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Systemic Candidiasis Contribution of Imaging: A Case Report and Bibliographic Review

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Abstract | **Case Report**

Systemic candidiasis is a severe invasive fungal infection that mainly affects immunocompromised patients and is associated with significant morbidity and mortality. Although Candida albicans remains a major pathogen, the epidemiology of invasive candidiasis has changed over recent decades, with an increasing incidence of non-albicans Candida species, some of which show intrinsic resistance or reduced susceptibility to commonly used antifungal agents. The clinical presentation is often nonspecific, usually consisting of persistent fever, deterioration of general condition, or sepsis-like manifestations in patients with predisposing factors such as neutropenia, malignancy, major surgery, broad-spectrum antibiotic therapy, central venous catheters, parenteral nutrition, or prolonged intensive care stay. Diagnosis remains challenging and relies on a combination of clinical, microbiological, histopathological, and imaging findings. Imaging plays a crucial role in detecting deep-seated organ involvement, assessing disease extent, guiding biopsy when feasible, and monitoring therapeutic response. Pulmonary candidiasis may present with diffuse randomly distributed micronodules, consolidations, cavitary lesions, or the halo sign. Hepatosplenic and renal candidiasis typically appear as multiple disseminated microabscesses, sometimes showing a bull's-eye or target appearance and peripheral enhancement. Osteoarticular candidiasis is rare and often manifests as a late complication of hematogenous dissemination, whereas central nervous system involvement may include microabscesses, granulomas, meningitis, ventriculitis, vascular complications, or abscess formation. Despite the nonspecific nature of most imaging findings, their recognition in the appropriate clinical context can strongly support early diagnosis and improve patient management. We report the case of a 3-year-old girl followed for acute myeloid leukemia (AML) and currently receiving chemotherapy, who presented with prolonged fever lasting more than 15 days, in whom the diagnosis of systemic candidiasis was confirmed.

Keywords: Systemic candidiasis; Invasive candidiasis; Candidemia; Candida albicans; Non-albicans Candida; Immunocompromised patients; Hepatosplenic candidiasis; Pulmonary candidiasis; Fungal microabscesses; Medical imaging.

INTRODUCTION

Invasive fungal diseases represent a major public health concern, particularly in immunocompromised patients, in whom they are associated with significant morbidity and a high risk of death, especially in the pediatric population [1]. Among these infections, species of the genus Candida represent the most frequent cause of fungal infections in humans [2-7]. Candidemia is of particular importance, as it is the fourth most common cause of nosocomial bloodstream infections in the United States and Europe [2-7]. Over the last two decades, the epidemiology of systemic candidiasis has changed significantly, with the emergence of non-albicans species, notably Candida glabrata, Candida krusei, Candida tropicalis, and Candida parapsilosis [2-7]. This evolution is probably favored by the widespread and sometimes inappropriate use of certain antifungal agents. In some centers, these species may account for up to 50% of all cases. Their clinical relevance is related to their intrinsic resistance or reduced susceptibility to several classes of antifungal drugs, which may complicate therapeutic management.

CASE REPORT

We report the case of a 3-year-old girl followed for acute myeloid leukemia (AML) and currently receiving chemotherapy, who presented with prolonged fever lasting more than 15 days, with severe neutropenia, in whom the diagnosis of systemic candidiasis was

confirmed. A chest, abdominal, and pelvic CT scan was performed to determine the cause and revealed.

At the pulmonary level, there were diffuse nodules and micronodules with a random distribution. Some nodules showed subtle peripheral ground-glass opacity, corresponding to the halo sign, while others were cavitated or in the process of cavitation **(Fig 1)**. No mediastinal lymphadenopathy was noted. Splenic involvement was characterized by nodular and micronodular lesions, including spontaneously hypoattenuating micronodules that showed no enhancement after contrast administration; some demonstrated thin peripheral enhancement after contrast injection. A few nodules also showed arterial-phase enhancement **(Fig 2)**. Similar hepatic micronodules were also noted **(Fig3).** A few pancreatic nodules were identified, showing a bull's-eye appearance on contrast-enhanced images **(Fig3**). This nodular and micronodular involvement was compatible with abscesses and microabscesses). The remainder of the examination was unremarkable.

The findings were concluded to represent pulmonary and hepatospleno-pancreatic involvement in the setting of systemic candidiasis.

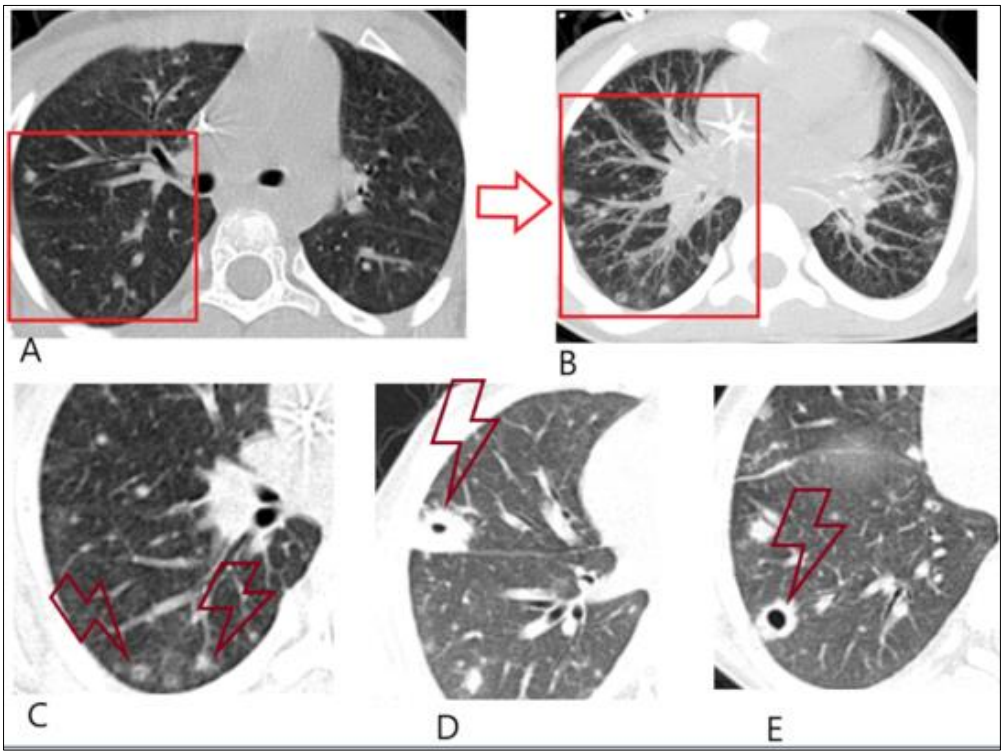

Figure 1: pulmonary involvement on CT scan:
A: diffuse micronodules with a random distribution (red square)
B: the same region in MIP mode
C: Nodules with faint signs of a ground-glass halo, some of which are beginning to excavate. (Arrows)
D and E: Excavated nodules (Arrows)

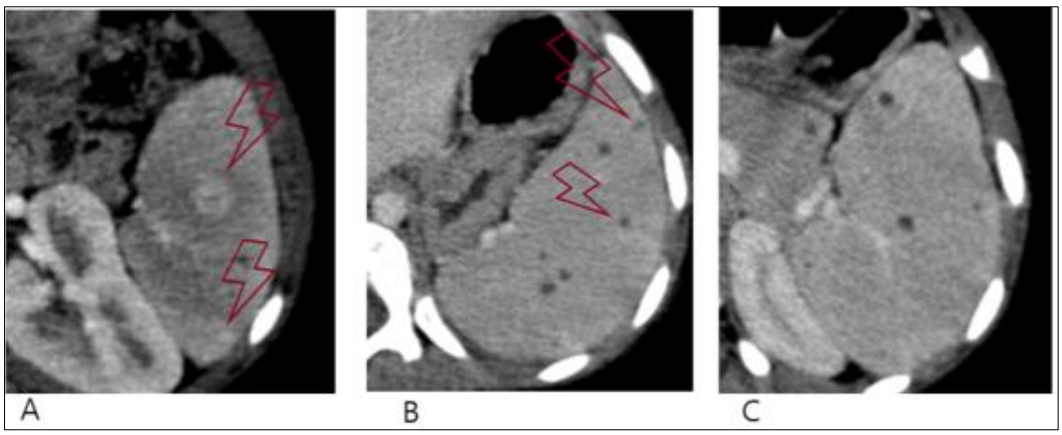

Figure 2: splenic involvement on CT scan after contrast injection:

Nodular and micronodular lesions, including spontaneously hypoattenuating micronodules that showed no enhancement after contrast administration (C); some demonstrated thin peripheral enhancement after contrast injection (B: Arrows). A few nodules also showed arterial-phase enhancement (A)

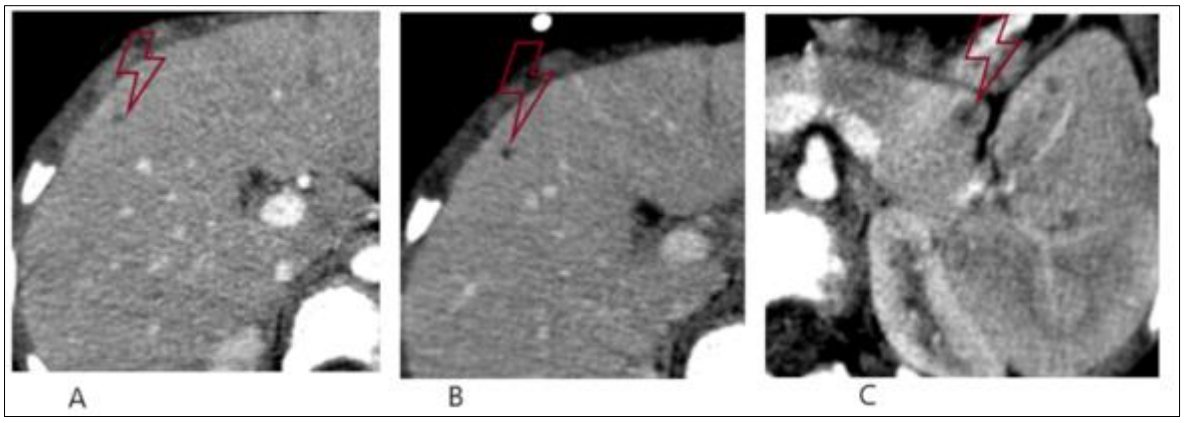

Figure 3: hepato-pancreatic involvement on CT scan after contrast injection:
A and B: A few hypoattenuating micronodules consistent with microabscesses in the liver (Arrows)
C: Nodular pancreatic lesion with a bull's-eye appearance

DISCUSSION

Risk Factors

Candidemia usually occurs in patients with one or more risk factors. Previous colonization by Candida is an important factor in the development of invasive infection [7-10,12]. The underlying clinical condition also plays a major role. Neutropenic patients, those with hematologic malignancies or solid tumors, patients who have undergone major surgery, diabetic patients, individuals infected with HIV, patients with chronic renal failure, and elderly subjects are at increased risk of systemic candidiasis.

These factors are compounded by numerous iatrogenic factors. The presence of central venous catheters, chemotherapy, radiotherapy, gastrointestinal surgery with disruption of mucosal barriers, broad-spectrum antibiotic therapy, parenteral nutrition, corticosteroid therapy, H2 blockers, prolonged intensive care unit stay, and mechanical ventilation are all factors that promote the occurrence of invasive candidiasis [7-10,12].

In neonates and children, specific additional risk factors should be considered, including prematurity, low birth weight, low Apgar score, and certain congenital malformations associated with immune deficiency, such as DiGeorge syndrome.

General Clinical Manifestations

Systemic candidiasis most often results from hematogenous dissemination and may present in several clinical forms: isolated candidemia, disseminated candidiasis, or infection localized to a single organ [1] [11]. Its clinical presentation is usually nonspecific. It may manifest as persistent fever, deterioration of general condition, or an infectious syndrome that does not respond to appropriate antibiotic therapy, particularly in a patient with risk factors.

Organ involvement is variable and may affect the lungs, liver and spleen, kidneys, osteoarticular system, eyes, myocardium, or central nervous system. Hepatosplenic candidiasis, also referred to as chronic disseminated candidiasis, is a classic form observed in neutropenic patients. Renal, osteoarticular, ocular, myocardial, and neurological involvement should be investigated according to the clinical and biological context.

Diagnostic Methods

The diagnosis of systemic candidiasis remains a major challenge. It is based on a combination of clinical, biological, microbiological, histological, and radiological arguments. Tissue biopsy, when feasible, can confirm fungal invasion. Blood cultures remain a reference examination in cases of candidemia, although their sensitivity may be limited, particularly in deep-seated or localized forms.

Serological antigen tests may raise the issue of distinguishing simple colonization from invasive candidiasis. PCR may provide greater sensitivity than blood cultures and allow earlier positivity, but its lack of specificity may sometimes limit interpretation. In this context, imaging plays an important role in diagnosis, assessment of disease extent, and follow-up. The main imaging modalities used are ultrasonography, computed tomography, and magnetic resonance imaging.

Pulmonary Candidiasis

Pulmonary involvement may occur as part of systemic candidiasis through hematogenous dissemination, or more rarely as primary Candida pneumonia [1] [13]. In systemic pulmonary candidiasis,

the mechanism is usually hematogenous, resulting in the formation of pulmonary microabscesses. The most suggestive radiological pattern is the presence of multiple nodules or micronodules with a miliary distribution [1]. Other abnormalities may also be observed, including ground-glass opacities, parenchymal consolidations, the halo sign, and cavitations. However, these findings remain nonspecific and may be seen in other infections, particularly invasive aspergillosis [7].

The halo sign corresponds to a pulmonary nodule or area of consolidation surrounded by ground-glass opacity. It is frequently described in angioinvasive fungal pneumonias [14]. Although initially associated with invasive pulmonary aspergillosis, it has also been reported in Candida infections.

Primary Candida pneumonia is rare [1] [13] [15]. Establishing a causal relationship between the isolation of Candida and a pulmonary infiltrate is a real challenge, as airway colonization is common. Radiologically, this form may manifest as a mass, parenchymal consolidations, or diffuse micronodular involvement.

In neonates, several histological patterns of pulmonary candidiasis have been described: an embolic form due to arterial invasion, a disseminated form due to capillary invasion, and a bronchopulmonary form due to invasion of the air spaces. Radiological abnormalities may include progressive consolidation, focal cavitary lesions, homogeneous pleural-based consolidation, extensive areas of homogeneous consolidation, or rounded pseudomasses with or without central necrosis, which may mimic invasive aspergillosis.

Other findings have been reported in pneumonias exclusively caused by Candida albicans: alveolar-type consolidations, sometimes associated with an interstitial component, bilateral nonsegmental homogeneous or heterogeneous poorly defined foci, bilateral lobar involvement, pleural effusions, and cavitary lesions [15-18]. Some authors consider the diffuse miliary nodular pattern to be an early manifestation of pulmonary candidiasis. Cases of allergic bronchopulmonary candidiasis related to Candida have also been reported [18].

Hepatosplenic Candidiasis or Chronic Disseminated Candidiasis

Hepatosplenic candidiasis, or chronic disseminated candidiasis, is a persistent and severe infection involving the liver, spleen, and sometimes other tissues. It occurs preferentially in neutropenic patients, particularly after recovery from neutropenia. When the involvement is limited to the liver and spleen, it is classically referred to as hepatosplenic candidiasis. Isolated splenic involvement remains rare.

Imaging plays a central role in diagnosis and follow-up. Hepatic and splenic lesions are typically multiple and small [15]. Histologically, the lesions may be associated with mild or absent inflammatory reaction, a usual suppurative response, or, more rarely, hepatic granulomas [19] [21]. Hepatic candidiasis is typically characterized by microabscesses containing yeast forms or pseudohyphae in the center of the lesion, surrounded by an area of necrosis and polymorphonuclear infiltration. During the healing stage, microabscesses may decrease in size and be associated with increased fibrous tissue.

Ultrasonography

Ultrasonography is an accessible, non-irradiating examination useful for the detection and especially the follow-up of chronic disseminated candidiasis [1] [15] [20]. However, its sensitivity may be limited, raising the question of the potential value of contrast-enhanced ultrasonography. The typical appearance consists of multiple small disseminated hypoechoic lesions, which may be difficult to distinguish from hepatic lymphoma, leukemic infiltrates, or metastases.

A characteristic appearance is the “bull’s-eye” or target sign, defined by a peripheral hypoechoic halo surrounding a central hyperechoic core [20]. Four main sonographic patterns have been described. The first is the “wheel-within-a-wheel” appearance, consisting of a peripheral hypoechoic rim, an inner echogenic zone, and a central hypoechoic nidus. The second is the bull’s-eye appearance, with a clearly visible hypoechoic rim and echogenic center. The third corresponds to multiple hypoechoic lacunae, often distributed between the hepatic veins without vascular compression or displacement. The fourth is the “echogenic focus,” represented by a single oval echogenic lesion, which may coexist with small lesions of the other patterns.

The “wagon-wheel” appearance is considered a variant of the first pattern, with echogenic spokes separated by hypoechoic areas and a central hypoechoic axis.

Computed Tomography

CT and MRI are generally superior to ultrasonography for the detection and characterization of lesions [1] [19] [23]. On CT, enhancement varies according to the stage of the disease: acute, subacute, or chronic. In the acute stage, the arterial phase, obtained approximately 25 to 35 seconds after contrast injection, is considered the most sensitive phase for detecting hepatic involvement. It may show a hyperdense rim surrounding a hypodense center, producing a bull’s-eye appearance, or sometimes a globally hyperdense lesion.

In the portal venous phase, obtained approximately 60 to 80 seconds after contrast injection, microabscesses most often appear as small hypodense

lesions, usually measuring 1 cm or less, sometimes ranging from 2 to 20 mm, with or without peripheral enhancement. Central enhancement may occasionally be observed. Some lesions may be isodense during the portal phase, and a double-target appearance is rarely reported. CT also allows assessment of disease extent, although the findings remain nonspecific and must be differentiated from other fungal, infectious, or tumoral lesions.

Magnetic Resonance Imaging

MRI is superior to CT for identifying hepatic lesions. When appropriate techniques are used, its sensitivity may reach 100% and its specificity 96%. In the acute stage of hepatosplenic candidiasis, lesions are usually round, measure less than 1 cm, and appear markedly hyperintense on T2-weighted images.

During follow-up, either during or after treatment, MRI may show a dark ring surrounding the initial lesions, with a non-enhancing center after gadolinium administration, corresponding to a necrotic core. In the subacute phase, the “dark ring sign” appears; histologically, this corresponds to a granuloma containing hemosiderin, responsible for low signal intensity on both T1- and T2-weighted images. In the chronic phase, lesions may become quadrangular, measure 1 to 3 cm, show globally low signal intensity on T1- and T2-weighted images, and lack diffusion restriction. Complete disappearance of hepatic abnormalities may occur after treatment.

Associated lesions may show nonspecific abscess-like features, with high T2 signal intensity, peripheral enhancement, and high signal intensity on diffusion-weighted imaging.

Renal Candidiasis

Renal fungal infections occur mainly in immunocompromised patients. Candida and Aspergillus are the most frequently involved pathogens in the kidneys. Renal involvement may result from hematogenous dissemination, with the formation of parenchymal microabscesses similar to those observed in the liver and spleen. These lesions appear hypoechoic on ultrasonography, hypoattenuating on CT, and hyperintense on T2-weighted MRI sequences.

Candiduria may represent the first manifestation of disseminated disease and should therefore be interpreted with caution in high-risk patients. Primary renal involvement is most often due to Candida albicans, the leading cause of fungal infections of the urinary tract. The mechanism is usually ascending and is favored by immunosuppression, antibiotic therapy, chronic urinary catheters, or obstructive uropathy. Clinical forms include pyelonephritis, perirenal abscess, sometimes associated with gas bubbles, hydronephrosis, and fungal bezoars.

Osteoarticular Candidiasis

Osteoarticular involvement due to Candida is rare. It is most often a complication of candidemia but may also occur after trauma or an iatrogenic procedure. Imaging helps determine the location and extent of disease, although radiological findings are generally nonspecific.

Osteoarticular candidiasis has a predilection for fibrocartilaginous joints, particularly costochondral, intervertebral, and sacroiliac joints. Monoarticular involvement is more frequent than polyarticular disease. Candida albicans arthritis is among the most common fungal arthritides in immunocompromised patients. Unlike bacterial arthritis, bone destruction is usually less pronounced.

Candida osteomyelitis is often a late manifestation of hematogenous dissemination. A review of 207 cases of Candida osteomyelitis in pediatric and adult patients between 1970 and 2011 reported bone destruction in 54% of cases, soft-tissue extension in 27%, increased uptake on bone scintigraphy in 23%, intervertebral disc-space narrowing in 21%, and epidural abscess in 12%. On MRI, decreased T1 signal intensity and increased T2 signal intensity are frequently observed.

In pediatric patients, the most commonly involved bones are the femur, humerus, vertebrae, and ribs. Most patients have at least two infected bones. In neonates, Candida osteomyelitis is generally multifocal and often associated with arthritis [15]. The most frequently involved joints are the knee and hip.

Central Nervous System Candidiasis

Central nervous system involvement is observed in a significant proportion of systemic candidiasis cases documented at autopsy. It may manifest as multiple microabscesses, granulomas, and, more rarely, meningitis. Other manifestations have been described, including fungal balls, ependymitis, macroabscesses, thrombosis, infarction, mycotic aneurysms secondary to vascular invasion, and demyelinating lesions.

In infants, cases of Candida meningitis and ventriculitis with progressive hydrocephalus have been reported. Imaging may occasionally show large lesions with ring enhancement, corresponding to Candida abscesses. After treatment, some lesions may calcify.

Differential Diagnosis

The radiological manifestations of systemic candidiasis are often nonspecific. The differential diagnosis depends on the lesion pattern and the organ involved. The main conditions to consider include invasive aspergillosis, other fungal infections, granulomatous infections, tuberculosis, metastatic lesions, septic emboli, and certain hematologic or

tumoral infiltrative diseases. Imaging interpretation must therefore always be correlated with the patient's underlying condition, clinical context, microbiological data, and laboratory findings.

CONCLUSION

Systemic candidiasis is a severe invasive infection whose prognosis largely depends on early diagnosis and prompt initiation of appropriate therapy. It occurs preferentially in immunocompromised patients, particularly in the presence of neutropenia, invasive devices, prolonged antibiotic therapy, or intensive care unit stay. Diagnosis is based on a combination of epidemiological, clinical, biological, microbiological, and radiological evidence. Although imaging findings are often nonspecific, imaging is essential for diagnosis, assessment of disease extent, and therapeutic monitoring. In systemic pulmonary candidiasis, diffuse randomly distributed micronodules represent a suggestive finding, sometimes associated with cavitary nodules, the halo sign, or consolidations. In visceral candidiasis, particularly hepatosplenic and renal forms, multiple disseminated microabscesses, bull's-eye or target appearances, and ring enhancement are important imaging features. Osteoarticular involvement preferentially affects fibrocartilaginous joints, long bones, vertebrae, and ribs, with frequent multifocal disease in children and less aggressive bone destruction than in bacterial infections. Finally, central nervous system involvement may manifest as microabscesses, granulomas, meningitis, ventriculitis, vascular complications, or true abscesses. Thus, despite the absence of absolute specificity of imaging signs, their recognition in an appropriate clinical context may guide early diagnosis and improve the management of patients with systemic candidiasis.

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