Molds are a frequent cause of morbidity and mortality in allogeneic hematopoietic stem cell transplant recipients and in patients with hematological malignancies. The most frequent molds involved in this setting are *Aspergillus* spp. and Zygomycetes [1]. *Aspergillus* and Zygomycetes infect the lower or upper respiratory tract after inhalation of spores. When host defenses are failing, the spores germinate and the hyphae invade the tissue. Because they also invade the vessels (Figure 1) and occlude the tissue, thrombosis results in infarction of the tissues, and necrosis is a hallmark of the disease whatever the localization. Most of the clinical and radiological signs are explained by tissue infarction.

High-resolution computed tomography (CT) scan allows earlier detection of pulmonary lesions in high-risk febrile patients. The typical CT scan aspects of invasive aspergillosis are presence of nodules. The lesions can be modified by presence of a halo sign (early phase), an air crescent sign (usually after recovery from neutropenia), or a cavity. The halo sign indicates a rim of ground glass opacity around a nodule with a progressive attenuation. At pathologic examination, the nodules represent foci of infarction, and the halo of ground glass opacity results from alveolar hemorrhage [2]. Presence of a halo sign around nodules was first described in invasive pulmonary aspergillosis [3]. It has also been reported in non-*Aspergillus* fungal infections, nonfungal infections, primary or metastatic neoplasms, inflammatory or systemic diseases, and iatrogenic injury such as transbronchial lung biopsy [4].

Based on data from a large clinical trial [5], Greene et al showed that nodules were present at baseline in 94% of the cases of invasive aspergillosis and that at least one macronodule (>1 cm) was surrounded by a halo sign in 64% of the cases with nodular lesions [6]. These results supported the decision by the European Organisation for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) consensus group to consider a nodule with a halo sign a strong radiological signal in favor of invasive aspergillosis in a patient with host factors predisposing to this infection [7]. However, a limitation of the analysis by Greene et al is that the presence of a nodule with a halo sign was a criterion for inclusion in the clinical trial, and therefore there might have been an overestimation of the rates of nodular lesion as well as of halo sign. In our local series of 208 consecutive cases of invasive pulmonary aspergillosis [8], 155 (75%) patients had at least one nodule on the first CT scan, and only 51% of them had a halo sign around the nodule. The consensus definitions for invasive fungal diseases have appropriately been updated in 2008 and have accepted that patients with a dense well-circumscribed lesion may qualify for invasive pulmonary fungal disease [7, 9]. Although not clearly stated, dense well-circumscribed lesions include nodules, non-nodular infarcts, and consolidations. Whether alveolar infiltrates are also included remains a debate, and clarification is expected from the next update.

Despite recent improvements in diagnosis and treatment of invasive aspergillosis, the mortality rate remains high, in the range of 30%–40% [5]. Because earlier onset of treatment has been associated with better outcome, any new diagnostic method can help to further improve the outcome. In 2005, Sonnet et al suggested that high-resolution multidetector CT angiography allows direct detection of angioinvasion in aspergillosis or mucormycosis by showing the vascular occlusion at a peripheral level [10]. Vascular occlusion has been defined as an interruption of a pulmonary artery at the border of a focal lesion without depiction of the vessel inside the lesion or peripheral to the lesion. Vascular occlusion was
detected on CT angiography in 4 of the 5 lesions with histologically proven fungal angioinvasion. Only 2 of the lesions had a halo sign on the CT scan, suggesting a superiority of the vascular occlusion sign in detecting invasive mold infections. In all 9 lesions in which angioinvasive infection was excluded, CT angiography showed patent vessels. Final diagnoses in these 9 cases were scar tissue, hematoma, lymphoma, atypical mycobacterium infection, or diffuse alveolar damages. The authors concluded that high-resolution multidetector CT angiography can directly depict vessel occlusion in the setting of suspected fungal infections.

In this issue, Stanzani et al report their experience with CT pulmonary angiography in diagnosis of pulmonary mold diseases in patients with hematological malignancies [11]. Thirty patients with a suspicion of invasive mold disease were enrolled. The CT angiography was performed after the basal high-resolution CT scan had shown a nodule (≥10 mm). Interestingly, results have been correlated with final diagnosis using the EORTC/MSG criteria [9]. Twenty-one patients had proven, probable, or possible invasive molds disease. Nineteen (90%) had a positive vascular occlusion sign. Fifteen patients had no invasive mold disease, and only one had a positive vascular occlusion sign. The sensitivity of the sign to detect an invasive mold disease is 83%, and the specificity is 93%. These performances are similar to those observed by Sonnet (80% and 100%, respectively) [10]. These results place the occlusion sign at the same level of performance for the diagnosis of invasive disease as the serum galactomannan detection test for invasive aspergillosis [12]. The vascular occlusion sign probably deserves a place among the criteria defining invasive mold disease.

We must also highlight the limitations with routine angiography in patients suspected of invasive mold disease. Contrast-induced acute kidney injury, usually defined by an increase of serum creatinine of ≥0.5 mg/dL or by >25% increase over baseline creatinine value within 48 hours following contrast exposure, is the third most common cause of hospital acquired acute renal failure [13, 14]. Incidence of contrast-induced acute kidney injury has been estimated to be 3% in patients without risk factors but can rise to 30% among patients aged >70 years or with chronic renal disease, diabetes mellitus, congestive heart failure, or hypotension. Occurrence of a contrast-induced acute renal failure has major consequences for patients, including need for dialysis and increased mortality [14, 15]. Patients at risk of invasive mold disease certainly are at increased risk of contrast-induced acute kidney injury because of prior or concomitant exposure to nephrotoxic agents such as aminoglycosides, glycopeptides, cytotoxic agents, or immunosuppressants. They also often have diabetes mellitus, a significant risk factor for zygomycosis.

In addition to nephrotoxicity, others adverse events are also possible after contrast media injection. In a recent review of the tolerance of iodinated contrast media administration in 1514 patients, Lapi et al reported immediate (within 1 hour after injection) or delayed (>1 hour and up to 1 week) adverse events in 172 (11.3%)
patients [16]. Thirty-four (2.2%) patients experienced immediate events that included nausea, vomiting, headache, hypotension, bronchospasm, glottal obstruction, local or generalized urticaria, palpebral edema, rash, and itching. Most immediate events occurred in patients who received monomeric low-osmolar contrast media (iodipamide, iomeprol, iobitridol), while only three immediate events were recorded in patients receiving dimeric iso-osmolar media (iodixanol). Delayed events occurred in 144 (9.5%) patients, with a higher incidence in patients receiving dimeric iso-osmolar media. Delayed events included skin events similar to the immediate skin events, diarrhea, fever, myalgia, arthralgia, and abdominal pain. However, despite the overall high incidence of adverse events, all but one were mild or moderate.

Increased irradiation dose can also be a concern. Before deciding for angiography, Stanzani et al first realized a high-resolution CT scan without contrast. Angiography was only performed if a dense nodule (≥10 mm) was present on a basal CT scan. This double CT scan is mandatory to avoid exposure to contrast media if there is no dense lesion on the basal CT scan. It leads, however, to a double radiation exposure. Because response assessment of invasive pulmonary mold diseases is mainly based on radiology [17], patients may be exposed to cumulative high radiation dose. Options to limit total radiation dose are to reduce the number of follow-up CT scans and to use low-dose follow-up CT scans. Low-dose CT scans may be associated with a slight decrease in image accuracy that is unlikely to affect the response assessment of lesions previously identified by standard-dose CT scans [18].

A technical limit of the approach proposed by Sonnet et al and Stanzani et al is the size of the lesion [10, 11]. Small (<10 mm) or very peripheral nodules are not exhaustively assessable by angiography. In both studies, the CT scan was a 16-multidetector scan. Currently CT scanners often have 32, 64, or even 128 detectors. This technical improvement should result in an improvement in detection of smaller lesions.

Angioinvasive aspergillosis is the most common pattern of invasive aspergillosis in neutropenic patients, stem cell transplant recipients, and patients receiving steroids [19]. A second pattern of the disease, more frequent in non-neutropenic patients, is airway invasive aspergillosis. CT scan aspects of airway invasive disease are airspace consolidations, also called Aspergillus bronchopneumonia, and a “bud in tree” pattern [20]. No vascular occlusion is expected at the early stage of an airway invasive aspergillosis, and therefore CT pulmonary angiography is useless.

In conclusion, the vascular occlusion sign is a sensitive and specific sign of angioinvasive pulmonary mold disease. The diagnostic performance of this sign seems better than that of the halo sign and close to the performance of the serum galactomannan test for invasive aspergillosis. The need for iodinated contrast media administration requires excluding from this approach patients with a higher risk of contrast-induced acute kidney injury.

Note

Potential conflicts of interest. All authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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