

# Chronic Necrotizing Pulmonary Aspergillosis in Pneumoconiosis\*

## Clinical and Radiologic Findings in 10 Patients

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**Study objective:** To characterize clinical, radiographic, and CT findings of chronic necrotizing pulmonary aspergillosis (CNPA) in patients with pneumoconiosis.

**Methods:** We studied 10 patients with pneumoconiosis who were seen at Asahi Rosai Hospital and received a clinical diagnosis of CNPA during a 15-year period, and detailed the long-term clinical and radiologic courses of four cases.

**Results:** All patients were men, ranging in age from 48 to 77 years (mean, 60.1 years). Their occupational histories included pottery making (n = 9) and coal mining (n = 1). Chest radiographic findings by the International Labor Organization profusion grading system were greater than category 2. All patients were symptomatic, with a productive cough, hemoptysis, and dyspnea. Serum findings were positive for the *Aspergillus* antibody in seven patients. The radiologic findings consisted of parenchymal infiltrates and cavities mostly containing mycetoma, which generally involved the upper lobes. The disease progressed slowly; in one patient, broad destruction of the lung was observed after > 10 years without antifungal administration. Most of the patients experienced clinical and radiologic improvement after receiving antifungal therapy, by oral, inhaled, or intracavitary administration.

**Conclusions:** Chronic persistent or progressive upper-lobe infiltrates and cavities in patients with pneumoconiosis should raise the possibility of CNPA. Early diagnosis and initiation of effective therapy are recommended to achieve a better outcome. (CHEST 2002; 121:118-127)

**Key words:** Aspergillus; chronic necrotizing pulmonary aspergillosis; pneumoconiosis

**Abbreviations:** CNPA = chronic necrotizing pulmonary aspergillosis; ILO = International Labor Organization

The fungus *Aspergillus* is widely present in soil, water, and decaying organic matter, so that humans are at high risk of exposure via inhalation. Its pathogenicity is low, however, and primary aspergillosis rarely occurs in man. In recent years, the number of patients with deep-seated mycosis has been increasing because of the increase in the elderly population, lowered immunity due to malignant tumors and prolonged steroid administration, and microbial substitution induced by the use of various antibiotics. The contribution of aspergillosis

to deep-seated mycosis is increasing, and this is causing a problem partly because there are not very many effective antifungal agents.<sup>1</sup> Generally, pulmonary infections caused by *Aspergillus* organisms have been categorized into three basic forms: invasive, saprophytic, and allergic, based on the relation between the immune response of the host and the virulence of *Aspergillus*.<sup>2-5</sup> Intermediate forms might also be encountered; in 1982, Binder et al<sup>6</sup> proposed the term *chronic necrotizing pulmonary aspergillosis* (CNPA) for an indolent destructive form secondary to local invasion of the lung parenchyma by *Aspergillus* species. Binder and colleagues<sup>6</sup> described pneumoconiosis as the underlying disease most likely to be complicated by CNPA, but details have been lacking. We report our experience with 10 pneumoconiosis patients with CNPA observed from 1984 through 1998.

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## MATERIALS AND METHODS

Of the 804 patients with pneumoconiosis seen at Asahi Rosai Hospital during the period from January 1984 to December 1998,

10 patients received a diagnosis of CNPA. We retrospectively examined their background factors, clinical features, and methods of diagnosis. Chest radiographs and CT scans obtained before diagnosis from as far back as possible were collected to analyze the process of advancement of lesions on images. The diagnosis was clinically established from typical chest radiograph and CT findings, including persistent or progressive infiltrative and cavitary lesions, positive serum findings for the *Aspergillus* antibody, and isolation of *Aspergillus* species from expectorated sputum, bronchoscopic or percutaneous needle aspirates, or washed fluid from forceps and biopsy specimens obtained by bronchofiberscope, according to the criteria of Binder et al<sup>6</sup> for the clinical definition. Serum *Aspergillus* antibodies were determined using the method of Ouchterlony.<sup>7</sup>

## RESULTS

The characteristics of the 10 patients are presented in Table 1. All 10 patients were men, with

ages at diagnosis ranging from 48 to 77 years (average age, 60.1 years). Their occupational histories included pottery making (n = 9) and coal mining (n = 1). As the underlying disease apart from pneumoconiosis, one patient had a history of pulmonary tuberculosis and four patients had tuberculous pleurisy. One patient had a history of chemotherapy and radiotherapy for cancer of the tongue, and one patient had received long-term administration (4 years) of betamethasone (0.5 to 2 mg/d) aimed at improvement of respiratory function (Table 1).

All patients were symptomatic, with sputum production (n = 10), coughing (n = 8), hemoptysis (n = 5), dyspnea (n = 4), chest pain (n = 2), fever (n = 1), and general fatigue (n = 1; Table 1). Ac-

**Table 1—Clinical Characteristics of the 10 Cases\***

Case No.	Age, yr†/Sex	Occupational History	Previous Illness/Background	Symptoms	ILO Radiologic Category, SO/LO	Predominant Radiologic Findings	Delay in Diagnosis, mo‡	Outcomes
1	55/M	Pottery making	Tongue cancer (chemotherapy and radiotherapy)	H	2/–	RUL infiltrate with cavity and mycetoma	124	Improved
2	77/M	Pottery making	History of tuberculous pleurisy	S, C	2/–	RUL infiltrate with cavity and mycetoma	133	Improved, but died of aspiration pneumonia
3	48/M	Pottery making	History of pulmonary tuberculosis	C, H	1/–	RUL infiltrate with cavity and mycetoma	Indeterminate	Improved
4	58/M	Pottery making	History of tuberculous pleurisy, oral steroid therapy (betamethasone, 0.5 to 2 mg/d for 4 yr)	C, H, D	2/–	RUL infiltrate with cavity and mycetoma	Indeterminate	Improved
5	56/M	Coal mining	History of tuberculous pleurisy	H, D	2/B	LUL infiltrate with cavity and mycetoma	36	Improved
6	65/M	Pottery making		S, C, chest pain	2/–	RUL infiltrate with cavity and mycetoma, RML and LLL infiltrates	Indeterminate	Improved
7	57/M	Pottery making		S, C, fever, fatigue	3/–	BUL infiltrate with cavity and mycetoma	Indeterminate	Improved
8	61/M	Pottery making	History of tuberculous pleurisy	S, C, D	2/B	LUL infiltrate with cavity	22	Improved
9	68/M	Pottery making		C, H	1/–	RUL infiltrate with cavity and mycetoma	31	Improved
10	56/M	Pottery making		S, C, D, chest pain	2/–	LLL infiltrate with cavity and mycetoma	Indeterminate	Unknown

\*M = male; S = sputum; C = cough; H = hemoptysis; D = dyspnea; SO = small opacities; LO = large opacities; RUL = right upper lobe; LUL = left upper lobe; RML = right middle lobe; LLL = left lower lobe; BUL = bilateral upper lobe.

†Age at diagnosis.

‡Duration between the first symptoms or signs and the diagnosis of CNPA.

According to the classification of chest radiographs defined by the International Labor Organization (ILO) for pneumoconiosis, two patients were in category 1 on profusion of small opacities, seven patients were in category 2, one patient was in category 3, and two patients were in category B of large opacities (Table 1).

Blood examination at diagnosis revealed that total WBC counts were within the normal range in all patients, and erythrocyte sedimentation rates were  $> 15$  mm/h in seven patients. C-reactive protein values were elevated slightly in six patients, and serum findings were positive for *Aspergillus* antibodies in seven patients.

On chest radiographs, infiltrative and cavitory lesions were observed in all patients. The locations of the main lesions were the right upper lobe ( $n = 6$ ), left upper lobe ( $n = 2$ ), left lower lobe ( $n = 1$ ), and bilateral upper lobes ( $n = 1$ ). Intracavitary masses, consistent with mycetomas, were detected in nine patients. One patient also had infiltrates in the right middle and left lower lobes apart from the main lesion (Table 1). The range and character of lesions changed slowly over time in all patients. Examination of past radiograph findings revealed that four patients (cases 1 to 4) had infiltrates that initially appeared in lung fields as small opacities alone, which subsequently progressed to cavitory lesions with mycetomas. In three patients (cases 5 to 7), pulmonary cysts or thin-walled cavities were already present in the available past chest radiographs. Main lesions appeared from these preexisting cystic or cavitory spaces, with changes in the range and character of the lesions. In three patients (cases 8 to 10), chest radiographs obtained before the appearance of lesions were not available. Four cases (cases 1, 2, 6, and 8) with unique radiographic features, which could be followed in detail by chest radiographs and CT scans, are presented in the following paragraphs.

In case 1, the chest radiograph at first examination revealed only diffuse small opacities in the bilateral upper and middle lung fields; however, an infiltrate appeared in the right apex of the lung. The chest radiograph showed gradual progression of the right apical infiltrate, adjacent pleural thickening, and a new right upper nodular infiltrate (Fig 1, *top left, A*). The chest CT scan at diagnosis indicated worsening of the infiltrates in the right upper lobe (Fig 1, *top right, B*). After initiation of antifungal treatment, the chest CT showed improvement of the infiltrates and pleural thickening. In the process, a cavity formed in the center of the infiltrates, accompanied by a mycetoma (Fig 1, *bottom left, C*). Subsequently, the cavitory lesion diminished and the mycetoma disappeared (Fig 1, *bottom right, D*).

In case 2, the chest radiograph at first examination revealed only diffuse small opacities in the bilateral upper and middle lung fields; however, the chest CT scan showed an infiltrate in a part of the right upper lobe concomitant with the presentation of the symptoms (Fig 2, *top left, A*). The right upper lobe infiltrate gradually deteriorated with extensive pleural thickening (Fig 2, *top right, B*). The inside of the infiltrate necrotized resulting in formation of several cavities that had irregular-shaped mycetomas (Fig 2, *bottom left, C*). After initiation of antifungal treatment and intracavitary washing, there was a collapse of the intracavitary structures and thinning of the cavity walls. The cavities expanded and occupied the majority of the right upper lobe (Fig 2, *bottom right, D*).

In case 6, the chest radiograph at first examination revealed a right upper cavitory lesion with an adjacent infiltrate and right lower and left middle lung field infiltrates in the background of small opacities (Fig 3, *top left, A*). Some cysts were observed in the right upper lung field in a previous chest radiograph. The lesions deteriorated gradually, and the chest CT scan at diagnosis showed a right upper lobe infiltrate with associated pleural thickening (Fig 3, *top right, B*). After initiation of antifungal treatment, the patient experienced clinical and radiographic improvement. The chest CT scan indicated a cavity within the infiltrate and a mycetoma (Fig 3, *bottom left, C*). Subsequently, the mycetoma disappeared and the cavitory lesion continued to improve (Fig 3, *bottom right, D*).

In case 8, the chest radiograph at first examination revealed a left upper lung field infiltrate with adjacent pleural thickening in the background of small opacities (Fig 4, *top left, A*). The infiltrate deteriorated gradually, and the chest CT scan at diagnosis indicated a left upper lobe infiltrate with associated pleural thickening (Fig 4, *top right, B*). After initiation of antifungal treatment, symptoms and chest radiographic findings improved. The chest CT scan revealed a cavity within the infiltrate and dilated bronchi (Fig 4, *bottom left, C*). Subsequently, thinning of the cavity walls was observed (Fig 4, *bottom right, D*).

In eight patients (cases 1 to 6, 8, and 9), tuberculous lesions were strongly suspected at first and antituberculous agents were administered. Mycobacterial pathogens, however, were not isolated by culture on multiple sputum examinations, and chest radiographic findings failed to show improvement.

In all patients, *Aspergillus* was isolated several times from clinical specimens such as sputum and bronchoscopic samples. In case 2, *Aspergillus* was isolated from cavity puncture fluid taken percutaneously. In case 8, a transbronchial lung biopsy dem-

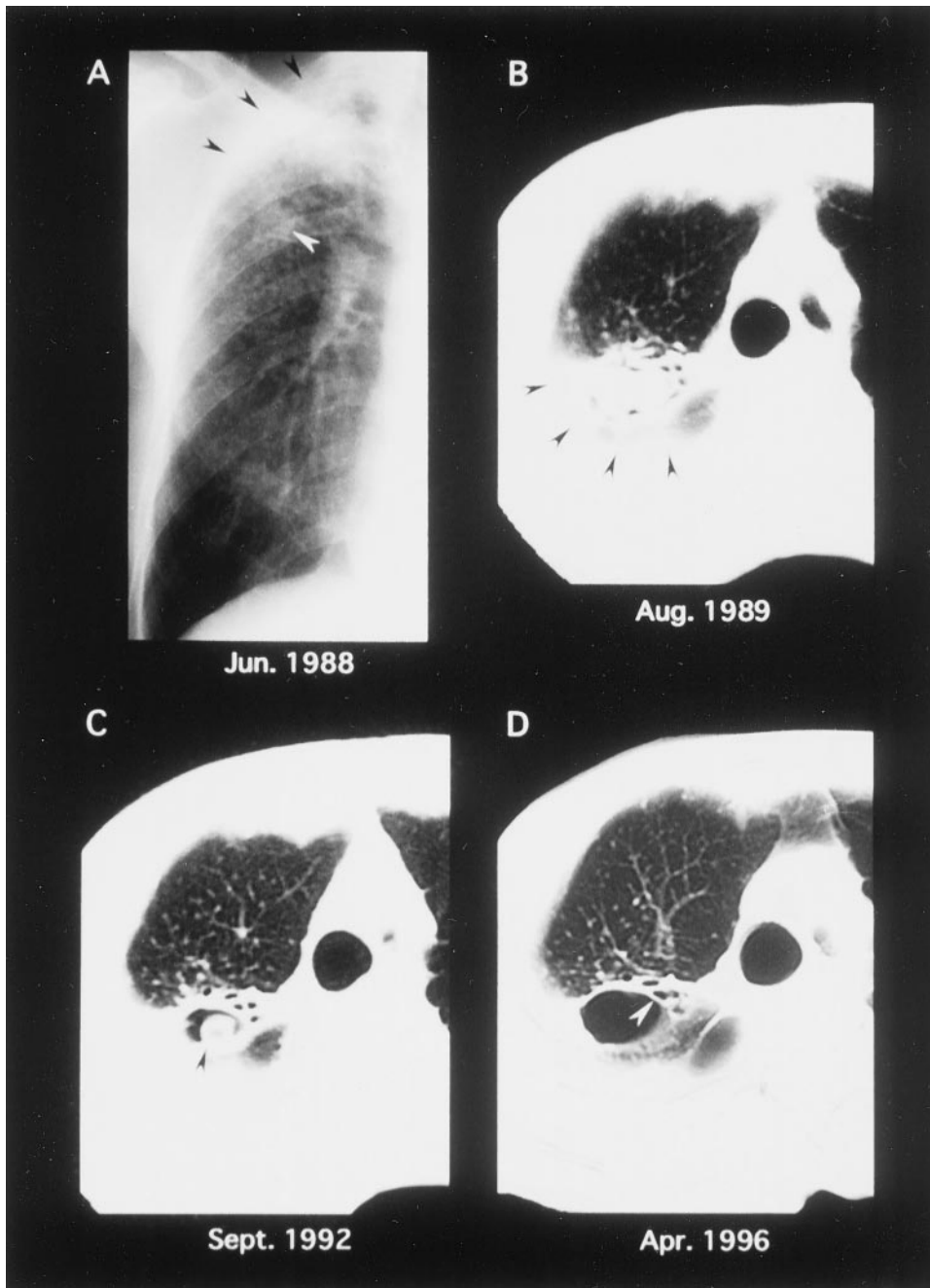


FIGURE 1. Patient 1. *Top left, A:* Chest radiograph (June 1988) showing an apical infiltrate with adjacent pleural thickening (black arrows) and a nodular infiltrate (white arrow) in the right upper lung zone. *Top right, B:* Chest CT scan (August 1989) showing an infiltrate containing an air bronchogram on the dorsal side of the right upper lobe, accompanied by pleural thickening and an infiltrate of the lung parenchyma immediately beneath the pleura (arrows). *Bottom, left, C:* After initiation of antifungal treatment, chest CT scan (September 1992) shows the infiltrate diminished and cavitated, with a mycetoma (arrow) capped by air anteriorly and laterally. *Bottom right, D:* Chest CT scan (April 1996) showing thinner cavity wall and dilated bronchi (arrow).

onstrated *Aspergillus* surrounded by numerous inflammatory cells and granulation in the lung parenchyma. Fungal cultures resulted in growth of *Aspergillus fumigatus* in four patients (cases 2, 5, 6, and 10). No other bacterial, fungal, or mycobacterial pathogens could be isolated.

Adequate data were available in five cases for judging the duration between the first symptoms or chest radiograph findings and the diagnosis of CNPA. The duration ranged from 22 to 133 months (Table 1).

Antifungal agents were administered to all patients

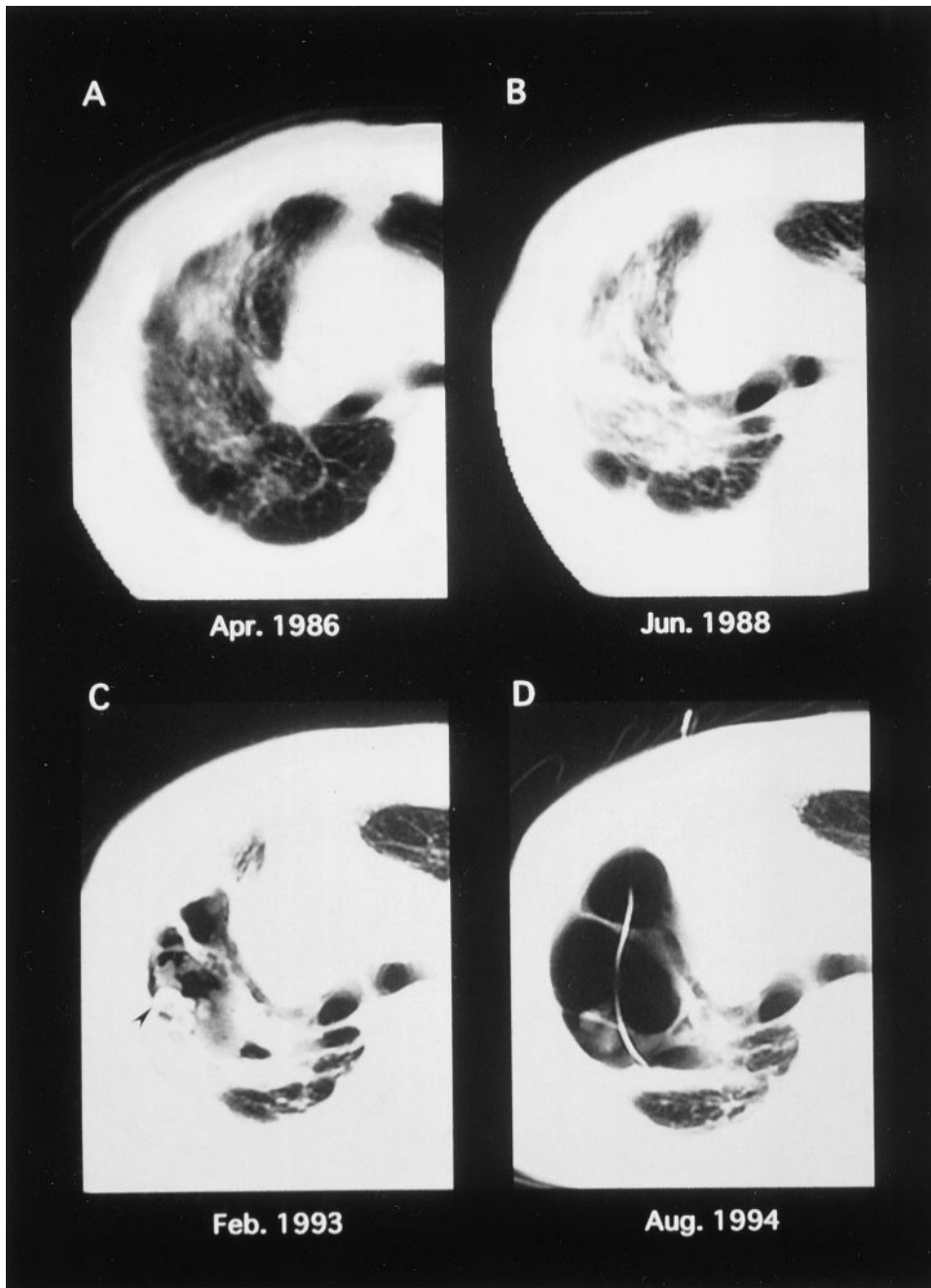


FIGURE 2. Patient 2. *Top left, A:* Chest CT scan (April 1986) showing an infiltrate in the right upper lobe with small opacities in the background. *Top right, B:* Chest CT scan (June 1988) showing infiltrate expanded to occupy the entire right upper lobe, accompanied by pleural thickening. *Bottom left, C:* Chest CT scan (February 1993) showing formation of cavities with several small intracavitary masses (arrow) inside the infiltrate. *Bottom right, D:* After initiation of antifungal treatment and intracavitary lavage, chest CT scan (August 1994) shows collapsed intracavitary structures and thinner cavity walls. A catheter for lavage is observed in the cavities.

by oral administration, inhalation, or intracavitary administration. In nine patients, radiographic and symptomatic improvement was confirmed and there was good control of hemoptysis. The other patient (case 10) could not be followed up because he stopped attending the hospital (Table 1).

Patient 2 died from respiratory failure due to aggravation of aspiration pneumonia, and an autopsy was performed. A large cavity measuring 10 cm in maximum diameter occupied most of the right upper lobe. There was no mycetoma in the cavity. Histologic sections demonstrated no invasion by *Aspergil-*

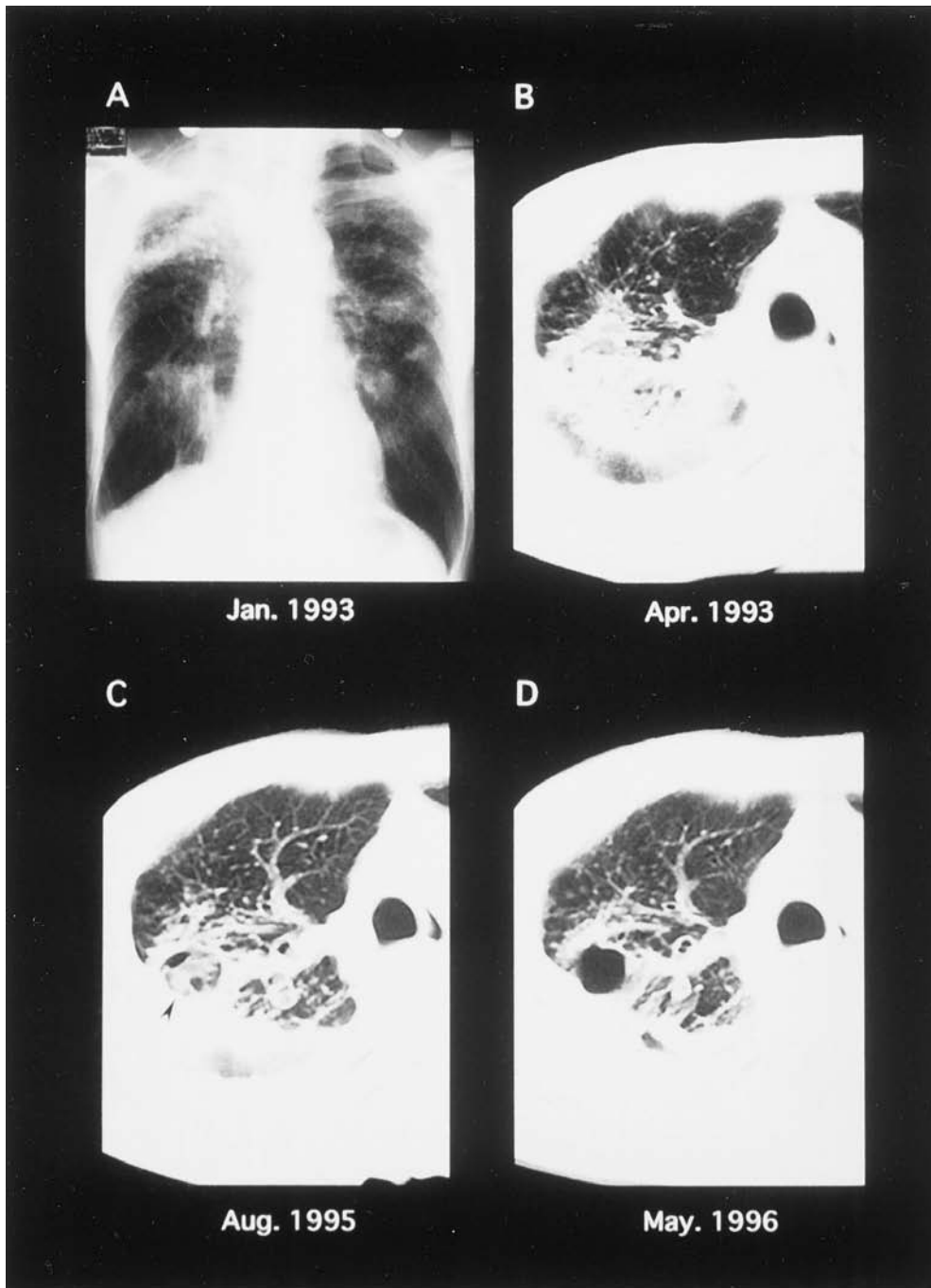


FIGURE 3. Patient 6. *Top left, A:* Chest radiograph (January 1993) showing right upper lung zone infiltrate surrounding preexisting cysts and right lower and left middle lung zone infiltrates with small opacities in the background. *Top right, B:* Chest CT scan (April 1993) showing an infiltrate containing an air bronchogram in the right upper lobe, accompanied by adjacent pleural thickening. *Bottom left, C:* After initiation of antifungal therapy, chest CT scan (August 1995) shows diminished infiltrate forming a cavity with a mycetoma (arrow). *Bottom right, D:* chest CT scan (May 1996) showing disappearance of mycetoma and the cavitory infiltrate diminished further.

lus into the cavity wall or the surrounding lung parenchyma. Acid-fast stain results of the cavity wall were negative, and there was no evidence of mycobacterial infection. No disseminated *Aspergillus* infection was detected in other organs.

#### DISCUSSION

According to the description of Binder et al,<sup>6</sup> CNPA occurs primarily in middle-aged persons who often have underlying pulmonary disease, such as

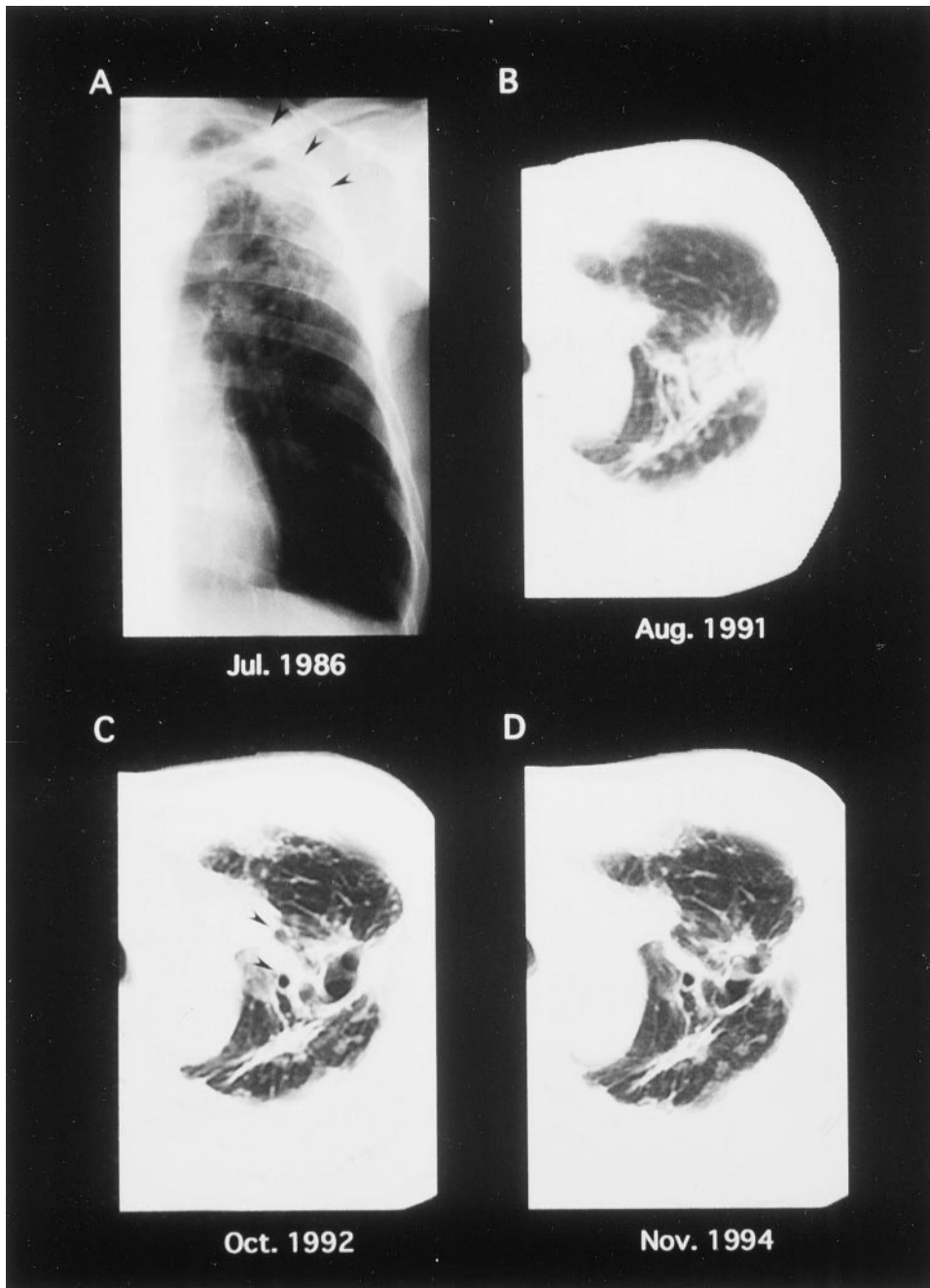


FIGURE 4. Patient 8. *Top left, A:* Chest radiograph (July 1986) showing an infiltrate with associated pleural thickening (arrows) in the left upper lung zone, with small opacities in the background. *Top right, B:* Chest CT scan (August 1991) showing an infiltrate with adjacent pleural thickening in the left upper lobe. *Bottom left, C:* After initiation of antifungal therapy, chest CT scan (October 1992) shows cavity formed within the infiltrate and dilated bronchi (arrows). *Bottom right, D:* Chest CT scan (November 1994) shows thinner cavity wall.

chronic obstructive lung disease, a history of pulmonary tuberculosis, cystic lung disease, previous resectional surgery, and pneumoconiosis. In addition, CNPA is observed in patients with some evidence of mild systemic immunodeficiency, including diabetes mellitus, collagen disease, or low-dose steroid ther-

apy. While *Aspergillus* invades the lung parenchyma and causes tissue necrosis in the host with lowered systemic or local resistance, the course progression is slow, differing from that of acute aspergillus pneumonia. The most frequent complaints are nonspecific symptoms such as sputum, cough, fever, and

general fatigue. Diagnostic confirmation requires histologic evidence of lung tissue invasion by septate hyphae, consistent with *Aspergillus* species; however, this is often difficult to obtain. Therefore, Binder et al<sup>6</sup> proposed the following clinical diagnostic criteria: (1) chronic symptoms for > 30 days prior to the institution of therapy; (2) the growth of *Aspergillus* species from clinical specimens, such as lung biopsy samples, bronchoscopic or percutaneous lung aspirates, or sputum; (3) failure to detect other bacterial, fungal, or mycobacterial pathogens, and failure to respond to antibacterial or antimycobacterial therapy; (4) chest radiograph abnormalities, most often localized on the upper lobes and showing infiltrates and cavities, often with mycetomas, due to tissue necrosis; and (5) a clinical response to specific antifungal therapy. Isolation of *Aspergillus* is sometimes difficult.<sup>4</sup> In such cases, the presence of serum *Aspergillus* antibody, reported to show positive rates of 83 to 100%,<sup>8,9</sup> is useful to support the diagnosis because of the high sensitivity and specificity.

In the present cases, the disease progressed slowly, taking a long course in all patients. While *Aspergillus* species were isolated from clinical samples, no other pathogenic microorganisms, including *Mycobacterium tuberculosis*, were detected. Chest radiographs and CT scans mostly demonstrated infiltrative and cavitory shadows in the upper lobes. The patients were symptomatic with a productive cough, hemoptysis, and fever. Serum findings were positive for *Aspergillus* antibody in 7 of 10 patients. On the basis of these clinical findings, we diagnosed pulmonary aspergillosis in patients with pneumoconiosis as CNPA.

All patients received antifungal therapy by oral administration, inhalation, or intracavitary administration, and the recovery and stabilization of disease were confirmed in all cases except patient 10. In patient 2, in whom it took 133 months until diagnosis of CNPA, even though disappearance of the intracavitary contents, thinning of the cavity walls, and resolution of infiltration were observed after the initiation of specific therapy, enlargement of the cavities and broad destruction of the lung were still apparent at autopsy. This suggests that early diagnosis and treatment are important for management of CNPA, as Saraceno et al<sup>10</sup> described.

The most radical and curative treatment for pulmonary aspergillosis is surgical resection. Especially in cases where patients have hemoptysis, surgery might be indicated.<sup>11-13</sup> In the case of patients with pneumoconiosis, however, the indication and the surgical forms of pulmonary resection should be carefully considered, taking into account the possibility of serious complications during and after the operation brought about by impaired lung functions

and severe pleural adhesions. In these patients, medical treatment with antifungal agents was first performed, and surgery was considered for patients who were resistant to the medical treatment. As the result, the control of hemoptysis was favorable in all cases except patient 10, there were no deaths from hemoptysis, and no surgery was performed.

A pathologic diagnosis of CNPA requires the demonstration of invasion of lung parenchyma by septate hyphae typical of *Aspergillus* species on biopsy specimens, but fungal invasion was not demonstrated in these cases. In patient 2, at autopsy, invasion of lung tissue surrounding the cavities by *Aspergillus* was not apparent. This indicates therapeutic efficacy because thinning of the cavity walls and resolution of the infiltrates by fungal therapy had already been observed radiographically. Although there have been reports of pathologic examination in terms of diagnosis, the disease process, and the effectiveness of therapy for CNPA,<sup>14-16</sup> the numbers of patients were limited. Further studies with a larger series of cases are thus needed.

The most frequent chest radiographic and CT findings of CNPA are upper-lobe areas of consolidation, multiple nodular opacities, and pleural thickening.<sup>16-18</sup> Including the four cases detailed above, we followed up and assessed the radiographic and CT findings of CNPA in nine patients with pneumoconiosis. The first finding was infiltration with air bronchograms, and then expansion of the infiltrate and adjacent pleural thickening appeared. Subsequently, tissue necrosis was induced inside the infiltrate, resulting in cavity formation with eventual development of mycetomas. After beginning antifungal treatment, collapse and disappearance of mycetomas, thinning of the cavity wall, improvement of the infiltrate, and dilatation of the bronchi were observed. In seven patients (cases 1 through 7), chest radiographs obtained before the onset of CNPA were available. In cases 1 through 4, only small opacities due to pneumoconiosis were detected. In cases 5 through 7, cysts or thin-walled cavities were already present and infiltration appeared around them. In cases 8 through 10, chest radiographs before the onset of CNPA were not available; therefore, the presence of preexisting cystic or cavitory spaces could not be confirmed.

As background factors, a history of pulmonary tuberculosis, tuberculous pleurisy, and chemotherapy and radiotherapy for cancer of the tongue were encountered in the present series. Tuberculosis was not active, however, and left no tuberculous cavity. One patient (case 4) received long-term oral corticosteroids. In four patients (cases 6, 7, 9, and 10), pneumoconiosis was the only risk factor. In two of

these patients, however, we confirmed the presence of preexisting cysts in the same region as the main lesions. There are various opinions on the formation of cavities.<sup>6,17–19</sup> From the findings of the present study, it appears possible that *Aspergillus* invades the lung parenchyma and forms a cavity as a result of lung necrosis, suggesting that pneumoconiosis contributes to the onset of CNPA. We cannot, however, rule out that a history of other diseases and other abnormalities, which most patients had, might participate in the onset of CNPA. The ILO radiographic classification of small opacities was greater than profusion category 2 in 8 of 10 patients, and the occurrence of CNPA was prominent in patients with progressive pneumoconiosis. Further studies with larger numbers of patients are needed to substantiate whether the frequency of CNPA is higher in patients with pneumoconiosis.

Nomoto et al<sup>20</sup> tested for *A fumigatus* in sputum from patients with coal workers' pneumoconiosis using nested polymerase chain reaction amplification of the *Asp fI* gene and reported that colonization of the respiratory tract with *A fumigatus* might be associated with pneumoconiosis. The group of pulmonary diseases caused by *Aspergillus*, which is essentially nonpathogenic or very weakly pathogenic for humans, is considered to be closely associated with the state of the host defense system, particularly the failure of nonspecific defense, rather than the pathogenicity of the fungus. In patients with pneumoconiosis, highly advanced pulmonary fibrosis with extensive organic disorders of the respiratory tract might be associated with abnormalities in the pulmonary defense mechanism. Thus, the respiratory tract is easily colonized and invaded by *Aspergillus*. Because severe systemic immunosuppression is not a feature, however, infiltration by *Aspergillus* is confined to local invasion with indolent progress. Binder et al<sup>6</sup> reported that patients who were easily affected with CNPA have local defects in pulmonary defenses stemming from structural lung disease and/or mild lowered immunologic functions, and pneumoconiosis is the disease consistent with those factors.

Patients with pneumoconiosis suffer frequently from pulmonary tuberculosis, which markedly aggravates their prognoses.<sup>21</sup> The most frequent symptoms of pulmonary tuberculosis are fever, chronic cough, sputum production, and weight loss, with typical chest radiograph findings of progressive cavity infiltrates predominantly in the upper lung fields, closely resembling those of CNPA. Therefore, there are cases in which distinguishing the two diseases can be difficult. Pulmonary tuberculosis was wrongly diagnosed in 8 of 10 patients on the basis of

their clinical courses; and they were treated initially with antituberculous agents. Taguchi et al<sup>22</sup> reported that in three of five patients in whom *Aspergillus* was present in cavities in 196 autopsied patients with pneumoconiosis, although smear and culture findings were negative for *M tuberculosis* during follow-up, antituberculous therapy was performed and the tuberculous change was not confirmed at autopsy.

In conclusion, we propose that close observation, including differential diagnosis of CNPA, is needed when chest radiographs and CT scans show slow progressing upper-lobe infiltrates and cavities, often with mycetomas, in patients with pneumoconiosis. Additionally, the necessity for early diagnosis and initiation of effective therapy should be emphasized.

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