Clinical and radiologic manifestations of pulmonary cryptococcosis in immunocompetent patients and their outcomes after treatment

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PURPOSE
We aimed to investigate clinical and radiologic manifestations of pulmonary cryptococcosis in immunocompetent patients and their outcomes after treatment.

MATERIALS AND METHODS
We retrospectively reviewed the medical records, initial and follow-up chest computed tomography scans and/or radiographs for initial clinical and radiologic manifestations and outcomes following antifungal treatment of 12 immunocompetent patients diagnosed with pulmonary cryptococcosis between 1990 and 2012.

RESULTS
Twelve patients (age range, 21–62 years; males, eight patients (67%)) were included. Nine (75%) patients were asymptomatic, eight of whom had disseminated infection with central nervous system involvement. Initial pulmonary abnormalities consisted of single nodules/masses (n=5), single segmental or lobar mass-like consolidation (n=3), multiple cavitary and noncavitary nodules (n=1), and multifocal consolidation plus nodules (n=3). These lesions ranged from less than 1 cm to 15 cm in greatest diameter. Distinct subpleural and lower lung predominance was observed. Seven patients (58.3%) had one or more atypical/aggressive findings, namely endobronchial obstruction (n=4), calcified (n=1) or enlarged (n=4) mediastinal/hilar lymph nodes, vascular compression (n=1), pericardial involvement (n=1), and pleural involvement (n=2). Following antifungal therapy, radiologic resolution was variable within the first six months of eight nonsurgical cases. Substantial (>75%) improvement with some residual abnormalities, bronchiectasis, cavitation, and/or fibrotic changes were frequently observed after 12–24 months of treatment (n=6).

CONCLUSION
Pulmonary cryptococcosis in immunocompetent patients frequently causes disseminated infection with atypical/aggressive radiologic findings that are gradually and/or incompletely resolved after treatment. The presence of nonenhanced low-attenuation areas within subpleural consolidation or mass and the absence of tree-in-bud appearance should raise concern for pulmonary cryptococcosis, particularly in patients presenting with meningitis.

Pulmonary cryptococcosis is an emerging infection caused by Cryptococcus species complex, which are ubiquitous encapsulated yeasts found worldwide. The infection usually affects immunocompromised patients, particularly those with an impaired cell-mediated immune response (1, 2). In rare circumstances, the infection occurs in otherwise healthy individuals. According to previous studies from many countries in North America, Europe, and the East (3–11), most immunocompetent individuals have mild or no clinical symptoms with isolated pulmonary involvement through single or multiple small pulmonary nodules. These findings are somewhat different from the more aggressive clinical and radiographic findings described in isolated case reports among Thai immunocompetent patients (6, 12–14) and in a study from South America (3). Therefore, there might be potential differences in the clinical and radiologic characteristics of pulmonary cryptococcosis among different geographic regions and hospital settings. Although radiologic responses to treatment have been previously mentioned (3–6, 9–11), specific details regarding the radiologic changes in pulmonary cryptococcosis following antifungal therapy are still limited and are usually based on follow-up chest radiographs. This information led us to ascertain clinical and radiologic manifestations of pulmonary cryptococcosis among Thai immunocompetent patients and their outcomes following antifungal therapy.

Materials and methods

Study population
This retrospective study was approved by the Local Ethics Committee on Human Rights related to research involving human subjects at our institution. Patient consent was waived because the investigations and management were part of routine patient care, and patient confidentiality was strictly maintained by our methods.

We retrospectively searched our hospital database between 1990 and 2012 for adult patients (aged ≥18 years) who had evidence of cryptococcal infection and/or positive cryptococcal antigen (CRAG) tests in serum or cerebrospinal fluid (CSF). Patients with coexisting human immunodeficiency virus or other immunocompromised diseases (i.e., hematologic or solid organ malignancies, kidney transplantation, collagen vascular disease, diabetes mellitus, liver cirrhosis, and immunosuppressive therapy) or unavailable medical records were excluded. The criteria used for the diagnosis of pulmonary cryp-
Pulmonary cryptococcosis included the histopathological presence of the organism in a resected lung specimen or from a lung biopsy, a positive culture of a respiratory specimen for Cryptococcus spp., or a positive serum CRAG test, regardless of titer value, with clinical or radiographic evidence of active pulmonary disease. Disseminated infection was considered when there was an evidence of extrathoracic involvement—i.e., positive CSF culture for Cryptococcus spp., positive CSF CRAG test, or clinical or radiologic evidence of other organ involvement in addition to pulmonary disease.

During the study period, 24 apparently immunocompetent patients had documented cryptococcal infection. We further excluded 12 patients who did not meet our criteria for the diagnosis of pulmonary cryptococcosis, leaving 12 patients for analysis. The patients' medical records were retrospectively reviewed for their demographics (age, gender, occupation, tobacco smoking status, and exposure to pigeon excreta), clinical presenting symptoms (fever, headache, cough, sputum production, hemoptysis, weight loss, and night sweats), treatments (types and dosage of antifungal drugs and surgical intervention), clinical response and outcomes after antifungal treatment.

Laboratory data, including CRAG titers in serum and CSF; India ink-stained preparation; culture and/or molecular identification for Cryptococcus spp. from bronchoalveolar lavage fluid, blood, and CSF; and/or histopathology results of biopsy specimens (lung, lymph node, and skin), were also reviewed.

**Radiologic assessment**

All chest computed tomography (CT) and chest radiographs of these patients were retrospectively reviewed by two observers, and the results were reached by consensus. Both nonenhanced and contrast-enhanced chest CT scans were obtained in most patients. The CT scans were performed using various scanners, including an electron-beam CT scanner (Imatron, San Francisco, California, USA), as well as 4-slice (Lightspeed plus, General Electric Medical Systems, Milwaukie, Wisconsin, USA), 16-slice (Mx8000 IDT, Philips, Eindhoven, The Netherlands), and 64-slice (Sensation Cardiac 64, Siemens Healthcare, Erlangen/ Muenchen, Germany) multidetector CT scanners. The CT parameters (120 kVp, 80–220 mAs) and the slice thickness (2–10 mm) used were variable depending on the type of the CT scanner. All CT images were reconstructed with standard and high-spatial frequency algorithms for mediastinal- and lung-window displays, respectively.

Initial pulmonary parenchymal abnormalities were classified as a pulmonary nodule or mass (a rounded or oval-shaped opacity ≤3 cm or >3 cm in diameter, respectively), airspace consolidation (a nonrounded, subsegmental, segmental, or lobar opacity obscuring the underlying vascular structures), groundglass opacity (opacity without obscuration of the underlying vascular structures), miliary pattern, and centrilobular branching or tree-in-bud appearance.

The number and greatest dimension of the pulmonary nodules, masses, and consolidation were determined. The location of the abnormalities was defined based on the pulmonary lobes and zonal involvement (peripheral, subpleural or pleural-based, middle 1/3, or perihilar). The margins of the nodules/masses were classified as well- or ill-defined with a smooth, lobulated, irregular or spiculated border. The presence of air- or mucus-filled bronchograms, cavitation, calcification, the pattern of contrast enhancement (homogeneous or heterogeneous), the presence of enhancing vessels (the so-called CT angiogram sign) and nonenhanced low-attenuation areas within the masses or consolidated areas were determined whenever possible. Associated airway abnormalities (bronchial wall thickening, bronchiectasis, endobronchial obstruction) were assessed as present or absent.

Mediastinal or hilar lymphadenopathy (lymph node with a short axis diameter ≤10 mm), nodal calcification, pleural abnormalities (effusion, thickening, and calcification), cardiovascular abnormalities (pericardial effusion, vascular encasement/compression), and upper abdominal organ involvement were assessed.

Radiologic changes and/or outcomes after antifungal therapy were determined based on follow-up chest CT or chest radiographs <1 month, 1–3 months, >3–6 months, >6–12 months, >12–24 months, and >24 months after initiation of antifungal therapy. If more than one imaging modality were available, the latest CT or chest radiograph (when CT was unavailable) obtained in each period was used for analysis. In each patient, the improvement of parenchymal abnormalities was visually estimated by comparing the sizes and/or numbers of the pulmonary nodules, masses and/or consolidations with those observed on the initial imaging using a five-point scale as follows: 0, no improvement; 1, improved <25%; 2, improved 25%–50%; 3, improved >50%–75%; and 4, improved >75%. Resolution of extrapulmonary abnormalities, including re-establishment of airway and superior vena cava patency, as well as associated cavitation, cyst formation, calcification, air bronchogram, bronchiectasis, and fibrotic change (the presence of architectural distortion and a parenchymal scar) were also determined from CT.

**Results**

**Clinical manifestations and pathological findings**

Eight (66.7%) of the 12 patients were men. The patients’ median age was 51 years (range, 21–62 years). Six patients worked in agricultural fields of rice or fruits, and two were construction laborers. Four patients had an exposure to pigeon excreta. Three of the male patients were...
current smokers, and one was a former smoker. Nine patients (75%) were symptomatic. The common presenting clinical symptoms included headache (n=5), fever (n=4), and chronic cough (n=4). The median onset of clinical illness was 2.5 months (range, 0.5–8 months) prior to presentation.

Cryptococcomas (fibrogranulomatous nodules with multinucleated giant cells and numerous yeasts) were found in the surgical specimens of two patients. Pathological examination of the lung biopsy specimens (Fig. 1) revealed histiocyte aggregations or poorly formed granulomas with numerous yeasts within histiocytes and minimal inflammatory response (n=5) and coexisting fibrosis (n=3). Sputum (n=3), bronchoalveolar lavage fluid (n=2), and/or CSF (n=7) cultures yielded *C. neoformans var. grubii* (serotype A) in seven patients (58.3%). Cultures were unavailable in the remaining patients.

As shown in Table 1, eight patients (66.7%) had disseminated infection to the central nervous system (CNS), including cryptococcal meningitis (n=8), and cranial nerve (n=1) and cerebral (n=1) involvement. Cutaneous (n=1) and probable splenic (n=1) involvement were also observed.

**Initial radiologic manifestations**

As shown in Table 1, initial radiologic abnormalities were determined based on chest CT findings in eight patients and chest radiographic findings in four patients (no. 1–4). The median interval between initial chest radiographs or initial chest CT and definitive diagnosis was 12 days (range, 3–66 days). Nine (75%) of the 12 patients had unilobar involvement of a single pulmonary nodule/mass (n=5, Fig. 1), a single segmental or lobar mass-like consolidation (n=3, Figs. 2, 3), or a cluster of cavitary and noncavitary pulmonary nodules (n=1). The remaining three patients (25%) had multilobar involvement by multiple subsegmental/segmental areas of consolidation plus small nodules (Fig. 4). Distinct peripheral, subpleural, or pleural-based involvement was observed with all single lesions and most multiple lesions. The lower lung zones were involved in 11 patients (91.6%), and the right middle lobe was involved in seven patients (58.3%). These lesions ranged from <1 cm up to 15 cm in greatest diameter. All of the single pulmonary nodules/masses and most of the multiple pulmonary nodules/masses were solid in appearance and had a rather well-defined but slightly lobulated or irregular mar-
gin. Air bronchograms and/or small air-filled cavities within the nodules/masses were frequently visible on CT in seven cases (58.3%). Flecks of calcification within the pulmonary mass were observed in one case (Fig. 1a, 1b). Multiple small, calcified nodules were found in one case. Surrounding groundglass opacity, the so-called CT halo sign, was evident in two patients (Fig. 4a). No fibrotic change, bronchiectasis, isolated groundglass opacity, miliary pattern, or tree-in-bud appearance was observed.

Table 1. Summary of initial clinical and radiologic manifestations of 12 patients with pulmonary cryptococcosis

<table>
<thead>
<tr>
<th>Patient no. (Age [years]/gender)</th>
<th>Year</th>
<th>Clinical presentation</th>
<th>Disseminated infection with CNS involvement</th>
<th>Initial serum/CSF CRAG test or titers</th>
<th>Imaging modality</th>
<th>Site of lesion(s)</th>
<th>Mode of biopsy (site)</th>
<th>Associated findings in the pulmonary lesion</th>
<th>Radiologic findings</th>
<th>Additional CT findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (41/F) 1990 headache, +</td>
<td>1:64/1:64</td>
<td>CXR RLL surgery (lung)</td>
<td>single (3.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2 (21/M) 1990 headache +</td>
<td>1:4/1:16</td>
<td>CXR RML NA</td>
<td>single (3.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3 (33/M) 1997 headache, hearing loss, weakness, ataxia +</td>
<td>1:1024/1:512</td>
<td>CXR RML NA</td>
<td>single (2.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4 (59/M) 1998 chronic cough +</td>
<td>1:128/1:32</td>
<td>CXR LLL TBBX</td>
<td>multiple (1.0–2.5)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>5 (51/F) 2002 asymptomatic +</td>
<td>1:1024/1:128</td>
<td>CT RLL TBBX (lung)</td>
<td>single (7.4)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>splenic nodules</td>
<td></td>
</tr>
<tr>
<td>6 (53/M) 2003 chronic cough +</td>
<td>+ve/1:128</td>
<td>CT all TBBX (lung)</td>
<td>multiple (1.25)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>minimal pleural effusion and thickening</td>
<td></td>
</tr>
<tr>
<td>7 (62/M) 2007 chronic cough, fever, weight loss -</td>
<td>+ve/-ve</td>
<td>CT RUL, RML, TTNA, TBBX</td>
<td>multiple (0.2–2.0)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8 (58/F) 2007 fever, weight loss -</td>
<td>+ve/-ve</td>
<td>CT RML TBBX (LN)</td>
<td>single (15.0)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>vascular compression</td>
<td></td>
</tr>
<tr>
<td>9 (51/M) 2008 headache, fever, ataxia, blurred visions +</td>
<td>&gt;1:1024/1:1024</td>
<td>CT RML TTNB (lung, skin)</td>
<td>single (8.0)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>calcified LN, calcified nodules in liver and small bowel, left eyelid and intracerebral nodules</td>
<td></td>
</tr>
<tr>
<td>10 (48/F) 2009 headache, chronic cough, hemoptysis, fever, pleuritic chest pain, weight loss +</td>
<td>1:1024/1:512</td>
<td>CT lingula TTNB (lung)</td>
<td>single (7.8)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>pericardial effusion and thickening</td>
<td></td>
</tr>
<tr>
<td>11 (40/M) 2010 asymptomatic -</td>
<td>1:128/-ve</td>
<td>CT RML, RLL TBBX (lung)</td>
<td>multiple (0.2–0.9)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>minimal pleural effusion, calcified nodules</td>
</tr>
<tr>
<td>12 (54/M) 2012 asymptomatic -</td>
<td>-ve/-ve</td>
<td>CT LLL surgery (lung)</td>
<td>single (2.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*non-diagnostic result, ≥10 mm in short axis diameter.

AB, air bronchograms; CNS, central nervous system; CRAG, cryptococcal antigen; CSF, cerebrospinal fluid; CT, computed tomography; CXR, chest radiograph; EBO, endobronchial obstruction; F, female; LAA, low-attenuation area; LLL, left lower lobe; LN, lymph node; M, male; NA, not available; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; TBBX, transbronchial biopsy; TTNA, transthoracic needle aspiration; TTNB, transthoracic needle biopsy; +, present; -, absent; +ve, positive CRAG titer but not quantified; -ve, negative CRAG titer.
Following intravenous contrast enhancement, most nodules larger than 1 cm showed mild but homogeneous contrast enhancement, whereas all large masses or consolidated areas exhibited heterogeneous enhancement in association with a CT angiogram sign, nonenhanced low-attenuation areas and/or mucus-filled bronchograms (Figs. 1c, 2a, 3b). Obstruction of the segmental or lobar bronchi within the pulmonary mass or the area of postobstructive pneumonitis was also evident in four patients (33.3%) (Figs. 1b, 1c, 3b).

Six (50%) of the 12 patients had at least one extrapulmonary CT finding, consisting of calcified lymph nodes (n=1, Fig. 1a, 1b), enlarged mediastinal/hilar lymph nodes ranging from 10 to 38 mm in short axis diameter (n=4, Figs. 2a, 3a), compression of the superior vena cava and distal right pulmonary artery (n=1, Fig. 3a), and involvement of the pericardium (n=1, Fig. 2a), pleura (n=2), and extrathoracic organs (n=2).

Clinical and radiologic outcomes after treatment

Two patients (no. 1 and 12) underwent lobectomy because of uncertainty in the clinical diagnosis and had no radiographic evidence of recurrence after surgery. Ten patients (no. 1–10) required induction with intravenous amphotericin B, and six of them subsequently received oral fluconazole. Two patients (no. 9 and 12) received only oral fluconazole. The duration of oral fluconazole in eight patients ranged from 4–52 months (median, 33 months).

Because of obstructive hydrocephalus, two patients (no. 1 and 3) required ventriculoperitoneal shunts. Patient no. 3 also had permanent hearing loss and visual impairment. Patient no. 6 with extensive pulmonary cryptococcosis developed respiratory failure shortly after admission and required mechanical ventilation for two months. The patient subsequently improved but eventually required home oxygen therapy. Other symptomatic patients had clin-
ical improvement within a month of treatment. All patients remained alive at the time of hospital discharge (n=2) or their last visit (n=9), ranging from two months to 107 months (median, 42 months).

Eight of the remaining patients had available follow-up chest CT scans and/or chest radiographs, with a range of 0.5–100 months (median, 29 months) after antifungal treatment. Based on available chest CT and/or chest radiographs in each period, radiologic resolution following antifungal therapy was variable within the first six months (Table 2). Half of the cases showed slight improvement (<50%) of parenchymal abnormalities, including endobronchial obstruction and postobstructive pneumonitis, within one month of treatment. Further but gradual improvement along with interval development of air bronchograms and/or bronchiectatic changes (n=4), cavitation (n=4), and/or fibrotic changes (n=5) in the resolving lesions was usually observed thereafter.

Notably, one patient (no. 8) developed a small cavity, groundglass opacity, and tree-in-bud appearance at the right upper lobe four months after antifungal treatment. The lesions subsequently proved to be due to coexisting tuberculosis. After dual treatment with antifungal and antituberculous drugs, there was partial resolution of both pulmonary tuberculosis and cryptococcosis along with gradual reduction in nodal sizes (Fig. 3c, 3d).

In six patients, substantial improvement (>75%) along with complete resolution of pericardial (Fig. 2b) and pleural involvement were evident after 12 months of treatment. However, all of them had some residual pulmonary parenchymal and/or nodal abnormalities, as well as fibrotic and/or bronchiectatic changes in the affected regions after 24 months of treatment. As shown in Fig. 4c, 4d, there was subsequent development of several subpleural and/or intraparenchymal cysts in the right lung, diffuse groundglass opacity in the remaining lung parenchyma, smooth right pleural thickening, and interval calcifications of bilateral lower paratracheal nodes in one patient (no. 6).

**Discussion**

To the best of our knowledge, our study is the first original study describing pulmonary cryptococcosis among immunocompetent patients in Southeast Asia. As shown in our study, our patients had a wider range of clinical and radiologic manifestations, ranging from asymptomatic colonization to disseminated infection than those reported previously. In contrast to the previous studies from other countries in which most cases were asymptomatic and had isolated or limited pulmonary involvement (3–6, 8–11), most of our patients had either symptomatic or disseminated infection with more aggressive and/or atypical radiologic manifestations at the initial presentation. Although most of our patients also had unilobar pulmonary involvement, a finding that was different from previous studies showing multiple lesions, multilobar, or bilateral pulmonary involvement (5–10), and the sizes of the pulmonary nodules, masses and/or consolidations in our patients were more variable, ranging from <1 cm up to 15 cm in greatest diameter. The distinct peripheral, subpleural, and lower lung predominance in the present study was similar only to the findings reported by Fox and Müller (6) and Yang et al. (8) but was in contrast to other previous studies showing upper or middle lung predominance mimicking tuberculosis (5, 10) or no lobar predilection (4, 9).
Cavitation and air-filled bronchograms within nodules or consolidation, observed in 58.3% of our cases, have been variably demonstrated in previous studies, ranging from 0% to 42% of cases (4–11, 15). Nonenhanced, low-attenuation areas within the areas of consolidation or masses, previously shown to represent gelatinous collections of large numbers of fungal organisms or rarely ischemic necrosis (12, 15, 16) were also frequently demonstrated on CT images in our study but have rarely been described (17). Calcification within the pulmonary lesion, as shown in one of our cases, is also rare (14, 15, 17, 18). Surrounding groundglass opacity or the CT halo sign, as found in our study, and isolated groundglass opacity (6, 8–11, 17) can be observed. Although centrilobular or satellite nodules have been described (6, 8), tree-in-bud appearance was observed neither in the present nor in previous studies (6–9). Therefore, we suggest that the presence of nonenhanced low-attenuation areas within the areas of consolidation or mass having peripheral, subpleural and lower lung predominance, as shown in the present study, should raise the concern for pulmonary cryptococcosis, particularly in a patient presenting with meningitis.

Endobronchial obstruction in association with other pulmonary abnormalities, similar to our cases, have been described (14, 19), and, unexpectedly, appeared to be more common in immunocompetent patients (19). However, the incidence of direct airway involvement remains unknown (19).

Of interest, more than half of our cases had extrapulmonary findings, including lymphadenopathy, vascular compression, and pericardial or pleural involvement, at the initial presentation. Although lymphadenopathy can be found on CT (5, 6, 8) and can occur in up to two-thirds of immunocompetent patients presenting with cryptococcal pneumonia (15), massive lymphadenopathy causing vascular compression, similar to that in one of our patients, has been reported in only one case in the Korean literature (20). Calcifications of the lymph nodes (14, 15, 17) and/or intracerebral lesions, as found in two of our patients at the initial presentation and after antifungal therapy, are also unusual (21). However, it should be noted that cryptococcosis and tuberculosis might coexist, as presented in one of our cases and in the recent study of Huang et al. (22). Therefore, it might be impossible to exclude other coexisting infections, particularly in the tuberculosis endemic region (22).

Pericardial involvement, as demonstrated in one of our cases, is rarely demonstrated in immunocompetent or immunocompromised hosts (12, 13, 23). As with previous studies, pleural effusion is also uncommon, found in less than 10% of cases, and is often small in size (3–10, 18).

Because *C. neoformans* had been isolated from soils in various parts of Thailand (24), patients who had been working in agriculture or construction fields might have been exposed to a potentially large amount of the fungus, a finding that might explain the relatively extensive disease among Thai patients (12, 13). Different from previous studies in which *C. gattii* occurs mainly in immunocompetent patients in subtropical or tropical countries (1, 6, 25), *C. neoformans var. grubii* (serotype A) was found to be the major organism in the present study, most likely due to a higher prevalence of this variety in Thailand (26). Nevertheless, greater outdoor exposure in men and suppression of the *in vitro* growth of *C. neoformans* by estrogens might explain the male predilection observed in our study and in most of the previous studies (2, 6, 8, 9) and might explain the sporadic case reports from Thailand (12–14).

The presence of poorly formed granulomas in approximately half of our patients, instead of well-formed granulomas with epithelioid or multinucleated giant cells typically found in immunocompetent hosts (6, 16), might reflect the difference or minor functional defect in the host’s immune response (27), posing a risk for extensive disease or dissemination in an apparently immunocompetent patient. Therefore, we speculated that the variation in the amount of fungal exposure (3, 12, 15–18), the differences in *Cryptococcus* varieties and their virulence factors in different geographic regions (1, 2, 6, 26), and the variation of an individual host’s immune response (2, 16, 27) might influence the difference in clinical features and course of the infection among our patients. However, incomplete data on *Cryptococcus* species or serotypes, histopathological findings, and immunological studies in the present and previous studies precluded further analysis. The issues regarding the effect of *Cryptococcus* varieties on clinical and radiologic features and the risk of extrapulmonary dissemination need further determination.

Following antifungal therapy, we found variable radiologic resolution within the first six months, and substantial improvement (>75%) was usually evident after 12 months of treatment, compared with the more rapid clinical response. As demonstrated in the current and a few recent studies (3, 9, 11), it should be noted that the incomplete and/or gradual radiologic resolution with some residual abnormalities and/or fibrotic scars was a frequent observation among the nonsurgical cases. We speculated that the presence of granulomatous inflammation with fibrosis or a fibrocaseous center demonstrated in the current study and in previous studies (3, 6, 10, 12, 16, 17) should be attributed to a slow regression and incomplete resolution of the radiologic abnormalities and to the development of fibrotic changes, similar to those found in tuberculosis (28). Interval development of cavitation, air bronchograms and/or bronchiectatic changes within the resolving lesions, found in the present study and in
previous studies (6), might be due to dislodgement or drainage of necrotic lung parenchyma and/or gelatinous collection of the fungal organisms. Check-valve bronchiolar obstruction or diffuse pulmonary fibrosis may lead to thin-walled cysts or pneumatocele formation (29, 30) as demonstrated in one of our patients.

As demonstrated in the current study and in previous studies (3, 9, 11), complete radiologic resolution can be achieved only after surgical resection. In an operable case with isolated or persistent pulmonary involvement, particularly in cases with an uncertain diagnosis, surgical intervention may be justified to obviate the need for long-term antifungal treatment (11, 25). Nevertheless, the specific treatment and optimal duration of antifungal therapy for pulmonary cryptococcosis in immunocompetent patients are beyond the scope of our study.

The main limitation in our study was the small number of patients. However, this emphasized the rare occurrence of pulmonary cryptococcosis among immunocompetent patients. Its retrospective nature was another important limitation. Therefore, the initial radiologic images, including the CT technique, as well as types and the timeline of follow-up imaging studies were incomplete and were quite variable among our cases. Nonetheless, our study still provided some useful information that should aid in the diagnosis, treatment, and follow-up of the specific disease entity.

In conclusion, we observed a wide range of clinical and radiologic manifestations, ranging from asymptomatic colonizaion to disseminated infection, of pulmonary cryptococcosis among Thai immunocompetent patients. Atypical and/or aggressive pulmonary and extrapulmonary involvement, mimicking other more common diseases, was also common. Our findings were different from those reported from other geographic regions; thus, both radiologists and clinicians should be aware of these possibilities. Although the radiologic findings are not specific, the presence of nonenhanced low-attenuation areas within the areas of consolidation or mass with peripheral, subpleural and lower lung predominance and the lack of tree-in-bud appearance on CT should raise concern for pulmonary cryptococcosis, particularly in a patient presenting with meningitis. Importantly, the radiologic resolution of pulmonary cryptococcosis following antifungal therapy was usually gradual and incomplete. Some residual abnormalities, including bronchiectasis, cavitation and/or fibrotic scars, were frequently observed, most notably on CT. Based on our experiences, chest CT may play a role in the diagnostic evaluation and follow-up of severe cases with atypical or aggressive radiologic findings and those requiring long-term antifungal treatment.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References