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CLINICAL INVESTIGATION

Seven cases of localized invasive sino-orbital aspergillosis

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Abstract
Purpose To describe the clinical manifestations and prognoses in 7 patients with invasive sino-orbital aspergillosis (ISOA).
Methods This was a retrospective study of consecutive patients who were diagnosed as having ISOA at the Gifu University Hospital and Gifu Municipal Hospital between January 1993 and December 2015. Data were collected on demographics, initial manifestations, examination findings, treatments, clinical course, and outcomes.
Results The median age of the 7 patients with ISOA was 68 years; 5 of them had diabetes. The initial symptoms were reduced blurred vision (57%), unilateral headaches (43%), unilateral abnormal sensations or numbness of the periorbital area (43%), and external ophthalmoplegia (43%). The medical department that the patients first visited was the ophthalmology department in 57% of the cases. The initial CT showed bone destruction in 71% and calcification in 14% of the patients. Six of the 7 cases were misdiagnosed. The definitive diagnosis of ISOA was made by histopathologic examinations of the biopsy specimens, with an average of 2.6 biopsies. All patients received aggressive antifungal treatments after the diagnosis. However, the final visual outcome was no light perception in 86% and death related to the ISOA in 43% of the patients. Patients who were older at the onset had lower survival rates.
Conclusions The prognosis for patients with ISOA is poor in terms of both vision and life. Ophthalmologists are often the first examiner. ISOA should be considered in the differential diagnosis for patients with a gradually progressive orbital mass, unilateral headaches, numbness of the periorbital area, and a decrease in visual acuity of unknown origin.

Keywords *Aspergillus* · Invasive sino-orbital aspergillosis · Fungal sinusitis

Introduction

Though a rare disease, the incidence of invasive sino-orbital aspergillosis (ISOA) is reportedly increasing owing to the growing number of aged individuals and immunocompromised patients who are treated with steroids or immunosuppressive drugs [1]. ISOA can progress to severe illness, with mortality rates of 40–80% [2–4].

ISOA has diverse signs and symptoms [5, 6]; the main clinical manifestations are headaches, eye and periorbital pain, facial paresthesia, blepharoptosis, visual disturbances, and ophthalmoplegia. Thus, ophthalmologists have a higher chance of being the first to examine patients with this disease than do otolaryngologists or neurosurgeons [6, 7]. Many ophthalmologists, however, are unfamiliar with the disease because of its rarity and difficulty of diagnosis. This lack of knowledge can lead to a delay in diagnosis or to misdiagnosis, which could lead to blindness and even death [4].

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We report the clinical manifestations, examination findings, differential diagnoses, treatments, and outcomes of 7 patients with histopathologically confirmed ISOA.

Patients and methods

This was a retrospective study of 7 consecutive patients diagnosed as having ISOA at the Gifu University Hospital and Gifu Municipal Hospital between January 1993 and December 2015. The following information was collected from the medical records: age, sex, medical history, signs and symptoms, duration of symptoms, medical department first visited by the patient, initial visual acuity, computed tomography (CT) and magnetic resonance imaging (MRI) findings, initial diagnosis, number of biopsies, interval to definitive diagnosis, level of β-D-glucan, treatment, and outcome of vision and life. The study was approved by the institutional review board of each institute.

Results

Basic demographics

The median age of the 7 consecutive patients with localized ISOA was 68 years (range 26–76 years), and 6 of the 7 patients (85.7%) were aged over 50 years (Table 1). There were 6 men and 1 woman. Five patients (71.4%) had diabetes; 2, hypertension; 1, spinal disease; 1, stroke; and 1, hyperuricemia. Nobody suffered from diseases that led to immunodeficiency. All patients had unilateral sino-orbital aspergillosis (SOA) at the first presentation, and 3 patients (42.9%) developed bilateral lesions during the follow-up period. The diagnosis in case 3 was invasive *Aspergillus* sinusitis on the left side, which had been treated at another hospital 1.5 years earlier. The patient then developed it on the right side and visited our hospital. In 3 patients (42.9%), the HbA1c level was higher than the normal cut-off value of 6.5% at the initial presentation [Japan Diabetes Society (JDS)]. The medical department first visited by the patients was the ophthalmology department in 4 (57.1%), the neurosurgery department in 2 (28.6%), and the otorhinolaryngology department in 1 (14.3%). The median interval between the onset of symptoms and the first visit to our hospital was 69 days.

Initial signs and symptoms

The initial signs and symptoms were a decrease in vision in 4 (57.1%), unilateral headaches in 3 (42.9%), unilateral abnormal sensation or numbness in the periorbital area in 3 (42.9%), external ophthalmoplegia in 3 (42.9%), double

Table 1 Demographics and initial manifestations

Case no.	Age, year/sex	Side of lesion	Medical history	HbA1C, %	Medical department at first visit	Interval between onset of symptoms and first visit (days)		Initial manifestations
						A certain medical institute	Our hospital	
1	26/F	L	None	NA	Ophthalmology	0	70	Decreased vision, double vision, proptosis, external ophthalmoplegia
2	76/M	L	DM, backbone disease	6	Neurosurgery	10	50	Unilateral headache, abnormal sensations of the periorbital area, proptosis, external ophthalmoplegia
3	67/M	R	HTN, stroke, invasive sino-orbital aspergillosis on the left side	NA	Ophthalmology	0	110	Decreased vison, blurred vision
4	70/M	L (→B)	DM	6.8	Otolaryngology	0	0	Unilateral headache, nasal congestion, staggering
5	57/M	L (→B)	DM	6.7	Ophthalmology	30	84	Decreased vision, double vision, numbness of the periorbital area, external ophthalmoplegia
6	68/M	L	DM, HTN, hyperuricemia	8.5	Neurosurgery	19	69	Unilateral headache
7	73/M	R	DM	5.6	Ophthalmology	2	7	Decreased vision, abnormal sensations and numbness of the periorbital area, visual field abnormalities

L left, *R* right, *B* bilateral, *DM* diabetes mellitus, *HTN* hypertension, *NA* no available data

Table 2 Examination findings and initial diagnosis

Case no.	Imaging at presentation		Intracranial extension Presentation/during follow-up examination	Orbital, paranasal, cavernous sinus involvement	β-D glucan, pg/mL		Serum aspergillus antigen	Initial diagnosis	Use of steroid/ radiation before diagnosis
	CT	MRI			Initial	Definitive diagnosis			
1	Bone destruction, mass infiltrating into the left orbit	Ill-defined, heterogeneous mass, isointense to muscle on T1-weighted images and hypointense on T2-weighted images	−/+	Left orbit, right maxillary, sphenoid, bilateral frontal, ethmoid	NA	NA	NA	Orbital tumor, idiopathic orbital inflammation, ocular sarcoidosis, lymphoma	+/+
2	Bone destruction, mass reaching apex	Ill-defined, heterogeneous mass, isointense to muscle on T1-weighted images and hypointense on T2-weighted images	−/+	Left ethmoid, sphenoid, left cavernous sinus	15.3	<5	Negative	Idiopathic orbital inflammation, lymphoma, bacterial sinusitis	+/+
3	Soft tissue mass reaching apex	Ill-defined, homogeneously enhanced mass, hypointense on both T1- and T2-weighted images	−/−	Right ethmoid, right cavernous sinus	64	117	Positive	Tolosa-Hunt syndrome, idiopathic orbital inflammation	+/−
4	Bone destruction, calcification, mass infiltrating into anterior cranial fossa	Slightly heterogeneous mass, isointense to muscle on T1-weighted images and hypointense on T2-weighted images	+/+	Left maxillary, anterior cranial fossa	NA	87.5	Positive	Fungal sinusitis	−/−
5	Bone destruction, osteosclerosis, soft tissue mass infiltrating into orbit and skull	Ill-defined, homogeneous mass, isointense to muscle on T1-weighted images and hypointense on T2-weighted images	+/+	Left orbit, left frontal, ethmoid, maxillary	NA	>300	NA	Malignant tumor	−/−
6	Bone destruction, soft tissue mass expanding inferior orbital fissure	Ill-defined, heterogeneously enhanced mass, isointense to muscle on T1-weighted images and hypointense on T2-weighted images	−/−	Left ethmoid, maxillary, sphenoid, left cavernous sinus	NA	284.2	Positive	Bacterial sinusitis	−/−
7	No abnormalities found initially	No abnormalities found initially	−/+	Right sphenoid	NA	45.3	NA	Retrobulbar neuritis, PION, Tolosa-Hunt syndrome	+/−

CT computed tomography, *MRI* magnetic resonance imaging, *PION* posterior ischemic optic neuropathy, *NA* no available data

vision in 2 (28.6%), and proptosis in 2 (28.6%) patients (Table 1). Additionally, 1 patient each had blurred vision, nasal congestion, staggering, and visual field abnormalities. The initial visual acuity was better than 20/30 in 5 (71.4%) and hand movements in 2 (28.6%) of the patients.

Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) were performed in all patients at the initial examination (Table 2). Five patients (71.4%) had ill-defined lesions. The initial CT findings indicated bone destruction in 5 patients (71.4%) (Fig. 1) and calcification in 1 patient (14.3%). The initial MRI examination showed hypointensity in the T1-weighted images in 1 patient (14.3%), and hypointensity in the T2-weighted images in 6 patients (85.7%) (Fig. 1). Although no CT and MRI abnormalities were detected in case 7 at the initial examination, mucosal hypertrophy in the sphenoidal sinus and soft tissue shadows in the cavernous sinus were detected 2 months later (Fig. 1). Intraorbital expansion of the lesions was confirmed in 2 (28.6%), intracranial extension in 2 (28.6%), and cavernous sinus invasion in 3 (42.9%) patients at the initial examination (Table 2).

Initial diagnosis and treatments before definitive diagnosis

Tumor, idiopathic orbital inflammation, ocular sarcoidosis, lymphoma, bacterial sinusitis, Tolosa-Hunt syndrome, retrobulbar neuritis, and posterior ischemic optic neuropathy (PION) were considered as the initial diagnosis (Table 2). However, only 1 patient (case 4) was suspected by the radiologists to have a fungal infection because of the presence of dense calcification in the initial CT images.

The treatments before the definitive diagnosis were radiation in 2 (28.6%), systemic steroid in 4 (57.1%), and antibiotics in 2 (28.6%) patients with some overlapping treatments (Table 2).

Biopsy and definitive diagnosis

Biopsies were performed for all the patients other than the patient of case 3, and *Aspergillus* organisms were histopathologically detected in all the specimens (Table 3; Fig. 2). Diagnostic biopsy in case 3 was not performed at our institution because the patient had been histopathologically diagnosed as having *Aspergillus* sinusitis at another hospital 1.5 years earlier. The number of biopsies performed was 1 in 3 patients and more than 2 in 3 patients (average 2.6 times).

A definitive diagnosis of ISOA was made from the histopathologic examinations of the biopsy specimens

Fig. 1 Radiologic features in invasive sino-orbital aspergillosis. ▶ Computed tomography (*left*) and magnetic resonance imaging (*middle and right*). *Case 1* A 29-year-old woman with double vision. CT (**a**) and T1-weighted MRI (**b**) showed a mass infiltrating into the left orbit and sinusitis in the ethmoid. *Case 2* A 76-year-old man with temporal headache for 10 days. CT (**c**) and T1- and T2-weighted MRI (**d**, **e**) showed a soft tissue mass reaching the left apex. *Case 3* A 67-year-old man with blurred vision for a few weeks. CT (**f**) and both enhanced T1- and enhanced T2-weighted MRI (**g**, **h**) showed a soft tissue mass reaching the right apex and extending into the cavernous sinus. *Case 4* A 70-year-old man with temporal headache, nasal congestion, and staggering. CT (**i**) showed calcification in the left maxillary sinus. T1-weighted MRI (**j**) showed a heterogeneous mass. Enhanced T2-weighted MRI (**k**) showed thickening of the mucosa in the left maxillary sinus and a mass infiltrating the anterior cranial fossa. *Case 5* A 57-year-old man with double vision and decrease in vision for 30 days. CT (**l**) and T1-weighted MRI (**m**) showed a homogeneous mass extending from the orbit to the anterior cranial fossa on the left. T2-weighted MRI **(n)** showed a hypointense mass in the muscle. *Case 6* A 68-year-old man with temporal headache for a few weeks. CT (**o**) and T1-weighted MRI (**p**) showed a soft tissue mass in the left ethmoid and sphenoid sinuses. T2-weighted MRI (**q**) showed the mass enhanced. *Case 7* A 73-year-old man with visual field abnormalities in the right eye. CT (**r**) and both T1- and T2-weighted MRI (**s**, **t**) showed no abnormal findings at presentation. CT (**u**) showed a soft tissue mass in the right sphenoid sinus 1.5 month after presentation. T1-weighted MRI showed enhancement of the sphenoid sinus on the right (**v**) and a hypointense mass around the right apex (**w**)

except in case 3 (Table 3). Only for case 7, which was of the most recently diagnosed patient, was a polymerase chain reaction (PCR) test performed on formalin-fixed, paraffin-embedded sections to identify the *Aspergillus* species, and the results showed that *A. fumigatus* was the causative organism. Cases 1 to 6 were not identified to the level of the *Aspergillus* species because formalin-fixed, paraffin-embedded sections were not available. The median interval between the presentation at our institution and the time of definitive diagnosis for all the cases other than case 3 was 59 days (range 24–1018 days).

β-D-glucan and *Aspergillus* antigen

The serum β-D-glucan level just after the detection of *Aspergillus* was 45.3 to >300 pg/mL, which is higher than the standard range, in 5 of 6 patients (83.3%) (Table 2). There was no medical record of the serum β-D-glucan level in case 1. After the detection of the *Aspergillus* organisms, its antigen was positive in the blood of 3 of 4 patients (75%).

Treatments and outcomes

After the definitive diagnosis was made, all the patients were treated with several antifungal drugs (Table 3). The antifungal drugs used were intravenous amphotericin-B, oral itraconazole, intravenous micafungin, and intravenous

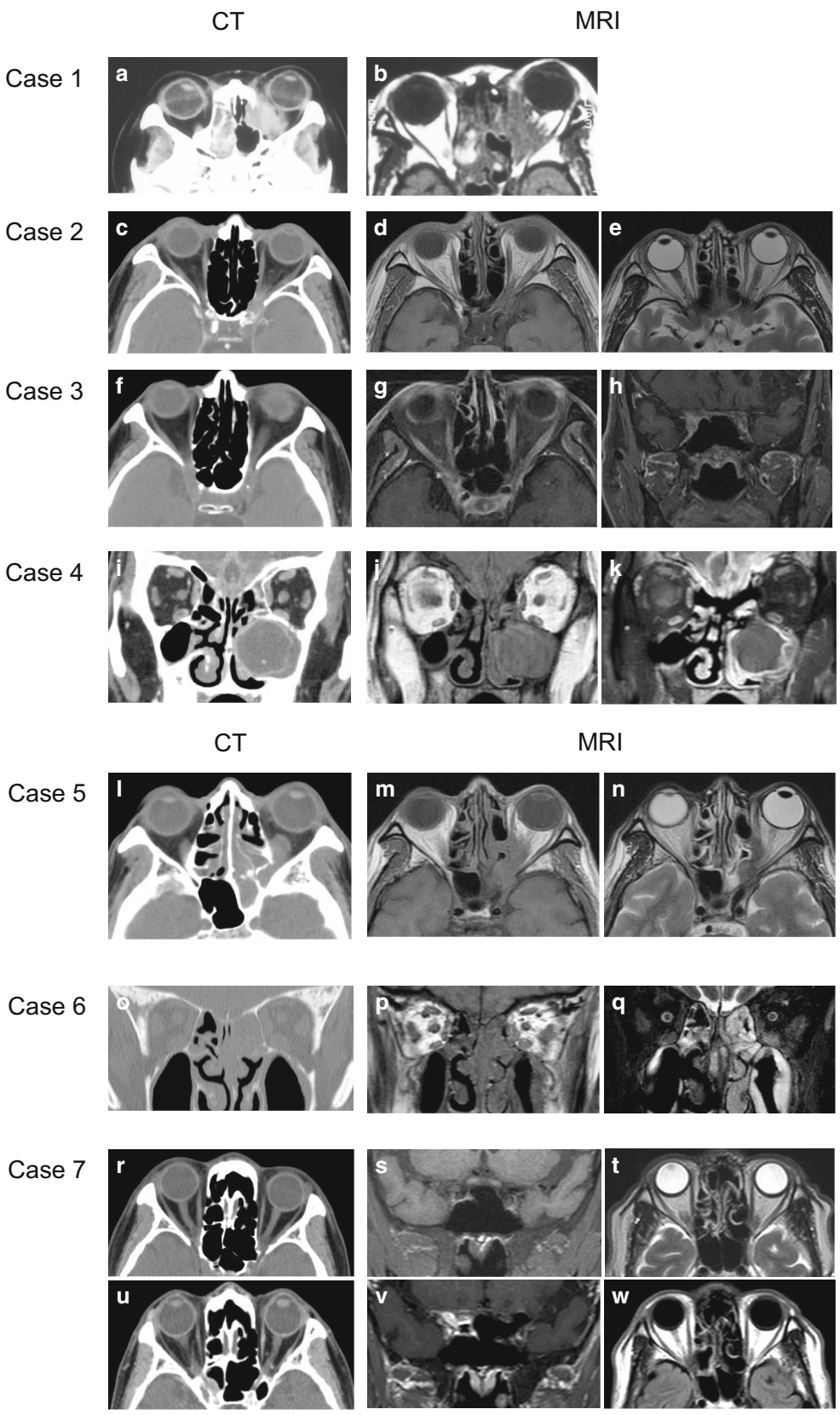
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Table 3 Biopsy, definitive diagnosis, and treatment

Case no.	No. of biopsies	Etiologic fungus	Interval between presentation at our institutions to time of definitive diagnosis (days)	Medical treatment			Adverse effects of medical treatment
				Antifungal agent	Total amount of dose used, mg	Daily dose (mg/day) * the total number of dosing days	
1	7	*Aspergillus* species	1018	AMPH	4200	30 * 40 + 25 * 120	–
				ITCZ	249,400	200 * 1247	
				FLCZ	48,000	400 * 120	
2	2	*Aspergillus* species	82	AMPH	418	11 * 38	–
				ITCZ	26,200	200 * 131	
				MCFG	51,900	300 * 173	
3	0	*Aspergillus* species	0	ITCZ	10,400	200 * 52	–
				MCFG	8550	150 * 53 + 100 * 6	
4	1	*Aspergillus* species	24	L-AMB	2950	100 * 2 + 200 * 4 + 150 * 13	–
				MCFG	25,400	150 * 8 + 300 * 80 + 200	
				VRCZ	32,420	560 + 300 * 93 + 240 * 4 + 200 * 15	
5	4	*Aspergillus* species	35	AMPH	822.5	45 * 10 + 22.5 * 16 + 12.5 * 1	Renal impairment, digestive symptom, photophobia
				ITCZ	59,200	200 * 296	
				VRCZ	184,000	800 * 5 + 600 * 1 + 400 * 448 + 200 * 1	
6	1	*Aspergillus* species	11	MCFG	1200	150 * 8	–
				VRCZ	95,700	400 * 125 + 300 * 35 + 200 * 176	
7	1	*Aspergillus fumigatus*	108	ITCZ	42,000	200 * 210	Liver dysfunction
				MCFG	19,500	300 * 65	
				VRCZ	8400	400 * 21	

AMPH amphotericin-B, *ITCZ* itraconazole, *MCFG* micafungin, *L-AMB* liposomal amphotericin-B, *VRCZ* voriconazole

or oral voriconazole. None of the patients had intraocular or intraorbital medical treatment and surgery.

The final outcome was no light perception, including phthisis bulbi, in 6 eyes (85.7%), and 20/600 in 1 eye (Table 4). There were signs of damage to the oculomotor nerve in 5 (71.4%), to the trochlear nerve in 4 (57.1%), to the trigeminal nerve in 4 (57.1%), and to the abducens nerve in 5 (71.4%) patients during the follow-up period. Five patients (71.4%) eventually had an intracranial extension of SOA; 3 of them (60%) died, and the average interval between the onset of symptoms and death was 327 days (range 187–433 days). In total, 4 of the 7 patients (57.1%) died during the follow-up period. The patient of case 3, who did not have an intracranial extension, unexpectedly died at 1555 days of follow-up, but the cause of death was not stated in the medical record. The patient of case 1 was followed for 3234 days but was lost after that. This patient also had depression and articulation disorder related to intracranial extension of *Aspergillus* and attempted suicide once during this period. The patients of cases 5 and 6 are still alive with no disease recurrence over 3129 and 2414 days of follow-up, respectively.

Discussion

We have presented the clinical manifestations and outcomes of 7 cases of ISOA, which is the largest number of cases among the previous reports in Japan. The reported risk factors for SOA were advanced age, diabetes mellitus, use of corticosteroids or immunosuppressive agents, hematologic malignancy, neutrophil defect, HIV infection, excessive environmental exposure to fungi, and transplantation [3, 4, 8]. In this study, 5 patients (71.4%) had diabetes mellitus and were aged over 65 years. However, none had diseases that compromise immunity.

The signs and symptoms of eyes with orbit and orbital apex SOA often precede those of the sinuses [2, 4]. Therefore, ophthalmologists have a greater chance to be the first to see patients with SOA [7]. Thurtell et al. [6] reported that 6 of 10 patients (60%) with SOA had initially visited an ophthalmologist, which is similar to our finding in 4 of 7 cases (57.1%).

The clinical manifestations of invasive fungal sinusitis including *Aspergillus* are varied and nonspecific [2]. The reported common signs and symptoms are proptosis

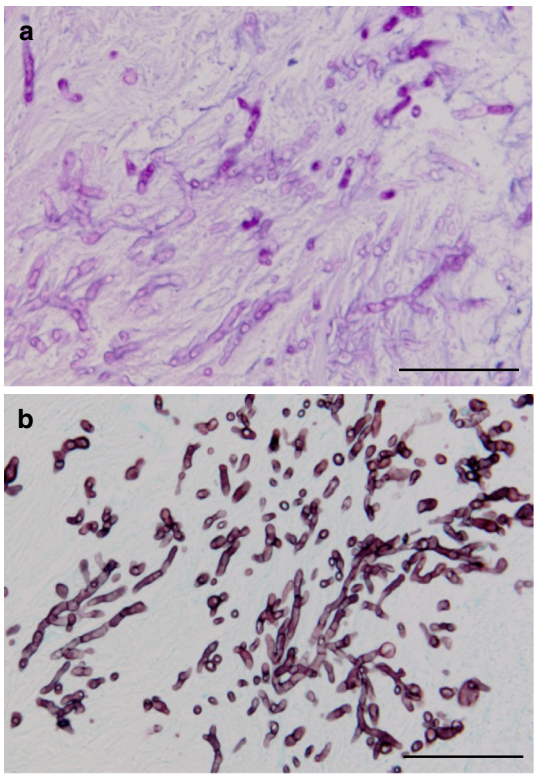

Fig. 2 Histopathologic findings of sino-orbital aspergillosis (case 7). Periodic acid-Schiff stain (**a**) and Grocott stain (**b**) showing dichotomously branching fungal hyphae. *Bar* 50 μm

[4, 6, 9], periocular swelling [9], pain located on one side of the head or retrobulbar area [1, 6, 8], disorders of eye movements [6], and decreased vision [4]. In our patients, the most common symptoms at presentation were blurred vision (4 patients [57.1%]), followed by unilateral headache (3 patients [42.9%]), unilaterally abnormal sensation or numbness of the periorbital area (3 patients [42.9%]), and external ophthalmoplegia (3 patients [42.9%]). Thus, persistent unilateral pain or abnormal sensation in the head or the retrobulbar area should alert clinicians to the possibility of SOA. According to the literature [4, 6, 10], symptoms related to sinus involvement such as rhinorrhea, epistaxis, nasal congestion, and nasal crusting are rare at presentation, which is consistent with our results.

Previous studies reported on the advantages of both CT and MRI in the diagnosis of suspected sino-orbital fungal infections (Table 5) [3–5, 11–14]. The presence of dense calcification is particularly suggestive of aspergillosis [4]. Calcifications in the CT images were reported to be present in 50% [11], 53% [12], 77% [13], and 88% [14] of patients with *Aspergillus* sinusitis. In the MR images of suspected aspergillosis, heterogeneous lesions and hypointense signals on both the T1- and the extremely T2-weighted images are reliable signs for this disease [3–5, 13]. However, calcification of the CT images was detected in only 1 of our patients (14%) and hypointense signals on both the T1- and the T2-weighted images were detected in another patient (14%) only. The reason for such differences in the incidence between our study and those of other studies is unknown. Although calcification in the CT images and hypointensity in the MR images are highly indicative of aspergillosis, it should be noted that their absence does not rule it out [7], as shown in our cases. Sinus aspergillosis is rare and difficult to distinguish from other similar diseases radiologically [14].

New diagnostic markers for invasive fungal infections, such as serum *Aspergillus* galactomannan and β-D-glucan, are reported to be useful for early diagnosis of invasive fungal infections [1, 15, 16]. In our study, the serum β-D-glucan level exceeded the normal limits in 83.3% of the patients. Thus, the level of serum β-D-glucan should be determined for patients having the early signs and symptoms of aspergillosis: unilateral and persistent headache, periorbital pain, facial numbness, ptosis, and disorders of ocular movements of unknown origin.

A definitive diagnosis of SOA is ultimately made by histopathologic examination of biopsy specimens with support from the clinical findings and CT and MR images.

Table 4 Outcomes

Case no.	Visual acuity		Involved cranial nerves	Survival outcome	Interval between onset of symptoms and death (days)	Period of follow-up examination (days)
	Initial	Final				
1	20/25	0 (phthisis)	II III IV V VI	Unknown	NA	3234
2	20/25	0	II III IV V VI	Dead	361	311
3	HM	20/600	II	Dead[a]	1555	1454
4	20/20	0	II V	Dead	187	187
5	HM	0	II III IV VI	Alive	NA	3129
6	20/25	0	II III VI	Alive	NA	2414
7	20/30	0	II III IV V VI	Dead	433	426

HM hand motions, *NA* no available data

[a] Cause of death unknown

Table 5 Characteristics on image findings

	Invasiave sino-orbital mycosis	Bacterial sinusitis	Sarcoidosis	Idiopathic orbital inflammation	Malignant lymphoma	Tolosa-Hunt syndrome	Bacterial cellulitis
CT	Ill-defined, heterogeneous, irregular mass, low-density mucus and calcification in sinus, thickening of nasal or sinus mucosa, bone destruction and erosion, osteosclerosis	Mucosal thickening and fluid in sinus	Diffuse, relatively defined, low-density, homogeneously enhanced mass	Ill-defined, irregular, heterogeneously enhanced mass	Ill-defined, irregular, diffuse mass, molding around normal structures without deforming them, that is isodense to extraocular muscle	No abnormal findings on plain images, slight soft tissue changes possibly on high resolution images	Ill-defined, irregular, homogeneously enhanced mass
MRI	Ill-defined, homogeneously enhanced mass, that is hypointense on T1-weighted images and extremely hypointense on T2-weighted images	Thickening mucosa that is isointense to soft tissue, hypointesive fluid in sinus on T1-weighted images, both mucosa and fluid are extremely hyperintense on T2-weighted images	Homogeneously enhanced mass, that is isointense to gray matter on both T1- and T2-weighted images	Ill-defined, homogeneously enhanced mass, that is isointense to extraocular muscle on T1-weighted images and hyperintense on T2-weighted images	Ill-defined, homogeneously enhanced mass, that is isointense to white matter and extraocular muscle on T1-weighted images and isointense to fat on T2-weighted images	Enlarging, homogeneously enhanced cavernous sinus, that is isointense to gray matter and extraocular muscle on T1-weighted images, hyperintense to muscle and isointense to fat on T2-weighted images	Ill-defined, homogeneous mass, that is isointense to optic nerve and extraocular muscle on T1-weighted images and hyperintense on T2-weighted images

CT computed tomography, *MRI* magnetic resonance imaging

However, Dhiwakar et al reported a sensitivity of 33% for incisional biopsy from the paranasal sinuses [10]. Six of our patients with an average of 2.6 biopsies were finally diagnosed as having aspergillosis by the histopathologic findings. Similar to a previous report [10], only 3 of these patients (50.0%) were diagnosed after the first biopsy, and the others required repeated biopsies. The necessity of repeated biopsies may be due to 3 problems: the staining method, preconceptions, and sampling errors. Fungi including *Aspergillus* are frequently not stained with hematoxylin-eosin (HE), and special stains such as periodic acid-Schiff (PAS) are better in making them visible [4, 5, 7, 8, 17]. In case 1, the first to sixth biopsy specimens were stained with HE, and that of the seventh was stained with HE, PAS, and Grocott stains. Every section of the first to sixth biopsies revealed some abnormalities such as dense hyaline connective tissue with foreign body giant cells, fibrous connective tissue with inflammatory cell infiltration, and loose connective tissues without cell components. A definitive diagnosis of aspergillosis was made by the seventh biopsy specimen stained with PAS and Grocott staining, although the report of the seventh biopsy sections stained with HE were similar to those of the first to sixth biopsies. *Aspergillus* is generally considered to be a harmless saprophyte that is ubiquitous in our environment [18]. In case 2, *Aspergillus* organisms were detected on the first biopsy but were considered normal flora. The samples were reported to be inflammatory responses, and such preconceptions probably led to the misdiagnosis. Biopsies were taken 3 times in case 5, and all of the samples were stained with PAS. The histopathologic changes of the specimens were concluded to be tissue inflammatory responses, and *Aspergillus* organisms were finally detected on the fourth biopsy. This could probably be classified as a sampling error. PCR is also valuable in cases in which either the culture results are negative or culturing is not performed [19, 20]. In case 7, the most recent case, PCR was performed using formalin-fixed, paraffin-embedded sections, and *A. fumigatus* was detected.

SOA is often misdiagnosed as being a variety of diseases, such as optic neuritis, temporal arteritis, bacterial cellulitis, malignant tumor, lymphoma, idiopathic orbital inflammation, and the Tolosa-Hunt syndrome. Thus, it is often treated with steroids and radiation [4–6, 8]. In our study, 4 patients were initially treated with systemic steroids for presumed idiopathic orbital inflammation and/or Tolosa-Hunt syndrome, and 2 of 3 patients were misdiagnosed as having a malignant tumor and underwent radiation therapy. We recommend that biopsies be done to identify the causative organism before the use of steroids or radiation.

Thurtell et al. [6, 21] reported that amphotericin B is considered the gold standard agent to treat SOA; however,

its use is limited because of the associated complications, such as nephrotoxicity. Itraconazole and voriconazole have now replaced amphotericin B. However, 4 of the 7 patients in our study treated with combinations of amphotericin B, itraconazole, and/or voriconazole eventually died, and 3 of these 4 patients died of intracranial extension. Before the introduction of antifungal therapy, these 3 patients received systemic steroid therapy for presumed inflammatory disease. The progression of the signs and symptoms should be carefully monitored during such empirical treatments. Even though antifungal agents are used, changes in the symptoms should be carefully monitored because of the increase in the number of fungi having low susceptibility to antifungal drugs [22, 23] and the problem of the penetration of antifungal drugs through the blood–brain barrier [2]. Newer antifungal agents are needed to control this severe infection. In 2016, Aggarwal et al. [21] reported that no definite treatment protocols existed for orbital aspergillosis, but a complete surgical debridement was recommended as the primary treatment in patients with orbital aspergillosis [21]. Involvement of the bone, blood vessels, and orbital structures, however, limits this approach. Radical surgical debridement of the sinuses and skull base area is rarely performed in Japan, unlike in advanced Western countries. Surgical intervention treatment might have rescued some of our patients.

Invasive fungal sinusitis has a very poor prognosis for both vision and life. The rate of permanent loss of light perception was reported to be 80% [24] and 100% [6]. The death rate was reported to be 50% [1], 60% [6], and 71% [8]. In our study, the rate of loss of light perception was 86% (6 of 7 eyes). The cause of the sudden death in case 3 was not known. Death related to SOA occurred in 3 of our 7 patients (43%). Differences between the deceased patients (cases 2, 4, and 7) and the surviving patients (cases 1, 5, and 6) in terms of the medical history or presence or absence of intracranial invasion were not observed, but the age at onset (median age, 73 vs 57 years) clearly differed between these 2 groups. Patients with older age at onset had a higher mortality rate, which is similar to previous reports [4, 9].

To conclude, ISOA has nonspecific clinical manifestations and poor prognoses for both vision and life. Diabetes mellitus and onset at age >65 years were risk factors for ISOA, and older age at onset may have a poor prognosis. Histopathologic examinations by repeated biopsies with support from the clinical findings and CT and MR images are necessary for a definitive diagnosis. Ophthalmologists are often the first to examine these patients, and ISOA should be considered in the differential diagnoses of patients with a gradually progressive orbital mass, unilateral persistent headache, unilateral numbness of the periorbital area, and decrease in visual acuity of unknown origin.

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