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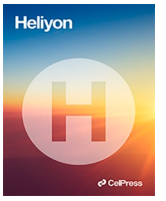

Case report

Pulmonary granulomas and Mendelson syndrome in an immunocompromised patient

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ABSTRACT

Granuloma formation is generally correlated with infection. Pulmonary granulomas caused by foreign bodies aspiration are uncommon. The clinical and radiologic features of such cases often lack specificity, which makes it difficult to distinguish from malignancy. Aspiration is usually not considered in the differential diagnosis of patients presenting with mass-like abnormalities on chest imaging. Occult aspiration history, diverse clinical manifestations, atypical imaging findings, and limited availability of pathogen detection techniques make the precise diagnosis a substantial challenge. Herein, we describe an older patient presenting with chest pain and worrisome lung masses/nodules that proved to be pulmonary granulomas caused by foreign matters aspiration. In addition, the patient developed Mendelson syndrome due to acute macroaspiration. Lung tissue metagenomics next-generation sequencing (mNGS) revealed *Streptococcus intermedius*, a normal flora of the oropharynx. The aim of this case was to underscore the importance of considering aspiration as a potential differential diagnosis of patients presenting with pulmonary granulomas, especially in patients with recurrent pneumonia or predisposing factors. In addition, mNGS act as a potential, rapid, and effective technique for diagnosing aspiration-related syndrome, showing satisfactory performance in identifying pathogens.

1. Introduction

A granuloma is defined as a conglomeration of macrophages and/or epithelioid cells with or without auxiliary features such as inflammatory leukocyte infiltration or necrosis [1]. Granuloma formation is generally correlated with infectious diseases. *Mycobacterium* and fungi infection are the most common causes of pulmonary granulomas [2]. Distinguishing between infectious and non-infectious causes is often the critical role of pathologists, and in most cases, has greatest impact on clinical management. Pulmonary granulomas caused by foreign bodies aspiration are uncommon. The clinical and radiologic features of such cases often lack specificity, which makes it difficult to distinguish from malignancy [3]. Aspiration defined as the inhalation of oropharyngeal

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secretions or gastric contents into the larynx and lower respiratory tract [4]. Occult aspiration history and limited availability of pathogen detection techniques also make the diagnosis of aspiration-related pulmonary disease a substantial challenge [5]. Herein, we describe an older patient presenting with chest pain and worrisome lung masses/nodules that proved to be pulmonary granulomas caused by foreign matters aspiration. Microbiota analysis revealed that the most abundant microbiota in lung tissues was *Streptococcus intermedius*, a normal flora of the oropharynx [6]. Notably, the patient developed Mendelson syndrome due to acute macroaspiration. It may alert the pathologists and radiologists to consider aspiration in the differential diagnosis of patients presenting with malignant-appearing lung masses, especially in patients with recurrent pneumonia.

2. Case presentation

A 68-year-old man was admitted to the hospital after having left chest pain for 2 weeks. One day before hospital admission, a chest computed tomography (CT) scan in outpatient clinic showed soft tissue density masses in the posterior basal and lateral basal segment of the lower lobe of the left lung, with sizes of 4.2 cm*2.8 cm and 1.8 cm*1.4 cm, respectively (Fig. 1A–C). Notably, multiple lymph nodes (maximum measured approximately 0.7 cm) were found in the mediastinum and right hilar area. He was admitted to the hospital for further diagnosis and treatment. He did not have a fever, cough, night sweats, or hemoptysis. He has hospitalized for pneumonia several times in the past year. He has lost approximately 17 kg of body weight in the past year. The patient undergoing moderate malnutrition according to the Global Leadership Initiative on Malnutrition 2019 and Nutritional Risk Screening-2002. Besides, he suffered from nasopharyngeal carcinoma chemoradiotherapy, prostatic cancer, gastroesophageal reflux disease, diabetes mellitus, and hypotension episodes.

At the time of admission, physical examination showed temperature of 36.5 °C, heart rate of 84 beats/min, blood pressure of 149/93 mmHg, and respiratory rate of 20 breaths/min. SpO2 was 95 % on room air. Lung examination revealed coarse breath sounds with scattered moist rales bilaterally, especially in the left lung. Laboratory examination showed increased levels of high sensitivity C-reactive protein (hsCRP) to 35.77 mg/L, procalcitonin (PCT) to 0.11 ng/ml, interleukin-6 (IL-6) to 13.80 pg/ml, and erythrocyte sedimentation rate (ESR) to 116 mm/h. The serum 1,3-β-d glucan test (G test) (236.12 pg/ml) and galactomannan test (GM test) (3.226) were positive. However, microscopy and culture of sputum, bronchoalveolar lavage (BAL) fluid, and peripheral blood failed to identify any responsible bacteria, fungi, or mycobacteria. Tuberculosis infectious T-lymphocyte spot assay (T-SPOT-TB) was negative. Real-time fluorescent polymerase chain reaction (PCR) test for SARS-CoV2 and EB virus were negative. An antibody panel, covering 11 respiratory pathogens (*respiratory syncytial virus*, *adenovirus*, *influenza virus A/B*, *parainfluenza virus*, *Mycoplasma pneumoniae*,

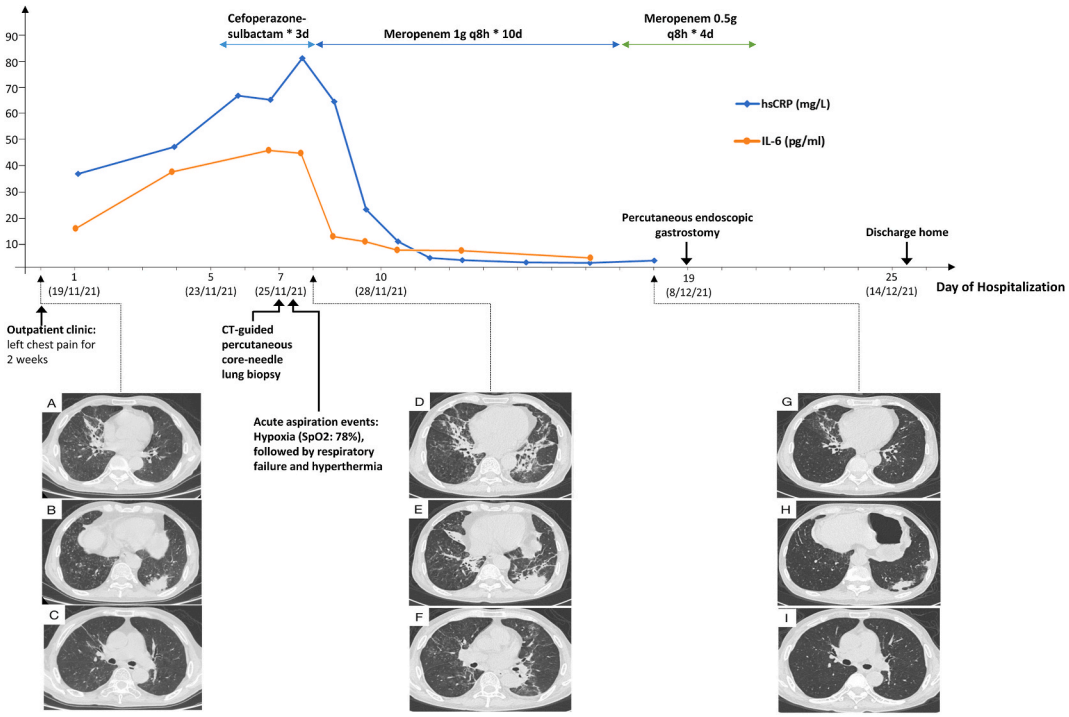

Fig. 1. Timeline of displaying the progression of the patient's condition, key diagnoses, and treatment interventions. A-C (One day before hospital admission) showed nodules/masses-like abnormality in left lower lobe. D-F (on the 7th day of admission) showed more consolidation in the bilateral lower lobe, new ground glass density shadows, and a small amount of pleural effusion in the left lung. G-I (on the 18th day of admission) showed left lower lobe consolidation remarkably smaller, diffuse centrilobular nodules in the bilateral lung fields decreased, and the new onset ground-glass opacity disappeared, considering inflammatory absorption. hsCRP: high sensitivity C-reactive protein, IL-6: interleukin-6.

Chlamydia pneumoniae, *coxsackievirus A/B*, *Echovirus*, and *Legionella pneumophila*) were negative. On the 5th day of admission, the patient showed higher levels of hsCRP (46.31 mg/L) and IL-6 (34.87 pg/ml) than before. To prevent the exacerbation of aspiration related syndrome, the patient was empirically treated with cefoperazone-sulbactam.

On the 7th day of admission, he underwent CT-guided percutaneous core-needle lung biopsy and histopathological examination showed pulmonary granulomas embedded with foreign bodies and secondary organizing pneumonia (Fig. 2A–C). Special stains for microorganisms including Grocott methenamine silver (GMS), periodic acid-Schiff (PAS), and acid-fast staining were negative. Subsequently, lung tissue specimen and oropharyngeal swab were sent for metagenomics next-generation sequencing (mNGS). The mNGS of lung biopsy reported *Streptococcus intermedius*, *Senotrophomonas acidaminiphila*, *Citrobacter freundi*, and *Pseudomonas aeruginosa*, whereas the mNGS of oropharyngeal swab showed *Acinetobacter junii*, *Corynebacterium kroppenstedtii*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Sphingomonas paucimobilis* and *Rothia kristinae*. Microbiota analysis revealed that the most abundant microbiota in lung tissues and oropharyngeal swab was the *Streptococcus anginosus* group (SAG), including *S. intermedius*, *S. anginosus*, and *S. constellatus* (Fig. 3).

Four hours after lung biopsy, the patient developed hypoxia (SpO2: 78 %), followed by respiratory failure (arterial blood gases: PH 7.42, PO2 59 mmHg, PCO2 46 mmHg), heart rate of 106 beats/min, and hyperthermia (Tmax 39.5 °C), with hsCRP up to 80.72 mg/L and IL-6 up to 41.63 pg/mL. After careful history-inquiry, the patient disclosed that he had drink 400 ml of enteral nutritional powder within 5 minutes and then lay flat before the severe hypoxia. Mendelson syndrome, also known as "aspiration pneumonitis", was suspected. A repeat chest CT showed more consolidation in the bilateral lower lobe, new ground glass density shadows in the upper lobe of the left lung, the apical segment of the upper lobe and the dorsal segment of the lower lobe of the right lung, and a small amount of pleural effusion in the left lung (Fig. 1D–F). Subsequently, antibiotics escalation to meropenem (1g, q8h, po) for 10 days and then changed to meropenem (0.5g, q8h, po) for 4 days. He received non-invasive mechanical ventilation for 23 minutes, and then switched to high-flow oxygen inhalation due to intolerance. 10 days after, the patient exhibited gradual improvement with absorption of the ground glass opacities in the bilateral lung fields (Fig. 1G–I). On the 20th day of admission, the patient underwent percutaneous endoscopic gastrostomy and discharged 6 days later. In the 12-month follow-up, the patient did not develop any aspiration-related

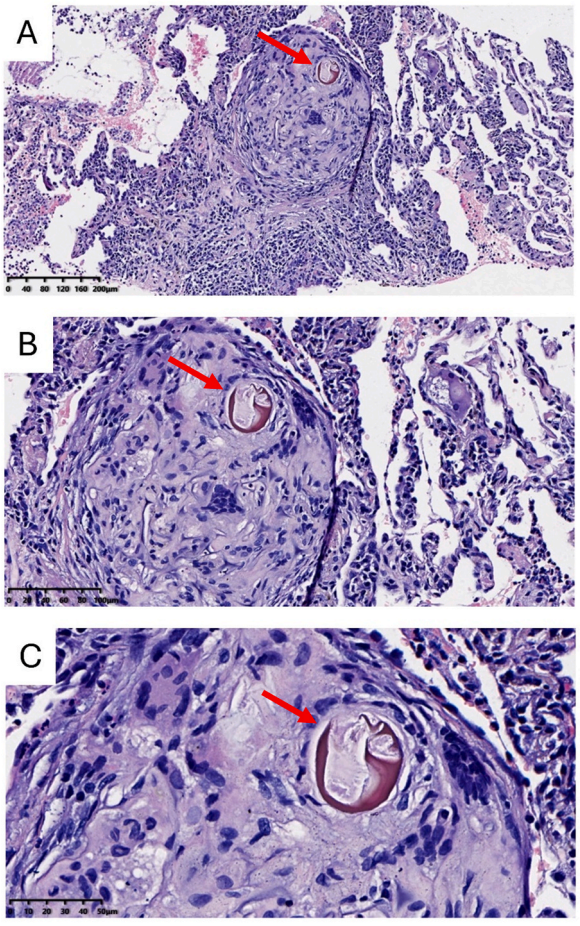

Fig. 2. Histologic examination of lung tissue. The hematoxylin and eosin (H&E) stain showed granulomatous inflammation embedded with foreign bodies and secondary organizing pneumonia (A 40X, B 100X, C 400X). The location of the foreign body is indicated by an arrow.

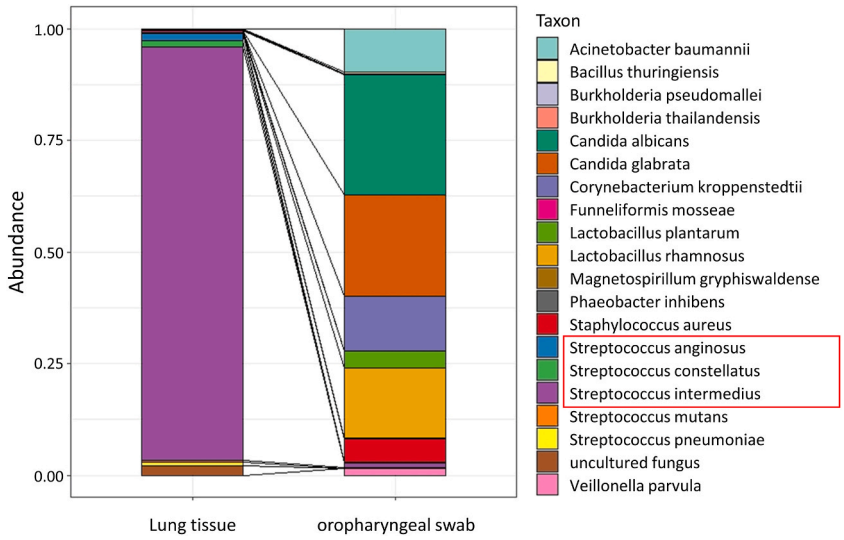

Fig. 3. Microbiota analysis in lung tissue and oropharyngeal swab. Microbiota analysis revealed that the most abundant microbiota in lung tissues and oropharyngeal swab was the *Streptococcus anginosus* group (SAG), including *S. intermedius*, *S. anginosus*, and *S. constellatus*.

pulmonary syndrome.

3. Discussion

The current study described a chronic and acute phase of aspiration-related syndrome in a 68-year-old man with silent and obvious aspiration events. Currently, there is still a lack of clinical practice guidelines for the diagnosis and management of aspiration-related lung disease. In most cases, diagnosis presumptively relies on characteristic clinical histories, risk factors, and radiologic findings. However, aspiration was suspected clinically in only 9 % of patients in whom aspiration was confirmed on lung biopsy [7]. Aspiration-related lung disorders are associated with a wide spectrum of radiologic phenotypes, such as bronchiolitis, patchy consolidation, mass, atelectasis, centrilobular nodules, and patchy ground-glass opacities [3]. Aspiration is usually not considered in the differential diagnosis of patients presenting with mass-like abnormalities on chest CT. However, our patient was diagnosed with aspiration-related lung disease as the pulmonary granulomas caused by foreign bodies entering the lungs. The manifestations of peripheral airways and lung parenchyma damage caused by chronic and acute aspiration were revealed by chest CT and histopathological examination. It may alert the clinicians and radiologists to consider aspiration in the differential diagnosis of patients presenting with worrisome nodules/masses on chest imaging, especially in patients with predisposing factors.

A granuloma is a conglomeration of multiple inflammatory cells [1]. Identifying the cause or disease association of granulomatous lesions is usually arduous due to the granulomatous lesions are lack of specificity unless the triggering factors can be ascertained within the granuloma or via culture. In the present study, histopathological examination showed pulmonary granulomas embedded with foreign bodies and secondary organizing pneumonia. Granuloma, a common finding of routine diagnostic pathology in lung biopsy to assess lung nodules, is most common seen in infectious diseases, especially mycobacteria and fungi. Certainly, it is crucial to exclude this possibility through culture, serology, and special staining, as was done in this study. This reaction may also be showed in vasculitides, immunologic diseases, Crohn's disease, and berylliosis [2,8].

In the present case, conventional microbiological tests failed to find responsible pathogens. Microbiota analysis of lung tissue and oropharyngeal swab based on mNGS data indicated the pathogenic role of SAG, including *S. intermedius*, *S. anginosus* and *S. constellatus*, are normal flora of the oropharynx, gastrointestinal and urogenital tract [6,9]. It has been reported that SAG bacteremia is associated with a higher risk of developing infections, ranging from mild (e.g., sinusitis and dental abscesses) to severe involving the head and neck regions, lungs, abdomen, and soft tissues infections [10]. *S. intermedius* predominantly impacts the head and neck, respiratory tract, and central nervous system, exhibiting a proclivity for abscess formation and deep tissue infections [11]. In the context of lung infections, the prevailing clinical manifestations attributable to *S. intermedius* encompass fever, cough, chest pain, and dyspnea [12]. Several mechanisms for *S. intermedius* infection have been postulated, with the aspiration of oropharyngeal secretions being of notable significance. Risk factors associated with *S. intermedius* infection encompass age, male, periodontal disease, chronic obstructive pulmonary disease, and diabetes mellitus, consistent with our observations [12,13]. There is no doubt regarding the involvement of SAG in the pathogenesis of lung disease. The treatment regimen should encompass aforementioned pathogens and empirically select amoxicillin clavulanic acid, ampicillin sulbactam, fluoroquinolones, and carbapenems according to the severity of the condition. Furthermore, ceftriaxone and levofloxacin are the prevailing empirical antibiotics employed for treating *S. intermedius* lung infections [12]. In this case, prior to obtaining the results of lung tissue mNGS, the patient had started cefoperazone-sulbactam therapy. Cefoperazone, a third-generation cephalosporin antibiotic, exhibits significant antimicrobial activity against cocci.

However, the detection of SAG in routine clinical examinations poses a challenge. Conventional cultures usually underestimate the pathogenic impact of these causative pathogens [14]. mNGS, a hypothesis-free, unbiased, culture-independent, high-throughput sequencing technology, exhibits the capability to concurrently detect all potential pathogens (including bacteria, fungi, viruses, and parasites) within a sample, particularly those of rare or unknown microorganism [15]. The samples employed for mNGS analysis are flexible, including BALF, peripheral blood, pleural effusion, respiratory secretions, cerebrospinal fluid, tissue, etc. In this case, conventional microbiological tests, immunological tests, and PCR test were all negative, while mNGS results supplied the evidence of SAG. Furthermore, the patient has had multiple positive results for G test and GM test. BALF mNGS did not find any fungus, and both the fungal smear and culture of the BALF were negative. Based on these examination results, the positive serum and BALF GM tests were suspected due to the aspiration of inhaled materials into the lungs, with no active fungal infection present. Our findings suggest that mNGS serves as a valuable adjunct to conventional culture techniques, offering a precise diagnostic approach to identify pathogens lacking typical characteristics. The clinical metagenomics enables more precise treatment strategies and holds the potential to improve clinical outcomes.

The clinical symptoms of aspiration generally depend on the frequency, size, volume, and characteristic of aspirated substances [16]. Hypoxemia with dyspnea is commonly associated with acute macroaspiration with acute lung damage and diffuse alveolar injury. The lung damage may be attribute to the toxic effects of hydrochloric acid on alveolar cells rather than aspirated foreign matters. Ground-glass opacities is a frequent radiological pattern of diffuse alveolar injury, as described in this case [17]. It is an inflammatory reaction that has been labeled as Mendelson syndrome, also known as aspiration pneumonitis. The treatment of aspiration pneumonitis has not markedly altered since Mendelsohn first described it in the 1950s [16]. Clinical management is supportive and includes suction to clear the airway, oxygen to correct hypoxemia, and mechanical ventilation support if necessary [5]. It has been recommended that routine antibiotics are not necessary unless patients are taking acid-suppressing drugs [5]. In this case, the patient was immunosuppressed and had gastroesophageal reflux disease. He's being treated with omeprazole. In addition, cefoperazone treatment is not effective and the antibiotic escalation to meropenem.

This study highlighted the precise diagnosis of chronic and acute phase of aspiration-related syndrome through comprehensive analysis of clinical, radiological, pathological, and microbiological evidence. It may alert the clinicians and radiologists to consider aspiration in the differential diagnosis of patients presenting with worrisome nodules/masses on chest imaging, especially in patients with predisposing factors. Moreover, the utilization of mNGS provides a clinically actionable diagnostic method that holds the potential to yield improved clinical outcomes by identifying the causative pathogens.

Ethics statement

This study protocol was reviewed and approved by the Ethics Committee of Peking University First Hospital (approval number 2021-124). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Data availability statement

All relevant data has been presented in the manuscript and further inquiry can be directed to the corresponding author.

CRediT authorship contribution statement

Hui Xu: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Ruixue Zhang:** Investigation, Formal analysis, Data curation. **Xiaoxue Zhang:** Investigation, Formal analysis, Data curation. **He Wang:** Writing – review & editing, Data curation. **Yan Xiong:** Writing – review & editing, Data curation. **Bo Zheng:** Writing – review & editing, Data curation. **Zhi Zhang:** Writing – review & editing, Investigation, Funding acquisition. **Lianjun Lin:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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