Cardiothoracic Imaging

Black Fungus and beyond: COVID-19 associated infections

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ABSTRACT

Globally, many hospitalized COVID-19 patients can experience an unexpected acute change in status, prompting rapid and expert clinical assessment. Superimposed infections can be a significant cause of clinical and radiologic deviations in this patient population, further worsening clinical outcome and muddling the differential diagnosis. As thrombotic, inflammatory, and medication-induced complications can also trigger an acute change in COVID-19 patient status, imaging early and often plays a vital role in distinguishing the cause of patient decline and monitoring patient outcome. While the common radiologic findings of COVID-19 infection are now widely reported, little is known about the clinical manifestations and imaging findings of superimposed infection. By discussing case studies of patients who developed bacterial, fungal, parasitic, and viral co-infections and identifying the most frequently reported imaging findings of superimposed infections, physicians will be more familiar with common infectious presentations and initiate a directed workup sooner. Ultimately, any abrupt changes in the expected COVID-19 imaging presentation, such as the presence of new consolidations or cavitation, should prompt further workup to exclude superimposed opportunistic infection.

1. Introduction

Since December 2019, the coronavirus disease 2019 (COVID-19) pandemic has affected over 539 million people, with over 6.3 million deaths worldwide.[1] The pathogen responsible is a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that primarily affects the respiratory tract and shares a similar genetic identity with SARS-CoV from 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) from 2012. Most infected individuals present with mild to moderate disease; however, patients with underlying comorbidities may require hospitalization with intensive care and mechanical ventilation, predisposing them to secondary infections.

Throughout the course of hospitalization, COVID-19 patients can undergo changes in clinical status for a variety of reasons, such as thromboembolic disease, medication adverse effects, and vasculopathy. Nevertheless, it is imperative that clinicians consider common infections in the differential diagnosis and recognize their typical imaging and clinical features to avoid missing the opportunity to diagnose a highly preventable disease. Ultimately, any unexpected changes in the radiographic presentation of COVID-19, such as development of new consolidations or cavitation, should prompt further serologic workup to exclude superimposed opportunistic infection.

Although the common pulmonary sequelae of COVID-19 have been widely reported, thorough documentation on the manifestations and radiologic findings of secondary infections is still lacking. Many COVID-19 imaging features are nonspecific or atypical, thus accurate diagnosis and optimal treatment of co-infections in COVID-19 patients is a challenging task. By describing case studies of COVID-19 patients with superimposed infections and elucidating the most frequently reported imaging findings of opportunistic infections in COVID-19, we aim to help clinicians identify opportunistic infections earlier and greatly improve patient outcome.

2. Imaging of COVID-19

Before highlighting the radiologic findings of superimposed infections, we must first identify the common pulmonary imaging findings of COVID-19 infection. Chest imaging has been shown to play an important role in both diagnosis and management of COVID-19 patients. On Chest X-ray (CXR), typical findings are lung consolidation (57.7%), ground-glass opacities (GGOs, 62.8%), nodules (23.5%), and reticular-nodular opacities (66.6%), with frequent bilateral involvement.[2] More nonspecific findings include hilar or vascular congestion (39.3%), cardiomegaly (29.9%), pleural effusion (16.6%), and pneumothorax (2.4%).[3–6] Other studies have noted predominant peripheral and lower zone distribution and a peak severity 10–12 days from symptom onset.[7] On Computed Tomography (CT), COVID-19 pneumonia typically presents as multifocal bilateral peripheral, ground-glass opacities with or without consolidation, superimposed on interlobular/intralobular septal thickening (crazy-paving pattern). As the disease progresses, many features of organizing pneumonia may be present such as pulmonary opacities and consolidations with peri-lobular or peri-bronchovascular distribution, bronchiectasis, reticulation, interstitial or airspace nodules, interlobular septal thickening, reversed halo sign, and halo sign.[8] Cavitation, pleural or pericardial effusion, and lymphadenopathy are rare but sometimes observed as well.[9] While in most cases a clinical and radiologic reversal process begins and lung lesions regress, some patients can develop secondary infections with non-COVID-19 pathogens.[10]

2.1. Bacterial superinfections

The most common bacterial pathogens superimposed on COVID-19 infection include *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Acinetobacter baumannii*. However, most COVID-19 publications oftentimes scarcely report secondary or concomitant bacterial infections (4.8–15%).[11,12]

Streptococcus pneumoniae is the leading cause of community-acquired pneumonia (CAP). The invasive form of such infection, which mainly affects immunocompromised patients and the elderly, has a mortality rate ranging from 10 to 36%. Suspected pneumococcal infection is confirmed by bacterial isolation in sputum or blood cultures or detection of the C-polysaccharide antigen in urine. In a recent study, *S. pneumoniae* was deemed to be the most common co-infecting pathogen with a 59.5% coinfection rate in COVID-19 patients.[13]

The typical radiologic appearance of pneumococcal pneumonia is that of a unilateral lobar consolidation, but it can less commonly present as bilateral or interstitial infiltrates. Lesions suggestive of pneumococcal pneumonia can often mimic or be obscured by other lung infections, such as COVID-19. Therefore, radiologic features alone are not sufficient to reliably confirm or exclude bacterial pneumonia. Recently, Zhou et al.[14] attempted to differentiate CT features of COVID-19 and pneumococcal pneumonia and suggested that ground-glass opacities, the crazy paving sign, and abnormally thickened interlobular septa were more prevalent in COVID-19 than *S. pneumoniae*. While these CT findings are not definitive, they may lead clinicians towards accurate diagnosis when faced with this diagnostic dilemma.

In a case series of COVID-19 patients with superimposed pneumococcal pneumonia proven by positive urine pneumococcal C-polysaccharide antigen, the primary symptoms were fever, cough, and dyspnea.[16] Radiologic findings on CXR in three cases showed bilateral interstitial infiltrates, bilateral consolidative infiltrates, and unilateral lobar consolidative infiltrates, respectively.[16] A chest CT scan was obtained for the latter patient, which revealed unilateral ground-glass opacities suggestive of organizing pneumonia. Ultimately, the authors concluded that clinicians should be cognizant of a potential association between SARS-CoV-2 and pneumococcus, in order to avoid both misdiagnosis and delay of specific antibiotic therapy. In addition, it is

imperative that patients at high risk for superimposed pneumococcal infection obtain their pneumococcal vaccine for prevention.[13]

Pseudomonas aeruginosa is another common biofilm-forming opportunistic pathogen that co-infects COVID-19 patients causing exacerbation of illness (Fig. 1). Qu et al. reported that *P. aeruginosa* isolated from sputum and Bronchoalveolar lavage (BAL) demonstrates novel epigenetic markers that could lead to excessive biofilm formation, resulting in increased antibiotic resistance and prolonged colonization in COVID-19 patients.[15]

Legionella has also been reported to coinfect COVID-19 patients. A Japanese case study from early 2020 reported an 80-year-old male with legionella and COVID-19 co-infection.[16] This patient presented to the emergency department seven days after symptom onset with malaise, cough, and diarrhea after returning from a Nile cruise. Due to the strong association between cruise ships and Legionnaires' disease, legionella infection was suspected, and urinary antigen test returned positive. RT-PCR for COVID-19 also came back positive. Interestingly, CXR was not clinically significant, but chest CT showed patchy, peripheral GGOs bilaterally (Fig. 2). Unfortunately, this patient was intubated 5 days after admission and passed away 10 days later.

There are also other reported cases of gram-negative bacterial infections from the Enterobacteriaceae family superimposed on COVID-19. Fig. 3. shows chest CT scans of two patients with COVID-19 infection (confirmed by RT-PCR positivity on oropharyngeal swabs), who concomitantly developed Klebsiella pneumonia. While initial chest CT of these patients revealed typical patterns of COVID-19, subsequent CT scans demonstrated new parenchymal opacities, coarse reticular pattern, and evolution of previous ground-glass opacities to form new air space consolidations. BAL culture in both patients came back positive for Klebsiella infection. Ammar et al.[17] also reported similar cases of superimposed Klebsiella pneumonia, with CT images revealing large cavitation and emerging consolidation on top of previously seen ground-glass opacities, interlobular septal thickening (resulting in crazy paving appearance), cystic changes, and traction bronchiectasis. Jose and Desai[18] reported a case of superimposed *E. coli* infection in a 62-year-old healthy male with no significant medical history. He presented to the ED with fever, cough, and body aches and tested positive for COVID-19. As he was clinically stable and CXR returned negative, he was discharged home. Five days later, he presented again complaining of dyspnea, diaphoresis, spiking fevers, and diarrhea since his previous visit. Another CXR was obtained and indicated a focal consolidation in the left upper lung, bilateral airspace opacities, and low lung volumes. Blood cultures returned positive for imipenem-resistant *E. coli*. He continued to deteriorate and unfortunately passed away due to multiple organ dysfunction secondary to superimposed *E. coli* infection. Fig. 4 showcases the chest X-rays from his initial visit on day 1 to his subsequent admission on day 5.

In co-infection cases, oftentimes the radiologist is the first to point in the direction of probable diagnosis and initiate further work up, thus expediting appropriate care. The above-described scenarios suggest that in the appropriate clinical setting, new-onset or an abrupt change in imaging features should raise the suspicion for secondary bacterial infections, warranting aggressive microbial investigation.

2.2. Fungal superinfections

2.2.1. Invasive Aspergillus

Aspergillus species oftentimes cause life-threatening superinfections, particularly in patient populations with risk factors such as glucocorticoid use, prolonged leukopenia, lymphopenia, chronic obstructive pulmonary disease (COPD), inherited immunodeficiencies, allogeneic stem cell/solid organ transplant, hemopoietic malignancy, and severe COVID-19 infection (defined as severe pneumonia, requiring ICU care, in elderly, or with multiple comorbidities).[19,20] Recent studies have shown that patients with severe COVID-19 are at a higher risk of invasive pulmonary aspergillosis (IPA), even without the use of
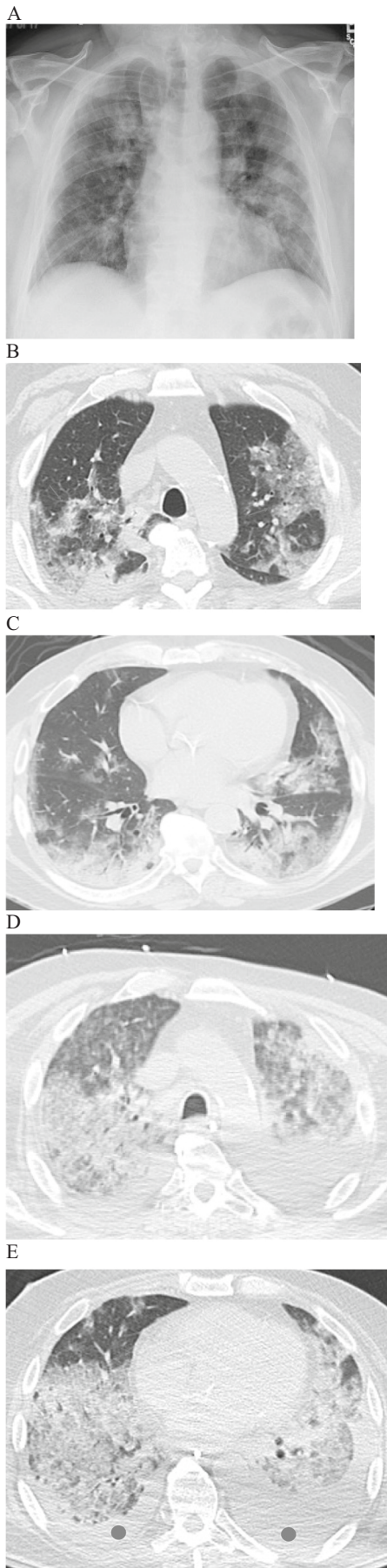
A

B

C

D

E

(caption on next column)

Fig. 1. A 62-year-old male presented with acute hypoxemia with positive PCR for COVID -19. Initial frontal radiograph (A) shows multifocal peripheral predominant patchy opacities, which was confirmed on axial CT images (B and C) as basilar and peripheral predominant ground glass opacities with early superimposed consolidations (arrows), commonly seen in COVID-19 pneumonia. He was placed on supplemental oxygen with nasal cannula and started on hydroxychloroquine. On the 2nd day of admission, severe acute chest pain, hypotension and worsening respiratory failure required transfer to ICU, intubation and mechanical ventilation with initiation of empiric therapy for bacterial pneumonia. Further work up confirmed myocardial infarction and emergent left circumflex coronary artery stenting was performed. Over next week, his oxygen demands increased and follow up CT (D and E) demonstrated more confluent consolidations bilaterally along with new pleural effusions (circles). Subsequent, bronchial lavage/pleural cultures came consistent with Pseudomonas aeruginosa and antibiotic therapy was changed to Meropenem. Patient subsequently improved and discharged two weeks later to rehab on oxygen support.

immunosuppressing medications.

In a case report by Witting et al.,[21] IPA occurred after treatment with tocilizumab in a previously immunocompetent man with COVID-19-related acute hypoxemic respiratory failure. The patient's initial CXR showed bilateral opacifications, and consequent nasopharyngeal PCR was positive for SARS-CoV-2. A few days later, he developed acute hypoxemic respiratory failure, and he continued to deteriorate despite mechanical ventilation and remdesivir treatment. Given persistent fever and hypoxemia, elevated inflammatory markers, and serial CXRs revealing progressive bilateral opacifications, tocilizumab was administered. After initially improving, the patient developed recurrent shock and fever, and CXR showed increased opacification at lung bases. Consequent fungal cultures and BAL confirmed Aspergillus infection, and CT scan demonstrated large bilateral cavitary lesions with aspergillomas. After treatment with voriconazole and micafungin, the patient gradually improved. Thus, it is imperative to consider opportunistic infection as a differential diagnosis prior to initiating immunosuppressive therapies.

In another case report by Nasri et al.,[22] a fatal case of probable invasive pulmonary aspergillosis was described in an acute myeloid leukemia patient co-infected with SARS-CoV-2 and further complicated by acute respiratory distress syndrome (ARDS). This patient presented post chemotherapy with a dry cough, dyspnea, fever, and subsequent positive COVID-19 RT-PCR test. On day 8, High-Resolution Computed Tomography (HRCT) scan demonstrated multiple vessel-related nodular opacities with ground-glass halo in a central and peripheral distribution, with bilateral pleural effusion (Fig. 5). Serum galactomannan antigen (GM) test was positive. Thus, diagnosis of probable IPA with COVID-19 pneumonia was confirmed, and intravenous liposomal amphotericin B was administered.

Recently, authors have suggested that the radiologic characteristics of pulmonary aspergillosis include one of the following four patterns on CT: dense, well-circumscribed lesions with or without a halo sign, air crescent sign, cavity, or wedge-shaped and segmental/lobar consolidation.[23] However, the radiologic presence of IPA can differ based on type and level of immunosuppression. For example, nodules or infiltrates with a halo sign are frequently seen on CT among neutropenic patients but are nonspecific for IPA in other groups.[24] In nonneutropenic patients with IPA, common CT findings include bronchopneumonia, segmental/subsegmental and patchy consolidation, cavitation, pleural effusions, ground-glass opacities, tree-in-bud opacities, and atelectasis. In addition, the air crescent sign is a late and nonspecific sign among this patient population.[25]

Ultimately, imaging alone is not a reliable criterion to diagnose patients with COVID-19-associated pulmonary aspergillosis (CAPA), as radiologic features of COVID-19 pneumonia can mimic IPA, and vice versa. In addition, common features of IPA such as the halo sign are not sufficient to diagnose CAPA without mycological evidence, as the halo sign suggests local infarction, an intrinsic component of severe COVID-
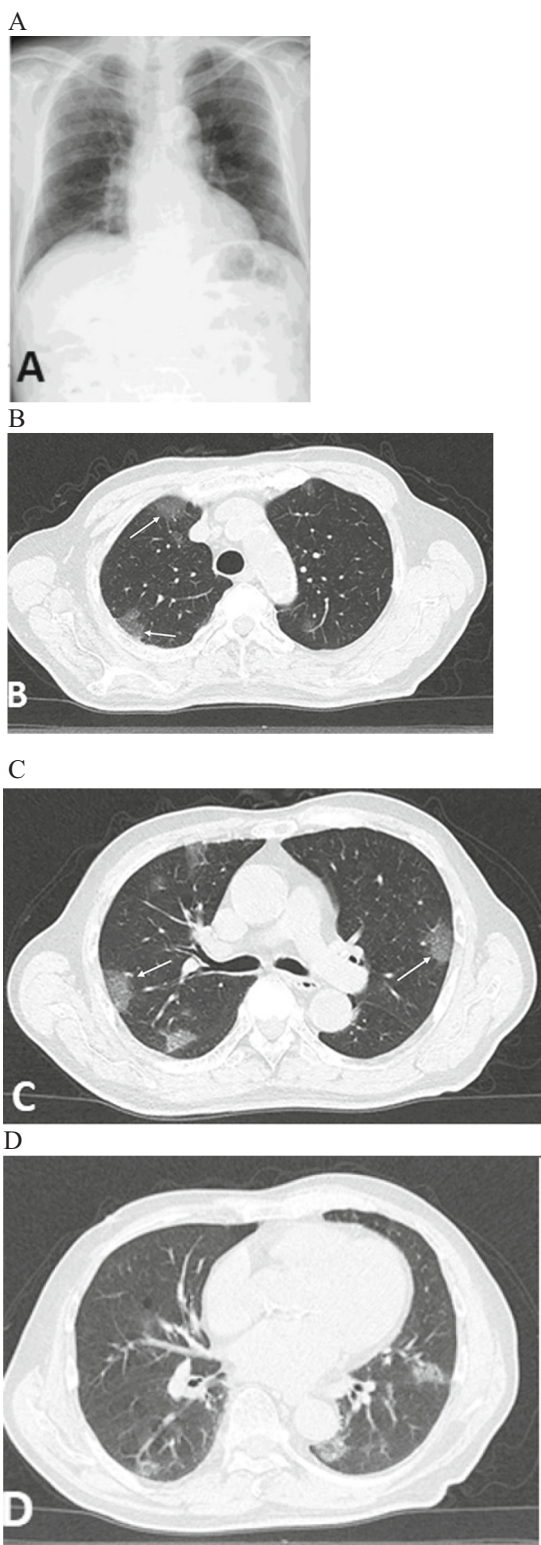
Fig. 2. SARS-CoV-2 and Legionella Co-infection. Frontal chest radiograph (A) of a patient with severe acute respiratory derangement and confirmed SARS-CoV-2 and Legionella co-infection, reveals no significant abnormality. However, on axial CT scan images (B, C and D) obtained on day 7 of illness, there are bilateral subpleural predominant patchy ground-glass opacities (arrows), which are typical for COVID-19 and no definite imaging clues to suggest co-infection. Figures reproduced with permission from Arashiro T, Nakamura S, Asami T, et al. SARS-CoV-2 and Legionella co-infection in a person returning from a Nile cruise. J Travel Med. 2020;27(3): 053.

19-related thrombosis. In response to these limitations, certain authors suggest that the presence of multiple pulmonary nodules or lung cavitation in critically ill COVID-19 patients should prompt a full investigation for IPA, as these radiologic findings are rarely seen in COVID-19 alone.[26] Fig. 6 identifies a case of mixed bacterial and fungal infections superimposed on COVID-19.

2.2.2. Histoplasmosis

While most reports of fungal infection concurrent with COVID-19 have been invasive aspergillosis, there is emerging literature on histoplasmosis and SARS-CoV-2 co-infection. For instance, Basso et al. reported a case of COVID-19 associated histoplasmosis in Southern Brazil.[27] The patient in question was a 43-year-old woman with a 21-year history of HIV infection and poor adherence to antiretroviral treatment. She presented to the emergency department with cough, fever, dyspnea, and disorientation, but RT-PCR for COVID-19 was negative. Initial chest CT showcased bilateral ground-glass opacities, diffuse bronchial wall thickening (arrow heads), and multiple centrilobular nodules (circles in 7A). Abdominal CT was also performed and indicated hepatosplenomegaly. The patient was given empiric therapy for neurotoxoplasmosis and discharged. 8 days later, she returned to the hospital with worsening symptoms and RT-PCR for COVID-19 was now positive. Chest and abdominal CT scans were re-ordered with the former showing worsening of pulmonary micro nodularity and ground glass opacification (circles in Fig. 7C). The latter scan reported retroperitoneal lymphadenopathy and hepatosplenomegaly with numerous splenic hypodense nodules (circle in Fig. 7D). At this point, urine sample result was positive for *H. capsulatum* antigen (galactomannan) and she was put on a twice-daily oral itraconazole regimen and discharged on request.

In another case report in a COVID-19 patient from Argentina with past history of HIV[28]; initial chest CT demonstrated a bilateral diffuse micronodular interstitial pattern, suggestive of superimposed miliary histoplasmosis. Interestingly, Bertolini et al.[29] noted both miliary-pattern infiltrates and bilateral peripheral multifocal ground-glass opacities in a different HIV patient with COVID-19 and histoplasmosis co-infection. Ultimately, these cases show the importance of pre-emptively testing for fungal infections, especially in endemic areas and in high-risk patients.

Of interest, few case studies have suggested that COVID-19 may trigger the development of acute pulmonary histoplasmosis after resolution of COVID-19 infection.[30] Thus, clinicians should be aware of this differential diagnosis in patients from endemic areas with persistent fever and cough even after COVID-19 recovery.

2.2.3. Mucormycosis (Black Fungus)

Mucormycosis is a life-threatening opportunistic fungal infection caused by Mucorales, with a clinical hallmark of tissue necrosis resulting from angioinvasion and subsequent thrombosis. The infection primarily affects immunocompromised patients and can be classified into different clinical forms based on anatomic location, including pulmonary, sinusitis, gastrointestinal, cutaneous, and disseminated disease. Unlike invasive aspergillosis, the prognosis of mucormycosis has not improved significantly over recent decades, primarily due to issues isolating the causative fungi, the lack of reliable diagnostic biomarkers, and the limited efficacy of antifungal agents against Mucora.[31] As this disease has a high mortality rate, early diagnosis and a high index of suspicion are crucial to promptly initiate necessary therapeutic interventions.

Recent studies have reported co-infection with mucormycosis in hospitalized COVID-19 patients (CAM) with oftentimes fatal outcomes.[32] While many of these patients may have multiple risk predisposing them to this infection, the immune alteration caused by SARS-CoV-2 itself, coupled with immunosuppressant and high-dose steroid use for COVID-19 treatment, also increases fungal infection susceptibility.[33] Garg et al., reported a probable pulmonary mycosis in a patient with diabetes and end-stage renal disease that had initially presented with COVID-19 pneumonia. Initial CXR showed typical COVID-19
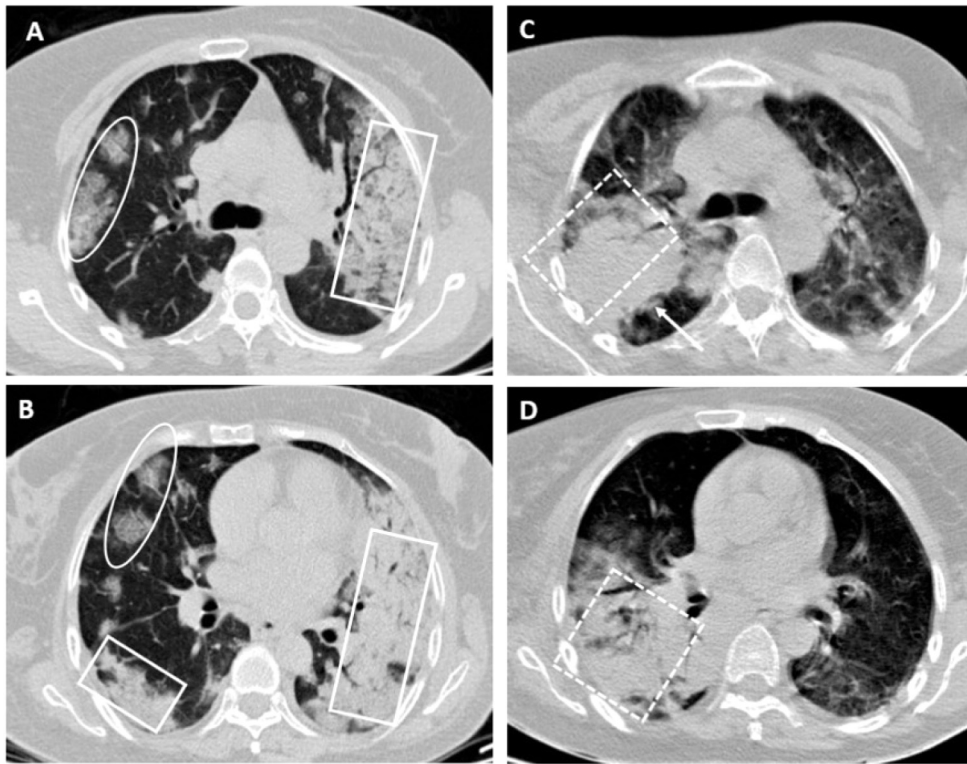
Fig. 3. Bacterial (Klebsiella) superinfection in COVID-19. A 54-year-old female patient with RT-PCR positive COVID-19 pneumonia (A, B). First CT scan upon admission (day 1) shows multifocal patchy ground-glass opacities (circles) and consolidations (boxes), mostly in left lung. He underwent treatment by antiviral agent and corticosteroids and improved significantly. On day 11, he underwent a second CT scan (C, D) due to persistent low O_2 saturation without fever or cough which demonstrated new air space consolidations in right upper and right lower lobes (dotted boxes) with a decrease in ground-glass opacites. A bulging fissure sign is also noted (arrow in C). Culture of bronchoalveolar lavage confirmed superimposed Klebsiella infection.
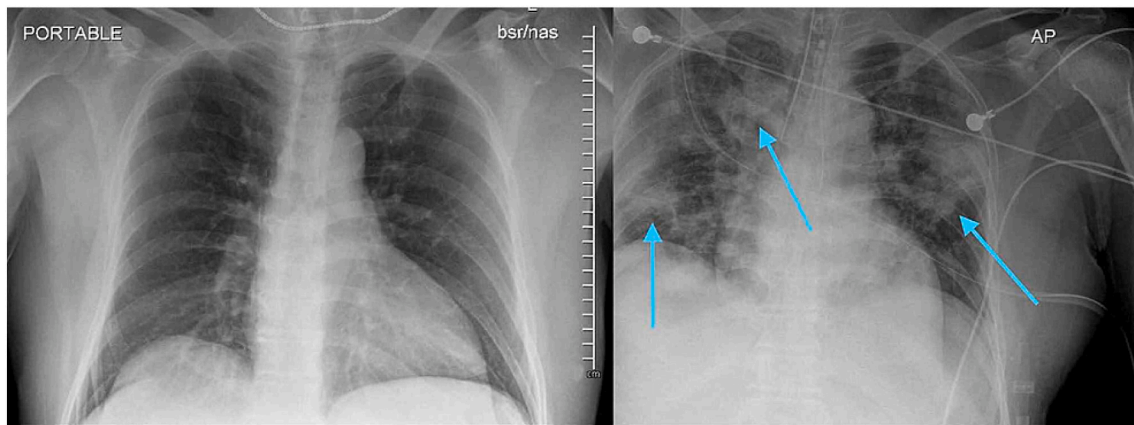

Fig. 4. SARS-CoV-2 and E.Coli Co-infection. A 62-year-old healthy male with RT-PCR positive COVID-19 pneumonia. Comparison of chest X-ray changes on day 1 (left) and day 5 (right) of presentation. CXR on day 5 (right) indicated a focal consolidation in the left upper lung, bilateral airspace opacities, and low lung volumes. Figure reproduced with permission from Jose M, Desai K (May 29, 2020) Fatal Superimposed Bacterial Sepsis in a Healthy Coronavirus (COVID-19) Patient. Cureus 12(5): e8350. doi:10.7759/cureus.8350.

infiltrates including bilateral, diffuse interstitial opacities and cardiomegaly, and subsequent RT-PCR was positive for SARS-CoV-2. After 14 days of therapy with intravenous dexamethasone, remdesivir, and supportive therapies, there was clinical improvement and radiologic resolution. However, three days later, the patient developed new cough with expectoration, and burning micturition. A CXR 21 days after admission showed a pulmonary cavity with intracavitary contents in the right upper lobe, also confirmed by subsequent CT, and associated with minimal right-sided pleural effusion. Rhizopus microspores were then isolated in the sputum, and the patient was treated with liposomal amphotericin B for probable pulmonary mucormycosis. His symptoms improved, and he was discharged 54 days after initial hospitalization. A few additional similar case reports have been reported with COVID-19-associated pulmonary mucormycosis.[34–36]

2.2.4. Radiologic findings of Mucormycosis

2.2.4.1. Pulmonary mucormycosis.
After comparing chest CT scans of patients with lung mucormycosis to scans of patients with invasive lung aspergillosis, certain authors report that the following radiologic findings favor diagnosis of pulmonary mucormycosis over pulmonary aspergillosis: ≥10 pulmonary nodules, pleural effusion, and reverse halo sign.[37–39] In addition, reverse halo sign was much more common in patients with mucormycosis than in those with aspergillosis (54% versus 6%, respectively), whereas some airway-invasive features, such as clusters of centrilobular nodules, peribronchial consolidations, and bronchial wall thickening, were more common in patients with aspergillosis. In immunocompromised hosts, authors report that the CT reverse halo sign is one of the strongest indicators of pulmonary
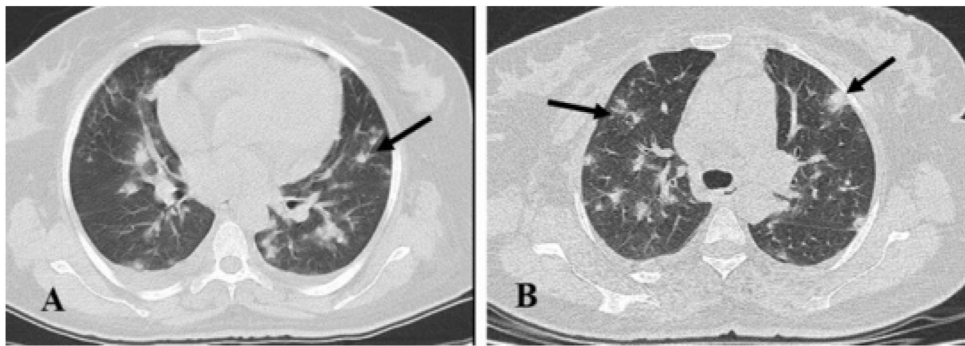
Fig. 5. Aspergillosis superinfection in COVID-19. A 42-year-old female patient with newly diagnosed Acute Myeloid leukemia who recently underwent standard combination chemotherapy. Axial chest CT images (A, B) on day 8 revealed multiple vessel-related nodular opacities with ground glass halo with central and peripheral distribution(arrows in A and B) with small bilateral pleural effusion (stars in A).The imaging findings are more typical for an invasive fungal infection and atypical for COVID-19. She tested positive for SARS-CoV-2 and *Aspergillus fumigatus.* Figure reproduced with permission from Nasri E, Shoaei P, Vakili B, Mirhendi H, Sadeghi S, Hajiahmadi S, Sadeghi A, Vaezi A, Badali H, Fakhim H. Fatal Invasive Pulmonary Aspergillosis in COVID-19 Patient with Acute Myeloid Leukemia in Iran. Mycopathologia. 2020 Dec;185(6):1077–1084.
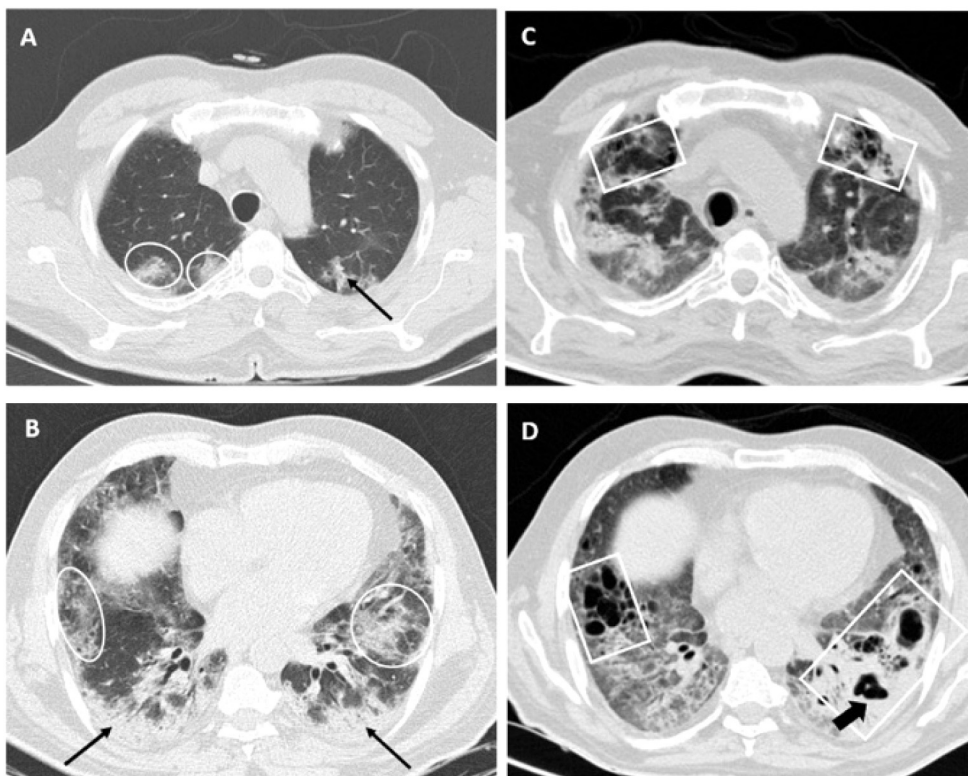

Fig. 6. Mixed fungal and bacterial co-infection in COVID-19 pneumonia. Initial axial chest CT images (A, B) on first day of admission reveal bilateral multifocal patchy ground-glass opacities (circles) and consolidations (arrows) with peripheral predominance. Following standard treatment by remdesivir and corticosteroid and partial improvement he developed fever, dyspnea and low O_2 saturation. Second CT scan images ((C, D)) on day 14 show multifocal new parenchymal cavities in upper and lower lobes along with coarse reticular pattern. Air-fluid level is also seen in left lower lobe cavities. The imaging findings are suggestive of necrotizing pneumonia. He underwent bronchoscopy and culture of bronchoalveolar lavage revealed mixed fungal (aspergillosis) and gram-negative (Klebsiella) infection.

mucormycosis.[40] Although these radiologic features are not pathognomonic, elucidating more specific imaging findings may aid physicians in reaching the correct diagnosis sooner and pre-emptively starting antifungal therapy. Table 1. describes common imaging findings of COVID-19 associated pulmonary mucormycosis published so far.

2.2.4.2. Rhino-orbital-cerebral mucormycosis. Apart from pulmonary manifestations, mucormycosis can also commonly present clinically in the form of rhino-orbital-cerebral infection (Fig. 8). This is a rapidly progressive, fatal infection, which can spread cranially into the brain, laterally into the cavernous sinus and orbits, and inferiorly to the palate. In addition, it can invade the arterial lamina, causing thromboembolism and subsequent tissue infarction. Thus, immediate treatment includes early surgical debridement to stop the spread of fungal infection along with amphotericin B pharmacotherapy. Clinically, the hallmark of this form is necrotic eschars and patients often complain of peri-orbital edema, ophthalmoplegia, blurry vision, headache, proptosis, sinusitis,

and facial pain or numbness.

Radiologically, rhino-orbital-cerebral mucormycosis may mimic routine uncomplicated sinusitis on cranial CT, thus, a negative CT cannot exclude the disease. Cranial MRI is more sensitive than CT for identifying cerebral and orbital involvement, and contrast-enhanced MRI has utility in tracking the spread of perineural infection which appears as high T2 signal and/or post contrast enhancement along the nerve. Another key MRI finding is the black turbinate sign, which represents devitalized mucosa leading to a hypointense mucosal appearance.[41] Table 2. shows the main reported imaging features of rhino-orbital-cerebral mucormycosis in COVID-19 patients.

Alekseyev et al.[42] reported a case of rhino-orbital-cerebral mucormycosis concurrent with COVID-19 pneumonia in a 41-year-old man with past medical history of type 1 diabetes mellitus. His initial chest X-ray revealed atelectasis and pneumonia primarily in the left lung, but follow-up chest CT demonstrated peripheral bilateral lung infiltrates. He complained of deep aching pain in the nose radiating down to throat,
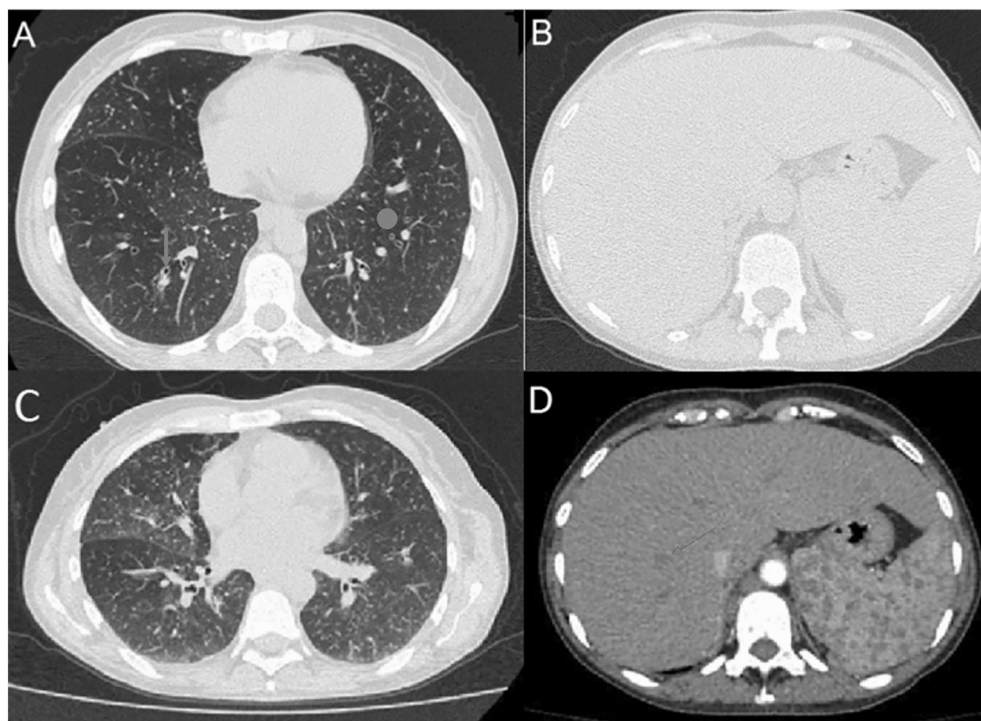
Fig. 7. Superimposed Histoplasmosis infection on COVID-19. A 43-year-old woman with a 21-year history of HIV infection and poor adherence to antiretroviral treatment recently tested positive for COVID-19. Initial chest CT axial image (A) shows bilateral ground-glass opacities, diffuse bronchial wall thickening (arrow), and multiple centrilobular nodules (circles). 8 days later, Chest (C) and abdominal CT (D) were re-ordered due to worsening symptoms, which show worsening of pulmonary micro nodularity and ground glass opacification. Hepatosplenomegaly with numerous splenic hypodense nodules (circle in Fig. 7D) are visualized, concerning for disseminated granulomatous infection. Patient tested positive for urinary H. capsulatum antigen. Figure reproduced with permission from Basso RP, Poester VR, Benelli JL, et al. COVID-19-Associated Histoplasmosis in an AIDS Patient. Mycopathologia. 2021;186 (1):109–112.

Table 1
Spectrum of radiologic findings in pulmonary mucormycosis.

Authors	Radiologic findings
Garg et al.[35]	- Initial CXR: bilateral diffuse interstitial opacities (COVID-19) and cardiomegaly
	- CXR 21 days after admission: a cavity with intracavitary contents in the right upper zone,
	- Chest CT: a thick-walled cavity in the right upper lobe associated with minimal right-sided pleural effusion
Placik et al.[38]	- Initial CXR: patchy opacities throughout the lungs concerning for viral pneumonia (typical SARS-CoV-2 pneumonia without any evidence of right upper lobe lesions).
	- CXR 2 weeks after admission a large right pneumothorax with mediastinal shift.
	- Repeat chest X-ray after CT-guided chest tube placement: persistent right pneumothorax.
	- Repeat CXR after second chest tube: only mildly improvement of the right pneumothorax.
	- Chest CT confirming the cavitary lesion and persistent pneumonia despite the presence of 2 chest tubes.: a persistent right pneumothorax and a large air-filled bullous process in the posterior right upper lobe, suspicious for bronchopulmonary fistula.
Pasero et al.[39]	- Chest CT: buried cavitary lesions in the lingula of the left lung upper lobe
	- Cranial CT: non-encephalic lesions+ opacification of the left maxillary sinus+ thickening with sclerosis of sinus walls (corpuscular material in the left maxillary sinus, which was not proven to be mucormycosis)
	- Repeat Chest CT, after 16 days antifungal therapy: a rupture of the cavities previously observed in the pleural space + bilateral pleural effusion.

which led to cranial CT scan and MRI showing chronic sinusitis and intracranial abscess in the infratemporal fossa with cavernous sinus enhancement. On initial debridement, evidence of mucormycosis was found. After his first surgery, a repeat MRI demonstrated the disease's progression intracranially and now involved the right cavernous sinus with thrombophlebitis. He was started on IV heparin for the cavernous vein thrombosis. Prior to a second surgery, a second COVID-19 RT-PCR returned negative. He no longer had any signs of COVID-19 pneumonia, and treatment was now focused on the rhino-orbital-cerebral mucormycosis. A few similar case reports of COVID-associated with mucormycosis have also been recently published.[43–46]

2.3. Pneumocystis jirovecii pneumonia

Pneumocystis jirovecii pneumonia (PCP) is a common opportunistic infection affecting immunocompromised patients, that shares numerous clinical and radiologic characteristics with COVID-19 (Fig. 9). In terms of radiographic findings, both PCP and SARS-CoV-2 infection frequently present as multifocal ground-glass opacities, making the radiologic differentiation extremely challenging, especially in the immunocompromised patient. Furthermore, consolidation, nodules, cysts, and spontaneous pneumothorax may also occur with PCP. In advanced-stage disease, up to 33% of patients develop pneumatoceles, which can aid clinicians in diagnosis.[47]

In a case study by Bhat et al.,[48] a severely immunocompromised 25-year-old patient was reported to have concurrent COVID-19 and PCP infection. CXR showed a large right pneumothorax and extensive interstitial disease, and subsequent chest CT scan revealed apical cystic changes, diffuse GGOs, dense consolidation, and pneumothorax. PCP was confirmed by bronchoscopic detection of the Pneumocystis antigen, and the patient improved after initiating appropriate therapy. Ultimately, it is imperative that physicians are aware of potentially treatable co-infections (such as PCP) in patients with severe COVID-19 who develop persistent or worsening clinical symptoms, especially when the immune status is compromised. Table 3 shows a summary of the common radiologic findings reported in patients infected with concomitant COVID-19 and PCP.[49–53]
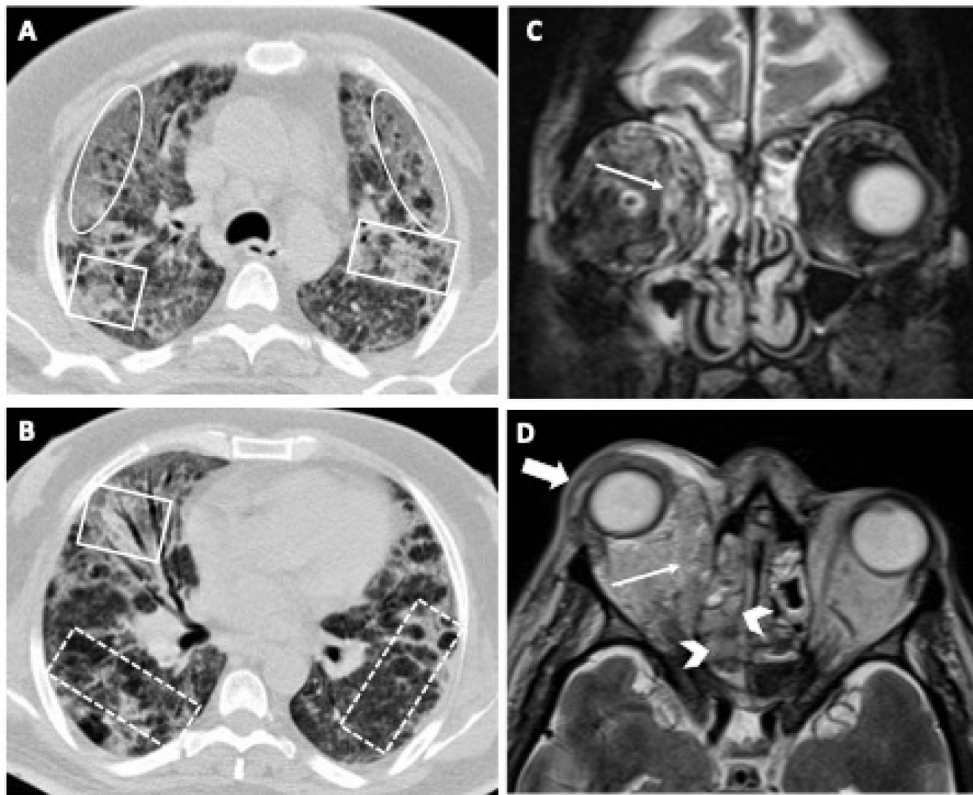
Fig. 8. Rhino-orbital Mucormycosis in COVID-19. A 55-year-old male patient with recent RT-PCR positive COVID-19 pneumonia and history of longstanding poorly controlled diabetes mellitus. Chest CT scan (A, B) at the second week of infection upon ICU admission show extensive bilateral confluent consolidations (boxes), ground-glass opacities (ovals) and coarse reticular pattern (dotted boxes) associated with interstitial septal thickening suggestive for subacute phase of COVID-19 infection. He underwent standard of care treatment with remdesivir and corticosteroid. On day 4 of admission, he developed right sided proptosis, chemosis, and periorbital edema. Coronal (C) and axial (D) T2-weighted images from orbital MRI show opacification of bilateral frontal and ethmoidal sinuses as well as right maxillary sinus with areas of internal relative T2-weighted hypointense signal (arrowheads), typical for mucormycosis. An ill-defined lesion is depicted in medial right orbit (thin arrows) involving extra and intraconal spaces leading to proptosis of globe (thick arrow). Paranasal sinus culture confirmed rhino-orbital mucormycosis. He eventually died during admission following intracranial spread of fungal infection.

2.4. Parasitic infections

While both bacterial and fungal infections have been shown to be associated with COVID-19 infection, there is relatively scarce literature on parasitic co-infection. Having said that, recent studies have noted superimposed Strongyloidiasis infection in immunocompromised COVID-19 patients, even after just a single high dose of dexamethasone or short courses of low dose glucocorticoids.[57] Strongyloidiasis is often asymptomatic in immunocompetent patients, but can present with mild respiratory or gastrointestinal symptoms, and a linear pruritic rash known as larva currens.[54] However, in an immunocompromised host, a disseminated infection can occur, potentially causing sepsis or meningitis on top of the previously mentioned symptoms.[57] As both COVID-19 and Strongyloidiasis infections share many of the same radiologic and clinical findings, such as bilateral lung infiltrates and dyspnea, fever, and gastrointestinal symptoms, respectively, diagnosis of co-infection can be challenging. Thus, clinicians are urged to obtain a thorough clinical history and have higher clinical suspicion in migrants or patients with previous history of travel, barefoot walking, or poor sanitation.

A case report by Lier et al.[55] discussed a 68-year-old patient who presented after eight days of chills, myalgia, dyspnea, and nausea. It is important to note that this patient resided in Connecticut but had emigrated from Ecuador twenty years prior. Upon hospital admission, RT-PCR was positive for COVID-19 and CXR showed patchy airspace opacities in the mid to lower lung zones bilaterally. The next day, the patient developed respiratory failure requiring intubation along with one dose of Tocilizumab (once, intravenous at 8 mg/kg) and three courses of Methylprednisolone (40 mg intravenous every 8 h). On hospital day 18, this patient developed fever, confusion, and eosinophilia. Serpiginous tracks on chocolate agar raised suspicion for strongyloidiasis but Strongyloides serology came back negative at this time point. CXR on day 21 revealed unchanged multifocal pulmonary opacities bilaterally. The patient progressively worsened and was diagnosed with possible meningitis associated with disseminated strongyloidiasis infection after tocilizumab treatment for COVID-19. Chest CT scan on hospital day 30 was notable for widespread peripheral GGOs and right lower lobe peribronchial consolidation. Repeat Strongyloides serology on day 38 was finally positive. After extensive treatment, this patient was discharged to a skilled nursing facility after over 40 days of hospitalization. Ultimately, it is imperative that patients within endemic areas and with risk factors are pre-emptively tested for these parasites prior to beginning immunosuppressive therapy.

2.5. Viral co-infections

2.5.1. Influenza

Certain authors have also begun to identify influenza co-infection in COVID-19 patients. In a study conducted by researchers at the University of Edinburgh of 6382 COVID-19 patients, 583 patients were found to have confirmed co-infections, with 227 of them from influenza viruses.[56] Interestingly, these authors indicated that COVID-19 patients who were co-infected with influenza viruses were twice as likely to require mechanical ventilation and had a much higher risk of mortality compared to COVID-19 infection alone. While the exact mechanism of these findings has yet to be elucidated, there may be some synergy between Influenza A virus (IAV) and SARS-CoV-2, as IAV replicates in type 2 pneumocytes, cells that SARS-CoV-2 primarily infect.[57] In addition, mice studies conducted by Bai et al.[58] demonstrated the IAV infection prior to COVID-19 ultimately increased SARS-CoV-2 viral entry and infectivity. This data ultimately indicates that an acute influenza infection may create a hospitable environment for SARS-CoV-2 and ultimately exacerbate COVID-19 infection.

As far as radiographic findings present in COVID-19 and influenza viruses, Ozaras et al.[59] reported that the majority of patients with confirmed co-infection showcased standard COVID-19 radiographic findings, such as patchy GGOs and consolidation opacities, nonspecific peripheral lesions in both lobes, bronchial wall thickening, and shrinking lesion contour. However, one patient demonstrated radiographic findings more representative of influenza findings with cluster-like

Table 2

Reported radiologic findings in Rhino-orbital-cerebral Mucormycosis

Authors	Radiologic findings
Alekseyev et al.[45]	- CXR: atelectasis and pneumonia (left lobes>right lobes).
	- chest CT: displayed peripheral bilateral lung infiltrates and chronic sinusitis.
	- Cranial CT & MRI: Intracranial abscess in the infratemporal fossa with cavernous sinus enhancement and mucormycosis extension into the sinuses
	- a repeat MRI: the disease progression intracranially and with the involvement of the right cavernous sinus with thrombophlebitis.
Mehta et al.[46]	- Chest CT: CT scan showing extensive peripheral ground-glass opacities in both lungs.
	- MRI of the brain, orbits, & paranasal sinuses: a soft tissue swelling in the right preseptal, malar, premaxillary, and retrobulbar regions (hyperintense on T2 and FLAIR) + bulky right extraocular muscles, mild right proptosis+ sinusitis (in the form of significant mucosal thickening in the right frontal, maxillary, and ethmoidal sinus).
Mekonnen et al.[47]	- Head CT: soft tissue window: maxillary and ethmoid sinusitis, asymmetric contrast enhancement and stranding of the intraconal and extraconal orbital fat on the right compared to the left side, and subtle enlargement and enhancement of the right inferior and medial rectus muscles. Bone window: bony dehiscence of the lamina papyracea along the right medial orbital wall.
Werthman-Ehrenreich et al.[48]	- Chest CT: left lower lobe consolidation consistent with pneumonia.
	- Face CT: significant for moderate bilateral maxillary and ethmoid sinus mucosal thickening + mucosal opacification of the ostiomeatal units.
	- Brain MRI: multifocal infarction (extensive multifocal signal abnormality with edema, and evidence of ischemia and infarction, highly suspicious for invasive rhino-orbital-cerebral mucormycosis).
	- Head & neck MRA: unremarkable.
	- repeat brain MRI: fundal brain abscess (previously noted regions of cerebral edema had evolved into multiple encapsulated complex fluid collections predominantly in the bifrontal region, suspicious for invasive mucormycosis)
Maini et al.[49]	- Brain & orbit MRI: an ill-defined heterogeneous soft tissue signal intensity (hypointense on T1W-imaging) + polypoidal mucosal thickening involving left maxillary and ethmoid sinuses+
	a breach in the posterior portion of left lamina paprycea with altered signal intensity involving conal and extra-conal infero-medial portion of the left orbit.
	+ displacement of adjacent medial and inferior rectus
	+ retrobulbar soft tissue fat stranding and edema with resultant displacement of left eyeball anteriorly leading to proptosis. It was also found to be closely abutting the left optic nerve
Index case Fig. 6.	- Chest CT: extensive bilateral confluent consolidations, GGOs, and coarse reticular pattern, associated with interstitial septal thickening, suggestive for subacute phase of COVID-19 infection.
	- Orbital MRI T2-weighted sequence: opacification of frontal and ethmoidal sinuses and right maxillary sinus showing relative T2-weighted hypointense appearance+ an ill-defined lesion in medial right orbit, involving extra and intraconal spaces, leading to proptosis of globe

GGOs, central lesions that favor inferior lobes, an absence of bronchial wall thickening, and non-shrinking lesion contour. Other authors report that certain CT findings such as pleural effusion and bronchiectasis are more common in influenza, whereas other radiologic findings such as crazy-paving sign, vascular enlargement, linear opacification, and pleural thickening are more common in COVID-19 pneumonia.[60] While these findings may not always hold true, the presence of new-onset pleural effusion or bronchiectasis in a COVID-19 patient may prompt further workup for superimposed influenza infection.

2.5.2. Dengue

As Dengue fever has been shown to coinfect hosts with influenza in the past, it is not unexpected that recent studies have reported superimposed Dengue fever in COVID-19 patients. Interestingly, Carosella et al.[61] reported that in Buenos Aires, rates of Dengue fever in 2020 surpassed case counts from the past decade combined. Cardona-ospina et al.[62] have noted similar findings in certain endemic areas, with dengue reports outnumbering or mimicking the number of COVID-19 cases. Yet, other authors have also reported that in certain regions, the
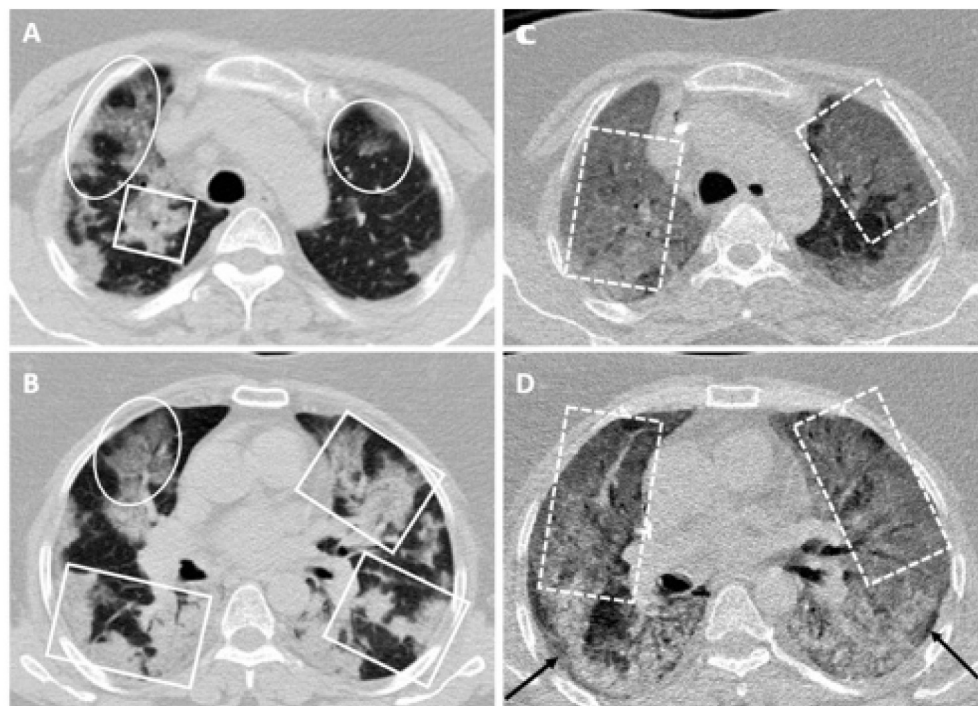

Fig. 9. Pneumocystis pneumonia (PCP) in COVID-19. A 57-year-old female patient with RT-PCR positive COVID-19 pneumonia. Axial CT scan images (A, B) on day 1 show bilateral multifocal consolidations (boxes) and patchy ground-glass opacities (circles) with dominant peripheral distribution in the upper lobes and the superior segments of lower lobes. The patient did not respond well to routine standard of care treatment and corticosteroids were continued. Due to persistent hypoxemia and respiratory distress second CT was obtained on day 18 of admission in ICU (C, D), which shows new/worsened extensive bilateral confluent ground-glass opacities and fine reticular pattern (dotted boxes) with previously noted consolidations not clearly visualized. Relative subpleural sparing is also noted in the superior segment of lower lobes (arrows). Diagnostic bronchoscopy was canceled due to respiratory distress. Considering the new imaging findings, he underwent treatment trial for pneumocystis pneumonia (PCP) and dramatically improved and discharged.

Table 3
Chest imaging findings in concomitant COVID-19 and PCP

Authors	Imaging findings
Bhat et al.[51]	- CXR: a large right pneumothorax + extensive interstitial disease. - Subsequent chest CT: apical cystic changes+ diffuse GGOs, dense consolidation+ pneumothorax
Coleman et al.[52]	- CT: extensive subpleural and para-mediastinal cystic changes+ subpleural GGOs, bilaterally, most prominent in the upper lobes with relative sparing of the lung bases, consistent with PJP. Incidental interstitial lung fibrosis and paraseptal emphysema was also reported.
Rubiano et al.[53]	- Initial CXR: diffuse hazy opacities (heterogeneous bilateral lung opacities with scattered air bronchograms, but the opacities were less dense than expected for COVID-19 and for his level of hypoxemia).
Menon et al.[54]	- Chest CT: diffuse bilateral GGOs+ patchy bands of atelectasis+ small nodular foci of consolidation with a distribution suggestive of a viral pneumonia. Subtle cystic changes were also seen in the affected regions
Mang et al.[55]	- CXR: diffuse GGO of both lungs + consolidation in the left lower lobe - CT: Diffuse bilateral GGOs, consolidations, and crazy-paving pattern, typical for COVID-19. As a potential sign for subacute manifestation, airway changes, pleural changes, fibrosis, and nodules were present. Fine reticular changes suspicious for a co-pathogen.
Cai et al.[56]	- Chest CT: pneumonia in the right upper lobe of lungs, concerning for COVID-19. - Multiple Following CT series: significant absorption lesions in lungs➔ new GGOs and patchy shadows in the lungs➔ total absorption of lung lesions ➔increased lesions➔ worsening lung lesions➔significant absorption of lesions on her lungs,
Index case. Fig. 7.	- Initial CT: bilateral multifocal consolidations and patchy GGOs with dominant peripheral distribution in the upper lobes and superior segments of lower lobes. - Repeat CT: extensive bilateral confluent GGOs and fine reticular pattern at the same locations. Relative subpleural sparing is also noted in superior segments of the lower lobes.

opposite phenomenon has shown to be true, with cases of COVID-19 skyrocketing while dengue cases have plummeted. More recently, Lustig et al. noted serological cross-reactivity in dengue and COVID-19, thus the reported data may be flawed by considerable false positives.[63]

In addition to the serological cross-reactivity, dengue and COVID-19 have radiologic and clinical similarities, thus accurate diagnosis/treatment of dengue viral superinfection in COVID-19 patients is a difficult endeavor. COVID-19 manifests as an acute undifferentiated febrile illness (AUFI), and in many endemic regions, dengue virus is considered the most common cause of an AUFI.[64] In addition, leukopenia with lymphopenia presents in both early Dengue and early COVID-19 infection.[62] As far as symptomatology, both Dengue and COVID-19 often have fever, malaise, myalgia, gastrointestinal symptoms, and headache. However, viral exanthem may aid physicians in reaching the correct diagnosis, as this is a clinical finding typically seen with Dengue fever and infrequent in COVID-19 infection.

In a case report by Bicudo et al.,[65] a 56-year-old female presented to the hospital after 12 days of anosmia, sore throat, mild dyspnea, headache, and fever. RT-PCR for COVID-19 was subsequently positive and IgG and IgM antibody tests for Dengue were negative. Chest CT upon admission noted few peripheral GGOs bilaterally which were felt to be correlating with COVID-19. Three days later, she developed a pruritic, erythematous maculopapular rash and diarrhea/nausea in addition to her previous symptoms. At this time point, repeat RT-PCR for both Dengue and COVID-19 returned positive as did IgG and IgM antibody tests for Dengue fever. This patient did not have severe COVID-19 or Dengue fever infection and was discharged after supportive treatment and 6 days of hospitalization. Ultimately, this case emphasizes that the diagnosis of one viral infection does not preclude the presence of another viral infection, and testing for prevalent pathogens should be performed in endemic regions, irrespective of their COVID-19 status.

In terms of radiological manifestations, published case reports of Dengue and COVID-19 co-infection describe a scarcity of imaging findings. Normal chest imaging, pleural effusion, or COVID-19-related ground-glass opacities have been reported by some authors in such clinical setting.[66–68] While radiology oftentimes doesn't play an active role in diagnosis of Dengue fever, imaging can be useful in elucidating extra-pulmonary manifestations (ie. hepatomegaly, splenomegaly, and ascites) in the absence of serological results. Interestingly, Tiwari et al.[69] reported a pediatric case of COVID-19 encephalitis with Dengue shock syndrome (DSS). Her CXR showed reticulonodular opacities in bilateral lung fields without any evidence of pleural effusion and both RT-PCR for COVID-19 and serum Dengue antigen test were positive. Contrast-enhanced brain CT was performed, which revealed ill-defined hypodensities in the bilateral frontal lobes, right parietal lobe, bilateral temporal lobe, basal ganglia, corpus callosum, midbrain, and pons,

suggestive of viral encephalitis (Fig. 10). These imaging findings were suggestive of COVID-19-associated encephalitis with concomitant DSS. Ultimately, physicians must be aware of viral co-infections in endemic areas with overlapping outbreaks and consider the possibility of detrimental viral synergy.

3. Discussion

Beyond the potential link between Dengue virus and SARS-CoV-2, many authors have begun to question whether these superimposed infections were coincidental or if COVID-19 infection increases the risk of subsequent infection. While the exact link between COVID-19 and other pathogens has yet to be fully elucidated, any severe infection can create the perfect environment for secondary pathogens to grow. For example, a critically ill COVID-19 patient may be immunocompromised (steroid-mediated, COVID-19 mediated, or due to underlying comorbidities), have increased glucose levels (can be attributed to steroid use, diabetes, increased cortisol levels), hypoxic (due to COVID-19 infection or underlying comorbidities), and have an acute acidemia (due to diabetic ketoacidosis, metabolic acidosis), creating the ideal environment for secondary infection.[70] In addition, many patients who are reported to have superimposed infections already have a variety of high-risk factors for co-infection, such as prolonged hospitalization, lung damage due to complex inflammatory processes, and mechanical ventilator use.[71] Yet, further research is necessary to evaluate whether synergy exists between COVID-19 and other pathogens on the molecular scale as the exact relationship between COVID-19 and other forms of infections is not well understood at this time.

Ultimately, there are limitations inherent within the discussion of superimposed infection in COVID-19 patients. While each patient presented here tested positive for at least two organisms, co-detection may not always equate to co-infection. A positive antigen or RT-PCR test may occur in the pre-symptomatic period, well after acute infection, or just be indicative of a latent pathogen.[72] In addition, diagnosing based on CT findings alone may be problematic, as COVID-19 pneumonia can mimic various other lung pathologies. The presence of ground glass opacities, typically with a peripheral multifocal subpleural distribution in lower lobes, has been reported to be the primary radiologic feature of COVID-19 pneumonia on CT.[73] However, chest CT may not reveal distinct patterns in all patients as CT findings of COVID-19 pneumonia are often nonspecific and variable throughout the disease course, thus engendering a diagnostic dilemma.[74] Therefore, while CT is a valuable tool in COVID-19 diagnosis, its findings should be interpreted in the context of clinical presentation, ancillary imaging findings, and follow-up CT imaging to avoid misdiagnosis.
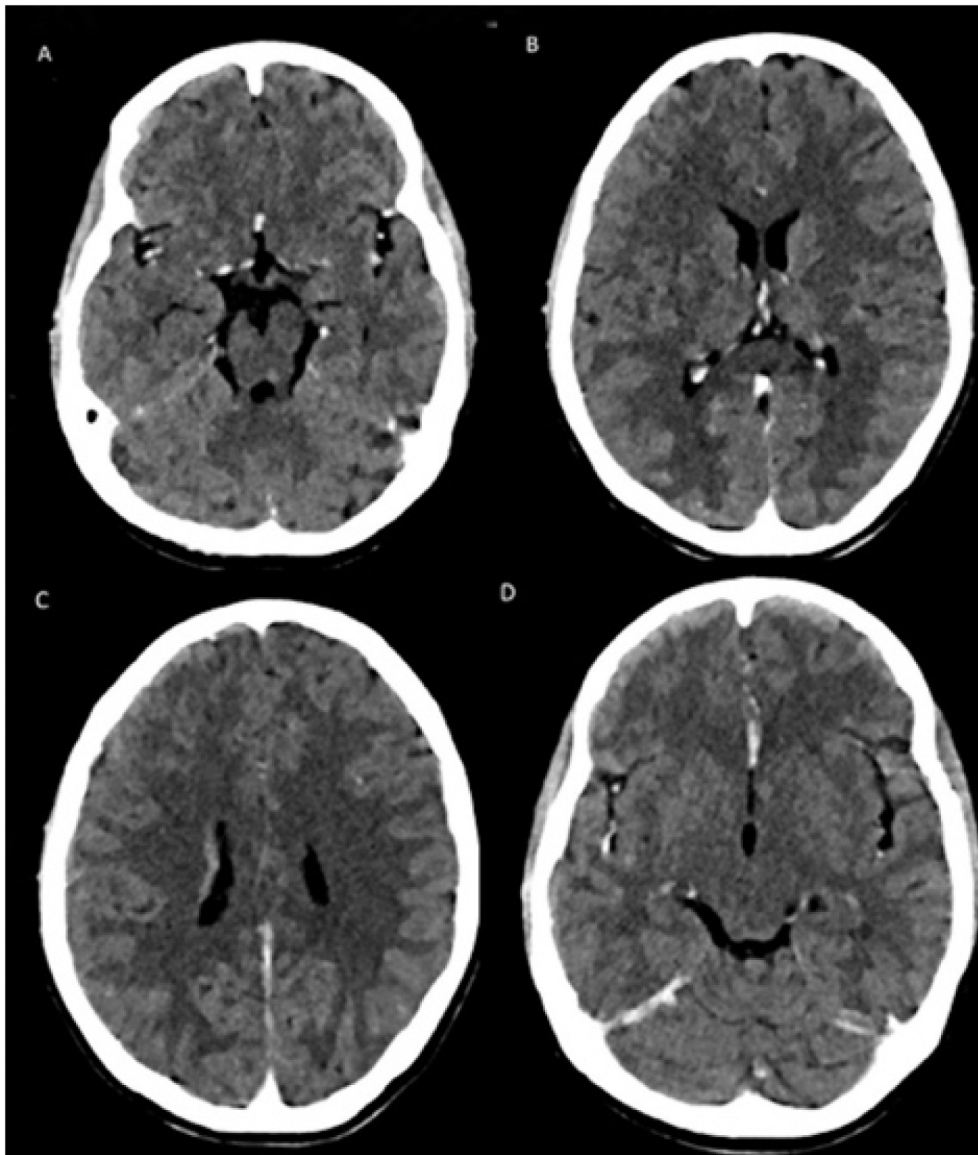
Fig. 10. COVID-19-associated Encephalitis with Dengue Shock Syndrome. A 14-year-old female presented with high-grade fever, headache and vomiting and respira- tory distress and hypotensive shock. Nasopharyngeal PCR testing for SARS-CoV-2 and serum dengue NS1 antigen were tested positive. Contrast-enhanced axial CT images showing ill-defined marked hypodensities in Mid-brain, thalamus, corpus callosum and bilateral periventricular area, basal ganglia and bilateral frontal lobes. Given the clinical context, lab testing results and patient's demographics (resident of an endemic for Dengue fever), the image findings are suggestive of viral encephalitis.

Figure reproduced from Tiwari L, Shekhar S, Bansal A, Kumar P. COVID-19 with dengue shock syndrome in a child: co-infection or cross-reactivity? BMJ Case Rep. 2020 Dec 21;13(12): e239315 with permission from BMJ Publishing Group Ltd.

4. Conclusion

In addition to the widespread turmoil caused by the SARS-CoV-2 virus alone, viral, bacterial, parasitic, and fungal pathogens have co-infected hospitalized COVID-19 patients, further increasing morbidity and mortality. However, clinically differentiating COVID-19 and its progression from co-infection, remains challenging. Thus, it is imperative that any acute change in either clinical or radiographic presentation prompts an investigation into superimposed infection and that the index of suspicion for concomitant infection is greater in high-risk cases, especially immunocompromised patients. Given the new delta variant of SARS-CoV-2, combining imaging and laboratory findings, epidemiologic data, and detailed clinical history can ultimately provide the best opportunity for a positive clinical outcome. Ultimately, familiarity with various CT patterns associated with common opportunistic infections will aid decision-making when facing challenging clinical cases of co-pathogens superimposed on COVID-19 infection, allowing early diagnosis and initiation of appropriate treatment.

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Declaration of competing interest

The authors declare they have no conflict of interest in this study.

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