in lung abscesses.[3] Studies demonstrate that anaerobic lung abscesses are typically dominated by *anaerobic streptococci*, Fusobacterium *nucleatum*, and Prevotella *melaninogenica*.[2,4] However, no systematic data exist on the clinical features of *T. forsythia-associated* lung abscesses, with only isolated case reports documented.[5,6] This profound knowledge gap underscores the necessity of our study. Herein, we present four cases of mNGS-confirmed *T. forsythia* lung abscesses (the largest series to date) and highlight their common clinical and imaging features. The demographic and basic clinical characteristics of these cases are summarized in Table 1.

Patients and Methods

Study Population

This retrospective study was conducted at the Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University from April 2023 to May 2024. Lung abscess was defined as a cavitary lesion >2 cm in diameter on computed tomography (CT). Inclusion criteria: All adult patients (≥18 years) with radiologically confirmed lung abscesses during the study period were screened. Exclusion criteria: (1) Incomplete clinical/imaging records; (2) Abscesses with confirmed non-infectious etiology (eg, malignancy, vasculitis). The pathogen identification protocol: All patients underwent conventional cultures of sputum. Bronchoalveolar lavage fluid (BALF) mNGS testing was performed when initial empirical antibiotic therapy failed (persistent fever/radiographic progression at 72 hours). Four cases with mNGS-confirmed *T. forsythia* as predominant pathogen were included.

Ethics Statement

The Ethics Committee of Hangzhou TCM Hospital approved this work, which involved retrospectively reviewing medical records (Approval No.: 2024KLL215). The requirement for consent from the study participants was waived by the ethics committee because the study was retrospective. This study was conducted in accordance with the Declaration of Helsinki. All patient data were de-identified and anonymized to ensure privacy and confidentiality. The data were handled in accordance with the hospital's data protection policy and relevant ethical guidelines.

Data Collection

Demographic characteristics, medical history, clinical symptoms, laboratory findings, and imaging results were collected for each patient. Laboratory tests included complete blood count (CBC), C-reactive protein (CRP), and procalcitonin (PCT) levels. CT scans were performed at admission and during follow-up to assess disease progression and treatment response. Non-contrast chest CT scans were routinely performed for all patients using a 256-slice multidetector CT scanner with a standardized protocol: 120 kVp, automated tube current modulation, 1.0–1.5 mm slice thickness, and reconstruction with both lung (width: 1500 HU; level: −600 HU) and mediastinal (width: 350 HU; level: 40 HU) algorithms. Contrast-enhanced CT was performed in all patients using a non-ionic contrast agent (iohexol, 350 mgI/mL) administered via a power injector at a dose of 1.5 mL/kg body weight and a flow rate of 2.5–3.0 mL/s, with imaging acquired in the portal venous phase (approximately 60–70 seconds post-injection). The definition of clinical cure is the resolution of all baseline symptoms (cough, fever, hemoptysis) for ≥72 hours, along with normalization of CRP (<10 mg/L), with radiographic improvement (reduced cavity size/consolidation) serving as supportive evidence.

Microbiological Analysis

Sputum and BALF samples were obtained via bronchoscopy and subjected to conventional bacterial cultures. Additionally, mNGS was performed on BALF to identify microbial pathogens. mNGS was performed at Hangzhou Matridx Biotechnology Co., Ltd., China, using clinically validated protocols: BALF samples underwent mechanical homogenization (BSP-100 Oscillator, Hangzhou Matridx Biotechnology Co.,Ltd.) followed by co-extraction of total nucleic acids for DNA/RNA pathogens; dual libraries were constructed through fragmentation and adapter ligation, then sequenced on Illumina NextSeq 550 (2×75 bp). Bioinformatic analysis involved host DNA subtraction (GRCh38.p13)

Table 1 Demographic and Baseline Clinical Characteristics of the Patients

No.	Gender	Age (Years)	Smoking/ Drinking History	Underlying Disease	Symptom at Onset	WBC ($\times 10^9$/L)	CRP (mg/L)	PCT (ng/mL)	Lesion Location	Chest CT Findings	Treatment Drugs	Days of Therapy	Prognosis
1	Female	46	No/No	None	Cough, chest pain	17.2	110.0	0.05	Left upper lobe	Consolidation, Calcification, Air bronchogram, Cavity	TZP combined with MTZ for 13 days, LVX for four days	17	Cured
2	Male	68	Yes/Yes	Hypertension, ALD	Cough, fever, hemoptysis	12.4	99.1	0.08	Bilateral upper lobes	Consolidation, Air bronchogram, Cavity	TZP combined with MXF for six days, AMC combined with MTZ for ten days, Tienam for four days, MXF for 72 days	92	Cured
3	Male	49	Yes/No	Hypertension	Cough, fever, hemoptysis, chest pain	9.5	54.9	0.05	Left upper lobe	Consolidation, Cavity, Mediastinal lymphadenopathy	TZP combined with MTZ for 12 days, MTZ for four days, AMC for eight days	20	Cured
4	Male	57	Yes/Yes	Hypertension, Diabetes	Cough, hemoptysis	17.7	105.9	0.05	Left upper lobe	Consolidation, Cavity, Pleural effusion	TZP for four days, AMC for 52 days, MTZ for four days	56	Cured

Abbreviations: WBC, White blood cell count; CRP, C-reactive protein; PCT, procalcitonin; CT, computed tomography; TZP, Piperacillin-tazobactam; MTZ, Metronidazole; LVX, Levofloxacin; ALD, Alcoholic liver disease; MXF, Moxifloxacin; AMC, Amoxicillin-clavulanate.

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and microbial classification against combined GenBank NT/NR plus curated clinical databases (35,257 species) using KRAKEN2/Bracken. Pathogen significance required: (1) ≥10 unique reads mapped to a species,(2) combined with either relative abundance ≥1% of microbial reads or RPM >5× negative control, and (3) passing quality control (Q30>80%, PhHV-1 recovery ≥80%).

Results

General Characteristics

The study included four patients (1 female, 3 males) aged 46 to 68 years (Table 1). Three patients had a history of hypertension, one had alcoholic liver disease, and one had diabetes mellitus. Three patients had a long history of smoking, and all had periodontitis (n=3) or dental caries (n=1). Two patients had a history of drinking. None of the four patients received immunosuppressive therapy, including glucocorticoids.

Clinical Manifestations of the Onset

All patients presented with respiratory symptoms, most notably cough and expectoration (4/4, 100%), while fever >38°C and chest pain each occurred in 50% of cases (2/4, 50%). Strikingly, hemoptysis was observed in three patients (3/4, 75%). Two patients (Cases 2 and 3) manifested concurrent hemoptysis and high fever (≥39°C).

Laboratory and Radiological Findings

Leukocytosis was observed in Cases 1 (White Blood Cell Count, WBC: 17.2×10^9/L), 2 (WBC: 12.4×10^9/L) and 4 (WBC: 17.7×10^9/L), while Case 3 had normal WBC counts. CRP levels were markedly elevated in all patients (range: 54.9–110.0 mg/L). PCT remained within normal limits (≤0.08 ng/mL) in all cases. The locations of lung abscesses in the four patients were as follows: three cases in the upper lobe of left lung and one case in the upper lobes of both lungs. On imaging, consolidation and cavitation were present in all cases. Other findings included air bronchograms (2/4), pleural effusion (1/4), calcification (1/4), and mediastinal lymphadenopathy (1/4). Contrast-enhanced chest CT was performed in three patients, all of whom demonstrated heterogeneous enhancement with central non-enhancing hypodense areas, suggestive of necrotic components. Detailed lung images of four patients are shown in Figures 1–4.

Microbiological Findings

Conventional cultures of sputum and BALF were negative in all cases. However, mNGS identified *T. forsythia* as the predominant pathogen in all patients, with sequence counts ranging from 32383 to 249236 (Table 2). Co-detection of other oral pathogens (eg, *Porphyromonas gingivalis, Treponema socranskii, Campylobacter rectus*) and viruses (eg, *Epstein–Barr virus, cytomegalovirus*) was also observed.

Treatment Outcomes

All four patients met predefined clinical cure criteria through tailored antibiotic regimens, though therapeutic courses varied significantly in duration (17–92 days). Initial intravenous therapy (primarily piperacillin-tazobactam with metronidazole) was followed by oral transition in most cases. Case 2 required prolonged multidrug adjustment (92 days) due to complications (hemoptysis and recurrent fever), while others showed faster responses. The prognosis for all four patients was satisfactory. Radiologic recovery lagged behind clinical improvement. All four patients achieved complete resolution of clinical symptoms, with significant radiographic improvement observed in three cases (Figures 1–4). Although the clinical symptoms of Case 3 were resolved through treatment, radiographic improvement remained limited at the 1-week follow-up (Figure 3). Regrettably, the patient declined subsequent chest CT imaging surveillance as recommended. At the 3-month clinic review, Case 3 maintained clinical recovery with no respiratory symptoms and normalized CRP (2.1 mg/L). While definitive radiographic resolution could not be confirmed, sustained wellness supports therapeutic success.

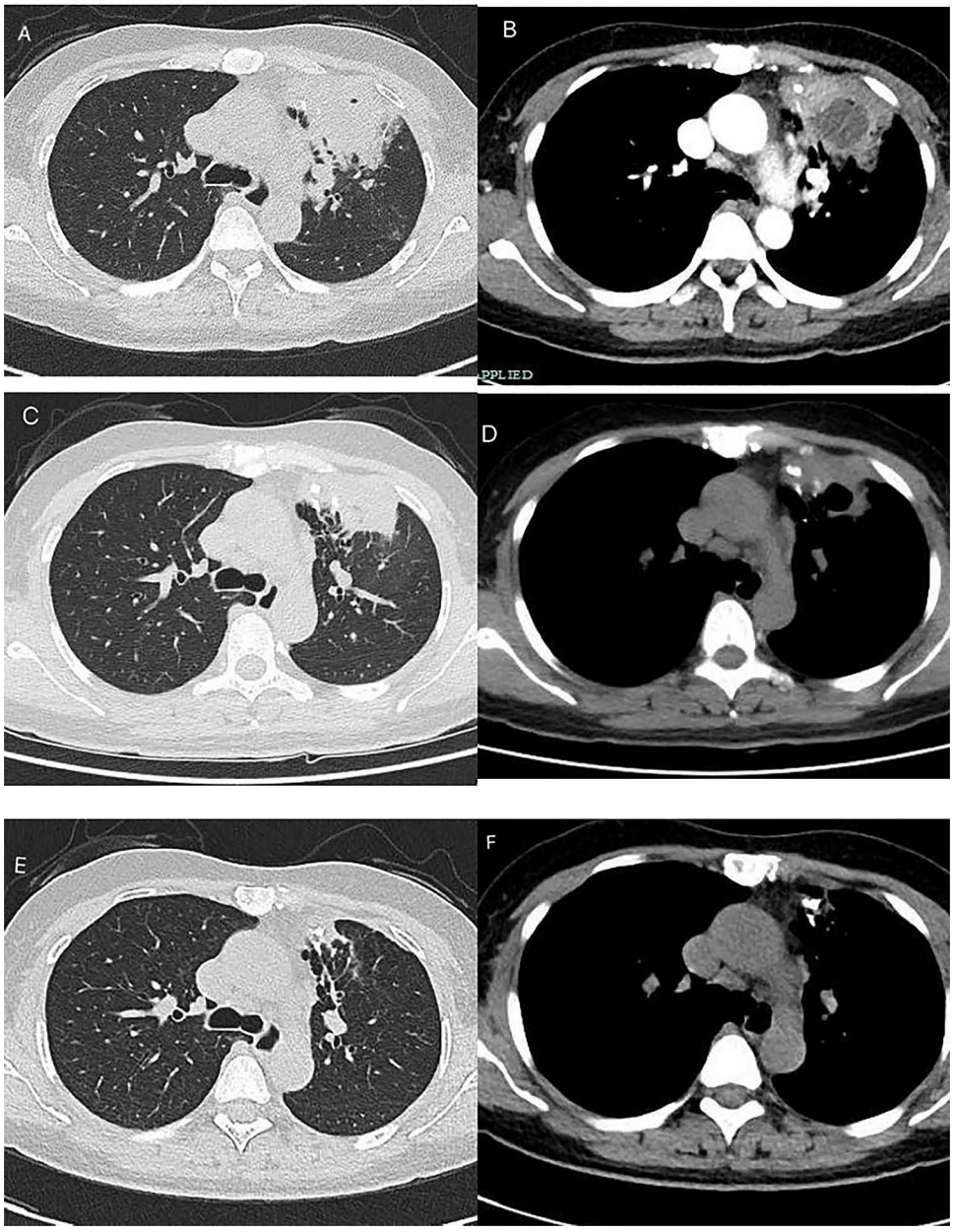

Figure 1 Serial chest CT images of Case 1: (**A**) and (**B**) On the day of admission, (**C**) and (**D**) 10 days after treatment, (**E**) and (**F**) Three months after treatment.

Discussion

A lung abscess represents a localized suppurative infection within the pulmonary parenchyma, characterized by necrotic cavitation and typically demonstrating air-fluid levels on imaging.[4] These infections can progress to systemic involvement, including life-threatening sepsis. While various pathogens may cause lung abscesses, contemporary research indicates aerobic bacteria—particularly *Enterobacterales, non-fermenting Gram-negative bacilli*, and *Gram-positive cocci*—predominate in current case series.[7–9] The diagnostic identification of anaerobic pulmonary abscesses remains clinically challenging due to cultivation difficulties. Notably, *T. forsythia*, a predominant anaerobic oral commensal, has been well established as a key periodontal pathogen.[10] Despite its oral prevalence, clinical data regarding *T. forsythia-associated* pulmonary abscessation remain remarkably limited. To our knowledge, this study provides the first systematic characterization of *T. forsythia-associated* lung abscesses in adults, representing the largest case series reported to date.

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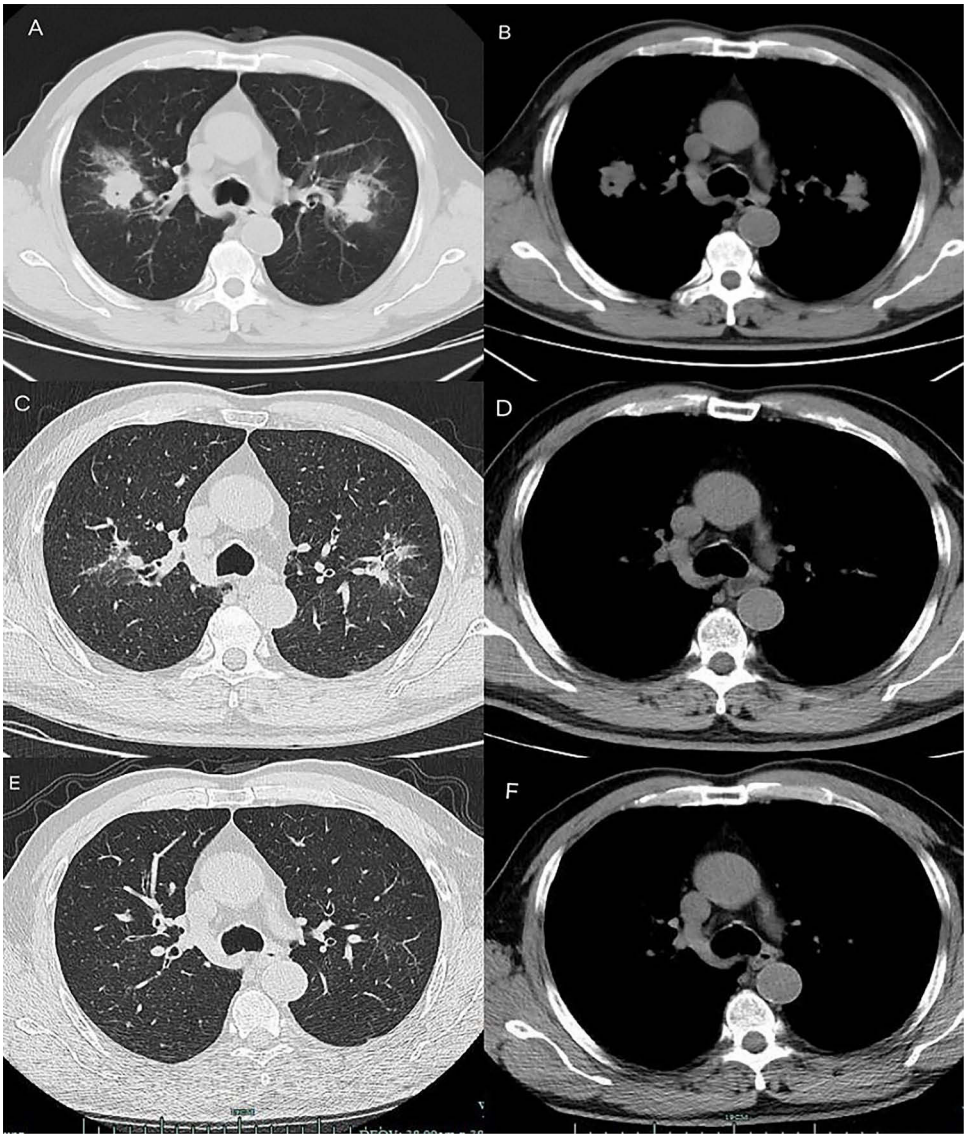

Figure 2 Serial chest CT images of Case 2: (**A**) and (**B**) On the day of admission, (**C**) and (**D**) Two months after treatment, (**E**) and (**F**) Ten months after treatment.

In our case series, three of four patients (75%) had a long history of smoking, leading us to hypothesize that smoking may represent a potential risk factor for *T. forsythia-associated* lung abscesses. This observation is supported by existing literature: Lv et al[5] documented a confirmed case of *T. forsythia* pulmonary abscess in a chronic smoker, while Stewart et al[11] reported a polymicrobial empyema involving *T. forsythia, Fusobacterium nucleatum*, and suspected *Actinomyces species* in another long-term smoker. Periodontal research provides mechanistic insights, as demonstrated by a key study[12] revealing significant differences in subgingival microbial profiles between smokers and non-smokers. Current smokers exhibited markedly increased colonization by periodontal pathogens including *Parvimonas, Fusobacterium, Campylobacter*, and *Bacteroides species*, with *T. forsythia* detection being exclusive to active smokers. Furthermore, Delima et al[13] demonstrated that smoking cessation leads to decreased levels of various oral pathogenic microorganisms. The association between oral pathologies and pulmonary anaerobic infections is well documented. Previous investigations have shown that poor oral hygiene correlates with elevated obligate anaerobic bacterial burdens in pneumonia patients,[14] while poor dental status has been independently associated with lung abscess development.[15,16] Based on this evidence, we speculate that smoking might contribute to *T. forsythia* pulmonary infections through its detrimental effects on oral microbiome composition and local mucosal defenses.

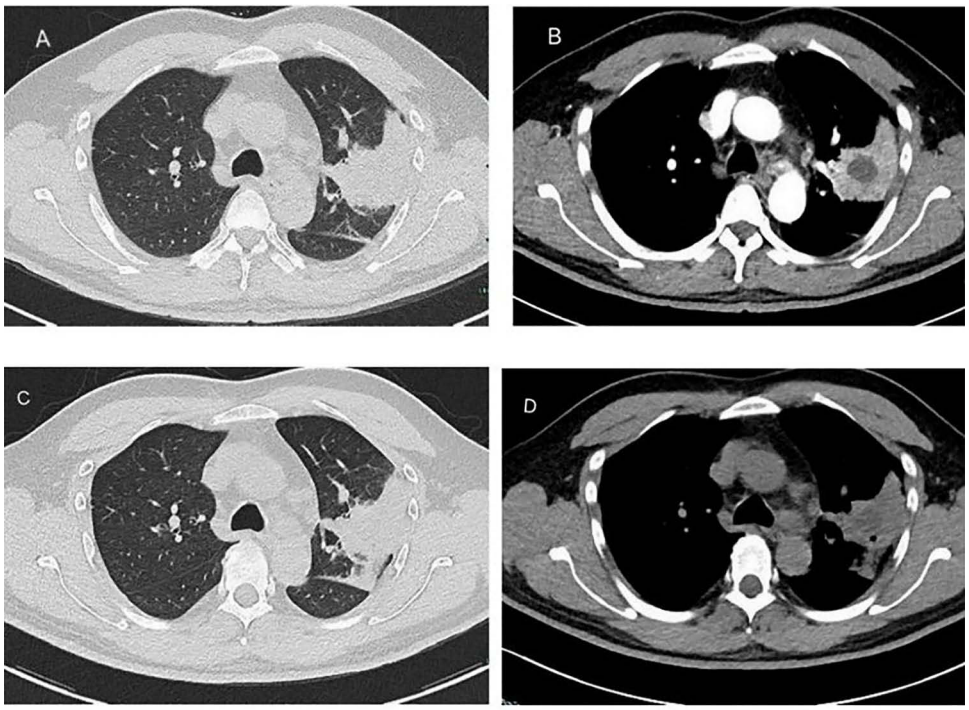

Figure 3 Serial chest CT images of Case 3: (**A**) and (**B**) On the day of admission, (**C**) and (**D**) One week after treatment.

Lung abscesses are generally classified into aspiration lung abscesses and hematogenous lung abscesses based on the route of infection. Hematogenous lung abscesses are usually caused by aerobic bacteria (such as *Staphylococcus aureus*) that spread through the bloodstream. The lesions are multiple and have no fixed distribution pattern, which is significantly different from the anaerobic bacterial infection and focal distribution of aspiration-related abscesses. Aspiration of oropharyngeal secretions is the predominant mechanism for lung abscesses caused by oral anaerobic bacteria, as supported by microbiological and clinical evidence.[17] Based on the strict anaerobic nature of *T. forsythia*, its primary ecological niche within the subgingival biofilm, the consistent detection of co-pathogens indicative of oral flora polymicrobial infection via mNGS in all our cases, and the exclusive upper lobe localization of the abscesses (3/4 in left upper lobe, 1/4 bilateral upper lobes), we propose that aspiration is the most plausible translocation route for *T. forsythia* in this series. The prevalent history of periodontitis/dental caries (100%) and smoking (75%) might contribute by potential increasing the oral bacterial burden (including *T. forsythia*) and potentially impairing mucosal defenses and respiratory clearance mechanisms, thereby facilitating aspiration and subsequent pulmonary infection establishment. Therefore, the pathogenesis of *T. forsythia*-associated lung abscesses in these patients might involve aspiration of pathogenic oral microbiota, facilitated by underlying poor oral health and smoking.

In our case series, patients presented with non-specific respiratory symptoms including cough, fever, chest pain, and hemoptysis. Notably, we found hemoptysis occurred in 3/4 cases (75%), a markedly higher frequency than reported in typical lung abscesses (10–20%).[3] Two patients (Cases 1 and 3) presented with concurrent hemoptysis and high fever, suggesting severe parenchymal involvement. All four cases demonstrated periodontal pathology, with three patients exhibiting periodontitis and one having dental caries. Radiographically, all abscesses were localized to the upper lung lobes, consistent with a previous report by Miao et al.[6] The exclusive upper lobe localization (left upper lobe: 3 cases; bilateral upper lobes: 1 case) aligns with established aspiration anatomy. In recumbent positions, aspirated oropharyngeal secretions gravitate toward dependent lung zones: the posterior segments of upper lobes and superior segments of lower lobes. This distribution is documented as a characteristic of aspiration-related infections.[2,17] Pulmonary consolidation was the predominant imaging finding, present in all four cases (100%). Contrary to Miao et al's findings,[6] which reported negative inflammatory markers in *T. forsythia* pulmonary abscesses, our series demonstrated significant systemic inflammation: all four patients showed markedly elevated CRP levels, three exhibited leukocytosis, and all four had elevated neutrophil percentages. This

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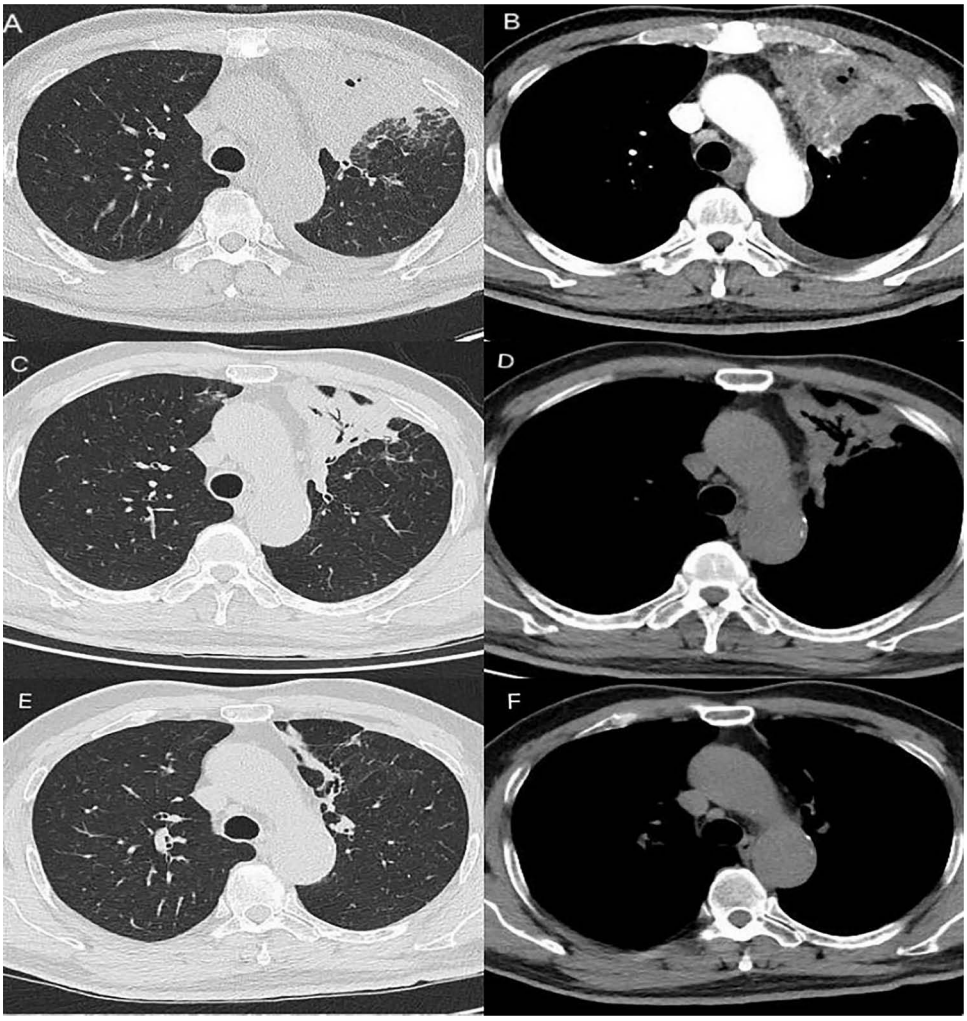

Figure 4 Serial chest CT images of Case 4: (**A**) and (**B**) On the day of admission, (**C**) and (**D**) One month after treatment, (**E**) and (**F**) Six months after treatment.

discrepancy may reflect differences in disease severity or host response. Current evidence suggests *T. forsythia* possesses significant pro-inflammatory potential. In vitro studies demonstrate that *T. forsythia* infection elevates serum inflammatory markers in murine models,[18,19] likely mediated through its unique rough-type lipopolysaccharide (LPS) that potently activates macrophage inflammatory responses.[20,21] The dissociation between markedly elevated CRP and normal PCT levels observed in all our patients is noteworthy and may provide additional pathophysiological insights. PCT is a biomarker highly specific

Table 2 The Result of Bronchoalveolar Lavage mNGS

No.	mNGS Detected Pathogene	Sequence Counts
1	*Tannerella forsythia*	105639
	Porphyromonas gingivalis	11479
	Campylobacter rectus	450
	Pseudoramibacter alactolyticus	133
	Treponema lecithinolyticum	81
	Veillonella atypica	35
	Parvimonas micra	28
	Prevotella salivae	19

(*Continued*)

Table 2 (Continued).

No.	mNGS Detected Pathogene	Sequence Counts
2	*Tannerella forsythia*	249236
	Porphyromonas endodontalis	6660
	Treponema socranskii	2064
	Prevotella salivae	1189
	Campylobacter rectus	1085
	Streptococcus parasanguinis	653
	Epstein-Barr virus	571
	Veillonella parvula	300
	Human betaherpes virus 7	256
3	*Tannerella forsythia*	182792
	Treponema socranskii	26697
	Porphyromonas gingivalis	24888
	Epstein-Barr virus	4329
	Schaalia cardiffensis	718
	Catonella morbi	349
	Cytomegalovirus	292
	Prevotella oris	207
	Human betaherpes virus 7	119
	Cardiobacterium hominis	68
	Streptococcus parasanguinis	64
	Veillonella atypica	51
	Escherichia coli	26
4	*Tannerella forsythia*	32383
	Porphyromonas endodontalis	1804
	Epstein-Barr virus	179
	Campylobacter rectus	117
	Streptococcus constellatus	63
	Cytomegalovirus	25

Abbreviation: mNGS, metagenomic next-generation sequencing.

for systemic bacterial infections, particularly those caused by aerobic bacteria, and is strongly induced in response to endotoxins like LPS in sepsis.[22] In contrast, CRP is a general acute-phase reactant elevated in a wide range of inflammatory conditions, including localized infections.[23] The normal PCT levels in our series, despite significant local inflammation (high CRP), suggest that *T. forsythia* lung abscesses may primarily represent a localized suppurative process without significant bacterial dissemination or a systemic endotoxin-mediated response. This could be attributed to the nature of the pathogen and the infection: (1) *T. forsythia* is an anaerobic bacterium causing a contained abscess, potentially limiting the release of inflammatory mediators into the systemic circulation; (2) The unique rough-type LPS of *T. forsythia* may exhibit different immunostimulatory properties compared to the potent endotoxins of Gram-negative enteric bacilli, which are classic potent inducers of PCT.[21] Therefore, the biomarker profile (elevated CRP + normal PCT) in *T. forsythia* lung abscess might reflect an intense local inflammatory response to anaerobic infection without concomitant bloodstream invasion or classic sepsis syndrome. While the localized nature of the abscess and the unique immunobiology of *T. forsythia* LPS provide plausible explanations, the precise mechanisms underlying this dissociated inflammatory response warrant further investigation.

As a nutritionally fastidious bacterium, *T. forsythia* requires exogenous N-acetylmuramic acid (MurNAc) for growth and proliferation.[24] In the oral cavity, commensal bacteria such as *oral streptococci* and *Actinomyces spp*. provide essential MurNAc and muropeptide fragments for *T. forsythia* through specific surface molecular interactions.[25] Yoneda et al[26] demonstrated synergistic virulence between *Porphyromonas gingivalis* and *T. forsythia*, showing enhanced abscess formation in murine models. This pathogenic cooperation may explain our clinical findings: mNGS of bronchoalveolar lavage fluid from

all four patients revealed polymicrobial infections containing various odontogenic anaerobic pathogens alongside *T. forsythia*. In our study, *Porphyromonas* species were detected in the BALF of all four patients via mNGS, with high sequence counts. Among them, *Porphyromonas gingivalis* was identified in two cases, while *Porphyromonas endodontalis* was found in the other two. The mNGS detection of Epstein–Barr virus (EBV) and Cytomegalovirus (CMV) in several cases warrants careful interpretation. The clinical significance of EBV/CMV co-detections remains limited despite elevated reads in Case 3 (EBV:4,329). CT scans do not show typical viral pneumonitis patterns like diffuse ground-glass opacities or peribronchial thickening. Crucially, all patients achieved complete clinical recovery without any antiviral therapy, demonstrating that EBV/CMV did not contribute significantly to the disease process.

mNGS represents an advanced high-throughput nucleic acid sequencing technology that has emerged as a powerful tool for comprehensive microbial identification.[27,28] Compared to conventional culture methods, mNGS demonstrates superior diagnostic sensitivity, particularly for challenging pathogens including *Mycobacterium tuberculosis*, viral agents, anaerobic bacteria, and fungi.[29] Notably, this contrasts with targeted molecular methods (eg, 16S rRNA sequencing or species-specific PCR). Targeted 16S rRNA sequencing can detect anaerobic bacteria with high sensitivity but requires bacterial universal primers and lacks broad pathogen coverage beyond bacteria.[30] Similarly, species-specific PCR (eg, for *T. forsythia*) offers high specificity yet demands a priori clinical suspicion to select primers.[31] Crucially, both methods encounter difficulties in dealing with polymicrobial infections due to issues with primer bias and limited multiplexing capacity.[30,31] In contrast, mNGS's untargeted approach enables the simultaneous detection of *T. forsythia*, co-pathogens, and opportunistic viruses without hypothesis-driven primer design. In our retrospective analysis, mNGS successfully identified causative pathogens in all four lung abscess cases where traditional diagnostic methods (sputum culture and bronchoalveolar lavage fluid culture) yielded negative results. This technology offers particular advantages in detecting polymicrobial infections.[32] Lung abscesses are frequently the result of mixed infections involving multiple bacterial species.[33] Given that lung abscesses typically result from mixed bacterial infections, mNGS may become an essential diagnostic modality for determining abscess etiology. However, mNGS cannot reliably differentiate true infection from microbial colonization, requiring clinicians to correlate findings with clinical manifestations and ancillary tests (eg, imaging characteristics). Unlike conventional culture, mNGS currently cannot provide antibiotic susceptibility data. Interpretation requires careful integration with the clinical context. The disadvantages of mNGS also include higher cost and bioinformatics complexity. While these limitations exist, ongoing technological advances may address these challenges, potentially establishing mNGS as a cornerstone in pulmonary infection diagnostics.

The selection of appropriate antimicrobial therapy is critical for effective management of lung abscesses. In our study, the empirical regimen of piperacillin-tazobactam combined with metronidazole was initiated prior to mNGS results. In accordance with the 2019 ATS/IDSA guidelines for severe community-acquired pneumonia,[34] we initiated empirical therapy with piperacillin-tazobactam to cover potential *Pseudomonas aeruginosa* and other Gram-negative pathogens, supplemented with metronidazole due to clinical suspicion of anaerobic involvement (eg, aspiration or radiographic findings suggestive of abscess/empyema), pending results from mNGS. This combination provides broad-spectrum coverage against common aerobic bacteria while ensuring potent activity against anaerobes, which is paramount given the strong association between upper lobe abscesses, oral pathologies, and aspiration. Notably, *T. forsythia* is resistant to the antibiotic fosfomycin, primarily due to the absence of MurAB enzymes, which are involved in the biosynthesis of MurNAc.[35] Similar to other red complex bacteria, *T. forsythia* frequently harbors tet(Q) and tet(32) genes, potentially conferring resistance to tetracycline-class antibiotics such as doxycycline.[36] In vitro susceptibility testing demonstrated 100% sensitivity of *T. forsythia* to moxifloxacin while revealing resistance rates of 25.6% to both amoxicillin and metronidazole, and 21.0% to azithromycin.[37] Clinical evidence supports these findings, with a trial in periodontitis patients showing a significant reduction in *T. forsythia* levels following moxifloxacin treatment.[38] Additional studies of peri-implant inflammation have reported general sensitivity to metronidazole but approximately 20% resistance rates to both amoxicillin and clindamycin, with no observed strains resistant to both amoxicillin and metronidazole.[39] The subsequent mNGS results robustly confirmed the rationality of our empirical strategy by identifying *T. forsythia* as the predominant pathogen and revealing polymicrobial infections containing various odontogenic anaerobes in all cases, which necessitated combined anaerobic-aerobic coverage. In most cases (Cases 1, 3, and 4), the clinical response to the initial regimen was satisfactory, and the therapy was consolidated based on mNGS findings. In contrast, for Case 2 with

severe symptoms (hemoptysis and recurrent fever), the mNGS finding of an exceedingly high sequence count of *T. forsythia* (249,236 reads) provided a microbiological basis for further escalating and prolonging antimicrobial therapy. This therapeutic approach resulted in significant clinical improvement in all patients.

The significant variation in treatment duration observed in our series (17 to 92 days) highlights a critical challenge in managing anaerobic lung abscesses: the absence of standardized treatment duration guidelines. This deficiency stems from several interrelated factors. Firstly, the historical and ongoing difficulty in microbiological diagnosis—due to the fastidious nature of anaerobes and the low yield of conventional cultures—has precluded the large-scale, pathogen-specific studies needed to establish evidence-based durations. Secondly, the disease itself is highly heterogeneous; the extended 92-day course in Case 2 was directly attributable to the management of severe symptoms, specifically massive hemoptysis and recurrent high fever, which necessitated multiple antibiotic adjustments. Notably, Case 2 also exhibited the highest bacterial burden as reflected by the markedly elevated sequence counts (249,236), which may have contributed to the more severe clinical presentation and the prolonged treatment required. In contrast, the shorter courses (17–56 days) in the other three patients reflect an uncomplicated clinical course with favorable response to initial empiric therapy. Thirdly, the decision to cease antibiotics relies on subjective clinical assessment and imperfect markers, as radiographic resolution notoriously lags behind clinical cure, and we lack validated biomarkers for microbiological eradication. While IDSA/ATS guidelines provide general recommendations for community-acquired pneumonia and lung abscess management, specific evidence-based protocols defining optimal treatment length for anaerobic lung abscesses, particularly those involving fastidious organisms like *T. forsythia*, are lacking.[34] Current practice often relies on individualized decisions based on clinical response (symptom resolution, fever defervescence), inflammatory marker normalization (eg, CRP), and radiographic improvement. This individualized approach, while pragmatic given the heterogeneity of patient factors and disease severity, inherently leads to substantial variation in antibiotic exposure duration, as demonstrated in our cases. Future studies focusing on objective markers of microbiological eradication and tissue healing are warranted to establish more evidence-based, standardized duration recommendations for anaerobic lung infections, potentially reducing unnecessary antibiotic exposure and associated risks.

This study has several notable limitations that warrant explicit emphasis: (1) Selection bias risk: Despite consecutive screening of all lung abscess patients, final cohort selection depended on mNGS-confirmed *T. forsythia* detection, potentially underrepresenting culture-positive cases. (2) Lack of control group: As an observational case series, this study lacks comparator groups (eg, *non-T. forsythia* abscesses). (3) Unverified microbiological findings: The absence of confirmatory tests (PCR, immunohistochemistry, or culture) for mNGS results remains a critical methodological constraint. (4) Incomplete radiographic follow-up: Long-term CT was unavailable for Case 3, precluding definitive resolution assessment despite clinical recovery. (5) Retrospective single-center design: Small sample size (n=4) and institutional specificity may affect generalizability. Collectively, these limitations necessitate cautious interpretation of findings.

Conclusion

This study presents the largest reported case series (n=4) of *T. forsythia*-associated lung abscesses, serving as a hypothesis-generating exploration rather than definitive evidence. Key observations in this cohort include: (1) Concomitant oral pathologies and smoking history (75%) were common comorbidities; (2) clinical manifestations were non-specific, while chest CT predominantly revealed consolidations and cavitary lesions; (3) mNGS proved valuable for rapid pathogen identification; and (4) Favorable short-term outcomes were achieved with appropriate antimicrobial therapy regimens in these cases. These findings generate three key hypotheses for validation: (1) Oral dysbiosis as a potential risk factor for *T. forsythia* pulmonary translocation; (2) mNGS-guided therapy improving anaerobic abscess outcomes; (3) Smoking potentiating *T. forsythia* virulence. To validate these mechanisms and establish clinical guidelines, prospective multicenter studies are critically needed.

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Disclosure

The authors report no conflicts of interest in this work.

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