Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Case report

Typical CT findings of COVID-19 pneumonia in patients presenting with repetitive negative RT-PCR

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ABSTRACT

Multiple polymerase chain reaction (RT-PCR) is considered the gold standard diagnostic investigation for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19).

However, false negative multiple polymerase chain reaction (RT-PCR) results can be diagnostically challenging. We report three patients with history of fever and different clinical signs. During the height of the pandemic in Italy (March to May 2020), these patients underwent chest computed tomography (CT) scans that showed lung alterations typical of COVID-19 with multiple negative RT-PCR tests and positive serology for SARS-CoV-2. Two of the three patients showed residual pneumonia on CT after the onset of the first clinical signs. One patient presented with diarrhoea without respiratory symptoms. These cases suggest that in the COVID-19 pandemic period, to provide an earlier specific treatment in patients with positive serology, a chest CT scan can be useful in those presenting with a fever or a history of fever associated with persistent mild respiratory symptoms or with abdominal complaints despite repeated negative RT-PCR results.

Introduction

Coronavirus disease 2019 (COVID-19), a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, Hubei Province, China. Despite travel restrictions, border controls, and quarantine measures adopted in many countries, the disease has rapidly spread around the world.

COVID-19 usually manifests with clinical symptoms related to pneumonia and, in fatal cases, with acute respiratory distress syndrome (ARDS). In some cases, asymptomatic and gastrointestinal or genitourinary complaints have been described as emerging presentations.[1–4] To date, although multiple polymerase chain reaction (RT-PCR) is considered the gold standard diagnostic for SARS-CoV-2, there have been reports of low sensitivity ranging from 42% to 71%.[5–8]

False negative RT-PCR results are also a major concern for the clinical management of patients, especially for asymptomatic or mildly symptomatic individuals who continue to infect others while unaware of their increased transmission risk.[5,8–11]

In the presence of persistent clinical signs, additional diagnostic tools should therefore be considered.

We report three patients presenting with mild clinical signs and radiological findings typical of COVID-19 infection despite repeated negative RT-PCR results in the presence of positive serology.

Case presentations

The first case is a 60-year-old man who was referred to our emergency department due to mild dyspnoea. No history of

Abbreviations: ARDS, Acute respiratory distress syndrome; CLIA, chemiluminescent immunoassay; CT, computed tomography; COVID-19, coronavirus disease 2019; CRP, C-reactive-protein; GGOs, ground-glass opacities; NP/OP, nasopharyngeal and oropharyngeal; RT-PCR, polymerase chain reaction; RDT, rapid diagnostic test; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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previous lung pneumonia was reported. Forty days before the onset of respiratory symptoms, he had a fever for seven days (39 °C) after close contact with COVID-19 patients. Ten days after the first episode of fever, nasopharyngeal and oropharyngeal (NP/OP) swabs were performed by a family doctor who was negative for SARS-CoV-2. Ten days later, a second NP/OP swab was also negative; 20 days later, when the patient was admitted to our institution, further NP/OP swabs in the emergency room were also negative. He also presented with very mild lymphocytosis (3.27 × 10ˆ3/μL; normal range values are 1.5–3.0 × 10ˆ3/μL) and a mildly elevated C-reactive-protein (CRP) value (8 mg/dL; normal range values are 0–5 mg/dL). Arterial blood gas revealed an SpO_2 of 94%. A rapid diagnostic test (RDT) was performed to detect the presence of SARS-CoV-2 IgG and negative IgM antibodies.

To determine an appropriate treatment and considering the positive epidemiological history (contact with COVID-19 patients), the previous presence of fever, persistent mild dyspnoea and the presence of SARS-CoV-2 IgG antibodies, a chest computed tomography (CT) scan was performed (Fig. 1). The CT scan showed the appearance of a typical COVID-19 radiological pattern according to international radiological guidelines,[12] including ground glass opacities (GGOs) in both inferior lobes (Fig. 2) and the right middle lobe with posterior and subpleural distribution. Treatments with hydroxychloroquine sulfate and corticosteroid (methylprednisolone, 4 mg twice daily orally for 5 days) were administered with improvements in clinical conditions.

The second case is a 52-year-old woman who came to our emergency department due to persistent diarrhoea. Thirty days before the onset of the abdominal symptoms, she reported having had a fever for 14 days (38–40 °C). On the tenth day of the fever, NP/OP swabs were negative for SARS-CoV-2 infection and were still negative 12 days later. Haematological evaluation on admission was normal, and the CRP value was in the normal range (2.9 mg/dL; normal range values are 0–5 mg/dL). Arterial blood gas revealed an SpO_2 of 98%. Faecal specimens were negative for salmonella/shigella/yersinia. On the basis of the previous persistent fever and diarrhoea, NP/OP swabs were performed in the hospital and were found to be negative for SARS-CoV-2. However, a rapid serological test confirmed the presence of SARS-CoV-2 IgM and IgG. A thoracic-abdominal CT scan showed residual pneumonia with some GGOs on both lungs; no abdominal alterations were seen on the abdominal CT scan (Fig. 3). Antiviral (lopinavir/ritonavir) treatment with antibiotic therapy was therefore started.

The third case is a 40-year-old woman who came to the emergency department having had a fever for seven days together with mild dyspnoea. NP/OP swabs performed by the family doctor two days prior to admission were negative for SARS-CoV-2. Her laboratory values showed mild lymphopenia (1.3 × 10ˆ3/μL; normal range values are 1.5–3.0 × 10ˆ3/μL), and platelet counts were at the lower limit range (150,000/mmˆ3) (normal range values 150,000–400,000/mmˆ3). The CRP and D-dimer values were in the normal range. Arterial blood gas revealed an SpO_2 of 90%. An RDT detected the presence of SARS-CoV-2 IgM. Therefore, a chest CT scan was performed, which showed bilateral and multilobar involvement of GGOs with predominance in the superior lobes and the middle lobe with peripheral and peribroncovascular distribution suggesting probable COVID-19 infection[12] (Fig. 4). Alternative differential diagnoses, including organizing pneumonia, influenza pneumonia, drug toxicity and connective tissue disease, but positive serology confirmed COVID-19 infection, and treatment with hydroxychloroquine sulfate in association with lopinavir/ritonavir and low molecular weight heparin was started. Tocilizumab therapy was also administered (8 mg in two intravenous infusions) to reduce inflammatory responses.

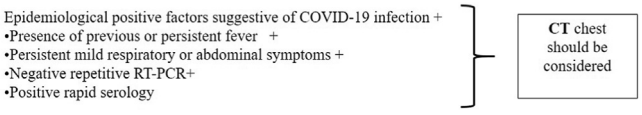

Figure 1. Clinical conditions to proceed to chest CT.

However, her NP/OP swabs performed seven and ten days later at our hospital continued to be negative for SARS-CoV-2. Twenty days later, a chest CT scan showed a reduction in the GGOs (Fig. 4), and the serological test with chemiluminescent immunoassay (CLIA) detected the presence of SARS-CoV-2 IgG 15.72 (normal value 1) and negative IgM 0.9 (normal value 1).

Discussion

RT-PCR is usually used to confirm the microbiological diagnosis of SARS-CoV-2; however, its sensitivity depends on several factors, including the quality of the sampling, the sensitivity of the test kit, and the viral burden at the time of specimen collection.[1,9–15] To date, several studies have reported a high sensitivity with CT scans, suggesting that they should be used in the diagnosis of COVID-19 together with RT-PCR.[7,8,15] The reported sensitivities and specificities of CT scans for COVID-19 vary widely from “60%–98%” and “25%–63%”, respectively.[7,8,16,17]

Current international radiological guidelines, including those from the Centers for Disease Control (CDC), the American College of Radiology (ACR) and the British Society of Thoracic Imaging (BSTI), do not recommend CT scans to diagnose COVID-19; instead, viral testing remains the only specific method of diagnosis.[6,18,19] However, CT scans can be considered a diagnostic method when RT-PCR tests are not available, in the case of false-negative PCR assays and in areas with a high prevalence of COVID-19.[6,11,12,15,20–25]

The CDC guidelines indicate that even if radiological findings are suggestive of COVID-19, the viral test is required; however, in all our cases, we performed a serological test together with a CT scan to determine specific treatments. As CT features tend to peak later (days 6–11) in the disease course,[24] two of our patients presented after a long period of persistent clinical signs (all had fever), and a CT scan was performed later. In some cases, CT scans may highlight the first stage of COVID-19 before a positive RT-PCR test.[7] Therefore, CT scans can be useful both in the early stage of COVID-19 and in symptomatic patients in the chronic phase, as they can reveal residual pneumonia.[7,25]

The imaging features on chest CT usually vary depending on the time of scanning, disease stage during the follow-up, patient's age, immunity status, underlying diseases, and drug interventions.[2]

Treatment with COVID-19 is currently based on anti-inflammatory and immunomodulatory drugs to reduce the immune response and antiviral drugs and to monitor coagulation function. Respiratory and circulation support are used for severe patients.[2,5]

The use of a low-dose CT scan for the diagnosis of viral pneumonia enables patients with suspected SARS-CoV-2 infection to be quickly treated, thus optimizing patient management.[26] The use of CT scans could also be very helpful in revealing *complications* of *COVID-19*, such as pneumomediastinum, pneumothorax, lung pulmonary embolism, and ARDS.[2,27] Typical CT findings in individuals with COVID-19 have been reported to be GGOs, particularly on the peripheral and lower lobes, and bilateral multiple lobular and subsegmental areas of consolidation.[12,26,28] Combinations of peripheral and central distribution have also been reported.[12,28]

Non-typical CT findings have included pleural effusion, masses, cavitations and lymphadenopathies, which would therefore suggest alternative diagnoses.[12,29]

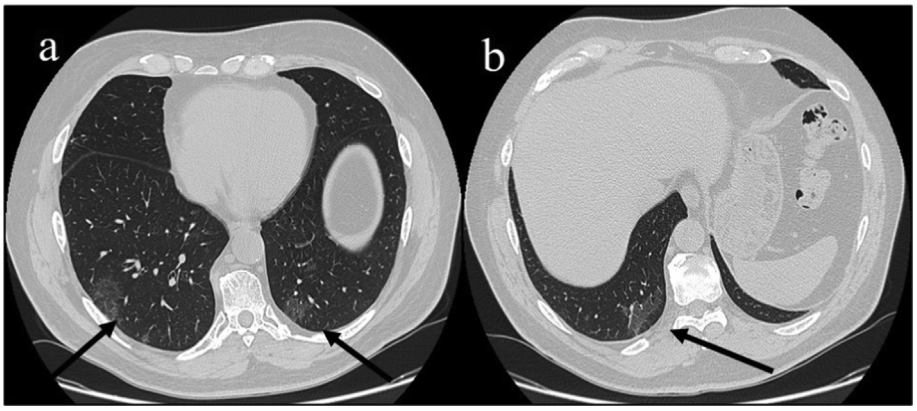

Figure 2. Images a,b represent GGOs (black arrows) in a typical radiological pattern with peripheral and posterior distributions in the inferior lobes on the chest CT scan of the first patient.

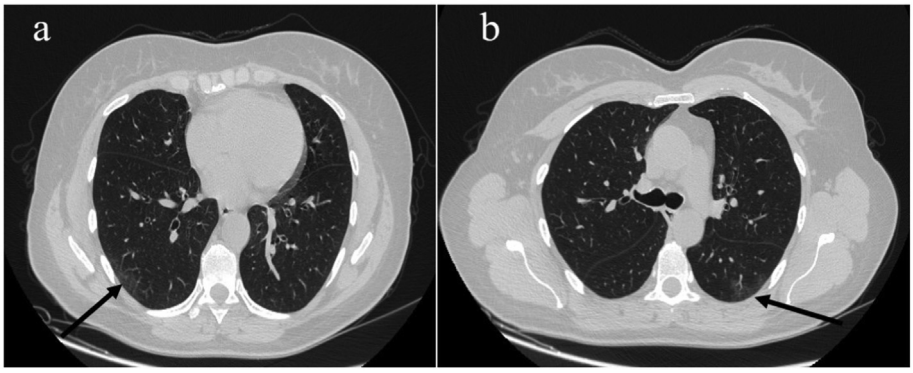

Figure 3. Images a,b describe some GGOs (black arrows) with the typical peripheral distribution in the inferior lobes on the chest CT scan of the second patient.

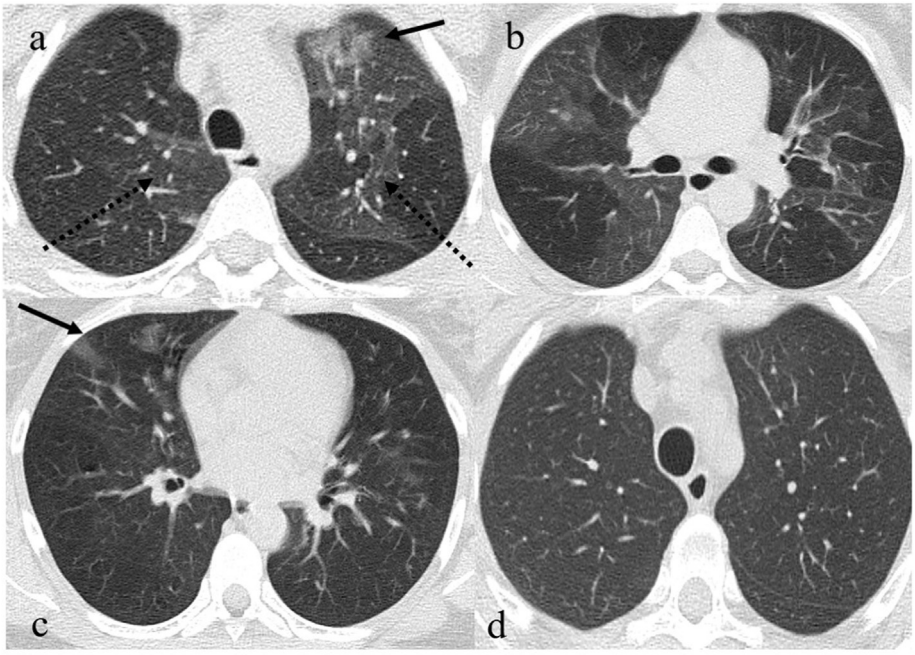

Figure 4. Chest CT scan of the third patient describing GGOs with a peripheral distribution (black arrow) and also a peribroncovascular distribution (black dotted arrows) in the superior lobes (a); GGOs with a peripheral, posterior distribution and also a peribroncovascular distribution in the superior and inferior lobes (b); GGOs with a peripheral distribution in the right middle lobe (c); resolution at 20 days after therapy of the previous GGOs in the superior lobes.

Residual pneumonia with GGOs in two of our patients was visible more than 30 days after the onset of the initial symptoms; these patients had never been referred for previous pneumonia.

Serological platforms are also useful to confirm SARS-CoV-2-specific antibody responses to reveal past infections, for rapid case identification, and in RT-PCR-negative patients, especially those who present later during the disease.[30–35] The accuracy of serological tests is near 100% when samples are obtained 20 days after infection or first symptoms.[32] Pooled specificities range from 96.6% to 99.7%.[31] An RDT is typically a qualitative (positive or negative) lateral flow immunoassay with rapid time to results but with a low sensitivity of 66.0% (49.3%–79.3%), despite the high specificity (87–100%).[31,36] Ong et al.[37] showed that the sensitivity of RDT improved in patients with at least seven days of symptoms. Therefore, due to its high specificity, an RDT is considered a primary and rapid screening tool for COVID-19 and can accelerate decision making in the emergency room.[37,38] CLIA is usually a quantitative, lab-based test with high sensitivity and specificity. The pooled sensitivity in measuring IgG or IgM using CLIA is 97.8% (46.2%–100%), and the specificity is approximately 98–100%.[31,33,39]

In two of our cases, clinicians used only rapid serological tests. In the third case, clinicians also used a quantitative test for the recent history of the disease and to quantify the immune response.[33] It has been reported that IgM antibodies are detectable approximately 10 days after the onset of symptoms and increase rapidly. IgG antibody concentrations closely follow the IgM response. Seroconversion is typically within the first 3 weeks.[33,35]

If a subject with a COVID-19 exposure history has positive IgM and IgG, this is indicative that the infection began more than 14 days previously and the immune system is actively producing antibodies.[40] In these symptomatic cases, as in our second case, a chest CT can be useful because it can reveal lung alterations; thus, specific therapies can be used to treat the long-term activation of the immune response. Our cases support the importance of performing a chest CT in COVID-19 patients presenting with laboratory alterations,[5] persistent respiratory symptoms or abdominal complaints who have had positive serology results despite repeated negative RT-PCR results.[38]

Conclusions

A multimodality approach including chest CT and serological platforms was found to be useful in confirming the COVID-19 diagnosis in symptomatic patients with repeated negative repetitive RT-PCR results.[38] A CT scan can be useful both in the acute and chronic phases in COVID-19 patients because it can reveal early alterations in the lungs and residual pneumonia.

Conflict of interest statement

The authors report no conflict of interest.

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All procedures performed in the studies involving human participants were in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the patients. The authors would like to thank all of the emergency services, nurses, doctors, and other medical workers from Italy and the rest of world for their efforts to combat the COVID-19 outbreak. No funding was received.

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