

CASE REPORTS

Intracranial invasive fungal aneurysm due to *Aspergillus* sinusitis successfully treated by voriconazole plus internal carotid artery ligation therapy in an aged woman

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Abstract

A fungal carotid aneurysm is an infrequently occurring infectious aneurysm that is usually treated by antifungal therapy plus surgical debridement of the infected vessel. We herein report an extremely rare case involving a patient with a medical history of bladder cancer treated by Bacillus Calmette–Guérin (BCG) who developed a fungal aneurysm of the internal carotid artery and thrombosis of the superior ophthalmic vein caused by maxillary *Aspergillus* sinusitis. The patient was successfully treated by antifungal, anticoagulant, and antiplatelet drugs combined with internal carotid artery ligation therapy. Internal carotid artery fungal aneurysm is associated with a high mortality rate, but the present case suggests that it can be successfully treated by antifungal therapy combined with a less invasive endovascular therapy.

Keywords: Fungal carotid aneurysm, bladder cancer, Bacillus Calmette–Guérin, less invasive endovascular therapy, antibiotics

INTRODUCTION

Among intracranial infectious aneurysms, fungal aneurysm is estimated to account for 14% of all carotid infectious aneurysms.¹ The standard treatment of intracranial mycotic aneurysm is surgical debridement of the infected vessel in combination with antifungal therapy¹; however, the mortality rate in previously reported cases of *Aspergillus* aneurysm was high.² We herein report a case involving an aged woman with bladder cancer treated by Bacillus Calmette–Guérin (BCG) who developed an intracranial fungal aneurysm and thrombosis of the superior ophthalmic vein due to maxillary *Aspergillus* sinusitis. She was successfully treated by antifungal, anticoagulant, and antiplatelet drugs combined with internal carotid artery (ICA) ligation therapy.

CASE REPORT

An 82-year-old Japanese woman with a medical

history of bladder cancer treated by BCG (Immunobladder® Intravesical at 80 mg/week into the bladder for six courses followed by Immunobladder® Intravesical at 40–80 mg every 3 months) for 4 years developed general fatigue and fever of up to 37.7°C as her first infection symptom (Day 1). On the following day (Day 2), she developed severe pain around her right eye, and both eyelids became swollen. On Day 4, her right eye showed vertical and adducted disturbances with eyelid ptosis. On Day 5, she was admitted to a local hospital, where head magnetic resonance imaging (MRI) showed a right ICA aneurysm and thrombosis in the bilateral superior ophthalmic veins (Figure 1C, Day 5, circle and arrow). She subsequently developed a severe headache on Day 8 with left maxillary sinusitis accompanied by calcification that was confirmed on a computed tomography scan (Figure 1D, white arrow). Therefore, she was transferred to our neurosurgery department

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to receive endovascular treatment on Day 19. On admission (Day 19), she showed right side mydriasis, an absent light pupillary reflex, complete external ophthalmoplegia and an absent corneal reflex in the right eye, and sensory disturbance in the region of the right ophthalmic nerve. A laboratory blood test showed a mild inflammatory reaction with an erythrocyte sedimentation rate of 27/60 mm (1/2 h), but her white blood cell count and C-reactive protein level were within the reference range (4,880 μ L and 0.07 mg/dL, respectively). Cerebrospinal fluid analysis showed a mildly elevated protein level (64 mg/dL) but a normal cell count (0/ μ L) and glucose level (63 mg/dL; serum glucose, 103 mg/dL).

Because the patient was suspected to have cavernous sinus syndrome due to systemic infection, she was admitted to our department on Day 22. She was 148.0 cm tall and weighed 34.0 kg; her body weight had decreased by 5 kg in 6 months, and her body mass index was 15.5 kg/m². Neurological examination showed that her pupils were anisocoric and round (3.0/4.0 mm R/L) with a body temperature of 36.7°C, blood pressure of 122/68 mmHg, pulse rate of 85/min, and no murmur in the right orbit. She showed right ptosis and complete vertical and adducted palsy of the right eye (Figure 1A, Day 5). The light reflex in the right eye was absent. Her visual field and visual acuity were normal. An antiplatelet drug (aspirin, 100 mg/day) was started on Day 22 for thrombosis in the bilateral superior ophthalmic veins. On Day 24, digital subtraction angiography (DSA) and balloon test occlusion were performed by the attending neurosurgeons. DSA showed a 12-mm-diameter, irregularly shaped aneurysm in the C4 area of the right ICA (Figure 1B).

On Day 25, transnasal antral lavage was performed to treat the left maxillary sinusitis, and an approximately 15-mm-diameter gray granuloma was removed (Figure 1D, black arrow). Thereafter, an antifungal drug (liposomal amphotericin B, 50 mg/day) and anticoagulant (heparin, 10000 IU/day) were started on Day 25; the heparin was switched to apixaban (10 mg/day) after 15 days. On day 27, microscopic examination of the granuloma derived from the left maxillary sinus led to a pathologic diagnosis of an *Aspergillus* fungal ball because hematoxylin and eosin staining and Gomori methenamine silver staining showed many *Aspergillus* mycelia (Figure 1E). Despite these therapies, head MRI on Day 30 showed expansion of the right ICA aneurysm (Figure 1C, Day 30, circle and arrows). Thereafter,

on Day 40, the serum *Aspergillus* antigen titer became high, reaching 0.5 (+) (cut-off, ≥ 0.5); the Candida antigen titer was negative and the β -D glucan level was still low (<6.0 pg/ml). Voriconazole (600 mg/day) was then started for sterilization of *Aspergillus*.

On Day 64, DSA and MRI showed further expansion of the right ICA aneurysm from 12 to 16 mm in diameter (Figure 1B and C, Day 64). Because of the patient's old age, complication of bladder cancer treated by BCG immunotherapy, and large aneurysm, minimally invasive surgery was chosen for treatment of the ICA aneurysm. The cervical portion of the right ICA was neurosurgically ligated to block the inflow of the aneurysm on Day 72, and the aneurysm was successfully diminished on Day 120 (Figure 1C, Day 120). Two years after ICA ligation, the patient's right ptosis and external ophthalmoplegia improved (Figure 1A), and she showed no recurrence of the right ICA aneurysm on head MRI.

DISCUSSION

Infectious aneurysms represent only 2% to 5% of all intracranial aneurysms.³ Among intracranial infectious aneurysms, fungal aneurysms are estimated to account for 14% of all carotid infectious aneurysms.⁴ Therefore, the present case of an intracranial fungal aneurysm caused by left maxillary *Aspergillus* sinusitis is extremely rare. Most mycotic aneurysms of the ICA due to mycotic sinusitis show direct invasion from the sphenoidal sinus to the same side of the ICA via the cavernous sinus. In the present case, however, the left maxillary *Aspergillus* sinusitis led to a contralateral right ICA aneurysm by intravenous invasion via the cavernous sinus (Figure 1C, D). This was supported by both the high serum titer of *Aspergillus* antigen and isolation of *Aspergillus fumigatus* from the right maxillary sinus abscess. *Aspergillus* causes infectious vasculitis and thrombus, resulting in hemorrhagic infarction, brain abscess, sudden massive hemorrhage, and aneurysm formation.¹ The patient's superior ophthalmic vein thrombosis occurred by formation of a thrombus due to fungal infection and circulation disorder by the right ICA aneurysm via the cavernous sinus, which also resulted in headache, ptosis, and external ophthalmoplegia (Figure 1A, Day 5; Figure 1B and C).

A previous manuscript reported that invasive fungi, such as *Aspergillus* species or fungi that cause mucormycosis, induced the formation

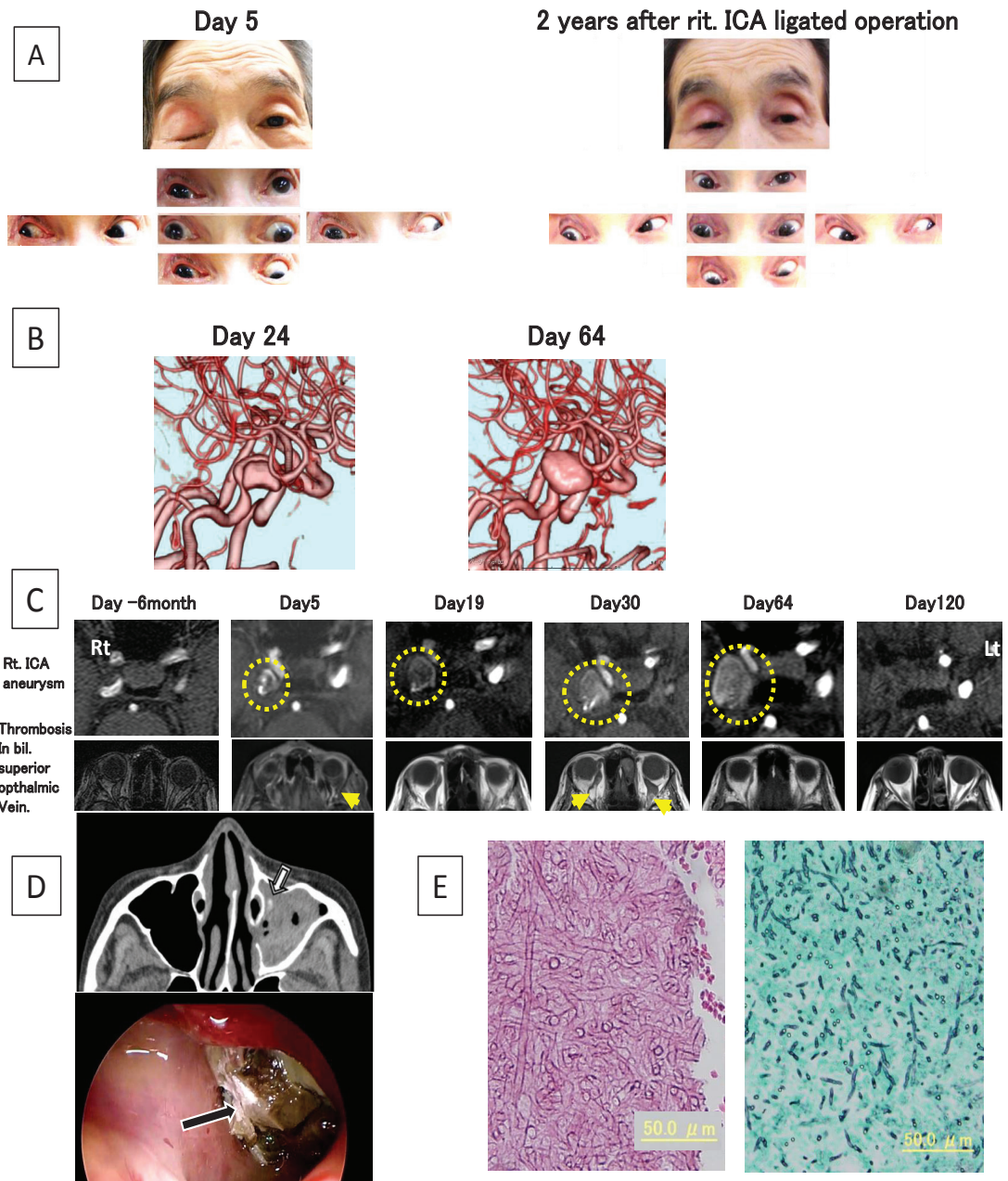


Figure 1. Clinical course of the patient in the present case. (A) On Day 5, the patient's right eye showed vertical and adducted disturbances with eyelid ptosis. However, 2 years after treatment by antibiotic, anticoagulant, and antiplatelet drugs combined with less invasive internal carotid artery (ICA) ligation therapy, her right ptosis and external ophthalmoplegia improved. (B) Digital subtraction angiography showed a growing right internal carotid aneurysm from Day 24 (c, 12 mm) to Day 64 (d, 16 mm). (C) Head T2-weighted magnetic resonance images showed a right internal carotid artery aneurysm (dotted circles) and thrombosis in the bilateral superior ophthalmic veins (arrows). (D) Head computed tomography showed left maxillary sinusitis accompanied by calcification (white arrow). A fungal mass was detected at the left maxillary sinusitis on transnasal antral lavage (black arrow). (E) Histopathology of the granuloma in the left maxillary sinus. Hematoxylin and eosin staining and Gomori methenamine silver staining showed many *Aspergillus* mycelia.

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Previous reports of intracranial invasive aspergillus aneurysm

Author (Year of publication)	Age/Sex	clinical presentation	site of aneurysm (s)	Antifungal therapy	Interventional procedure	outcome	associated diseases
1 Watanabe T (2008)	15 M	headache, right hemiplegia	lt. ICA	micafungin + amphotericin B	endovascular coil embolization	Survived	severe aplastic anemia, DM
2 Negro E (2013)	22 F	headache, visual impairment	lt. ACA	voriconazole →liposomal amphotericin B	none	Died due to cerebral aneurysm ruptured	acute myeloid leukemia
3 Ahmad RA (2014)	39 M	lower extremity embolus	no records	amphotericin B →voriconazole + micafungin	endovascular coil embolization	Survived	mechanical AVR, pacemaker implantation
4 Bowers CA (2015)	76 F	headache	lt. ICA	none	none	Died due to cerebral aneurysm ruptured	rheumatoid arthritis, giant cell arteritis
5 Ogawa M (2015)	83 M	headache, facial diplegia, rt. retrobulbar neuritis	lt. ICA	none	none	Died due to cerebral aneurysm ruptured	inflammatory pseudotumor of the clivus, left maxillary sinusitis
6 Yuki S (2015)	77 M	rt. reduced visual acuity, rt omnidirectional ocular motility disorder	rt ICA	amphotericin B + micafungin → voriconazole + micafungin	trapping of rt. ICA + STA-MCA bypass	Died due to cerebral aneurysm ruptured	none
7 Yamaguchi J (2016)	79 M	rt. decreased visual acuity	rt ICA	amphotericin B → micafungin	high-flow bypass from ECA to MCA	Survived	retrobulbar optic neuritis, DM
8 Muraoka S (2016)	56 M	fever, headache	rt. PCA	voriconazole	Endovascular treatment of the ruptured aneurysm occlusion	Survived	paramasal sinusitis
9 Winterholler M (2017)	64 M	diplopia, vertigo, dysarthria, unstable gait	BA	voriconazole	none	Died due to cerebral aneurysm ruptured	sphenoidal sinusitis, DM
10 Varghese B (2018)	65 M	headache, chills, worsening delirium	bil. MCA	posaconazole + caspofungin + amphotericin B + anidulafungin	none	Died due to cerebral aneurysm ruptured	hemophagocytic lymphohistiocytosis, pulmonary aspergillosis
11 Present case (2018)	82 F	general fatigue, fever up	rt. ICA	amphotericin B → voriconazole	rt. ICA ligation	Survived	bladder cancer treated by BCG

bil: bilateral, ICA: internal carotid artery, PCA: posterior cerebral artery, BA: basilar artery, lt: left, MCA: middle cerebral artery, rt: right, STA-MCA: superficial temporal artery-middle cerebral artery bypass, ECA: external carotid artery, AVR: aortic valve replacement, BCG: Bacillus Calmette-Guérin, DM: diabetes mellitus

Figure 1F. Previous reports of intracranial invasive aspergillus aneurysm

of an ICA fungal aneurysm, especially in immunocompromised hosts.¹ Our patient was not immunocompromised, but she had received BCG therapy for bladder cancer. BCG therapy is an effective treatment for bladder cancer and rarely induces serious complications, such as sepsis, infectious aortic aneurysm, and iliopsoas abscess.⁵ However, two previous case reports described a ruptured fungal ICA aneurysm (due to *Mycobacterium bovis* and *M. tuberculosis*) after BCG therapy for bladder cancer.^{6,7} In these cases, the body weight had decreased by 5 kg in 6 months due to anorexia after BCG therapy, however, the relationship between BCG therapy and fungal infection was not clear.

The standard treatment of an intracranial fungal aneurysm is surgical debridement of the infected vessel in combination with antifungal therapy.¹ Previous case reports showed high mortality rates among patients with intracranial invasive *Aspergillus* aneurysms, especially those treated by only antifungal therapy (Figure 1F). In the present case, after transnasal antral lavage for the left maxillary sinusitis, an antifungal drug (liposomal amphotericin B, 50 mg/day) and anticoagulant (heparin, 10000 IU/day) were quickly started. After confirmation of positive serum *Aspergillus* antigen, the patient began treatment with voriconazole, which is recommended as the first-choice antifungal agent for aspergillosis by the Infectious Diseases Society of America. However, the patient's aneurysm increased in size. Therefore, a less invasive endovascular therapy for the ICA aneurysm was chosen because she was a high-risk patient for open surgery (old age and complication of bladder cancer treated by BCG immunotherapy). Finally, she was successfully treated by the combination of a less invasive surgical and medical treatment with antifungal, anticoagulant, and antiplatelet drugs. The present case suggests that invasive *Aspergillus* sinusitis and aneurysm with thrombosis of the superior ophthalmic vein can be successfully treated by antifungal, anticoagulant, and antiplatelet drugs combined with less invasive ligation therapy.

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DISCLOSURE

Conflict of interest: None

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