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Coronavirus-associated bronchiolitis in an immunocompetent adult with anti-glomerular basement membrane disease

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ABSTRACT

A 19-year-old male presented with a 1-month history of cough. Initial computed tomography scan of the chest demonstrated fairly diffuse centrilobular nodules with extensive tree-in-bud nodularity in both lungs. His nasopharyngeal sample for respiratory viruses was positive for coronavirus 229E by respiratory viral reverse-transcriptase polymerase chain reaction (RT-PCR). Within 48 hours of admission, the patient presented with hemoptysis and subsequent hypercapnic and hypoxemic respiratory failure requiring transfer to the intensive care unit for mechanical ventilation. He also developed acute renal failure and was initiated on plasma exchange and Methylprednisolone for possible renal-pulmonary syndrome. These therapies were discontinued when his first serum anti-GBM was negative. After 40 days of mechanical ventilation, the patient recovered fully and was discharged home. Three months after, he again developed acute renal failure with active sediment associated with a significantly elevated anti-GBM level. There were no pulmonary symptoms. He was diagnosed with anti-glomerular basement membrane disease on renal biopsy. This is an unusual case of acute bronchiolitis and respiratory failure presumed secondary to the low-pathogenic coronavirus 229E in an immunocompetent adult patient. The temporal association of the coronavirus infection and the first onset of anti-GBM disease may suggest a connection in the pathogenesis of these two diseases.

RÉSUMÉ

Un homme de 19 ans présentait une histoire de toux depuis un mois. Une tomographie thorax a révélé des nodules centrolobulaires assez diffus et une nodularité bourgeonneuse étendue dans les deux poumons. Son échantillon nasopharyngé pour les virus respiratoires s'est révélé positif pour le coronavirus 229E par RT-PCR. Moins de 48 heures après son admission, le patient a présenté une hémoptysie et une insuffisance respiratoire hypercapnique et hypoxémique nécessitant son transfert à l'unité des soins intensifs pour y être traité par ventilation mécanique. Il a aussi développé une insuffisance rénale aiguë et a été traité par échange plasmatique et par méthylprednisolone pour un possible syndrome pneumorénal. Ces thérapies ont été arrêtées au moment du premier sérum anti-MBG négatif. Après 40 jours de ventilation mécanique, le patient avait entièrement récupéré et a donc reçu son congé. Trois mois plus tard, il a à nouveau développé une insuffisance rénale aiguë avec un sédiment actif, associé à un taux d'anti-MBG significativement élevé. Il n'y avait pas de symptômes pulmonaires. Il a reçu un diagnostic de maladie des anticorps anti-membrane basale glomérulaire suite à une biopsie rénale. Il s'agit d'un cas inhabituel de bronchiolite et d'insuffisance respiratoire présumée secondaire au coronavirus 229E faiblement pathogène chez un patient adulte immunocompétent. L'association temporaire entre l'infection par coronavirus et la première apparition de la maladie anti-MBG pourrait suggérer un lien entre la pathogénèse de ces deux maladies.

KEYWORDS

Coronavirus; anti-glomerular basement membrane (anti-GBM); bronchiolitis

Learning objectives

1. To describe clinical and radiographic presentation of coronavirus-related acute bronchiolitis.
2. To recognize a possible association between coronavirus respiratory infection and anti-GBM disease.

Pre-test questions

1. What are the radiological features of acute bronchiolitis on chest computed tomography?
2. What is the clinical presentation of coronavirus respiratory infection?

Case presentation

A 19-year-old male presented with a 1-month history of cough. His past medical history included seasonal allergies with rhinitis and seizure disorder for which he took Divalproex. He previously worked briefly as a welder. He smoked marijuana regularly and started smoking cigarettes six months ago. No recent travel history. His oxygen saturation at rest was 95% on 5 L of supplemental oxygen, blood pressure was 109/55 mmHg, and heart rate was 116 beats per minute. His chest exam was unremarkable. His arterial blood gases showed pH 7.43, pCO₂ 37 mmHg, pO₂ 80 mmHg, and HCO₃ 24 mmol/L. On presentation, RT-PCR by multiplex NAT was positive for coronavirus 229E in his nasopharyngeal sample. Chest X-ray demonstrated a diffuse nodular pattern, and CT chest further showed diffuse centrilobular nodules with tree-in-bud nodularity in both lungs consistent with bronchiolitis (Figure 1A and B).

Around 48 hours after admission, the patient developed gross hemoptysis and was intubated for hypercapnic and hypoxemic respiratory failure. He developed acute renal failure and became anuric, and continuous renal replacement therapy was subsequently initiated. With the concern of possible pulmonary-renal syndrome, the patient was empirically treated with one run of plasma exchange and Methylprednisolone 1 g daily for 3 days. These measures were discontinued after his anti-GBM and ANCA, collected prior to the initiation of these therapies, were negative. The patient was continued on intravenous Linezolid, Micafungin, Oseltamivir, and Trimethoprim/Sulfamethoxazole. Repeat CT chest nine days later showed persistence of diffuse nodularity with development of mild bronchiolectasis at several lung segments (Figure 2). Expecterated sputum was negative for organisms and endotracheal aspirate demonstrated *Candida albicans*. Inspection during bronchoscopy showed copious purulent secretions. There was a rise in red blood cell count in sequential bronchoalveolar lavage (BAL) aliquots. Cell count from BAL showed white blood cell count $1256 \times 10^6/L$ with 92% neutrophils, 5% eosinophils, 3% monomacrophages, and 1% basophils. Bronchial bacterial cultures were negative. Cytology was negative for malignant cells. Acid-fast bacilli smear and mycobacterial cultures were negative. Nineteen days post-admission, a follow-up BAL viral culture was negative.

The patient required mechanical ventilation for 40 days. The patient recovered completely and was discharged home. Repeat chest X-ray at the time of discharge revealed complete resolution of lung abnormalities.

Three months post-discharge, the patient re-presented with acute renal failure associated with hematuria and proteinuria. He did not present with any pulmonary symptoms and his chest X-ray was unremarkable. His anti-GBM was found to be 96 U/ml, and ANCA was negative. He underwent a renal biopsy which confirmed the diagnosis of anti-glomerular basement membrane glomerulonephritis with diffusely crescentic (94% of the glomeruli demonstrated crescents) and necrotizing features. The patient received a total of 36 plasma exchanges and completed a course of intravenous cyclophosphamide. His anti-GBM level became

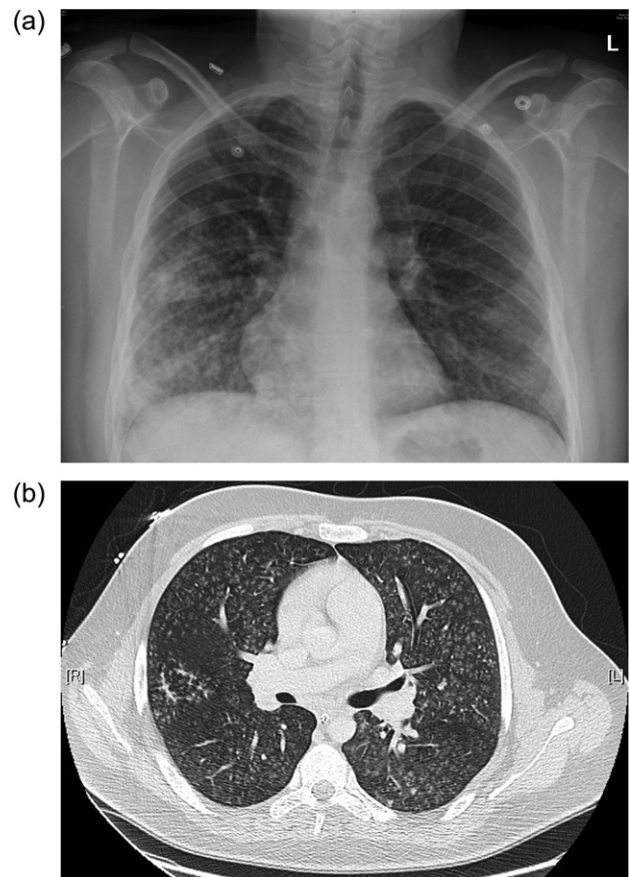


Figure 1. At the time of presentation, chest X-ray (A) demonstrated confluent opacities with a nodular pattern particularly in the right lung. Transverse axial thin section CT image (B) of the lungs obtained at the level of the right and left main bronchi demonstrating fairly diffuse centrilobular nodules with extensive tree-in-bud nodularity in both lungs without any zonal predominance.

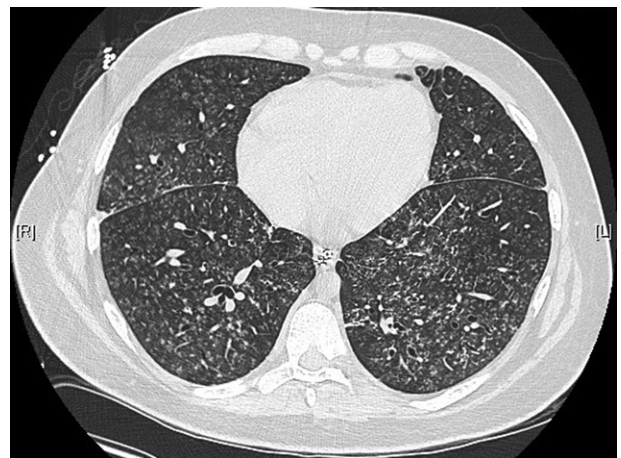


Figure 2. Repeat CT chest scan nine days post admission showed development of bronchiolectasis in posterior segments at the lung bases. There was also cylindrical bronchiectasis in the lingual and mild varicoid bronchiectasis in the lateral segment of the right middle lobe.

undetectable and his glomerular filtration rate is in the stage 4 chronic kidney disease range.

Discussion

Our clinical case described the presentation of acute bronchiolitis presumed secondary to Coronavirus-229E (HCoV-

229E) infection in an immunocompetent adult patient. Coronaviruses (CoV) are positive-stranded RNA viruses in the Coronaviridae family and can be classified as possessing high or low pathogenicity. The clinical course of highly pathogenic Coronaviruses such as the well-known SARS-CoV and MERS-CoV in humans starts with fever and cough for several days, followed by hypoxemia and pneumonia-like symptoms, and progression to acute respiratory distress syndrome which often results in death.¹ At the other end of the spectrum, Coronaviruses of low pathogenicity including HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU typically cause mild, self-limiting cold-like respiratory illness. However, severe consequences such as pneumonia and acute respiratory distress syndrome have been described in some cases.²⁻⁴ Gaunt et al. has found the lack of association between HCoV-229E and significant respiratory symptoms in healthy individuals. This may be in part due to infrequent respiratory viral testing in the adult population. In their study, 70% of the HCoV-229E strains were detected in samples from immunocompromised patients.⁵

In the literature, the sensitivity and specificity of multiplex RT-PCR assay for CoV are 71.4% and 99.4%, respectively,⁶ which suggests that the positive result in our patient likely represented a true finding. However, there are few studies directly comparing positive RT-PCR viral results to respiratory illness. Therefore, the clinical significance of viral detection in patients with pneumonia is often unclear, and may represent persistent viral shedding post-infection, an infection limited to the upper respiratory tract, or one that also involves the lower respiratory tract. To address this question, Self et al. conducted a prospective study that investigated the prevalence of viruses in upper respiratory tract of patients with community-acquired pneumonia compared to asymptomatic patients using nasopharyngeal RT-PCR. They found that CoV were detected significantly more commonly in patients with pneumonia than in asymptomatic controls which implies that most CoV detections are associated with illness, although this was not as dramatic as for other viruses such as RSV, influenza, and human metapneumovirus.⁷ Nonetheless, our patient's radiological findings demonstrated bronchiolitis, an inflammatory response of the distal bronchioles, with centrilobular nodules and tree-in-bud involving multiple lung lobes.⁸ In the nine-day interval between the two CT chest studies, our patient had developed bronchiectasis and mild bronchiectasis. These patterns are very suggestive of an infectious etiology. Common causes of acute bronchiolitis include infection, aspiration, toxic inhalation such as smoking, and connective tissue diseases.⁹ A retrospective study of patients hospitalized with lower respiratory tract infection characterized by diffuse acute bronchiolitis revealed that the most common infectious etiologies were *M. pneumoniae*, influenza virus, *H. influenzae*, respiratory syncytial virus, rhinovirus, and *S. pneumoniae*.¹⁰ Various causes of acute bronchiolitis may have similar pathological findings. Due to the self-limiting course of acute infectious bronchiolitis, this disease is rarely diagnosed with biopsy specimens but rather, on the basis of clinical symptoms, laboratory findings, and chest imaging. In our patient, an

open lung biopsy was not pursued as the patient was clinically improving and the test result would not change his management. In general, majority of the patients recover from acute bronchiolitis without any complications. In rare cases, healing of viral bronchiolitis can lead to fibrous obliteration of small airways.¹⁰

One of the most interesting aspects of this case was the temporal association of the coronavirus infection and the onset of anti-GBM disease. Anti-GBM antibody disease is most often idiopathic but can occasionally follow pulmonary infections or injury. Infectious agents have long been suspected as causative, for example, influenza and Dengue virus have been reported in the literature.^{11,13-15} However, no specific infectious entity has been consistently linked to the disease. One hypothesis to explain this association is that an infection can trigger formation of antibodies reactive with the basement membranes, or can lead to an antigenic alteration that enhances the immunogenicity of the basement membrane antigens.¹³

Anti-GBM disease is caused by circulating autoantibodies directed against alpha-3(IV)NC1, a major component of glomerular, alveolar, and other specialized basement membranes.¹¹ This mechanism leads to glomerulonephritis associated with rapidly progressive renal failure and in 40-60% of the cases, alveolar hemorrhage.¹² The presence of the latter is termed Goodpasture's syndrome. Diffuse alveolar filling pattern from hemorrhage can be nonspecific. Radiological features of Goodpasture's syndrome can range from diffuse nodular opacities with no zonal predominance but sparing of costophrenic angles and apices, to ill-defined areas of ground glass opacification.^{16,17} However, diffuse bronchiolitis is not a typical presentation in this disease, therefore making it difficult to reconcile our patient's radiological findings with alveolar hemorrhage on bronchoscopy.

The initial serum anti-GBM level could have been a false negative even without the interference of the corticosteroids and plasma exchange. False negative anti-GBM has been previously reported particularly in disease associated with intact renal function and in mild pulmonary disease, which was not consistent with our patient's presentation. The mechanism behind a negative result may be explained by the entrapment of high affinity of autoantibodies in lung tissue resulting in low circulating anti-GBM antibody level below the ELISA detection limit.¹⁸ False negatives can also occur when circulating antibodies are generated to GBM antigens other than alpha-3(IV)NC1. Despite these factors, ELISA is overall a well-validated technique for detection to circulating anti-GBM antibodies.¹⁹ In one study, the sensitivity and specificity of serum anti-GBM are 41.2% and 85.4%, respectively.²⁰

This emphasizes the importance of tissue biopsy to confirm diagnosis, particularly when the anti-GBM is negative in the appropriate clinical context. Finally, it is interesting to note that if our patient's initial presentation was that of Goodpasture's disease, his second presentation had excluded pulmonary involvement. This highlights the possibility of a mixed spectrum of anti-GBM disease.

Post-test

1. What are the radiological features of acute bronchiolitis on chest computed tomography?
The most common CT findings in acute bronchiolitis include diffuse centrilobular nodules with extensive tree-in-bud nodularity, and bronchiolectasis or bronchiectasis.
2. What is the clinical presentation of coronavirus respiratory infection?
Different strains of Coronavirus can lead to a variable spectrum of clinical presentation. It ranges from self-limiting upper respiratory tract illness symptoms to pneumonia and respiratory failure.

Disclosure statement

The authors have no financial disclosures or conflicts of interest to declare.

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