

## Case Report

# Clinical Case with Negative Polymerase Chain Reaction (PCR) and Suspicious Chest Computed Tomography (CT) Images SARS-CoV-2 Infection or Not

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**Abstract:** Background: The SARS-CoV-2 infection has polymorphic clinical presentations. The real time PCR is the reference diagnostic test; however, it can only detect presence of virus for a specific window of time. Case: We report a clinical case in a patient aged 66 years. His clinical history included known hypertension for 10 years and ischemic stroke. He had no known contact with infected persons. He initially presented with a productive cough, fever, shortness of breath on exertion, intense asthenia and palpitations. The real time PCR with upper airway samples was conducted on days 18 and 20 of the onset of symptoms and was negative. Despite chest CT abnormalities, the patient was not considered to be infected SARS-CoV-2 according to national recommendations for diagnosis and treatment in Benin. He was discharged from the treatment centre. Readmitted 7 days later to the emergency room for respiratory distress, the patient died. Conclusion. Diagnosis of SARS-CoV-2 infection can be difficult. In the context of typical clinical presentation, chest CT features of viral pneumonia may be strongly suspicious for SARS-CoV-2 despite negative real time PCR results. In order to improve the diagnostic and therapeutic strategy for SARS-CoV-2 infection in Benin, chest CT and other diagnostic tests/ criteria should be adopted.

**Keywords:** SARS-CoV-2, Real Time PCR, False Negative, Chest CT

## 1. Introduction

On 31 December 2019, China notified WHO about a cluster of pneumonia cases of unknown causes in Wuhan, Hubei province. The causative pathogen, was later identified and named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group of the

International Committee on Taxonomy of Viruses based on its phylogeny, taxonomy, and established practices [1, 2] (Since then, the SARS-CoV-2 has spread worldwide and was declared a pandemic by the WHO on March 11, 2020 [3]. Africa is one of the last continents to be affected by SARS-CoV-2 with relatively few reported cases and deaths. In Benin, where 210 cases have been reported [4], the national reporting and treatment strategy remains based on

confirmation of cases by real time PCR. Several data in the literature report false negative results by real time PCR [5- 9]. In these cases, the use of other diagnostic tools such as chest Computed Tomography (CT) and serological tests is necessary. Chest CT has proven to be a credible alternative diagnosis in patients with typical images [6, 7, 10]. We report a clinical case in a patient with typical chest CT scan images with two negative real time PCR test. The analysis of the clinical, chest CT and evolutionary data of this patient may change the management and prevention of the infection in our country.

## 2. Case

The patient was a male, aged 66 years, weighing 82 kgs for a height of 187cm. He lived 133 km from the city of Cotonou, where the highest number of cases of SARS-CoV-2 infection have been recorded in Benin. His clinical history included known hypertension for 10 years and ischemic stroke. He had no known contact with anyone infected with SARS-CoV-2 and no cases had been identified in his city of residence at the time of his symptoms. He initially presented with a productive cough, fever of 38.5°C, then secondarily with shortness of breath on exertion, intense asthenia and palpitations. He was admitted 5 days later, for intensive care in his hometown hospital and treated for pulmonary embolism associated with pneumonia with enoxaparin (8,000 UI twice a day) and antibiotics (Roxithromycin 150 mg + Amoxycillin/Clavulanic acid 1g, twice a day).

After a 5-day stay in intensive care with clinical stabilization, he was transferred under rivaroxaban (15mg twice a day) to Cotonou for CT scan and was admitted to the cardiology department of the "Centre National Hospitalier et Universitaire Hubert Koutoukou Maga" (CNHU-HKM). He presented a sudden deterioration of his clinical condition on the day of admission with respiratory distress SpO<sub>2</sub> of 80% and a fever of 40°C. He was given non-invasive respiratory assistance with high concentration oxygen by mask. The patient's biological data are summarized in Table 1. The ECG showed no particularities other than bi-atrial overload and isolated ventricular extrasystole. The echocardiographic findings were signs of an acute pulmonary heart with RV/LV ratio at 0.87, pulmonary artery systolic pressure (PASP) using tricuspid valve velocity at 50 mmHg. Kinetics and function of the left ventricle were good. There was no significant mitro-aortic valve disease or pericardial effusion.

Table 1. Biological data.

|                               | Patient values (ULN) |
|-------------------------------|----------------------|
| D-dimer (ng/l)                | 10,000 (20X ULN)     |
| Complete blood count (CBC)    | 15.7                 |
| Hemoglobin (grams/dl)         | 305                  |
| Platelets (billion/l)         | 18,7                 |
| White blood cells (billion/l) | 91                   |
| Neutrophils (%)               | 4                    |
| Lymphocytes (%)               |                      |

|                                 | Patient values (ULN) |
|---------------------------------|----------------------|
| Protonin Ic (ng/l)              | 37 (2.6X ULN)        |
| Blood urea nitrogen (BUN) (g/l) | 0.17                 |
| Creatinine (mg/l)               | 11.5                 |
| C-Reactive Protein (CRP) (mg/l) | 82.3 (5.6X ULN)      |
| real time PCR (test1)           | negative             |
| real time PCR (test2)           | negative             |

ULN: Upper Limit Normal; PCR: Polymerase Chain Reaction.

The chest CT scan showed the following abnormalities: Frosted glass lung areas bilateral asymmetrical predominantly posterior lung more pronounced on the right, of mixed topography, diffuse condensation on the right with lower lobe aerial bronchogram (figure 1 and figure 3), ground-glass opacity, central basal posterior left, focal lung infarction (figure 2), lower lobar pulmonary embolism and sub-segmental and segmental (figures 3 and figure 4), dilatation of right cavities, low-abundant pleural fluid effusion on the right (figure 3).

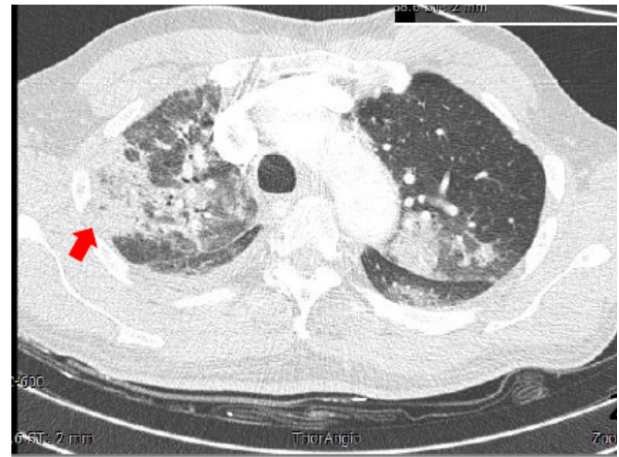


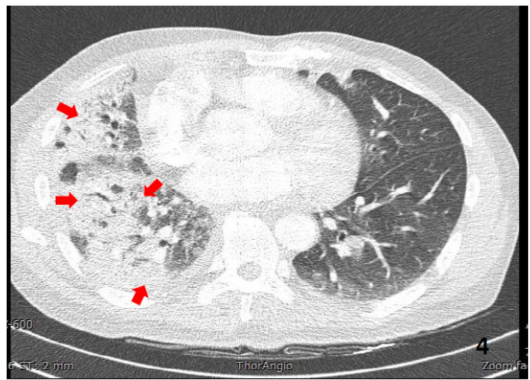
Figure 1. Chest CT imaging.

Frosted glass lung areas bilateral asymmetrical predominantly posterior more pronounced on the right (red arrows).



Figure 2. Chest CT imaging.

Ground-glass opacity, central basal posterior left (blue arrow), Focal Lung Infarction (star).



**Figure 3.** Chest CT imaging.

Diffuse lung condensation on the right with lower lobe arial bronchogram (red arrows).



Cardiovascular abnormalities: Left segmental embolism (red arrows).

**Figure 4.** Chest CT imaging.

Based on the chest CT scan results a SARS-CoV-2 infection was suspected, and the patient was transferred to the national SARS-CoV-2 management center in accordance with national policy. The disinfection procedures of the room and of the equipment were made and the 4 contacts patients put isolation as recommended.

Confirmatory testing by real time PCR with oropharyngeal samples was performed on days 18 and 20 of the onset of symptoms at the national SARS-CoV-2 management center. real time PCR results were negative twice. The patient was not considered to be infected with SARS-CoV-2 and was not treated as such. He was discharged from the treatment centre and returned home. Readmitted to the emergency room for respiratory distress 7 days later, the patient died.

### 3. Discussion

This clinical case in a patient with a history of hypertension and cerebrovascular disease highlights several points for comment, including:

1. the patient's clinical symptomatology and medical history,
2. the diagnosis of SARS-CoV-2 infection,
3. the therapeutic regimen and hospital management of the patient and the possible consequences of a falsely

negative result for SARS-CoV-2.

#### 3.1. The Patient's Clinical Symptomatology and Medical History

The patient presented with respiratory symptoms and fever suggestive of pulmonary embolism and/or pneumonia. Pulmonary embolism is one of the common clinical presentations or complications of SARS-CoV-2 infection as reported in several data in the literature [11-15]. SARS-CoV-2 is associated with a high thromboembolic risk, with several factors being incriminated: prolonged immobilization, inflammation responsible for a state of hypercoagulability and endothelial dysfunction. High levels of D-dimer ( $> 1$  g/L) were strongly correlated with high intra-hospital mortality [16] or 6 times the upper limit of normal [17]. The patient described in the clinical case had a D-dimer level of 20 times the upper limit of normal.

The patient was 66 years old, had hypertension and stroke in his history. Elderly patients with a cardiovascular history appear to be more affected with a poor prognosis than in the absence of cardiovascular disease as reported in the literature. Indeed, SARS-CoV-2 has a dual effect at the cardiovascular level: the infection will be more intense if the host has cardiovascular comorbidities and the virus itself can cause potentially fatal cardiovascular damage [18]. In a study of 138 cases of SARS-CoV-2 infection in the Wuhan region of China, 64 patients (46.4%) had at least one predominantly CV comorbidity, hypertension was present in 31.2% of subjects, diabetes in 10.1% of subjects and cardiovascular infection in 14.5% of patients [19]. In this study, the forms of SARS-CoV-2 that stayed in the Intensive Care Unit (ICU) were higher in patients with hypertension (50.3%), diabetes (22.2%), heart disease (25%) and cerebrovascular disease (16.7%) [19]. Higher excess mortality occurred in the group of patients with a cardiovascular history (10.5%) compared to patients with underlying chronic respiratory disease (6.3%).

#### 3.2. Diagnosis of SARS-CoV-2 Infection in the Patient

The confirmation of the diagnosis of SARS-CoV-2 infection was not made by the real time PCR test, which was negative twice. Several data in the literature report false negative results by real time PCR [5-9]. A recent study showed that the mean duration of viral clearance in patients with SARS-CoV-2 in China was 20 days [20]. The real time PCR is the reference test because it is very specific. However, this technique lacks sensitivity. False-negative results are related to low viral load, the quality and timing of sampling (e.g. during the early phase of infection and then during the symptom resolution phase), the presence of PCR inhibitors, virus mutation and transport conditions [21]. When the test returns negative, it must be repeated and at different sites. The study by Wang et al. compared the performance of real time PCR viral RNA testing at different collection sites on 1070 samples obtained from 205 patients with confirmed SARS-CoV-2 based on a combination of compatible symptoms and characteristic radiological signs. The most

sensitive specimen appeared to be bronchoalveolar lavage (93%), followed by sputum (72%). The widely used nasal swab real time PCR appeared to be less sensitive (63%) and should be repeated to reduce the incidence of false negatives [22]. In the clinical case patient, the swab was taken from the oropharynx.

It was the chest CT images that made the diagnosis by finding two characteristic anomalies: ground-glass opacity with peripheral distribution and condensation. The pulmonary embolism found may be an evolving complication. Indeed, pulmonary embolism is on the left while lesions of the pulmonary parenchyma predominate on the right.

In these cases, chest CT represents an alternative in symptomatic patients by showing typical lesions [6, 7, 10]. Ai T. et al. showed a sensitivity of 97% chest CT scan, based on positive real time PCR results. These same authors had 75% chest CT positive cases in real time PCR negative patients [23]. The specificity of the CT scan seems more modest, however a recent Chinese American study [24] has shown the possibility of distinguishing SARS-CoV-2 infection from other viral pneumopathies. The most discriminating features for SARS-CoV-2 pneumonia included a peripheral distribution (80% vs. 57%,  $p < 0.001$ ), ground-glass opacity (91% vs. 68%,  $p < 0.001$ ) and vascular thickening (58% vs. 22%,  $p < 0.001$ ).

Serological tests can also be performed if real time PCR is negative with a strong suspicion of SARS-CoV-2 infection. They detect antibodies specific for SARS-CoV-2 infection of IgM and IgG type [21]. These tests are not true diagnostic tests. The antibodies are not produced at the onset of infection, but somewhat later (from day 5 and day 10 of the onset of symptoms for IgM and IgG respectively) and thus one can miss out on newly infected cases. Furthermore, these tests do not tell whether a person is still infectious, unlike real time PCR tests, which also reveal the virus load in the sample. A positive result from these tests, however, proves contact with the virus, regardless of whether symptoms are present or not. Serological tests would have been of interest in this patient but were not available in the SARS-CoV-2 diagnostic system in Benin.

### 3.3. The Therapeutic Regimen and Hospital Management of the Patient and the Possible Consequences of a Falsely Negative Result for SARS-CoV-2

The patient in the clinical case was not considered to be infected with SARS-CoV-2 according to national recommendations for diagnosis and management despite compatible chest CT images. The management of this patient revealed gaps in the case management policy and failure to consider CT abnormalities in the definition of suspected SARS-CoV-2 infection. Several consequences can be noted for a patient falsely declared not infected with SARS-CoV-2 infection. Individuals with these results may relax physical distancing and other personal measures designed to reduce the transmission of the virus to others. In the case of clinicians, they may be sent to the frontlines of care and inadvertently transmit the virus to patients and colleagues, further straining the already precarious ability of the health care system to

respond to the pandemic [9].

## 4. Conclusion

SARS-CoV-2 infection with its polymorphic clinical presentations can be difficult to diagnose. In the context of typical clinical presentation, chest CT features of viral pneumonia may be strongly suspicious for SARS-CoV-2 despite negative real time PCR results. In order to improve the diagnostic and therapeutic strategy for SARS-CoV-2 infection in Benin, chest CT and other diagnostic tests / criteria should be adopted.

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