

# Orbital apex syndrome secondary to aspergilloma masquerading as a paranasal sinus tumor

## A case report and literature review

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### Abstract

**Rationale:** Orbital apex syndrome is a complex clinical disorder featuring a collection of cranial nerve deficits characterized by impairment of the extraocular muscles, the ophthalmic branch of the trigeminal nerve, and even the optic nerve. Sino-orbital aspergillosis is rare but aggressive infection. Surgical resection accompanied by antifungal medication is advised currently.

**Patient concerns:** We report a 61-year-old woman diagnosed as aspergilloma presenting with the characteristic manifestations and imaging features of orbital apex syndrome.

**Diagnoses:** Paranasal sinus tumor was misdiagnosed initially according to magnetic resonance imaging of the orbit. Finally aspergilloma was diagnosed by pathologic report.

**Interventions:** The anti-fungal medication, voriconazole, was administered immediately. Surgical excision was also done due to the poor response to medical treatment.

**Outcomes:** Postoperative follow-up showed no recurrence of aspergillosis but the vision was lost permanently.

**Lessons:** Invasive sino-orbital aspergillosis as an aggressive disease with highly invasive patterns and it may be misdiagnosed as tumors. To achieve better prognosis and survival, clinicians should be aware of this distinct manifestation.

**Abbreviations:** CNS = central nervous system, CRP = C-reactive protein, HIV = human immunodeficiency virus, IOP = intraocular pressure, OAS = orbital apex syndrome, SAH = subarachnoid hemorrhage.

**Keywords:** aspergilloma, orbital apex syndrome, paranasal sinus tumor

## 1. Introduction

Orbital apex syndrome (OAS) is a complex clinical disorder featuring a collection of cranial nerve deficits characterized by impairment of extraocular muscles, the ophthalmic branch of the trigeminal nerve, and the optic nerve.<sup>[1,2]</sup> OAS often presents with ophthalmoplegia and visual loss. It is an uncommon disease caused by orbital apex infiltration by infectious, inflammatory, vascular, or neoplastic processes. The incidence of each etiology varies in different reports. Infection of periorbital structures, paranasal sinuses, and central nervous system (CNS) may lead to OAS. The pathogens include fungi, such as Mucormycosis and Aspergillosis, bacteria, viruses, and spirochetes.<sup>[3]</sup> Early recognition and appropriate treatment is critical.

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Sino-orbital aspergillosis is rare but aggressive, usually occurring after paranasal sinus infection. It can be divided into invasive and noninvasive types. Invasive aspergillosis invades the tissue, causing bony erosion, and hematologic infections by invading vessels. However, noninvasive aspergillosis forms a mass-lesion or a ball of aspergillus, known as an aspergilloma. Invasive aspergillosis is often found in immunocompromised patients with neutropenia, long-term corticosteroid use, type 2 diabetes mellitus, hematologic malignancy, prosthetic devices, trauma, excessive environmental exposure to aspergillus, residence in an endemic area, or old age.<sup>[1,4]</sup> Noninvasive aspergillosis is typically found in immunocompetent patients. When the patient is immunocompromised, noninvasive aspergillosis can become invasive causing bony infiltration, as in our case. The clinical manifestations in the orbit include orbital inflammation, malignancy, and acute glaucoma.<sup>[5]</sup> Some case reports revealed the misdiagnosis of aspergilloma as tumor metastasis due to patient's history of malignancy.<sup>[6,7]</sup> This delayed treatment. However, aspergilloma complicated by OAS has been rarely addressed. This report illustrates the clinical presentations, pertinent radiographic findings, and treatment of such a case. The early identification of OAS and the underlying aspergilloma is possible with adequate imaging studies when its awareness is raised. The patient had given consent for the use of photographs for publication. The study was approved by institutional review board of Tri-Service General Hospital.

## 2. Case report

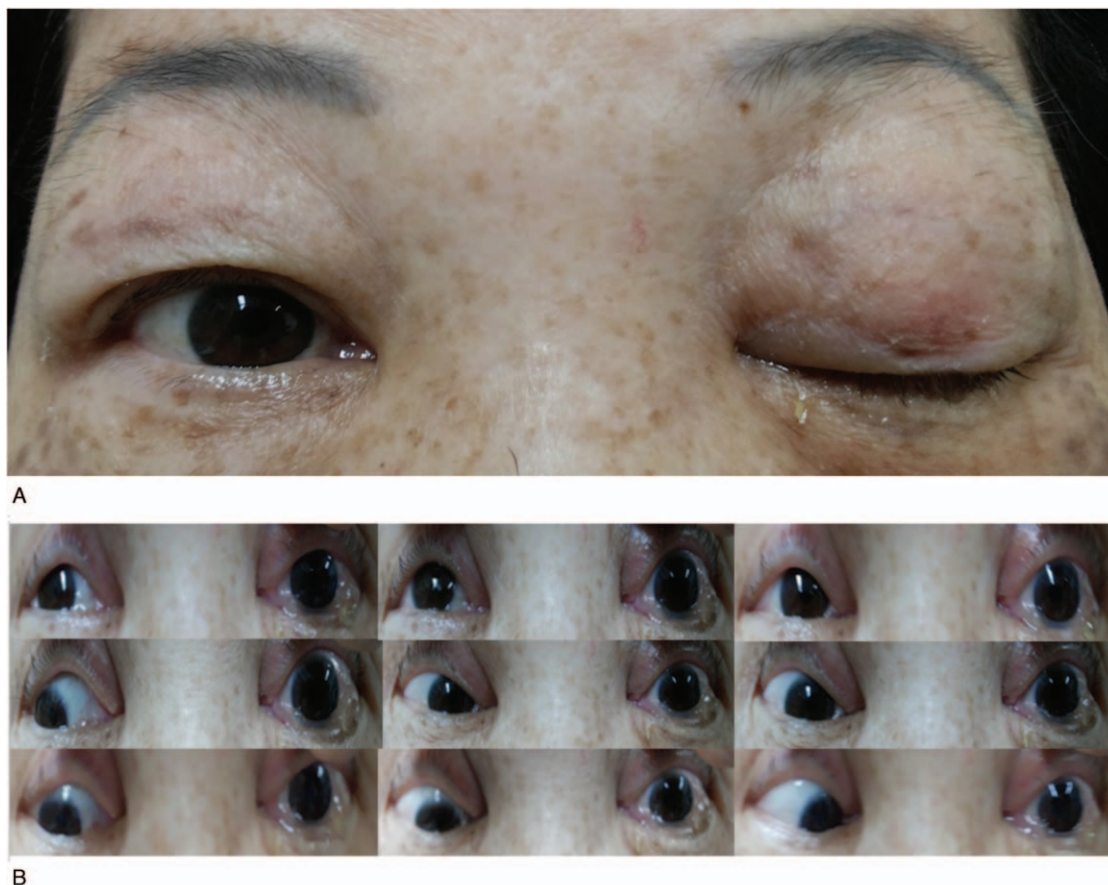
A 61-year-old woman, with the past history of chronic kidney disease and type 2 diabetes mellitus with poor glycemic control,

suffered from intermittent, purulent nasal discharge, and postnasal drip for many years without paying attention to it. She complained of headache on and off for 2 months, followed by progressive drooping of the left eyelid, a swollen, painful sensation, and blurring of vision in the left eye for 1 month (Fig. 1A). On ophthalmic examination, the right and left visual acuities were 3/60 and counting finger at 20 cm, respectively. The intraocular pressure (IOP) was 14 mm Hg in the right eye and 26 mm Hg in the left. Proptosis, complete ptosis, and nearly frozen ocular motility in all directions were noted (Fig. 1B). Biomicroscopic examination showed severe chemosis and the pupil showed positive relative afferent pupillary defect in the left eye. Fundoscopy revealed proliferative diabetic retinopathy in both eyes. Laboratory tests revealed leukocyte count of  $16,980/\mu\text{L}$  with neutrophil predominance, and high C-reactive protein (CRP) level of  $5.57\text{ mg/dL}$ . The computed tomography of the orbit without contrast showed mucoperiosteal thickening and soft-tissue collection in the left sphenoid, ethmoid, and maxillary sinuses, and bony defect in the anterior wall of the left sphenoid sinus (Fig. 2). The magnetic resonance imaging of the orbit without contrast further disclosed a 2-cm low-signal nodule in the left posterior ethmoid, and sphenoid sinuses, involving the left pterygopalatine fossa, the left cavernous sinus, and the inferior aspect of the left retrobulbar extraconal region (Fig. 3). This suggested a paranasal sinus tumor causing OAS. Due to the persistent chemosis and high IOP in the left eye, functional endoscopic sinus surgery for tissue biopsy and culture combined

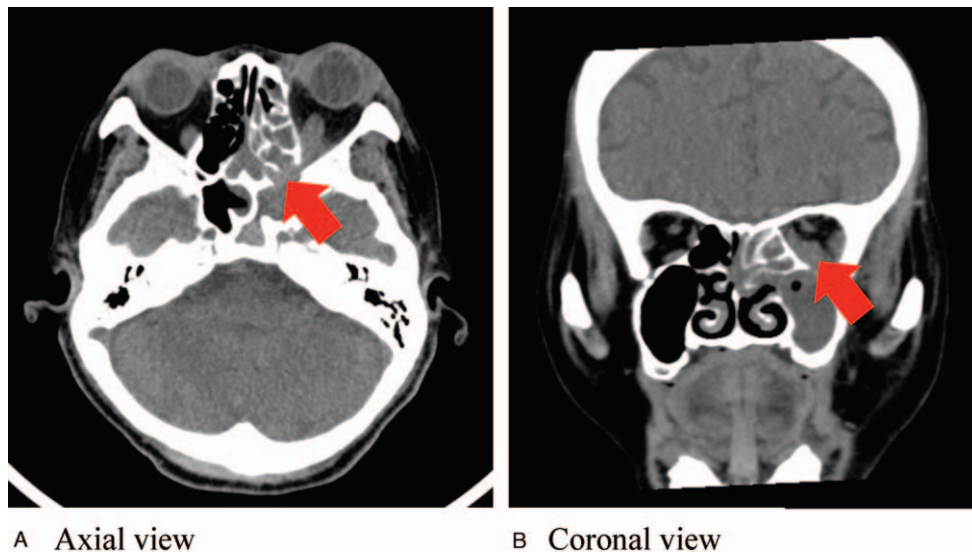
with decompression surgery were performed 3 days later since admission. The histopathological specimen from orbital and sinus tissues revealed fungal hyphae with septation surrounded by chronic granulomatous inflammation, suggesting *Aspergillus* species infection (Fig. 4). Therefore, we prescribed intravenous injection of the systemic antifungal, voriconazole: 200 mg every 12 hours for 1 month. After medical treatment, the ptosis and ophthalmoplegia persisted. The aspergilloma with necrotic tissue was, then, removed by surgery 1 month later. The patient continued to use oral voriconazole 200 mg every 12 hours for 1 month. The swelling and redness of left eye improved gradually without systemic infection; however, the visual acuity of left eye declined to no light perception at 1-year follow-up.

### 3. Discussion

OAS can be caused by many etiologies, including inflammation, infection, vasculitis, and malignancy. It can mimic optic neuritis, orbital cellulitis, and cavernous sinus syndrome, and the wrong treatment leads to poor visual outcome. Sino-orbital aspergillosis is uncommon but potentially lethal disease when complicated by CNS infection or subarachnoid hemorrhage (SAH) secondary to ruptured mycotic aneurysms. Many reports show that invasive sino-orbital aspergillosis is found in both immunocompromised and immunocompetent patients.<sup>[8–10]</sup> Regardless of immune status, sino-orbital aspergillosis can contribute to poor prognosis when treatment is delayed. Most patients present with infiltrative



**Figure 1.** (A) Picture of external eye demonstrating swelling and complete drooping of the left eyelid. (B) Extraocular movements demonstrating restriction in all directions.

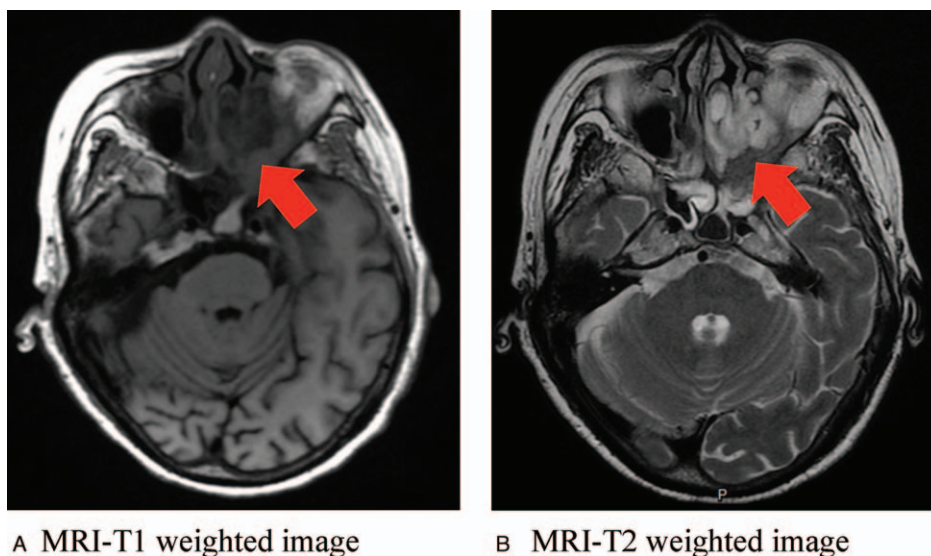


**Figure 2.** The computed tomography of orbit without contrast. (A) The axial view showing mucoperiosteal thickening and soft-tissue collection in left sphenoid, ethmoid, and maxillary sinuses, with bony defect over the anterior wall of left sphenoid sinus (arrow head). (B) The coronal view showing inferior rectus muscle enlargement (arrow head).

rather than mass patterns of aspergillosis in the orbital region. Aspergilloma, though noninvasive, may become invasive in immunocompromised patients. We present a case, immunocompromised due to type 2 diabetes mellitus and chronic kidney disease, who was misdiagnosed to have paranasal sinus tumor initially. Aspergilloma was diagnosed by pathologic report following which treatment with voriconazole was immediately started. Surgical excision was also done as the response to medical treatment was poor. However, the vision could not be recovered.

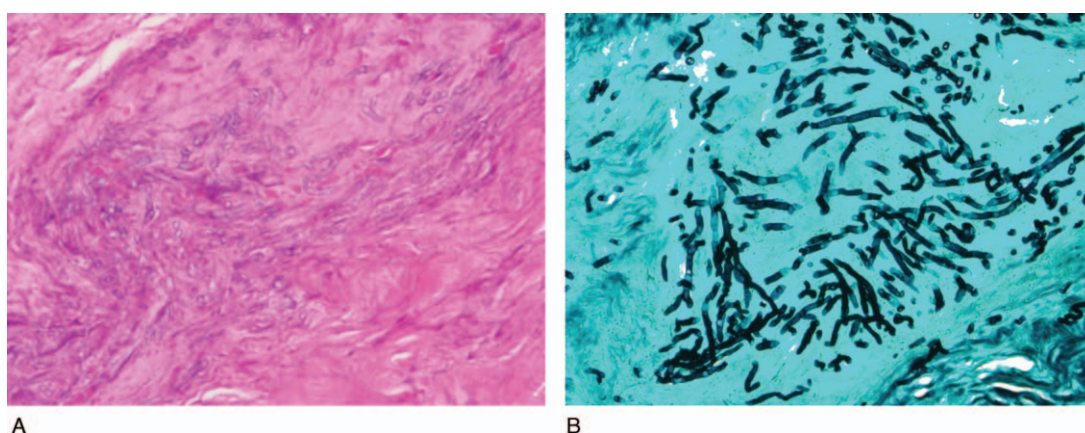
We conducted a systematic literature review covering the years 1970 to 2017 using the PubMed, Medline, Cochrane, and

Embase databases. All patients included in the review were diagnosed with OAS caused by aspergilloma. We identified 5 case reports with orbital complications. The presence of poor visual acuity, visual impairment, or blindness was described; however, patient details such as the visual acuity before and after treatment, the type of antifungal drugs used, and systemic diseases, were not available. The clinical characteristics and demographics of these 5 patients and our patient are listed in Table 1.<sup>[6,11–14]</sup> Of the 6 patients, 4 were immunocompromised and 2 were immunocompetent. The ages of these patients ranged from 43 to 65 years (immunocompromised patients: 52–64 years; immunocompetent patients: 43–65 years). All patients were male



**Figure 3.** Magnetic resonance imaging. (A) Axial T1 magnetic resonance imaging of the orbits without contrast showing 2 cm low-signal nodule in the left posterior ethmoid, sphenoid sinus, with involvement of the left pterygopalatine fossa, left cavernous sinus, and inferior aspect of the left retrobulbar extraconal region (arrow head). (B) Axial T2 magnetic resonance imaging of the same (arrow head).





**Figure 4.** Biopsy of orbital and sinus tissue showing fungal hyphae with septation and surrounding chronic granulomatous inflammation. (A) Hematoxylin and eosin stain,  $\times 400$ . (B) Grocott methenamine silver stain,  $\times 400$ .

except our case. All patients presented initially with visual impairment accompanied by headache, periorbital pain, ptosis, ocular motility impairment, proptosis, and disturbances in consciousness of varying severities. The immunocompromised patients included 1 case of cutaneous lymphoma, 1 of human immunodeficiency virus (HIV) infection, and 2 of type 2 diabetes mellitus. The patients with cutaneous lymphoma and diabetes mellitus survived after treatment, whereas we are unclear of the HIV patient's survival. However, among the immunocompetent patients, 1 case died from CNS infection. Among the patients with diabetes mellitus, excluding our case, we found only one Science Citation Index case report from 1970 to 2017.<sup>[11]</sup> On the basis of Table 1, there are several similarities between our case and the case reported by Cho et al,<sup>[11]</sup> including the age, initial visual acuity, clinical presentation, and image findings. They all had survived after surgical excision and antifungal treatment. The most important difference was final visual acuity, our case having poorer vision than the case reported by Cho et al.<sup>[11]</sup>

Prompt antifungal therapy should be applied; however, treatment is delayed in many patients due to faulty diagnosis. In our literature review, 1 patient misdiagnosed to have an orbital pseudotumor received steroid treatment,<sup>[12]</sup> the anti-inflammatory action of which though helpful initially, causes sharp

deterioration and increased risk of serious secondary infections. Aspergilloma may present with atypical manifestations. It can mimic orbital pseudotumor and as tumor metastasis in patient with a history of malignancy.<sup>[6]</sup> Having presented as a necrotic mass covering the entire bulbar surface, it was misdiagnosed as an orbital surface squamous neoplasia<sup>[13]</sup> in a HIV patient.

MRI can reveal the soft tissue structures in detail and is often used to evaluate the sino-orbital fungal infections, which have the propensity to invade the surrounding structures. The MRI findings in the sino-orbital aspergillosis are very distinctive. It reveals a mass lesion with the iso- to hypointense signals on T1-weighted images and extremely hypointense on T2-weighted images along with bright homogenous enhancement on post-contrast T1-weighted images.<sup>[15]</sup> Therefore, exquisite neuroimaging and surgical biopsy are warranted to confirm *Aspergillus* infection.

Unfortunately, permanent blindness<sup>[9,16–18]</sup> and high mortality rates<sup>[19–22]</sup> are reported even after immediate antifungal therapy. Amphotericin B is most used in sino-orbital aspergillosis, 40% to 60% of patients being responsive to it.<sup>[23]</sup> Due to the nephrotoxicity with long-term use, liposomal forms were developed.<sup>[24]</sup> Other antifungal drugs such as voriconazole and itraconazole, are also commonly used, independently or

**Table 1**

**Review of literature: clinical characteristics of patients with orbital apex syndrome caused by aspergilloma.**

Case	Age, y/Sex	Initial visual acuity	Symptoms	Administration of steroid	Administration of antifungal agents	Surgical excision or resection	Final visual acuity	Outcome	Systemic disease
Slavin <sup>[12]</sup>	65, male	20/25	Retro-orbital pain, diplopia, headache, impaired eye movement, Blepharoptosis	Yes	Amphotericin B	No	Unremarkable	Death	No
Naik et al <sup>[13]</sup>	52, male	No light perception	Pain, watering, frequent bleeding with discharge, rapidly increasing mass	No	Unremarkable	Yes	Unremarkable	Unremarkable	HIV
Cho et al <sup>[11]</sup>	64, male	Counting finger/50 cm	Rhinorrhea, diplopia, headache, ptosis, ophthalmoplegia	Yes	Amphotericin B	Yes	20/63	Alive	Type 2 diabetes mellitus
Cheko et al <sup>[6]</sup>	57, male	Unremarkable	Double vision, Ophthalmoplegia, Visual disturbance	Yes	Antifungal medication	Yes	Unremarkable	Alive	Cutaneous lymphoma
Moreno-Sanchez et al <sup>[14]</sup>	43, male	No light perception	Weakness of vision, Ptosis, Proptosis, Impaired eye movement	No	Amphotericin B, Caspofungin	Yes	Light perception	Alive	No
Our case	61, female	Counting finger/20 cm	Ptosis, Proptosis, Headache, Periorbital pain, Frozen eye movement	No	Voriconazole	Yes	No light perception	Alive	Type 2 diabetes mellitus, Chronic kidney disease

combined, in invasive sino-orbital aspergillosis. They are better tolerated with less systemic adverse effects than amphotericin B.<sup>[23,25]</sup> However, there is no prospective study comparing them for invasive aspergillosis. Surgical resection accompanied by antifungal medication is advised currently.<sup>[26]</sup> In our review, we found that the patients were alive after surgical intervention. The limitation of our literature review was the small case number with which the demographic tendency cannot be revealed.

#### 4. Conclusion

Our study highlighted invasive sino-orbital aspergillosis as an aggressive disease with highly invasive patterns. Aspergillomas may be misdiagnosed as tumors. The main treatment is surgical resection combined with early antifungal medication. To achieve better prognosis and survival, clinicians should be aware of this distinct manifestation.

#### Author contributions

**Conceptualization:** Yu-Min Chang, Yun-Hsiang Chang, Ke-Hung Chien, Chang-Min Liang, Ming-Cheng Tai, Shin Nieh, Ying-Jen Chen.

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**Writing – original draft:** Yu-Min Chang.

**Writing – review & editing:** Ying-Jen Chen.

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