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Original article

Recurrence of chronic pulmonary aspergillosis after discontinuation of maintenance treatment by antifungal triazoles

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ABSTRACT

Objective: To assess the prevalence and risk factors of recurrence of chronic pulmonary aspergillosis (CPA) after discontinuation of antifungal triazoles.

Method: We reviewed the medical records of CPA patients who achieved resolution of clinical and radiographic manifestations and stopped taking antifungal triazoles between June 2006 and June 2012 at Tokyo National Hospital. We evaluated whether there was CPA recurrence within 1 year after treatment cessation and investigated risk factors for relapse. The association of anti-Aspergillus antibody conversion with CPA recurrence was also reviewed.

Results: A total of 39 patients were included in this study and there was CPA recurrence in 14 patients. Compared with the Non-recurrence group, the Recurrence group exhibited 1) younger age ($p = 0.017$), 2) more than one lung lobe affected by CPA more frequently ($p = 0.008$), 3) longer duration needed to remit manifestations of chest radiograph ($p = 0.031$), 4) longer antifungal treatment duration ($p = 0.042$). The present study did not reveal an association between negative conversion of serum anti-Aspergillus antibody and recurrence risk. Multivariate logistic regression analysis revealed that patients with CPA with affected area of more than one lung lobe had increased risk (odds ratio, 10.20; 95% confidence interval, 1.49–69.77; $p = 0.018$).

Conclusion: CPA recurrence can be seen in about one-third of cases after discontinuing azole treatment. We should make decisions about treatment duration and follow up depending on the severity of each case, particularly on the expansion of CPA-affected area.

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1. Introduction

Chronic pulmonary aspergillosis (CPA) is a slow progressive disease caused by destruction of the lung by *Aspergillus* spp. CPA occurs in patients with underlying lung disease or mild immunosuppression and needs relatively long treatment duration. Although treatment in the acute phase consists of administration of various antifungal drugs such as liposomal amphotericin B and voriconazole, maintenance treatment consists of a prescription of

oral itraconazole or voriconazole in the majority of cases [1,2]. There have been some recommendations about the duration of maintenance treatment. Guidelines published by the Infectious Diseases Society of America say that antifungal treatment may be required for the 'long-term, perhaps lifelong' [3]. The American Thoracic Society statement recommends that treatment should continue until resolution or stabilization of all clinical and radiographic manifestations [1]. Treatment durations in previous studies evaluating the effectiveness of triazoles were within 1 year [8,11–13]. However, there have been few studies reporting the appropriate duration of treatment, prevalence of relapse and risk factors for recurrence.

In an attempt to reveal the prevalence of CPA recurrence after treatment discontinuation and risk factors for CPA recurrence, we performed a retrospective study of CPA patients at Tokyo National

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Hospital. We also evaluated whether conversion of serum anti-*Aspergillus* antibody was associated with CPA relapse because there have been several reports referring to the relationship between the titer of the antibody and stage of disease [4,5].

2. Patients and methods

2.1. Design

This was a retrospective cohort study evaluating CPA patients who were treated at Tokyo National Hospital. The hospital was found as sanatorium for tuberculosis patients and now plays a role as a core hospital for community health care. In patients with CPA, we reviewed whether there had been CPA recurrence within 1 year after treatment cessation and investigated risk factors for relapse. A patient was considered to have recurrence of CPA when new infiltration or wall thickening of lung cavity appeared at the site diagnosed as aspergillosis previously. We excluded cases in which other lung diseases including infection with other pathogens were considered. We divided the CPA patients into the Recurrence group and Non-recurrence group and determined risk factors for recurrence by comparing the clinical and radiologic manifestations mentioned below.

2.2. Patients

We investigated the medical records of CPA patients who achieved resolution of clinical and radiographic manifestations and discontinued antifungal triazoles between June 2006 and June 2012 at Tokyo National Hospital. Patients with CPA were defined as patients with the presence of: 1) underlying lung disease, 2) one or more of the following evidences suggesting *Aspergillus* infection: positive serum anti-*Aspergillus* antibodies, positive cultures of *Aspergillus* spp. from respiratory specimens including sputum and bronchial wash, or histological evidences of *Aspergillus* spp. in lung biopsy specimens, 3) slowly progressive chest CT abnormalities suggesting spp. infection such as lung infiltrations, thickening of cavity wall and fungus ball. Since meeting the “criteria 2”) was a prerequisite for the inclusion of this study, we selected patients using database of serum anti-*Aspergillus* antibody, pathological examinations and microbiological tests between January 2001 and June 2012, and reviewed treatment course examining whether treatment completed. Although triazole discontinuation might have been decided with various additional reasons by the physicians, we included, in this study, only those patients who met the recommendation for the discontinuation, i.e. clinical and radiological resolution. Patients were excluded if they discontinued medication for reasons other than CPA improvement or underwent resection of *Aspergillus* infection sites.

We checked chest images and clinical information including patients' sex, age, clinical symptoms, comorbidities, smoking history, pre-existing pulmonary disease, medication history and treatment duration. Treatment duration included not only the period of triazole administration, but also the duration of induction therapy by other antifungal drugs including intravenous triazole, micafangin and amphotericin B. Chest CT scans obtained before the initiation of treatment were reviewed; we evaluated the presence of fungal ball and whether the pathological change by aspergillosis extended over more than one lung lobe. We also evaluated the period needed to achieve remission of radiological findings of CPA. A patient was considered to have radiological remission if the infiltration or thickening of lung cavity improved and became stable on chest radiographs.

Table 1
Characteristics of the CPA patients.

	All (n = 39)	Recurrence (n = 14)	Non-recurrence (n = 25)	P value ^a
Median age (years old)(range)	59 (35–84)	55 (35–76)	61 (40–84)	0.017*
Never smoker (%)	8 (21%)	5 (36%)	3 (12%)	0.109
Male (%)	31 (79%)	9 (64%)	22 (88%)	0.109
BMI (kg/m ²) (range)	18.8 (14.1–26.2)	18.5 (14.9–21.1)	19.4 (14.1–26.6)	0.209
Preexisting lung disease				
Tuberculosis sequelae (%)	21 (54%)	9 (64%)	12 (48%)	0.504
Emphysema (%)	18 (46%)	7 (50%)	11 (44%)	NS
Bulla (%)	3 (8%)	0 (0%)	3 (12%)	0.540
NTM disease (%)	2 (5%)	1 (7%)	1 (4%)	NS
Postoperation (%)	2 (5%)	1 (7%)	1 (4%)	NS
Underlying extrapulmonary disease				
Diabetes mellitus	6 (15%)	1 (7%)	5 (20%)	0.391
Coronary heart disease	2 (5%)	0 (0%)	2 (8%)	0.528
HIV infection	1 (3%)	1 (7%)	0 (0%)	0.359
Positive sputum culture (%)	10 (26%)	2 (14%)	8 (32%)	0.279
Positive bronchial washing culture (%)	1 (3%)	0 (0%)	1 (4%)	NS
Hypha proven by TBLB (%)	2 (5%)	1 (7%)	1 (4%)	NS
Positive serum <i>Aspergillus</i> antibody	34 (87%)	12 (86%)	22 (88%)	NS
CT findings				
<i>Aspergilloma</i>	4 (10%)	2 (14%)	2 (8%)	NS
Expansion of CPA affected area >1 lung lobe	19 (49%)	11 (79%)	8 (32%)	0.008**

BMI: body mass index, NTM: nontuberculous mycobacteria, TBLB: transbronchial lung biopsy, CPA: chronic pulmonary aspergillosis.

* $p < 0.05$, ** $p < 0.01$.

^a The significance of differences between the Recurrence and Non-recurrence groups.

2.3. Anti-*Aspergillus* antibody

We compared the serum anti-*Aspergillus* antibody level at the times of treatment initiation and treatment completion. Whether negative conversion of anti-*Aspergillus* antibody by treatments affected CPA recurrence was evaluated. The serum antibody level was measured by the Ouchterlony method [6,7]. After patients' serum and *Aspergillus fumigatus* antigen were placed in adjacent wells cut in a diffusion gel, visible precipitation, indicating the presence of anti-*Aspergillus* antibody, was checked. The antibody was considered positive when the serum reacted either *A. fumigatus* culture filtrate antigen or *A. fumigatus* somatic antigen, 2 mg/ml and 20 mg/ml for each.

2.4. Statistical analysis

Data are shown as number of patients with percentage. Age, treatment duration and time needed for resolution of chest radiograph are shown as median and range.

Fisher's exact or Chi-squared test and Mann Whitney *U* test were used to compare patients' characteristics between the Recurrence and Non-recurrence groups. The risks for recurrence of CPA were evaluated by logistic analysis. $P < 0.05$ was considered as statistically significant.

2.5. Ethics

This study was reviewed and approved by the ethics committee of the National Hospital Organization, Tokyo National Hospital, and was conducted according to principles expressed in the Declaration of Helsinki.

3. Results

A total of 39 CPA patients (31 males and 8 never smokers) were eligible for this study. All patients were followed one year after treatment discontinuation without any deaths. Patients' clinical characteristics, laboratory data, microbiological findings and chest radiological findings are shown in Table 1. Age at the time of treatment initiation ranged from 35 to 84 years (median 59 years). No patient received immunosuppressive drugs including corticosteroids. There was one HIV-infected patient, but his immunity recovered by antiretroviral therapy when the diagnosis of aspergillosis was made. There were no patients with cancer. Eleven patients had positive *Aspergillus* spp. culture (10 sputum samples, 1 bronchial washing sample). The cultured *Aspergillus* species from 2 sputum samples and 1 bronchial wash was *Aspergillus niger*, and the others were *A. fumigatus*. Preexisting lung diseases are shown in Table 1. Tuberculosis sequela was seen most frequently (21 cases; 54%), followed by emphysema (18 cases; 46%).

Treatment duration ranged from 44 days to 3014 days, and the median duration was 778 days. There were several patients who changed prescriptions within the triazoles. Three patients switched from itraconazole to voriconazole because itraconazole was not effective. On the other hand, there were 2 patients who changed medication from voriconazole to itraconazole, because of side effects in 1 case and of ineffectiveness in the other. Finally, the triazole antifungal drug that was mainly used was itraconazole in 33 patients (85%) and voriconazole in 6 patients (15%) (Table 2). Itraconazole was prescribed as 200 mg once daily by capsules while voriconazole was prescribed as 200 mg twice daily in one patient and 150 mg twice daily in other patients.

In the present study, 14 patients experienced CPA recurrence (Table 1). The duration between treatment cessation and recurrence ranged from 47 days to 263 days (median was 160 days). In all 14 patients, manifestation of chest radiograph worsened, and 12 patients complained of symptoms at the time of recurrence. Table 1 shows the clinical and radiological characteristics between the Recurrence and Non-recurrence groups. Although there were no significant differences in smoking history, comorbidities and pre-existing lung disease, age was younger in the Recurrence group ($p = 0.017$). The Recurrence group patients had expansion of aspergillosis to more than one lung lobe on chest CT more frequently ($p < 0.01$) and needed longer duration to remit manifestations on chest radiograph in the treatment course ($p = 0.031$). The total antifungal treatment duration was also longer in the Recurrence group ($p = 0.042$). Triazole medication was restarted in

all patients in the Recurrence group, and manifestation of clinical symptoms and chest radiograph findings improved in 13 patients.

We investigated the association of recurrence risk with serum anti-*Aspergillus* antibody (Fig. 1). Serum anti-*Aspergillus* antibody was positive in 34 patients (87%) at the start of treatment. Among them, there were 16 patients whose anti-*Aspergillus* antibody became negative at treatment completion. One year after treatment end, although fewer patients experienced CPA recurrence in the negative conversion group compared with the positive group (32% vs. 50%), the difference was not significant ($p = 0.447$). In the negative conversion group of patients, anti-*Aspergillus* antibody became positive after CPA relapsed.

Because differences between the Recurrence and Non-recurrence groups were seen in age, expansion of aspergillosis on chest CT, total treatment duration and duration to remission on chest images as mentioned above, we evaluated these as risk factors by logistic regression analysis. The results are shown in Table 3. Expansion of aspergillosis and age were revealed as risk factors for reoccurrence. However, multivariate analysis indicated only expansion of the CPA-affected area to more than one lung lobe as a risk factor for recurrence.

4. Discussion

CPA is a persistent infectious disease that needs long treatment duration, and some of the patients need antifungal oral triazoles, e.g. itraconazole and voriconazole, as maintenance therapy for life long [3,8]. Although we need to clarify criteria for the possible completion of the triazole therapy and risks of CPA recurrence after the treatment completion, the data has been very scarce. We reviewed patients who discontinued triazole medication with remission of CPA to examine what patients' characteristics affect CPA recurrence, and tried to reveal who should be followed more carefully after treatment completion.

The present study revealed that there was CPA recurrence in one-third of patients within one year after treatment completion and indicated that CPA affected area was the only factor related to the relapse by the multivariate logistic regression analysis, other than difference of the age that was shown as possible risk by univariate analysis. The patients of the Recurrence group needed longer duration to remit on chest radiograph and they were treated for longer duration, although these characteristics were not proved as risks statistically. These trends seem to mean that more severe and refractory cases tended to relapse. Other studies have reported several CPA prognostic factors including body mass index [9] and nontuberculous mycobacteria co-infection [10], which were not revealed as significant factors for the relapse in this study probably because patients not achieving remission by the treatment were excluded in this study.

Different from several reports indicating the utility of the antibody for evaluating disease control [4,5], the present study did not reveal association of negative conversion of the antibody with the risk of the recurrence. We measured serum anti-*Aspergillus* IgG antibody that reflects disease control more weakly compared with serum IgA antibody according to the study by van Rens et al. We needed more number of patients to clarify the utility of anti-*Aspergillus* IgG antibody.

In this study anti-*Aspergillus* antibody test seemed useful to predict relapse of aspergillosis. Whereas negative conversion of the antibody by treatment was not sufficient enough to support treatment discontinuation, positive conversion during follow-up without triazole treatment was a good marker indicating relapse of the aspergillosis, together with symptoms and radiological deterioration. To prove association of positive conversion of the antibody with CPA recurrence, we needed to show that the

Table 2
Treatment of CPA patients.

	All (n = 39)	Recurrence (n = 14)	Non-recurrence (n = 25)	P value ^a
Main triazole prescribed for maintenance therapy				
itraconazole ^b (%)	33 (85%)	11 (79%)	22 (88%)	NS
voriconazole ^c (%)	6 (15%)	3 (21%)	3 (12%)	NS
Treatment duration (days)(range)	776 (44–3014)	999 (502–1964)	778 (44–3014)	0.042*
Treatment duration needed to achieve radiological remission (days)(range)	147 (7–876)	177 (51–876)	140 (7–779)	0.031*

* $p < 0.05$.

^a The significance of differences between the Recurrence and Non-recurrence groups.

^b Itraconazole capsules 200 mg once daily in all patients.

^c Voriconazole tablets 200 mg twice daily in one patient and 150 mg twice daily in other patients.

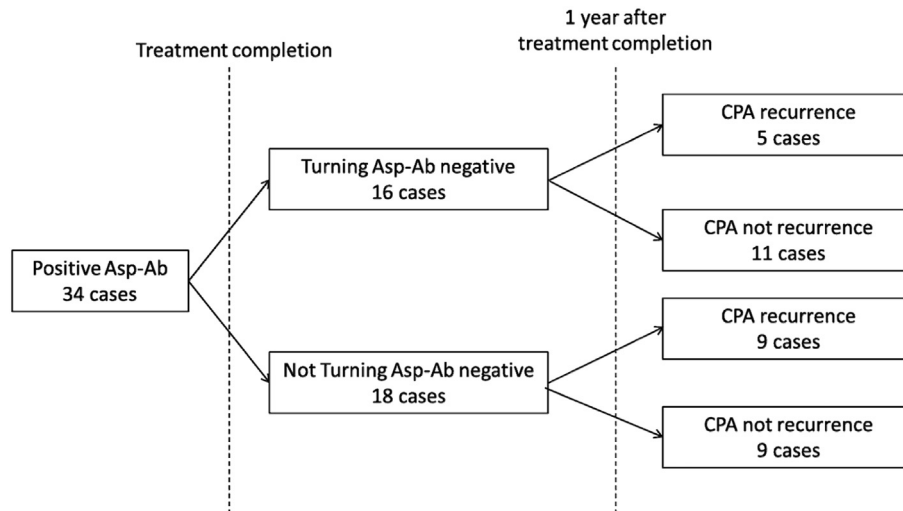


Fig. 1. Association of CPA recurrence within 1 year after treatment completion with serum *Aspergillus* antibody conversion. Asp-Ab: anti-*Aspergillus* antibody.

antibody remained negative in the Non-recurrence group of patients in whom anti-*Aspergillus* antibody was not measured after treatment completion in the present study. A further study that examines the antibody with schedule after treatment will be helpful.

One of the limitations of this study was that we could not determine the reasons for the cessation of the triazole treatment for each case. Although guidelines recommend to treat until resolution of clinical and radiological findings [1] and the cases elicited in the present study achieved those, physicians decided to complete treatment considering not only change of radiological manifestations and clinical resolutions, but also treatment durations, serum marker including anti-*Aspergillus* antibody, and other patients' characteristics such as underlying lung diseases and immunosuppression. The reason for the decision of treatment completion might have influenced the course and relapse of the disease, which we could not be defined in this study.

Second limitation was that the diagnosis as recurrence was made subjectively based mainly on radiological findings and symptoms. However, the evaluation was considered accurate because 1) the majority (13/14) of the Recurrence group was remitted by triazole retreatment and 2) the anti-*Aspergillus* negative conversion group of patients exhibited positive conversion of the antibody at the time of relapse.

Finally, it was unclear whether our observation duration, i.e. one year after treatment completion, was appropriate. Considering that not a few recurrences occurred in the second half of the observation period, we might have needed longer follow-up to determine when

the CPA tended to relapse frequently and how many patients experienced recurrence finally.

One of the unique points of the present report was relatively longer treatment duration reaching 778 days as a median, compared with previous studies investigating effectiveness of triazole therapy for CPA in which the duration was within about 1 year [8,11–13]. Triazole-resistant *Aspergillus* spp. is an increasing clinical problem [14] that can cause refractory diseases [15] and it has also been reported that the presence of triazole treatment history and longer treatment duration induces the resistance [16,17]. Tashiro et al. reported that triazole MICs against *A. fumigatus* clinical isolates increased in proportion to the duration of itraconazole treatment [16]. The longer treatment duration could have affected the prevalence of disease recurrence by increasing *Aspergillus* spp. resistance against triazole therapy in this study. We did not measure drug sensitivity of the *Aspergillus* spp. isolates. However, we considered triazole resistance as uncommon since restart of triazole medication improved majority of CPA relapse.

The other feature of the patients' characteristics was that tuberculosis sequelae were seen more frequently than that reported in the previous study [18]. The background of our hospital, founded as a sanatorium, might have affected the underlying disease variation.

The present study showed that CPA patients in whom aspergillosis affected more than one lung lobe had increased risk for CPA recurrence and needed more careful follow-up. In addition, conversion of negative anti-*Aspergillus* antibody to positive during follow-up observation without treatment could be a marker indicating CPA relapse. To investigate more accurate risk factors for recurrence, a prospective study defining CPA remission and treatment completion should be conducted.

Conflict of interest

None.

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Table 3
Logistic analysis of the risk for CPA recurrence.

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p value	OR (95%CI)	p value
Age	0.93 (0.86–0.99)	0.033*	0.92 (0.84–1.01)	0.064
Expansion of CPA affected area >1 lung lobe	7.79 (1.69–7.79)	0.008**	10.20 (1.49–69.77)	0.018*
Treatment duration needed to achieve radiological remission	1	—	1	—
Treatment duration	1	—	1	—

CPA: chronic pulmonary aspergillosis.

* $p < 0.05$, ** $p < 0.01$.

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