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Invasive Pulmonary Aspergillosis in Acute Leukemia: Characteristic Findings on CT, the CT Halo Sign, and the Role of CT in Early Diagnosis[1]

Invasive pulmonary aspergillosis (IPA) in immunocompromised patients is often difficult to diagnose. Many pathogens present initially with similar, nonspecific pulmonary findings. Air crescent formation has been reported to be highly suggestive of IPA in the appropriate clinical setting, but this is a late sign in an otherwise rapidly fatal infection. The authors reviewed the available chest computed tomography (CT) scans of nine patients with acute leukemia and documented IPA, including four patients with serial scans obtained during the course of infection. Typical CT findings of IPA were multiple inflammatory nodules, often with one large dominant mass, or a single peripheral masslike infiltrate. Cavitation or air crescent formation occurred late in the course of infection, usually at the time of bone marrow recovery from chemotherapy. CT scans obtained early in the course of infection in two patients demonstrated a distinctive feature of one or more pulmonary masslike infiltrates surrounded by a halo of low attenuation. These lesions subsequently progressed to cavitation or air crescent formation typical of IPA. While this CT halo sign may not be pathognomonic for *Aspergillus*, seen in the appropriate host, it may suggest early on the possibility of IPA.

Index terms: Aspergillosis, 60.2056 • Leukemia, complications, 60.341 • Lung, cavitation, 6.7225 • Lung, infection

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See also the paper by Gefter et al. (pp. 605–610) in this issue.

INVASIVE pulmonary aspergillosis (IPA) can occur in any severely immunocompromised or chronically debilitated host. By far, the most common clinical setting is the patient with prolonged granulocytopenia during treatment for acute leukemia (1–3). Early recognition of invasive fungal disease in such patients is imperative and may improve survival, but diagnosis is often difficult, and specific therapy with amphotericin can result in significant toxic side effects (2–5). Early clinical and plain film findings of IPA are nonspecific, with many other pathogens manifesting similar features. Sputum cultures are positive in less than 10% of patients with proven IPA, and results of serologic studies are often unreliable (4). Definitive diagnosis frequently requires aggressive, invasive biopsy procedures that are often prohibited by the patient's marked thrombocytopenia or compromised respiratory status (4, 6, 7). Any radiographic finding that might suggest *Aspergillus* as the infectious agent over other pathogens would be helpful in instituting earlier aggressive diagnostic and therapeutic measures.

Air crescent formation has been reported to be highly suggestive of IPA, but this is a late finding, coinciding with recovery from granulocytopenia and the resolution phase of the infection (8). To date, computed tomography (CT) scanning has not been extensively used for the evaluation of nonspecific pulmonary infiltrates in the immunocompromised host. After review of the CT scans of nine patients with acute leukemia and documented IPA, we found a potential role for CT in the early diagnosis of IPA. The spectrum of CT findings of IPA are presented as well as a typical pattern of progression seen on serial scans from four patients. We also describe two patients with CT scans obtained early in the course of infection that demonstrate a CT halo sign or zone of low attenuation surrounding a pulmonary mass. The halo sign preceded the development of typical cavitation or air crescent formation by 2 to 3 weeks. Although this sign may not prove to be specific for *Aspergillus*, it may indicate early on the possibility of IPA.

MATERIALS AND METHODS

The medical records, chest radiographs, and available chest CT scans of nine patients with documented IPA were reviewed. CT scans had been obtained with either a Siemens DR-3 scanner (5 sec, 450 mAs, 120 kVp, and 4-mm collimation; Iselin, N.J.) or an AS&E scanner (10 sec, 200 mAs, 125 kVp, and 4- or 8-mm collimation). All nine patients had acute leukemia being treated with induction therapy, augmentation therapy, or for relapse. All patients had received chemotherapy during or before the onset of infection and were granulocytopenic at the time of infection. Steroid therapy had been given to one patient intermittently, and one patient had

Table 1
Clinical Summary of Case Material

Case/Age (yr)/Sex	Diagnosis	Culture/Biopsy	Granulocytopenia and Broad-Spectrum Antibiotics	No. of CT Scans and Time Obtained During Course of Infection
1/30/M	AML	Sputum	+	3 early and late
2/40/F	AML	TNBA	+	4 early and late
3/57/M	AMM_oL	TNBA	+	5 early and late
4/49/M	AML	Sputum/naris	+	3 late
5/36/M	AML	TNBA	+	1 late
6/31/M	AML	TNBA	+	1 late
7/39/M	AML	Surgery	+	1 late
8/64/M	AML	Sputum	+	1 late
9/36/F	AML	TNBA	+	1 late

Note.—TNBA = transthoracic skinny-needle biopsy aspiration, AML = acute myelogenous leukemia, AMM_oL = acute myelomonocytic leukemia. Pluses indicate that the patient was granulocytopenic and receiving multiple antibiotics at the time of onset of infection.

received a bone marrow transplant. All patients had persistent spiking fevers despite broad-spectrum antibiotic therapy for both gram-negative and gram-positive bacterial organisms. In two patients, pleuritic chest pain preceded the development of pulmonary infiltrates. Hemoptysis occurred late in the course of infection in two patients.

The diagnosis of IPA was established bacteriologically or histologically in all nine cases by transthoracic skinny-needle biopsy aspiration (5), surgical lobectomy (1), or by positive sputum cultures (3). All nine patients survived their initial infection, though two subsequently died of progression of the leukemia and/or reinfection. A summary of the clinical case material is presented in Table 1. Representative case histories of two of the four patients with serial CT scans have been selected for demonstration.

Case 1. A 30-year-old man with acute myelogenous leukemia received induction chemotherapy with cytosine arabinoside (Cytosar-U; Upjohn, Kalamazoo, Mich.), daunomycin (Cerubidine; Ives Laboratories, New York), and amsacrine (Ben Venue Laboratories). Two weeks later, while the patient was granulocytopenic and receiving multiple antibiotics, persistent fever and pleuritic chest pain developed. Six days after the onset of symptoms, the chest radiograph showed for the first time a left upper-lobe masslike infiltrate. A CT scan obtained at the time of initial abnormality on chest radiograph (Fig. 1a) showed a peripherally placed 3-cm mass in the left upper-lobe with a surrounding zone of low attenuation forming a distinctive halo. These findings were suggestive of an inflammatory process. Several other similar but smaller nodules in both lungs were also found (Fig. 1b). Based on the finding of multiple inflammatory masses and the clinical setting, we made a presumptive diagnosis of IPA. A biopsy at the time could not be performed because of severe thrombocytopenia, and the patient was empirically treated with amphotericin. Multiple subsequent sputum samples yielded *Aspergillus flavus*. Six weeks after induction therapy and three weeks after the masslike infiltrate developed, bone marrow recovery occurred. A CT scan obtained 1 week later (Fig. 1c) showed cavitation of the left upper-lobe mass with formation of an air crescent and central sequestrum or fungus ball, which is characteristic of IPA. Cavitation of a second smaller right upper-lobe lesion was also seen. The patient's condition gradually improved while receiving extended amphotericin therapy, and a third scan (Fig. 1d) taken 1 month later showed reduction in the size and further organization of the cavitary lesions.

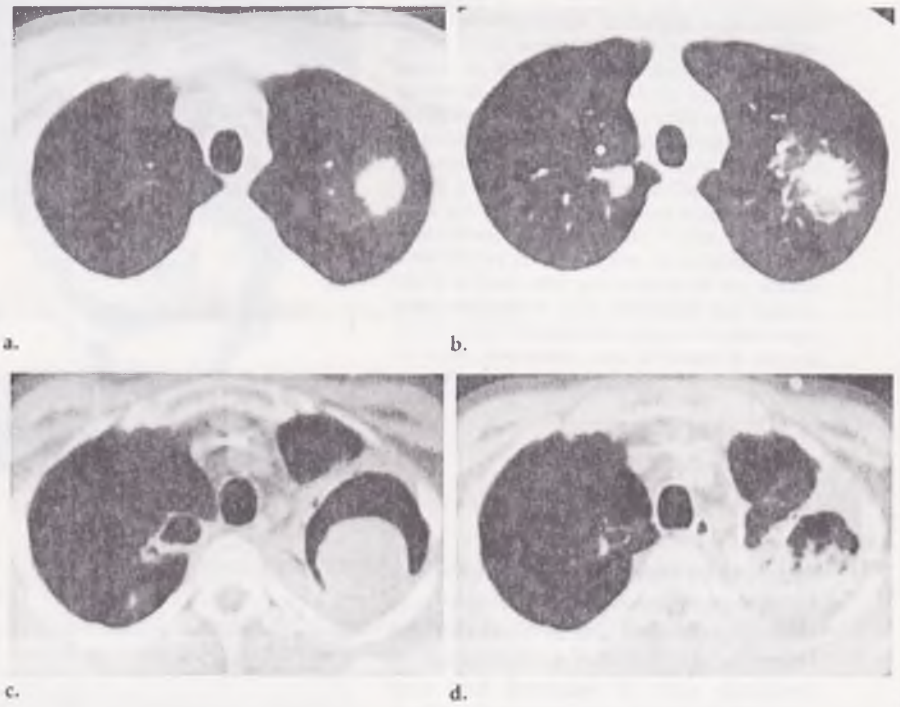

Figure 1. A 30-year-old man with acute myelogenous leukemia, pancytopenia, and new infiltrate on chest radiograph. **(a)** CT scan obtained early in the course of IPA infection shows an inflammatory mass with a halo sign or surrounding zone of low attenuation in the left upper lobe. **(b)** A second smaller but similar lesion in the right lung. **(c)** CT scan obtained 4 weeks later at the time of bone marrow recovery shows cavitation and air crescent formation in both lesions typical of IPA. **(d)** Follow-up scan during the recovery phase of IPA shows further organization and decrease in size of the cavitary lesion.

Case 2.—A 40-year-old woman with acute myelogenous leukemia received induction chemotherapy with cytosine arabinoside, daunomycin, and amsacrine, followed by augmentation therapy. Six weeks after her second course of chemotherapy, while granulocytopenic and receiving multiple antibiotics, the patient developed persistent fever. A chest radiograph revealed a new masslike infiltrate in the left upper lobe. A CT scan obtained at this time (Fig. 2a, 2b) showed a 5-cm round masslike infiltrate in the left upper lobe with a variable surrounding zone of low attenuation, compatible with peripheral air space filling. Areas of inhomogeneity and low attenuation could be seen within the center of the mass, suggestive of very early necrosis. A biopsy was not performed at this time because of severe thrombocytopenia, and the patient was empirically treated with amphotericin. Two and a half weeks later, bone marrow recovery began, and chest radiographs showed development of air crescent formation (Fig. 2c). A CT scan obtained 4 days later (Fig. 2d) demonstrated consolidation of the masslike infiltrate with no surrounding zone of low attenuation and the appearance of air within the mass compatible with cavitation. A transthoracic skinny-needle biopsy aspiration showed *Aspergillus* forms. Follow-up scans obtained 1

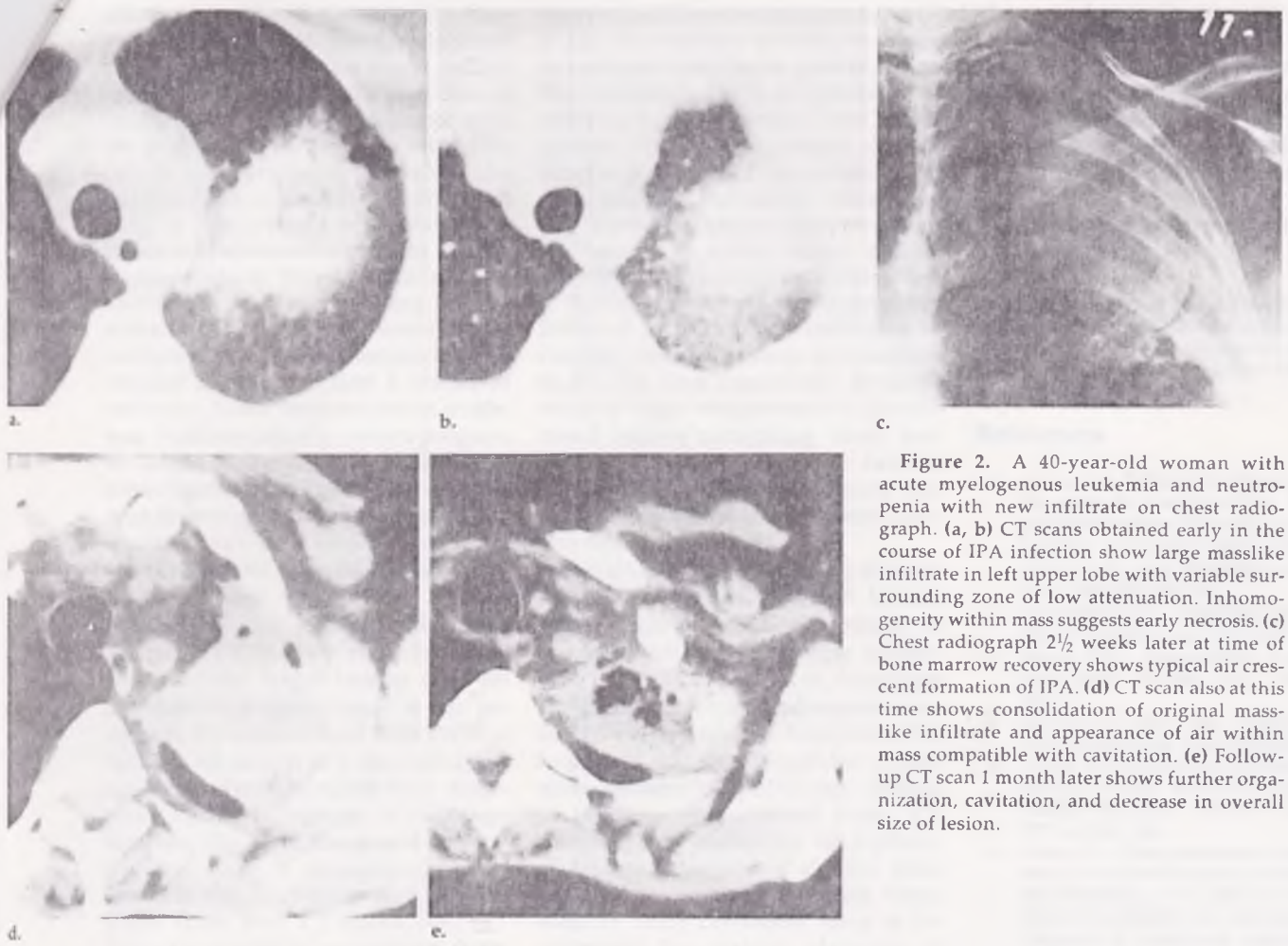

Figure 2. A 40-year-old woman with acute myelogenous leukemia and neutropenia with new infiltrate on chest radiograph. **(a, b)** CT scans obtained early in the course of IPA infection show large masslike infiltrate in left upper lobe with variable surrounding zone of low attenuation. Inhomogeneity within mass suggests early necrosis. **(c)** Chest radiograph 2½ weeks later at time of bone marrow recovery shows typical air crescent formation of IPA. **(d)** CT scan also at this time shows consolidation of original masslike infiltrate and appearance of air within mass compatible with cavitation. **(e)** Follow-up CT scan 1 month later shows further organization, cavitation, and decrease in overall size of lesion.

Table 2
CT Findings in IPA

Type of Involvement	No. of Cases
Multiple nodules with one larger, dominant mass	5/9
Single peripheral masslike infiltrate or nodule	4/9
Wedge-shaped segmental consolidation	1/9
Air crescent formation or cavitation	6
Organizing mass on late scans	6
Halo zone of low attenuation surrounding a mass or nodule on early scans	2

month later (Fig. 2e) showed further organization of the left upper-lobe process and a decrease in its overall size with more prominent central air collections.

RESULTS

A summary of some of the typical CT findings in IPA found in our nine patients is presented in Table 2. Two basic types of involvement were found—multiple nodules or fluffy masses with one larger, dominant masslike infiltrate (five cases), or a single masslike infiltrate or nodule usually peripherally placed (four cases). One patient's CT scan showed a wedge-shaped consolidation resembling a segmental infarct. Some form of cavitation or air crescent formation was found in six of the nine patients, usually coinciding with bone marrow recovery. CT scans obtained after bone marrow recovery, during the resolution phase of the disease, showed an organizing mass in six patients. As illustrated by the case reports, a characteristic pattern of progression of IPA emerged. Typically, one or more inflammatory nodules or masslike infiltrates with surrounding halos of low attenuation progressed to enlarged consolidations with subsequent cavitation or air crescent formation at or near the time of granulocyte recovery. Further organization or solidification of the lesions, with loss of surrounding halo of low attenuation and decrease in size occurred during the recovery phase of the leukemia and infection.

DISCUSSION

The pathologic features and natural history of IPA during the course of infection have been extensively studied by Orr et al. and others (4, 9). IPA is characterized by hemorrhagic infarction of lung tissue secondary to vascular invasion of *Aspergillus* organisms, causing thrombosis of small arterioles and sometimes larger pulmonary vessels. On macroscopic examination, the characteristic early lesions of IPA are 1- to 3-cm nodules or target lesions that have a central gray area of necrosis surrounded by a red peripheral ring from hemorrhage or hemorrhagic infarction. Often, a thrombosed artery can be seen at the edge of the lesion. Target lesions arise from endobronchial proliferation of *Aspergillus* organisms that spread transbronchially to adjacent pulmonary arterioles, with consequent thrombosis and ischemic necrosis of

small areas of lung. Correlation of autopsy findings with premortem chest radiographs reveals that target lesions correlate with the early nodules or small fluffy masslike infiltrates seen on plain films of patients with IPA (4). It is speculative whether the pathologically identified peripheral ring of hemorrhage or hemorrhagic infarction surrounding target lesions corresponds to the CT halo zone of low attenuation surrounding IPA lesions found on early CT scans. Chronologically, IPA target lesions usually present during the first 2 weeks of infection. Some lesions remain stable, but, characteristically, others progress to larger pulmonary consolidations with infarction, cavitation, or air crescent formation, on the average of 2–3 weeks later (4). Less commonly, wedge-shaped pleural-based infiltrates develop, representing hemorrhagic infarction of major pulmonary arteries (4). Retraction of the infarcted center of the target lesions with resorption of necrotic tissue at the periphery by white blood cells (WBCs) leads to formation of a sequestrum of dead tissue intermingled with *Aspergillus*. Filling in with air of the space between the dead tissue and the peripheral lung is thought to correspond to the air crescent sign seen on plain films and CT scans (10, 11). Since resorption of sequestrum is required, it is not surprising that air crescent formation is a relatively late radiographic finding coinciding with the recovery of WBCs.

Clinically, the onset of IPA is highly variable. The most common clinical presentation is unremitting fever or progression of pulmonary infiltrates despite therapy with broad-spectrum antibiotics (3). IPA can appear insidiously after a series of bacterial infections or present dramatically, being indistinguishable from an acute bacterial pneumonia (2). A common presentation is the onset of pleuritic chest pain with the appearance of one or more peripherally based infiltrates mimicking pulmonary emboli or septic emboli with infarction on chest radiographs (3, 4).

The plain film findings of IPA are also variable and nonspecific early in the course of the disease. Up to 25% of patients may have a normal chest radiograph at the onset of symptoms (3, 4, 12). The earliest lesions are single or multiple nodules or patchy, masslike infiltrates, often peripherally located (2, 4, 6, 11). Serial chest radiographs, then, demonstrate one of several patterns of progression. In some patients, the lesions remain stable. In others, they progress over several weeks to either larger diffuse consolidations and/or cavitation (2, 4, 6, 9). One of the more characteristic forms of progression is cavitation of existing nodules to form air crescents (8, 11, 13). Less commonly, development of large wedge-shaped pleural-based lesions mimicking bland pulmonary infarction occurs (4). Lesions identical to bronchopneumonia and diffuse interstitial pneumonitis have also been reported (2).

Serial CT scans in our study showed a similar progression of IPA lesions from single or multiple nodules or masslike infiltrates to larger pulmonary consolidations. Six of nine cases showed some form of subsequent cavitation or air crescent formation. We found CT scanning helpful in evaluating nonspecific pulmonary lesions in immunocompromised hosts. CT scanning may detect the multiplicity of lesions, identifying smaller nodules not appreciated on chest films; identify early cavitation; help in localization for optimal planning of transthoracic skinny-needle biopsy; and differentiate the extent of pleural versus pulmonary involvement. CT scanning during the recovery phase of leukemia and IPA infection has been used to monitor the conditions of patients to document regression in size and organization of lesions, which often require prolonged outpatient courses of amphotericin. CT scanning may also play a role in the early diagnosis of nonspecific pulmonary infiltrates in immunocompromised hosts. In the appropriate clinical setting, the CT halo sign of a zone of low attenuation surrounding a nonspecific pulmonary mass or masslike infiltrate may prove to be another clue to the early diagnosis of IPA in patients with leukemia. Further observation and study will be necessary to establish the specificity of the CT halo sign for IPA. If the development of a halo depends on small vessel invasion and thrombosis with lung infarction, then other fungi, such as mucormycosis, might be expected to cause similar findings (14). In the appropriate clinical setting, however, the CT halo sign may indicate the need for more aggressive measures to establish the diagnosis of invasive fungal disease and to initiate appropriate fungal treatment. ■

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