

Red Complex Bacteria as a Hidden Cause of Chronic Lung Abscess: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 59-year-old
Final Diagnosis: Lung abscess caused by Red Complex
Symptoms: Cough • recurrent hemoptysis
Clinical Procedure: —
Specialty: Pulmonology

Objective: Rare disease
Background: Common oral pathogens such as *Treponema denticola*, *Porphyromonas gingivalis*, and *Tannerella forsythia*, which form biofilms in the periodontal pockets, are classified together as Red Complex bacteria in Socransky's subgingival cluster model and are key pathogenic bacteria in periodontitis. Oral pathogens play a critical role in pulmonary infections, particularly in the pathogenesis of lung abscesses. Lung abscesses caused by Red Complex bacteria have rarely been described; to our knowledge, few cases have been reported to date.

Case Report: We present the first documented case of chronic lung abscess caused by Red Complex bacteria, with recurrent hemoptysis as the main symptom. The patient had chronic periodontitis and uncontrolled diabetes, and exhibited an indolent clinical course with consistently negative bacterial cultures. Chest computed tomography (CT) demonstrated a thick-walled cavity with minimal liquefactive changes in the right upper lobe. Red Complex bacteria in the bronchoalveolar lavage fluid and the lung tissue were identified by metagenomics next-generation sequencing (mNGS). The patient underwent intravenous penicillin therapy. The hemoptysis resolved completely coupled with improvement in clinical status and inflammatory markers. The chest CT demonstrated near-complete resolution of the lung abscess during follow-up.

Conclusions: Red Complex bacteria are rare pathogens in patients with periodontitis who develop culture-negative chronic lung abscesses accompanied by recurrent hemoptysis. This case report highlights this rare etiology and reveals a critical diagnostic limitation, as routine cultures frequently fail to detect these fastidious organisms. The incorporation of mNGS into the diagnostic algorithm for such cases can facilitate a definitive diagnosis and guide precise antimicrobial therapy.

Keywords: Lung Abscess • Sequence Analysis, DNA • *Treponema denticola* • *Porphyromonas gingivalis* • *Tannerella forsythia*

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Introduction

Treponema denticola, *Porphyromonas gingivalis*, and *Tannerella forsythia* are biofilm-forming bacteria commonly found in periodontal pockets [1]. These 3 species are classified together as the Red Complex in Socransky's subgingival cluster model, which groups subgingival bacteria into color-coded clusters (eg, Red, Orange) based on their bacterial profiles and association with the severity of disease [2]. The Red Complex is widely regarded as a key pathogenic consortium in periodontitis. A lung abscess is a pus-filled cavity resulting from necrosis of lung tissue, most commonly caused by bacterial infection. Lung abscess in adults is frequently the result of aspiration of oral pathogens into the lower respiratory tract and failure of host defense mechanisms to eliminate the contaminating bacteria. The oral pathogens play a central role in this chain of events [3]. A great challenge with identification of oral anaerobic bacteria is that they are difficult to culture using traditional methods. However, metagenomics next-generation sequencing (mNGS) has emerged as a critical tool for identifying such rare pathogens [4]. Although there are many reports of lung abscesses caused by periodontal pathogens, lung abscesses due to Red Complex bacteria remain exceptionally rare in the literature. In this report, we present what we believe to be the first documented case of a chronic lung abscess, characterized by recurrent hemoptysis as the primary clinical manifestation, caused by the Red Complex pathogens. This report aims to describe the clinical presentation, diagnostic process, and implications of a lung abscess caused by Red Complex pathogens.

Case Report

The patient was a 59-year-old man with poorly controlled diabetes (duration: 6 months) and a 30-year history of active smoking. He had developed cough and hemoptysis for 5 days and was admitted to the local hospital on 24 December 2023. He presented with a productive cough with blood-tinged sputum, and occasionally a few mouthfuls of blood, but no fever, chest pain, or dyspnea. A contrast-enhanced chest computed tomography (CT) revealed infection in the right upper lobe. Laboratory tests demonstrated mild leukocytosis (white blood cells: $11.24 \times 10^9/L$, reference range: $4\text{--}11 \times 10^9/L$) with neutrophil predominance (69%). Markers of inflammation were elevated, including a C-reactive protein (CRP) level of 35 mg/L (normal <5 mg/L) and an erythrocyte sedimentation rate (ESR) of 26 mm/hour (normal range: 0–15 mm/hour). Glycemic control was suboptimal, as evidenced by an elevated hemoglobin A1c (HbA1c) of 8.9% (reference: 4–6%). Repeated sputum cultures showed no bacterial growth. A provisional diagnosis of community-acquired pneumonia was established at the referring hospital, where empirical therapy with cefoxitin was initiated (rationale for antibiotic selection unavailable). However

clinical improvement was not observed. Bronchial artery embolization was performed for hemoptysis control, but symptoms recurred within 48 hours. Self-administered hemostatic agents failed to resolve the recurrent hemoptysis.

The patient was admitted to our institution on 21 April 2024. Contrast-enhanced chest CT revealed patchy shadowing with a thick-walled small cavity lesion in the right upper lobe, the consolidated lesion contained minimal hypodense liquefactive changes. While no distinct air-fluid level was evident, the imaging features were suggestive of lung abscess formation (Figure 1A). According to the characteristics of common pathogenic bacteria in lung abscesses, empirical antibiotic therapy with intravenous piperacillin-tazobactam (4.5 g every 8 hours) was initiated. Pre-treatment sputum and bronchoalveolar lavage fluid cultures repeatedly yielded negative results (specimens collected prior to antibiotic administration). Toward the conclusion of the 10-day antibiotic course, the patient's hemoptysis persisted. A repeat bronchoscopy was performed on 30 April 2024, during which bronchoalveolar lavage fluid (BALF) was obtained for both liquid-based cytology and mNGS analysis. The liquid-based cytology analysis showed ciliated columnar epithelial cell hyperplasia with abundant neutrophils and lymphocytes. These findings excluded malignant neoplasia and supported an infectious/inflammatory etiology. The mNGS analysis of BALF revealed a polymicrobial infection predominantly comprising periodontal pathogens, with *T. denticola* (sequence reads 744; relative abundance 12.13%) and *P. gingivalis* (sequence reads 1623; relative abundance 26.46%), additional species detected included *T. forsythia* (sequence reads 49; relative abundance 1.79%), *Prevotella buccae* (sequence reads 22, relative abundance 0.36%), *Alloprevotella rava* (sequence reads 16, relative abundance 0.26%), and *Bacteroides pyogenes* (sequence reads 9, relative abundance 0.15%). The above-mentioned bacteria are common oral bacteria, and the number in the oral cavity of patients with chronic periodontitis is significantly higher than in people without chronic periodontitis. Therefore, to further clarify whether the bacteria were pathogenic bacteria, CT-guided percutaneous lung biopsy was performed. The mNGS analysis of lung tissue suggested *T. denticola* (sequence reads 864; relative abundance 16.12%), *P. gingivalis* (sequence reads 1887; relative abundance 28.57%), and *T. forsythia* (sequence reads 234; relative abundance 7.27%) were likely responsible for the abscess. The microbiological profile of both specimens, demonstrating high abundances of fastidious anaerobic bacteria typically associated with dental biofilm, strongly indicates aspiration of oral pathogens and suggests periodontal disease-associated pulmonary infection. Subsequent pathological examination confirmed chronic suppurative inflammation in the affected lung tissue. A comprehensive dental evaluation revealed moderate chronic periodontitis (Figure 1B), further supporting the oral source pathogenesis. Based on the patient's poorly controlled

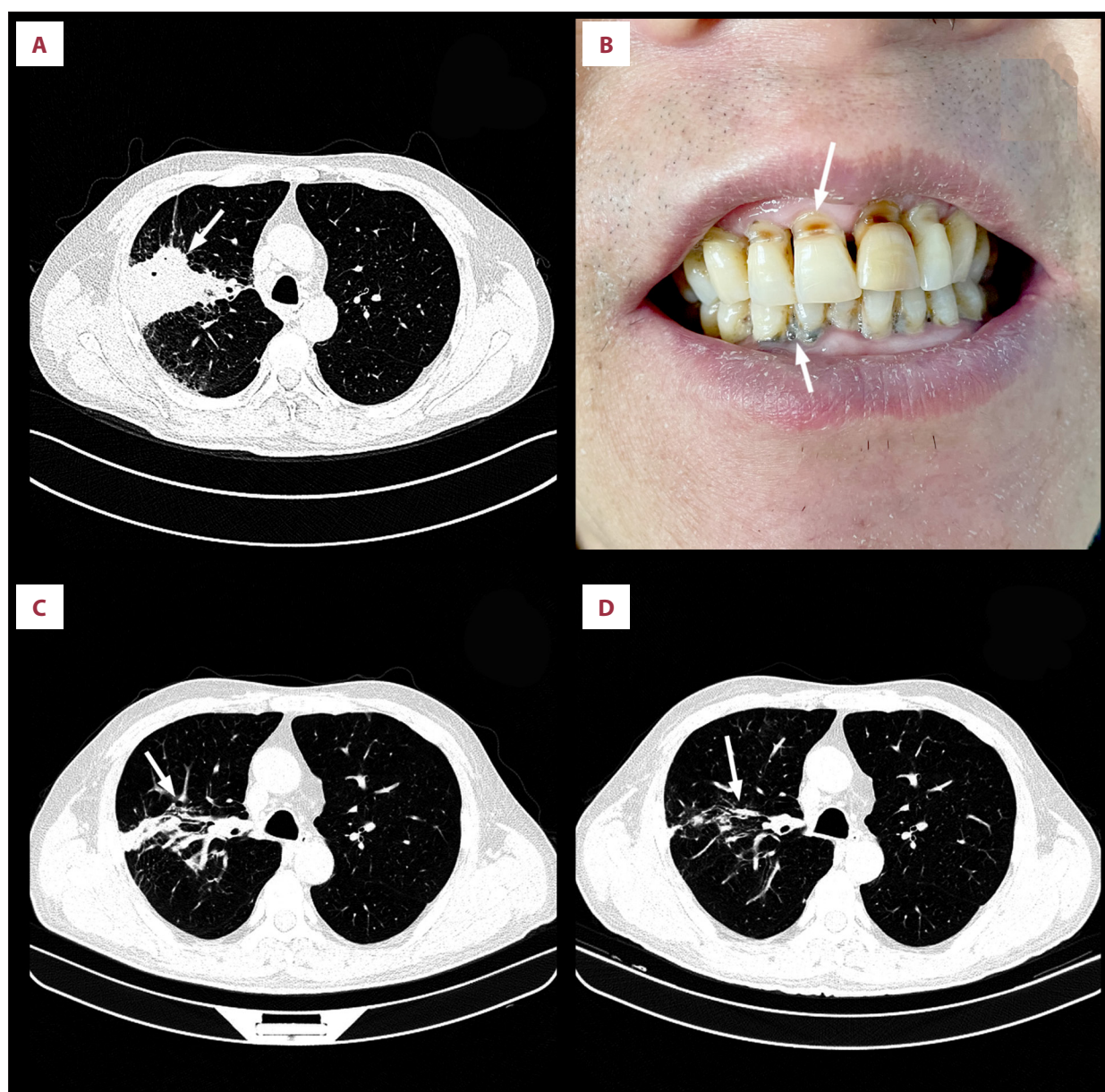


Figure 1. CT scans of the patient's chest during hospitalization and the patient's periodontal condition. **(A)** Chest CT scan on admission showing patchy shadowing with a thick-walled small cavity in the right upper lobe (arrow). The consolidated lesion contains minimal hypodense liquefactive changes. **(B)** Clinical photo of the patient's periodontal condition showing dental plaque (arrow), gingival recession (arrow), and alveolar bone resorption, consistent with a diagnosis of moderate chronic periodontitis. **(C)** Chest CT scan after 12 days of therapy showing significant reduction of the abscess lesion in the right upper lobe (arrow). **(D)** Chest CT scan after 54 days of therapy demonstrating near-complete resolution of the lung abscess (arrow). CT – computed tomography.

diabetes history (a known risk factor for severe infections), patient clinical characteristics, chest CT findings, and high microbial abundance (revealing predominant Red Complex organisms), a final diagnosis of lung abscess caused by Red Complex bacteria was made. Given the lack of established treatment guidelines for Red Complex bacteria and the absence of antimicrobial susceptibility data, empirical therapy

with penicillin was initiated. This decision was based on the anaerobic nature of these organisms and the known susceptibility of *Treponema* species to beta-lactams. The antimicrobial regimen was switched to penicillin sodium (4.8 million units intravenously every 6 hours) on 6 May 2024 with a plan to continue therapy for 6-8 weeks. The patient also received a 2% glucose chlorhexidine mouth rinse for chronic periodontitis.

His hemoptysis gradually decreased until its disappearance. Repeated CT of the chest after 12 days revealed a significant reduction of the abscess lesion (**Figure 1C**) coupled with improvement in clinical status and inflammatory markers. He was discharged on 5 June 2024, and no hemoptysis has occurred since. Oral amoxicillin (500 mg, 3 times/day) was continued until 28 June 2024. Repeated chest CT scans showed almost complete resolution of the lung abscess on 28 June 2024 (**Figure 1D**).

Discussion

Red Complex bacteria (*T. denticola*, *P. gingivalis*, and *T. forsythia*) form a consortium in the subgingival biofilm and are regarded as the principal periodontopathogenic bacteria. In patients with periodontitis, Red Complex bacteria as dominant species co-localize in subgingival plaque and exhibit strong synergistic effects in growth promotion, nutrient utilization, biofilm formation, and virulence [5]. The typical biofilm of dental plaque may serve as a reservoir of pathogenic bacteria for respiratory infection. Red Complex bacteria have been reported to be located on the surface of dense subgingival bacterial biofilms [6] and are easily released from bacterial biofilms and inhaled into the lower respiratory tract, especially in patients with periodontal disease. Many studies have reported on the pathogenicity of *P. gingivalis*; however, little attention has been paid to the virulence properties of *T. denticola*, particularly the pathogenicity of *T. denticola* in lung tissue. *T. denticola* expresses a wealth of virulence factors and dozens of virulence properties have been identified in this bacterium, as follows: motility, chemotaxis, adherence to host cells, colonization, lipopolysaccharides, toxins, and enzymes, among others [1]. These virulence factors mediate tissue penetration and destruction as well as evasion of host immune responses. Of the 3 species identified from the biopsy, only *T. denticola* is motile and able to respond chemotactically to environmental stimuli. Interestingly, *T. denticola* has been demonstrated to show chemotaxis to glucose [7], suggesting that our patient's poorly controlled diabetes mellitus constituted a major risk factor for Red Complex bacteria, especially *T. denticola* infection. Motility and chemotaxis are not considered to be classic virulence factors of bacteria. However, for *T. denticola*, these traits are likely essential for its survival and virulence, underpinning its role in disease progression [5]. *T. denticola* outer sheath vesicles (OSVs) have been proposed as long-range virulence factors capable of penetrating tissues more readily than the bacteria themselves. They contribute to host tissue damage through toxins and proteolytic enzymes. Additionally, OSVs facilitate immune evasion by initial contact with immune cells, thereby limiting clearance of the bacteria during subsequent encounters [8]. Dentilisin has been proposed to be a major *T. denticola* virulence factor. It contributes to disease progression

by disrupting or modulating intercellular host signaling pathways and degrading host cell matrix proteins [5]. Collectively, these virulence factors reveal a novel role for *T. denticola*; not merely as a contributor to tissue damage, but as a sophisticated orchestrator of pathogenesis that enables persistent colonization, immune evasion, and inhibition of host tissue repair within the complex host environment.

Earlier articles have suggested in general terms that periodontal pathogens are common pathogens of lung abscesses. The oral bacterial species frequently implicated are *A. actinomycetemcomitans*, *Actinomyces israelii*, *Capnocytophaga* sp., *Eikenella corrodens*, *Prevotella intermedia*, and *Streptococcus constellatus*. A published case report described a lung abscess caused by *P. gingivalis*, highlighting both the bacterium's vascular invasiveness and the importance of obtaining lower respiratory tract specimens through bronchoscopy with anaerobic culture [9]. Similarly, another article reported a culture-confirmed case of *P. gingivalis*-induced lung abscess [10]. In both cases, the diagnosis was established through bacterial culture methods, with *P. gingivalis* identified as the sole causative pathogen of the lung abscess.

In humans, pulmonary infections caused by Red Complex bacteria have been rarely reported in the literature and their pathogenicity and clinical features remain unclear. Therefore, further studies involving the collection of these bacteria and analysis of more clinical cases are necessary to better elucidate their clinical characteristics and pathogenic mechanisms. Here, we report the first complete case of chronic lung abscess caused by Red Complex bacteria with recurrent hemoptysis as the main symptom. Ryuta Kimizuka et al induced experimental pneumonia in mice by mono- and mixed infections with *P. gingivalis* and *T. denticola*, and found that the lung tissue from mice with mixed infections showed more severe lung abscess, with more hemorrhage and alveolar destruction [11]. Even low-dose mixed infections of *T. denticola* and *P. gingivalis* caused significant tissue damage [12]. In our case, with a mixed infection involving 3 species, a similar mixed-infection effect seems to have happened. The pathological findings we saw may be attributed to the unifying features of the Red Complex, which promote bacterial complex invasion in tissue, destruction of host defenses, and inhibition of tissue repair. Specifically, these features are: their robust extracellular proteolytic activity, production of toxic metabolites, and outer membrane (or sheath) vesicles. Given that *T. denticola* and *P. gingivalis* adhere strongly through specific interactions and exist in a symbiotic relationship, we hypothesize that the diagnostic approach in the above cases [9,10], in which *P. gingivalis* was identified as the sole causative pathogen of the lung abscess, may have missed additional species due to a lack of advanced techniques (anaerobic culture or mNGS), and that the infections may have in fact been due to Red Complex bacteria rather than solely

P. gingivalis. Research has also demonstrated that the relative loads of *T. denticola* and *P. gingivalis* are significantly higher in the periodontal pocket samples of patients with a history of active smoking than in those of non-smokers, with an increased susceptibility to infection [13]. Notably, our patient may represent a clinically relevant case that substantiates these findings, as he was an active smoker with lung abscess caused by Red Complex bacteria. However, we acknowledge the limitation that the relative loads of *T. denticola* and *P. gingivalis* in the periodontal pocket samples of patients were not quantitatively assessed in this case.

Red Complex bacteria, especially *T. denticola*, increase vascular permeability by activating the kallikrein-kinin system and disrupt blood coagulation by degrading fibrinogen, fibrin, and factor X [14]. These processes promote bleeding from the lesion site, and provide a source of nutrients conducive to the growth and virulence of Red Complex bacteria. In our case, recurrent hemoptysis was the main symptom. The above mechanism may be the cause of the hemoptysis. Therefore, we hypothesize that refractory hemoptysis may be a characteristic clinical feature of Red Complex bacterial pulmonary infections. This hypothesis warrants further validation through systematic collection, analysis using advanced techniques such as mNGS, and comparison of clinical characteristics from a large number of cases.

Currently, there are no established treatment guidelines for lung abscesses caused by Red Complex bacteria. With regard to lung abscess caused by oral anaerobic bacteria, clindamycin was considered the standard drug in the early 1980s [15]. The record of this drug was subsequently tarnished by its role in promoting *Clostridioides difficile* proliferation, causing pseudomembranous colitis, and at the same time, its therapeutic evaluation against anaerobic bacteria in polymicrobial infections like aspirational lung abscesses is limited by its concomitant activity against streptococci [16]. It should be acknowledged that metronidazole is a drug that is active against virtually all clinically important anaerobes, but does not work well in anaerobic lung infections [16]. Given the microbiological profile of the Red Complex, we initiated penicillin therapy. Concurrently, the patient underwent smoking cessation, glycemic control, and periodontal treatment to address underlying risk factors. Subsequent clinical improvement was observed. The optimal antimicrobial treatment regimen for Red Complex-associated lung abscesses requires further investigation,

including comprehensive in vitro susceptibility testing and systematic evaluation of treatment strategies in clinical practice. In summary, an integrated treatment strategy is essential.

Classical etiological descriptions of infection are based on culture results. However, the genome of *T. denticola* carries only a limited set of genes that are associated with biosynthetic pathways [17]; it is a slow-growing, fastidious, and highly fragile obligate anaerobe, making its cultivation and handling in the laboratory difficult [18]. This is the reason why specimens in our case were repeatedly found to be culture-negative, and why lung infections with *T. denticola* or other Red Complex bacteria have rarely been reported. Hence, it is important to keep in mind that culture-based methods are not sufficient for accurate identification of all bacterial species and determination of all causal agents of disease [19]. The cases we reported were diagnosed by mNGS detection. The mNGS method has multiple advantages, in that it can not only directly sequence the genome of the sample, but also has higher sensitivity and takes less time than traditional culture methods. In an additional role as an effective method, the use of mNGS contributes to diagnosis of rare pathogens and early target treatment.

Conclusions

For patients with periodontitis presenting with culture-negative chronic lung abscesses and recurrent hemoptysis, infection with Red Complex bacteria should be considered. This case underscores the limitations of routine cultures in diagnosing pulmonary infections involving fastidious organisms. The mNGS technique has emerged as a critical tool for identifying rare pathogens, enabling targeted therapy and improving clinical outcomes.

Informed Consent Statement

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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