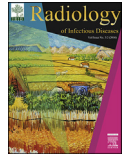


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Review

Clinical and imaging features of COVID-19

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Abstract

Since December 2019, multiple cases of 2019 coronavirus disease (COVID-19) have been reported in Wuhan in China's Hubei Province, a disease which has subsequently spread rapidly across the entire country. Highly infectious, COVID-19 has numerous transmission channels and humans are highly susceptible to infection. The main clinical symptoms of COVID-19 are fever, fatigue, and a dry cough. Laboratory examination in the early stage of the disease shows a normal or decreased white blood cell count, and a decreased lymphocyte count. While CT examination serves as the screening and diagnostic basis for COVID-19, its accuracy is limited. The nucleic acid testing is the gold standard for the diagnosis of COVID-19, but has a low sensitivity is low. There is clearly a divide between the two means of examination. This paper reviews the published literature, guidelines and consensus, and summarizes the clinical and imaging characteristics of COVID-19, in order to provide a reliable basis for early diagnosis and treatment.

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Keywords: Novel coronavirus; Coronavirus disease 2019; Clinical features; Image features

1. Introduction

Since December 2019, multiple cases of unexplained pneumonia have been reported in Wuhan, in China's Hubei Province. As the disease has spread, cases of COVID-19 have also been found across the whole of China and overseas. Nucleic acid detection of a patient's respiratory secretions identified the source of infection to be a new type of coronavirus, which was been defined as 2019 novel coronavirus (2019-nCoV) [1]. On 11 February 2020, the WHO officially named the disease caused by the novel coronavirus (2019-nCoV) as Coronavirus Disease 2019 (COVID-19) [2]. On February 22, 2020, China's National Health Commission announced the designation of the new coronavirus pneumonia

as Coronavirus disease. The disease is a new type B infectious disease (in accordance with the class A management, Infectious Disease Prevention and Control Law). Although there is considerable overlap between imaging manifestations of different viral pneumonia, comprehensive analysis of clinical features, epidemiology and laboratory examination results are of significance in improving the diagnosis of COVID-19.

2. Etiology and epidemiology

Coronaviruses form a large RNA virus family. The surface of virus particles is covered in many spines, and the virus particles as a whole resemble a crown, which is the origin of the name "coronavirus". Six subtypes have been found; of these, four are less pathogenic and generally lead to mild symptoms after infection; two subtypes can cause severe infections. The novel coronavirus is a new-type coronavirus that has not been previously been found in humans being. It is now considered to be a seventh subtype, but its genes have more than 85% homology with a SARS-like virus in bats. It has

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been speculated that the pathogenic mechanism of the virus may be that because the 2019-nCoV receptor and SARS-CoV receptor binding region (RBD) structure domain between the amino acid sequence and the prediction of protein structure are highly similar, 2019-nCoV can effectively use angiotensin-converting enzyme 2(ACE2) on alveolar type II epithelial cells as the receptor to invade cells, thus entering the bronchial epithelial cells to replicate and cause disease [3,4].

Current epidemiological investigations show the incubation period of COVID-19 to range from one to fourteen days, and in most cases to be three to seven days. The main source of infection is patients infected with the novel coronavirus infection. Patients with asymptomatic infection (incubation period) can also be a source of infection. Infection is mainly spread by respiratory droplets and contact. Exposed mucus membranes and unprotected eyes increase the risk of infection, and the detection of the virus in stool and urine samples from patients also suggests the possibility of fecal-oral transmission. There is a possibility of aerosol transmission under the condition of prolonged exposure to high concentrations of aerosols in a relatively closed environment [5–7]. At present, there are no reports of vertical transmission from mother to child.

3. Clinical and imaging

COVID-19 lacks specificity in both clinical manifestations and laboratory tests. The main clinical manifestations of the disease are fever, fatigue, and a dry cough, and in severe cases, multiple organ failure [7–9]. Its atypical symptoms may include myalgia and diarrhea. Laboratory tests have shown that the total number of white blood cells in early peripheral blood is normal or has decreased, and the lymphocyte count has progressively decreased; C-reactive protein and serum sedimentation rates were increased in most patients [7–9]. COVID-19 was confirmed by viral nucleic acid detection with strong specificity and poor sensitivity [10]. In order to improve the rate of positive nucleic acid detection, it is recommended to retain sputum and lower respiratory secretions as far as possible and promptly submit them for examination [7]. CT examination serves as the screening and diagnostic basis for COVID-19: chest imaging in the early stage shows multiple plaque shadows and interstitial changes, mostly seen in the peripheral lung and subpleural, and then developed into multiple ground glass shadows and infiltration shadows in both lungs. In severe cases, lung consolidation can occur, presenting as “white lung”, with rare pleural effusion and mediastinal lymph node enlargement [6,7].

4. Image features and staging

Since the outbreak of the COVID-19 epidemic in December 2019, the “Diagnosis and Treatment Scheme for Coronavirus Disease (Trial Version 5)” [6] recommended that suspected cases with pulmonary imaging characteristics be included for the first time in “clinical diagnosis” in Hubei Province. Pulmonary imaging is mainly performed by chest CT (particularly HRCT), supplemented by X-ray chest radiographs

[10,11]. CT examination is the main screening and diagnosis basis for COVID-19. The image changes basically reflect the inflammatory pathological process of lung tissue-exudation, proliferation, and metamorphism [12].

4.1. Image features

4.1.1. Ground-glass opacity (GGO)

GGO is a slightly higher density blurred image in the lungs, where the pulmonary blood vessels are visible. The pathological change of GGO is that the virus invades the bronchioles and alveolar epithelium, and replicates in the epithelial cells, causing the alveolar cavity to leak, and the alveolar wall or the alveolar space to become inflamed or thickened, with a distribution mainly around the lung and under the pleura [13,14].

4.1.2. Consolidation and air bronchi sign

As inflammation progresses, there is extensive involvement of alveoli and mucosal ulcers, followed by consolidation; when the body reacts strongly as to an inflammatory storm, large exudation occurs in the alveoli of both lungs, showing a “white lung” performance. Air bronchus sign refers to the phenomenon of dendritic low-density shadowing of air-containing bronchus in the consolidation of lung tissue, which is more common in the progress of the disease. The pathological basis is that the pathogen invades epithelial cells, causing inflammatory thickening and swelling of the bronchial wall, but without obstructing the bronchioles [15].

4.1.3. Paving stone sign

On high-resolution CT, the lobular interval thickening and interlobular interval line shadows are superimposed on a ground glass-like opaque background. They are called paving stones due to the resemblance of the forms to irregularly shaped paving stones. The pathological changes are lobular intervals and interlobular interstitial thickening, suggesting interstitial changes.

4.1.4. Fibrous lesions

During repair and healing of chronic inflammation or hyperplasia of the lung, fibrous components gradually replace the normal cellular components to form scars. Fibrous lesions can cause distracted bronchi or bronchiectasis and distorted travel.

4.1.5. Vascular thickening

Thickening vessels can be seen at the edge or the center of the lesion, and are observable at various stages of the disease.

4.1.6. Halo sign

The density of the lesion is slightly higher at the center and slightly lower at the edges. A thin circle of cloud-like ground glass shadow, which varies in thickness and changes like a halo surrounds the lesion. Pathological changes may be virus replication in epithelial cells [16].

4.2. Image staging and clinical typing

In “Diagnosis and Treatment Scheme for Coronavirus Disease (Trial Version 6)”, infection is classified according to its clinical symptoms and imaging manifestations [7]. There is a one-to-one correspondence between the imaging stage (early, advanced, and severe) and clinical classification (mild, general, and severe) in most patients with COVID-19. ① Early-stage and mild type (mild patients have mild clinical symptoms and no significant imaging findings such as pneumonia performance). ② Progressive stage and common type (general type patients have fever, respiratory tract symptoms, and imaging shows pneumonia). ③ Severe stage and severe type (Patients with shortness of breath and hypoxemia. The images mainly show diffuse lung lesions, some of which manifest “white lung” changes; the range of lesions within 24–48 h significantly progresses >50% [7]). There are, however, some cases which do not comply to the above one-to-one correspondence. ① Some cases have obvious imaging manifestations, but the clinical symptoms are atypical (Fig. 1). Among the close-contact cases diagnosed through screening as having COVID-19, most patients had no obvious clinical symptoms at the initial diagnosis, and the corresponding clinical symptoms appeared after a period of time; a few patients showed no obvious clinical symptoms for a long period, with the infection becoming “invisible”. However, the images of the above cases did show pneumonia at the time of screening, the signs of which were mainly ground glass and patchy shadows under the pleura or outside the lungs [17,18]. ② The clinical manifestations of some cases are typical, and no obvious manifestations of pneumonia were found on imaging examination (Fig. 2). This may relate to the virus being mainly located in the upper respiratory tract and not causing exudative lesions in the lung. Such patients should be diagnosed, isolated, and treated early to prevent transmission of the virus. ③ In some cases, the clinical symptoms are relieved, and the imaging manifestations have progressed (Fig. 3) [19]. The mismatch between clinical and imaging manifestations becomes a difficult problem for COVID-19 diagnosis. Therefore, comprehensive analysis of clinical data, epidemiology

and imaging performance is more helpful for the diagnosis of COVID-19.

4.3. Image expression is differentiated from nucleic acid detection

The gold standard for diagnosis of COVID-19 is a positive nucleic acid test with high specificity, and a low sensitivity of 30–50% [20]. It is common in clinical work to find that clinical and imaging findings support the diagnosis of COVID-19 while multiple consecutive nucleic acid tests are negative (Fig. 4). It has been reported that up to eight nucleic acid tests have been negative in infected patients before COVID-19 was finally diagnosed. Over-reliance on nucleic acid tests may lead to the misdiagnosis of patients who do in fact have COVID-19. This is not conducive to the control of the epidemic. Preliminary data from a designated virus hospital in Wuhan showed that the CT positive rate of clinically highly suspected cases was $\geq 90\%$, while the positive rate of nucleic acid tests was about 40%. This is due to the many factors which affect the nucleic acid test such as the course of infection, viral load, sampling method, detection reagents, and interpretation standards. Reagents in particular greatly affect the detection effect [21]. Therefore, nucleic acid test cannot be a factor in restricting the accurate diagnosis and treatment of diseases. The director of the radiology department of a hospital in Wuhan strongly recommends CT scan as the main diagnostic and screening basis for COVID-19. The “Diagnosis and Treatment Scheme for Coronavirus Disease (Trial Version 5)” [6] specifically formulated clinical diagnosis standards for patients in Hubei Province, and defined suspected cases with pneumonia imaging manifestations as “clinical diagnostic cases”, which reduced the risk of further spread.

With the exception of the above cases, some mild cases had no obvious imaging changes of pneumonia, but the nucleic acid test was negative (Fig. 5). The use of imaging pneumonia as a prerequisite for the diagnosis of COVID-19 may lead to clinicians focusing solely on patients with pneumonia and missing the diagnosis of infected patients who show no changes in pneumonia. The “Diagnosis and Treatment Scheme for Coronavirus Disease (Trial Version 4)” stipulates that [22]

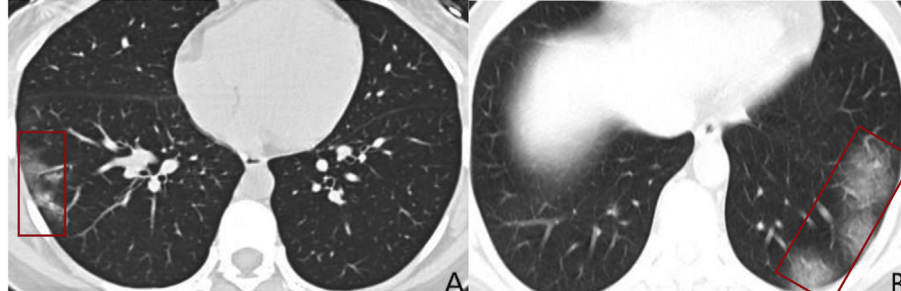


Fig. 1. Female patient, 30 years old, clinical symptoms are not typical, CT examination (A, B); image shows ground-glass exudation in both lungs (see the red frame).

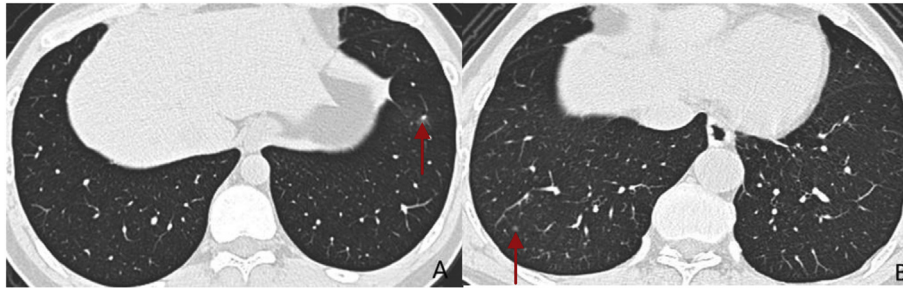


Fig. 2. Male patient, 23 years old; Clinical manifestations of fever, dry cough for 5 days, and fatigue for 2 days; relevant contact history; CT examination (A, B); no obvious signs of pneumonia were seen in either lung (see the red frame).

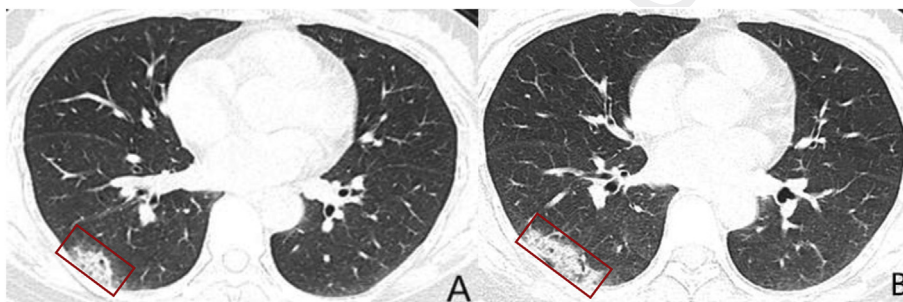


Fig. 3. Female patient, 38 years old, first examination (A); image shows solitary consolidative peripheral opacities with ground-glass density in right lower lobe; after 2 days (B); image shows progressive consolidative peripheral opacities in right lower lobe (see the red frame).

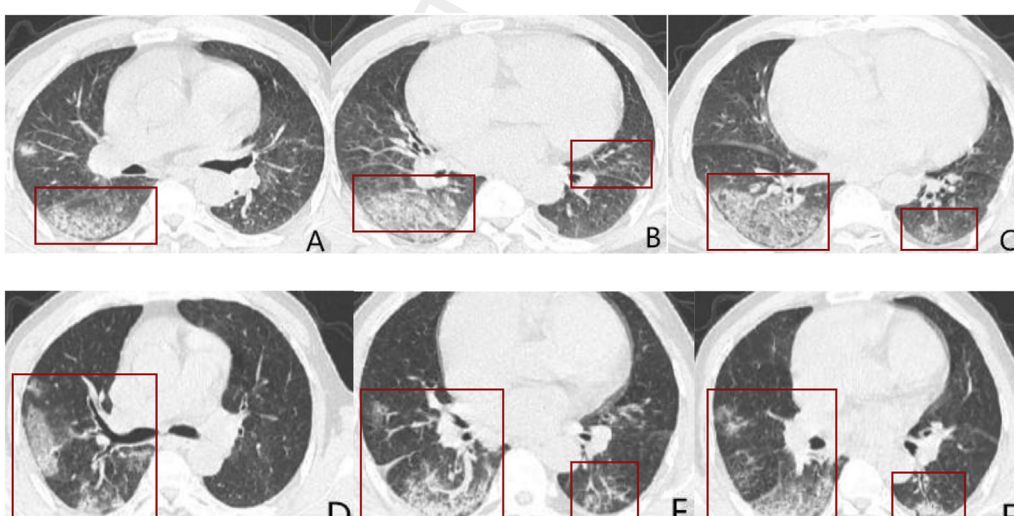


Fig. 4. Male patient, 60 years old, first examination (A–C); multiple exudative lesions in both lungs; the nucleic acid test was negative. Five days later (D–F); exudative lesions of both lungs, with a few lines of shadow; the nucleic acid test was positive. (With thanks to the First Affiliated Hospital of Xi'an Jiaotong University for providing this case) (see the red frame).

a patient who meets any one of the epidemiological history criteria and any two of the clinical manifestations can be included in suspected cases, and that an etiological test then be conducted. Such an approach is conducive to the detection of patients with COVID-19 [6,7].

4.4. Diagnostic value of imaging in COVID-19

Chest radiographs are suitable for primary hospitals which do not have CT machines, and for the bedside examination of critically ill patients. CT tomography, especially high-

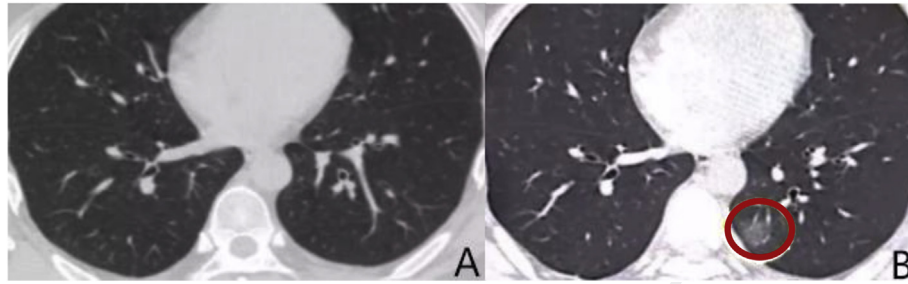


Fig. 5. Male patient, 44 years old, first examination (A); no obvious abnormality was found in both lungs; the nucleic acid test was positive. After 4 days (B); ground-glass exudation of left lower lobe. (With thanks to the First Affiliated Hospital of Xi'an Jiaotong University for providing this case) (see the red frame).

resolution CT, has no overlapping structural interference and can detect small lesions early. The value of a CT scan for COVID-19 lies in it being: the key technology for detecting the presence of lesions in the lungs; the important basis for the diagnosis and differential diagnosis of COVID-19; detecting important warning signals for patients with negative virus nucleic acid test; an important means to monitor COVID-19 treatment outcome (progression, stability, absorption); an early detection of other complications; the best follow-up method for patients following discharge [23]. As mentioned above, the CT scan occupies an important position in the diagnosis of COVID-19; in clinical work, however, we must perform CT examinations without affecting the premise of diagnosis, and we must not over-examine. Therefore, based on the observation of existing cases and combined with clinical experience, we recommend the following CT examination time window: ① Newly diagnosed patients with typical clinical manifestations and positive nucleic acid tests, with a negative chest CT scan at the initial diagnosis, and a review of chest CT scan within 3–5 days; ② Clinical diagnosis cases with atypical clinical manifestations and viral pneumonia characteristics. In addition to repeated nucleic acid tests, a chest CT is recommended for 5–7 days; ③ Non-critical confirmed cases: a chest CT scan is recommended at 5–7 days [24].

5. Differential diagnosis of COVID-19

The differential diagnosis of COVID-19 in “Diagnosis and Treatment Scheme for Coronavirus Disease (Trial Version 6)” primarily includes [7]: the need to distinguish mild manifestations from other respiratory infections caused by other viruses such as influenza viruses, adenoviruses, respiratory syncytial virus and other known viral pneumonia and mycoplasma pneumoniae infections. They should also be distinguished from non-infectious diseases such as vasculitis, dermatomyositis, and organizing pneumonia.

5.1. Other viral pneumonia

The imaging manifestations of viral pneumonia were mainly pulmonary interstitial changes accompanied by alveolar wall edema, while the CT manifestations were GGO, with

consolidation, thickening of interlobular septa, mesenchymal shadow, central lobular nodules, tree buds, air retention, and fiber cable shadow. There is significant overlap between the imaging manifestations of different viral pneumonia, so the final diagnosis should be combined with clinical data, epidemiology and laboratory results. Diagnosis depends on the detection of etiology.

5.1.1. Influenza A virus (H1N1)

Unilateral or bilateral multiple GGO, with or without consolidation, located in the bronchovascular bundle or subpleural (Fig. 6) [25,26]. It is difficult to distinguish the image from the new type of coronavirus pneumonia. However, the early stage of the new coronavirus pneumonia can be manifested as a small ground glass density shadow, or a small flake of ground glass density shadow can be seen in the thickened blood vessel shadow. This may be helpful for the early identification of H1N1 lesions.

5.1.2. Adenovirus pneumonia

Common in children. Multifocal GGO in both lungs with patchy consolidation, present a multisegmental pulmonary distribution trend (Fig. 7). Atelectasis can occur in children. It can sometimes be difficult to distinguish it from bacterial pneumonia [25,26].

5.1.3. Human parainfluenza virus pneumonia

A common cause of seasonal respiratory infections. Imaging findings are varied, and include multiple peribronchial nodules, consolidation of GGO and aerated bronchi (Fig. 8) [25,26]. The central distribution of the lesion is different from the characteristic subpleural distribution of new coronavirus pneumonia.

5.1.4. Respiratory syncytial virus pneumonia

Common in infants, congenital defects, immunosuppression and chronic lung disease. The central lobular nodule is the most characteristic image, and its occurrence rate is up to 50% (Fig. 9), which can be distinguished from the new coronavirus pneumonia. In addition, air consolidation (35%), GGO (30%), and bronchial wall thickening (30%) are seen. It is distributed in the central or surrounding area of the lung and presented bilateral asymmetric distribution [25,26].

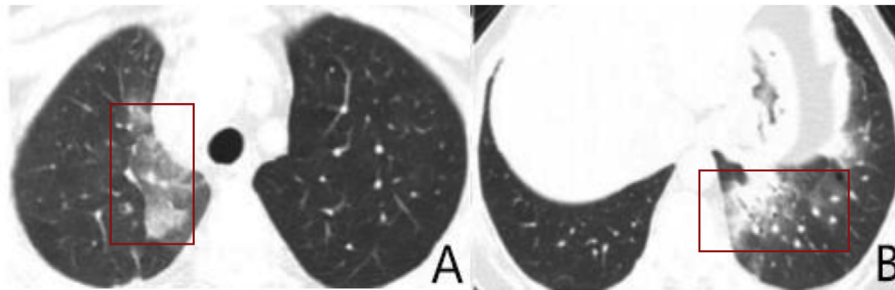


Fig. 6. Male patient, 17 years old, clinical manifestations of fever for 1 day, and dry cough for 3 days; no relevant contact history; CT examination (A, B); multiple exudates in both lungs; located in bronchovascular bundle or subpleural (see the red frame).

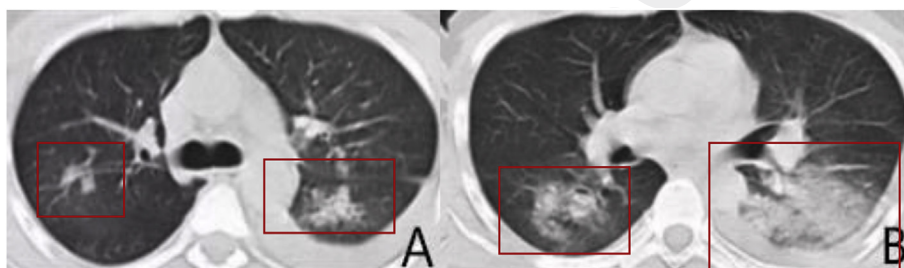


Fig. 7. Male patient, 23 years old, fever for 4 day, no relevant contact history; CT examination (A, B); multifocal GGO in both lungs with patchy consolidation, present a multisegmental pulmonary distribution trend; pleural effusion (see the red frame).

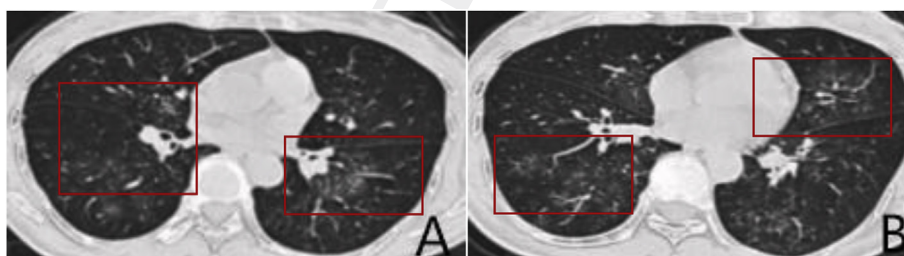


Fig. 8. Female patient, 37 years old, no relevant contact history; CT examination (A, B); multiple peribronchovascular nodules, consolidation of GGO, the distribution of lesions is different, mainly for the central nodules (see the red frame).

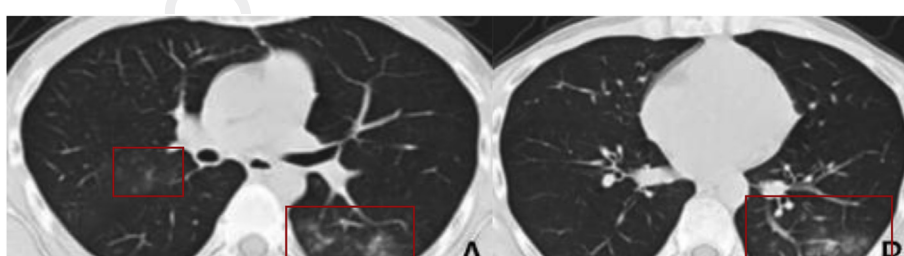


Fig. 9. Male patient, 25 years old, fever for 4 days, no relevant contact history; CT examination (A, B); central lobular nodule and GGO in both lungs, the distribution of lesions differs from that in COVID-19 (see the red frame).

5.2. Infectious pneumonia other than virus

5.2.1. *Mycoplasma pneumoniae*

Common in children and adolescents, image presenting as central lobular nodules, ground-glass opacity, consolidation, with thickening of bronchial wall, Bronchiole tree buds, hilar

and mediastinal lymph node enlargement [27]. Laboratory tests are positive for the mycoplasma antibody.

5.2.2. *Bacterial pneumonia*

There are no prodromal symptoms of upper respiratory tract infection, cough purulent sputum, bloody sputum or rust-

colored sputum, laboratory examination of increased white blood cell count, imaging features of single leaf segment or sub segment consolidation shadow. Treatment with antibiotics is good.

5.3. Non-infectious diseases

5.3.1. Mechanical pneumonia

Typical manifestations are bilateral subpleural patchy ground-glass opacity or consolidation, the air bronchi sign. In some lesions, the central ground-glass opacity, marginal ring or crescent shape consolidation presents an “anti-halo” sign, hilum and, mediastinal lymph node enlargement, as well as pleural effusion in a small number of cases [28].

5.3.2. Hypersensitivity Pneumonitis

Diffuse ground-glass opacities in both lungs. Central lobe nodules with fuzzy edges, mosaics perfusion and air retention in expiratory phase, lung field in chronic stage shows fine mesh shape shadow and stretch extension. The patient usually has a history of bird breeding or of occupational exposure [29].

5.3.3. Vasculitis

The manifestations are multiple nodules with cavitation, nodules connected to pulmonary vessels (nourishing vascular signs), halo or anti-halo signs, multiple consolidation, fiber cord shadow and ground glass density shadow diffuse distribution, the subpleural area is rare. It occurs mostly in the middle of the band with diffuse alveolar hemorrhage. Clinical manifestations can be hemoptysis, and pleural effusion is common [30]. A laboratory test of positive cANCA antibody is helpful in diagnosis.

6. Conclusion

COVID-19 is highly contagious and humans are generally susceptible to infection. While clinical and CT scans do share certain characteristics, there is some separation between a CT scan and a nucleic acid detection in some cases. Therefore, comprehensive analysis of the patient's epidemiological history, laboratory test results, clinical symptoms and imaging manifestations is necessary in order to effect early prevention, early detection, early diagnosis, early isolation, and early treatment.

Ethic statement

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

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