

# Cerebral Aspergillosis and Cerebral Candidiasis; A Retrospective Analysis of Clinicopathologic Features in Ramathibodi Hospital

Noppadol Larbcharoensub MD\*,  
Somphong Wongwichai BSc\*, Piriyaoporn Chongtrakool PhD\*\*,  
Atthaporn Boongird MD\*\*\*, Asawin Noinang MD\*\*\*,  
Siriorn Paritpokee Watcharananan MD\*\*\*\*, Supoch Tunlayadechanont MD\*\*\*\*\*,  
Rawiphan Witoonpanich MD\*\*\*\*\*, Suchart Phudhichareonrat MD\*\*\*\*\*

\* Division of Anatomical Pathology, Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

\*\* Division of Microbiology, Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

\*\*\* Division of Neurosurgery, Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

\*\*\*\* Division of Infectious Disease, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

\*\*\*\*\* Division of Neurology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University  
\*\*\*\*\* Department of Pathology, Prasat Neurological Institute, Bangkok, Thailand

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**Objective:** Determine and compare the clinicopathological findings of cerebral aspergillosis with cerebral candidiasis.

**Material and Method:** The medical records with cerebral aspergillosis and cerebral candidiasis in Ramathibodi Hospital between January 1997 and December 2008 were analyzed. The criterion for the diagnosis of cerebral aspergillosis and cerebral candidiasis was the evidence of fungal elements from histopathologic section. The age, gender, neurological manifestations, duration of symptom, associated underlying disease, predisposing risk factor, laboratory data, extent of systemic organ involvement and treatment outcome were analyzed.

**Results:** The present study included cerebral aspergillosis (n = 41) and candidiasis (n = 15). There were 23 male and 33 female patients. The mean and median ages at diagnosis were 39.7 and 45 years, respectively (range, 1 month to 87 years). The clinical presentations included alteration of consciousness (69.6%), fever (60.7%), weakness of the extremity (14.3%), cranial nerve palsy (12.5%), headache (12.59%) and seizure (5.4%). One third of the cases had underlying hematologic malignancy. The cerebral aspergillosis and cerebral candidiasis were associated with corticosteroids treatment in 32.1%. The frequent associated sites of fungal infection included the lungs (73.2%), alimentary tract (33.9%) and sinonasal tract (19.6%).

**Conclusion:** A diagnosis of cerebral aspergillosis and cerebral candidiasis requires a high index of suspicion especially in immunocompromised patients who presented with alteration of consciousness, fever, focal neurological deficit, headache, and seizure. The patients with cerebral aspergillosis and cerebral candidiasis manifest with similar clinicopathologic features. However, the sinonasal tract infection and abscess formation are more common in cerebral aspergillosis. Associated alimentary tract infection is commonly seen in cerebral candidiasis.

**Keywords:** Cerebral mycosis, Aspergillosis, Candidiasis, Fungus, Brain abscess

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**Correspondence to:**

Larbcharoensub N, Department of Pathology, Ramathibodi Hospital, Mahidol University, 270 Rama VI Rd, Ratchathewi, Bangkok 10400, Thailand.

Phone: 0-2354-7277, Fax: 0-2354-7266

E-mail: Noppadol\_1@hotmail.com

Cerebral mycosis has emerged as a catastrophic condition with high morbidity and mortality. Cerebral mycosis is difficult to be diagnosed and encompasses a wide clinical spectrum of disease<sup>(1)</sup>. Cerebral mycosis can be further subdivided into meningitis, ventriculitis, venous sinus thrombosis, vasculitis, cerebritis, abscess and granuloma. The diagnosis largely relies on clinical, radiological, histological and microbiological confirmation of fungal organism. Most of cerebral mycoses in non-human immunodeficiency virus (non-HIV)-infected-patients cause by *Aspergillus* spp and *Candida* spp<sup>(2,3)</sup>. At present, there are only a few epidemiological data regarding the fungal agents causing cerebral aspergillosis and cerebral candidiasis in Thailand<sup>(4-6)</sup>. The purpose of the present study was to determine and compare the clinicopathological findings in 56 cases of histologically verified cerebral aspergillosis and cerebral candidiasis seen in Ramathibodi Hospital.

#### Material and Method

This was a retrospective study of cerebral aspergillosis and cerebral candidiasis diagnosed on surgical and/or autopsy material from the Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, over the period of 12 years (1997-2008). All cases were seronegative for HIV.

All tissues were formalin-fixed and routinely processed for paraffin-embedding. Tissue sections, 4 mm thick, were cut. Routine hematoxylin and eosin (H&E)-stained sections were examined for histopathologic findings. Fungal morphology was delineated using special stains *i.e.* Gomori's methenamine silver (GMS), and periodic acid Schiff (PAS). The histopathologic diagnosis of cerebral aspergillosis and cerebral candidiasis were reviewed. Information obtained from the medical records including age, gender, neurological manifestations, duration of symptoms, associated underlying disease, predisposing risk factor, laboratory data, extent of systemic organ involvement and treatment outcome were analyzed. Patients were grouped based on causative fungal organisms. The results were presented in frequency and percentage or mean  $\pm$  SD for continuous data. A two-tailed Fisher's exact test was used to evaluate statistical significance between groups. The present study was approved by the committee on human research at Faculty of Medicine Ramathibodi Hospital (ID12-51-29).

#### Results

##### Patient characteristics

Fifty-six cases composing of 13 surgical cases and 47 autopsy cases met the inclusion criteria.

**Table 1.** Patients' characteristics with cerebral aspergillosis and cerebral candidiasis (n = 56)

Detail	Cerebral aspergillosis (n = 41)		Cerebral candidiasis (n = 15)		p-value
	No. of patients	Percent	No. of patients	Percent	
Mean age (years) $\pm$ SD	38.57 $\pm$ 23.06	-	42.81 $\pm$ 23.93	-	-
Gender					0.551
Male	18	43.9	5	33.3	-
Female	23	56.1	10	66.7	-
Duration of chief complaint					-
$\leq$ 1 week	31	75.6	13	86.6	-
1 week to 1 month	5	12.2	1	6.7	-
$\geq$ 1 month	5	12.2	1	6.7	-
Mean temperature at admission ( $^{\circ}$ C) $\pm$ SD	37.66 $\pm$ 0.90	-	37.89 $\pm$ 1.12	-	-
$\geq$ 38 $^{\circ}$ C	16	39.0	8	53.3	0.375
Neutropenia	10	24.4	5	33.3	0.514
Corticosteroids treatment	14	34.1	4	26.7	0.751
History of organ transplantation	5	12.2	1	6.7	1.000
Surgical treatment	12	29.3	1	6.7	0.150
Antifungal treatment	22	53.7	6	40.0	0.547
Mortality	36*	90.0	15	100.0	0.308

\* Total 40 cases, loss follow-up 1 case

Four cases were complete both surgical and autopsy studies. There were 41 cases of cerebral aspergillosis, and 15 cases of cerebral candidiasis, affecting patients between 1 month and 87 years with the mean and median ages of 39.7 and 45 years, respectively. There were 23 males and 33 females (Table 1).

### Clinical characteristics

The onset of symptoms ranged from one day to two months, 78.6% of cases were shorter than one week and 10.7% were longer than one month. The body temperatures (at the admission time) varied from 36°C to 40.5°C. Forty-three percent had a body temperature higher than 38°C. The mean and median body temperatures (at admission) were 37.7°C and 37.8°C, respectively. The details of patients' characteristic are presented in Table 1. The initial neurological symptoms were alteration of consciousness (39 cases, 69.6%), fever (34 cases, 60.7%), weakness of the extremity (8 cases, 14.3%), cranial nerve palsy (7 cases, 12.5%), headache (7 cases, 12.5%), seizure (3 cases, 5.4%) and blurring of vision (2 cases, 3.6%), are listed in Table 2.

### Underlying predisposing condition

Hematologic disease in 25 (44.6%) patients was the commonest underlying disease and 19 of 25 patients (76%) had hematologic malignancy including myeloproliferative and lymphoproliferative disorders. The other underlying diseases included systemic lupus erythematosus (SLE) (14 cases, 25%) and diabetic mellitus (7 cases, 12.5%) as shown in Table 3.

In the present series, neutropenia (neutrophils in peripheral blood < 1,000 cells/mm<sup>3</sup>) was described in 26.8% of cases. Another factor in the development

of cerebral aspergillosis and cerebral candidiasis was immunosuppression due to corticosteroids administered (32.1%). Six cases had a history of organ transplantation and placed on immunosuppressive agents. Associated opportunistic cytomegalovirus (CMV) infection and tuberculosis were represented in seven and one cases, respectively (Table 3).

### Organ involvement

The extent of systemic organ involvement included lungs (41 cases, 73.2%), cardiovascular system (19 cases, 33.9%), alimentary tract (19 cases, 33.9%), and others, as shown in Table 4. Evidence of maxillary, ethmoidal, and sphenoid sinusitis was present in 11 patients (19.6%). In four patients, orbital changes were evident which included enophthalmitis and periorbital cellulitis. All of sinonasal tract infections were caused by *Aspergillus* spp, documented by histopathology.

### Pathology

Intracranial disease on radiographic and/or autopsy findings included cerebritis (24 cases, 42.9%), vasculitis (20 cases, 35.7%), abscess (16 cases, 28.6%), meningitis (8 cases, 14.3%) and others, as shown in Table 5. The abscess formation commonly found in cerebral aspergillosis. Fungal vasculitis was characterized by the fungal organism in the vascular wall with inflammatory respond. Secondary cerebral infarction and/or hemorrhage may occur after vasculitis. The location of lesions commonly presented in the frontal lobe and others, as shown in Table 6. There was an uncommon case of mycotic aneurysm of the middle cerebral artery caused by *Aspergillus flavus*. This case was classified in the group of vasculitis.

**Table 2.** Neurological symptoms in the 56 patients with cerebral aspergillosis and cerebral candidiasis

Neurological symptoms	Cerebral aspergillosis* (n = 41)		Cerebral candidiasis* (n = 15)		p-value
	No. of patients	Percent	No. of patients	Percent	
Alteration of consciousness	27	65.9	12	80.0	0.513
Fever	24	58.5	10	66.7	0.759
Cranial nerve palsy	7	17.1	0	0	0.171
Headache	6	14.6	1	6.7	0.661
Weakness of the extremity	5	12.2	3	20.0	0.668
Seizure	3	7.3	0	0	0.556
Blurring of vision	2	7.3	0	0	0.556

\* The patients may have one or more than one neurologic symptoms

**Table 3.** Underlying predisposing conditions in the 56 patients with cerebral aspergillosis and cerebral candidiasis

Underlying diseases	Cerebral aspergillosis* (n = 41)		Cerebral candidiasis* (n = 15)		p-value
	No. of patients	Percent	No. of patients	Percent	
Myeloproliferative disorders	8	19.5	2	13.3	0.713
Lymphoproliferative disorders	5	12.2	4	26.7	0.229
Other hematologic diseases**	6	14.6	2	13.3	1.000
SLE	10	24.4	4	26.7	1.000
Diabetes mellitus	5	12.2	2	13.3	1.000
Hypertension	3	7.3	2	13.3	0.602
Cytomegaloviral infection	6	14.6	1	6.7	0.661
Chronic renal failure	2	4.9	1	6.7	1.000
Congenital immunodeficiency disease	1	2.4	1	6.7	0.468
Congenital heart disease	2	4.9	1	6.7	1.000
Dengue hemorrhagic fever	2	4.9	0	0.0	1.000
Cirrhosis	1	2.4	1	6.7	0.468
Solid malignancy	1	2.4	0	0.0	1.000
Myasthenia gravis	1	2.4	0	0.0	1.000
Tuberculosis	1	2.4	0	0.0	1.000

\* The patients may have one or more than one underlying diseases

\*\* Including thalassemia (documenting by hemoglobin typing) 2 cases, idiopathic thrombocytopenic purpura with splenectomy 2 cases and autoimmune hemolytic anemia 4 cases

SLE = systemic lupus erythematosus

**Table 4.** Infected organs in the 56 patients with cerebral aspergillosis and cerebral candidiasis

Underlying diseases	Cerebral aspergillosis* (n = 41)		Cerebral candidiasis* (n = 15)		p-value
	No. of patients	Percent	No. of patients	Percent	
Lung and respiratory tract	29	70.7	12	80.0	0.735
Cardiovascular system	16	39.0	3	20.0	0.220
Alimentary tract	10	24.4	9	60.0	0.024**
Sinonasal area	11	26.8	0	0	0.026**
Thyroid gland	9	22.0	3	20.0	1.000
Adrenal gland	4	9.8	0	0	0.565
Liver	4	9.8	3	20.0	0.370
Spleen	3	7.3	4	26.7	0.074

\* The patients may have one or more than one infected organs

\*\* p < 0.05

### Microbiology

Cultures were positive for fungal organisms in 38 cases out of 56 cases (67.9%) Multiple *Aspergillus* spp including *Aspergillus fumigatus* (17 cases), *Aspergillus flavus* (7 cases) and other species of *Aspergillus* (2 cases) were also implicated as causative agents. Multiple *Candida* spp were cultured including *Candida albicans* (11 cases), *Candida tropicalis*

(2 cases), *Candida glabrata* (1 case), *Candida parapsilosis* (1 case) and *Candida guilliermondii* (1 case). The details of microbiologic characteristics are presented in Table 7.

### Treatment

Overall, 13 patients received surgical treatment. Twenty-seven patients received intravenous

**Table 5.** Pathologic basis of disease in the 56 patients with cerebral aspergillosis and cerebral candidiasis

Chief symptoms	Cerebral aspergillosis* (n = 41)		Cerebral candidiasis* (n = 15)		p-value
	No. of patients	Percent	No. of patients	Percent	
Cerebritis	17	41.5	7	46.7	0.768
Abscess(es)	15	36.6	1	6.7	0.043**
Vasculitis	12	29.3	8	53.3	0.122
Meningitis	7	17.1	1	6.7	0.428
Ventriculitis	2	4.9	1	6.7	1.000
Venous sinus thrombosis	1	2.4	0	0	1.000
Granuloma	0	0	1	6.7	0.268

\* The patients may have one or more than one underlying diseases

\*\* p < 0.05

**Table 6.** Location of lesions in the 56 patients with cerebral aspergillosis and cerebral candidiasis

Location	Cerebral aspergillosis* (n = 41)		Cerebral candidiasis* (n = 15)		p-value
	No. of patients	Percent	No. of patients	Percent	
Frontal lobe	21	51.2	3	20.0	0.065
Parietal lobe	11	26.8	5	33.3	0.741
Temporal lobe	10	24.4	3	20.0	1.000
Occipital lobe	8	19.5	1	6.7	0.418
Basal ganglion	5	12.2	1	6.7	1.000
Cerebellum	9	22.0	6	40.0	0.193
Brainstem	4	9.8	3	20.0	0.370
Meninges	7	17.1	1	6.7	0.428
Diffuse brain	9	22.0	6	40.0	0.193

\* The patients may have one or more than one lesions

**Table 7.** Neurological symptoms in the 38 patients with cerebral aspergillosis and cerebral candidiasis

Fungal species	No. of patients
<i>Aspergillus fumigatus</i>	17
<i>Aspergillus flavus</i>	7
<i>Aspergillus spp</i>	2
<i>Candida albicans</i>	11
<i>Candida tropicalis</i>	2
<i>Candida glabrata</i>	1
<i>Candida parapsilosis</i>	1
<i>Candida guilliermondii</i>	1

\* The patients may have one or more than one fungal species

amphotericin B as soon as a diagnosis of cerebral mycosis was established. Two and seven patients

received itraconazole and voriconazole, respectively. Most patients died due to extensive fungal infection involving multiple organs, especially pulmonary infection causing respiratory distress and pulmonary hemorrhage. Five discharged-patients received both surgery and medical treatments including amphotericin B and voriconazole. One was discharged on request with good condition, but did not return for follow-up. Thus, treatment success was seen in four patients and the overall mortality was 93%.

### Discussion

Cerebral mycosis is a common opportunistic infection in immunosuppressed and debilitated hosts. The incidence of cerebral mycosis among autopsy cases ranges from 15.7 to 26.5%<sup>(4,7)</sup>. The overall incidence of cerebral mycosis is increased due to the

expansion of immunocompromised population at risk. An important finding from the clinicopathologically analyzed data is that hematologic malignancy is the major disease (13.4-38.5%)<sup>(7-9)</sup>. The other predisposing factors include neutropenia and received corticosteroids<sup>(1,4)</sup>. The authors' findings were similar to previous observation regarding the association between cerebral mycosis and neoplastic hematologic diseases as well as corticosteroids therapy<sup>(1,4)</sup>.

In the present study, the common neurological manifestation was alteration of consciousness, followed by fever, focal neurological deficit, headache, seizure, and blurring of vision. The duration of these presenting symptoms was highly variable ranging from days to months. The patients with cerebral aspergillosis and cerebral candidiasis manifested with similar clinical features. Most patients had clinical history, symptoms, signs and laboratory features suggestive of the immunodepletive condition. However, the diagnosis of cerebral mycosis cannot be made clinically in any of these immunodepleted patients. The clinicoradiologic correlation is essential and the surgical tissue biopsy should be promptly performed. The histopathology is one of the most reliable laboratory procedures to prove the diagnosis by showing the fungal elements and cellular reaction.

The numbers of various forms of cerebral mycosis have increased markedly. Reviews of reported cases indicated abscess formation of 5.4-50%, which is the common pathology in cerebral mycosis<sup>(2,3,11)</sup>. The abscess formation is more common in cerebral aspergillosis<sup>(11)</sup>. However, the authors observed a difference in pathology. The cerebritis was involved most frequently. This suggests that the early clinicoradiologic detection at the highest risk of being exposed to fungal organisms, on the basis of cerebral abscess formation takes time more than cerebritis<sup>(12)</sup>.

In the present study, the predominant cerebral mycosis demonstrated by histopathology and tissue culture was *Aspergillus* spp, followed by *Candida* spp. *Aspergillus* spp has a predilection to invade blood vessel walls and produces vasculitis and mycotic aneurysm. In the present study, angio-invasive *Aspergillus* spp is commonly found in the cerebral cortex, especially the frontal lobe. The angio-invasive nature of *Aspergillus* sp is directly related to its ability to destroy vascular walls, resulting in aneurysm formation, cerebral hemorrhage and subarachnoid hemorrhage<sup>(13)</sup>. The growth of fungal hyphae can produce thromboembolism, resulting in cerebral infarction. The diagnosis cannot be made by clinical

manifestations, but can only be judged by histopathologic demonstration of fungal elements and tissue reactions in a biopsy.

*Candida* spp are commensal of the gastrointestinal mucosae. *Candida* systemic infection needs overgrowth on mucosal surfaces and translocation through the hematogenous route causing cerebral candidiasis<sup>(14)</sup>. Moreover, *Aspergillus* spp are typically caused fungal sinusitis and can directly invade the skull base to the central nervous system, especially in the frontal lobe<sup>(5,6,15)</sup>. Analysis of the authors' data reveals that the statistically significant difference between patients with cerebral aspergillosis and cerebral candidiasis are the associated sinonasal tract and alimentary fungal infections, respectively.

Cerebral aspergillosis and cerebral candidiasis were clinically diagnosed in 50% of cases. In previous reports of systemic mycosis, infection was found to be the most frequently overlooked diagnosis, accounting for 36.1% of misdiagnosed cases<sup>(4)</sup>. The cerebral mycosis is more overlooked than systemic fungal infection. The increase use of immunosuppressive therapy has been complicated by serious cerebral mycosis. Their unusual clinical manifestations and the masking of signs and symptoms by another serious condition also resulted in these fungal infections being missed in such cases.

Treatments of cerebral aspergillosis and cerebral candidiasis require a combination of antifungal agents and extensive surgical intervention. The antifungal agents commonly used in Thailand are amphotericin B, fluconazole, itraconazole and voriconazole. All antifungal agents, with the exception of voriconazole, penetrate poorly into the brain. During the first seven years of the study, voriconazole was not yet available in Ramathibodi Hospital. Amphotericin B was chosen for treatment in all cases. Only one case had successful treated of cerebral aspergillosis<sup>(6)</sup>. Recent literature suggests the superiority of voriconazole with cerebral aspergillosis. Thirty-five percent response rate of voriconazole with cerebral aspergillosis has been reported<sup>(16)</sup>. In the authors' study, an improving survival rate of 26.3% has been reported in patients with cerebral aspergillosis in the last five years of study.

Cerebral mycoses are serious fungal infection with high morbidity and mortality rates. The clinical outcome of cerebral aspergillosis and cerebral candidiasis depends on prompt awareness of the diagnosis and early effective treatment. Current advances in medicine result in an increasing

population of severe immunocompromised patients at high risk for cerebral mycosis. The recent technology including radiography, serology for detecting the aspergillus galactomannan antigen and molecular approaches has improved the overall early diagnosis. Ongoing research efforts hope to capitalize on data derived from the sequencing of the fungal genome, which is aimed at identifying new targets and new methods for diagnosing the fungal infection. However, the histopathology and culture of specimens remain the gold standard for diagnosis and may reveal major unexpected findings that are of clinical importance and emphasis on evaluation in that it is necessary for the improvement of diagnosis, treatment, and prevention of infectious diseases. Successful antifungal therapy of cerebral aspergillosis and cerebral candidiasis depends on early initiation of antifungal agents and reversal of immunosuppression. The present study offers the unique opportunity to assess the epidemiology of cerebral aspergillosis and cerebral candidiasis over a twelve-year period in Ramathibodi Hospital.

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## การศึกษา วิเคราะห์ ลักษณะทางคลินิก และพยาธิวิทยา ของโรคติดเชื้อราในสมอง aspergillosis และ candidiasis ในผู้ป่วยโรงพยาบาลรามธิบดี

นพดล ลาภเจริญทรัพย์, สมพงษ์ วงศ์วิชัย, พิริยาภรณ์ จงตระกูล, อัถพร บุญเกิด, อัศวิน น้อยนาง, สิริอร วัชรานานันท์, สุพจน์ ตูดยาเดชาชนนท์, รวิพรรณ วิฑูรพนิชย์, สุชาติ พุทธิเจริญรัตน์

**วัตถุประสงค์:** ศึกษาลักษณะทางพยาธิวิทยาและทางคลินิกของโรคติดเชื้อราในสมอง aspergillosis และ candidiasis **วัสดุและวิธีการ:** ศึกษาเวชระเบียนผู้ป่วยในโรงพยาบาลรามธิบดี ตั้งแต่ มกราคม พ.ศ. 2540 ถึง ธันวาคม พ.ศ. 2551 ซึ่งได้ทำการตรวจวินิจฉัยเป็นการติดเชื้อราในสมอง มีเกณฑ์การวินิจฉัยโรคคือ การพบเชื้อราลูกกลมเข้าไปในเนื้อเยื่อ โดยการตรวจทางจุลพยาธิวิทยา รายงานนี้ทำการศึกษาข้อมูลด้านอายุ เพศ อาการแสดง ทางระบบประสาท ระยะเวลาก่อนเกิดโรค โรคประจำตัว ปัจจัยเสี่ยง ข้อมูลทางห้องปฏิบัติการ การแพร่กระจาย ของเชื้อราในอวัยวะภายใน และผลการรักษา

**ผลการศึกษา:** ผลการตรวจทางพยาธิวิทยา 56 ราย (เพศชาย 23 ราย เพศหญิง 33 ราย อายุเฉลี่ย 39.7 ปี ช่วงอายุตั้งแต่ 1 เดือน ถึง 87 ปี) ที่วินิจฉัยเป็นโรคติดเชื้อราในสมอง aspergillosis 41 ราย และโรคติดเชื้อราในสมอง candidiasis 15 ราย พบว่า อาการที่ผู้ป่วยมาพบแพทย์ คือ ระดับการรู้สติลดลง (69.6%) ไข้ (60.7%) อาการแขนขาอ่อนแรง (14.3%) อาการอัมพาตของเส้นประสาทสมอง (12.5%) ปวดศีรษะ (12.5%) และชัก (5.4%) ผู้ป่วยหนึ่งในสามมีโรคเมเร็งระบบเลือดและ/หรือต่อมน้ำเหลืองเป็นโรคประจำตัว ร้อยละ 32.1 พบว่ามีการใช้ยา corticosteroids พบว่าอวัยวะภายในที่ติดเชื้อาร่วมด้วย ได้แก่ ปอด (73.2%) ทางเดินอาหาร (33.9%) และโพรงอากาศไซนัส (19.6%)

**สรุป:** โรคติดเชื้อราในสมอง aspergillosis และ candidiasis พังสลายในผู้ป่วยที่มีภูมิคุ้มกันต่ำ ซึ่งมาพบแพทย์ด้วยอาการระดับการรู้สติลดลง ไข้ อาการแขนขาอ่อนแรง อาการอัมพาตของเส้นประสาทสมอง ปวดศีรษะ และชัก ผู้ป่วยทั้งโรคติดเชื้อราในสมอง aspergillosis และ candidiasis มีอาการแสดงและพยาธิสภาพส่วนใหญ่เหมือนกัน แต่กลุ่มการติดเชื้อในโพรงอากาศไซนัส และการสร้างเป็น abscess มักพบในโรคติดเชื้อราในสมอง aspergillosis ส่วนการติดเชื้อร่วมด้วยในระบบทางเดินอาหารมักพบในโรคติดเชื้อราในสมอง candidiasis

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