International Journal of Antimicrobial Agents 55 (2020) 106006

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

SARS-CoV-2 was already spreading in France in late December 2019

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ARTICLE INFO

Article history:
Received 14 April 2020
Accepted 25 April 2020

Keywords:
COVID-19
Coronavirus disease 2019
SARS-CoV-2
Intensive care unit
France

ABSTRACT

The COVID-19 epidemic is believed to have started in late January 2020 in France. Here we report a case of a patient hospitalised in December 2019 in an intensive care unit in a hospital in the north of Paris for haemoptysis with no aetiological diagnosis. RT-PCR was performed retrospectively on the stored respiratory sample and confirmed the diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Based on this result, it appears that the COVID-19 epidemic started much earlier in France.

1. Introduction

Following its onset in December 2019 in China, a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing COVID-19 (coronavirus disease 2019), has spread widely in many countries [1]. The World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020 [2]. France reported the first cases of SARS-CoV-2 infection on 24 January 2020 [3]. Both cases had a history of travel to Wuhan, China [4]. To the best of our knowledge, these two cases are believed to be the first confirmed cases in France. COVID-19 most commonly presents with influenza-like illness (ILI) [5]. While China was facing the COVID-19 outbreak, European countries were struggling with seasonal influenza [6]. Since clinical symptomatology between COVID-19 and ILIs is similar, we therefore decided to retrospectively look for SARS-CoV-2 in respiratory samples collected in the intensive care unit (ICU) of our hospital near Paris, France.

2. Methods

2.1. Selected records

The medical records of ICU patients admitted for ILI between 2 December 2019 and 16 January 2020 with a negative reverse transcription PCR (RT-PCR) performed at admission were retrospectively reviewed. Every respiratory sample collected in our hospital is frozen at −80 °C in a Thermo Scientific™ −86°C freezer and is stored for 4 years in case of a need for further analysis. Samples taken from patients with both ILI symptoms (fever >38.5 °C, cough, rhinitis, sore throat or myalgia) and pulmonary ground-glass opacity according to their medical record underwent SARS-CoV-2 RT-PCR. A description of sample selection is shown in Fig. 1.

2.2. Testing for COVID-19

SARS-CoV-2 RT-PCR was performed on 14 selected biobanks between 6–9 April 2020. RT-PCR was performed strictly according to the Charité protocol [7] targeting the E gene, encoding the envelope protein, pangenomic of SARS-CoV-1 and SARS-CoV-2, using a QuantStudio™ 7 Flex Real-Time PCR System (Thermo Fisher). A positive result (Fig. 2) was confirmed using a Gene finder® COVID19 Plus RealAmp Kit (IFMR-45) according to the manufac-

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https://doi.org/10.1016/j.ijantimicag.2020.106006
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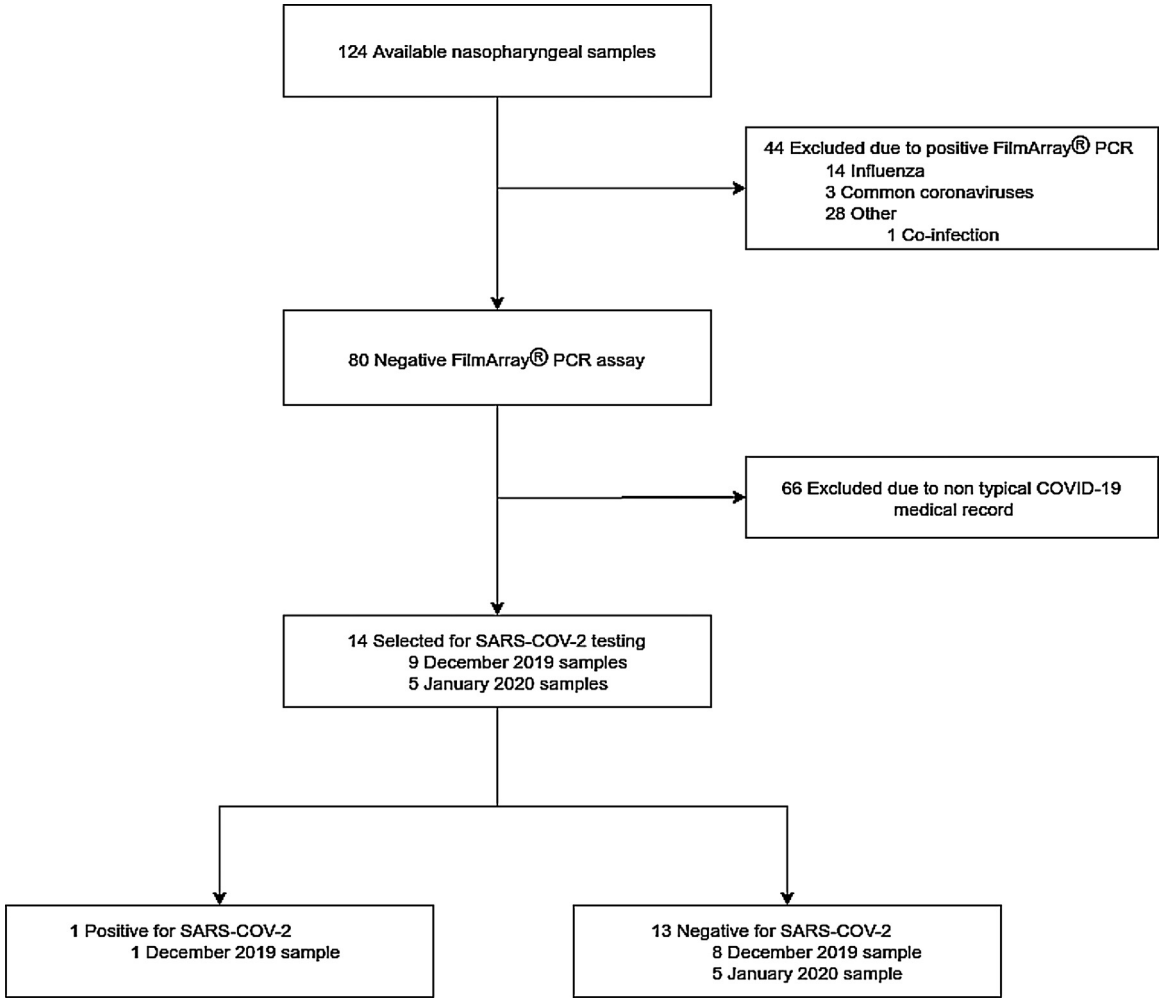

Fig. 1. Selection process for testing. COVID-19, coronavirus 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

turer's recommendations. This test targets three viral genes (RdRp, E and N encoding, respectively, the viral RNA-dependent RNA polymerase, envelope protein and nucleocapsid protein) as well as the cellular ribonuclease P gene in order to confirm the quality of the respiratory sample.

3. Results

During the study period, 14 (24%) of 58 patients admitted for ILI were included in the current analysis (Table 1). One sample taken from a 42-year-old unemployed male born in Algeria who had lived in France for many years was positive. His last foreign travel was to Algeria in August 2019. One of his children presented with ILI prior to the onset of his symptoms. His medical history included asthma and type II diabetes mellitus. He presented to the emergency ward on 27 December 2019 with haemoptysis, cough, chest pain, headache and fever, evolving for 4 days. Initial examination was unremarkable and chest computed tomography (CT) imaging revealed bilateral pulmonary ground-glass opacities in the inferior lobes (Fig. 3).

At admission, the patient had lymphopenia and elevated C-reactive protein (CRP) and fibrinogen, whilst the procalcitonin level was in the normal range. No pathogen was identified in sputum sample collected in the emergency ward. The patient was admitted to the ICU where he received antibiotic therapy and his clinical evolution was favourable until discharge on 29 December 2019.

4. Discussion

Here we report an observation of a SARS-CoV-2-infected patient 1 month before the first reported cases in France. On admission, the patient presented clinical signs and radiological patterns frequently observed previously in Chinese [9] and Italian [10] cohorts. Identifying the first infected patient is of great epidemiological interest as it changes dramatically our knowledge regarding SARS-CoV-2 and its spread in the country. Moreover, the absence of a link with China and the lack of recent foreign travel suggest that the disease was already spreading among the French population at the end of December 2019.

Further studies are required to evaluate the actual onset of SARS-CoV-2 in the French territory as well as the extent of SARS-CoV-2 contamination in the population during late 2019 and January 2020 and to explore the potential unnoticed deaths that could have happen at the time. As of 10 April 2020, COVID-19 is considered to be responsible for 86 334 cases and 12 210 deaths in France [11], but our findings suggest that these numbers could underestimate the actual burden of COVID-19. Two recent studies suggested that ~18–23% of patients infected with SARS-CoV-2 were asymptomatic [12] and that ~55% of infections were caused by unidentified infected persons [13]. The current results strongly support these two assumptions, suggesting that many asymptomatic patients were not diagnosed during January 2020 and contributed to the spread of this epidemic.

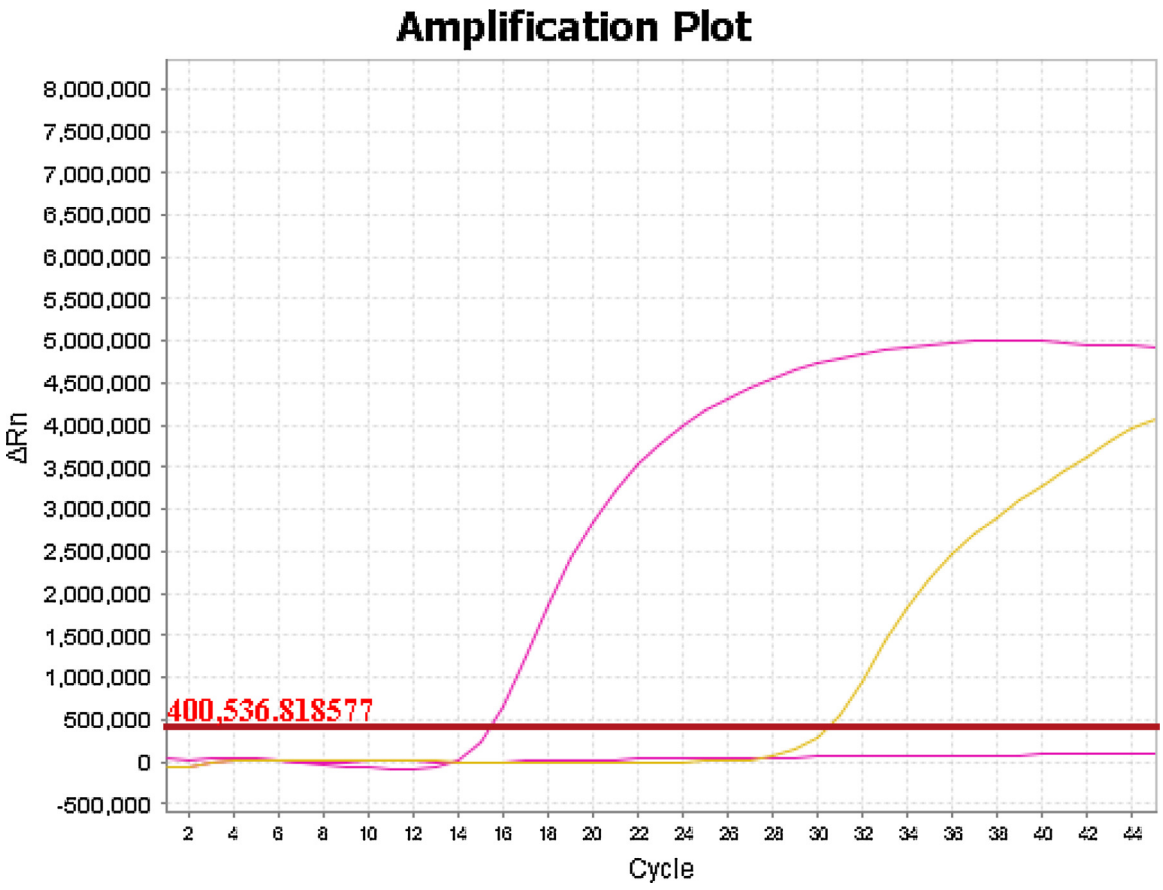

Fig. 2. Result of Charité protocol RT-PCR assay [11]: patient's curve in yellow; positive and negative test samples in purple.

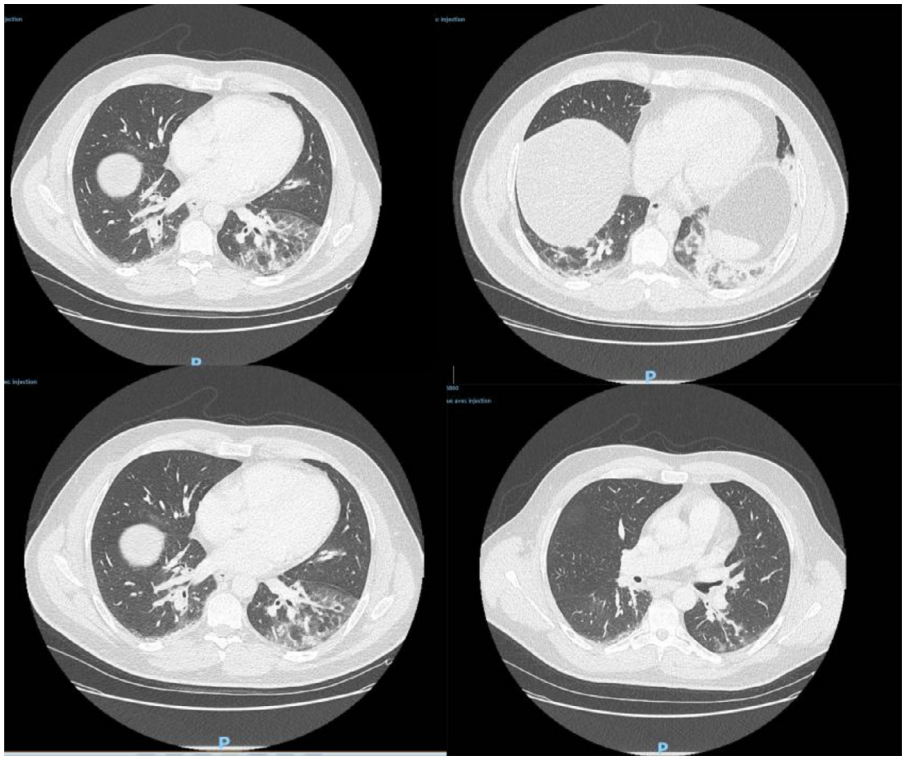

Fig. 3. Chest computed tomography (CT) images at baseline. Bilateral pulmonary ground-glass opacities appear in the inferior lobes.

Table 1
Clinical characteristics of the tested patients at baseline.

Patient no.	Age (years)	Sex	Medical history	SARS-CoV-2 RT-PCR result	Days from symptom onset to nasopharyngeal swab	Symptoms at disease onset	BMI (kg/m^2)	TLC ($\times 10^9$/L)	LDH (U/L)	hs-cTn (ng/L)	Fibrinogen (g/L)	CRP (mg/L)	PCT (μg/L)	Bacteriology finding	Presence of ARDS [a]	Ventilation	Days spent in the ICU	Outcome
1	63	M	Stroke, MI	Neg.	3	Fatigue, weight loss, fever, cough, dyspnoea	14.3	0.26	737	10	10.91	487	43.92	Blood cultures: *Streptococcus pneumoniae*	Yes	NIV	9	Favourable
2	67	M	HBP, T2DM, hyperthyroidism, SAS, ILD, arrythmia	Neg.	7	Dyspnoea	33.0	1.18	NA	NA	4.38	6	0.04	Not performed	Yes	NIV	12	Favourable
3	55	F	Steiner's myopathy	Neg.	3	Dyspnoea, fall, cough	11.3	1.29	NA	59	NA	NA	0.22	Bronchial aspiration: *Escherichia coli, Pseudomonas aeruginosa*	Yes	NIV	4	Death
4	43	F	None	Neg.	2	Dyspnoea	21.2	<0.1	189	9	4.01	148	0.8	Blood cultures: *Staphylococcus haemolyticus*	Yes	NIV	8	Death
5	42	M	T2DM, asthma	Pos.	5	Haemoptysis, cough, headache, chest pain, fever	NA	0.89	310	3	4.55	47	0.21	Not performed	No	Spontaneous	2	Favourable
6	77	F	AML, osteoporosis	Neg.	10	Hypoxaemia, polypnoea, febrile aplasia	22.1	1.03	740	11	5.43	240	0.55	Not performed	No	NIV	3	Death
7	53	F	T2DM, HBP	Neg.	3	Diarrhoea, dyspnoea, agitation	30.9	3.87	926	NA	3.04	NA	1.08	Not performed	No	Spontaneous	6	Favourable
8	74	F	Hemiparesis	Neg.	1	Dyspnoea, impaired consciousness	22.4	0.77	519	124	4.00	NA	0.77	Urinary colonisation with *E. coli*	No	NIV	7	Favourable
9	34	M	Obesity	Neg.	30	Cough, fatigue, fever, dyspnoea	36.9	3.52	821	394	6.88	3	NA	Toxocariasis	No	NIV	7	Favourable
10	37	F	Uterine carcinoma	Neg.	0	Haemoptysis	23.4	0.76	NA	NA	NA	NA	NA	Not performed	No	Spontaneous	1	Favourable
11	54	M	HIV	Neg.	4	Dyspnoea, chest pain	23.8	1.03	479	8	6.84	330	2.04	Sepsis and pneumonia with *S. pneumoniae*	Yes	NIV	2	Favourable
12	54	M	Sarcoidosis, SAS, T2DM, HBP	Neg.	13	Dyspnoea, fever, cough, haemoptysis, diarrhoea	27.9	0.69	615	68	5.62	173	0.64	None	Yes	NIV	4	Favourable
13	92	F	Pulmonary embolism	Neg.	NA	Cough, fall	17.6	0.63	NA	311	10.32	284	0.81	Not performed	Yes	NIV	5	Death
14	73	F	HBP, atherosclerosis, ILD	Neg.	1	Cough	21.4	1.56	1032	45	7.61	171	0.25	Negative	Yes	NIV	3	Favourable

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BMI, body mass index; TLC, total lymphocyte count; LDH, lactate dehydrogenase; hs-cTn, high-sensitivity cardiac troponin I; CRP, C-reactive protein; PCT, procalcitonin; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; MI, myocardial infarction; NIV, non-invasive ventilation; HBP, high blood pressure; T2DM, type 2 diabetes mellitus; SAS, sleep apnoea syndrome; ILD, interstitial lung disease; NA, not available; AML, acute myeloid leukaemia; HIV, human immunodeficiency virus.

[a] According to the Berlin definition [8].

Furthermore, since these results change our understanding of the dynamics of the epidemic, it also means that several models used to predict the evolution and outcomes of SARS-CoV-2 propagation might be based on biased data and would need to be adjusted to the actual profile of the epidemic [14].

This study has several limitations. First, owing to the retrospective nature of the analyses, medical records were not exhaustive and some relevant information might have been missing. Second, we are not able to rule out false-negative results due to the sensitivity of RT-PCR [15] and a technique of storage that may possibly impair the quality of samples [16]. To avoid any false-positive result, we took all of the usual precautions and also confirmed the result by two different techniques and staff. Third, we restricted our analyses to only a few samples and chose to limit the selected records to ICU patients with compatible symptoms and CT findings, although most patients actually have mild symptoms. Fourth, we restricted our analyses to patients with a negative multiplex PCR at the time even though cross-contamination has been described in the literature [17]. Finally, we conducted a monocentric study in the Northern Paris area, which faced a particularly high burden in this epidemic [18]. These limitations could explain why we were only able to identify one person infected with SARS-CoV-2 in our population.

Declarations

Funding: None.

Competing Interests: None declared.

Ethical Approval: Not required.

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