

Invasive Pulmonary Aspergillosis*

MRI, CT, and Plain Radiographic Findings and Their Contribution for Early Diagnosis

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A prospective study was conducted in 38 patients with nodular lesions on plain chest radiographs and the clinical suspicion of invasive pulmonary aspergillosis (IPA) to assess the diagnostic accuracy of magnetic resonance imaging (MRI) and computed tomography (CT). For early diagnosis of IPA (clinical signs and symptoms <10 days), CT scans with demonstration of the halo sign had a high sensitivity (16/22) and specificity (8/8). Magnetic resonance imaging performed at the same time revealed a relatively higher sensitivity (22/22), but a very poor specificity (0/8). Gadolinium-diethylene-triamine-pentaacetic acid (Gd-DTPA) enhanced images did not improve specificity. In the later course of infection (clinical signs and symptoms >10 days), MRIs showed typical nodular target-like lesions with Gd-DTPA en-

hancement of the rim area that was not seen in the early course of the disease or in patients with *Pseudomonas* or staphylococcal infection. In conclusion, MRI findings are not as characteristic as the CT halo sign in diagnosing IPA in the early course of the disease, but the MRI target sign with Gd-DTPA enhancement of the rim area and the "reverse target" on T₂-weighted images are strongly suggestive of IPA at a later stage of the disease. (*Chest* 1994; 106:1156-61)

Gd-DTPA=gadolinium-diethylene-triamine-pentaacetic acid; IPA=invasive pulmonary aspergillosis; MRI=magnetic resonance imaging

Key words: aspergillosis; CT; lung; lung nodules; MRI

Invasive pulmonary aspergillosis (IPA) has become an increasingly important cause of morbidity and mortality in myelosuppressed patients. IPA can occur in any severely immunocompromised or chronically debilitated host and is associated with fatality rates of 10 to 100 percent.^{1,2} By far, the major risk factor is prolonged granulocytopenia in patients undergoing intensive treatment for acute leukemia.^{1,3-5} Survival of these patients depends on early diagnosis and the institution of prompt therapeutic measures.⁶ However, the limitations of antemortem diagnosis of IPA are well known: sputum cultures are rarely positive in the early period of the disease^{1,3} and serologic tests are unreliable.^{1,7} Bronchoalveolar lavage yields a high percentage of true-positives, but also a small incidence of false-positives, which may be improved by the assessment of fungal antigens.⁸ For these reasons, correct antemortem diagnosis of IPA is rarely established in early infection. Therefore, noninvasive methods are needed to substantiate the clinical suspicion of IPA to initiate early antifungal therapy.

The present study was undertaken in order to de-

termine the diagnostic accuracy of computed tomography (CT) and magnetic resonance imaging (MRI) in the early and late stage of IPA.

METHODS

Between February 1990 and December 1992, 38 patients with the clinical suspicion of IPA were prospectively studied with CT and MRI. The clinical diagnosis of IPA was based on nodular lesions on plain chest radiographs and the clinical setting of fever, pneumonia, and granulocytopenia. There were 16 women and 22 men, ranging in age from 25 to 69 years (mean, 48 years). In 30 patients IPA was confirmed either histologically (n=20) and/or microbiologically (n=19). In eight patients, the diagnosis of *Pseudomonas* (n=6) and staphylococcal (n=2) pneumonia was established by microbiologic analyses.

For the purpose of this study, two groups were defined according to the stage of disease. A cutoff of 10 days was selected between early (<10 days) and late (>10 days) infection with *Aspergillus* species. This cutoff was determined on the basis of an increased risk for cavitation or progression of the disease. Group A comprised patients with nodular infiltrations that appeared on plain chest radiographs within 10 days after the onset of symptoms (fever, cough, dyspnea). This group included 30 patients: 22 with IPA, 6 with *Pseudomonas*, and 2 with staphylococcal pneumonias.

Group B was designed to evaluate the findings in the late course of IPA. This group included a total of 15 patients: 8 patients who turned out to have IPA with a clinical evolution longer than 10 days and had not yet undergone treatment with antimycotic agents and 7 of group A in whom follow-up studies were performed.

Twenty-one of 38 patients suffered from acute leukemia and 3 of 38 suffered from chronic leukemia. They were treated with cytotoxic agents (for induction/augmentation therapy or treatment for relapse). Three of 38 patients were treated with

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Table 1—Underlying Diseases of Patients With Suspected IPA (n=38)

Underlying Disease	Aspergillus	Pseudomonas/ Staphylococcus
Leukemia		
Acute myelogenous	15	3
Chronic myelogenous	3	
Acute lymphatic	3	
Bone marrow transplantation	3	1
Non-Hodgkin's lymphoma	3	
Small-cell lung carcinoma	3	
Esophageal carcinoma		1
Renal transplantation		2
HIV infection		1
Total	30	8

chemotherapy for non-Hodgkin's lymphoma, 3 of 38 were treated for small-cell lung cancer, and 1 was treated for esophageal cancer. Four of 38 patients had undergone bone marrow transplantation for non-Hodgkin's lymphoma (n=3) and chronic myelogenous leukemia (n=1), 2 were renal transplant recipients, and 1 had HIV infection.

The underlying diseases of the patients with suspected IPA are summarized in Table 1.

Thirty-five of 38 patients had marked prolonged granulocytopenia at the time the fungal infection was diagnosed (0 to 800 cell units/mm³). Thirty-seven of 38 patients were finally treated with broad-spectrum antibiotics and antimycotic agents (10 itraconazole, 27 amphotericin B). Eleven patients died of fungal infection and 2 patients died of bacterial infection.

All radiographic abnormalities and their sequential changes were assessed. A total of 483 pairs (anteroposterior and lateral projections) of chest radiographs (median, 12 pairs) were obtained in both study groups.

Fifty-three CT examinations were performed in 38 patients (38 initial and 15 follow-up CT studies). The CT scans were obtained with one of two scanners (Siemens DR-H or Siemens Somatom Plus S). Consecutive 8-mm-thick sections were obtained from the entire chest with additional 2-mm thin sections through any suspected fungal lesions. No contrast medium was administered. The CT images were viewed at lung (W, 1,200 HU; C, 800 HU) and mediastinal (W, 500 HU; C, 0 HU) windows.

Magnetic resonance imaging (38 initial and 15 follow-up studies) was performed with a 0.23 low field unit (Tomikon, Bruker, Karlsruhe, Germany). Conventional SE sequences were performed with electrocardiographic triggering for T₁-weighted (TR, 480 to 560 ms; TE, 20 ms) and T₂-weighted images (TR, 2,700 to 3,150 ms; TE, 75 to 125 ms). Gadolinium-diethylenetriamine-pentaacetic acid (Gd-DTPA, Schering, Berlin, Germany) was administered intravenously (0.1 mmol/kg) in all cases and T₁-weighted images were repeated. The whole chest was imaged; slice thickness was 8 mm, and intersection space was 4 mm in axial and coronal planes. The acquisition matrix was 256×256.

All patients of study group A and B had bronchoscopy and lavage fluid culture, and 12 of 38 had repeated bronchoscopic examination with a varying time interval of 5 to 8 days.

The diagnosis of IPA was proved in all patients either antemortem microscopically (in 19 of 30 by bronchoscopy and positive lavage fluid cultures) or histologically (in 8 of 30 by surgery and in 1 of 30 by percutaneous needle biopsy) or postmortem (in 11 of 30 by autopsy). In six patients the diagnosis was confirmed only at autopsy. Culture and necropsy diagnosis of IPA was made by the identification of the characteristic septated hyphae on hematoxylin-eosin, periodic acid-Schiff, or silver methenamine stains.

Plain radiographs, CT scans, and MRI studies were randomly presented to three readers and independently evaluated for the presence or absence of signs of IPA. The readers did not know the results of surgery, pathologic study, culture, or the results of other imaging modalities at the time of interpretation. The final diagnosis was based on the microscopic and/or histopathologic results, and a comparison to the imaging findings was made in every case.

The MRI findings 1 to 8 days before surgical resection (n=8) or autopsy (n=11) were correlated with the pathologic findings. This correlation could be done only in the late stage of infection.

RESULTS

Study Group A

Nodular lesions on plain radiographs were the radiologic inclusion criteria for the study (Fig 1, top left) and were present in all 30 patients. However, an air crescent sign that corresponds to a resolving pulmonary lesion with formation of a thin-walled cyst combined with the nodules was not observed in any case.

Computed tomographic studies revealed in 16 of 30 patients single or multiple nodular infiltrates with a halo sign that represents a zone surrounding a pulmonary nodule with an attenuation lower than that of the center of the infiltration (Fig 1, top right). All these patients were later confirmed as having early IPA (16 of 22). None of the patients with Pseudomonas or staphylococcal pneumonia showed this halo sign leading to a high specificity value (8 of 8). Nodular infiltrates with a hazy margin were not helpful for establishing the diagnosis of early IPA. Infiltrates with cavitation or air crescent sign were not present in patients with early disease.

Magnetic resonance imaging studies showed homogeneous nodular infiltrates with low/intermediate signal intensity on T₁-weighted and high on T₂-weighted images (Fig 1, bottom left) as a nonspecific finding. Isointense nodular lesions on T₁-weighted and lesions with a hyperintense center on T₂-weighted images (target-like) as well as nodules with an air crescent combined with an hyperintense center and rim on T₂-weighted images could not be shown in any patient. On images obtained after intravenous administration of contrast medium, all nodules showed homogeneous accumulation of Gd-DTPA (Fig 1, bottom right) without rim enhancement.

The true-positive and true-negative rates for the diagnosis of early IPA on plain radiograph, CT, and MRI are summarized in Table 2.

Study Group B

Plain radiographic findings in the late course of infection were similar to the early stage with nodular infiltrates in 11 of 13 patients (Fig 2, top left). An air crescent sign within a cavitation was present in two cases. Computed tomographic scans revealed nodular infiltrates with a halo sign (Fig 2, top right)

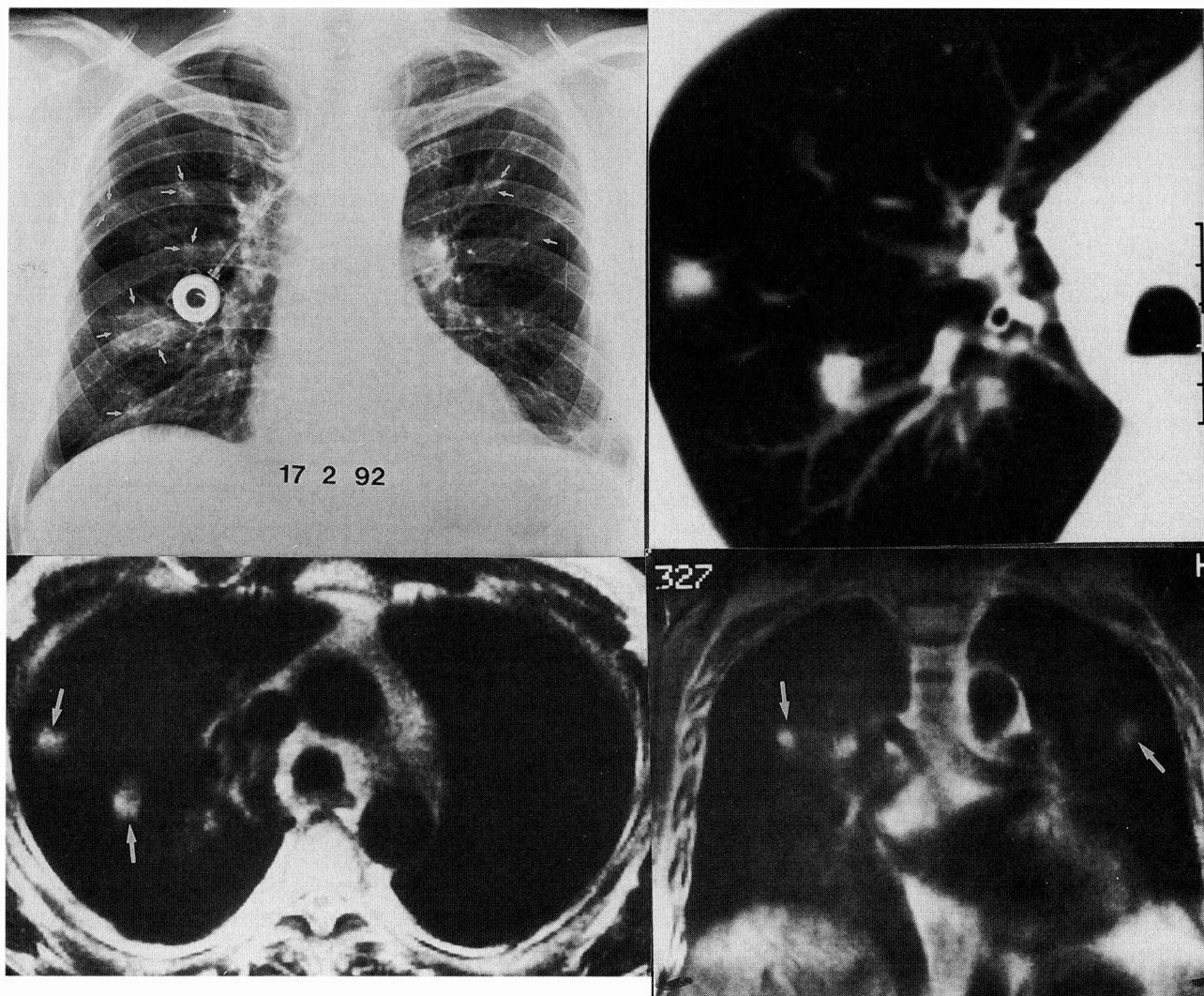


FIGURE 1. Early findings of invasive pulmonary aspergillosis. Top left, Nodular rounded infiltrates in the right and left lung on plain chest radiograph (*arrows*); top right, pulmonary CT shows nodules with halo in early IPA; bottom left, hyperintense lesions on T₂-weighted (3,150/100) (*arrows*); and bottom right, on postcontrast T₁-weighted images without rim enhancement (*arrows*).

in 3 of 13 patients. In the late course of IPA, stabilization of the rounded infiltrates or even progression to larger consolidations was in 7 of 13 cases presenting themselves as nodular lesions with hazy margins.

In 11 of 13 patients with late IPA, the rounded lesions showed a target-like appearance with homogeneous intermediate signal intensity on T₁-weighted images. The target-like appearance was not reliably recognized on T₁-weighted images. On postcontrast T₁-weighted images, there was marked enhancement of the rim ("target sign") (Fig 2, bottom left) and on T₂-weighted images a higher signal intensity in the center combined with a comparatively lower signal intensity in the rim outlined a characteristic feature that we call a "reverse target" (Fig 2, bottom right). Pseudomonas infections did not show the "target sign," but progressive healing of the rounded infiltrations with homogeneous low and homogeneous

high signal intensity on T₁- and T₂-weighted images, respectively, was observed. Taking into account that the series of 15 patients in group B included only two true-negative cases (*Pseudomonas* infection), the values of specificity are limited by the small patient number.

In 2 of 13 patients, there was cavitation and an air crescent sign of the initially nodular homogeneous infiltration with demonstration of a "target" on postcontrast T₁- and a "reverse target" on T₂-weighted images.

The diagnostic accuracy of imaging findings for the diagnosis of late IPA is listed in Table 3.

Magnetic resonance images could be correlated with histopathologic findings in 19 patients. The marked hyperintense areas on T₂-weighted images represented older hemorrhage and hemorrhagic necrosis permeated by hyphae of *Aspergillus*; the high

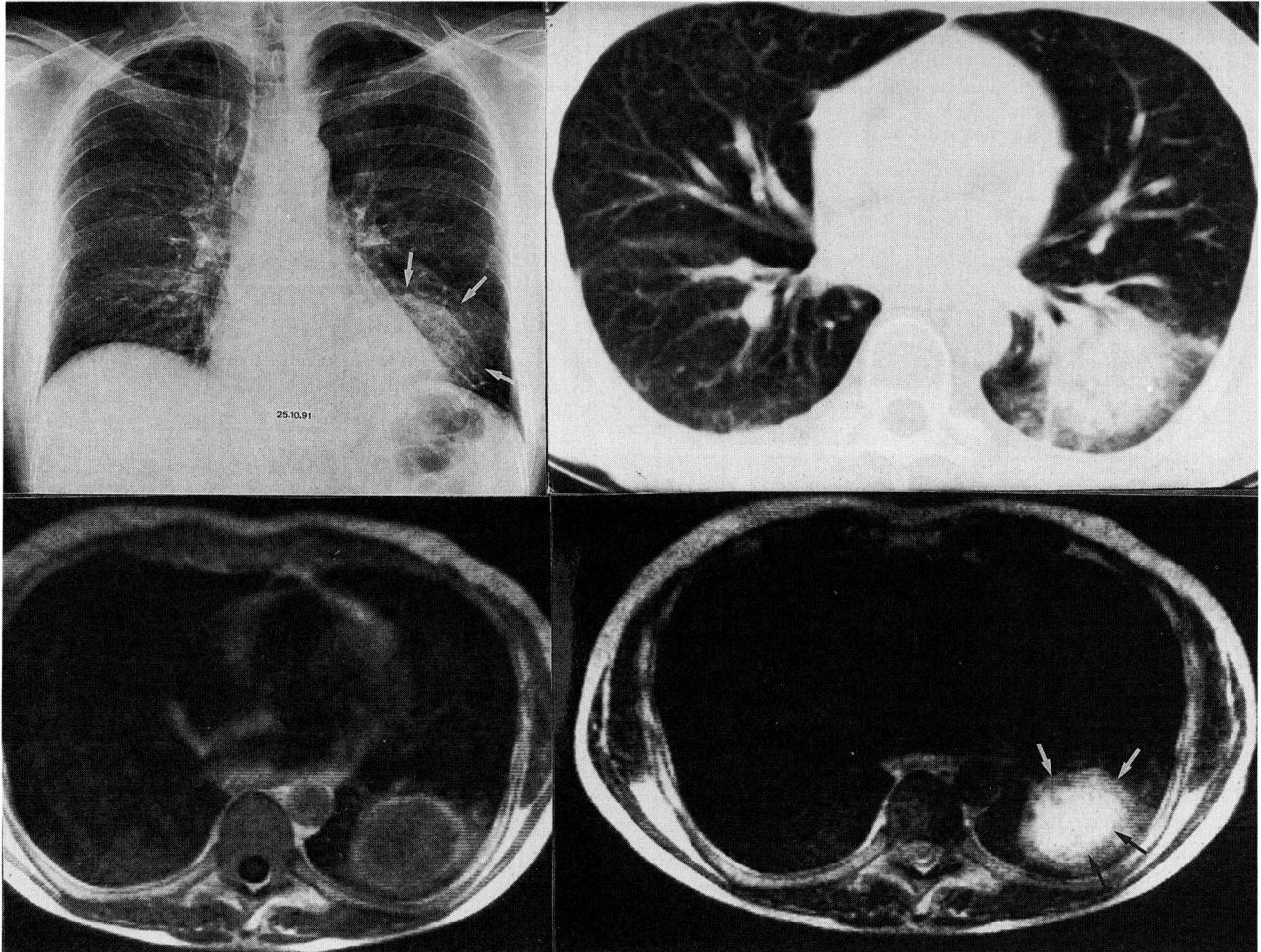


FIGURE 2. Findings in fully developed IPA (day 15 of infection). Top left, plain chest radiograph shows a nodular lesion in the left lower lobe (*arrows*); top right, CT evidence of a rounded infiltration with halo; bottom left, postcontrast T₁-weighted image shows enhancement of the rim surrounding an isointense center (“target sign”); and bottom right, axial T₂-weighted (3,150/75) image demonstrating a target-like lesion with hyperintense center (*black arrows*) and a rim of intermediate signal intensity (*white arrows*) corresponding to an aging hemorrhage (“reverse target sign”).

signal intensity of the rim represented fungus-induced infarction (Fig 2, bottom left).

The nodular lesions progressing into cavitations with air crescent signs later on showed communication with the bronchial system. The high signal tissue corresponded to parenchymal necrosis caused by permeating hyphae of *Aspergillus*.

In immunocompromised patients, there may be many infectious causes of nodular lesions besides pulmonary aspergillosis, *Staphylococcus*, or *Pseudomonas*, but in our two study groups, a wider spectrum of organisms leading to nodular infectious infiltrations could not be detected.

DISCUSSION

The usefulness of conventional radiography, CT, and MRI in establishing the diagnosis of early fungal infections has been studied by several authors.⁹⁻¹⁸

Conventional radiography in early IPA “uniform-

ly” shows single or multiple nodular infiltrates in all patients.⁹⁻¹¹ In the later course, there is stabilization in size and healing similar to a pulmonary infarction with the typical pattern of resolution fading from the periphery to form a linear scar related to the pleura or forming a thin-walled cyst with an air crescent sign.¹²⁻¹⁴

The spectrum of CT findings and their contribution to the management of IPA was summarized by Kuhlmann et al.¹⁵⁻¹⁷ the halo sign is strongly suggestive of IPA in its early course. In our two study groups, a CT halo sign was found in 16 of 22 patients with early infection and in 3 of 13 in later stages. While the CT halo sign was characteristic for the early course of disease, a positive halo sign was not observed in any of our eight patients with bacterial pneumonia. A larger series with nodular infiltrates caused by organisms other than *Aspergillus* species should be studied to clarify the specificity of the halo

Table 2—Sensitivity and Specificity of Imaging Modalities for Early (<10 Days) Diagnosis of IPA (n=30)

	Sensitivity	Specificity
Plain radiograph		
Single/multiple nodular lesions	22/22	0/8
Nodule(s) with air crescent	0/22	8/8
CT		
Nodule(s) with halo sign	16/22	8/8
Nodule(s) without halo sign	6/22	0/8
Nodule(s) with hazy margin	0/22	0/8
Nodule(s) with cavity	0/22	8/8
Nodule(s) with air crescent	0/22	8/8
MRI		
Homogeneous*	22/22	0/8
Target-like†	0/22	8/8
Air crescent	0/22	8/8
Gd-DTPA enhancement‡	22/22	0/8

*On T₁-weighted images, hypointense/isointense; on T₂-weighted images, hyperintense.

†On T₁-weighted images, isointense lesion; on T₂-weighted images, hyperintense center.

‡Homogeneous enhancement of the lesion. Rim enhancement only in the later course of infection.

sign.

The CT findings in the later course of IPA correspond to those of conventional radiography: rounded infiltrations that resolve like a pulmonary infarction from the periphery to form a linear scar related to the pleura or a thin-walled cyst that shows an air crescent sign when communicating with the bronchial system.¹²⁻¹⁶ As demonstrated in two of our patients, there may be progression to larger consolidations indicating an unfavorable course of the infection.

Magnetic resonance imaging characteristics of IPA have been studied by Herold et al¹⁸ in 11 patients with a total of 37 infiltrates. In this study, 34 nodules had a target-like appearance. The signal characteristic of the “target sign” consisted of a lower signal in the center compared with a higher signal intensity in the rim of a nodular infiltrate. With respect to age and signal appearance of the infiltrates, the authors concluded that nodular lesions with isointense rims on T₁-weighted images and hyperintense rims on T₂-weighted images were characteristic for lesions not older than 7 days. In our study, MRI features were nonspecific within the initial 10 days after the appearance of nodular infiltrates on plain radiographs showing no rim enhancement on T₂-weighted images. Nevertheless, the “target sign” was observed in all 13 patients in the late course of the disease (>10 days). These target-like infiltrates on T₂-weighted and on postcontrast T₁-weighted images were seen only after 10 or more days of infection in patients with fully developed or resolving IPA. A larger patients group, however, with nodules caused by other organisms other than *Aspergillus*, should be exam-

Table 3—Sensitivity and Specificity of Imaging Modalities for the Diagnosis of Late (>10 Days) IPA (n=15)

	Sensitivity	Specificity
Plain radiograph		
Single/multiple nodular lesions	11/13	0/2
Nodule(s) with air crescent	2/13	2/2
CT		
Nodule(s) with halo sign	3/13	2/2
Nodule(s) with hazy margin	7/13	0/2
Nodule(s) with cavity	1/13	2/2
Nodule(s) with air crescent	2/13	2/2
MRI		
Homogeneous	0/13	0/2
Target-like	11/13	2/2
Air crescent	2/13	2/2
Gd-DTPA enhancement (enhanced rim)	13/13	2/2

ined to determine the diagnostic value of the MRI findings.

Orr et al¹⁹ and Hruban et al²⁰ correlated radiographic and autopsy findings. The authors identified nodular (“target”) lesions as coagulation necroses surrounded by a rim of hemorrhagic infarction. The resulting microinfarction is usually spherical.

On the basis of the studies by Huber et al²¹ and Swensen et al,²² it was concluded that subacute hemorrhage and peripheral inflammatory reaction are responsible for the high signal intensity in the rim of nodular lesions on T₂-weighted images.¹⁸ The hyperintense center on T₂-weighted images is consistent with aging hemorrhage combined with necrosis. Postcontrast enhancement of the rim of nodular infiltrates is possibly associated with peripheral inflammation and hyperemia. The fact that there was no increased signal intensity in the rim of the nodular infiltrates on T₂-weighted images in the early course of infection may be due to a diffuse inflammatory reaction and hyperemia without *Aspergillus*-induced necrosis. This hypothesis is supported by the missing rim enhancement with Gd-DTPA in our 22 cases of early IPA (group A).

In conclusion, the demonstration of target-like nodular lesions on MRI is a typical, but by no means an early finding of IPA, as reported previously.¹⁸ The CT halo sign observed in patients with IPA is the most accurate sign for the early diagnosis of this fungal infection. Magnetic resonance imaging may be of diagnostic value in later stages of the disease and for the follow-up of nodular infiltrates of unknown etiology in immunocompromised patients. Considering the high mortality of patients with IPA, early institution of empiric therapy based on CT halo or MRI target sign as noninvasive imaging findings is advocated without confirming tissue diagnosis.

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