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Short Communication

A Case Series of Chronic Necrotizing Pulmonary Aspergillosis and a New Proposal

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SUMMARY: Chronic necrotizing pulmonary aspergillosis (CNPA) is an indolent, cavitating process in the lungs resulting from invasion of lung tissue by *Aspergillus* spp. However, most previous reports have not found any clear evidence of parenchymal invasion, and clinical distinction between CNPA and chronic cavitary pulmonary aspergillosis (CCPA) is difficult. We performed a histopathological study of lung specimens obtained by autopsy, surgical resection, or biopsy to clarify the characteristic pathological and clinical features of CNPA. We present 4 cases of proven CNPA, diagnosed by histological demonstration of tissue invasion by the fungus, and present its clinical features. These 4 patients were male, and the mean age was 62 years (range, 51–75 years). Their underlying conditions were chronic obstructive pulmonary disease (n = 3), sequelae of pulmonary tuberculosis (n = 2), and diabetes mellitus (n = 1). *Aspergillus* precipitation tests were positive for 3; and *Aspergillus* antigen tests were positive for 2 on admission, and subsequently, for all 4. The isolated pathogens were *Aspergillus niger* for 1 and *A. fumigatus* for 1. Initial radiographic findings were infiltrates or nodular lesions, which slowly progressed and cavitated before the appearance of fungus balls. Although CNPA has characteristic pathological features, it is clinically difficult to distinguish CNPA from CCPA. We propose to use the term chronic progressive pulmonary aspergillosis for both CNPA and CCPA.

Chronic necrotizing pulmonary aspergillosis (CNPA) is an indolent, cavitating process in the lungs caused by invasion of lung tissue by *Aspergillus* spp. (1). The diagnosis of CNPA is primarily confirmed by pathological evidence of tissue invasion by *Aspergillus* spp. (1,2). However, in previous reports, the majority of patients with CNPA have been diagnosed according to clinical criteria (3–6). We conducted a histopathological study of lung specimens obtained by autopsy, surgical resection, or biopsy to clarify the characteristic pathological and clinical features of CNPA, which was diagnosed in a total of 4 patients. This retrospective study was approved by the ethical committee of Nagasaki University Hospital.

Case 1: A 75-year-old man with cough, fever, and malaise was admitted to our hospital on August 30, 2010. He had chronic obstructive pulmonary disease (COPD) and a history of left pneumonectomy for intractable pulmonary tuberculosis and aspergilloma on April 15, 1993. *Aspergillus* precipitation test was positive and *Aspergillus* galactomannan was 2.210. Radiography revealed multiple bullae and pleural thickening in the right upper lobe (RUL). Despite broad-spectrum antibiotic therapy, subsequent chest computed tomography (CT) scans revealed increasing consolidation with cavities in RUL and ground glass opacity in the right middle lobe (RML) and right lower lobe (RLL) (Fig. 1A and 1B). The patient continued to deteriorate and died on September 27, 2010. Autopsy findings confirmed necrotic cavities in RUL. Histological examination revealed dichotomously branching septate hyphae in both fungus balls and necrotic lung tissue. Diffuse alveolar damage (DAD) was observed in the right lung distant from cavities. Examination with polarized light revealed abundant deposition of birefringent crystals in the cavity walls and the necrotic lung tissue (Fig. 1C). Crystal deposition was accentuated in the walls of blood vessels. In addition, crystals were observed in lung parenchyma distant from the cavity and in the tubules of both kidneys without fungal elements.

Case 2: A 51-year-old man was hospitalized owing to hemoptysis on March 30, 2007. He had a history of pulmonary tuberculosis and alcoholism. Radiography revealed a cavitary lesion in the left upper lobe (LUL) and nodular lesions in RUL (Fig. 2A). *Aspergillus* precipitation test was positive and *Aspergillus* galactomannan was 0.600. Bronchoscopy revealed a lingular bronchus that actually opened into a large cavity; the inner wall of the cavity showed an irregular black surface with white nodules (Fig. 2B). Biopsy specimens revealed necrotic lung tissue with septate hyphae and calcium oxalate crystals. Bronchial washings grew *Aspergillus niger*. After voriconazole (VRCZ) therapy, the cavity wall

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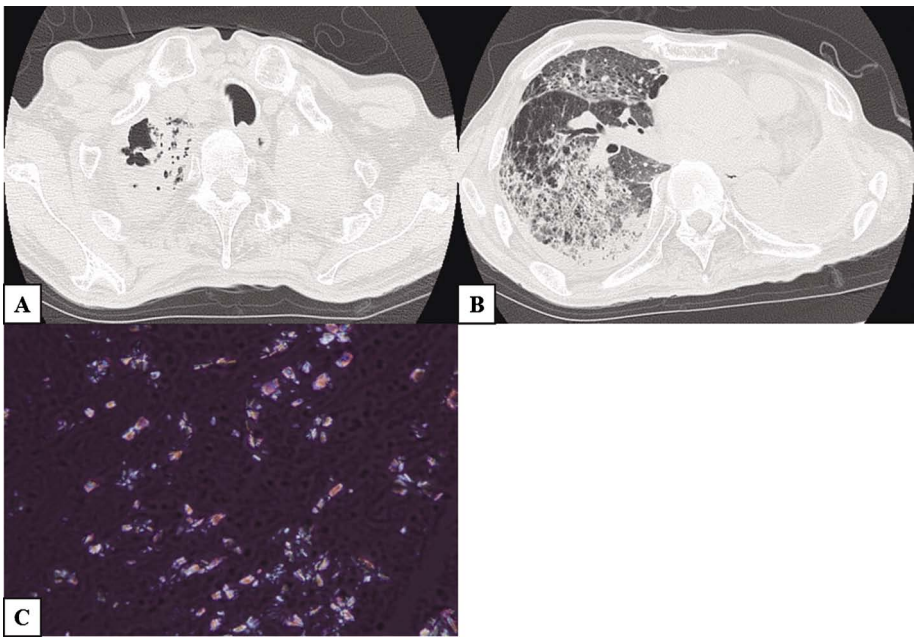

Fig. 1. (A) and (B) Chest CT scans of case 1 on September 11, 2010 showing consolidation with cavities in RUL and ground glass opacity in RML and RLL. (C) Polarized light examination of a tissue section revealed abundant deposition of birefringent crystals (partial polarization, hematoxylin and eosin stain; original magnification ×400). RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe.

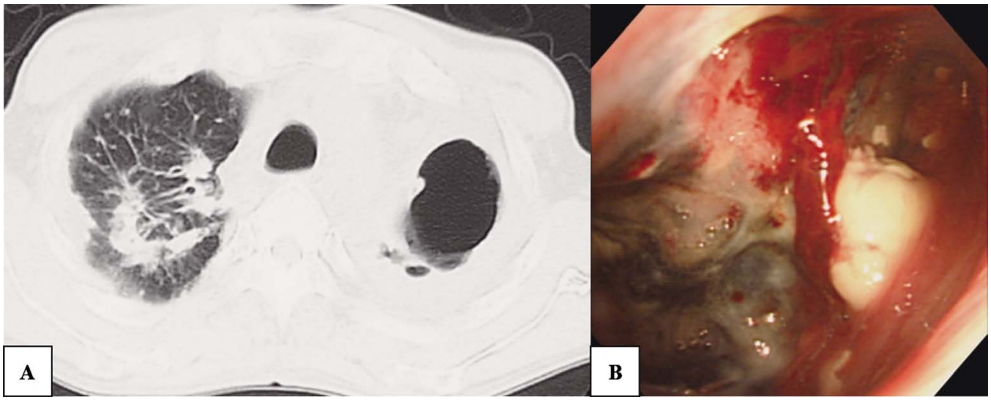

Fig. 2. (A) Chest CT scan of case 2 on April 3, 2007 showing a thick-walled cavity in LUL and nodular lesions in RUL. (B) Bronchoscopic examination of the cavity showing an irregular black surface and white nodules with bleeding. LUL, left upper lobe.

became thinner and the nodular lesions decreased.

Case 3: A 65-year-old man with COPD and diabetes mellitus (DM) presented with cough and fever. Radiography revealed a cavitary lesion and pericavitary infiltrates in the left lung. Despite broad-spectrum antibiotic therapy, fever persisted, the infiltrates increased, and the cavity wall thickened. The patient was admitted to our hospital on December 7, 2006. Culture of sputum and bronchial washing revealed *Aspergillus fumigatus* and *Pseudomonas aeruginosa*. *Aspergillus* precipitation test was positive and *Aspergillus* galactomannan was 2.391. Chest CT scans showed an LUL cavity with a fungus ball and infiltrates around the cavity (Fig. 3A). VRCZ, micafungin (MCFG), and broad-spectrum antibiotics were administered; however, the patient continued to deteriorate and died on December 30, 2006. Autopsy findings revealed multiple bullae and cavitary lesions containing necrotic materials in LUL. Microscopy revealed necrotic lung tissue invaded by septate hyphae and aspergilloma (Fig. 3B and 3C).

Case 4: A 56-year-old man with malaise was admitted to our hospital on February 8, 2010. The patient had COPD, and chest radiograph revealed multiple nodular shadows in both upper lobes. The nodular shadows were first detected in March 2004, without any symptoms. Because medical examination revealed no finding of malignancy, tuberculosis, mycosis, or any other disease, the patient was followed without therapy. Subsequent radiography revealed slow enlargement of the nodular lesions. Despite broad-spectrum antibiotic therapy, new nodular lesions, one of which was cavitated, appeared (Fig. 4A). *Aspergillus* precipitation test was positive and *Aspergillus* galactomannan was 0.457. Transbronchial biopsy and washing revealed no evidence of malignancy or specific inflammation. To make a decisive diagnosis, right upper lobectomy was per-

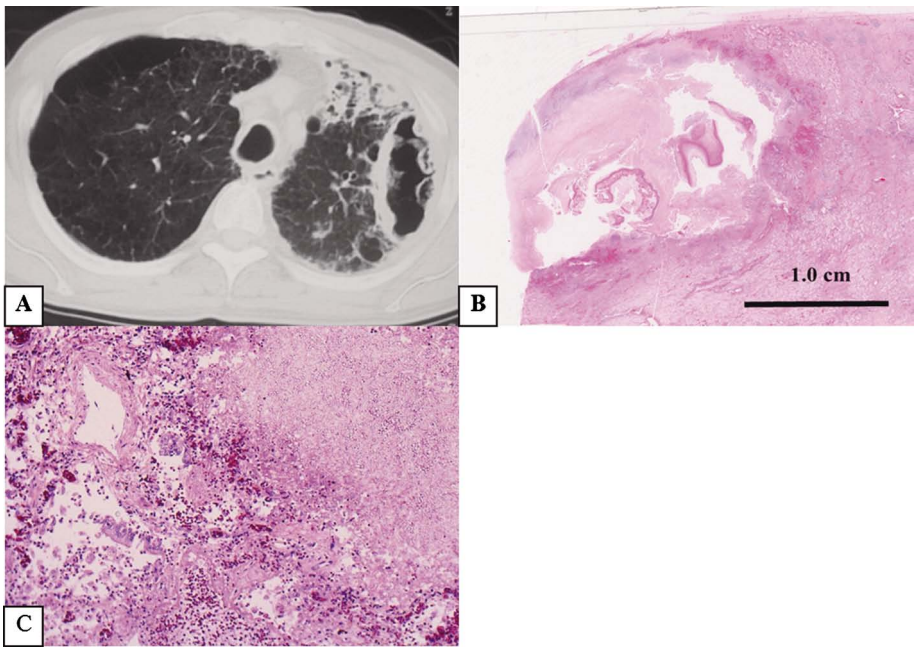

Fig. 3. (A) Chest CT scan of case 3 on December 1, 2006 showing a thick-walled cavity with fungus balls and pericavitary consolidation in LUL. (B) Autopsy specimen from LUL showing a cavity containing necrotic lung tissue and fungus balls (hematoxylin and eosin stain; original magnification loupe). (C) Lung parenchyma invaded by septate hyphae (hematoxylin and eosin stain; original magnification ×200).

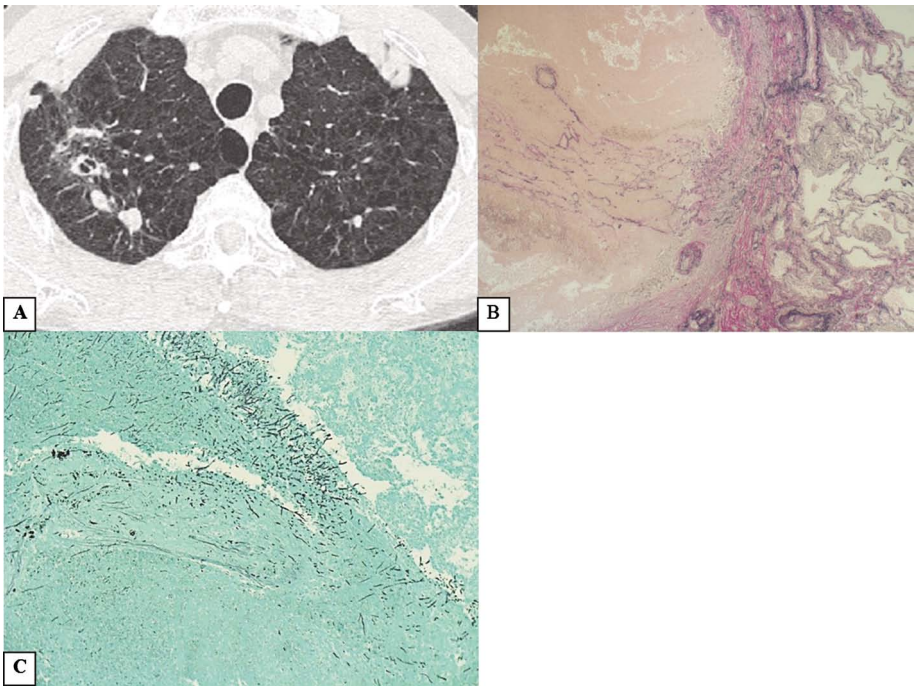

Fig. 4. (A) Chest CT scan of case 4 on November 4, 2007 showing nodular lesions, one of which is cavitated, in both upper lobes. (B) Resected specimen of RUL showing a necrotic nodule comprising necrotic lung tissue (elastica van Gieson stain; original magnification ×40). (C) Septate hyphae were demonstrated in necrotic lung tissue (Grocott stain; original magnification ×100).

formed on April 22, 2010. Macroscopy revealed a cavitary lesion and necrotic nodules. Histology of the necrotic nodule revealed necrotic lung tissue invaded by septate hyphae (Fig. 4B and 4C).

Denning et al. (7–9) classified subacute or chronic pulmonary aspergillosis (CPA) into 3 subcategories: subacute invasive pulmonary aspergillosis (IPA) or CNPA, chronic cavitary pulmonary aspergillosis (CCPA), and chronic fibrosing pulmonary aspergillosis (CFPA). CCPA is defined as the presence of one or more pulmonary cavities, with or without a fungus ball, with significant pulmonary or systemic symptoms and overt radiological progression. Thus, the clinical features of CCPA are similar to those of CNPA, and a key

pathological distinction is the presence of *Aspergillus* hyphae in lung tissue in CNPA, as opposed to the presence of *Aspergillus* hyphae within cavities in CCPA.

In the present study, 4 patients were diagnosed with CNPA. All 4 were males, and the mean age was 62 years (range, 51–75 years). Their underlying conditions included COPD, sequelae of pulmonary tuberculosis, and DM. Pathological examination revealed local invasion into cavity walls and lung parenchyma by *Aspergillus*. Because intracavitary masses, aspergillomas and/or necrotic lung tissue, were confirmed in all patients, we inferred that necrotic lung tissue invaded by this fungus gradually changes to fungus balls after necrotic materials are absorbed or excreted. Thus, necrotic lung tissue and aspergilloma may co-exist in the cavity. Pulmonary oxalosis was confirmed in 2 patients. Increased crystal deposits were observed surrounding and within blood vessel walls of the cavitary lesions. Associated blood vessels were often occluded by thrombi, and pulmonary hemorrhage or hemorrhagic infarction was observed around the cavities. *A. niger* and, to a lesser degree, other *Aspergillus* spp. are known to release oxalic acid (10,11), which complexes with free calcium ions in tissue and blood to form calcium oxalate. The crystals induce lipid peroxidation and iron-dependent oxidant generation, along with the release of various enzymes from neutrophils. Thus, the crystals may induce tissue injury, resulting in hemorrhagic infarction, coagulative necrosis, or DAD (12–14).

Aspergillus precipitation tests were positive for 3 patients. Although the majority of patients with CNPA have positive serum *Aspergillus* precipitin test results, this observation varies over time and may be negative at some points during the course of CNPA. *Aspergillus* antigen tests were positive (OD >0.5) for 2 patients on admission, and subsequently, for all 4. The high positivity of the test in our patients may be due to the severity of CNPA and repeated testing of blood samples.

Initial radiographic findings were infiltrates in 3 patients, which slowly progressed and cavitated, at which point fungus balls appeared. Another patient revealed multiple nodular lesions, which slowly enlarged and cavitated, following which a fungus ball appeared. The site of involvement was both upper lobes in 3 patients and RUL in 1. The rate of radiological progression in CNPA is measured in weeks or months; however, our case 4 had a more slowly progressive course over months to years. Thus, patients with CNPA do not always have subacute courses.

Perfect et al. (15) reported that the most common *Aspergillus* spp. identified in patients with CNPA was *A. fumigatus* (80%), followed by *A. niger* (10%). We previously reported that the most commonly isolated species in patients with CNPA was *A. fumigatus* (54%), followed by *A. niger* (24%) and *A. terreus* (10%) (16). However, these patients were not proven CNPA cases. In the present study of proven CNPA cases, *A. niger* was identified in 1 patient, and another patient was strongly suspected to be infected by *A. niger* because of extensive pulmonary oxalosis. Saraceno et al. (3) reported 6 cases with CNPA; 3 infected by *A. niger* and 3 infected by *A. fumigatus*. Although *A. niger* is less invasive than *A. fumigatus*, *A. niger* may be more likely to cause CNPA with cavities because of its tendency to produce calcium oxalate crystals (10). Finally, although CNPA has characteristic pathological and clinical features, it is difficult to clinically distinguish CNPA from CCPA, particularly if previous chest radiographs are not available. Moreover, the distinction between the two may have little significance with regard to treatment (17). Therefore, the term CPA is used for diseases including CCPA and CNPA (7,8). However, CPA may include simple aspergilloma (9), which develops in a preexisting pulmonary cavity with minor or no symptoms and radiological progression, and the therapeutic strategy for simple aspergilloma differs from that for CNPA or CCPA (17). The limitation of this study is that the number of cases was too small to draw conclusions regarding the clinical features of CNPA; however, our study reflected the scarcity of definite CNPA cases proved by pathological examination as well as the difficulty of acquiring tissues from actual CPA cases.

CNPA is considered as a ''sub-acute IPA'' owing to its progression in 1 to 3 months from the clinical point of view (7); however, CNPA was originally defined as CNPA by pathological findings, and chronicity was defined as duration of the disease process for more than 30 days prior to the initiation of therapy (1). Our cases actually indicated a longer progression rate of more than 3 months, and all CNPA cases may not progress at a ''sub-acute'' rate. ''Semi-invasive'' pulmonary aspergillosis defined by Gefter et al. may be a more suitable clinical alternative for CNPA (18), because it reflects the pathogenesis of this disease, such as the formation of a cavitary lesion followed by the appearance of a fungus ball. On the other hand, distinguishing between CNPA and CCPA is also difficult without pathological evidence and detailed information on the clinical and radiological courses. In addition, it is not important for management because the manner of treatment may not change. Hence, we propose to use the term ''chronic progressive pulmonary aspergillosis (CPPA)'' as a simple clinical diagnosis for CNPA and CCPA (excluding simple aspergilloma).

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Conflict of interest None to declare.

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