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## Case Report

# A case of influenza-associated invasive aspergillosis with cerebral hemorrhage due to infectious vasculopathy<sup>☆,☆☆</sup>

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## ABSTRACT

An invasive aspergillosis (IA) primarily occurs among immunocompromised patients. Recently with an influenzae infection prevalently spreading, influenzae-associated invasive aspergillosis (IAIA) has been reported occasionally. By contrast, neuroleptic malignant syndrome (NMS) occurs rarely in psychiatric patients who are treated with Olanzapine. We report a 43 years old male with psychiatric disorder who had developed IAIA followed by NMS and cerebral hemorrhage as the result of aspergillus invasion to cerebral vessels. He had also super-infection of COVID-19, 13 months later to be saved completely after invasive mechanical respiratory supports. From clinical aspects, we would emphasize that it is of importance to find earlier co-occurrence of IAIA patients with cerebral hemorrhage due to secondary infectious vasculopathy of IA.

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## Case report

A 43 years old male was admitted to the hospital with general weakness, pyrexia, and dyspnea. He had history of schizophrenia treated with atypical antipsychotic (Olanzap-

ine, 5mg/day). Three days before admission, he was diagnosed Influenza A with symptoms of sore throat, and pyrexia was diagnosed by Real-time RT-PCR assays. His timeline of clinical course after admission was shown in Fig. 1. On Day 1 as admission day, his chest computed tomography (CT) image showed “halo” sign in lung bilaterally and “air crescent sign”

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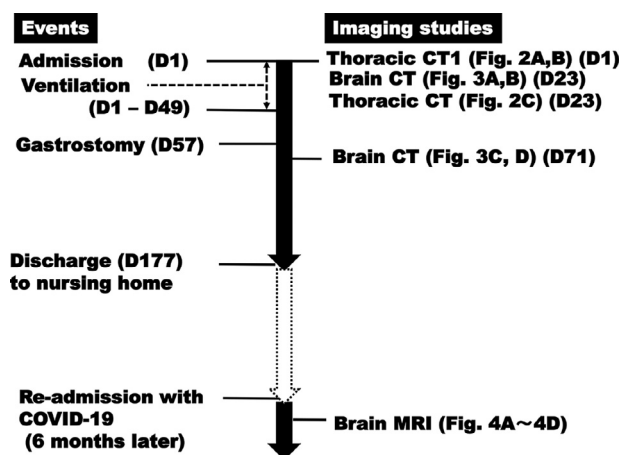
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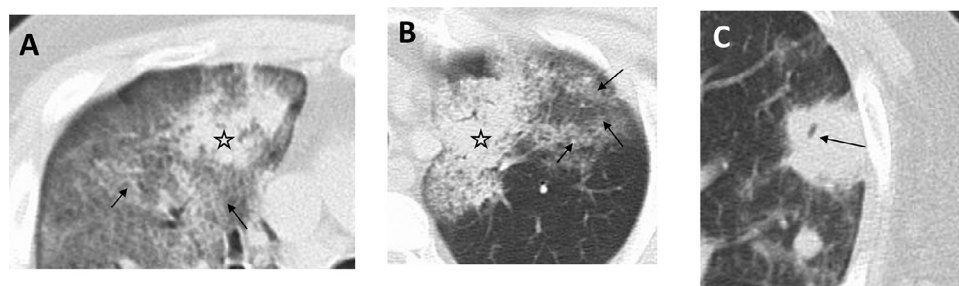


**Fig. 1 – Timeline.** Graphic illustration of the patient's Influenza-associated invasive aspergillosis (IAIA), neuroleptic malignant syndrome (NMS) and cerebral hemorrhage after disseminated cerebral aspergillosis occurred between Day 1 and Day 177. Abbreviations: Ab, antibody; Ag, antigen; ARDS, acute respiratory distress syndrome; *Asp. fum.*, *Aspergillus fumigatus*; BT, body temperature; CF, complement fixation test; COVID-19, SARS-CoV-2 infection disease; CT, computed tomography; IAIA, influenza-associated invasive aspergillosis; MCFG, Micafungin sodium; MLST, multi-locus sequence typing; NMS, neuroleptic malignant syndrome; PCR, polymerase chain reaction; TAZ, Tazobactam, Piperacillin Hydrate.

(Fig. 2A and B). His physical findings at admission were the follows: body temperature 38.7°C, heart rate 127 bpm, blood pressure 150/90 mmHg, respiratory rate 40 bpm, and arterial oxygen saturation (SpO<sub>2</sub>) 93%. His laboratory data showed that CPK 71,300 U/L, C-reactive protein 15.6 mg/dL, but no neutropenia was observed frequently associated in compromised hosts (Table 1). These were finding of rhabdomyolysis secondary from hyperthermia. As he developed severe dyspnea, ventilatory management was started on Day 1 with the diagnosis of severe acute respiratory distress syndrome (ARDS) with low PaO<sub>2</sub>/FiO<sub>2</sub> ratio (= 64.6 mm Hg/1.0). On Day 2, after confirming diagnosis of neuroleptic malignant syndrome (NMS) fulfilled with the following 6 criteria from phys-

ical findings (major criteria: + fever, + CPK elevation, minor criteria: + tachycardia, + hyper- or hypotension, + tachypnea, + hyperhidrosis), Dantrolene intravenously injection was continued for 3 days until resolving clinically by Day 9. On Day 10, laboratory of fungi infection showed serum (1→3) β-D-glucan of 208.0 pg/mL (ref, 0.0-20.0), and sputum multi-locus sequence typing (MLST) method for genotyping analysis confirmed the diagnosis of *Aspergillus fumigatus* (*Asp. fum.*). A serum antibody against *Asp.fum.* using complement fixation testing was strong positive (34 times; ref, <4 times). These latest 2 tests confirmed diagnosing bilateral pulmonary Infection with *Asp. fum.* associated with pre-occurrence of influenza infection. From his laboratory data and findings of radiological studies using thoracic CT (Fig. 2), he was diagnosed Influenza-associated Invasive pulmonary Aspergillosis (IAIA) (Fig. 1) which was treated with antifungal agent (micafungin sodium (MCFG), 100 mg/day) for 22 days. This antifungal treatment could successfully work to decrease serum β-D-glucan level from 208 to 16.1 pg/mL (Table 2). However, as with anisocoria appearance on Day 11 (pupil diameters: right 3.5 mm/left 2.5 mm) and brain CT taken urgently showed cerebral hemorrhage in the right frontal lobe on Day 23 (Fig. 3). The hemostatic agents were started until his conscious level recovered up to GCS score from 8 (M3V3E2) to 11 (M3V4E4) 3 days later. As he was managed with mechanical ventilation since admission and spontaneous respiratory function was not improved, tracheostomy was created on Day 29. On Day 57, gastrostomy was also created for nutritional support. After his general status was stabilized with anticonvulsants medication, he could discharge from our hospital to nursing home on Day 177. His tracheostomy was able to be closed 3 months later after discharge.

Under COVID-19 pandemic worldwide, 6 months later from discharge on Day 177, he got COVID-19 in January 2021 with symptoms of severe dyspnea and his SpO<sub>2</sub> dropped to 85% instead of O<sub>2</sub> inhalation (5 L/min) and returned to our hospital to treated with antiviral agent (Remdesivir 100 mg) given intravenously for 5 days. His signs and symptoms showed full recovery and discharged 14 days later (Fig.1). The magnetic resonance image (MRI) taken on Day 7 of COVID-admission showed that hemorrhagic mass in the right lobe seemed changing to aspergillosis abscess with peripheral ring-enhancing lesion in gadolinium- enhanced T1W Image (Fig. 4B).



**Fig. 2 – Thoracic computed tomography (CT) images (CT 1 in Fig.1).** (A, B) (both taken on Day 1) showed “halo” sign. The sign consists of 2 parts: a solid nodular core (☆) and a ground-glass perimeter of intermediate density (arrow). (C) (taken on Day 23) showed “air crescent sign” (arrow).

**Table 1 – The laboratory data on admission.**

(1) Plasma biochemistry				(3) Urinalysis	
CPK	71300 U/L	GOT	752 U/L	Osmolarity	350 mOsm/kg
GPT	105 U/L	LDH	2688 U/L	Appearance	clear
ALP	327 U/L	CH-E	244 U/mL	gravity	1.015
$\gamma$ -GTP	27 U/mL	Amy	96 U/mL	pH	6.5
TP	5.7 g/dL	Alb	2.9 g/dL	Protein	3+
T-Bil	0.6 mg/dL	BUN	17.9 mg/dL	Sugar	-
Cre	0.9 mg/dL	UA	9.4 mg/dL	Ketone	3+
Na	123.3 mEq/L	K	3.6 mEq/L	Blood	3+
Cl	87.2 mEq/L	Ca	7.5 mg/dL	WBC	-
IP	2.3 mg/dL	BS	94 mg/dL	UUN	492.8 mg/dL
T-cho	92 mg/dL	TG	198 mg/dL	Na	6.6 mEq/L
HDL-C	14 mg/dL	LDL-C	.46 mg/dL	Ketone	25.6 mEq/L
CRP	15.52 mg/dL	Mg	2.3 mg/dL	Cl	5.9 mEq/L
CK-MB	255.0 U/L	HbA1c	6%	Bacteria	Nil
NH4	82 $\mu$ g/dL				
(2) Complete Blood Count (CBC)					
WBC	9110 / $\mu$ L	RBC	$563 \times 10^4$ / $\mu$ L		
Neutro	77.7 %	Hb	16.8 g/dL		
Baso	1.1 %	Plt	$8.1 \times 10^4$ / $\mu$ L		
Lymph	15.8 %				
Mono	5.3 %				

**Table 2 – The laboratory data of fungal infection in our case.**

Day after admission	Ref	Day 1	Day 30	Day 36
(1→3) $\beta$ -D-glucan	0.0 - 20.0	208	16.1	
MLST genotyping	negative	Asp. fum.		
CF for Asp.Ab	< 4			X 34

Abbreviations: Ab, antibody; CF, complement fixation test; MLST, multi-locus sequence typing; Ref, reference value.

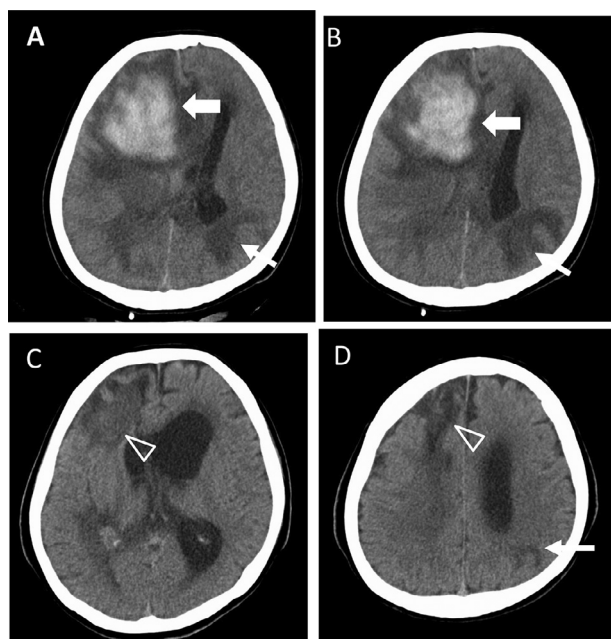
## Discussion

We would discuss this case from 3 aspects in accordance with the order of which this case has in his course: first IAIA, second neuroleptic malignant syndrome, and third cerebral hemorrhage. The written informed consent was taken from patient and this case report was approved by the hospital ethic committee and the approval number was 21-02.

### An invasive pulmonary aspergillosis as co-infection of influenza

Invasive pulmonary aspergillosis (IPA) occurs primarily among immunocompromised patients such as solid organ or stem cell transplantation, chemotherapy, or immune-suppressors [1] with neutropenia. However, as in our experienced case, he was immunocompetent without neutropenia, multicentric retrospective study showed that severe influenza is another risk factor to develop IPA necessary care in intensive care unit (ICU) [2]. In ICU settings, respiratory bacterial superinfection of influenza reported a common complication with high mortality [3,4]. Super-infection with *Aspergillus* spp. has

been increasingly reported since 2009/2010 influenza pandemic associated with higher mortality of 33%-67%. [5–7] The IAIA cause acute respiratory distress syndrome (ARDS) resulted from respiratory bacterial and viral super-infection with high mortality [8–10]. Moreover, patients with bone marrow transplantation have highest mortality rate of 87% [11]. Bicentric cohort study proved that predictor of severity and mortality in patients with IAIA are mechanical ventilation, vasoactive support, extracorporeal membranous oxygenation (ECMO), any complication. Our case had invasive mechanical ventilation support and ARDS diagnosed according to Berlin definition [5] and predicted poor outcome. To diagnose influenza-associated invasive aspergillosis (IAIA), an expert opinion has been proposed [2]. According to this, our case is diagnosed probable with finding of positive tracheal aspirate culture. In this proposal, the authors adopted not  $\beta$ -D-glucan, but galactomannan (GM) and PCR [12] as serum or brachial aspirate lavage (BAL) immunologic testing. As such, another practice guideline also recommends GM instead of  $\beta$ -D-glucan [13]. Comparing clinical use of the diagnostic methods among galactomannan (GM) antigen, PCR, and  $\beta$ -D-glucan, the latest of which we used to confirm diagnosis is comparable in term of diagnostic accuracy such as sensitivity (81.60%, 76.8%, and 76.9%, respectively) and specificity (91.6%, 75.0%, and 89.4%, respectively) [14]. From these, sensitivity and specificity of

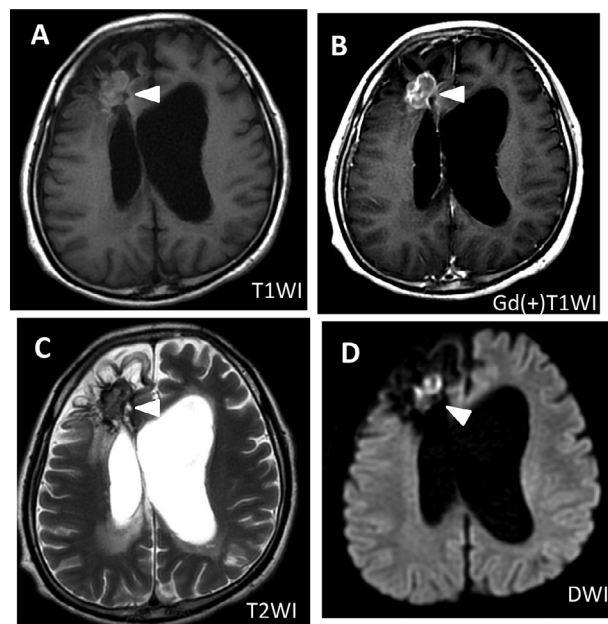


**Fig. 3 – Brain CT.** (A, B) Brain computed tomography (CT) taken on Day 1, showed hemorrhage with peripheral edema in the right frontal lobe (thick arrows), and the midline shift to the left existed. The mass in the left occipital lobe with peripheral low-density edema-equivalent lesion was also identified (arrows). (C) Brain CT (taken on Day 23) showed iso-density with low density surrounding area in the right frontal lobe (open triangle). (D) Brain CT (taken 11 months after his first admission) also showed the occipital lesion of the right frontal lobe. Abbreviations, CT: computed tomography.

$\beta$ -D-glucan seems similar or comparable with PCR which is included in diagnostic test in above mentioned proposal. It might be likely that not only GM and PCR but  $\beta$ -D-glucan could be candidate of diagnostic test because of its high feasibility and lower cost. The several meta-analyses and study [15] supported that (1→3)- $\beta$ -D-glucan assay is considered a useful diagnostic tool with knowledge of the limitations of the assay. [20–22]. Few studies have performed direct comparisons of 2 assays for diagnosis of IA in the same patients. One study favored the BG assay [16], one study favored the opposite [17], and another found no major difference between the 2 assays [18], and 2 showed moderate agreement between them [19,20]. Final decision might be made with the further prospective studies among larger patients with IA.

### Neuroleptic malignant syndrome in patients treated with Olanzapine

Neuroleptic malignant syndrome (NMS) is a life-threatening neurologic emergency associated with the use of antipsychotic (neuroleptic) agents and characterized by a distinctive clinical syndrome of mental status change, rigidity, fever, and dysautonomia. Its risk factors are psychiatric conditions,



**Fig. 4 – Brain MRI.** Four images of brain MRI, taken at COVID-admission when 6 months after his discharge on Day 177, showed mass in the right frontal lobe. Individual findings were as the follows: (A) T1WI showed heterogeneous (low- and high-intensity signal) inside with peripheral hypo-intensity (arrow). (B) Gadolinium-enhanced T1WI showed iso-intensity inside with peripheral ring-enhancing lesion (arrow). (C) T2WI showed heterogeneous (low- and high-intensity signal) inside with peripheral hypo-intensity (arrow). (D) DWI showed heterogeneous hyper-intensity signal inside (arrow). Abbreviations: DWI, diffusion weighted image; MRI, magnetic resonance imaging; T2WI, T2 weighted image.

acute catatonia, and extreme agitation are over-represented in patients who develop NMS [21]. Our case had psychiatric disorder and treated with Olanzapine which is reported in rarely introducing NMS [22]. Laboratory findings often reflect the clinical manifestations of NMS, with more severe rigidity leading to more profound creatine kinase (CK) elevation. CK levels above the upper limit of normal were noted in 76% of psychotic episodes in the patients with NMS [23]. In addition, infection is reported risk factor of NMS [24]. When patients with psychiatric disorders have infections including aspergillosis such as this case, NMS must be considered as a neurologic emergency.

### Cerebral hemorrhage and abscess formation as concurrence of aspergillus infectious vasculopathy in cerebral vessels

In the present case, he has developed cerebral hemorrhage (Fig.2A and B). In case series in patients with central nervous system aspergillosis [25], 6 of 34 cases did have subarachnoid hemorrhage. Its etiology was explained by Aspergillus in-

vades the large cerebral vessels and aneurysm is produced. In our case, the same explanation could be adapted to an etiology of his massive cerebral hemorrhage due to secondary infectious vasculopathy of IA. Another prominent finding in this case is that brain MRI findings taken in later period, 11 months after admission, seems difference from ordinal patients with cerebral hemorrhage. In usual case, post-cerebral hemorrhage lesion showed low-intensity in T2WI and is consistent with liquefied cyst. However, in our case, central area of hemorrhage lesion was iso-intensity inside with peripheral ring-enhancing area shown in gadolinium-enhanced T1W image (Fig. 2B). Considering the possible cause of an infectious vasculopathy by aspergillus invasion to cerebral greater vessels as cerebral hemorrhage, one possibility to explain this Gd-enhancing MRI finding is changing from cerebral hemorrhagic lesion to abscess formation as post-occurrence of infectious vasculopathy. As several studies reported of IA-related mortality varying from 21.5% to 66% [25–27], this mortality might be effect of invasive aspergillosis. A multicenter study reported an overall mortality in patients with IAIA in 90 days is 60.5% [25]. After dividing by days after occurrence, IA-related mortality seems decrease according to days from 97.6% to 86.7% and 58% within the first 14, 21, and 90 days, respectively [25]. Of the IA-related deaths, 66% occurred within 14 days and 83% within 21 days [25]. As the mortality of patients with co-occurrence of IAIA with cerebral hemorrhage seen in our case might be higher, this case presentation seems of importance to note and predict post-IAIA clinical courses. The authors also analyzed factors associated with IA-related death and found that chronic liver disease and voriconazole treatment were inversely risk factors. Contrary to our expectation, a disseminated IA was not stated a risk factor. However, as the authors did not analyze effects of cerebral hemorrhage or superinfection of IA with the other bacterial or viral infections unlikely to COVID-19 in our case, it remains unclear whether these are risk factors or not. The further investigations might be warranted to clarify effects of these factors on mortality. Giving the timeline of clinical course and radiological courses shown in Fig. 1, chronic fate of cerebral hemorrhage using CT, and MRI changing to aspergillus abscess due to infectious vasculopathy might be of value to predict clinical courses in IA patients (Fig. 3).

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## Patient consent

Informed consent was obtained from the patient for the publication of this case report.

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