Invasive fungal diseases in patients with hematological malignancies: Multidetector Computed Tomography findings in the most common sites of infections

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Learning objectives

To describe the most common sites of invasive fungal diseases (IFDs) in patients with hematological malignancies.

To review the role of MultiDetector Computed Tomography (MDCT) in the diagnosis of IFDs in such patients.

To resume typical MDCT imaging features of IFDs in immunocompromised patients.
Background

IFDs are a major cause of morbidity and mortality in patients suffering from hematological malignancies [1]. These patients have a compromised immune system, due to the disease itself, chemotherapy or stem cell transplantation procedure.

Most common sites of fungal infection in this setting are:

- low respiratory tract
- central nervous system (CNS)
- paranasal sinuses
- liver and spleen.

The most common pathogens causing IFD are *Aspergillus spp.* and *Candida albicans*.

According to US Mycoses Study Group (MSG) and the Infectious Disease Group of the European Organization for Research and Treatment of Cancer (EORTC) consensus group, three criteria are used to define IFD: host factors, clinical factors and microbiological factors [2]. These criteria also help to assign a degree of certainty to the diagnosis of IFD, namely "proven", "probable" and "possible" IFD. Proven IFD requires demonstration of fungal elements in diseased tissue. Probable IFD requires the presence of a host factor, a clinical criterion and a mycological criterion. If the mycological criterion is absent, but host and clinical criteria are met, IFD is considered possible [2]. Clinical criteria consider not only signs and symptoms but also imaging findings, resumed in table 1.

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Diagnostic criteria</th>
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<tbody>
<tr>
<td>Lower respiratory tract infection</td>
<td>Dense, well-circumscribed lesions(s) with or without a halo sign</td>
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<tr>
<td></td>
<td>Air-crescent sign</td>
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<td></td>
<td>Cavity</td>
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<tr>
<td>Sinonasal infection</td>
<td>Imaging showing sinusitis and 1 of the following 3 signs</td>
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<td></td>
<td>Acute localized pain (including pain radiating to the eye)</td>
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<td></td>
<td>Nasal ulcer with black eschar</td>
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Extension from the paranasal sinus across bony barriers, including into the orbit

CNS infection (1 sign)
Focal lesions on imaging
Meningeal enhancement on MRI or CT

Disseminated candidiasis (1 of the following 2 entities after an episode of candidemia within the previous 2 weeks)
Small, target-like abscesses (bull's-eye lesions) in liver or spleen
Progressive retinal exudates on ophthalmologic examination

Table 1. Clinical criteria for diagnosis of probable or possible IFD according to US Mycoses Study Group (MSG) and the Infectious Disease Group of the European Organization for Research and Treatment of Cancer (EORTC) consensus group [2]
Findings and procedure details

Lower respiratory tract infection

Chest CT detects typical infiltration patterns of pulmonary IFD such as lung nodules of 1 cm or more and lung masses and typical signs associated with nodules and masses [3]:

- halo sign
- reverse halo sign
- hypodense sign
- air crescent sign.

HALO SIGN

It is a typical early phase sign of pulmonary angio-invasive aspergillosis, consisting in a nodule or mass surrounded by an area of ground-glass opacity [4] as shown in Fig. 1 on page 8. This may result from pulmonary infarct with fungi (solid nodule) with blood in alveoli due to hemorrhage (ground-glass appearance).

In the appropriate clinical setting (hematological malignancy, profound neutropenia and persistent fever), the halo sign can be present before clinical symptoms and positive galactomannan results, and is highly specific for invasive aspergillosis. The prevalence of the halo sign is very high in the first days of disease and decreases over time. In one study in which patients were evaluated on day 0, 3, 7 and 14, the halo sign was present in 96%, 68%, 22% and 19% respectively. Therefore, it is very important to plan CT scanning early to get IFD detection on the basis of halo sign [3]. This sign may be associated also with Candida and Zygomycetes pulmonary infection. However the halo sign, when found within the first week of disease, is considered highly specific for angio-invasive aspergillosis due to higher prevalence of this cause in immunocompromised patients [5].

REVERSE HALO SIGN

Reverse halo sign consists in a focal area of ground-glass attenuation surrounded by a ring of consolidation (Fig. 2 on page 8). This appearance is due to a central area of hemorrhage and a peripheral solid ring of infarcted lung with inflammatory cells. Reverse halo sign is also an early phase sign of IFD, less common than halo sign, with prevalence of 1% in patients with invasive aspergillosis and 19% in patients with pulmonary zygomicosis [3].

HYPODENSE SIGN

It is a sign possibly found on subacute phase of pulmonary IFD, occurring 3-23 days after initial CT detection of IFDs. Due to its appearance time, it confirms fungal infection
rather than diagnose it or determine treatment [3]. Hypodense sign is represented by a central area of hypodensity in lung consolidations or nodules (Fig. 3 on page 9) due to central necrosis and dense fungal hyphae [5]. The hypodense sign is proved to be a precursor of the air crescent sign, anticipating it by a range of 2-19 days [6].

Hypodense sign may be seen on unenhanced CT, but is better appreciated on soft tissue window after contrast material injection.

AIR CRESCENT SIGN

This sign usually occurs 2-3 weeks after treatment initiation, is associated with neutropenia resolution and indicates a good prognosis [3]. The air crescent sign is characteristic of pulmonary angioinvasive aspergillosis when seen in the appropriate clinical setting. The hyphal form of the fungus invades the pulmonary vasculature resulting in pulmonary hemorrhage, arterial thrombosis, and eventual infarction. Over time, with retraction of the infarcted center and peripheral reabsorption of necrotic tissue by leukocytes, a central area of devitalized tissue is formed. The air crescent sign results when air fills the space between the devitalized tissue and the surrounding parenchyma (Fig. 4 on page 10). An opaque rim of hemorrhagic tissue peripheral to the radiolucency makes visualization of the air crescent possible [7].

CNS infection

Cerebral involvement in IFD results from hematogenous spread and occasionally from direct extension of infection from the paranasal sinuses or orbit. Aspergillus hyphae penetrate the vessel walls and cause local thrombosis resulting in cerebral infarction [8]. CT scan may reveal multiple cortical and subcortical areas of decreased attenuation. Brain infarction is usually hemorrhagic and in patients with severe neutropenia results in a rapid fatal outcome. In these cases, the lesions show little or no mass effect and minimal or absent contrast enhancement [9].

In most cases, however, patients have less severe neutropenia and infarcted parenchyma becomes infected with consequent abscess formation due to direct invasion of vessels wall by fungi [4]. Also fungal vasculitis, meningitis and mycotic aneurism may occur. Most common sites of cerebral abscesses are the cortico-medullary junction, basal nuclei, thalami and corpus callosum [9]. CT typically shows hypodense areas surrounded by ring enhancement (Fig. 5 on page 11). MRI allows detection of CNS abscesses as CT, but better demonstrates dural and meningeal enhancement or vascular infiltration, that may occur in case of paranasal sinusitis or orbit infiltration [9].

Sinonasal infection
Fungal disease of the paranasal sinuses is categorized into invasive or noninvasive forms. In immunocompromised patients acute invasive fungal sinusitis usually occurs [10] and *Aspergillus spp* are responsible for up to 80% infections in this group. MDCT shows hypoattenuating mucosal thickening or an area of soft tissue attenuation within the lumen of the involved paranasal sinus and nasal cavity, with predilection of unilateral involvement of the ethmoid and sphenoid sinuses (Fig. 6 on page 12). The infection may cause aggressive bone destruction with intracranial and intraorbital extension (Fig. 7 on page 12) [11]. Early changes cannot be differentiated from a nonspecific sinusitis [10] and bone erosion and mucosal thickening may sometimes be very subtle and nonsignificant [11]. MDCT is the tool of choice for the detection of osseous erosion, however MR imaging is superior in evaluating intracranial and intraorbital extension of the disease [12].

**Disseminated candidiasis**

Prolonged neutropenia and breach in mucosal integrity can lead to invasion of fungi from the gastrointestinal tract into the bloodstream and in particular into portal venous system. As a result, fungal micro-abscesses may be seen in the liver, spleen and kidneys, most commonly caused by *Candida spp*, but may also occur due to *Aspergillus spp* [13].

Fungal infection can cause multiple, small, scattered hypoattenuating nodules on MDCT (Fig. 8 on page 13) [14], which may be mimicked by metastases, lymphoma, pyogenic abscesses, and tuberculosis [13].

In case of hepatosplenic candidiasis typical MDCT findings are multiple, round lesions that may enhance centrally or may show central low attenuation and peripheral ring enhancement (Fig. 9 on page 14) [15].

Late-arterial phase CT evaluation provides a more accurate and sensitive method for diagnosis of chronic disseminated fungal infection, because the number and volume of lesions detected are significantly higher when compared with the portal venous phase [16]. However, CT appearance of fungal abscesses is similar to that of pyogenic ones and only a sample of the lesion enables definition of the pathogen.
Fig. 1: (A) Axial CT image shows two solid nodules surrounded by a perimeter of ground-glass opacity (halo sign) on upper and lower left pulmonary lobe. (B) Halo sign detected on HRCT at lower right pulmonary lobe.

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Fig. 2: (A) Axial HRCT reveals upper left lobe area of ground-glass opacity surrounded by solid ring (reverse halo sign). (B) In the same patient and exam of fig. 1 B, axial HRCT finding of reverse halo sign on left upper pulmonary lobe.

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**Fig. 3:** Axial CT shows a solid mass with central hypodense area (hypodense sign) on soft tissue manually adjusted window (A), better appreciated after endovenous contrast administration (B).

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Fig. 4: (A) Axial HRTC reveals a pulmonary cavitary process characterized by air surrounded by dense material along both its inner and outer margins (air crescent sign). (B) After 30 days, on a further HRCT, the lesion on Fig. 1 B shows small peripheral areas of initial cavitation.

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**Fig. 5:** Axial contrast enhanced CT reveals focal hypodense cerebral area with ring enhancement, associated with edema, at cortico-medullary junction on right temporo-occipital region (A) and at corona radiata on left side (B).

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![Axial contrast enhanced CT reveals focal hypodense cerebral area with ring enhancement.](image)

**Fig. 6:** Axial CT shows soft tissue attenuation in ethmoid and sphenoid sinuses (A). Also maxillary sinus is involved (B) with reduced thickness of medial bone wall (C).

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Fig. 7: CT reveals hypoattenuating mucosal thickening of left ethmoidal cells spreading into subcutaneous tissue of palpebra and orbit (A) that is also associated with reduced thickness of medial wall of orbit (B). On figure C orbit involvement with fat stranding and swollen appearance of medial rectus muscle can be better appreciated.

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**Fig. 8:** Axial contrast-enhanced CT on portal venous phase reveals multiple round hypoattenuating lesions on spleen (A) and on both kidneys (B) in a patient with disseminated candidiasis.

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**Fig. 9:** Axial late-arterial phase CT shows two round lesions with central low attenuation and peripheral ring enhancement on III and V hepatic segment.

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Conclusion

MDCT is a useful tool for the diagnosis of IFDs, allowing early detection of lesions in most common sites of infection.

Recognizing the most significant MDCT findings of IFDs is important to help the clinician in establishing an early diagnosis, enabling prompt institution of antifungal treatment and reducing morbidity and mortality of immunocompromised patients.
References


