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Case Report

Acute respiratory distress syndrome due to SARS-CoV-2 and Influenza A co-infection in an Italian patient: Mini-review of the literature

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ABSTRACT

A case of acute respiratory distress syndrome due to SARS-CoV-2 and Influenza A co-infection and a mini-review of the literature is reported. Even in COVID-19 epidemics, the early identification of concurrent respiratory pathogens is important to improve etiological diagnosis, preventive measures and patients’ clinical management and outcome.

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Introduction

In December 2019, a novel coronavirus, the severe acute respiratory syndrome coronavirus–2 (SARS-CoV-2) which causes a human disease named coronavirus disease (COVID-19) was identified in the pneumonia outbreaks in Wuhan, China, in December 2019 (Chan et al., 2020). It is currently expanding rapidly to several countries all-around the world, on February 21 the first person-to-person transmission in Italy was reported (Spina et al., 2020). Here, we report a case of SARS-CoV-2 and Influenza A co-infection and a mini-review of the literature.

Case presentation

A 56-year-old male general surgeon was admitted to the Lazzaro Spallanzani National Institute for Infectious Diseases in Rome, Italy, on March 6, 2020. He was a smoker, within the overweight range (29-body mass index), with a history of two episodes of acute myocardial infarction treated with coronary angioplasty and stenting. For 4 days, he had been complaining of fever, diarrhea and asthenia after winter ski week in Northern Italy. Two days after the onset of symptoms, a nasopharyngeal swab was positive for SARS-CoV-2 (genes E and S) and Influenza A. On March 6, a chest computed tomography (CT) scan revealed bilateral and multiples peripheral ground glass opacities. Blood tests showed lymphopenia (lymphocyte and monocyte cell count: 0.67 and 0.09 × 10^9/L respectively), C-reactive protein and serum fibrinogen levels were increased (43.3 g/L and 7980 g/L respectively). An arterial oxygen tension (PaO2)/fractional inspired oxygen (FiO2) P/F Ratio was 320. Oral oseltamivir (75 mg twice per day for 5 days) and lopinavir/ritonavir (400/100 mg twice per days for 14 days) were started together with antibiotic therapy (intravenous ceftriaxone 2 gr and oral azithromycin 500 mg per day) and intravenous methylprednisolone (40 mg twice daily for 5 days with tapered discontinuation). On day eight of hospitalization, he developed respiratory failure (P/F Ratio dropped to 202) and a second chest CT scan showed a worsening of the bilateral ground-glass opacities with fibrotic consolidation in both lower pulmonary lobes (Figure 1a). At that time, nasopharyngeal swabs were positive for SARS-CoV-2, only. The patient was transferred to the Intensive Care Unit (ICU) and non-invasive ventilation through continuous positive airway pressure (C-PAP) mask was started with positive end-expiratory pressure (PEEP) 7.5 mmHg and FiO2 40%. After three days, he was re-admitted to the High Isolation Unit and discharged in good clinical conditions with persistently negative nasopharyngeal swabs. A SARS-CoV-2 serology by an in house indirect immunofluorescence assay (IgA 1:1280, IgM 1:320 and IgG 1:80) was positive

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Colavita et al., 2019). During the following week, low-grade fever re-occurred with nocturnal sweats, a third CT scan showed a reduction of the ground glass areas with residual interstitial damage (Figure 1b) and a further nasopharyngeal swab was negative. Symptoms healed spontaneously few days later.

**Discussion**

Previous cases of viral pneumonia SARS-CoV-2 and influenza coinfection have been reported in literature. During the new coronavirus epidemic, a total number of 37 cases were described.

**Table 1**

Clinical characteristics of SARS-CoV-2 and influenza coinfection, COVID-19 epidemic.

| References          | Sex | Age | Comorbidities                | Coinfection   | Oseltamivir | Antivirals | Glucorticoids | ARDS | ICU | NIV | IMV | Outcome          |
|---------------------|-----|-----|------------------------------|---------------|-------------|------------|---------------|------|-----|-----|-----|-----------------|
| Azekawa et al. (2020) | F   | 78  | Dyslipidemia, hypothyroidism | Influenza A   | Yes         | No         | No            | No   | No  | No  | No  | Survived        |
| Blasco et al. (2020) | NA  | NA  | NA                           | Influenza A   | NA          | NA         | NA            | NA   | NA  | NA  | NA  | Survived        |
| Cuadrado-Payán et al. (2020) | M   | 53  | ERSD                         | Influenza A   | Yes         | Yes        | NA            | Yes  | No  | Yes | No  | Survived        |
|                     | M   | 78  | T2DM                         | Influenza A   | Yes         | Yes        | NA            | Yes  | No  | Yes | No  | Survived        |
|                     | M   | 56  | T2DM                         | Influenza A   | No          | No         | NA            | No   | No  | No  | No  | Survived        |
|                     | F   | 81  | ERSD                         | Influenza A   | Yes         | Yes        | NA            | Yes  | No  | Yes | No  | Survived        |
| de Souza Luna et al. (2020) | F   | 36  | NA                           | Influenza B   | Yes         | Yes        | NA            | Yes  | No  | Yes | No  | Survived        |
| Ding et al. (2020)   | F   | 47  | None                         | Influenza A   | Yes         | Yes        | Yes           | No   | No  | No  | No  | Survived        |
|                     | M   | 50  | Hypertension, cancer         | Influenza A   | Yes         | Yes        | Yes           | Yes  | No  | Yes | No  | Survived        |
|                     | F   | 66  | Hypertension, CVD, HBV       | Influenza B   | Yes         | Yes        | No            | No   | No  | No  | No  | Survived        |
|                     | M   | 39  | HBV                          | Influenza B   | Yes         | Yes        | Yes           | No   | No  | Yes | No  | Survived        |
|                     | F   | 49  | None                         | Influenza A   | Yes         | Yes        | No            | No   | No  | No  | No  | Survived        |
| Garazzino et al. (2020) | F   | 78  | NA                           | Influenza A   | Yes         | Yes        | NA            | Yes  | NA  | NA  | NA  | NA              |
| Hashemi et al. (2020) | M   | 75  | NA                           | Influenza A   | Yes         | Yes        | NA            | Yes  | NA  | NA  | NA  | Dead            |
| Khodamoradi et al. (2020) | F   | 74  | Hypertension, CVD            | Influenza A   | Yes         | Yes        | No            | No   | No  | No  | No  | Survived        |
|                     | M   | 40  | None                         | Influenza A   | Yes         | Yes        | No            | No   | No  | No  | No  | Survived        |
|                     | M   | 64  | None                         | Influenza A   | Yes         | Yes        | No            | No   | No  | No  | No  | Survived        |
|                     | M   | 50  | None                         | Influenza A   | Yes         | Yes        | NA            | Yes  | No  | Yes | No  | Survived        |
| Kim et al. (2020)    | NA  | NA  | NA                           | Influenza A   | NA          | NA         | NA            | NA   | NA  | NA  | NA  | NA              |
| Konala et al. (2020b) | M   | 57  | Hypertension, T2DM, CVD, AICD | Influenza A   | Yes         | Yes        | No            | No   | No  | No  | No  | Survived        |
|                     | F   | 35  | Sickle cell trait            | Influenza A   | Yes         | Yes        | No            | No   | No  | No  | No  | Survived        |
|                     | F   | 68  | T2DM, hypertension, GERD     | Influenza B   | Yes         | Yes        | NA            | Yes  | No  | Yes | No  | Dead            |
| Konala et al. (2020a) | F   | 66  | T2DM, CVD, hypertension, CKD | Influenza A   | Yes         | Yes        | NA            | Yes  | No  | Yes | No  | Survived        |
| Nowak et al. (2020)  | NA  | NA  | NA                           | Influenza A   | NA          | NA         | NA            | NA   | NA  | NA  | NA  | NA              |
| Pongprukul et al. (2020) | M   | 61  | None                         | Influenza A   | NA          | NA         | NA            | NA   | NA  | NA  | NA  | NA              |
| Richardson et al. (2020) | NA  | NA  | NA                           | Influenza A   | NA          | NA         | NA            | NA   | NA  | NA  | NA  | NA              |
| Wehl et al. (2020)   | NA  | 4   | None                         | Influenza A   | No          | No         | NA            | No   | No  | No  | No  | Survived        |
|                     | NA  | <17 | NA                           | MP, Influenza  | NA          | NA         | NA            | NA   | NA  | NA  | NA  | NA              |
| Wu et al. (2020)     | M   | 69  | None                         | Influenza A   | Yes         | Yes        | No            | Yes  | No  | Yes | No  | Survived        |
| Zhu et al. (2020)    | NA  | NA  | NA                           | 2 pts Influenza A | NA  | NA         | NA            | NA   | NA  | NA  | NA  | NA              

SARS-CoV-2: severe acute respiratory syndrome coronavirus-2, COVID-19: coronavirus disease-19, CVD: cardiovascular disease, HBV: hepatitis B virus, NA: not available, ARDS: Acute Respiratory Distress Syndrome, ICU: Intensive Care Unit, NIV: non-invasive ventilation, IMV: invasive mechanical ventilation, T2DM: type 2 diabetes mellitus, AICD: automatic implantable cardioverter defibrillator, RSV: Respiratory syncytial virus, MP: Mycoplasma pneumonia, ESRD: end-stage kidney disease, CKD: chronic kidney disease, GERD: gastroesophageal reflux disease.
Table 1 summarizes the characteristics of the coinfected patients. Fourteen cases belonged to epidemiological studies and clinical data were not available. All patients had a similar clinical presentation (fever, cough and shortness of breath) and 9 of them (9/37, 24.3%) presented a progressive worsening with ARDS. Furthermore, six patients needed ICU monitoring and were subsequently discharged in good clinical conditions with the exception of three patients who died.

Even during a pandemic scenario, several respiratory pathogens should be considered in the diagnostic algorithm, for an early etiologic identification and appropriate treatment. SARS-CoV-2 and influenza viruses share common route of transmission, same season occurrence and overlapping clinical features (Lai et al., 2020; Chow et al., 2019). Indeed, SARS-CoV-2 exhibits prevalent human-to-human transmission through close contact with an estimated R0 of 3.28 and a median of 2.79 with IQR of 1.6 (Liu et al., 2020).

Respiratory symptoms are always the initial manifestations of both SARS-CoV-2 and influenza infections which could progress towards ARDS. Recently, ground-glass opacities and a higher median PaO2/FIO2 (198.2 vs 107.0) were observed in COVID-19-induced respiratory cases rather than H1N1 patients (Tang et al., 2020).

Nevertheless, a timely identification of the two co-infections is needed in relation to difference in treatments and prognosis. Antiviral therapy is currently available for influenza infection (i.e. oseltamivir, zanamivir, and peramivir) while experimental off-label drugs (i.e. lopinavir/ritonavir, chloroquine, and hydroxychloroquine) have been commonly used in COVID-19 treatment. In particular, the boosted protease inhibitor lopinavir/ritonavir has been previously associated with significantly fewer adverse clinical outcomes for the treatment of SARS and furthermore, in association with the Interferon Beta-1b, it has been demonstrated to be effective in animal studies against the Middle East Respiratory Syndrome (Chu et al., 2004; Chan et al., 2015). Considering the severity of the clinical picture and the prompt availability of lopinavir/ritonavir in our Institute, clinicians opted for this treatment although the antiviral effects remain to be determined (Cao et al., 2020).

Despite a recent report on beneficial effect of steroids treatment in COVID-19 patients who develop ARDS, its routinely use remains controversial with lack of an accurate assessment of the harm/benefit balance (Wu et al., 2020a).

The epidemiological situation in Italy in February 2020 and the recommendations in use at that time allowed a timely identification of our patient with a prompt hospitalization and subsequent diagnostic investigations. Therefore, the early antiviral treatments of both influenza and SARS-CoV-2, together with a brief steroid course and oxygen supplementation, had an impact on the patient’s outcome avoiding the progressive worsening and the evolution towards the severe ARDS phase. In conclusion, even in epidemic setting, the early and prompt identification of concurrent respiratory pathogens is important in order to improve etiologic diagnosis, preventive measures and patients’ clinical management and outcome. Further studies are needed to better understand the pathogenic role of viral coinfestions in respiratory diseases.

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Ethical approval
This study was approved by the Spallanzani Institute Ethical Board and patient’s written informed consent for publication was collected.

Conflict of interest
All authors have no conflict of interest to declare.

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