Medical Imaging and Timely Diagnosis of Invasive Pulmonary Aspergillosis

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(See the article by Greene et al. on pages 373–9)

Reliable and timely diagnosis of invasive pulmonary aspergillosis (IPA) remains an interesting clinical challenge. At present, the in vivo clinical diagnosis of IPA is based on (1) host risk factors for the acquisition of this disease; (2) microbiological data, including the results of molecular diagnostic techniques; and (3) clinicoradiological data. The European Organization for Research and Treatment of Cancer/Mycoses Study Group incorporated these criteria into consensus diagnostic guidelines intended for clinical and epidemiological research involving patients with hematological malignancies or stem cell transplants [1]. In this issue of Clinical Infectious Diseases, Greene et al. [2] present high-resolution CT imaging data from a large series of patients with definite and probable IPA from the Global Comparative Aspergillosis Study, to assess the prevalence of the halo sign and to correlate imaging findings at presentation with therapeutic response. This study corroborates the importance of the CT scan in the diagnostic elaboration of infection and respiratory symptoms in a population of patients with a high a priori likelihood of developing invasive, opportunistic fungal infections. The majority of the patients had hematological immunosuppressive conditions; only 14% of patients had non-hematological immunosuppressive conditions. It was found that most patients (94%) presented with nodular lesions, and 61% of patients presented with a halo sign. Furthermore, the outcomes of patients presenting with a halo sign were significantly better than those of patients with other radiological abnormalities. This study provides large-scale confirmation of the diagnostic value of early CT scanning of the chest in patients with severe neutropenia who are developing respiratory symptoms suggestive for IPA, as was established by Caillot et al. [3]. Timely recognition of IPA shortens the delay before institution of appropriate therapy, creating an opportunity for curing the disease at an early stage with an inoculum amenable to antifungals. The CT halo sign appears early during the course of IPA, whereas the air crescent sign occurs later and is less useful for early diagnosis [4]. Approximately half of the patients in the Global Comparative Aspergillosis Study did not have neutropenia at the time of enrollment in the treatment protocol. The high prevalence of the halo sign in this series of patients supports its diagnostic value even for severely immunocompromised patients without severe neutropenia.

However, some caution is warranted, because the halo sign is part of the criteria used to make the diagnosis of probable IPA; these findings represent, in some ways, a self-fulfilling prophecy. Furthermore, the database of the Global Comparative Aspergillosis Study consists of a cohort of highly selected patients, subject to per-protocol diagnostic procedures that are not a reflection of everyday clinical practice. One should keep in mind that the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria are not evidence-based or autopsy-proven methods of diagnosing invasive fungal infections that have been established through well-designed multivariate analysis. In fact, large prospective studies are needed to establish evidence-based predictive criteria and to validate the proposed diagnostic algorithm. Subira et al. [5] reported that, in a series of autopsy-proven IPA cases in patients with hematological malignancies, only 36% of patients received antemortem diagnoses of IPA based on the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria. A similar finding was reported by Hachem et al. [6], in a series of patients with cancer who had autopsy-proven IPA: 47% of cases met the criteria for probable or proven IPA according to the widely accepted European
Organization for Research and Treatment of Cancer/Mycoses Study Group guidelines. These data suggest that the commonly used definitions of IPA may lack sensitivity, resulting in an underestimation of the burden of IPA, even in the highly susceptible patient group with hematological malignancies or stem cell transplants.

To put the findings of the current study into perspective, recent data indicating a change in the epidemiological profile of IPA need to be considered. There is increasing evidence that not only is IPA a devastating infectious complication in patients with immunosuppression caused by hematological malignant disease and its treatment, but it also may occur in other poorly defined patient risk groups. In particular, recent studies indicate that IPA may be considered to be an emerging problem in critical illness. In a retrospective study in the setting of a medical intensive care unit, Meersseman et al. [7] found microbiological or histopathological evidence of *Aspergillus* infection in 6.7% of patients; 108 cases could be classified as IPA, and 64% of these cases were in patients who did not have an underlying hematological malignancy. This observation has been confirmed in other studies in intensive care units [8, 9]. In a single-center series of 88 cases of IPA, 47% of cases were found in the intensive care unit, and 41% of the patients were non-neutropenic, having predisposing conditions such as chronic obstructive pulmonary disease, asthma, connective tissue disease, and solid organ transplantation [10]. The impact of infection with *Aspergillus* species in the critically ill is of the same order of magnitude as that in patients in hematological wards, and an attributable mortality of ~20% has been suggested [9–12]. Medical imaging findings in critically ill patients are far less pathognomonic, with nodular lesions found in one-third of patients in one study [9]. In the Meersseman et al. [7] study, a halo sign was found in 17% of patients; this precludes its usefulness in the early detection of IPA in patients without hematological malignancies and other predisposing immune deficits. Moreover, the contribution of the CT scan for diagnosis in this population is affected by many confounding factors, such as pneumonia, atelectasis, and pleural effusions. Nonneutropenic patients seem to have frequent intermittent bacterial or viral pneumonopathy [10].

In conclusion, the findings of Greene et al. [2] confirm the important role of the CT scan in the early diagnosis of IPA in severely immunocompromised patients with hematological disease. In this patient group, the halo sign is an early and typical radiological abnormality characteristic of IPA, indicating a stage of disease with better odds of therapeutic success. The value of medical imaging for early diagnosis of IPA in patients with other predisposing immune deficiencies is less clear; the further development of noninvasive molecular diagnostic techniques may be helpful in the timely recognition of this often fatal disease in patients with less typical radiological findings.

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**References**


