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Review article

Common radiological findings in fungal infections in hematological patients – Review

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ABSTRACT

Introduction: Invasive fungal infections are correlated with an increase in mortality rate among hematological patients. A correct diagnosis based on clinical manifestations may be very time consuming, while a delay in an appropriate treatment can have a negative impact on the further course of the disease.

Aim: The aim of this study is to present the most common radiological findings seen in CT or MRI which may help in making an accurate diagnosis.

Material and methods: A thorough literature search concerning the nature of invasive fungal infections, their clinical manifestations and methods of their radiological imaging were reviewed.

Results: An early diagnosis based on radiological imaging is crucial since radiological modalities are able to reveal lesions that can suggest ongoing fungal processes.

Discussion: There is a relationship between an early diagnosis of fungal lesions in CT imaging (i.e. the halo sign or micro- and macro-nodules) and an increase in the survival rate of hematological patients. Moreover, radiological methods of imaging can determine the degree of severity, especially the invasion of the infection into soft tissues, orbital cavities, brain and vasculature.

Conclusions: Early and systematic radiological assessment of hematological patients with increased risk of fungal infection result in an accurate diagnosis and have a positive impact on the decrease of mortality rate of immunocompromised patients.

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1. Introduction

Fungal infections are significant cause of mortality among immunocompromised patients. They mainly have an opportunistic character, therefore, rarely affect individuals with normal immunological system. The major factor predisposing progression of a fungal infection is a severe and long-lasting neutropenia, caused both by advanced stage of the disease and the treatment itself. Paradoxically, the new methods of treatment such as bone marrow and other organs transplantations, application of invasive diagnostic methods and a broad spectrum antibiotic therapy caused an increase in invasive fungal infection incidence. This may be due to prolongation of the immunocompromised patients' life. Although *Candida* and *Aspergillus* remain the most common causes of infection, in recent years the increased frequency of infections caused by other species of fungi were reported, particularly Mucor and/or Fusarium.[1–6] The symptoms of fungal infections are not specific and often difficult to distinguish from bacterial ones. Furthermore, an incorrect diagnosis and inappropriate treatment have a negative impact on the further course of the disease which can even lead to a fatal outcome. Radiological modalities are able to reveal lesions that can suggest ongoing fungal process such as: micro- and macro-nodules with the halo sign, reversed halo sign, tree in bud sign, air crescent sign, ground glass opacity, crazy-paving sign, microabcesses, bull's eye sign or black turbinate sign. Therefore, an early diagnosis based on radiological imaging, especially computed tomography (CT) and magnetic resonance imaging (MRI), is crucial.

2. Aim

The aim of this study is to introduce the most common radiological symptoms which may be helpful in an accurate diagnosis.

3. Material and methods

In this study a wide range of medical literature concerning the nature of invasive fungal infections, their clinical manifestations and methods of their radiological imaging were reviewed.

4. Results

An early diagnosis based on radiological imaging is crucial because radiological modalities are able to reveal lesions that can suggest ongoing fungal processes.

5. Discussion

5.1. *Halo sign*

The best radiological diagnostic method in case of invasive mycosis that is able to suggest infection at the early stage of the disease is high-resolution CT (HRCT). Micro- and macro-nodules with the halo sign can be the earliest lesions seen in HRCT as far as lungs are concerned (Figs. 1 and 2). The halo sign was initially described by Kuhlman et al. in patients with severe leukemia who suffered from advanced invasive pulmonary aspergillosis (IPA) while its definition was formulated in 1996.[7] The halo sign denotes a ground glass opacity surrounding the circumference of the nodule or consolidated area.[8] Histopathologically, it is a focus of pulmonary infarction

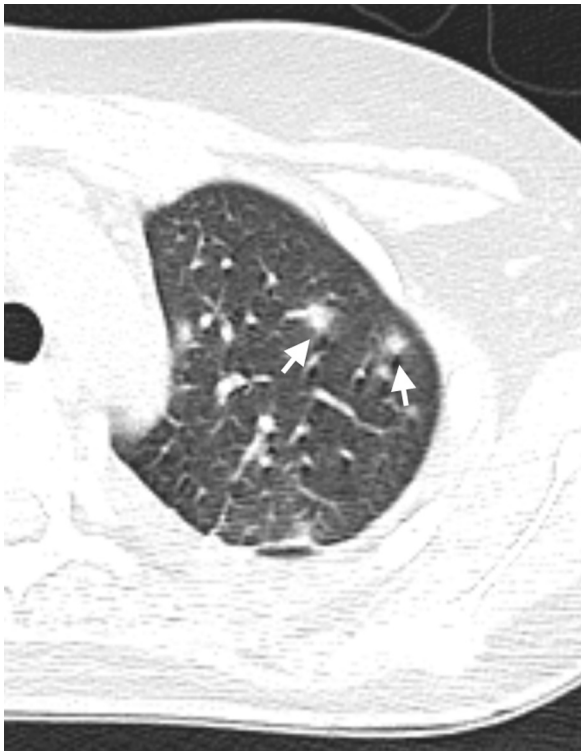

Fig. 1 – Pulmonary fungal infection in 16-year-old female patient with acute lymphoblastic leukemia. Nodules with halo sign visible on chest CT scan (arrows).

Fig. 2 – 28-Year-old hematological female patient with pulmonary fungal infection. Chest CT scan with multiple, confluent nodules with halo sign (arrows).

surrounded by alveolar hemorrhage. In patients with severe neutropenia, *Aspergillus* causes invasion of small and middle size pulmonary vessels resulting in their closure and consequently ischemia and necrosis of parenchyma. The area of necrosis corresponds to nodular lesions while bleeding particularly corresponds to the halo sign, both visible in HRCT.[9,10] The characteristic feature of the halo sign is its tendency to fade away with the course of the disease. Caillot et al. traced the evolution of lesions in lungs using CT imaging in 25 hematological patients with neutropenia and IPA. The authors concluded that approximately 96% of patients presented the halo sign in the first days of the infection. This value started fading away in the next few days down to 19% after 14 days of infection.[11]

Greene et al. published a study in which the halo sign was found in 61% of hematological patients with IPA. Consequently, an appropriate treatment was applied which resulted in significant clinical improvement and a decrease in mortality rate.[12]

The reports presented above underline the importance of an early and systematic radiological examination in patients with increased risk of fungal infection progression.

It is possible to observe the reversed halo sing in patients with IPA using CT.[13] It can be described as a spherical lesion with a ground glass opacity characteristic which is surrounded by a ring of consolidation. From histological perspective, the central portion corresponds to inflammatory lesions in the area of alveolar septum, while the peripheral portion corresponds to an organizing pneumonia within the alveolar ducts.[14]

5.2. *Nodules*

The most common pulmonary lesions are micro- and macro-nodules (Fig. 3a) which can be surrounded by a halo. Micro-nodules are lesions smaller than 1 cm in diameter, while macro-nodules reach sizes above 1 cm. Their position may be centrilobular, alongside perilymphatic vessels or even completely random.

As the disease progresses, cavitary lesions can develop within the nodules (Fig. 3b) which cause a separation of the central area of necrosis from normal pulmonary parenchyma. This results in a formation of air crescent sign. This type of lesion is most frequently observed in the latter phase of the disease a few days or weeks from the initial infection.[14] Moreover, they are related to an increased number of neutrophils in the blood.[14] It is a sign of convalescence of the organism which absence is strictly connected to a decrease in the survival rate of patients.[15]

5.3. *Consolidation and tree in bud sign*

The area of consolidation (Fig. 4a) relates to a condensation of pulmonary parenchyma which can be observed in both CT and X-ray. It is caused by fluid accumulation within the pulmonary alveoli which may take a form of transudate, similarly to heart failure case, or an exudate common in infections (including fungal ones) and/or tumors. Cavitary lesions with air crescent sign may also occur within consolidation areas (Fig. 4b). Those lesions are a less common image in case of IPA; however, they can also be reported in other mycoses, such as *Candida*.

The characteristic feature for the tree in bud sign (Fig. 5) is the presence of numerous, small centrilobular nodules and branching linear opacities of similar caliber originating from a single stalk.[16] At first this sign was attributed to lesions in the course of tuberculosis. However, it has been observed in many other diseases including infections, immunological disorders or congenital disorders. In case of fungal process, it is most commonly seen in infections caused by *Aspergillus fumigatus*.[16]

5.4. *Ground glass opacity and crazy-paving sign*

HRCT can also show lesions with ground glass opacity and crazy-paving sign (Fig. 6). The ground glass opacity is a hazy area of increased attenuation in pulmonary parenchyma caused by thickening of alveolar septum and pulmonary alveoli or by presence of fluid inside them. The crazy-paving sign is a thickening of interlobular septae observed on a ground glass opacity background.

It is important to notice that all these lesions are not characteristic for any invasive fungal disease and they can be observed in many infections caused by different species of

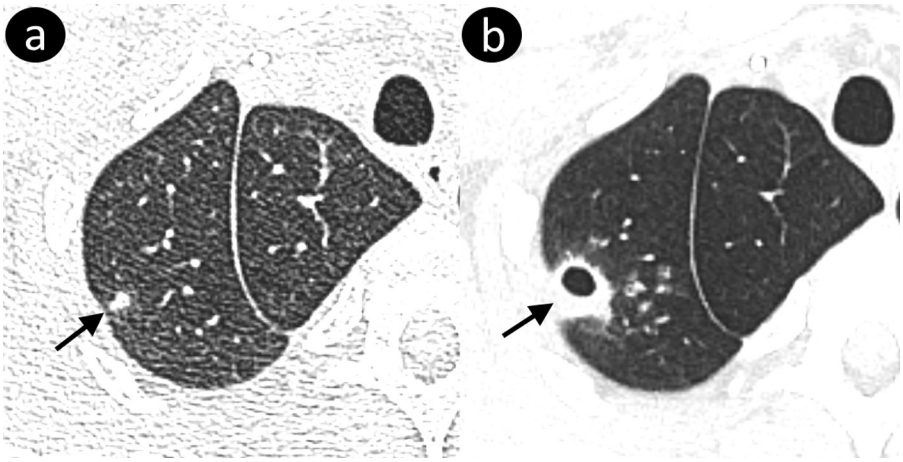

Fig. 3 – Pulmonary aspergillosis. Patient with acute myeloid lymphoma with micronodule (arrow) visible on CT scan (a). Follow-up CT, after one month, the cavitary lesion (arrow) appeared in the place of micronodule (b).

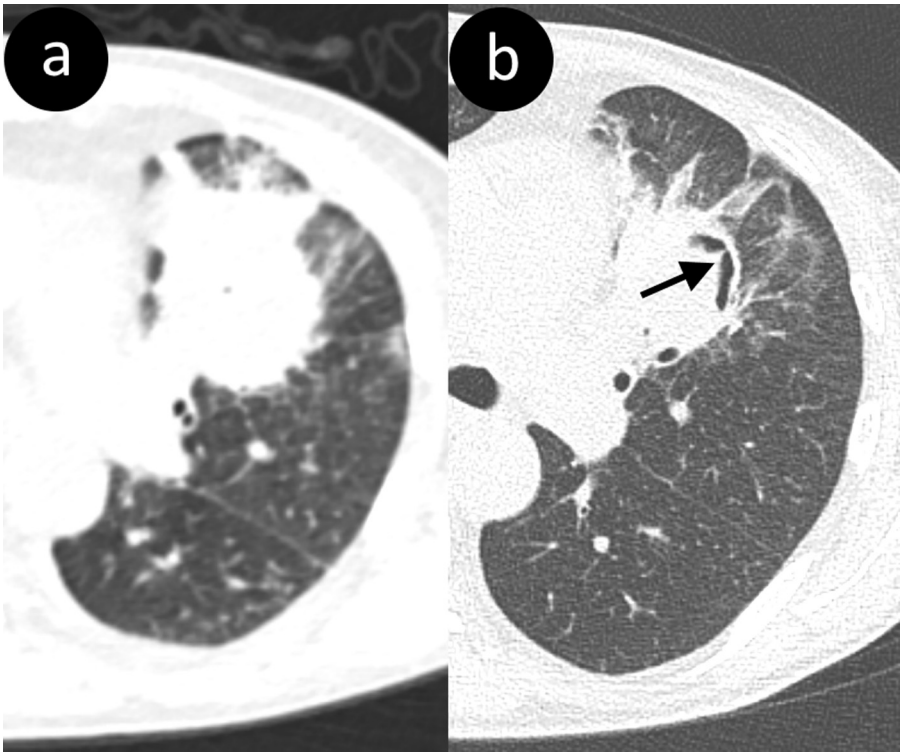

Fig. 4 – 55-Year-old female with acute myeloid lymphoma patient with pulmonary aspergillosis. Chest CT image with the area of parenchyma consolidation in left upper lobe (a). Follow-up CT revealed cavitary lesion with air crescent sign (b, arrow).

fungi i.e. in IPA, candidiasis (Fig. 7), cryptococcosis or mucormycosis.[10] Furthermore, the symptoms mentioned above are not specific and can occur in pulmonary edema, bacterial pneumonia, tumors or allergic diseases.

5.5. *Microabscesses*

Fungal infections of the liver and spleen usually occur as part of a disseminated fungal disease in immunocompromised patients.[17] The hepatosplenic involvement in fungal disease is characterized by the presence of microabscesses, which are usually caused by *Candida albicans*, less common by cryptococcosis, mucormycosis, histoplasmosis and rarely by aspergillosis.[17,18] MRI can be very helpful in monitoring the

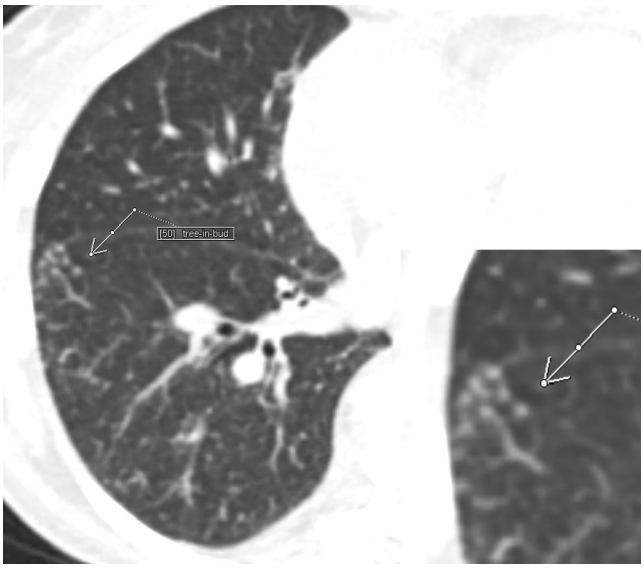

Fig. 5 – Tree-in-bud sign (arrow).

Fig. 6 – 55-Year-old female patient with ground glass opacity (arrow).

Fig. 7 – Pulmonary candidosis. 51-Year-old female with myeloma. CT image with visible parenchymal consolidation and ground glass opacity.

treatment response to antifungal therapy and in assessing the stage of the disease which are divided into acute, subacute post-treatment and chronic healed.

Acute fungal hepatic abscesses appear as multiple small lesions (<1 cm), which are mildly hypointense in T1-weigted images and hyperintense in T2-weighted images, with subtle contrast enhancement. In the subacute postreatment stage, lesions are mildly to moderately T1 and T2 hyperintense surrounded by a dark halo sign. After contrast administration there is mild enhancement of the abscess, which can contain a non-enhancing central portion corresponding to necrosis, known as 'bull's eye sign.' Healed abscesses can be presented as irregular and polygonal lesions, minimal T1 hypointense and T2 isointense, to mildly hyperintense with subtle or no enhancement.[18]

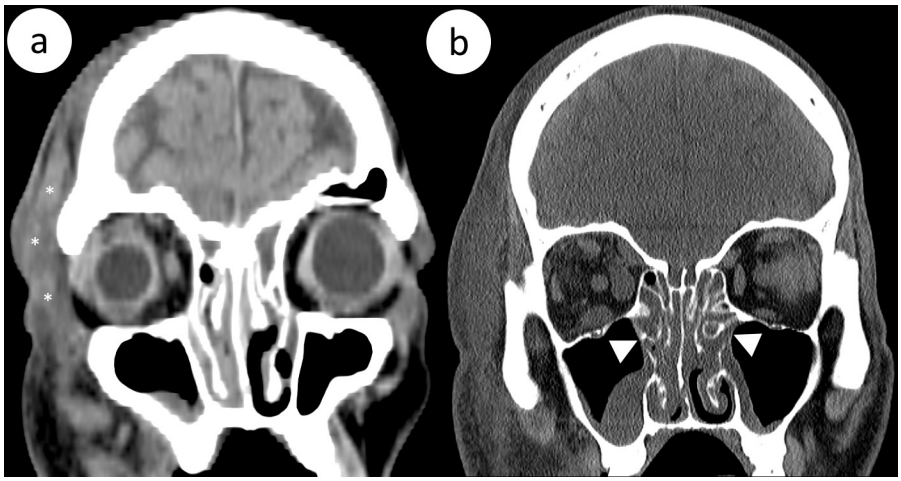

Fig. 8 – Mucormycosis. Male patient with acute myeloid lymphoma. Thickening of craniofacial soft tissue (a, asterisks) and mucosal thickening of ethmoidal cells and maxillary sinuses (b, arrowheads).

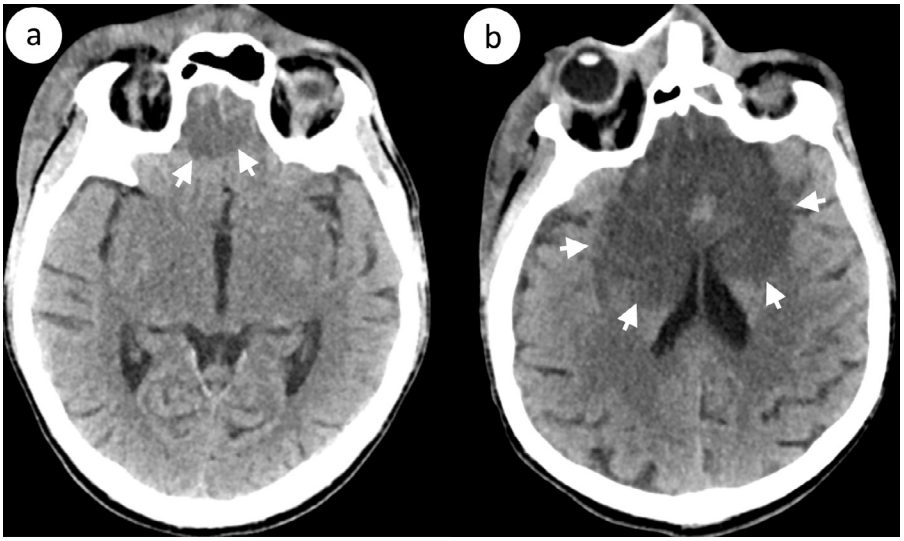

Fig. 9 – Mucormycosis in patient with acute myeloid lymphoma. Head CT presented hypodense focus of both frontal lobes (a, arrows). Follow-up examination revealed progression of hypodense area in brain (b, arrows).

5.6. *Rhinocerebral mycosis*

Radiological modalities such as CT and MRI became important tool in diagnosis of rhinocerebral mycosis. The most common fungi species that affect the brain are: *Aspergillus*, *Mucor*, *Cryptococcus*, *Candida* and *Blastomyces*.

The thickening of isodense paranasal sinuses mucosa is the most commonly observed sign present in CT imaging (Fig. 8).[19] Although CT does not always indicate the fungal etiology, it is able to demonstrate features which indicate a more invasive course of the disease i.e. bone destruction and edema of soft tissues. CT can be a useful tool in determination of the size of brain involvement in which edema, or focal hemorrhage may be found. In more severe stages of infection, hypodense areas can be revealed which can suggest brain tissue infarction (Fig. 9). The presence of such lesions and continuous exacerbation of patient's clinical condition should prompt further diagnostics, including MRI.

The MRI image of involved sinuses depends on the amount of water, protein and fungal elements. The lesions in T2-weighted images usually present a decrease of signal or are isointense. The lesions in T1-weighted images are isointense in the majority of cases. However, after contrast medium application the necrotic mucosa does not enhance which gives so-called 'black turbinate sign' (Fig. 10). In advanced stages of the disease, MRI allows to observe how fungal infection spreads into orbital cavities and adjacent tissues with enhancement after contrast medium administration. When CNS is involved enhancement of meninges and diffusion restriction in DWI sequence of brain tissue can be stated (Fig. 11).

Invasive fungal disease may also manifest as focal neurological lesions including brain abscess or microhemorrhage. Angioinvasive fungi species may lead to weakening of the vascular wall and thus development of mycotic aneurysms.[17]

Fig. 10 – Mucormycosis. 39-Year-old male patient with acute myeloid lymphoma. Contrast enhanced T1-weighted images in MRI detected isointensive necrotic lesions of ethmoidal cells, right orbit, nasal cavity and frontal lobes of brain. Lesions did not enhance after contrast medium administration – the black turbinate sign (a, b, c, arrows) and presented low signal of T2-weighted images (d, arrow).

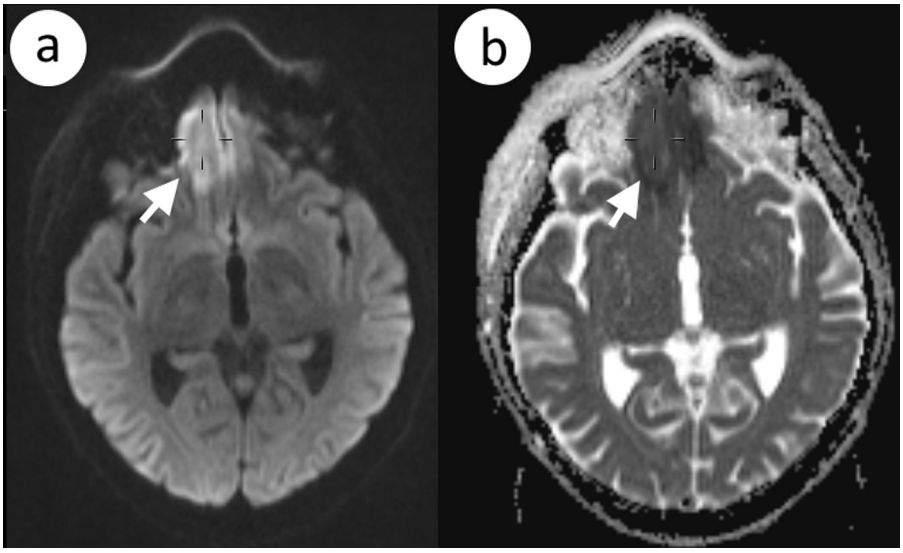

Fig. 11 – Mucormycosis. MRI shows diffusion restriction on DWI sequence with *b* value of 1 000 s/mm^2 (a, arrows) and ADC map (b, arrow).

5.7. *Diagnosis*

Radiological symptoms such as the presence of nodules with or without the halo sign or cavitary lesions were included in diagnostic criteria of fungal infections created by European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG).

The presence of radiological lesions and/or positive fungal markers imply a probable fungal infection.[20,21] However, it is important to remember that the ultimate confirmation of fungal disease relies either on biopsy of the lesion or positive mycological culture from the sterile sites including blood, tissue or cerebrospinal fluid.

6. Conclusions

Fungal infections are a serious problem in hematological patients. Severe neutropenia is a major infection risk factor. A late diagnosis increases the mortality rate among those patients.

Radiological imaging methods, especially CT and MRI, can be very useful in current diagnostics. Although imaging is very unspecific, it still can suggest the fungal etiology. Some lesions i.e. the halo sign or nodules suggest an early stage of a disease which allows introduction of effective treatment and improvement of patient's general condition and survival.

Moreover, these radiological modalities are able to accurately determine how extensive the disease is by showing its spread into soft tissues, orbital cavities, CNS and revealing bone destruction.

EORTC/MSG included radiological symptoms in their diagnostic criteria and considered them as possible diagnosis of fungal infection.

In conclusion, early and systematic radiological assessment of hematological patients with increased risk of fungal infection have a significant meaning, result in accurate diagnosis and have a positive impact on decreasing mortality rate of immunocompromised patients.

Conflict of interest

None declared.

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