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Case report

A case series of coinfection with SARS-CoV-2 and influenza virus in Louisiana

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ABSTRACT

Severe acute respiratory syndrome coronavirus–2 (SARS-CoV-2) is the novel coronavirus initially detected in Wuhan, China, and is responsible for the worldwide pandemic coronavirus disease 2019 (Covid-19). Influenza is a common endemic respiratory virus that causes seasonal outbreaks of respiratory illness. There are currently few reports in the literature describing patients with coexisting infections. This case series of 4 patients identified at our single institution in Louisiana highlights the patient characteristics, laboratory findings, and outcomes in patients with both Covid-19 and influenza infection.

1. Introduction

Severe acute respiratory syndrome coronavirus–2 (SARS-CoV-2) is the novel coronavirus first detected in Wuhan, China that is responsible for the worldwide pandemic coronavirus disease 2019 (Covid-19). Since initial detection of the virus, more than 3 million cases have been confirmed worldwide with approximately 1 million cases confirmed in the United States [1]. Influenza is a viral infection that is associated with seasonal outbreaks of respiratory illness particularly during the winter months, and appears to be similar to Covid-19 in terms of transmission characteristics [2,3]. The United States Centers for Disease Control (CDC) estimates that influenza has resulted in 9–45 million cases, and 12,000–61,000 deaths annually since 2010 [4].

The common clinical manifestations of patients with influenza virus include fever, cough, rhinitis, sore throat, headache, dyspnea, myalgia, and radiographic evidence of pneumonia, which are similar to those of Covid-19 patients. Covid-19 and influenza infection demonstrate varying degrees of disease severity, from mild symptoms to severe respiratory illness leading to death. Factors associated with increased risks of severe influenza and complications of influenza include an age of 5 years or younger or of 65 years or older, and the presence of chronic medical conditions. The presence of coexisting medical conditions have also been reported to correlate with more severe disease in Covid-19 patients [4].

There have been few reports in the literature of patients with Covid-19 and influenza coinfection, and the effect on disease severity or outcomes in these patients have yet to be established. We performed a single institution retrospective review of Covid-19 positive patients who presented to Baton Rouge General Medical Center in Baton Rouge, Louisiana. A total of 4 patients out of 81 positive Covid-19 patients who presented to our institution between March 27 to April 18, 2020 were identified to have coinfection with influenza virus. The aim of this case series is to present patient characteristics, laboratory findings, and outcomes in patients with Covid-19 and influenza coinfection to provide further insight on this novel disease.

1.1. Case presentations

1.1.1. Case 1

A 66-year-old Caucasian male healthcare worker with a medical history of diabetes mellitus and hypertension presented to our hospital on March 26, 2020 from home with 1 week complaints of progressive shortness of breath, cough with minimal expectoration, fevers, and watery diarrhea. On presentation, he had a temperature of 99.7 °F, heart rate of 92 beats/minute, respiratory rate of 24 breaths/minute, blood pressure of 120/85 mmHg, and oxygen saturation of 96% on room air. Physical exam was significant for tachypnea without accessory muscle use and decreased breath sounds at the bilateral lung bases. Admission laboratory studies revealed an acute kidney injury, a normal WBC with lymphopenia, mildly elevated aspartate aminotransferase (AST), and elevations in several inflammatory markers (Tables 1 and 2). He was also found to have an abnormal troponin of 0.535 ng/mL with a normal electrocardiogram. Chest radiograph showed an infiltrate in the left lower lobe with mild vascular congestion (Fig. 1). The rapid influenza

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Table 1
Admission laboratory studies.

	Case 1	Case 2	Case 3	Case 4	Reference ranges
BUN	33	27	20	24	7–18 mg/dL
Creatinine	2.17	1.28	5.94	1.28	0.5–1.2 mg/dL
Albumin	2.7	3.1	2.2	3.3	3.4–5.0 g/dL
Total protein	7.2	8.9	8.2	8.3	6.4–8.6 g/dL
ALT	41	38	6	32	16–61 U/L
AST	56	62	24	53	15–37 U/L
Alkaline phosphatase	82	52	92	41	45–117 U/L
Bilirubin total	0.6	0.7	0.4	0.9	0.2–1.0 mg/dL
WBC count	6.23	7.48	8.17	4.33	4.0–11.0 K/μL
Absolute lymphocyte count	940	1160	1030	730	1180-3740/μL
Hemoglobin	14.6	11.7	9.9	15.5	11.2–15.7 g/dL
Hematocrit	44.6	38.4	33.5	48.5	34.1–44.9%
Platelet count	188	284	243	181	150–400 K/μL
Troponin	0.535	<0.015	<0.015	N/A	0.000–0.045

BUN: blood urea nitrogen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; WBC: white blood cell; N/A: not applicable.

Table 2
Inflammatory markers.

	Case 1	Case 2	Case 3	Case 4	Reference ranges
CK	312	665	57	N/A	26–192 U/L
LDH	280	450	305	N/A	84–246 U/L
CRP	5.17	15.6	20.80	N/A	0.00–1.00 mg/dL
Ferritin	491.3	938.7	1725	N/A	8.0–252.0 ng/mL
D-dimer	0.53	0.79	2.14	N/A	0.00–0.39 μg/mL

CK: creatine kinase; LDH: lactate dehydrogenase; CRP: *C*-reactive protein; N/A: not applicable.

diagnostic test (RIDT) returned positive for influenza B infection via nasopharyngeal swab. The patient also tested positive for SARS-CoV-2 via reverse–transcriptase–polymerase-chain–reaction (RT–PCR) of a nasopharyngeal swab. He was treated with 5 days of azithromycin oral 250 mg/day. The patient remained febrile for the first 3 days of hospitalization and then remained afebrile for the remainder of his hospitalization. The patient was discharged home on day 6 and did not require supplemental oxygen during his hospitalization.

Case 1 (A): infiltrate in the left lower lobe with mild vascular congestion; Case 2 (B): patchy diffuse bilateral pulmonary infiltrates; Case 3 (C): infiltrates of the right lung base and right perihilar region; Case 4 (D): streaky opacities within the lower lungs fields bilaterally.

1.1.2. Case 2

A 60-year-old African American female healthcare worker with a medical history of diabetes mellitus and hypertension presented to our hospital on April 4, 2020 with a 2 week history of fevers, cough, malaise, myalgias, and progressive shortness of breath. On presentation, she had a temperature of 99.1 °F, heart rate of.

106 beats/minute, respiratory rate of 21 breaths/minute, blood pressure of 110/51 mmHg, and oxygen saturation of 76% on room air. She was placed on 20 L high-flow nasal cannula with improvement in her saturations to 96%. Physical exam was significant for bilateral coarse breath sounds. Initial laboratory testing revealed a normal WBC with mild lymphopenia, and elevations in AST and several inflammatory markers (Tables 1 and 2). Chest radiograph revealed patchy diffuse bilateral pulmonary infiltrates (Fig. 1). Her RIDT returned positive for influenza B via nasopharyngeal swab. She also tested positive for SARS-CoV-2 that was obtained via outpatient RT–PCR assay of a nasopharyngeal swab 5 days prior to presentation. The patient was admitted to the intensive care unit (ICU) and initiated on intravenous (IV) levofloxacin 750 mg/day, IV vancomycin 1.25 g/twice daily, oral oseltamivir 75 mg/twice daily, and oral hydroxychloroquine 400 mg/twice daily for one day and 200 mg/twice daily for 4 days. She also received a one time dose of IV methylprednisolone 60 mg and was transitioned to oral prednisone 40 mg/day. On day 2 of hospitalization she was transferred to the general medical ward on 4 L nasal cannula. Levofloxacin and vancomycin were discontinued after 2 days. She remained afebrile throughout hospitalization. On day 5 of hospitalization she was maintaining oxygen saturations of 98% on room air and was discharged home with 2 L of supplemental oxygen as needed. She completed 5 days of prednisone, hydroxychloroquine, and oseltamivir.

1.1.3. Case 3

A 62-year-old African American female with a medical history of end-stage renal disease on hemodialysis, anemia of chronic kidney disease, diastolic heart failure, hypothyroidism, diabetes mellitus, and chronic left foot ulcer presented to our hospital on April 17, 2020 from a nursing home with 1 day complaints of cough, dyspnea, and fevers. The patient's roommate was reported to be recently diagnosed with Covid-19 infection. The patient was recently initiated on antibiotics with IV vancomycin 1g/daily and oral metronidazole 500 mg/three times daily for a left foot ulcer on April 13, 2020 to complete a total of 10 days. Upon presentation, she had a temperature of 102 °F, heart rate of 83 beats/minute, respiratory rate of 27 breaths/minute, blood pressure of 110/51 mmHg, and oxygen saturation of 87% on room air. She was placed on 2 L of supplemental oxygen with improvement in her oxygen saturations to 95%. Physical exam was significant for tachypnea with accessory muscle use and decreased breath sounds at the bilateral lung bases. Initial laboratory testing revealed a normal WBC with mild lymphopenia and elevations in several inflammatory markers (Tables 1 and 2). Chest radiograph revealed infiltrates of the right lung base and right perihilar region (Fig. 1). RIDT via nasopharyngeal swab returned positive for influenza A infection. The patient also tested positive for SARS-CoV-2 via RT–PCR assay of a nasopharyngeal swab. She was initiated on IV levofloxacin 750 mg/day in addition to the continuation of vancomycin and metronidazole antibiotics. The patient was also started on oral hydroxychloroquine 400 mg/twice daily for one day and 200 mg/twice daily for 4 days and oral oseltamivir 75 mg/twice daily for 5 days. Levofloxacin was discontinued on day 2 of hospitalization. The patient improved throughout her hospitalization and was successfully weaned off of supplemental oxygen to room air, and remained afebrile after 3 days of initial hospitalization. She completed 5 days of oseltamivir and hydroxychloroquine. The patient was discharged to the nursing home after 6 days of hospitalization.

1.1.4. Case 4

A 58-year-old African American male with no significant past medical history presented to the emergency department on April 13, 2020 with increasing dyspnea, intermittent body aches, and cough for 5 days duration. He initially presented to an urgent care facility 1 day prior where he was diagnosed with influenza A via RIDT of a nasopharyngeal swab. He was given azithromycin 500 mg/day for one day, 250 mg/day for 4 days, and instructed to self-isolate at his home. However, the patient's symptoms worsened, which prompted his presentation to the emergency department. Upon presentation, the patient had a temperature of 99.9 °F, heart rate of 91 beats/minute, respiratory rate of 17 breaths/minute, blood pressure of 115/61, and oxygen saturation of 94% on room air. On physical exam, his breathing was non-labored and lung sounds were clear to auscultation bilaterally. Chest radiograph showed streaky opacities within the lower lungs fields bilaterally. Repeat RIDT via nasopharyngeal swab on admission was positive for influenza B and negative for influenza A infection. The patient was deemed to be clinically stable and was discharged home from the emergency department. He was discharged home with a 7 day course of amoxicillin-clavulanate 875-125mg/day. Subsequent SARS-CoV-2 RT-PCR testing returned positive following discharge.

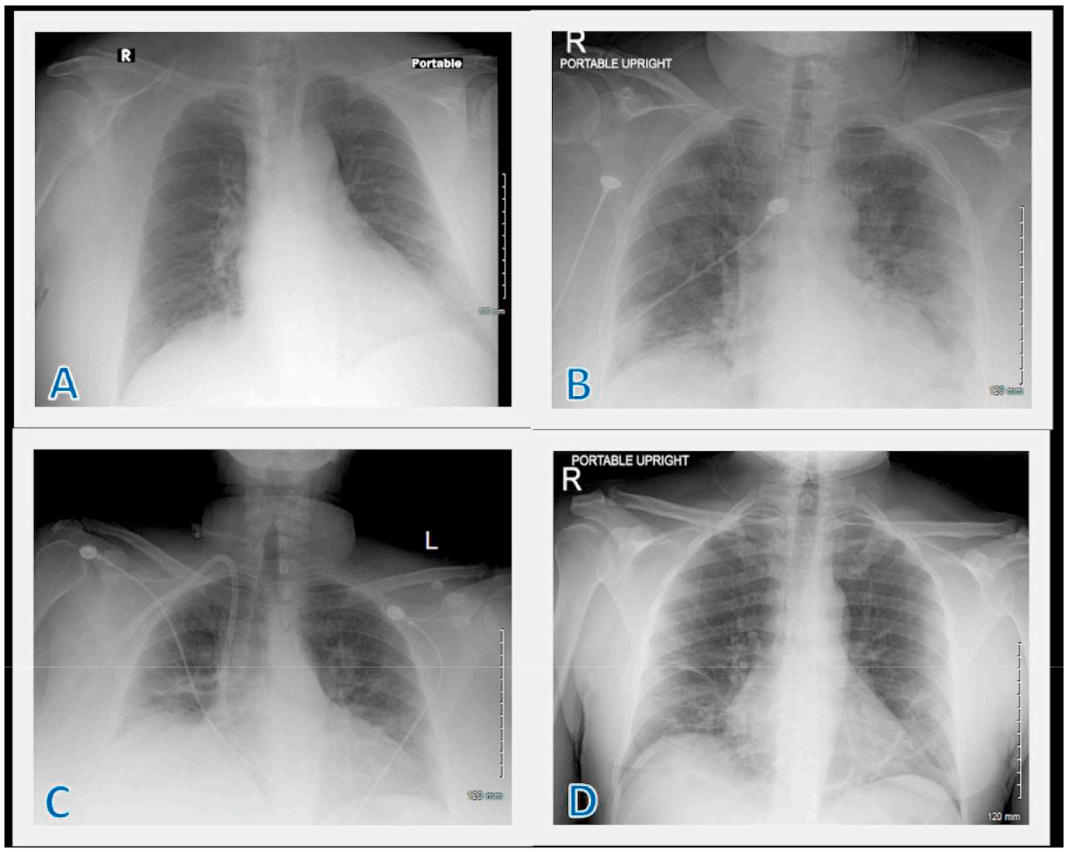

Fig. 1. Chest radiographs.

2. Discussion

Severe acute respiratory syndrome coronavirus–2 (SARS-CoV-2) is the novel coronavirus that causes the pandemic known as coronavirus disease 2019 (Covid-19) and is responsible for approximately 3 million cases and 200,000 deaths worldwide. Influenza is a common endemic respiratory virus that causes seasonal outbreaks of respiratory illness, particularly during the winter months. SARS-CoV-2 and influenza viruses cause varying degrees of disease severity, from mild symptoms to severe respiratory illness requiring mechanical ventilation and even death. There have been few reports in the literature of patients with Covid-19 and influenza coinfection, and the effect on disease severity or outcomes in these patients has yet to be established.

In this case series, we identified 4 cases of coinfection with influenza out of the 81 positive Covid-19 patients who presented to our institution, with an incidence rate of 4.9%. While no official numbers exist as far as rates of influenza coinfection, review of the literature suggests that the rate ranges anywhere from 0.08 to 90%, depending on region. In a retrospective chart review performed by Zhou and Ding at a single hospital center in Wuhan, China, the authors found that nine out of 1054 (0.9%) patients who tested positive for Covid-19 also tested positive for influenza [5]. In another cohort of cases from the same region, 5 out of 115 (4.35%) patients who tested positive for Covid-19 also tested positive for influenza [6]. On the contrary, a double-center study conducted by Xing and Li found that rates of coinfection in Qingdao, China were much higher than that in Wuhan, as much as up to 60% for influenza A and 53% of influenza B, although the sample sizes were considerably smaller in this particular study.

[7]. The authors suggested that localities with more temperate climates (i.e Qingdao) may have higher rates of coinfection with influenza and other respiratory viruses than places in subtropical climates. While a majority of novel coronavirus studies have been performed in China, other places around the globe have also reported simultaneous influenza infection with Covid-19. In a sample of 116 specimens from multiple sites in Northern California who were positive for SARS-CoV-2, 1 (0.9%) was found to test positive for influenza A [8]. In a retrospective study conducted in New York City, investigators found a coinfection rate of only 0.08%, however it is important to note that only 13% of Covid-19 positive samples were tested for influenza [9]. Furthermore, a case-series published in Iran reported four cases of coinfection with Covid-19 and influenza A [10].

The rapid influenza diagnostic test (RIDT) is an antigen detection assay that can detect influenza viral antigens in 10–15 minutes. Most rapid influenza diagnostic tests have a sensitivity of 50–79% for detecting influenza virus antigens and greater than 90% specific [11]. Sensitivity of RIDTs to detect influenza B viral antigens is lower than for detection of influenza A viral antigens. Tests with low to moderate sensitivity and high specificity have the potential to produce false negative results more commonly than false positive results, especially during peak influenza activity in the community. In contrast, false-positive RIDT results are less likely, but can occur especially during periods of low influenza activity. When interpreting RIDT results it is important for clinicians to consider that a positive result means that an influenza viral antigen was detected, but does not necessarily mean a viable influenza virus is present or that the patient is contagious. Clinicians are advised to consider the clinical presentation when interpreting the results of RIDTs. This may pose diagnostic difficulties considering the similar presentation of Covid-19 and influenza infections. Interestingly, the patient discussed in case 4 had a positive RIDT for influenza A and negative for influenza B initially, and then on repeat testing returned positive for influenza B and negative for influenza A. In order to further address these potential issues follow up with confirmatory tests such as RT-PCR or viral culture may be beneficial.

The ages of the patients identified in this case series ranged from 58 to 66 with the average age being 61.5 years (Table 3). The 3 patients

Table 3
Patient characteristics and outcomes.

	Case 1	Case 2	Case 3	Case 4
Age— years	66	60	62	58
Gender	Male	Female	Female	Male
BMI [a]	38.5	40.7	58.9	26.7
Race	Caucasian	African American	African American	African American
Co-existing medical conditions	Diabetes mellitus Hypertension	Diabetes mellitus Hypertension	Diabetes mellitus Diastolic heart failure End-stage renal disease	None
ICU	No	Yes	No	No
Oseltamivir	No	Yes	Yes	No
Antibiotic therapy	Yes	Yes[b]	Yes[b]	Yes
Hydroxychloroquine	No	Yes	Yes	No
Length of stay—days	6	5	6	0
Outcome	Discharged	Discharged	Discharged	Discharged

[a] The body-mass index is the weight in kilograms divided by the square of the height in meters; N/A: not applicable.
[b] In both cases, antibiotic therapy for viral pneumonia was discontinued after two days of hospitalization.

who were classified as obese (i.e body mass index (BMI $\geq$ 30.0)) were admitted to the hospital, as opposed to the patient with a BMI of 26.7 who was discharged home from the emergency department. Furthermore, the 2 patients who met criteria for severe obesity (BMI $\geq$ 40) required supplemental oxygen, with 1 of them requiring ICU level of care. This is consistent with previous reports linking obesity to more severe illness and complications from Covid-19, which is thought to be due to increased expression of cytokines leading to a dysregulated inflammatory response. It is also reported that obesity can impair the adaptive immune response to both the SARS-CoV-2 virus as well as the influenza virus [12]. In regards to co-existing medical conditions, all 3 of our hospitalized patients had multiple comorbidities, with the most common being diabetes mellitus and hypertension. This is also consistent with studies linking comorbid conditions to disease severity in Covid-19 as well as influenza [13,14].

Previous studies have suggested a correlation between severe disease with lymphopenia and elevations in several inflammatory markers [15]. Inflammatory markers were not obtained for 1 patient who was discharged from the emergency department. The patient described in case 2 who required ICU admission demonstrated higher elevations in their inflammatory markers CK, LDH, and ferritin. The patient in case 3 also demonstrated higher inflammatory markers, although was being treated with IV antibiotics prior to admission for an underlying infection. Lymphopenia was common in our patient population and was seen in all 4 patients. Elevations of AST on admission were also observed in 3 of our patients. There are currently no reports in the literature discussing the specific significance of inflammatory marker elevations in patients with influenza and Covid-19 coinfection. One retrospective study of 5 patients with Covid-19 and influenzavirus coinfection found that these patients did not appear to show more severe disease based on the laboratory findings, imaging studies, and patient prognosis [6]. Our patients demonstrated similar clinical outcomes, with all 4 patients being discharged; although, 1 patient required ICU admission, she did not require mechanical ventilation and was transferred out of the ICU after 2 days. (Table 3). The average length of stay was 4 $\pm$ 3 days, with 1 patient being discharged from the emergency department. There is currently very limited data concerning patients with Covid-19 and influenza coinfection; although, our small case series also suggests that the presence of coinfection alone does not appear to result in more severe disease presentations. This finding may be attributed to the small sample size studied along with failure to accurately identify all hospitalized patients with coinfection. Further reports are needed to investigate the impact of coinfection on disease severity and guidance on clinical management.

3. Conclusion

The SARS-CoV-2 and influenza viruses have been known to cause mild to severe respiratory illness. There is a sparsity in the literature concerning coinfection of these two respiratory viruses and their impact on clinical outcomes. Here we reported 4 cases of patients with coinfection of Covid-19 and influenza. Our study did not demonstrate more severe disease with coinfection. Due to lack of cotesting for both Covid-19 and influenza in every patient, we estimate the incidence of coinfection to be higher in the general population. We also estimate the incidence to be variable by region due to climate differences. This case series highlights the necessity of further clinical reporting and guidance on clinical management.

Consent

Patient consents were obtained for this case series.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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