SHORT COMMUNICATION

Diagnosis of COVID-19 pneumonia despite missing detection of viral nucleic acid and initially inconspicuous radiologic findings

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Abstract
The diagnosis of coronavirus disease 2019 (COVID-19) is mainly based on a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) result. PCR samples are obtained from upper or lower respiratory tract specimens. However, the sensitivity of PCR is known to have some limitations. We report on a patient who was admitted to our hospital with dyspnea, fever, cough, and history of contact with a SARS-CoV-2 infected relative. The initial chest computed tomography (CT) showed only minimal changes and SARS-CoV-2 PCR from a nasopharyngeal swab sample was negative. PCR results obtained from further nasopharyngeal swabs, qualified sputum samples, and from a lower respiratory tract specimen also remained negative. At day 13 after admission, a second chest CT showed radiological findings suspicious for viral pneumonia. Finally, serologic results showed high levels of immunoglobulin G and immunoglobulin A antibodies against the S1 domain of the SARS-CoV-2 spike protein, and the patient was diagnosed with COVID-19 pneumonia.

KEYWORDS
COVID-19, pneumonia, SARS-CoV-2

1 INTRODUCTION

Since the first recognition of pneumonia of unknown etiology in Wuhan (December 2019) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread around the world.1-3 The disease caused by this virus has been named coronavirus disease 2019 (COVID-19). To identify COVID-19 patients highly sensitive and specific diagnostic tools are important. Up to now, COVID-19 diagnosis is mainly based on polymerase chain reaction (PCR) results, and the respective specimens are usually obtained from the upper or lower respiratory tract.4,5 However, the sensitivity of PCR has its limitations and we and others have observed false-negative PCR results in the past.6-8 The sensitivity of chest computed tomography (CT) seems to be somewhat higher.9 However, radiologic findings are not highly specific for COVID-19, as other viruses or diseases can cause similar radiologic phenomena.10 A further diagnostic option is the detection of antibodies directed against SARS-CoV-2 epitopes (eg, the S1 domain of the SARS-CoV-2 spike protein) in patients sera.11

2 CASE REPORT

A 79-year-old male patient was admitted to our hospital due to fever (38.5°C) and cough. The medical history of the patient included hypertension, diabetes, coronary heart disease, cerebral and peripheral vascular disease, and condition after a lower leg amputation. The patient was admitted to our hospital on 10th April 2020.

On admission, the patient presented with dehydration, fever, cough, and drowsiness. Vital parameters were normal, with a heart rate of 60/minute, respiratory rate of 22/minute, and peripheral oxygen saturation of 94%. A close relative of the patient was only
recently (about 2 weeks before the patient’s admission) diagnosed to be SARS-CoV-2 positive. Laboratory findings included a slight elevation of C-reactive protein (CRP: 26 mg/L; normal range: <5mg/L) and d-dimer levels (390 ng/mL; normal range: <250 ng/mL), with a normal procalcitonine level (PCT: 0.11 ng/mL; normal range: <2 ng/mL). Importantly, white blood cell counts (WBC) and lymphocyte counts were in a normal range (WBC: 6.0/nL; normal range: 4.3-10/nL; lymphocytes: 42.8%; normal range: 20.5%-51.1%), and high sensitive troponin was slightly elevated (42 pg/mL; normal range: <14 pg/mL).

We suspected COVID-19 pneumonia and performed a chest CT scan as well as a nasopharyngeal swab for SARS-CoV-2 PCR testing (Real Star SARS-CoV-2 PCR Kit; Altona Diagnostics GmbH, Hamburg, Germany). The CT scan showed only minimal changes, namely a very small ground glass opacity in the left upper lobe (Figure 1A). SARS-CoV-2 PCR came up with a negative result. Thus, at this point, we could not truly confirm the suspected diagnosis of COVID-19 pneumonia (despite the history of close contact to a SARS-CoV-2 positive relative).

The patient was transferred to our isolation ward for further diagnostics and treatment. We started an intravenous volume substitution with crystalloids. The patient received an empiric antibiotic treatment with levofloxacin and the patient’s condition slightly improved. The concomitant medication of the patient included amlopidine, ramipril, bisoprolol, simvastatin, pregabalin, pantoprazole, clopidogrel, and acetylsalicylic acid. However, after an initial improvement, fever persisted. We performed an antipyretic treatment with paracetamol. Blood cultures, urine cultures, cultures from qualified sputum, and laboratory screening for atypical pneumonia (legionella, mycoplasma, and chlamydia) remained negative. We, therefore, collected another nasopharyngeal swab as well as a qualified sputum sample for SARS-CoV-2 PCR testing. Again, the results were negative.

During the further course of treatment, the patient complained about a shortage of breath and required oxygen supplementation. He developed a lymphocytopenia (WBC: 6.0/nL, lymphocytes: 14.1%) and an increase in CRP levels (164.8 mg/L). We performed another chest CT at day 13 after admission. This CT scan showed bilateral, multilobular ground-glass opacities, and crazy paving with a predominant peripheral and posterior distribution, as well as beginning consolidations, consistent with the diagnosis of viral pneumonia (Figure 1). At day 14, we collected the patient’s serum for SARS-CoV-2 antibody (immunoglobulin A [IgA] and immunoglobulin G [IgG]) detection and a specimen from the lower respiratory tract (deep tracheal aspiration) for PCR. Again, the PCR was negative for SARS-CoV-2. However, the serologic testing by an anti-SARS-CoV-2 IgG and IgA ELISA (EUROIMMUN AG, Luebeck, Germany), came up with a highly positive ratio for both, IgG and IgA. These clinical, radiologic, and laboratory findings finally led to the diagnosis of COVID-19 pneumonia.

During the further disease course, the patient received a supportive treatment, which consisted of a careful fluid substitution (with crystalloids) and antipyretic medication (with paracetamol). Further, the patient received oxygen supplementation as required.

Up to now the clinical condition of the patient has very much improved and no more oxygen supplementation is necessary. The chest CT scan performed at day 21 after admission shows an improvement of CT-morphological changes of COVID-19 (Figure 1). The patient was discharged on 6th May 2020 in a stable condition.

3 CONCLUSION

We here report on pneumonia that was initially suspected to be SARS-CoV-2 negative, based on a series of negative PCR results. The chest CT, performed on admission, only showed a very discrete ground-glass opacity in the left upper lobe. However, the patient’s history and clinical presentation were suggestive for COVID-19 diagnosis. Clinical and laboratory findings, a second chest CT, and the detection of high levels of IgA and IgG antibodies against SARS-CoV-2 finally confirmed the diagnosis of COVID-19 pneumonia.

Educational points from this case:

1) A negative PCR does not necessarily exclude a SARS-CoV-2 infection
2) Chest CT-findings can be inconspicuous at the very beginning of COVID-19 pneumonia
3) Laboratory findings, such as lymphocytopenia can be absent during the early phase of SARS-CoV-2 infection

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