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CASE REPORT

Organizing Pneumonia with NGS False-Positive Imaging Resembling Tuberculosis: a Case Report

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SUMMARY

Background: **Organizing pneumonia (OP) is a pathologic concept characterized by the formation of granulation tissue from fibroblasts, myofibroblasts, collagen, and fibrotic exudate in the respiratory fine bronchi, alveolar ducts, and alveoli. The clinical imaging of mechanized pneumonia is variable, and histopathological examination is required to clarify the nature of the lesion when imaging is atypical. We report a case of OP with imaging resemblance to pulmonary tuberculosis and false-positive next-generation sequencing (NGS), which was first misdiagnosed as pulmonary tuberculosis.**

Methods: **Appropriate laboratory tests, alveolar lavage fluid NGS, chest CT, bronchoscopy, percutaneous lung puncture, pathology.**

Results: **Chest CT showed a nodular high-density shadow in the lower lobe of the right lung. According to the chest CT, bronchoalveolar lavage was performed in the dorsal segment of the right lower lobe of the lung. NGS of lavage fluid: the sequence number of Moraxella osseae was 1,423; the sequence number of Prevotella melanogaster was 1,129. Based on lung histopathology, fibrous emboli and necrotic material were seen in the alveolar lumen, and the final diagnosis of the OP was confirmed.**

Conclusions: **It should be noted that physicians should not blindly believe the NGS result report. When the diagnosis is not clear and anti-infection treatment is ineffective, lung tissue should be obtained promptly for pathological examination to obtain pathological evidence to differentiate from misdiagnosed diseases.**

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KEYWORDS

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CASE REPORT

The patient was an elderly female, 66 years old, who was admitted to the hospital on 2022-02-24 with the main cause of chronic cough and coughing of large amounts of white pus sputum for 7 years with 7 days of aggravation. The patient had a history of pneumonia as a child that was not cured. Seven years ago, she began to have a cough and cough with large amounts of white pus sputum, which was especially aggravated in the morning and reduced during the day and night, without medication. She took moxifloxacin at home for 3 days

(the exact dosage is not known), but the effect was not good. Today, she came to our hospital for further diagnosis and treatment, and on 2022-01-30, we checked the chest CT: (Figure 1A - B): nodule-like high-density shadow and striated shadow in the lower lobe of the right lung with unclear borders, and inflammatory lesions were considered. History: previous "iliac fossa abscess surgery" for lumbar spine tuberculosis for more than 30 years; "hypothyroidism" for more than 5 years, treated with oral eugenol 42.5 μg/day; self-reported "coronary heart disease". She has a history of "coronary heart disease" for more than 5 years and usually takes 1 bag of heart-raising pellets 3/day and 1 tablet of coenzyme Q10 3/day for treatment; denies any history of hypertension or diabetes. Physical examination: T36. 1°C, P80 times/minute, R19 times/minute, BP114/81 mmHg, normal face, no congestion in the pharynx, scattered wet rales could be heard in the right lung, no significant abnormalities on cardiac and abdominal examination, negative hepatic jugular venous reflux sign, no edema in both lower limbs. The blood count: white blood cells [WBC] 2.3 x 10^9/L, neutrophils [NEU] 0.99 x 10^9/L, lymphocytes [LYM] 0.85 x 10^9/L, blood cell classification: red blood cells, platelets morphology did not show significant changes. C-reactive protein (C-reactive protein, CRP), calcitoninogen and sedimentation were normal. Serum Aspergillus-specific antigen test (GM test): (-). Sputum general bacterial culture and identification: Haemophilus parainfluenzae +, Neisseria desiccation +, Streptococcus streptococcus +++; sputum fungal culture and identification: no fungal growth in culture for 7 days.

On 2022-03-01, a bronchoscopy was performed under general anesthesia. Pathology of right lower lung lavage fluid: columnar epithelial cells, histiocytes, and lymphocytes were found in the specimen sent for examination, and no clear malignant components were seen; pathology of right lower lung clamp examination: no clear malignant components were seen. Cytological analysis of lavage fluid: a small number of erythrocytes, a small number of lobulated granulocytes, reticuloendothelial cells and lymphocytes were seen in lavage fluid. Next-generation sequencing (NGS) of microorganisms in the lavage fluid: the sequence number of Moraxella osseae was 1,423; the sequence number of Prevotella melanogaster was 1,129 (Figure 3E); the lavage fluid was negative for X-Pert.

After a combination of NGS results, piperacillin-tazobactam sodium 4.5 g IV 2/day and bromhexine 4 mg IV 2/day were given to resolve sputum, etc. On 2022-03-07, the chest CT was repeated and compared with the initial chest CT, which showed no significant changes in the nodular hyperdense shadow and striae in the right lower lobe of the lung. However, the patient was discharged with improved symptoms. After discharge, she continued to use clindamycin palmitate dispersible tablets 150 mg orally 3/day for anti-infection treatment for 1 month.

On 2022-05-01, a comparison of the chest CT at our outpatient clinic with the initial chest CT on 2022-01-30 suggested (Figure 2C - D) that the nodular hyperdense shadow in the lower lobe of the right lung was more than before, and the striated shadow was slightly more than before, considering that the inflammatory lesion was more progressive than before. The patient was admitted to our department for further treatment. The patient was admitted to our department for further treatment. The adjuvant examination: white blood cell [WBC] 2.9 x 10^9/L, neutrophil [NEU] 1.67 x 10^9/L, lymphocyte [LYM] 1.06 x 10^9/L, CRP 3.2 mg/L, hematocrit 31 mm/ht, microbial rapid dynamic test: G-lipopolysaccharide < 5 pg/mL, 1-3-beta-D glucan < 10 pg/mL, blood cell classification: white blood cells, red blood cells, platelet morphology did not show significant changes. Sputum culture: Klebsiella pneumonia subsp. pneumonia, Haemophilus parainfluenzae +, Neisseria desiccation +, Streptococcus straw green +++. Considering that the patient's inflammatory lesion was more progressive than before, a CT-guided lung tissue puncture was performed on 2022-05-06. Lung tissue NGS did not detect pathogenic bacteria; lung tissue X-pert was negative. The patient's tuberculin test (Purified protein derivative, PPD): (-) and T-cell assay for TB infection was negative. Histopathology of right lung puncture (Figure 4F - G): lung tissue was sent for examination, and fibrous emboli and necrotic material were seen in the alveolar cavity, considering organizing pneumonia. Special staining results: antacid stain (-), hexamine silver (-), and periodic acid-Schiff stain (PAS) (-). Combined with the histopathological findings of the lung puncture, the diagnosis was revised: organizing pneumonia. The patient had a history of lumbar spine tuberculosis for many years and old tuberculosis foci in the lung and mediastinum were considered on chest CT imaging. Rifampin 0.6 g orally 1/day, isoniazid 0.3 g orally 1/day, pyrazinamide 0.5 g orally 3/day were applied as prophylactic anti-tuberculosis treatment, and methylprednisolone sodium succinate 40 mg intravenously 1/day was added. After 7 days of combined treatment with the above drugs, the chest CT was repeated on 2022-05-19 compared with that on 2022-05-01 (Figure 5H - I): nodule-like high-density shadow and striae shadow in the lower lobe of the right lung was reduced, and the inflammatory lesion was considered to be absorbed more than before. After discharge from the hospital, oral prednisone treatment was continued based on preventive anti-tuberculosis treatment. At follow-up, the patient's symptoms improved significantly and the lesion was significantly more resorbed than before.

DISCUSSION

Microbial next-generation sequencing (NGS) technology is the use of high-throughput sequencing technology and bioinformatics analysis of all pathogens in a sample, independently of the pure culture of microorgan-

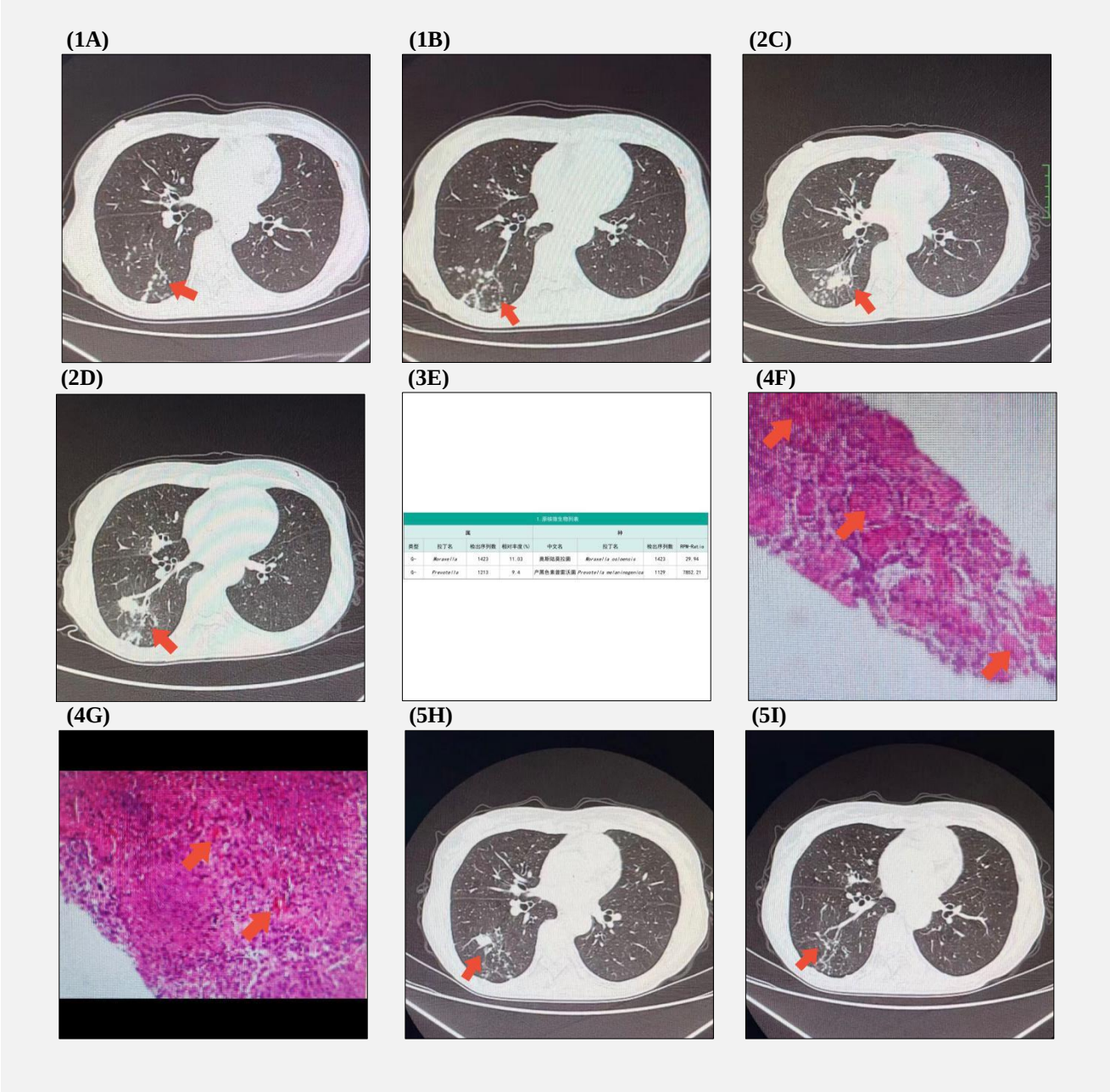

Figure 1. The patient's 2022-01-30 chest CT findings: nodule-like high-density shadow and striae shadow in the lower lobe of the right lung with unclear borders, considering inflammatory lesions (Figure 1A - B). Figure 2. Right lower lobe of the lung nodular-like high-density shadow increased more than before, and the striated shadow increased slightly more than before, considering inflammatory lesions progressed more than before (Figure 2C - D). Figure 3E. Alveolar lavage fluid NGS results suggesting Moraxella oxytoca sequence number 1,423; Prevotella melanogaster sequence number 1,129. Figure 4. Lung tissue sent for examination suggested that fibrous emboli and necrotic material were seen in the alveolar cavity (Figure 4F - G). Figure 5. Nodular hyperdense shadow and striae shadow in the lower lobe of the right lung were reduced compared with the previous one, considering the inflammatory lesion was absorbed compared with the previous one (Figure 5H - I).

isms [1]. It can obtain all microbial information in a sample efficiently, rapidly, and accurately. However, several studies reported that even though NGS has a specificity of 98% for detecting Mycobacterium tuberculosis [2], it may also detect colonized or non-pathogenic microorganisms, and there are problems with operational procedures and complex data analysis leading to false-positive results [3,4]. In this case, the NGS test of alveolar lavage fluid by fiberoptic bronchoscopy result showed Moraxella oxytoca with a sequence number

of 1,423 and Prevotella melanogaster with a sequence number of 1,129, and the patient was negative for PPD and T-cell test for tuberculosis infection, which did not exclude false negative or positive lagging test results. Initially, anti-infective treatment was tentatively given according to NGS results, and the patient showed significant improvement in clinical symptoms, but the inflammation on chest imaging was more progressive than before on review. The patient was considered to have a specific pathogenic bacterial infection or non-infectious factors and was given a CT-guided lung aspiration biopsy for pathological examination, and finally the diagnosis of organizing pneumonia was confirmed by the lung histopathological results, which resolved after 1 week of glucocorticoid treatment.

Typical pulmonary tuberculosis can be diagnosed by clinical manifestations (afternoon fever, night sweats, hemoptysis, cough, sputum, chest pain, wasting, etc.), positive antacid bacillus examination, and pulmonary imaging. However, due to the increasing drug resistance of Mycobacterium tuberculosis, atypical clinical manifestations, "different images with the same disease" or "different disease with the same image" in chest imaging, and low positive rate of routine sputum bacteriological examination, the confirmation rate is still low, resulting in a high misdiagnosis rate of pulmonary tuberculosis [5,6]. The imaging features of typical pulmonary tuberculosis are "three more", i.e., multifocal, polymorphic, and calcified, and "three less", i.e., fewer masses, less accumulation, and less enhancement. As a type of tuberculosis, atypical pulmonary tuberculosis has atypical imaging and clinical symptoms, and no antacid bacilli can be found temporarily in laboratory tests [7,8]. In this case, the chest CT showed progressive pulmonary solid lesions in the dorsal and posterior basal segments of the lower lobe of the right lung, which showed multiple nodular foci, hairy glass-like with exudative shadows. In combination with the previous history of "lumbar spine tuberculosis", it was initially considered that there was a possibility of recurrence of tuberculosis, which could be misdiagnosed as pulmonary tuberculosis.

OP is a pathological concept in which fine bronchi, alveolar ducts, and alveolar cavities are seen to be composed of polyps of loose connective tissue encapsulating fibroblasts, budding granulation tissue that can continue from one alveolus to adjacent alveoli through Cohn's foramen. The lesions are centered in the small airways and extend distally [9,10]. In 2002, the American Thoracic Society/European Society of Respiratory Diseases proposed to classify OP as Cryptogenic Organizing Pneumonia (COP) and or Secondary Organizing Pneumonia (SOP) [11]. Once pathology defines OP, the causative underlying cause needs to be clarified. SOP can be caused by infection, connective tissue disease, malignancy, drugs, inflammatory bowel disease, solid organ transplantation, radiotherapy, inhalational injury, etc. [9,12]. After a thorough and detailed examination, COP can be diagnosed if no underlying cause of the disease is found. Existing studies have concluded that infection is the most common secondary cause of SOP. In a study by Melloni et al., 57% of patients with SOP had a history of recurrent respiratory tract infections [13]. Other causes that can cause SOP are tuberculosis [14,15], tumors, etc.

CONCLUSION

The lessons we learned from the patient's case are: (1) NGS technology is a technique that can accurately and efficiently capture all microbial information in a sample, which is beneficial for determining infection by rare pathogens in the lung and for accurate diagnosis and prognosis. However, its use in clinical practice is not a panacea, and many problems need to be solved. For example, the airway is an open channel, so alveolar lavage fluid specimens are not sterile body fluid specimens, and many colonized bacteria are often present in the specimens, so not all detected bacteria require interventional treatment. Secondly, NGS is performed by directly extracting all nucleic acid substances from the sample, and both live and dead bacteria can be detected. Clinicians need to consider whether the pathogenic bacteria need to be treated in conjunction with the patient's clinical symptoms and relevant tests and imaging results. If the diagnosis is not clear and anti-infection treatment is ineffective, lung tissue should be obtained for pathological examination in time to obtain pathological evidence to differentiate the disease from misdiagnosis and reduce the patient's pain and economic pressure.

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Ethical Approval:
This study was approved by the ethics committee of North China University of Science and Technology Affiliated Hospital. All procedures performed in the studies were in accordance with the ethical standards. Informed consent was obtained.

Declaration of Interest:
No conflicts of interest.

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