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CT imaging of HIV-associated pulmonary disorders in COVID-19 pandemic

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ABSTRACT

Opportunistic infections in people living with human immunodeficiency virus (HIV) are readily detected with thoracic computed tomography (CT), but differential diagnosis remains a challenge. The global COVID-19 pandemic further exacerbates the issue, with SARS-CoV-2 having overlapping CT findings with infections common in HIV patients and complicating prior epidemiological data. We present a pictorial review of CT findings associated with COVID-19-mimicking opportunistic infections that can be encountered in HIV patients. PubMed database was searched for the complete list of relevant conditions, and a Venn diagram was constructed to highlight overlapping entities. The diagram showed five major disease groups: viral pneumonia, fungal pneumonia, bacterial pneumonia, sarcoidosis, and lung cancer. As these pathologies possess a wide range of features, the findings were grouped as "typical" and "other" for easier comprehension with provided relevant epidemiological data and discrepancies observed in available literature. The review highlights the importance of a specific approach to differential diagnosis in immunocompromised patients compared to immunocompetent hosts and the utility of follow-up scans.

1. Introduction

The human immunodeficiency virus (HIV) causing acquired immunodeficiency syndrome (AIDS) was simultaneously and independently discovered in 1985 by two groups.[1] Initially it was named as lymphadenopathy-associated virus (LAV) by the team of Luc Montagnier[2] and human T-lymphotropic virus type III (HTLV-III) by Robert Gallo et al.[3] Prior to 1996 and the development of effective antiretroviral therapy (ART, or HAART, highly active antiretroviral therapy), AIDS-related disorder was a fatal, mainly because of numerous opportunistic infections (OIs).[4] The full spectrum of HIV-associated pulmonary infections has been described in several comprehensive reviews.[5–7] The incidence of HIV complications, as well as the life expectancy of people living with HIV (PLHIV), have changed with the advancement in ART and primary prophylaxis usage.

In 1990s, Pneumocystis pneumonia (PCP) was the most common opportunistic infection in AIDS patients in Europe.[8] After PCP prophylaxis adoption, the incidence of the infection has been decreased.[9] That, and the introduction of HAART, has led to bacterial pneumonia becoming the most frequent type of HIV-associated infections in developed countries.[10]

Recently, a novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) was discovered that became a cause of global coronavirus disease 2019 (COVID-19) pandemic. COVID-19 shares computed tomography (CT) findings and clinical manifestations with the infections that are common among PLHIV, closely resembling PCP. It makes differentiation of infection causes difficult even for domain experts. Here we present a pictorial review of typical CT findings associated with COVID-19-mimicking opportunistic infections that can be encountered in AIDS patients.

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2. Materials and methods

In this review, we used a formal approach to define a list of AIDS-related OIs that share CT findings with COVID-19 in order to minimize potential author bias.

First, we searched the PubMed database to identify the HIV-associated lung diseases detectable by CT, using the query ("AIDS-Related Opportunistic Infections"[mh] OR AIDS related opportunistic infections OR HIV-Related Opportunistic Infections) AND ("Tomography, X-Ray Computed"[Mesh Terms] OR computed tomography) AND (thorax[mh] OR thorac* OR chest). The relevant conditions are summarized in Supplementary Table A. No exclusion criteria were applied during this and the following step of search.

The second step was to search the PubMed database to identify diseases with findings similar to COVID-19 CT, using the query ("COVID-19" OR "COVID-19"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR "coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND ("Diagnosis, differential"[Mesh] OR mimic* OR differential diagnosis) AND ("tomography, X-ray computed tomography"[Mesh Terms] OR computed tomography. The COVID-19-mimicking conditions are summarized in Supplementary Table B.

The third step was the building of Venn diagram (Fig. 1) to determine the shared pathological entities between Tables A and B, forming the list of conditions with similar radiographic features that could be observed in HIV-positive patients amid the COVID-19 pandemic.

The literature selection was performed by screening the abstracts and full texts of the studies. We also performed snowballing to identify articles missed in the search. If several articles with a common research question and similar results were found, the most recent study was included in the review. To minimize the selection bias, each study was independently screened by two reviewers, and the discrepancies were resolved through discussion or after consultations with the third reviewer.

The representative CT studies with target diseases were selected from the Unified Radiological Information Service (URIS) of the City of Moscow. The use of depersonalized CT studies as illustrative material was approved by the Independent Ethical Committee of the Moscow Regional Office of the Russian Society of Radiologists and Radiographers.

3. Results

According to the analyzed published data, the list of conditions with overlapping CT findings between HIV-related pulmonary diseases and COVID-19-mimicking entities consisted of five major disease groups: viral pneumonia, fungal pneumonia, bacterial pneumonia, sarcoidosis, and lung cancer (Fig. 1). Within viral pneumonias, cytomegalovirus pneumonia was singled out as having distinctive CT signs in comparison with other viral infections (Fig. 1). For the same reasons, PCP and invasive aspergillosis were separated from other types of fungal pneumonia (Fig. 1).

3.1. Viral pneumonia

HIV-positive patients are at risk of the viral respiratory infections that are frequent among the general population. Before the COVID-19 era, the most common viral infections in patients admitted to the intensive care unit were influenza A virus and rhinovirus.[11] COVID-19 pandemic shifted the distribution, with SARS-CoV-2 becoming the most detected respiratory tract pathogen.[12] In 2020–2021, the decrease in influenza virus incidence reached up to 100% in comparison to pre-pandemic years, depending on the region.[13–15] The following 2021–2022 season has brought the return of influenza, although the incidence was lower than seen before the pandemic.[16] The decline in the flu incidence is not associated with a decrease in testing for influenza, being instead attributed by CDC to COVID-19 mitigation measures, such as lockdown policies, face mask wearing, and increased ventilation of indoor spaces.[16,17]

There are scarce data on the yearly dynamics of viral infections prevalence other than flu and COVID-19. The current increase of influenza activity indicates a possible activation of other pathogens. The latter include herpes simplex virus, parainfluenza virus, respiratory syncytial virus, and adenovirus. These should be considered in the differential diagnosis when evaluating COVID-19 for HIV patients with respiratory symptoms. It is also important to bear in mind the possibility of cytomegalovirus pneumonia that occurs almost inclusively in immunocompromised patients.[18]

With the exception of COVID-19- and cytomegalovirus-associated pneumonia, viral pneumonia radiographic signs do not noticeably distinguish between different infections.[19]

Typical CT features are nonspecific and include patchy, multifocal or diffuse ground-glass opacities (GGOs) (Fig. 2A-B), interlobular septal or bronchial wall thickening as well as patchy, multifocal consolidation

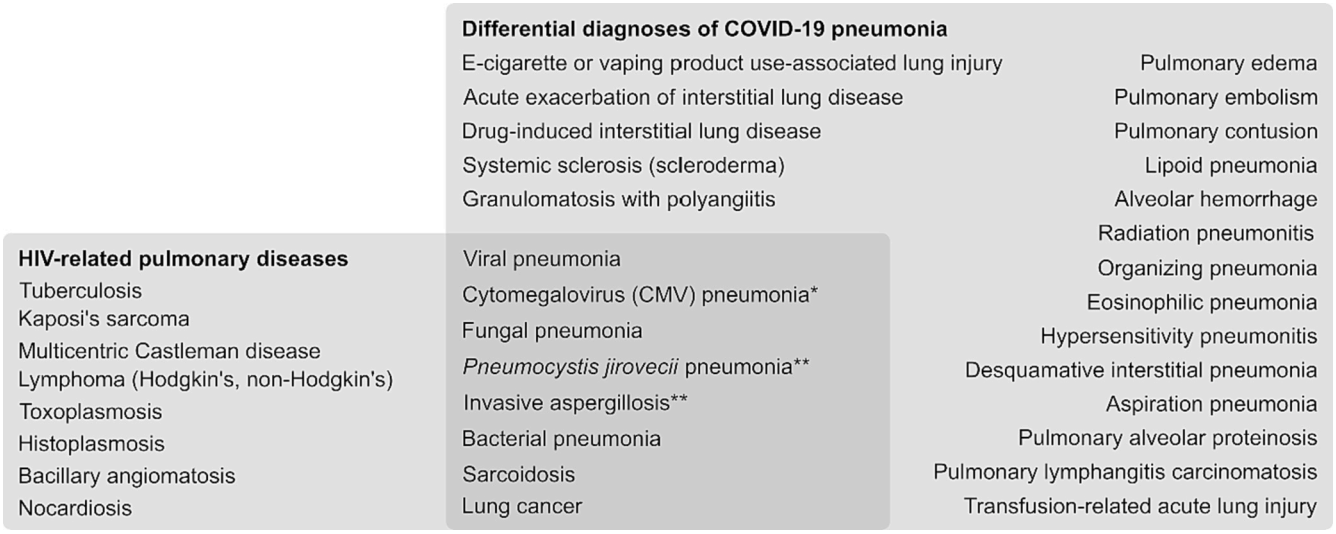

Fig. 1. Venn diagram showing the pulmonary diseases in PLHIV sharing CT findings with CIVID-19-mimicking conditions. Symbol * denotes viral pneumonia with distinctive CT signs. Symbol ** denotes fungal pneumonia with distinctive CT signs.

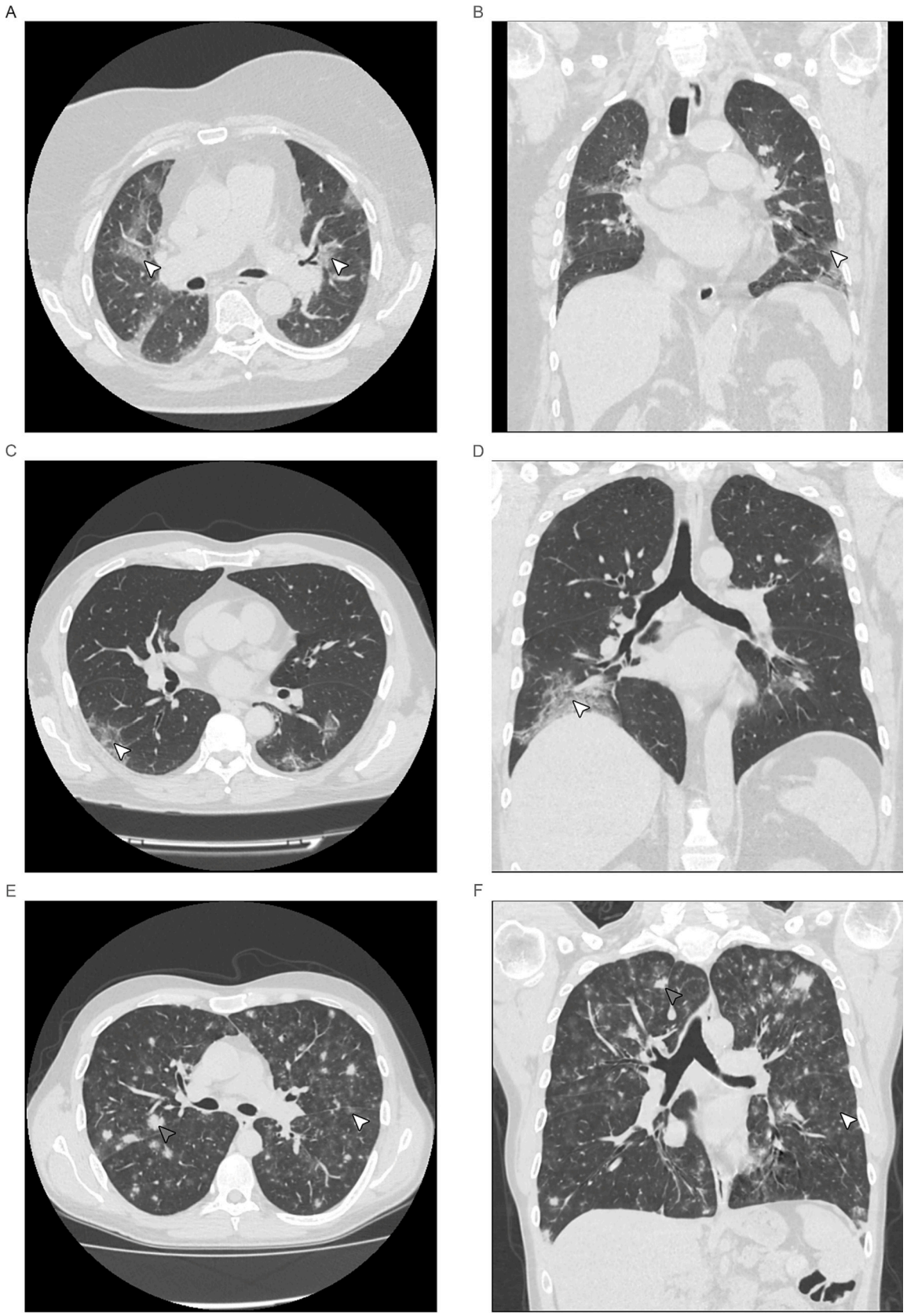

Fig. 2. Typical CT findings associated for different types of viral pneumonia. *A*, *B*: axial and coronal views of patchy GGOs (arrows) in 82-years-old woman with viral pneumonia caused by influenza A; *C*, *D*: axial and coronal images of GGOs with bilateral and peripheral distribution and interlobular septal thickening (arrows) in 47-years-old man with COVID-19-associated pneumonia; *E*, *F*: axial and coronal views of diffuse heterogenous GGOs (white arrows) with focal consolidationmultiple nodules (dark arrows) in 42-years-old man with CMV pneumonia.

corresponding to disease course.[20]

Other CT features include small centrilobular nodules, tree-in-bud opacities and small bilateral pleural effusion.[20]

3.2. COVID-19 pneumonia

Kerkhoff AD et al. showed that HIV-infected individuals may have an increased risk for severe COVID-19-related outcomes.[21] The risk appears to be driven by older age and comorbidities, mostly hypertension, obesity or hyperlipidemia, chronic obstructive pulmonary disease, and diabetes.[22] While the CT features of COVID-19 are non-specific, there are patterns that are typical for the subfamily of coronaviruses.[23]

Typical CT features include bilateral GGOs with apicobasal and peripherial distribution as well as subpleural involvement (Fig. 2C-D).

Other CT features reflect the disease course and complications: crazy paving sign (GGOs with thickened interlobular septa), coalescent consolidations, subpleural lines and pleural effusions.

Cytomegalovirus (CMV) is widespread among general population, with prevalence ranging from 45% to 100%, depending on the geographic region.[24] CMV pneumonia occurs almost inclusively in immunocompromised patients, including AIDS patients, most commonly following bone marrow and solid organ transplantation.[18] Prior to the introduction of HAART, CMV was associated with high early mortality, being one of the most dangerous OIs for PLHIV.[25] Currently, there is a controversy considering clinical significance of CMV as a pulmonary pathogen in HIV-positive patients. Some sources claim that the CMV significance is not fully defined,[26] and that CMV pneumonitis is uncommon in patients with HIV.[27] On the other hand, Tanaka et al. reported that the CMV coinfection in patients with AIDS in Japan is frequently occurring and has one of the highest mortality rates among the other major AIDS-defining diseases, namely PCP, candidiasis, and active tuberculosis.[28]

CMV pneumonia has several CT features distinguishing the disease from other etiologies of viral pneumonia.[19]

Typical CT features include bilateral basal heterogenous GGOs with subpleural sparing, small centrilobular nodules (Fig. 2E-F).

Other CT features include halo sign and interlobular septal thickening.

Unfortunately, the CT findings and clinical features are similar between CMV and adenovirus pneumonia, potentially complicating the final diagnosis.[29]

3.3. Fungal pneumonia

While invasive fungal infections (IFIs) are an important cause of opportunistic pneumonias in HIV patients, there are scarce and conflicting data on the incidence and mortality rate of IFIs. Some sources claim that 47% of AIDS-related deaths are attributed to IFIs.[30] Contrary to that, a large prospective cohort study in Japan revealed that the fungal pneumonia mortality in PLHIV was about 4%.[31] The reported values of IFIs incidence among HIV patients vary widely depending on the country; even within the studies performed in the same geographic area the observed epidemiology can be significantly different.[32–35] The observed inconsistency in reported incidence values may due to uneven distribution of diagnostic tests, resulting in frequent misdiagnosis.[36] The true burden of IFIs may be significantly underestimated, both in developing and developed world.[36] According to the review of Sousa-Neto et al., *Pneumocystis jirovecii* pneumonia (PCP) is the most common IFI among HIV-positive individuals worldwide.[37] Other frequently reported IFIs in HIV patients are cryptococcosis, histoplasmosis, and invasive pulmonary aspergillosis (IPA).[32] While cryptococcosis and histoplasmosis do not share CT findings with COVID-19, there are overlapping radiographic signs between COVID-19 pneumonia, PCP, and IPA.

Pneumocystis pneumonia is caused by ascomycetes fungi *Pneumocystis jirovecii*, formerly known as *Pneumocystis carinii*. The pathogen almost exclusively colonizes human lungs and causes clinical symptoms only in patients with weakened immune system.[38] Typical CT findings differ from other fungal infections in that the predominant findings are GGOs with subpleural sparing[20] (Fig. 3A-B) and "crazy paving": patchy or geographic GGOs with smooth septal line thickening.[39] Thin-walled cystic lesions are commonly identified with CT,[40] appearing during the chronic phase of PCP in the areas previously affected by GGO and being responsible for pneumothorax development.[40] Other findings include pulmonary consolidation, interstitial markings, and adenopathy.[39,41] Pleural effusions are extremely uncommon, and should prompt suspicion of another pathogen.[39]

Invasive pulmonary aspergillosis (two forms, angioinvasive and airway-invasive) has different findings depending on the disease stage. Typical CT findings include multiple ill-defined peripheral nodules that gradually coalesce into larger masses or areas of lobular to diffuse consolidation.[40] At the early stages of the disease the nodules are surrounded by a rim of ground-glass opacity, forming the halo sign[40] (Fig. 3C-D). The halo sign decreases over time, being replaced with cavitation, including the "air crescent sign", which usually indicates good prognosis.[39,40] Additionally, angioinvasive aspergillosis is associated with cavitation and pulmonary infarcts peripheral to the nodules.[39,40] Airway-invasive pulmonary aspergillosis manifests on CT scans with patchy areas of consolidation and crazy paving with a peribronchial distribution and three-in-bud pattern.[39,40] In rare cases, crazy-paving pattern can also be observed in patients with invasive aspergillosis[42] (Fig. 3C-D).

3.4. Bacterial community-acquired pneumonia

In the era of highly active antiretroviral therapy, bacterial community-acquired pneumonia (bCAP) remains a frequent clinical event: episodes of bCAP were observed in 2.1% of HIV-infected patients during a mean follow-up time of 16 months in the Strategies for Management of Antiretroviral Therapy trial.[43]

Even with antibacterial therapy, bCAP still represents an important cause of morbidity and mortality in HIV-infected individuals[44] with mortality being in range between 6% and 15%,[45] and morbidity of 0.53–0.56 cases/100 person-years.[45] Bacterial pneumonia in HIV-infected patients is also associated with permanent decline in lung function, and a higher risk of lung cancer.[46]

The clinical presentation of pneumonia is usually the same as in the HIV-negative population; however, there is a tendency for rapid progression.[47]

Typical CT features include unilateral focal consolidation with air brochogram sign (Fig. 4A, B).[47,48]

Other CT features include cavitation,[49] pleural effusion and lymphadenopathy. GGOs may be present in the earliest course of the disease[50] (Fig. 4C, D). Pleural empyema may be present in *Staphylococcus aureus* pneumonia.[47]

3.5. Pulmonary sarcoidosis

Pulmonary sarcoidosis in HIV is rare[51]; moreover, HIV with persistent viremia is associated with lower risk of incident sarcoidosis in comparison with general population..[52] However, earlier studies suggest that sarcoidosis may be recurrent[53] or newly diagnosed[54] in patients receiving HIV treatment. Further complicating the diagnosis, HIV treatment may induce sarcoidosis-like reactions,[55] requiring lesion biopsy to guide treatment. The CT features of newly diagnosed sarcoidosis in HIV patients resemble the findings in general population.[54] Unfortunately, pulmonary sarcoidosis has a wide spectrum of appearances in CT, earning "Great Pretender"[56] or "Master Mimicker"[57] monikers.

Typical CT features are related to the lymphatics involvement and include hilar and mediastinal lymphadenopathy, upper- and middle-zone perilymphatic micro- and macronodules with subsequent fibrotic changes (Fig. 5).[56]

Atypical CT features vary significantly and include GGOs, linear or

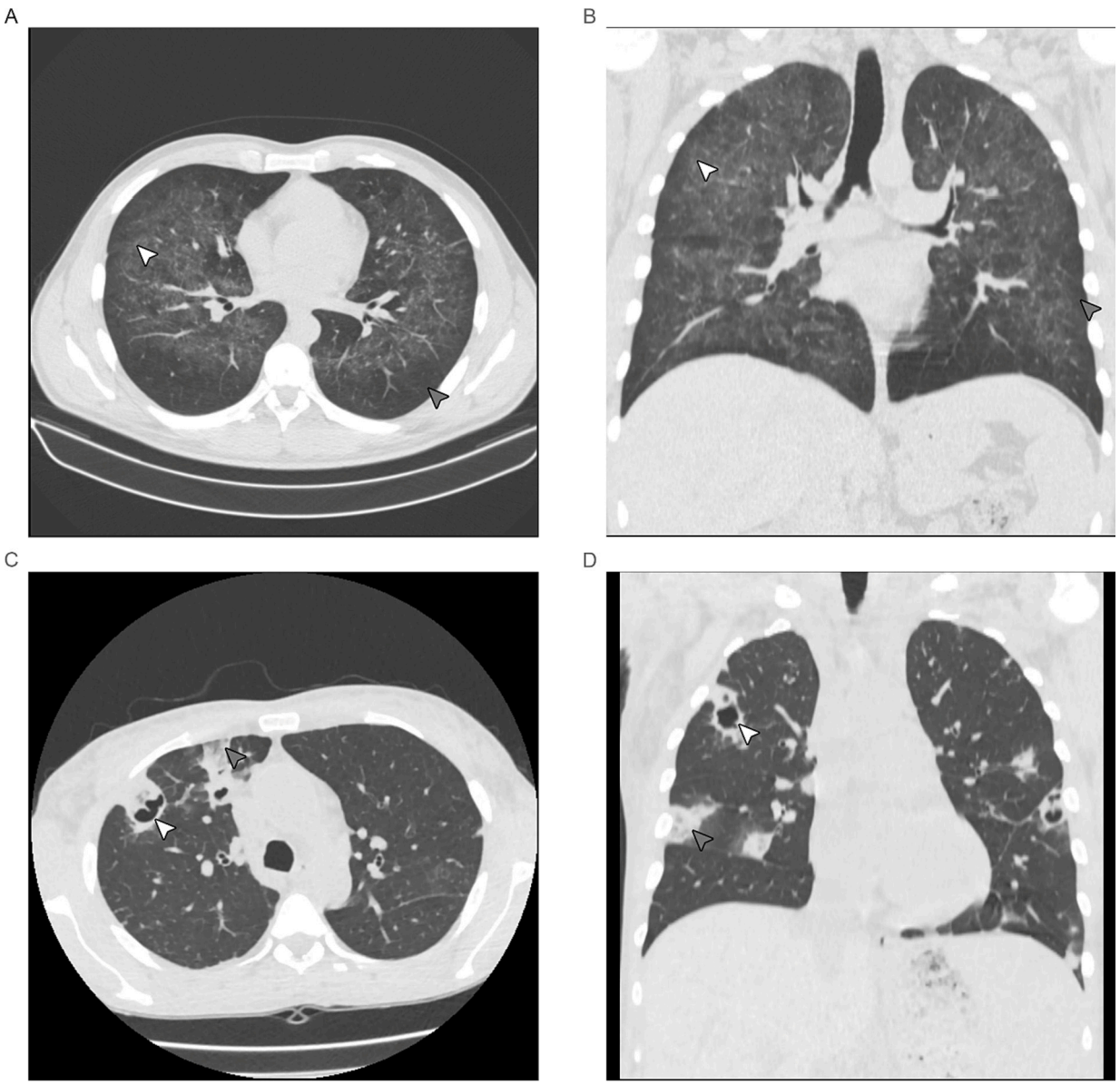

Fig. 3. CT findings in different types of fungal pneumonia. *A*, *B*: axial and coronal views of GGOs (white arrows) with subpleural sparing (dark arrows) in 38-years-old man with PCP; *C*, *D*: axial and coronal views of cavitation with halo sign (white arrows) and crazy-paving sign (dark arrows) in 38-years-old woman with invasive pulmonary aspergillosis.

miliary opacities, airspace consolidation, fibrocystic changes and pleural disorders.[58]

3.6. Lung cancer

HIV-positive individuals have 1.7-fold increased lung cancer risk in comparison with the general population.[59] Clinical and radiographic characteristics are similar between HIV infected and uninfected patients.[60] However, lung cancer in HIV infected patients is more aggressive and develops at younger age compared with uninfected patients.[6,61]

Lung cancer lesions occur more frequently in the upper lobes, with a predilection for the right lung.[62] However, the distribution could arise from the fact that perihilar and paramediastinal regions can be difficult to evaluate.[63] As a result, most missed parenchymal lesions tend to locate in the lower lobes.[64] By the location of the primary lesions, lung cancers can be categorized as central type or peripheral type.[65] Unfortunately, there is ambiguity about what to consider a "centrally located" tumor, causing a lack of agreement between physicians and unnecessary invasive staging for some patients.[66]

Non-calcified pulmonary nodules are typical computed tomography findings associated with early stages of lung cancer. Depending on the attenuation values, lung lesions can be classified as solid (Fig. 6A-B) and subsolid (Fig. 6C-D) nodules. Subsolid nodules include both pure ground-glass nodules and mixed part-solid (halo) types. Consolidation is also frequent on lung cancer CT scans.[67] It has been proposed that lung cancer with a consolidation <50% of the maximum tumor diameter could be a valuable predictive factor for early lung cancer.[68] However, the threshold was derived from retrospective studies; prospective study of Suzuki et al. proposed a consolidation-to-tumor ratio of ≤25% as a factor associated with early lung cancer.[69] which was confirmed in later studies.[70,71]

Rarer manifestations of early lung cancer are single or multiple "cystlike" airspaces with areas of consolidation or ground glass abutting the wall of the cystic part or interspersed between the cystic components.[71]

Typical presentations of advanced lung cancer stages are nodules and

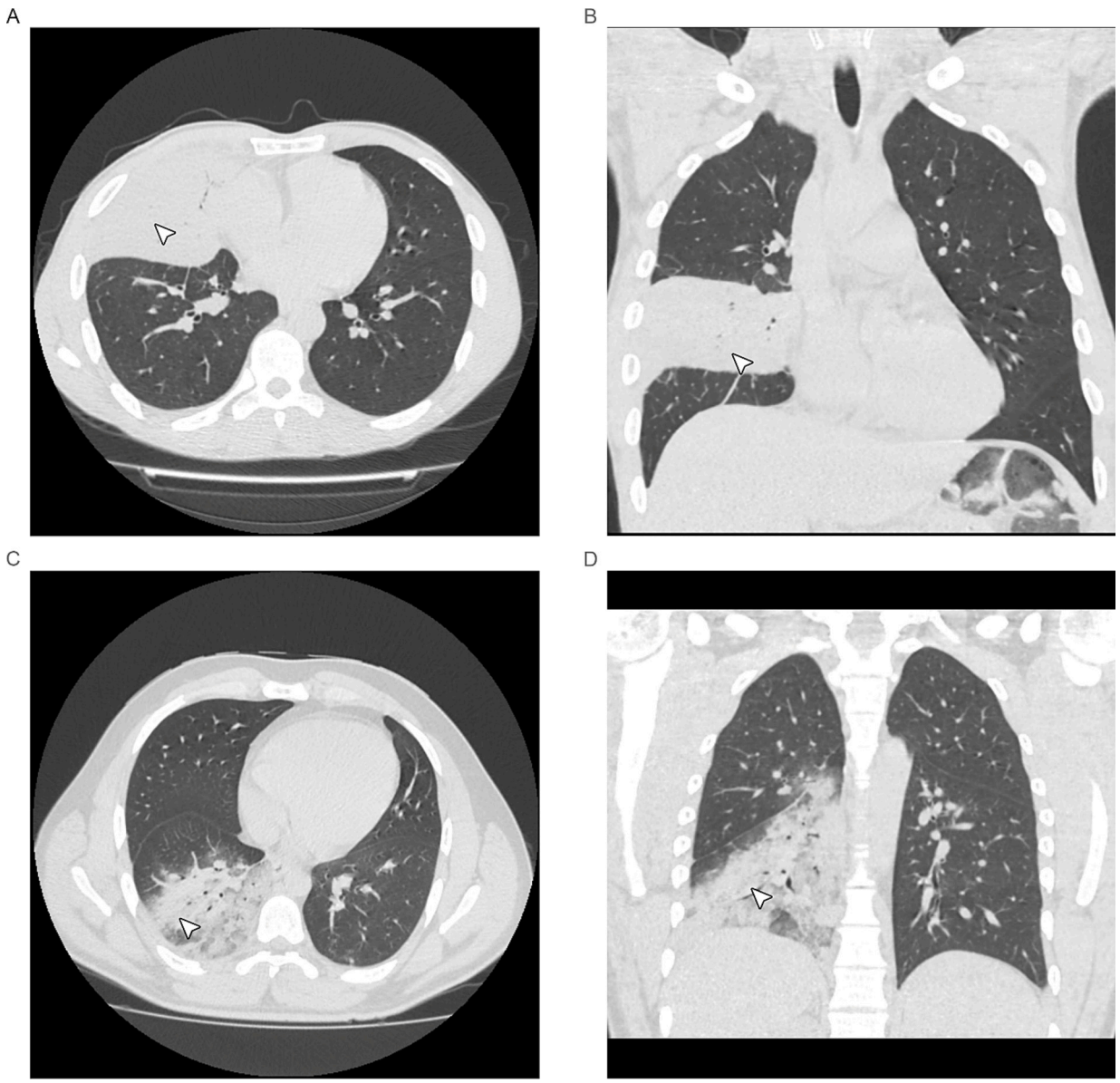

Fig. 4. Typical and COVID-19-mimicking CT findings for bacterial pneumonia. *A*, *B*: axial and coronal views showing unilateral lobar consolidation (arrows) in 44-years-old man with bacterial pneumonia; *C*, *D*: axial and coronal views of unilateral lobar GGOs with superimposed heterogenous consolidations (arrows) in 26-years-old man with bacterial pneumonia.

masses larger than 4 cm, with invasion into adjacent central/mediastinal or peripheral structures and involvement of lymph nodes/metastasis (Fig. 6E-F).[72,73] Other common findings observed on the later stages are obstructive pneumonia and atelectasis[74] and pleural effusion[75] (Fig. 6E-F).

4. Discussion

This pictorial review summarizes the current literature on non-enhanced chest CT findings resembling COVID-19-associated pneumonia that can be observed in HIV infected patients. For PLHIV, we identified five major COVID-19-mimicking disease groups: viral pneumonia, fungal pneumonia, bacterial pneumonia, sarcoidosis, and lung cancer (see Fig. 1).

Bilateral ground glass opacities and subpleural involvement are common in *COVID-19 pneumonia* (see Fig. 2C-D). Less frequent findings are crazy paving sign, coalescent consolidations, subpleural lines, and pleural effusions.

4.1. Differences between COVID-19 and other viral pneumonias

Patchy, multifocal, or diffuse GGOs are typical CT findings associated with *viral pneumonia* (see Fig. 2A-B); the main distinguishing pattern observed in COVID-19 is the apicobasal or peripheral distribution of ground glass opacities (see Fig. 2C-D, A-B). Findings that are common for viral pneumonias and uncommon in COVID-19 pneumonia, appearing only in severe COVID-19, include interlobular septal or bronchial wall thickening, and patchy, multifocal consolidation that can progress with the disease course.

Bilateral GGOs are typical both for COVID-19 and *CMV pneumonia*, but the latter has basal GGO distribution with subpleural sparing accompanied by small centrilobular nodules (see Fig. 2C-D, E-F).

4.2. Differentiating between fungal, viral pneumonias, and COVID-19

There are no typical CT findings associated with *fungal pneumonias*, but each of the four most common IFIs in PLHIV has its own set of

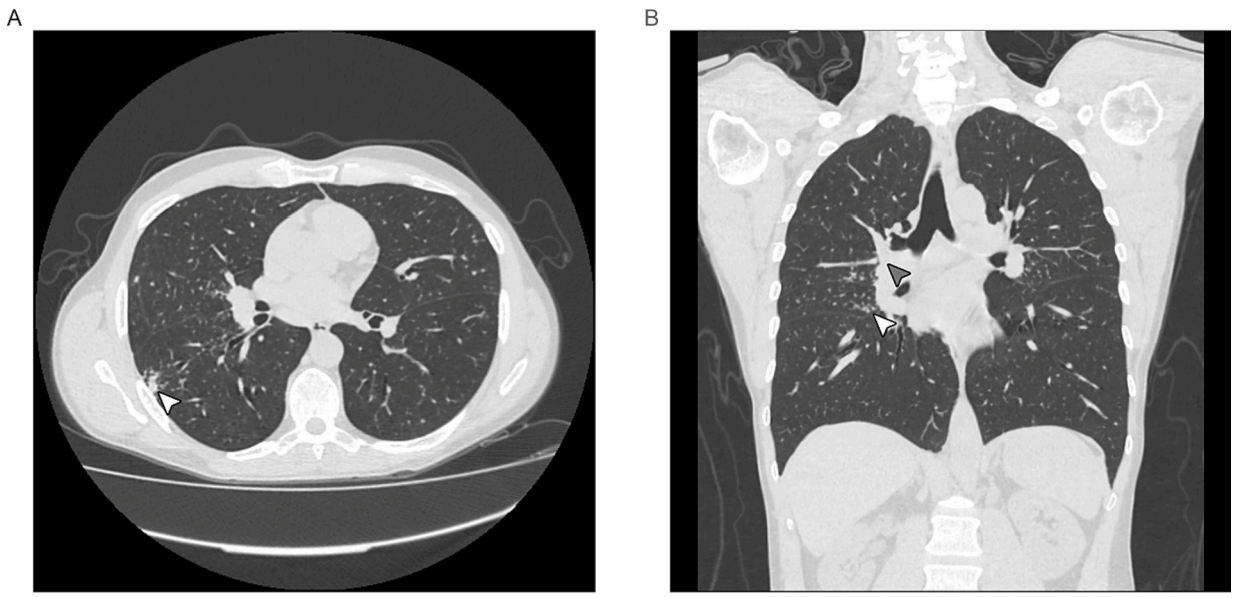

Fig. 5. Typical CT findings for pulmonary sarcoidosis. *A*: Axial view showing perilymphatic micronodules coalescing into micronodule in the right subpleural zone in 45-years-old man with sarcoidosis; *B*: coronal CT image of hilar lymphadenopathy (dark arrow) and perilymphatic micronodules (white arrow) in the same patient.

characteristic features. The CT features of ***PCP*** are similar to the coronavirus infection, however GGOs in PCP are usually extensive and predominate in a central distribution with subpleural sparing (see Fig. 2C-D, Fig. 3A-B). The other distinctive CT features of PCP are interstitial markings; chronic phase of PCP is often associated with occurrence of thin-walled cystic lesions.

Invasive pulmonary aspergillosis in HIV infected patients appears at early stages as multiple ill-defined peripheral nodules surrounded by halo sign. With the progress of IPA, halo sign decreases, being replaced first by the hypodense sign, and then by the air crescent sign (see Fig. 3C-D). Meanwhile, the nodules gradually coalesce into larger masses or areas of lobular or diffuse consolidation (see Fig. 3C-D).

4.3. The non-specific features of bacterial pneumonia

The CT findings in acute histoplasmosis and *bacterial pneumonia* are very similar, consisting of acute consolidation and lymphadenopathy (see Fig. 4). The presence of calcified pulmonary nodules is highly suggestive of current or previous histoplasmosis, while in bacterial pneumonia consolidations gradually disappear with patient's recovery.

4.4. Adding sarcoidosis and lung cancer to the list

The characteristic CT findings seen in pulmonary *sarcoidosis*, distinguishing it from viral, fungal, and bacterial pneumonias, include symmetric hilar and mediastinal adenopathy, and well-defined nodules 2–5 mm in size, with a perilymphatic distribution along the bronchovascular bundles, interlobular septa, interlobar fissures, and subpleural regions (see Fig. 5).

Findings associated with *lung cancer* include non-calcified solid and subsolid pulmonary nodules, the size of which depends on the stage of the disease (see Fig. 6). The nodule persistence during few weeks follow-up is a strong diagnostic sign of lung cancer. Advanced lung cancer manifests on CT scans with obstructive pneumonia, atelectasis, and pleural effusion (see Fig. 6E, F).

4.5. For immunocompromised patients, a different diagnostic approach is needed

Several CT findings observed in immunocompromised patients are not pathognomonic for the same diseases in immunocompetent population. For example, cryptococcosis manifests in immunocompetent patients with multiple well-defined nodules, which are uncommon in immunocompromised hosts. Infections such as cryptococcosis, PCP, pulmonary candidiasis occur predominantly in immunocompromised patients.[40] When the CT signs associated with these pathologies appear in immunocompetent hosts, they may be caused by other conditions, such as malignancy, inflammatory noninfectious pulmonary disease, COVID-19, and iatrogenic disease.[48] Detailed clinical information should be provided to the radiologist for the optimal interpretation of the CT scans. When nodules are detected on CT images, follow-up scans are a useful tool to determine therapy changes, specify the diagnosis, and rule out lung cancer.

4.6. Imaging significance and complications

According to retrospective study of Kowalska et al., the presence of typical or atypical radiological changes is associated with poor prognosis for HIV infected patients with COVID-19 coinfection.[76] Findings such as consolidation, nodules, cysts, and spontaneous pneumothorax occurring in the course of COVID-19 should raise the suspicion of secondary infection, and HIV-positive patients should undergo a broad differential diagnosis 106.[76] Primary coinfections in COVID-19 are rare.[77] This is also true for HIV-positive patients; to date, there have been only case reports published on concomitant COVID-19, HIV, and other disease, typically represented by fungal pneumonia or tuberculosis.[78,79] However, when there is a lack of clinical improvement, unusual CT findings can hint on the probability of secondary infection. For example, results of Wu et al. suggest considering the coexistence of PCP with other infection when pleural effusion was present in an immunocompromised patient.[80] Our review provides a list of typical and rare findings for each of the disease groups included, which may assist in the detection of such cases.

4.7. Limitations of the review

First, due to several occasions of conflicting data in the published literature, we have not included into review the CT features of the diseases that were reported in some papers and not mentioned in other studies. This could potentially lead to some rare but specific CT signs not being mentioned in the proposed list. However, the listing of all rare findings would significantly and unnecessary complicate the data

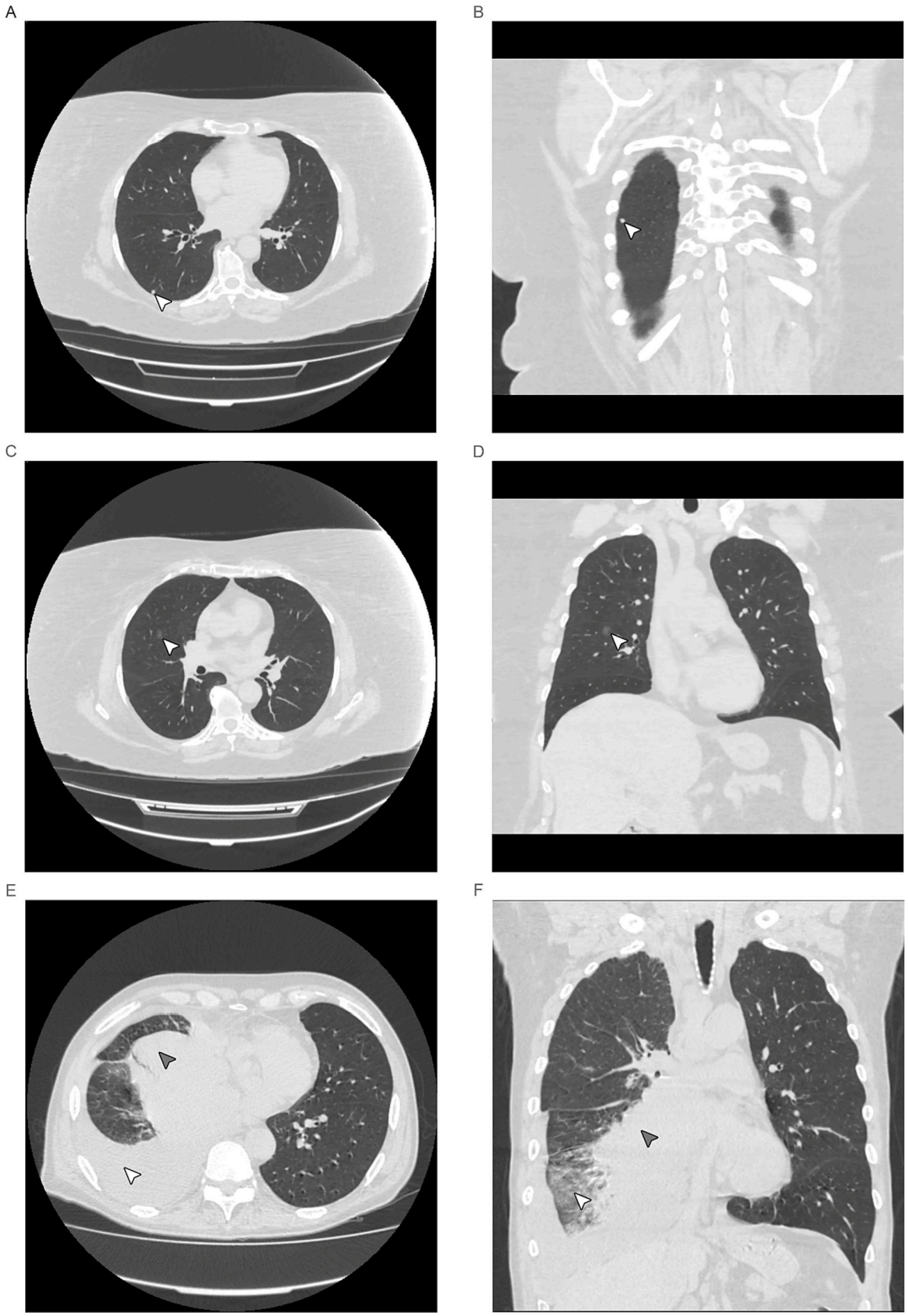

Fig. 6. Typical CT findings for lung cancer. *A*, *B*: axial and coronal views of solid nodule (arrows) in 78-year-old woman with early-stage lung cancer; *C*, *D*: axial and coronal views of subsolid nodule in the same patient; *E*: axial CT image showing large soft-tissue mass invading pericardium (dark arrow) and right-sided pleural effusion (white arrow) in 65-year-old man with advanced lung cancer; *F*: coronal view showing large hilar soft-tissue mass (dark arrow) and perifocal infiltrative changes (white arrow) in the same patient.

provided in the review. Second, due to peculiarities of the URIS architecture, we have had limited access to the clinical and demographic data of the CT studies used as illustrated material for the review. Because of that, we could not find examples of cases associated with rare combinations of confirmed pathologies. However, we have provided the references to the published literature containing relevant high-quality imaging data.

5. Conclusion

In the COVID-19 era, HIV patients with pulmonary diseases should undergo a broad differential diagnosis including viral pneumonia (with the careful attention on COVID-19 and CMV), fungal pneumonia (prioritizing PCP and invasive aspergillosis), bacterial pneumonia, sarcoidosis, and lung cancer. Follow-up scans for the assessment of radiological changes are a useful tool to specify the diagnosis and predict the outcomes for the patients. The appearance of unusual findings on chest CT suggests considering the coexistence of primary pathology with secondary infection. This review provides radiologists with carefully selected non-conflicting descriptive and pictorial data that may assist the diagnostic decision making.

CRediT authorship contribution statement

Liya R. Abuladze: conceptualization, methodology, writing, visualization, investigation. **Ivan A. Blokhin**: conceptualization, methodology, writing, visualization, investigation. **Anna P. Gonchar**: conceptualization, methodology, writing, visualization, investigation. **Mariya M. Suchilova**: writing, editing. **Anton V. Vladzimirskyy**: reviewing and editing, supervision. **Victor A. Gombolevsky**: reviewing and editing, supervision. **Eleonora A. Balanyuk**: supervision. **Oksana G. Ni**: supervision. **Dmitry V. Troshchansky**: supervision. **Roman V. Reshetnikov** – data curation, writing, reviewing, editing, and supervision.

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