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A Case Series of Patients Coinfected With Influenza and COVID-19

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Abstract

Coronavirus disease 2019, also called COVID-19, is a global pandemic resulting in significant morbidity and mortality worldwide. In the United States, influenza infection occurs mainly during winter and several factors influence the burden of the disease, including circulating virus characteristics, vaccine effectiveness that season, and the duration of the season. We present a case series of 3 patients with coinfection of COVID-19 and influenza, with 2 of them treated successfully and discharged home. We reviewed the literature of patients coinfected with both viruses and discussed the characteristics, as well as treatment options.

Keywords

coronavirus disease 2019, COVID-19, influenza A, influenza B, acute respiratory distress syndrome

Introduction

Coronavirus disease 2019, also called COVID-19, is a global pandemic resulting in significant morbidity and mortality. The cluster outbreak of cases of pneumonia from severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) was reported in December 2019 in Wuhan, China.[1] The COVID-19 has spread across the world at a fierce pace, and the United States has the highest number of infected patients, which led to the highest mortality in the world.[2]

The influenza pandemic occurs in the winter, and the mode of transmission is the same as that of COVID-19. The most common clinical symptoms in influenza are fever, cough, shortness of breath, fatigue, headache, and myalgia, which are similar to COVID-19.[3] There have been only a few cases of coinfection from influenza and COVID-19 reported before. In this article, we describe 3 cases of coinfected cases of influenza and COVID-19 in the United States.

Case Series

Patient 1

A 57-year-old male presented to the emergency department with a complaint of on and off fever as well as dry cough going on for 2 weeks and worsening shortness of breath for 2 days. He initially had a dry cough, which later became productive with brownish sputum. The fever was associated with headaches, sore throat, and myalgia and did not subside with ibuprofen and paracetamol. He denied any recent sick contact or recent travel. The patient's past medical history was significant for hypertension, diabetes mellitus, and myocardial infarction–automatic implantable cardioverter defibrillator (AICD) insertion. The patient denied any history of smoking, alcohol use, or illicit drug use.

On admission, the patient had a temperature of 101.3 °F, pulse rate of 123 beats per minute, respiratory rate of 22 breaths per minute, blood pressure of 100/90 mm Hg, and

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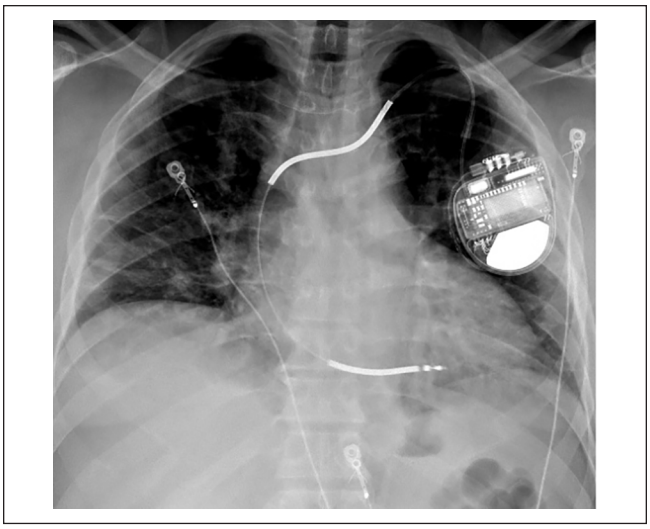

Figure 1. Chest X-ray showing septal bilateral patchy lung infiltrates.

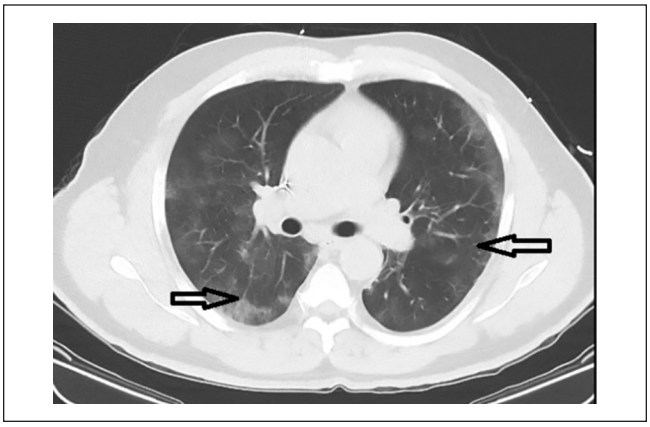

Figure 2. Computed tomography of the chest without contrast showing patchy bilateral ground-glass opacities in the periphery of both lungs.

oxygen saturation of 92% on room air. Physical examination was significant for right basal crackles and palpable AICD.

The electrocardiogram showed sinus tachycardia without ST-T wave changes and normal QTc interval. Chest X-ray showed septal bilateral patchy lung infiltrates versus atelectasis (Figure 1). The patient underwent computed tomography (CT) of the chest without contrast, which showed patchy bilateral ground-glass opacities in the periphery of both lungs (Figure 2) with suspicion for COVID-19 given clinical symptoms and radiological findings.

The patient was admitted to the medical floor for treatment of pneumonia as well as to rule out COVID-19 infection. Influenza and COVID-19 nasopharyngeal swabs were sent. The patient was started on 3 L of oxygen via nasal cannula with oxygen saturations above 95%. He was started on antibiotics with ceftriaxone and azithromycin. The patient

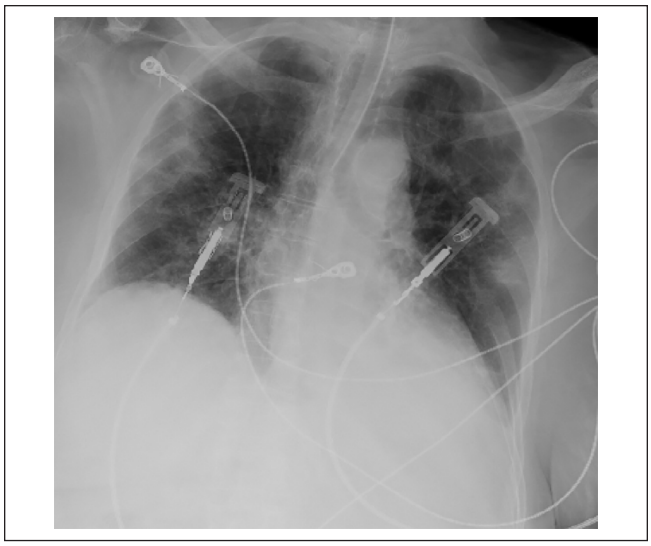

Figure 3. Chest X-ray showing moderate bilateral alveolar infiltrates right more than left.

was positive for both COVID-19 and influenza A. The patient was then started on oseltamivir along with hydroxychloroquine with QTc monitoring after an infectious disease and pulmonary consult. The patient completed a 5-day course of ceftriaxone, azithromycin, hydroxychloroquine, and oseltamivir. The patient remained afebrile and was saturating above 95% on room air for 72 hours and was discharged home.

Patient 2

A 35-year-old female presented with fever, headaches, dry cough, worsening shortness of breath, and diarrhea for 5 days. The highest recorded fever at home was 104 °F, which responded to acetaminophen. The patient worked as an airline manager and has not traveled, but has come in contact with a large number of international travelers. Her past medical history was significant for sickle cell trait.

On admission, the patient's temperature was 103.3 °F, pulse rate of 121 beats per minute, respiratory rate of 18 breaths per minute, blood pressure of 117/70 mm Hg, and oxygen saturation of 97% on room air. Physical examination was significant for tachycardia, respiratory distress, and fine crackles on the left lower chest on auscultation.

The electrocardiogram showed sinus tachycardia at a ventricular rate of 121 beats per minute without ST-T wave changes along with normal QTc intervals. A portable chest X-ray reported moderate bilateral alveolar infiltrates right more than left (Figure 3). CT scan of the chest without contrast revealed extensive scattered bilateral infiltrates right greater than left (Figure 4). Given the patient's history as well as radiological findings, COVID-19 was suspected.

The patient subsequently tested positive for influenza A and COVID-19. Blood and urine cultures revealed no

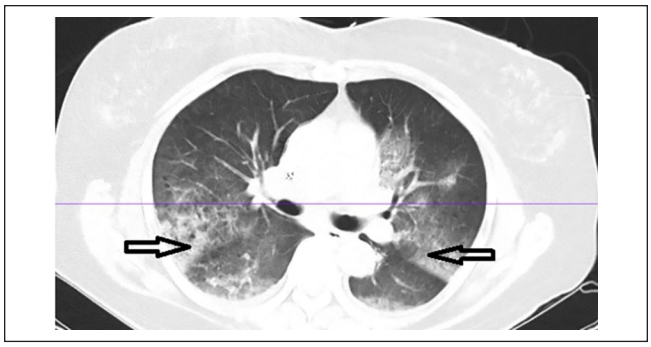

Figure 4. Computed tomography of the chest without contrast showing extensive scattered bilateral infiltrates right greater than left.

growth. The patient was treated with intravenous (IV) ceftriaxone, IV azithromycin, and oseltamivir. She also received hydroxychloroquine after COVID-19 was positive. Corrected QTc interval was monitored regularly. After consecutive 6 days of fever, the patient remained afebrile from day 7 onward. Oxygen saturation was maintained with oxygen 2 to 3L via nasal cannula. The patient was discharged home after she reported symptomatic improvement in shortness of breath and fever.

Patient 3

A 68-year-old female presented to the emergency department with a chief complaint of altered mental status and worsening shortness of breath along with mild diarrhea. Detailed history could not be elicited because of altered mental status. Her past medical history was significant for diabetes mellitus, hypertension, and gastroesophageal reflux disease.

On arrival to the emergency department, the patient was saturating 62% on room air, which improved to 90% with oxygen via a nonrebreather mask. The patient was tachycardic and tachypneic on the presentation at 119 beats per minute and respiratory rate at 28 breaths per minute, respectively. Her temperature was 102 °F, blood pressure of 100/82 mm Hg. Physical examination was significant for a confused patient in acute distress with tachypnea and tachycardia along with bibasal crackles. The patient's condition continued to deteriorate and required intubation and ventilation due to respiratory muscle fatigue.

A portable chest X-ray revealed mild-to-moderate pulmonary venous congestion, hazy airspace opacities bilaterally, which may represent diffuse pneumonia versus alveolar edema and very small bilateral pleural effusions (Figure 5). CT of chest without contrast showed extensive scattered bilateral infiltrates (Figure 6). Electrocardiogram revealed a ventricular rate of 112 beats per minute with a corrected QTc interval of 450 ms.

The patient tested positive for COVID-19 and influenza A and was treated with ceftriaxone, azithromycin,

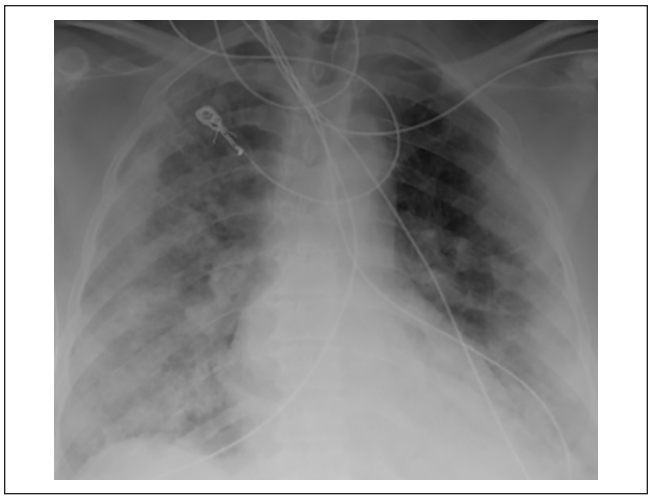

Figure 5. Chest X-ray showing mild-to-moderate pulmonary venous congestion, hazy airspace opacities bilaterally.

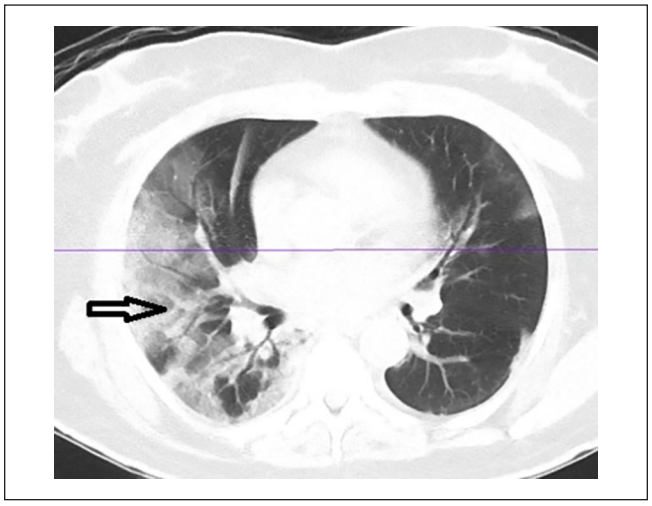

Figure 6. Computed tomography of the chest without contrast showing extensive scattered bilateral infiltrates.

hydroxychloroquine. The patient also had acute kidney injury with a history of chronic kidney disease and improved with IV hydration. The patient, unfortunately, had a cardiac arrest on day 1 of admission with unsuccessful cardiac resuscitation.

The laboratory testing for all patients are summarized in Table 1. All patients had lymphopenia along with elevated C-reactive protein, erythrocyte sedimentation rate, creatinine kinase, fibrinogen, D-dimer, interleukin-6 levels, lactic acid, and lactate dehydrogenase.

Discussion

The novel coronavirus spike (S) protein attaches to the membrane-bound angiotensin-converting enzyme 2 (ACE 2) and cleaved by serine proteases to gain access into the human

Table 1. Summary of Laboratory Abnormalities.

Parameters	Reference range	Patient 1	Patient 2	Patient 3
Hemoglobin	11-15 (g/dL)	14.4	14.9	16.5
Hematocrit	35-46 (%)	41.9	33.5	39.3
WBC	4.5-11 (10^3/μL)	8.4	5.3	8.9
Lymphocytes	22-48 (%)	16.0	12.0	17.7
Neutrophils	40-70 (%)	77.6	82.9	72.5
ESR	0-20 (mm/h)	67	60	80
Sodium	136-145 (mmol/L)	139	134	136
Potassium	3.5-5.1 (mmol/L)	4.7	4.4	5.7
BUN	9.8-20.1 (mg/dL)	12.2	9.9	22.3
Creatinine	0.57-1.11 (mg/dL)	1.35	1.11	1.55
Glucose	70-105 (mg/dL)	100	117	433
HbA1c	4.8-5.6 (%)	6.5	5.7	7.4
Phosphorus	2.3-4.7 (mg/dL)	3.2	3.8	4.1
Magnesium	1.6-2.6 (mg/dL)	2.3	2.2	2.3
Ferritin	30-400 (ng/mL)	507	300	410
Lactate dehydrogenase	125-220 (U/L)	339	337	1046
Creatine kinase	29-168 (U/L)	630	483	2430
C-reactive protein	0-10 (mg/L)	97	39	43
Troponin I	0.00-0.03 (ng/mL)	$<$0.03	$<$0.00	0.05$>>$0.06
Fibrinogen	193-507 (mg/dL)	692	567	476
D-dimer	0-500 (ng/mL)	1040	1974	4215
IL-6	0.0-15.5 pg/mL	283.7	205.5	1154.8
B-natriuretic peptide	10-100 (pg/mL)	80	$<$10	70.97
Lactic acid	0.5-1.9 (mmol/L)	3.1	3.4	3.5
Influenza	Type A Ag/Ab Type B Ag/Ab	Positive, type A antigen PCR: positive	Positive, type A antigen PCR: positive	Positive, type B antigen PCR: positive
SARS-CoV-2	PCR	Positive, PCR	Positive, PCR	Positive, PCR

Abbreviations: WBC, white blood cells; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; HbA1c, hemoglobin A1c; IL, interleukin; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus 2.

cell.[4] ACE 2 is widely distributed in the lungs, kidneys, gastrointestinal tract, oral, and nasal mucosa. COVID-19 causes activated T-cell response and increased pro-inflammatory cytokines levels. In severe cases, these increased levels can cause a cytokine storm and damages healthy tissue than the virus.[4,5]

COVID-19 causes mostly fever, cough, sore throat, and shortness of breath, which in most cases are self-limiting. Some individuals harbor the virus and are asymptomatic. They play a crucial role in the spread of the virus in the community.[1]

COVID-19 primarily affects the lungs causing dyspnea, hypoxia, and can cause severe infections resulting in acute respiratory distress syndrome (ARDS). In severe cases, patients often need intensive care unit admission causing multi-organ failure and death.[1]

COVID-19 co-circulates in the environment along with other respiratory viruses and, most importantly, influenza. The study from a hospital in Wuhan, which analyzed the epidemiological, demographic, and laboratory data from the COVID-19 and influenza cases visited between January 2017 and February 2020. There was a decreased number of influenza A and B cases in 2020 compared with the previous years. COVID-19 interfered with the seasonal influenza epidemic. There were 9 coinfection cases of influenza and COVID-19 reported in 1054 cases.[6] As per Centers for Disease Control and Prevention estimates from 2018-2019, approximately 35 million people were infected with influenza that resulted in approximately half million hospitalizations. Thirty-four thousand patients died from influenza last year.[3]

A double-center study was done in China to analyze coinfections of common respiratory pathogens in COVID-19. A total of 68 patients with SARS-CoV-2 infection were recruited, 38 from Wuhan and 30 from Quingdao. Among them, 24 (80%) patients from Quingdao had an immunoglobulin M antibody against 1 respiratory pathogen, compared with only 1 patient in Wuhan. The most common respiratory pathogens detected were influenza A, influenza B in the majority of cases, followed by *Mycoplasma pneumonia* and *Legionella pneumophilia*. This shows that the coinfection pattern differs significantly depending on the geographic area.[7]

In an experience described by Wuhan, only 5 patients among 115 were coinfected with influenza and COVID-19. In those 5 patients, 3 patients had influenza A, and 2 patients had

Table 2. Multiple Treatment Options Under Investigation for COVID-19.

Drug used	Phase/number of study participants	Type of study	Mode of administration
Standard treatment with or without lopinavir plus ritonavir, with or without arbidol	Phase 4/125	Open-labelled, randomized controlled clinical trial	Oral
Hydroxychloroquine sulfate vs placebo	Phase 4/202	Two-arm, open-label, pragmatic randomized controlled trial	Oral
Colchicine or placebo	Phase 3/6000	Randomized, double-blind, placebo-controlled multicenter study	Oral
Convalescent plasma	Phase 2/20	Open-label, phase 2A single center clinical trial	IV
Lopinavir/ritonavir, ribavirin and interferon-β-1b combination vs lopinavir/ritonavir alone	Phase 2/70	Prospective open-label randomized controlled trial	Lopinavir/ritonavir, ribavirin—oral, interferon-β-1b—subcutaneous
Recombinant human interferon-α-1b (low-risk group) Recombinant human interferon-α-1b and thymosin-α-1 (high-risk group)	Phase 3/2944	Open-label, nonrandomized, parallel assignment	Recombinant human interferon-α-1b—nasal Thymosin-α-1—subcutaneous
Mesenchymal stem cell in treating pneumonia patient's vs placebo with standard treatment in both arms	Phase 1/20	Open-label, nonrandomized, parallel assignment	IV
Natural killer cells treatment in pneumonia patient's vs placebo with standard treatment in both arms	Phase 1/30	Open-label, nonrandomized, parallel assignment	IV
Anti-SARS-CoV-2-inactivated convalescent plasma	NA	Prospective observational case only	IV
Favipiravir combined with chloroquine phosphate vs favipiravir vs placebo	Phase 2/3—150	Multicentered, 3-armed, randomized, double-blinded, controlled study	Both drugs—oral
Nitric oxide gas inhalation therapy for mechanically ventilated patients with severe acute respiratory syndrome vs placebo	Phase 2/200	Multicenter randomized controlled trial with 1:1 individual allocation	Inhalation
Low-dose chloroquine vs high-dose chloroquine	Phase 2b/200	Phase IIb, double-blind, randomized adaptive clinical trial	Oral
Sargramostim vs placebo along with standard of care in both arms	Phase 4/80	Prospective, randomized, open-label, interventional study	Inhalation or IV
Remdesivir 5 days vs 10 days along with SOC	Phase 3/400	Open-label, randomized, parallel assignment	IV
Remdesivir 5 days vs 10 days along with SOC	Phase 3/600	Open-label, randomized, parallel assignment	IV
Vitamin C	Phase 2/140	Open-label, randomized, parallel assignment	IV
DAS181	Phase 3/250	Randomized placebo-controlled study, parallel assignment	Nebulizer, inhalation
Sarilumab	Phase 2-3/250	Randomized, double-blind, placebo-controlled, parallel assignment	IV
Pirfenidone	Phase 3/294	Open-label, randomized, parallel assignment	Oral
Sarilumab	Phase 2-3/300	Randomized, double-blind, placebo-controlled, parallel assignment	IV

(continued)

Table 2. (continued)

Drug used	Phase/number of study participants	Type of study	Mode of administration
Remdesivir vs lopinavir/ritonavir vs interferon-β-1A vs hydroxychloroquine vs SOC	Phase 3/3100	Randomized, multicenter, adaptive parallel assignment	Remdesivir—IV, lopinavir/ritonavir—oral, interferon-β-1A—subcutaneous, hydroxychloroquine—oral
Escin vs SOC	Phase 2-3/120	Double-masked, nonrandomized, parallel assignment	Oral
Bevacizumab	Phase 2/20	Open-label, single group assignment	IV
Fingolimod	Phase 2/30	Open-label, nonrandomized, parallel assignment	Oral
Favipiravir combined with tocilizumab vs favipiravir vs tocilizumab	150	Open-label, multicenter, randomized, parallel assignment	Favipiravir—oral Tocilizumab—IV
Hydroxychloroquine + azithromycin vs hydroxychloroquine	Phase 3/440	Open-label, randomized, parallel assignment	Oral
Darunavir and cobicistat	Phase 3/30	Open-label, randomized, parallel assignment	Oral
BCG vaccine	Phase 3/4170	Two group, multicenter, open-label randomized parallel assignment	Intradermal
Combination of lopinavir/ritonavir and interferon-β-1b	Phase 2-3/194	Recursive 2-stage group sequential multicenter placebo-controlled double-blind randomized parallel assignment	Lopinavir/ritonavir—oral, interferon-β-1b—subcutaneous

Abbreviations: IV, intravenous; SARS-CoV-2, severe acute respiratory distress syndrome coronavirus 2; NA, not applicable; SOC, standard of care; BCG, Bacillus Calmette-Guérin.

influenza B. All the patients had a fever, cough, and shortness of breath. Two patients developed fatigue, myalgia, headache, and expectoration. Three patients had pharyngalgia, which appeared more in the patients who developed coinfection. Only 1 patient developed chest pain and hemoptysis. The laboratory data revealed lymphocytopenia and elevated C-reactive protein in 4 patients, elevated transaminases, and procalcitonin levels in 2 patients. Lymphocyte count improved during the remission of the disease. The renal function and coagulation function was normal in these patients. Only 1 patient among the 5 patients developed ARDS and needed noninvasive-assisted ventilation and improved. The chest CT of the patient who developed ARDS had significant ground-glass opacities and subsegmental areas of consolidation that correlated with the clinical picture. Acute liver injury was noted in 3 patients and diarrhea in 2 patients. All patients were treated with antiviral therapy, including oseltamivir, antibiotic therapy, and received supplemental oxygen. Three patients were treated with glucocorticoids. No one needed care in intensive care unit, and all the patients were discharged home.[8]

Wu et al reported a case of a 69-year-old male who presented with fever and dry cough after visiting Wuhan during the time of the COVID-19 outbreak. The patient's CT revealed ground-glass consolidation in the right lung inferior lobes. COVID-19 was suspected, nasopharyngeal swab specimen resulted negative for SARS-CoV-2 on repeated testing, but yielded positive for influenza A. The patient was discharged on oral oseltamivir and was instructed to remain in isolation at home. Subsequently, in a week, the patient developed ARDS and lymphopenia. Repeated testing by nasopharyngeal swab and sputum sample was negative. The patient was subsequently intubated, and finally, bronchoalveolar lavage fluid was tested positive for SARS-CoV-2. This case highlights that both influenza and SARS-CoV-2 mimic the clinical picture, and often the diagnosis of COVID-19 can be missed with false-negative tests for the upper respiratory specimen. If the suspicion for COVID-19 is high, repeated testing should be performed.[9]

Four cases of coinfection with SARS-CoV-2 and influenza were reported from Iran. Three of the patients were males, relatively younger, except for 1 patient, and only 1 patient has comorbidities. All the patients had a cough, dyspnea, and fever, while the majority had headache and myalgia. One patient had gastrointestinal symptoms. The majority had lymphopenia and elevated inflammatory markers. All the patients had radiological abnormalities. Significant renal failure was noted in 1 patient, and liver failure was noted in 2 patients. No outcomes were described in the patients.[10]

There is no proven therapy for COVID-19 till now; meticulous supportive care holds key. The patients are getting treated with hydroxychloroquine, azithromycin, as seen in our case series and in severe cases, interleukin-6 antibodies. Novel nucleoside analog-like remdesivir was also used. The treatment with steroids is controversial. There have been many emerging and experimental therapies described. Many clinical trials are underway across the globe to check the efficacy of different medications in COVID-19. In a few centers, the convalescent serum has been used. Patients with influenza should be treated with oseltamivir. Multiple clinical trials are under investigation as summarized in Table 2.[11]

Influenza and SARS-CoV-2 cause mostly similar symptoms, and the coinfection did not significantly worsen the symptoms or outcomes.

Conclusion

Influenza and SARS-CoV-2 coinfection can occur in patients with similar symptoms. The coinfection did not significantly worsen the symptoms and outcomes. It is essential to recognize coinfections as the treatment can be completely different. Patients should get vaccinations for common respiratory pathogens if available, to reduce the risk of coinfection.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article. For patient 3, consent was obtained from next of kin.

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