CASE REPORT

Case Report: Co-infection with SARS-CoV-2 and influenza H1N1 in a patient with acute respiratory distress syndrome [version 1; peer review: 1 approved, 1 approved with reservations]

Lekbir Baala1,2*, Dalila Benzekri-Lefevre3*, Laurent Bret1, Clémence Guillaume1, Laura Courtellemont1, Abdelkrim El Khalil4, Thomas Guery1, Sophie Iquel1, Olivier Perche1,2, Khalid Khadre5, Thomas Brungs1, Julien Decker1, Thomas Francia1, Julie Bois1, Benoit Delamare1, Jérôme Guinard1, Laurence Got1, Sylvain Briault1,2, Thierry Boulain3, Eric Legac1

1Pole de Biopathologie, CS 86709, 45067 Orléans CEDEX, France, Centre Hospitalier Régional d'Orléans, 14 Avenu de l'Hôpital, Orléans, France
2UMR7355 INEM Immunologie et Neurogénétique Expérientiales & Moléculaires, CNRS & Université d'Orléans, 3B rue de la Ferollerie, Orleans CEDEX 2, 45071, France
3Service de Médecine Intensive Réanimation, Pole Métiers de l'Urgence, Centre Hospitalier Régional d'Orléans, 14 Avenu de l'Hôpital, CS 86709, Orléans, 45067, France
4Service de Pneumologie, Centre Hospitalier Régional d'Orléans, Orléans, 45067, France
5Service de Radiologie, Centre Hospitalier Régional d'Orléans, Orléans, 45067, France

* Equal contributors

Abstract
Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and has been a global public health concern. Co-infection of SARS-CoV-2 and other respiratory syndrome has been rarely reported. We report coinfection of SARS-CoV-2 and 2009 H1N1 Influenza strain in a French patient with pneumonia leading to acute respiratory distress syndrome. The patient also had a medical history of pulmonary sarcoidosis with a restrictive ventilatory syndrome, which would be a supplementary risk to develop a poor outcomes. This case highlights the possible coinfection of two severe SARS-CoV-2 and influenza H1N1 viruses, which presents a higher risk to extend the care duration. The overlapping clinical features of the two respiratory syndromes is a challenge, and awareness is required to recommend an early differential diagnosis.

Keywords
Co-infection, SARS-CoV-2, Influenza H1N1
This article is included in the Disease Outbreaks gateway.

This article is included in the Coronavirus collection.

Corresponding author: Lekbir Baala (lekbir.baala@chr-orleans.fr)

Author roles: Baala L: Conceptualization, Data Curation, Investigation, Validation, Writing – Original Draft Preparation; Benzekri-Lefevre D: Data Curation, Formal Analysis, Investigation, Validation; Bret L: Conceptualization, Data Curation, Investigation, Writing – Original Draft Preparation; Guillaume C: Data Curation, Investigation, Validation; Courtellemont L: Data Curation, Investigation, Validation; El Khalil A: Data Curation, Investigation, Validation; Guery T: Investigation, Validation, Visualization; Iquel S: Formal Analysis, Visualization; Perche O: Data Curation, Investigation, Software, Writing – Original Draft Preparation; Khadre K: Data Curation, Validation; Brungs T: Data Curation, Validation; Decker J: Data Curation, Validation; Francia T: Data Curation, Validation, Visualization; Bois J: Data Curation, Investigation, Validation; Delamare B: Data Curation, Formal Analysis, Investigation; Guinard J: Data Curation, Investigation, Validation; Got L: Data Curation, Investigation, Supervision, Validation; Briault S: Conceptualization, Data Curation, Investigation, Validation, Writing – Original Draft Preparation; Boulain T: Data Curation, Supervision, Validation; Legac E: Data Curation, Project Administration, Supervision, Validation

Competing interests: No competing interests were disclosed.

Grant information: This study was supported by Centre Hospitalier Régional d'Orléans (CHRO).

Copyright: © 2020 Baala L et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Baala L, Benzekri-Lefevre D, Bret L et al. Case Report: Co-infection with SARS-CoV-2 and influenza H1N1 in a patient with acute respiratory distress syndrome [version 1; peer review: 1 approved, 1 approved with reservations] F1000Research 2020, 9:1482 https://doi.org/10.12688/f1000research.26924.1

First published: 18 Dec 2020, 9:1482 https://doi.org/10.12688/f1000research.26924.1
**Introduction**

Coinfections involving SARS-CoV-2 and respiratory viruses influenza viruses (A or B) have been rarely reported. To date, there is no published case with a co-infection between SARS-CoV2 and influenza H1N1.

**Case report**

A 41-year-old man presented to the hospital’s emergency unit with fever and cough that has been progressing for several days. The SARS-CoV-2 RT-PCR test was positive on March 22nd 2020. On March 24th 2020, the patient had developed a dyspnea aggravation and was taken care of by a medical unity at home. He has a medical history of pulmonary sarcoidosis with a restrictive ventilatory syndrome, which was being treated with Methotrexate (15mg per week) and folic acid (0,4mg one tablet per day). He also had malaria in 2004 from a trip to Central Africa.

Physical examination on the 24th March revealed a respiratory rate of 41 breaths/minute (normal range (NR) 12–20 breaths/minute) and oxygen saturation SpO2 of 75% (reference range (R-R) 95–100%) on ambient air. The SpO2 became at 96% when given mask flow oxygen at a rate of 12l/ minute. The patient was transferred to the emergency room with 97% SpO2, body temperature 37.2°C, and respiratory rate of 30 breaths per minute. The patient presented with superficial polypnea, dyspnea with little effort, difficulty in speaking and bilateral “crackles”. Neurological and cardiovascular examinations were normal.

On supplemental oxygen (12l/min), arterial blood gas analysis revealed pH 7.50 (R-R 7.35–7.45), PCO2 35 mmHg (NR 35–45 mmHg), PO2 88 mmHg (NR 75–100 mmHg), HCO3- 27.3 mmol/l (R-R 22–26 mmol/l), and SaO2 94.4% (R-R 95–100%). The patient was then transferred to intensive care unit (ICU). Respiratory panel tests were negative for adenovirus (subtypes 2, 3, 6, 7.1 and 8), coronavirus (229E, HKU1, NL63 and OC43), human metapneumovirus, rhinovirus, enterovirus, MERS-CoV, parainfluenza virus (1,2,3 and 4), respiratory syncytial virus, and Bordetella pertussis and parapertussis. However, influenza A, subtype influenza A-H1 variant 2009, was positive.

A chest computed tomography scan revealed a predominant left interstitial lung condensation syndrome. Routine laboratory tests revealed higher parameters during patient hospitalization: creatine phosphokinase 2999 U/l (R-R 30–200U/l); gamma glutamyl transferase 119 U/l (R-R 12–64U/l); D-Dimers, which has increased two fold in one week, 3620 ng/ml: 75mg twice/day) for influenza H1N1 infection. Klebsiella pneumonia infection was treated using Meropenem (intravenous dose) for sedation and 120mg of Celocurine for curarization. Enoxaparin (40mg /day) was administered by subcutaneous injection as a preventive anticoagulation up to April 1st and increased to 80 mg/day according to the patient being overweight (Body Mass Index 33.8) and to evolution of biological criteria (D-Dimers 1890ng/l, Fibrinogen 10.82g/l, platelets 528x10e9/l). Unfractionated heparin was used as relay according to the high probability of pulmonary embolism. Mechanical ventilation was used with several sessions of prone position and then oxygen therapy on April 19th. He was treated with hydroxychloroquine for 10 days (Plaquenil, 200mg every eight hours), and by Oseltamivir (4 days, oral suspension 6mg/ml: 75mg twice/day) for influenza H1N1 infection. Venous echodoppler performed on April 14th found no thrombosis and no pulmonary embolism.

On April 19th, the patient was transferred to the pulmonology department where he has a good respiratory evolution allowing oxygen weaning on April 23rd. He was discharged on April 28th, receiving kinesitherapy treatment, and taking a preventive anticoagulant therapy (Enoxaparine 4000 IU /0.4ml once daily by SC injection) for three weeks. The patient was integrated into the post COVID-19 rehabilitation program.

**Discussion**

We report, to the best of our knowledge, the first case of coinfection with SARS-CoV-V2 and seasonal influenza H1N1. The low incidence rate of this co-infection reported in France may be explained by the late screening for COVID-19, which started in France in March 2020, which corresponds with the tapering off period for H1N1. The prolonged intensive care and detection of SARS-CoV-2 viral RNA on the bronchoalveolar sample for at least three weeks might be explained by patient immunosuppression caused by lung polyinfection (viral, bacterial and fungal) and probably by his medical history of pulmonary sarcoidosis with a restrictive ventilatory syndrome.

Bacterial coinfections in COVID-19 patients have been reported in nine studies with a rate of 8% (62/806) of bacterial/fungal co-infection cases. A few cases have been reported with co-infection with SARS-CoV-2 and influenza viruses (A or B)\(^2\)\(^-\)\(^4\). Ding et al. has reported coinfected patients with SARS-CoV-2 and influenza virus and showed similar clinical characteristics as those patients with COVID-19 only, hence content (Table 1). The number of leukocytes and neutrophils underwent fluctuations with high rates between April 7th and 10th (Figure 1). In this period, bacteriological examination culture revealed infection by additional pathogens, with the presence of yeasts (Candida albicans) and bacteria (Klebsiella pneumoniae) in bronchial sampling, probably with nosocomial origin.
Table 1. Laboratory findings in the patient with coinfection of SARS-CoV-2 and influenza H1N1. NA: data not available.

<table>
<thead>
<tr>
<th>Laboratory parameters (reference range)</th>
<th>March, 26</th>
<th>March, 26</th>
<th>March, 31</th>
<th>April, 03</th>
<th>April, 04</th>
<th>April, 07</th>
<th>April, 10</th>
<th>April, 11</th>
<th>April, 12</th>
<th>April, 13</th>
<th>April, 15</th>
<th>April, 17</th>
<th>April, 24</th>
<th>April, 24</th>
<th>May, 06</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes (4-10x10^9/l)</td>
<td>8.8</td>
<td>12.4</td>
<td>11.8</td>
<td>11.5</td>
<td>11.5</td>
<td>11.5</td>
<td>11.5</td>
<td>11.5</td>
<td>11.5</td>
<td>11.5</td>
<td>11.5</td>
<td>11.5</td>
<td>11.5</td>
<td>11.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Hemoglobin (13-17 g/dl)</td>
<td>13.4</td>
<td>12.7</td>
<td>12.1</td>
<td>12.2</td>
<td>12.2</td>
<td>12.2</td>
<td>12.2</td>
<td>12.2</td>
<td>12.2</td>
<td>12.2</td>
<td>12.2</td>
<td>12.2</td>
<td>12.2</td>
<td>12.2</td>
<td>12.2</td>
</tr>
<tr>
<td>Hematocrit (40-54%)</td>
<td>40.7</td>
<td>38.9</td>
<td>36.4</td>
<td>35.2</td>
<td>33.9</td>
<td>33.9</td>
<td>33.9</td>
<td>33.9</td>
<td>33.9</td>
<td>33.9</td>
<td>33.9</td>
<td>33.9</td>
<td>33.9</td>
<td>33.9</td>
<td>33.9</td>
</tr>
<tr>
<td>Mean corpuscular volume (80 µm^3)</td>
<td>26.5</td>
<td>26.1</td>
<td>NA</td>
<td>NA</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
</tr>
<tr>
<td>Mean corpuscular haemoglobin concentration (27-32 pg)</td>
<td>26.5</td>
<td>26.1</td>
<td>NA</td>
<td>NA</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
</tr>
<tr>
<td>Red cell distribution width (12-16%)</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
<td>80.6</td>
</tr>
<tr>
<td>Platelets (150-450x10^9/l)</td>
<td>126</td>
<td>NA</td>
<td>180</td>
<td>528</td>
<td>599</td>
<td>516</td>
<td>437</td>
<td>382</td>
<td>336</td>
<td>296</td>
<td>231</td>
<td>184</td>
<td>528</td>
<td>516</td>
<td>516</td>
</tr>
<tr>
<td>Total neutrophils (1.80-8x10^9/l)</td>
<td>7.98</td>
<td>11.23</td>
<td>10.83</td>
<td>8.69</td>
<td>8.75</td>
<td>8.75</td>
<td>8.75</td>
<td>8.75</td>
<td>8.75</td>
<td>8.75</td>
<td>8.75</td>
<td>8.75</td>
<td>8.75</td>
<td>8.75</td>
<td>8.75</td>
</tr>
<tr>
<td>Total lymphocytes (1.40-4x10^9/l)</td>
<td>0.68</td>
<td>0.73</td>
<td>0.5</td>
<td>0.88</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td>Total monocytes (0.20-1x10^9/l)</td>
<td>0.13</td>
<td>0.36</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
</tr>
<tr>
<td>D-Dimers (40-500 ng/ml)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3620</td>
<td>4240</td>
<td>4240</td>
<td>4240</td>
<td>4240</td>
<td>4240</td>
<td>4240</td>
<td>4240</td>
<td>4240</td>
<td>4240</td>
<td>4240</td>
</tr>
<tr>
<td>Blood creatinine (64-104 µmol/l)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Urea (3.2-7.4 µmol/l)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>9.9</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
</tr>
<tr>
<td>Creatine phosphokinase (30-200 UI/l)</td>
<td>2999</td>
<td>1473</td>
<td>602</td>
<td>415</td>
<td>560</td>
<td>560</td>
<td>560</td>
<td>560</td>
<td>560</td>
<td>560</td>
<td>560</td>
<td>560</td>
<td>560</td>
<td>560</td>
<td>560</td>
</tr>
<tr>
<td>Aspartate aminotransferase (5-34 UI/l)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gamma glutamyl transpeptidase (12-64 UI/l)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total bilirubin (5-21 UI/l)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Figure 1. Dynamic profile of laboratory findings in patient with coinfection including SARS-CoV-2 and influenza H1N1. RdRp: RNA-dependent RNA polymerases; N: envelope protein N; S: Spike protein; CpK: creatine phosphokinase; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; Mar: March; Apr: April; #: Total count. The values between parentheses ‘()’ in the ordinate axis correspond to the reference range values.
not all patients need ICU\(^1\). However, in a report by Cuadrado-Payán \textit{et al.}, all COVID-19 patients studied attended the emergency unit but had medical history of hypertension, end-stage kidney disease, or type 2 diabetes\(^2\).

The co-detection of SARS-CoV-2 and Influenza H1N1 in our case demonstrates the challenge to screen in the onset of the respiratory illness for a panel of viruses, which have overlapping clinical patterns and might exacerbate clinical symptoms, increase morbidity and prolong ICU stay. Hence, this case highlights the higher risk and poor outcomes caused by co-infection and the importance to achieve a differential diagnosis of respiratory distress syndromes, to limit contamination and adapt therapeutic strategies.

**Consent**

Written informed consent was obtained from the patient for the publication of this article and any associated images.

**Data availability**

All data underlying the results are available as part of the article and no additional source data are required.

---

**References**

Open Peer Review

Current Peer Review Status: ? ✓

Version 1

Reviewer Report 20 July 2021

https://doi.org/10.5256/f1000research.29738.r86503

© 2021 Sadki K. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Khalid Sadki
Laboratory of Human Pathologies Biology, Faculty of Sciences, Mohammed V University, Rabat, Morocco

The work submitted by the authors is an interesting case report. They report a French patient co-infected by two severe viruses, SARS-CoV-2 and 2009 H1N1 Influenza strain.

The most important physical examination and diagnostic tests are reported in the case report. The methodology followed is well reported. However, data concerning the genetic investigations for both viruses is missed. It is recommended to discuss it, taking into consideration the specific phenotype observed in this case.

Is the background of the case's history and progression described in sufficient detail? Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes? Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment? Partly

Is the case presented with sufficient detail to be useful for other practitioners? Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immunology and immunogenetics

I confirm that I have read this submission and believe that I have an appropriate level of
expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 21 June 2021

https://doi.org/10.5256/f1000research.29738.r86504

© 2021 Lansbury L. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Louise E. Lansbury

1 Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK
2 NIHR Nottingham Biomedical Research Centre, Nottingham, UK

In this case report, Baala et al. describe the clinical course of a patient with a history of pulmonary sarcoidosis who was co-infected with SARS-CoV-2 and influenza A (H1N1) virus and developed acute respiratory distress syndrome, requiring a prolonged ICU stay. The case is generally well-described and a useful reminder that the clinical presentation of SARS-CoV2 and influenza infections may overlap, and of the importance of the timely recognition of co-infection of SARS-CoV2 with other respiratory pathogens. However, the authors may wish to consider the following points:

Abstract:
- Please clarify the sentence: “Co-infection of SARS-CoV-2 and other respiratory syndrome has rarely been reported”. Do you mean: “Co-infection with SARS-CoV2 and other respiratory pathogens”?
- Italicisation of ‘respiratory distress syndrome’ is not required (also italicised in the title)

Introduction:
- “To date, there is no published case with a co-infection between SARS-CoV-2 and influenza H1N1”. This can no longer be claimed as there are now several reports of co-infections with these viruses from several countries.

Case Report:
- “The SARS-CoV-2 RT-PCR test was positive on March 22nd 2020.” Is there information on the date of onset of symptoms in relation to the timing of this test?
- Did the patient receive the seasonal influenza vaccine prior to the 2019-2020 influenza season?
- Would it be possible to present the chest CT-scan?
- How many days had the patient been in ICU before Candida albicans and Klebsiella pneumoniae were first isolated?
The authors indicate that an infection with *Enterococcus faecalis* infection was also treated; what was believed to be the source of this infection?

**Discussion:**

○ As per the previous comment, this is no longer the first case report of a co-infection with SARS-CoV-2 and influenza A (H1N1). However, the fact that it occurred in a patient with a history of pulmonary sarcoidosis is perhaps more original and may be worth emphasising more in the discussion (and perhaps also in the title?).

○ The effect of SARS-CoV-2 and influenza co-infection on prognosis could perhaps be considered in a little more detail in the Discussion. The studies cited (Ding *et al.*, Cuadrado-Payán *et al.*) indicated that the clinical and analytic courses of their patients did not differ from patients infected only with SARS-CoV-2. However, other studies have suggested that co-infection may be associated with worse outcomes (e.g. see Stowe *et al.* and Hashemi *et al.*).

Overall, I believe the case study contributes to the literature on patients who are co-infected with SARS-CoV-2 and influenza as there are many uncertainties regarding these patients. I support indexing but would recommend the clarifications I have suggested are considered.

**References**


**Is the background of the case's history and progression described in sufficient detail?**

Yes

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**

Yes

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**

Partly

**Is the case presented with sufficient detail to be useful for other practitioners?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Respiratory pathogens

I confirm that I have read this submission and believe that I have an appropriate level of
expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com