Invasive Orbital Apex Aspergillosis with Mycotic Aneurysm Formation and Subarachnoid Hemorrhage in Immunocompetent Patients

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■ BACKGROUND: **Invasive orbital apex aspergillosis (IOAA) is an aggressive form of aspergillus infection that usually affects immunocompromised patients. It can cause orbital apex syndrome and, if not treated promptly, may progress rapidly causing fatal complications. Subarachnoid hemorrhage (SAH) secondary to ruptured mycotic aneurysms is a very rare complication of invasive aspergillosis. We aim to describe our management and the outcome of six immunocompetent patients with IOAA with subsequent SAH secondary to ruptured mycotic aneurysms.**

■ PATIENTS AND METHODS: **A retrospective review was undertaken of charts of patients treated for orbital involvement with aspergillosis between January 2003 and December 2015 at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. We identified all immunocompetent patients with IOAA who developed vascular complications.**

■ RESULTS: **Six immunocompetent patients with IOAA complicated by SAH secondary to ruptured mycotic aneurysms were identified in the study period. Four patients were female, and patients' age ranged between 14 and 53 years (mean, 33.7 ± 13.4 years). All patients presented with progressive retro-orbital headache, visual impairment, and ophthalmoplegia; four had proptosis. Two patients had vasospasm and brain infarction. Antifungal therapy was used in all patients, and 4 underwent emergency craniotomy and clipping of an aneurysm. Five patients died as a consequence of SAH and infarction.**

■ CONCLUSIONS: **IOAA is a serious disease that commonly causes catastrophic and fatal vascular complications.**

INTRODUCTION

Invasive orbital apex aspergillosis (IOAA) is a rare clinical entity, especially in immunocompetent patients.[1] The diagnosis of invasive aspergillosis can be challenging because of the wide variety of clinical presentations and the relative rarity of the disease.[1,2] Invasive aspergillosis can lead to intracranial complications including meningitis, meningoencephalitis, brain abscess, skull base osteomyelitis, cavernous sinus thrombosis, infarctions, and rarely, mycotic aneurysms.[3]

Orbital apex syndrome (OAS) is a constellation of findings characterized by paralysis of extraocular muscles and facial hypoesthesia due to multiple cranial nerve palsies, including the optic (cranial nerve [CN] II), the oculomotor (CN III), the trochlear (CN IV), and the abducens (CN VI) nerves, and the ophthalmic branch of the trigeminal nerve (CN V_1).[4] OAS can be caused by traumatic injuries, tumors of the orbit or adjacent structures, vasculitis, inflammatory diseases, or infections.[4,5] Bacterial, viral, and fungal infections have been reported to cause OAS.[5] Invasive fungal infection, caused by aspergillosis and mucormycosis, is a rare cause of OAS that usually affects immunocompromised hosts with sinus involvement[4,6]; however, some cases have been reported in immunocompetent individuals.[1]

The formation of mycotic aneurysms and subsequent subarachnoid hemorrhage (SAH) is a very rare complication of

Key words
- Aspergillosis
- Cerebral infarction
- Fungal infections
- Orbital apex syndrome
- Subarachnoid hemorrhages

Abbreviations and Acronyms
CN: Cranial nerve
CNS: Central nervous system
CSF: Cerebrospinal fluid
CT: Computed tomography
ICA: Internal carotid artery
IOAA: Invasive orbital apex aspergillosis
MRI: Magnetic resonance imaging
OAS: Orbital apex syndrome
SAH: Subarachnoid hemorrhage

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invasive aspergillosis.[3,6] This potentially fatal clinical complication of IOAA is reported rarely in immunocompetent patients.[7] In this study, we describe the clinical and radiologic characteristics, management, and outcome of 6 immunocompetent patients diagnosed in our institution with IOAA presenting with OAS complicated by SAH secondary to ruptured mycotic aneurysms.

MATERIALS AND METHODS

This was a retrospective chart review study at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. Medical records of patients treated for orbital aspergillosis between January 2003 and December 2015 were reviewed. Patients with pathologically proven IOAA that presented with vascular complications were included.

Standardized data collection form was used to collect relevant data, including patients' demographics, clinical presentation, comorbidities, radiologic features, pathology findings, diagnosis, treatment, complications, and outcome.

Inclusion/Exclusion Criteria

Study inclusion criteria were as follows: 1) patients with IOAA presenting with vascular complications (ischemic or hemorrhagic stroke, or SAH); 2) absence of clinical and radiological evidence of active otic or sinonasal disease; 3) absence of immunosuppression or any systemic disease; and 4) confirmation of diagnosis by either an evidence in histopathology or culture of surgically excised specimens or by cerebrospinal fluid (CSF) culture or serology test of galactomannan antigen.

We used the same magnetic resonance image (MRI) and computed tomography (CT) studies primarily performed to evaluate the extent of the invasive infection to assess the paranasal sinuses and otic involvement as they offered adequate visualization down to the maxillary sinuses and mastoid air cells. Pulmonary involvement was determined by reviewing patients' admission chest radiographs and charts for respiratory manifestations. Immunocompetency was determined by assessing patients and assuring the absence of any concomitant or previous chronic diseases. Patients were labeled immunocompetent if they were free from diabetes mellitus, alcoholism, advanced liver or kidney disease, malignancy, leukopenia, treatment with immunosuppressive or corticosteroid medications, organ transplantation, human immunodeficiency virus infection, or intravenous drug abuse.

Investigations

Routine investigations performed for all patients included complete blood count, liver, and renal functions tests, fasting blood sugar, and chest radiographs. Erythrocyte sedimentation rate and C-reactive protein levels were ordered in 3 patients. Radiologic studies included axial and coronal CT scan of the brain and paranasal sinuses and MRI of the brain without and with intravenous contrast administration in all patients. Computed tomography angiography (CTA), magnetic resonance angiography, and catheter angiography were performed to delineate the vascular complications.

Management

Treatment was initiated immediately after evaluation of radiologic studies and when IOAA was suspected. Patients were treated with antifungal therapy, initially with intravenous liposomal amphotericin B, followed by either oral voriconazole or itraconazole. An orbitofrontal craniotomy was performed in 4 patients to clip an aneurysm and debride the granuloma from the orbital apex and the middle cranial fossa. Two patients underwent external ventricular drainage because they presented with a Glasgow Coma Scale score less than 8 and with SAH and massive obstructive hydrocephalus and cerebral infarctions.

Histologic and Microbiological Diagnosis

The diagnosis was established by the recovery of aspergillus on fungal culture media and on histologic and immunohistochemical staining examinations of the specimen. In addition, CSF samples were obtained in 3 patients and were used to confirm the diagnosis through CSF cultures or serology tests of galactomannan antigen.

Outcome

Clinical follow-up data were obtained from medical records to determine the outcome and complications of the disease including worsening of preexisting neurologic deficits and the development of any postoperative complications.

RESULTS

From January 2003 through December 2015, we identified a total of 22 patients with orbital aspergillus infection. Sixteen patients were excluded for the following reasons: 9 patients had extensive and active sinonasal disease with medial orbital extension; 4 patients had localized aspergillosis of the orbital apex without intracranial extension; 1 patient had fungal meningitis, and 2 immunocompromised patients had intracranial disease causing carotid artery occlusion and massive infarction. Only 6 patients fulfilled our inclusion criteria.

The age of the 6 eligible patients ranged from 14 to 53 years with a mean of 33.7 $\pm$ 13.4 years. Four of the 6 eligible patients were female. Unilateral orbit involvement was seen in 5 patients (4, the left orbit, and 1, the right), and 1 patient had bilateral disease. All patients presented with a severe headache, visual impairment, and ophthalmoplegia, whereas proptosis was evident in 4 patients. The duration of symptoms before patients' presentation ranged between 8 and 22 days (Table 1).

Radiologic findings are summarized in Table 2. CT scans of the fungal infections showed hyperdensity associated with bone destruction. On noncontrast MRI, the disease showed low signal on T2-weighted images and intermediate-to-low signal on T1-weighted images. Restricted diffusion and heterogeneous enhancement with gadolinium also were noted. Considerable-size extraconal disease was seen, resulting in exophthalmos. Depending on the involvement of the orbital apex with superior or inferior orbital fissures, various combination of nerve involvement was demonstrated by ophthalmologic clinical examination.

On clinical and radiologic evidence of IOAA and confirmation of the diagnosis by histopathology or tissue culture, aggressive antifungal therapy was started. The middle cranial spread of infection was seen in all cases within 3–10 days of presentation. Sudden deterioration of patients' condition prompted reimaging by CT between days 4 and 7 after admission, which revealed SAH in all cases. Ruptured mycotic aneurysms were identified in all patients.

Table 1. Demographic and Clinical Characteristics of 6 Patients with Invasive Orbital Apex Aspergillosis

Clinical Details	*n*
Age, years	
Range	14–53
Mean ± SD	33.7 ± 13.4
Sex	
Male	2
Female	4
Presentation	
Side of affliction	
Right	1
Left	4
Bilateral	1
Duration before onset	8–22 days*
Severe headache	6
Proptosis ($n = 4$)	
Unilateral	3
Bilateral	1
Diplopia	3
Visual impairment	6
Ophthalmoplegia	6
Hypoesthesia of the face	4

*Two patients not available; 8, 13, 22, and 9.

Table 2. Radiologic Characteristics* of 6 Patients with Invasive Orbital Apex Aspergillosis

Spread of disease to the middle cranial fossa	6
Subarachnoid hemorrhage	6
Aneurysms	
ICA	3
ACA	1
PCA	1
BA	1
Infarction	
Anterior circulation territory	1
Posterior circulation territory	1
Clinical outcome	
Death	5
Complete monocular blindness and ophthalmoplegia	1

ICA, internal carotid artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery.
*Combination of computed tomography, magnetic resonance imaging, and angiographic findings.

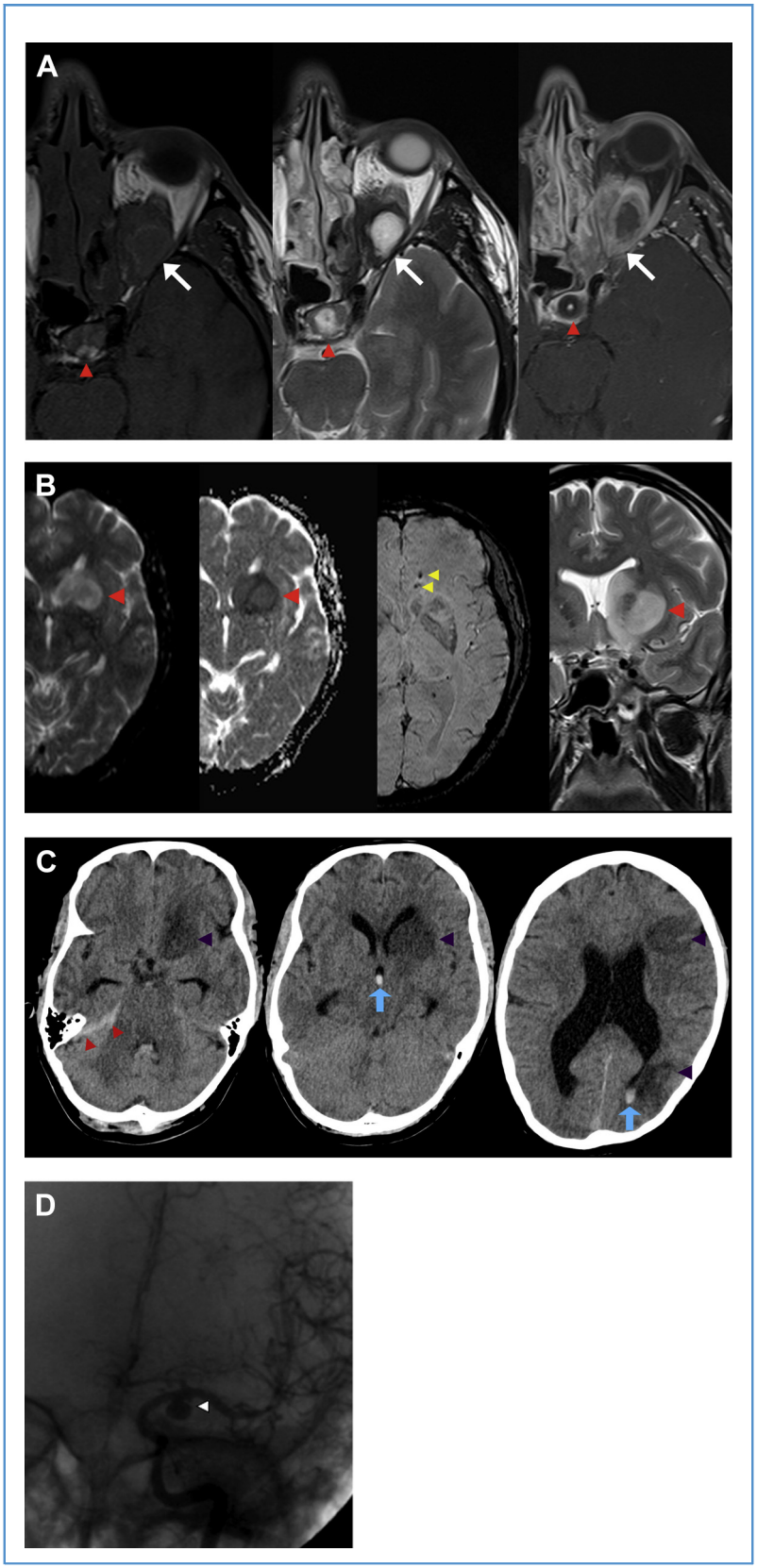
CTA was performed in 5 patients and showed aneurysms of the circle of Willis; 2 distal internal carotid artery (ICA) aneurysms, 1 anterior cerebral artery an aneurysm, 1 posterior cerebral artery aneurysm, and 1 basilar artery aneurysm. In the sixth patient, another ICA aneurysm was identified with the use of catheter angiography as the patient presented before the availability of CTA as a screening test for cerebral aneurysms in our institution. CSF was obtained from external ventricular drain in 2 patients, and a spinal tap was done in another patient. Two patients tested positive for CSF (one positive culture and one positive galactomannan antigen).

The mortality was high despite aggressive medical and surgical treatment. Five patients died within 12 days to 7 weeks after diagnosis. Two of them presented with poor Glasgow Coma Scale scores secondary to SAH and massive cerebral infarctions. They did not improve despite aggressive medical therapy and CSF drainage. Four patients underwent successful clipping of the aneurysms and debridement of the granuloma. In 2 clipped ICA aneurysms, they were appeared as berry aneurysms with a well-defined wide neck that required clipping using 2 fenestrated clips encasing and preserving the ICAs. In the third case, an ICA fusiform aneurysm was trapped with Sundt's encasing clip. The last case was a distal fusiform anterior cerebral artery aneurysm and was clipped proximally because the distal artery was very small. Despite successful surgery, all 4 cases had a progressive local disease and subsequently died of massive strokes as the result of progression of the disease and sequela of SAH. One patient survived the episode of infection; however, he was left with monocular blindness. **Figure 1** illustrates one of the cases in our series.

DISCUSSION

Aspergillus is a common mold that usually causes disease in immunocompromised patients. *Aspergillus fumigates* is the most common causative species isolated from human infections.[3] Inhalation of spores is the usual route of infection, giving the organism access to the bronchopulmonary tree and paranasal sinuses.[3] Invasive aspergillosis can be a localized or hematogenous spread infection.[8-10] Localized infection is associated with ulceration and destruction of the sinus with bone erosions and spread to adjacent structures.[9,11] Invasive disseminated infections are seen most commonly in immunocompromised patients and are usually fulminant and affect multiple organ systems.[5,8,9,11] A few reports of invasive orbital aspergillosis in immunocompetent patients have been reported in the literature.[11]

Patients with IOAA usually present with visual impairment, headache, periorbital pain, periorbital swelling, proptosis, and ophthalmoplegia along with cranial nerves impairment.[1,9] The clinical presentation among immunocompetent patients is widely variable and may hinder the establishment of the diagnosis.[1,11] For instance, in a case series of 4 immunocompetent patients and review of 17 additional previously published cases with sino-orbital invasive aspergillosis, 6 patients initially were misdiagnosed as temporal arteritis.[8] The history of vague, persistent unilateral pain localized to one side of the head or retro-orbital area, unilateral headache, and increase in C-reactive protein or erythrocytes


A
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sedimentation rate without other findings in immunocompetent patients led to the wrong diagnosis of temporal arteritis.[8] Many immunocompetent patients with invasive orbital aspergillosis have the history of paranasal sinus infection while others may present without any sinus symptoms.[1,3,11] None of our reported patients were having any clinical or radiologic evidence of active sinus infection at the time of the diagnosis.

OAS is a constellation of findings due to retro-orbital paralysis of extraocular muscles from infiltration of the oculomotor, trochlear, and abducens nerves.[4] Other findings include facial hypoesthesia due to involvement of the ophthalmic branch of the trigeminal nerve, and frequently visual impairment secondary to involvement of the optic nerve.[4] Invasive fungal infection is an important, albeit very rare, cause of OAS and usually is secondary to sinus infection in immunocompromised patients.[4] Aspergillus species is the most common causative fungus.[5] Invasive aspergillosis causing OAS in immunocompetent individuals is a very rare disease that is scarcely reported in literature.[12,13] All of our patients presented with a headache and symptoms of OAS that included visual impairment and ophthalmoplegia. Exophthalmos secondary to enlarging fungal mass was evident in 67% of our patients ($n = 4$) (**Table 1**).

The formation of intracranial mycotic aneurysms secondary to invasive aspergillosis is an extremely rare complication.[3,14] Intracranial mycotic aneurysms can result from either direct invasion of the fungi from an adjacent source of infection or hematogenous dissemination from a primary focus, usually in the lungs.[14,15] Neurosurgical procedures were also reported to introduce aspergillus into the central nervous system (CNS).[14,16] Aspergillus invades the cerebral blood vessels and causes intense inflammation of the arterial wall leading to thrombosis, dilation, rupture, and mycotic aneurysm formation.[14,15] A previous review of literature reported that 60% of patients with positive microscopic diagnosis of CNS aspergillosis had a triad of aspergillosis mycotic aneurysm, brain infarction, and granuloma formation.[14] The production of elastases by aspergillus species facilitates invasion to the arterial wall by digesting elastin.[14] This focal inflammatory destruction of the arterial wall may subsequently result in aneurysmal dilatation or vascular rupture causing SAH.[14] Invasive orbital aspergillosis causing mycotic aneurysms and subsequent SAH is an extremely rare disease in immunocompetent patients.[7] Mycotic cerebral aneurysms secondary to invasive aspergillosis are often large and isolated fusiform aneurysms and frequently affect the proximal segments of the major cerebral arteries at the skull base, as our cases.[3,17]

The clinical presentation of IOAA is widely variable and nonspecific, especially among immunocompetent patients. The nonspecific presentation, rarity of IOAA, absence of sinus involvement, and low index of suspicious may hinder the establishment of the diagnosis of IOAA.[1] It often is difficult to differentiate invasive aspergillosis mass lesions from other lesions radiologically, even with MRI.[14,15] Invasive orbital aspergillosis appears in CT scans as ill-defined, heterogeneous, hyperdense mass or as a heterogeneous infiltration of orbit.[1] Bone changes such as remodeling or erosions also can be seen on CT scans.[1] The presence of calcifications on CT scan, especially when their density is exceeding 2000 Hounsfield units, is particularly suggestive of aspergillosis.[18] In noncontrast MRI, invasive orbital aspergillosis usually produces low-intensity to iso-intensity signals on T1-weighted images and low-intensity signals on T2-weighted images.[1] Enhancement in postgadolinium MRIs is seen with restricted diffusion.[1,9,19] CTA or cerebral angiograms may help to diagnose and follow-up mycotic aneurysms secondary to invasive aspergillosis.[14] Cerebral infarction also is seen frequently as a complication of CNS vascular involvement by aspergillosis.[3,7]

Although CT and MRI can suggest aspergillosis, a definitive diagnosis should be made only after histologic confirmation of the operative specimens. High rates of negative biopsy results have been reported, and more than one biopsy may be needed.[8,9,20] Biopsies from hypodense areas may improve the efficacy and accuracy of biopsies.[8,18] In vitro culture of aspergillus species, the gold standard method of diagnosis, requires 2–6 days of incubation.[9] Also, the presence of galactomannan antigen (a major cell wall protein of *Aspergillus*), detection of *Aspergillus flavus*-specific DNA, and the identification of 1,3-β-D-glucan have been reported

Figure 1. Case illustration: A 43-year-old woman presented with a headache and left visual impairment and diplopia of 3 weeks' duration. (**A**) Axial magnetic resonance imaging (MRI) demonstrated a dumbbell-shaped lesion in the left orbital apex. The lesion was predominantly hypointense, with a rim of hyperintense signal suggesting a fungal etiology (*white arrow*) on T1-weighted (*left image*), with a rim of low signal with central necrosis appearing hyperintense on axial T2-weighted image (*middle image*), and marked peripheral enhancement of the lesion following the administration of intravenous gadolinium (*right image*). Note that the sinus component of the lesion is almost negligible compared with the orbital apex lesion (*red arrowhead*). The patient subsequently had right hemiparesis while on adequate antifungal therapy, and follow-up MRI, particularly, axial diffusion-weighted, and apparent diffusion coefficient and coronal T2-weighted images (**B**) scan demonstrated basal ganglia infarctions (*orange arrowhead*) and petechial hemorrhage (*yellow arrowhead*). This was presumed to be due to a combination of an intra-axial extension of the infection and vasospasm. (**C**) Axial nonenhanced computed tomography scan showed the advancing infarctions (*purple arrowheads*), subarachnoid hemorrhage (*orange arrowheads*) and intraventricular bleed (*blue arrows*). (**D**) Left internal carotid artery aneurysm (*arrowhead*) was demonstrated on digital subtraction angiography scan.

to be associated with cerebral aspergillus infection.[21-23] These nonculture based methods aim at early diagnosis of invasive aspergillosis and help at the beginning of initiation of treatment for this commonly fatal condition.[21] In particular, CSF galactomannan has showed high diagnostic performance results in detecting cerebral aspergillosis.[23] It was reported to be positive in a child with mycotic intracerebral aneurysms.[24] Such tests, however, are not available widely and are time-dependent.[22] In most cases of mycotic aneurysms secondary to aspergillosis, CSF analysis is nonspecific and shows pleocytosis with an increase in protein content.[15,22]

Debridement of the invasive fungal mass followed by intravenous amphotericin B is considered the treatment of choice of IOAA.[3] In cases of OAS, the presence of vital structures around the lesion may hinder complete surgical debridement.[19] When choosing an antifungal agent, amphotericin has the greatest rate of side effects.[3,19] Increasing reports have shown that some triazoles are emerging as better-tolerated, effective alternatives or add-ons.[19,25] Initial therapy with voriconazole in patients with invasive aspergillosis has led to better responses and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with amphotericin B.[26] Sasindran et al.[27] reported an 8-year-old boy who was diagnosed with IOAA who was treated successfully with voriconazole resulting in complete resolution of symptoms.[27] Itraconazole is also a better tolerated antifungal than amphotericin B but it should not be used in cases of pulmonary involvement.[25] Mycotic aneurysms secondary to invasive aspergillosis can respond to medical therapy and may resolve without surgery.[28]

CONCLUSIONS

We presented a series of 6 immunocompetent patients with IOAA that was complicated by SAH. Despite aggressive surgical and medical therapy, the outcome was poor. Five of the 6 patients have died, and the only survivor was left with monocular blindness. Therefore, IOAA is a progressive disease that is inevitably fatal when not diagnosed early. Late diagnosis, after the fungus has spread intracranially and involved the neurovascular structures usually result in fatal SAH or infarction. Therefore, early diagnosis of IOAA with the prompt eradication of localized intraorbital fungal disease is essential to improve the prognosis.

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