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Atypical imaging patterns during lung invasive mould diseases: lessons for clinicians

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The imaging patterns of invasive mould diseases have become more diverse due to the increasing diversity of immunosuppressive conditions and this reinforces the need for knowledge of various potential presentations according to the clinical situation. https://bit.ly/44yI18P

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Abstract

Imaging of pulmonary invasive mould diseases (IMDs), which represents a cornerstone in their work-up, is mainly based on computed tomography (CT). The purpose of this review is to discuss their CT features, mainly those related to aspergillosis and mucormycosis. We will especially focus on atypical radiological presentations that are increasingly observed among non-neutropenic emerging populations of patients at risk, such as those receiving novel anticancer therapies or those in the intensive care unit. We will also discuss the interest of other available imaging techniques, mainly positron emission tomography/CT, that may play a role in the diagnosis as well as evaluation of disease extent and follow-up. We will show that any new airway-centred abnormality or caveated lesion should evoke IMDs in mildly immunocompromised hosts. Limitations in their recognition may be due to potential underlying abnormalities that increase the complexity of interpretation of lung imaging, as well as the non-specificity of imaging features. In this way, the differentials of all morphological/metabolic aspects must be kept in mind for the optimal management of patients, as well as the benefit of evaluation of the vascular status.

Introduction

Invasive mould diseases (IMDs) of the lungs, in particular invasive aspergillosis and mucormycosis, are well-known complications among patients with haematological cancer, including chemotherapy-induced neutropenia and allogeneic haematopoietic stem cell transplantation (HSCT). Because of the non-specific clinical symptoms and the low sensitivity of mould biomarkers (*e.g.* galactomannan), imaging of the lungs is a cornerstone for initial detection as well as follow-up of IMDs. Some highly suggestive radiological patterns of IMDs, such as well-circumscribed density with or without a halo sign or air crescent sign, have been well described in this population [1]. However, it is acknowledged that the computed tomography (CT) pattern of invasive pulmonary aspergillosis (IPA) can vary depending on the profile of haematological patients. It may include signs of angio-invasive IPA in leukaemic and neutropenic patients, *i.e.* typically a macronodule with or without a halo sign, or signs of broncho-invasive IPA in non-neutropenic patients, including allogeneic HSCT, *i.e.* centrilobular micronodules and alveolar consolidation [2].

In addition, IMDs are nowadays increasingly recognised with some specificities among patients with other causes of immunosuppression resulting from novel anticancer therapies, such as tyrosine kinase inhibitors (TKIs), salvage therapy with chimeric antigen receptor (CAR) T-cells or from prolonged immunosuppressive therapies for solid-organ transplant (SOT). Moreover, IPA and mucormycosis have emerged as complications among intensive care unit (ICU) patients with severe influenza or coronavirus disease 2019 (COVID-19) infections [3, 4]. The imaging presentation of pulmonary IMDs in these non-neutropenic patients includes a wide spectrum of non-specific patterns, which cannot be easily distinguished from other bacterial/viral infections or non-infectious lung disorders. These atypical patterns of IMDs are particularly challenging for the clinicians as they may result in delayed diagnosis, which can negatively affect the outcome of these patients.

In this review, we will describe classic imaging features of IMDs observed in neutropenic patients as well as evolving aspects according to specific clinical situations outside of neutropenia. We will also discuss the potentials of other available imaging techniques, in particular positron emission tomography (PET)/CT and magnetic resonance imaging (MRI).

Imaging modality for IMD diagnosis and follow-up

Although chest radiography is widely available and easy to perform at the patient's bed, the sensitivity for IMD detection is low. It is therefore unsuitable for accurate diagnostic and therapeutic decisions (supplementary material S1).

In case of suspicion of IMD, a chest CT with thin slices (~1 mm) at deep inspiration is required [5]. A non-contrast CT is first performed and, in case of any focal non-peripheral abnormality >1 cm, a second CT acquisition with intravenous contrast administration (figure 1) has been proposed by Stanzani *et al.* [6]. In their study, angio-CT increased the diagnostic sensitivity and specificity for IMDs compared with native CT, by allowing the detection of angio-invasion within the lesion [6]. A direct contrast-enhanced CT may be performed in case of suspicion of IMD in the absence of contraindication *versus* a non-contrast CT that allows displaying suggestive morphological features by itself. However, it should always take into account that contrast-enhanced CT may be a source of additional effective radiation dose compared with non-contrast CT in which a lower dose may be used and this is particularly relevant for survivors of childhood leukaemia or in young SOT recipients (supplementary material S2). Post-processing tools may increase the diagnostic yield of CT scans. In particular, maximum intensity projection (MIP) post-processing, which ighlights the highest densities within a slab, may allow easier recognition of the vessel occlusion sign within the suspected IMD nodule on mediastinal windowing of a contrast-enhanced CT [6, 7].

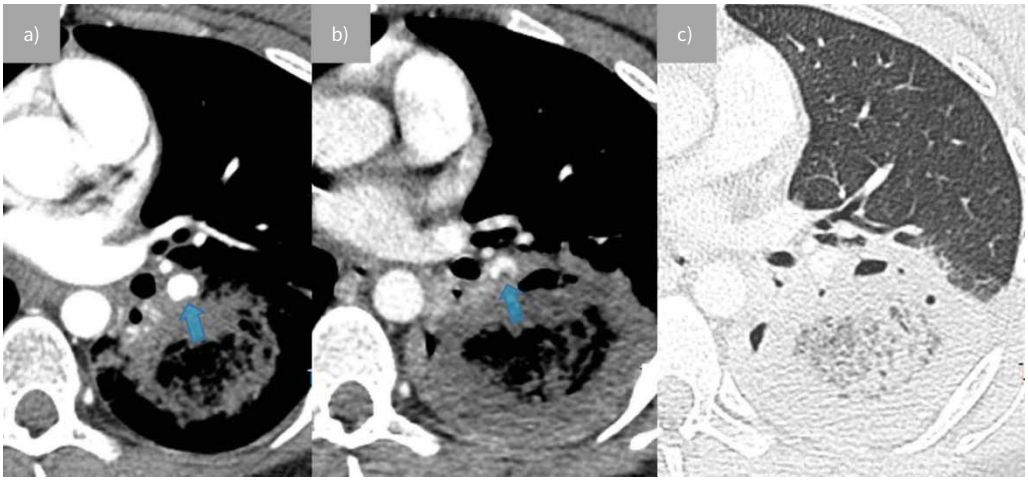

FIGURE 1 a, b) Two successive axial computed tomography slices in mediastinal windowing with intravenous contrast showing the occurrence of an intraluminal defect in a left lower pulmonary artery branch (arrows) adjacent to a necrotic mass related to an angio-invasive mucormycosis of the left lower lobe. This occurred during agranulocytosis secondary to induction chemotherapy for acute lymphoid leukaemia. c) On lung windowing, the presence of a bird's nest sign, referring to the appearance created by a reverse halo sign with associated irregular and intersecting areas of stranding or irregular lines within the ground-glass area.

In addition, MIP post-processing reformats greatly help to detect and evaluate the profusion of micronodules on lung windowing (supplementary material S3) [8]. Furthermore, CT volumetric measurement of lung nodules may be used to quantify the evolution of nodules on follow-up studies. Of note, low-dose CT (<1 mSv) may be appropriate for this task with current equipment. These approaches should be further investigated to delineate the optimal strategy for IMD diagnosis and follow-up at the cost of minimal radiation exposure.

On the other hand, the role of PET/CT has not been completely determined in the assessment of lung IMDs. While keeping in mind the potential additional radiation dose (supplementary material S2), PET/CT appears to be a promising technique for IMD extent work-up, except for the central nervous system [9]. In the series of Ankrah *et al*. [10], comparing ^{18}F-FDG-PET/CT with anatomy-based imaging methods, satellite or secondary IMD lesions not seen on conventional imaging were detected in 49% of PET/CT studies. There was a benefit of ^{18}F-FDG-PET/CT in the management of the disease in 74% of cases [10]. Of interest, latest-generation high-sensitivity silicon photomultiplier detector PET/CT increases lesion detection with novel acquisitions at deep apnoea (breath-hold on inspiration) and very low CT radiation dose (supplementary material S2). In all cases, it must be kept in mind that the observed ^{18}F-FDG uptake may simulate a tumour or may be related to another infection [11]. Another limitation of PET/CT to emphasise is the non-specific signal of the local metabolic avidity in the case of recent surgery (*i.e.* <1 month), in particular for mucormycosis, which might alter the quality of assessment in early follow-up (supplementary material S4) [12].

^{18}F-FDG-PET/CT may be useful to guide treatment, evaluate response to antifungal therapy (particularly in cases of azole resistance and co-infections such as aspergillosis–mucormycosis) or to assess the potential activity of a lesion that would require a surgical approach (*e.g.* before an allograft) and may help to decide when to stop antifungal therapy in selected conditions. Regarding disease relapse, CT usually allows to suspect it by itself.

In addition, ^{18}F-FDG-labelled autologous leukocyte PET/CT may be helpful for the detection and extensive work-up of mucormycosis, as illustrated by a few case reports [13], and experimental approaches on specific *Aspergillus* sp. siderophore tracing have been developed [14].

Next, if MRI has currently no place for the diagnosis or follow-up of pulmonary IMDs, this could change in the future with new low-field equipment, which has the capability of better spatial resolution, along with new developments of ultra-short echo sequences for lung imaging [15].

Chest ultrasound can be an interesting diagnostic tool, but very limited data are available for the diagnosis of IMDs. Owing to the non-specificity of any pleural effusion, ultrasound may be used to enable a tap and *Aspergillus* ssp. antigen testing.

Imaging features on CT

Nodules with or without a halo sign

In IPA, typically nodules of various size may be seen. In particular, macronodules with a size ⩾10 mm have been shown to have a high positive predictive value for the diagnosis of angio-IPA in immunocompromised hosts (figure 2) [16]. An even more suggestive presentation of IPA is the halo sign in a concordant clinical setting. When a peripheral halo sign is present, the solid central part of the nodule likely represents the pulmonary infarction secondary to mould angio-invasion, while the surrounding halo of ground-glass opacity (GGO) represents the local alveolar haemorrhage (figure 2). The halo sign is a variable, transient and early radiological feature in IPA, and some series have associated the halo sign to a better prognosis [16, 17]. During neutropenia, this finding has been shown to have the highest positive predictive value for IPA [7, 18].

While the number of nodules does not allow a clear distinction between IPA and mucormycosis, a few studies suggested that the presence of more than 10 nodules is more suggestive of mucormycosis [19]. However, due to the high spatial resolution of current CT allowing confident detection of tiny millimetre-size nodules, numerous nodules may also be observed in IPA.

Reverse halo sign

A reverse halo sign, defined as the presence of a focal ring-shaped area of GGO within a peripheral rim of consolidation, firstly suggests the diagnosis of mucormycosis, although this may be encountered in other IMDs in immunocompromised hosts as well as in other conditions [20–22]. The bird's nest sign, which

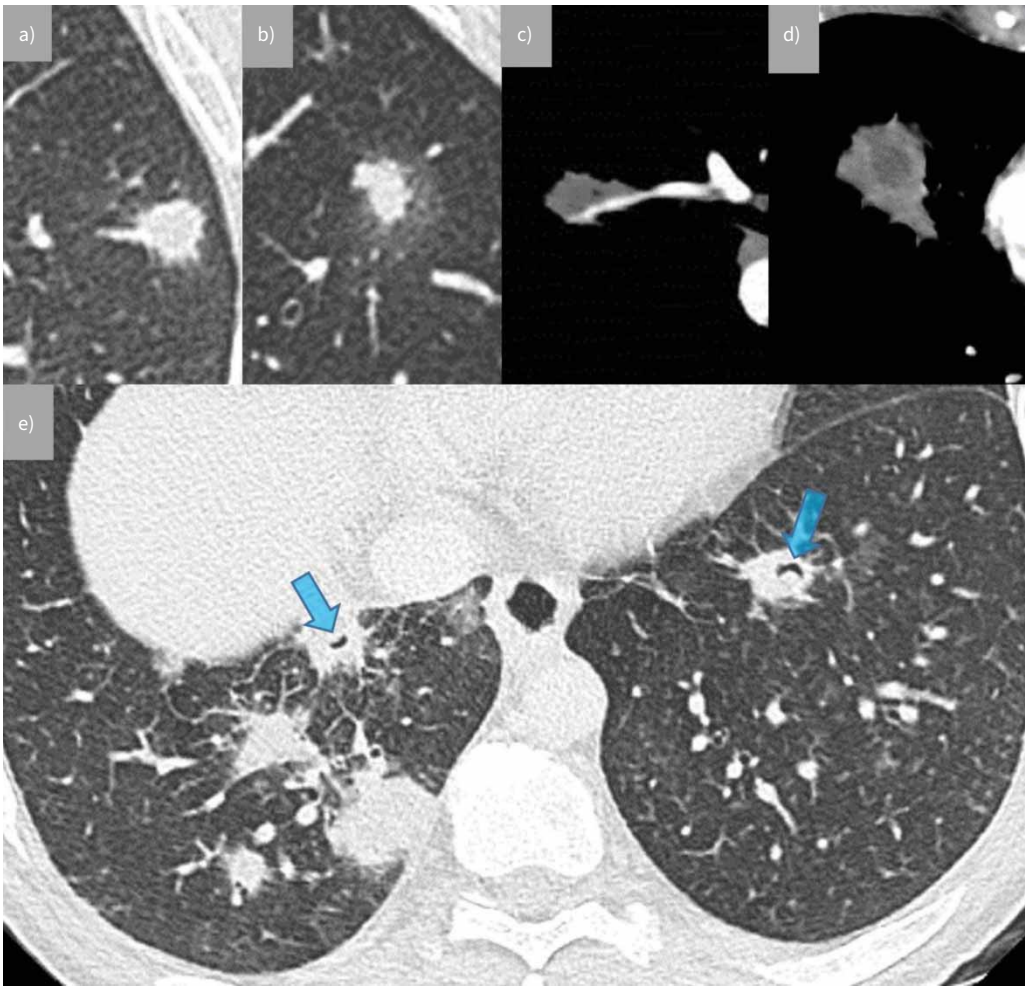

FIGURE 2 a) Invasive pulmonary aspergillosis (IPA) expressing as a new macronodule of 14 mm with slight irregular margins on a computed tomography (CT) image with lung windowing. Note the absence of a halo sign in the left upper lobe that does not reject the diagnosis. This occurred during prolonged agranulocytosis in a patient with acute myeloid leukaemia. b) Nodule with a halo sign and slight irregular borders related to an IPA of the left upper lobe during prolonged neutropenia in the context of salvage chemotherapy for relapse of acute lymphoid leukaemia. c) Axial CT slice in mediastinal windowing with intravenous contrast showing a sharply demarcated focal lesion of the middle lobe in contact with an irregular pulmonary vessel. This occurred in a patient with multiple myeloma following induction chemotherapy with an autologous bone marrow transplant programme and proven IPA. d) Axial CT image with mediastinal windowing with intravenous contrast showing a well-defined focal lesion of the middle lobe with a hypodense component confirmed as IPA. This occurred during prolonged agranulocytosis after induction chemotherapy for acute lymphoid leukaemia. e) Multiple nodules of variable size and mass are visible in the lower lobes on this axial CT image with lung windowing, with an air crescent sign in two of them (arrows). This occurred in the context of IPA–mucormycosis co-infection in a patient with acute myeloid leukaemia at the end of agranulocytosis following induction chemotherapy.

consists of reticulations inside a thick outer rim in an immunocompromised patient, also strongly suggests mucormycosis [6, 23, 24]. Vascular involvement with direct invasion of the neighbouring vessel has to be carefully looked at when the bird's nest sign is present (figure 1).

Hypodense sign

The hypodense sign is related to a well-defined hypodense area (<30 HU) within a focal lesion with a peripheral enhancement on mediastinal CT viewing (figure 2) [25, 26]. This aspect, which reflects a necrotic component, is highly suggestive of pulmonary IMDs in an immunocompromised patient setting, despite lacking specificity.

Vascular involvement

The depiction of an occlusion or lack of opacification by using contrast medium administration within a focal lesion, called the "vessel occlusion sign", reinforces the probability of IMD. According to Stanzani *et al.* [6], the sensitivity of this sign does not apply for peripheral nodules <10 mm in angio-invasive aspergillosis [7]. In our experience, irregular vascular walls should also be considered (figure 2). Septic bacterial pulmonary emboli, especially related to *Staphylococcus aureus* infection, represent the main differential diagnosis [27]. Pseudo-aneurysm may also be seen. This visualisation of vascular involvement potentially allows us to discover the origin of an haemoptysis or help to predict its risk [28].

Air crescent sign and cavitated nodules

The air crescent sign is a late and variable sign of angio-invasive aspergillosis, frequently observed at neutrophil recovery, typically occulting 2–3 weeks after treatment [29]. It is a crescent- or half-moon-shaped air collection in the periphery of a cavitary nodule (figure 2) or mass [30]. The air crescent sign is considered as a good prognostic radiological pattern [16].

In moderately immunocompromised patients, any new caveated nodule should suggest the possibility of an IMD. Interestingly, this presentation is not far from that of subacute invasive aspergillosis, formerly called chronic necrotising pulmonary aspergillosis, described by Denning *et al.* [31] in moderately immunosuppressed patients.

Airway-centred anomalies

Airway-centred anomalies may indicate a broncho-invasive aspergillosis. Several aspects may be encountered. First, peribronchial focal lesions may be seen, albeit these are not specific. Although commonly described in non-neutropenic patients [2], including persons living with HIV (PLWH) at a late stage of the infection [32], such lesions were shown to be a common finding of early IPA in haematological cancer patients with prolonged (⩾10 days) neutropenia [33].

In proximal airways, any new circumferential thickening of the trachea and/or the proximal bronchial tree should also suggest the possibility of a tracheobronchial invasive presentation of an IMD, and promptly motivate a bronchoscopy with mucosal and submucosal biopsies of the proximal airways. Invasive *Aspergillus* tracheobronchitis is also classically described in early (<1 year) lung transplant, in particular at the site of surgical sutures [34]. It may also be observed in mild immunocompromised patients following lung surgery as well as in PLWH at a late stage of the disease [35] or as a complication of influenza [4, 36]. A following submucosal fistulae may occur secondarily (figure 3).

On the other hand, bronchial stump aspergillosis is an infection involving the granulation tissue surrounding the sutures of lung resection that usually affects non-immunocompromised patients within the first year after pulmonary resection [37]. It may be asymptomatic or manifest as haemoptysis,

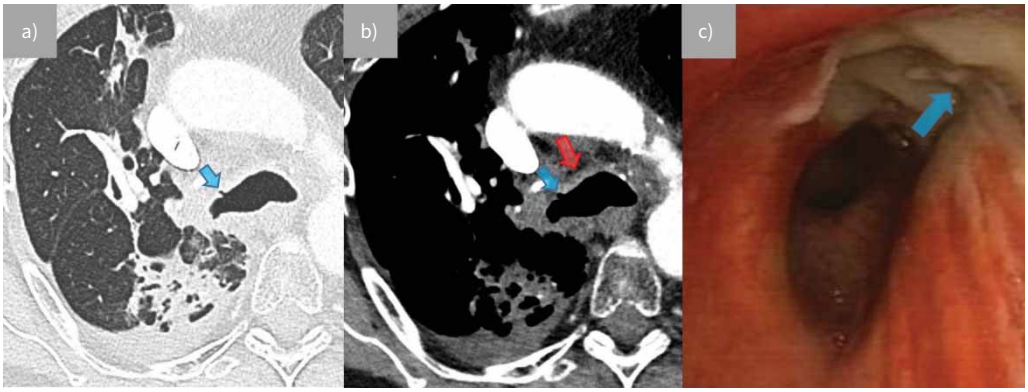

FIGURE 3 a, b) Axial computed tomography images with a) lung and b) mediastinal windowing after intravenous contrast in a patient treated for locally advanced non-small cell lung cancer showing a circumferential thickening of the distal trachea and main bronchi (red arrow) with a submucosal fistula (blue arrows), better seen with lung windowing in a), that was confirmed as airways invasive aspergillosis. c) Endoscopic view of the fistula (blue arrow) arising from the distal part of the trachea.

expectoration of a fungus mass, necrotic material or suture thread, cough, putrid sputum, asthma exacerbation and acute dyspnoea [37].

Other features

Pleural effusions may be observed during invasive aspergillosis and represent a poor prognosis indicator [38]. In addition, they are frequently observed during mucormycosis, although without any specificity [19].

Differentials

Each of the previously described imaging features may be related to a large number of disorders in the immunocompromised host, including other infectious diseases (*e.g.* viral: cytomegalovirus and herpesvirus) or non-infectious diseases (*e.g.* neoplasms, post-transplant lymphoproliferative disorders, acute fibrinous and organising pneumonia) [39]. Differentials of tracheobronchial invasive IMDs include other infectious causes (viral and bacterial) as well as immune-related tracheitis secondary to immune checkpoint inhibitor (ICI) therapy [40]. A precise analysis of the clinical context and biological results has to be integrated with the radiological analysis to retain the diagnosis of IMD [41], and it is important to note that IMDs can be mistaken as cancer recurrence/progression in patients with lung cancer because of mimicking both radiological and clinical characteristics [42].

IMD radiological patterns in specific clinical settings

Novel anticancer therapy

TKIs, such as ibrutinib, are used for the treatment of haematological cancers, such as lymphomas and acute myeloid leukaemia, and have recently been associated with the development of IMDs [43, 44], in particular IPA [45]. In this context, the CT aspect of lung IMDs is similar to that observed during prolonged neutropenia with a high incidence of concomitant cerebral aspergillosis [46, 47]. Nevertheless, imaging studies in this clinical setting are lacking.

Alemtuzumab is a monoclonal antibody targeting the protein CD52 and used for the treatment of multiple sclerosis and refractory lymphoproliferative disorders. It has been associated with an increased risk of IMDs [48, 49], but the risk seems to be higher for disseminated candidiasis [50]. Similarly to TKIs, the imaging pattern of IMDs has been poorly described in this clinical context.

ICIs have revolutionised the treatment of cancer in the last decade. Although it has been estimated that ~7% of patients receiving ICIs either in monotherapy or in combination will develop serious infection due to opportunistic infections, IMDs remain uncommon (0.8%) [51]. Most IMDs are related to the high-dose and prolonged corticosteroid therapy (>1 $mg \cdot kg^{-1}$) required for the management of immune-related toxicities [51]. In addition to the overlap of clinical signs, in the case of lung immune-related toxicity, an exhaustive lung parenchymal and bronchial analysis remains a challenge due to the presence of immune-related CT features that may alter IMD suspicion and recognition. Furthermore, the appearance of IMDs can mimic cancer progression when faced with new pulmonary nodule(s) or mass cavitation [52]. On the other hand, ICIs are studied in animal models as synergic therapy with antifungal drugs for IMDs [53].

CAR T-cells are a salvage treatment for some advanced malignancies, including lymphoma, myeloma and leukaemia. It is currently estimated that IMDs, which mostly follow the conditioning regimen for the management of cytokine release syndrome, account for 3–11% of treated patients [54–59]. No radiological specificities are described.

Intensive care unit

The diagnosis of IMDs in the ICU is particularly challenging because of the lack of sensitivity and specificity of clinical and radiological signs [60]. While influenza is a well-known independent risk factor for IPA in the ICU [61], a variable incidence of IPA has been reported among COVID-19 patients [62]. Rouzé *et al*. [63] found that IPA was twice as frequent in intubated patients with influenza than in COVID-19. An appearance of an invasive tracheobronchitis form has been described as a common manifestation of influenza-associated pulmonary aspergillosis with a very high mortality rate [36]. During severe influenza, the occurrence of new cavitary nodules should also suggest the possibility of an IMD [4] and these aspects are schematised in figure 4.

During COVID-19 pneumonia, independently of pneumatoceles that may occur [64], any new caveated nodular lesion should suggest the possibility of an IMD (figure 5). In this setting, no other peculiar CT pattern has been attributed to IMDs (figure 4). This highlights that a definitive diagnosis may be a challenge [65].

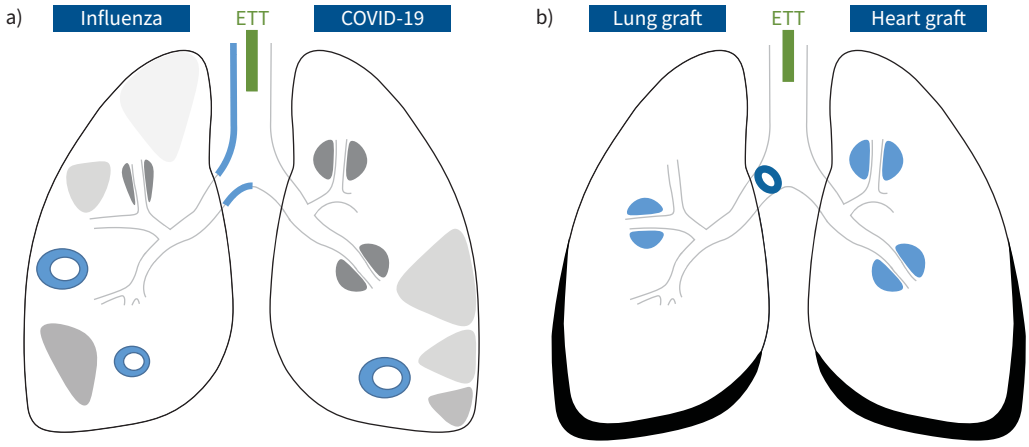

FIGURE 4 a) Influenza infection and coronavirus disease 2019 (COVID-19) complicated by invasive mould disease (IMD). Influenza infection: the various levels of lighter grey represent patchy ground-glass areas and the dark grey areas represent peribronchial alveolar consolidations due to influenza virus. *De novo* cavitated nodules requiring exclusion of mould infection (blue), as well as newly conferential thickening of trachea and main bronchi (blue). COVID-19: the various levels of lighter grey represent predominant basal subpleural patchy ground-glass areas and the dark grey areas represent peribronchial alveolar consolidations due to severe acute respiratory syndrome coronavirus 2. *De novo* cavitated nodules requiring exclusion of mould infection (blue). b) Lung and heart grafts complicated by IMD. Lung graft: concomitant pleural effusions (black) are frequent and anastomotic mould infection is a main finding (dark blue). Concerning parenchymal IMD, lung transplant recipients are likely to show peribronchial consolidations (blue). Heart graft: concomitant pleural effusions (black) are frequent. Concerning pulmonary IMD, cardiac transplant recipients are likely to show peribronchial consolidations (blue). ETT: endotracheal tube.

COPD patients

IPA complicating COPD exacerbations is rarely documented, partly because access to lower respiratory tract samples for testing is limited, fungal culture in expectoration has low predictive value and tests assessing circulating antigen in serum are usually negative [66]. However, up to 1–4% of COPD exacerbations may be complicated by IPA [67–69]. Radiological features of IPA in patients with COPD include non-specific new bilateral infiltrates, which later in the course may cavitate [66, 70]. The development of these radiological features, especially in the context of a recent high cumulative dose of corticosteroids, should prompt to investigate a potential diagnosis of IMD [68, 69].

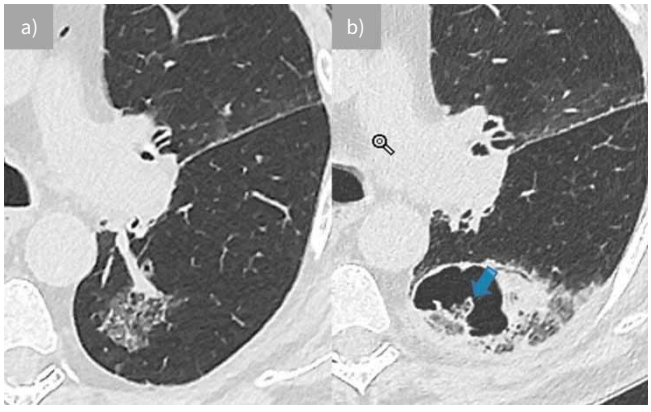

FIGURE 5 a) Axial computed tomography with lung windowing showing a newly appeared ground-glass focal opacity at the apical segment of the left lower lobe in a patient with a concomitant non-severe coronavirus disease 2019 infection in the context of advanced urothelial cancer. b) A cavitary lesion developed 10 days later with an alveolar consolidation in the same area. Note the intraluminal material (blue arrow). Histopathological results confirmed a semi-invasive *Aspergillus fumigatus* infection.

SOT recipients

SOT recipients are a well-known population at risk for IMDs, mainly regarding *Aspergillus* ssp. Although the overall IPA incidence in this setting remains below 10%, at least in non-lung transplanted patients [71, 72], the mortality rate is still high, mainly in liver transplant recipients [71, 73]. Regarding pulmonary IMDs, SOT recipients are likely to show peri-bronchial consolidations or GGOs and less likely macronodules, mass-like consolidations, halo signs and air crescent signs [74].

Of note, in heart and lung transplantation, concomitant pleural effusions are frequent [72] and may alter the recognition of IMD-compatible features (figure 4). Additionally, in a setting of lung transplantation, IMDs, mostly caused by *Aspergillus* spp., may involve the site of suture between the host main bronchi and pulmonary graft, *i.e.* anastomotic infection (figure 4 and supplementary material S5), or the lung parenchyma [34]. Single-lung transplant and airway colonisation with *Aspergillus* spp. within 1 year post-transplant are associated with a higher risk of IPA [75].

Congenital immunodeficiency disorders

Chronic granulomatous disease (CGD) and hyper-IgE syndrome (HIES) are the most frequently congenital, or primary, immunodeficiency disorders associated with IMDs [76].

In CGD, neutrophil, monocyte, macrophage and dendritic cell function is impaired due to an inherited mutation of superoxide anion production. The incidence of IMDs is high and estimated at between 20% and 40% [76, 77].

In HIES, the decreased production of interferon-γ in response to infectious stimuli due to an inherited mutation leads to an increased susceptibility to IMDs [76], with an estimated incidence up to 28% in autosomal-dominant signal transducer and activator of transcription 3 (STAT3) deficiency [78]. The radiological pattern of pulmonary IMDs in this specific clinical context is poorly described [79].

Points for clinical practice

- The imaging patterns of IMDs have become more diverse due to the increasing diversity of immunosuppressive conditions.
- Imaging of IMDs is mainly based on CT.
- Any new airway-centred abnormality or caveated lesion should evoke IMDs in mildly immunocompromised hosts.
- Limitations in their recognition may be due to potential underlying abnormalities that increase the complexity of interpretation of lung imaging, as well as the non-specificity of imaging features.

Conclusions

The imaging patterns of IMDs have become more diverse due to the increasing diversity of immunosuppressive conditions and treatments. Along with the expansion of the patient populations at risk of IMDs, this reinforces the need for knowledge of various potential presentations according to the clinical situation, with a crucial role of a multidisciplinary approach.

In particular, any new airway-centred abnormality or caveated lesion should evoke IMDs in mildly immunocompromised hosts. Limitations in their recognition may be due to potential underlying abnormalities that increase the complexity of interpretation of lung imaging, as well as the non-specificity of imaging features. In this way, the differentials of all morphological/metabolic aspects must be kept in mind for the optimal management of patients, as well as the benefit of evaluation of the vascular status.

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Biotest and Takeda; and advisory board participation with Syneos, all outside the submitted work. A. Bergeron reports lecture honoraria from AstraZeneca and Novartis; travel support from Boehringer and AstraZeneca; and advisory board participation with Enanta, all outside the submitted work. C. Beigelman-Aubry reports lecture honoraria from Gilead, outside the submitted work. All other authors have nothing to disclose.

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