Orbital Apex Inflammatory and Infectious Diseases

12

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Abstract

Infectious disease is one of the numerous causes of orbital apex disorders. In this chapter, the author will discuss the clinical features, diagnosis, and treatment of several infectious conditions which are associated with significant visual morbidity and **even** mortality. The impact of the COVID-19 pandemic will also be highlighted.

Keywords

Orbital apex syndrome · Bacterial sinusitis · Aspergillosis · Mucormycosis · COVID-19 · Herpes zoster ophthalmicus

Orbital apex disorders can be divided into superior orbital fissure syndrome, cavernous sinus syndrome, and orbital apex syndrome (OAS). All three syndromes share common characteristics of damage to the oculomotor nerve, trochlear nerve, and abducens nerve, along with the ophthalmic division of the trigeminal nerve. Patients with cavernous sinus syndrome also exhibit hypoesthesia in the distribution of maxillary division of the trigeminal nerve and Horner's syndrome due to involvement of sympathetic chain next to the cavernous segment of the internal carotid artery. On the other hand, patients with OAS experience visual disturbance additionally as a consequence of optic nerve dysfunction. With disease progression, superior orbital fissure syndrome can evolve into either OAS or cavernous sinus syndrome [3, 21]. Orbital apex disorders can be caused by a wide range of disease entities, infection affecting the orbital structures is one of them. The pathogens include bacteria, fungi, viruses, spirochetes, mycobacterium, and parasites. Making a prompt and accurate diagnosis with administration of appropriate treatment is crucial to save the vision and lives of patients. In this chapter we will discuss some of these conditions.

12.1 Bacterial Infections

Orbital apex syndrome commonly occurs as a complication of bacterial sinusitis. It is usually associated with orbital cellulitis. Orbital infection can be classified, with respect to the orbital septum, into preseptal (periorbital) and post-septal (orbital) infection [7]. The orbital septum works as a barrier against the spread of periorbital infection into the orbit; therefore, orbital apex disorder is unlikely to happen as a complication of preseptal cellulitis. Pansinusitis or ethmoid sinusitis occurs frequently in 86–98% of cases of orbital cellulitis. Other causes of orbital cellulitis are surgery, anesthesia, trauma, dental infection, and middle ear infection. Apart from causing orbital cellulitis, sinusitis can lead to other serious complications like orbital abscess and subperiosteal abscess [50]. Further extension of the infection into intracranial structures may lead to meningitis, subdural empyema, epidural abscess, or septic cavernous sinus thrombophlebitis [66].

OAS originating from isolated bacterial sinusitis without concurrent orbital cellulitis is less common. It is presumably because the pathogens can penetrate more readily through the thin sinus walls adjacent to the anterior orbit instead of the thick ethmoidal and sphenoidal walls [14]. Several case examples are listed below.

A 63-year-old woman with a history of metastatic breast cancer and diabetes mellitus (DM) presented with initial involvement of the trigeminal and abducens nerves, which had rapidly progressed to involve the optic and oculomotor nerves. Her visual acuity further declined to no perception of light despite appropriate antibiotics and surgical interven-

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tion. Magnetic resonance imaging (MRI) of the orbit showed pansinusitis and enhancement of the optic nerve. Cultures of blood and surgical specimens yielded methicillin-sensitive *Staphylococcus aureus* [64].

Kusunoki et al. reported a 60-year-old woman with diabetic nephropathy and heart disease who was diagnosed as OAS due to pansinusitis with *Pseudomonas aeruginosa* infection [36].

Colson and Daily described a 49-year-old man, with a history of DM and chronic sinusitis, who developed OAS and cavernous sinus thrombosis concomitantly due to mixed infection with *Staphylococcus aureus* and *Pseudomonas aeruginosa*. His affected optic nerve demonstrated microinfarctions due to arterial thrombosis [14]. Another case with mixed growth of bacteria occurred in a 58-year-old diabetic man who was hospitalized for right herpes zoster ophthalmicus and methicillin-sensitive *Staphylococcus aureus* osteomyelitis of his toe. During the course of treatment, he developed left OAS secondary to left sphenoid sinusitis. Subsequent MRI of the orbit demonstrated extension of inflammatory soft tissues towards the orbital apex and cavernous sinus, with enhancement of retro-orbital fat, rectus muscles, and optic nerve. Computed tomography (CT) showed bony erosion of the lateral wall of the sphenoid sinus. Sphenoidotomy with drainage yielded methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*. This man unfortunately died because of multiorgan failure [87].

The last example is a 68-year-old woman with acute myelogenous leukemia and migraine who complained of severe headache around 2 weeks after chemotherapy. With a CT angiogram and MRI showing mucosal thickening of ethmoid and sphenoid sinuses, which was initially thought to be insignificant, she was treated as a migraine attack. Two weeks later, she presented with typical features of OAS. She was found to have an interval progression of the mucosal thickening and bony erosion into the orbital apex. Erosion into the cavernous segment of the internal carotid artery resulted in thrombosis. She was treated with broad-spectrum antibiotics and antifungals. Sinus drainage finally revealed *Streptococcus viridans* [6].

These case examples illustrate a few crucial points. First, susceptible patients are often immunocompromised like having DM or malignancy. Second, prognosis can be very guarded despite appropriate interventions. Pfeiffer et al. have reviewed six analogous case reports [64]. Five patients presented with no light perception and only one patient made minimal visual recovery, from no light perception to hand motion. Third, presentation can be insidious and clinical signs and radiographic findings can be subtle, so that a high index of suspicion is necessary. Actually previous case reports have suggested that among patients with OAS secondary to sinusitis, the absence of overt orbital pathology on imaging or at surgery portends a better visual prognosis than patients who have apparent masses at the orbital apex [14]. Once bacterial infection is suspected, parenteral broad-spectrum antibiotics which cover *Staphylococcus aureus* (including MRSA), streptococci, and gram-negative bacilli such as *Pseudomonas aeruginosa* should be initiated promptly. Management should also include endoscopic nasal surgery and biopsy for histopathology and culture. Finally, it is essential to rule out invasive fungal infection because it shares similar clinical features and carries significant morbidity and mortality. Empirical antifungal therapy might be considered while waiting for the laboratory results.

12.2 Fungal Infections

Similar to bacterial infections, orbital apex disorders caused by fungi usually come after paranasal sinus infection. Fungal rhinosinusitis can be divided into two broad categories, namely, invasive and noninvasive, depending on the potential of the fungal hyphae to invade the adjacent tissues through the epithelium. Besides, further subdivision can be made based on the chronicity of the illness—acute (less than 4 weeks) and chronic (more than 4 weeks). Hence, fungal rhinosinusitis can be classified into six subgroups [18].

1. *Noninvasive fungal rhinosinusitis*
   (a) Saprophytic fungal infestation
   (b) Fungal ball
   (c) Allergic fungal rhinosinusitis
2. *Invasive fungal rhinosinusitis*
   (a) Acute invasive fungal rhinosinusitis
   (b) Chronic invasive fungal rhinosinusitis
   (c) Chronic granulomatous invasive fungal rhinosinusitis

Lee et al. reported a case series of 30 patients with orbital mycoses encountered in an Australian subtropical population over three decades. Most patients (87%) had invasive diseases, often with poor visual and survival outcomes. OAS was initially observed in 27% of patients. Common causative pathogens included *Mucorales* (N = 16) and *Aspergillus* (N = 8). Common risk factors included hematological disorders (myelodysplastic syndrome and aplastic anemia), hematological malignancies, neutropenia, corticosteroids use, and DM [39].

Fungal spores are abundant in the atmosphere. In normal subjects, inhaled fungal spores form part of the normal sinonasal flora without causing overt diseases, because these fungi are killed by neutrophils, monocytes, and macrophages. In immunocompromised individuals, a more fulminant and invasive disease may emerge. In immunocompetent individuals, *Aspergillus* tends to cause noninvasive fungal rhinosinusitis. However, there are a number of exceptions

reported in the literature. From 2000 to 2011, 11 cases of rhino-orbital-cerebral mucormycosis (ROCM) affecting immunocompetent hosts have been published. Among them, nine cases were due to *Apophysomyces elegans* [71].

12.2.1 Aspergillosis

Sino-orbital aspergillosis is a relatively uncommon cause of orbital apex disorders, but it remains an important differential diagnosis due to its aggressive clinical course. Inhalation of fungal spores released into the atmosphere is the typical route of infection. Paranasal sinuses are the usual portal of entry. *Aspergillus fumigatus* is the most frequent species isolated in human infections, followed by *A. flavus* [17]. As mentioned before, aspergillosis can be divided into invasive and noninvasive forms.

Invasive aspergillosis can either follow a fulminant or an indolent course. The fungal hyphae invade the sinus mucosa, orbital tissue, and spread along the skull base. It may produce bony destruction, hematogenous spread to other organs by vascular invasion, and intracranial extension via the orbital fissures or the optic canal. Cases of permanent blindness have been reported even with immediate antifungal therapy. Fatal outcomes can occur when the condition is complicated by central nervous system infection or subarachnoid hemorrhage (SAH) secondary to ruptured mycotic aneurysms. For example, Yip et al. reported a 73-year-old woman, who was maintained on long-term corticosteroids for her rheumatoid arthritis and presented with OAS. Massive fatal SAH suddenly occurred 5 days after endoscopic removal of the orbital apex lesion, due to a ruptured mycotic aneurysm [88]. Huang and Gui described a DM patient with simultaneous orbital apex and cavernous sinus invasions who was treated with voriconazole, surgery, and anticoagulant [26]. Perineural spread along the optic nerve to involve the optic chiasm has also been reported [42].

Immunocompromised individuals are typically more susceptible to invasive aspergillosis. Prolonged neutropenia, use of corticosteroids or other immunosuppressive agents, malignancies, allogeneic hematopoietic stem cell transplantation, and solid organ transplantation are the major risk factors for aspergillosis. DM, acquired immunodeficiency syndrome, severe burns, prosthetic devices, trauma, excessive environmental exposure, residence in endemic areas, drug abusers, alcoholics, liver cirrhosis, and elderly are other risk factors [41, 42]. Though less common, invasive aspergillosis can also be found in immunocompetent hosts [42, 49, 60].

Fungal ball, also known as aspergilloma, is one manifestation in patients with noninvasive aspergillosis. Typically, this happens in patients with intact immunity. Nevertheless, when host defenses are weakened, noninvasive aspergillosis can turn itself into an invasive form [13, 56]. Because of its nonspecific clinical and radiographic appearance as well as its potentially invasive and aggressive nature, misdiagnosis of aspergilloma as primary malignancy [60, 90] or metastasis [12] can occur. It can also mimic orbital pseudotumor [8] when the commencement of corticosteroid therapy may cause worsening rather than beneficial effects. Chang et al. reported a 61-year-old woman with uncontrolled DM whose MRI initially suggested paranasal sinus tumor. Tissue biopsy subsequently revealed *Aspergillus* and chronic granulomatous inflammation. Her vision was permanently damaged despite treatment with voriconazole and surgery. The authors have also conducted a systematic literature review from 1970 to 2017 and identified five case reports of OAS caused by aspergilloma [10].

Imaging is of great importance for establishing an anatomical diagnosis. CT may reveal intraluminal calcifications which are almost pathognomonic for aspergillosis, but it is present in only 50% of patients [40, 41]. In MRI, aspergillosis appears as iso- to hypointense signals on T1-weighted images, iso- to extremely hypointense signals on T2-weighted images, and intense homogenous (and rarely ring) enhancement on post-contrast T1-weighted images [74].

Tissue biopsy remains the gold standard for definitive diagnosis. Direct microscopy, preferably using optical brighteners, histopathology, and culture, are all recommended [79]. Septate fungal hyphae branching at 45° angle are typical of aspergillosis. These are best visible using periodic acid-Schiff (PAS) or Grocott-Gomori methenamine silver (GMS) stains. Unfortunately, the sensitivity of microscopy is rather low, between 33% and 50%, and repeated biopsy may be necessary. Serological markers such as serum galactomannan and (1→3)-β-D-glucan can be helpful, but their reliability can be limited by false-positive results. Polymerase chain reaction (PCR) provides a high sensitivity and specificity, hence reducing the need for repeated biopsies. Furthermore, PCR can hasten the initiation of the appropriate therapy. It can also be utilized to identify genetic mutations that confer resistance to triazole therapy [40].

Treatment of sino-orbital aspergillosis has evolved substantially over decades. In the past, radical surgical resection of the affected tissues or even orbital exenteration was considered the standard of therapy. However, radical surgery guarantees neither disease control nor patient survival. Recently, reports of satisfactory outcomes using combinations of less radical surgery and systemic antifungal therapy have been published [58]. Functional endoscopic sinus surgery with debridement is currently advised. It is also recommended to reverse the immunosuppression if possible.

Systemic antifungal agents consist of polyenes, triazoles, and echinocandins. The overall response rate to antifungal therapy is 40–60%. Amphotericin B is widely used, but due

to its nephrotoxicity, it is getting out of favor. Other antifungals such as voriconazole and itraconazole can also be considered alone or combined with amphotericin B. Voriconazole showed a high efficacy, low-toxicity profile, and its availability in both intravenous and oral formulations which allows for more management flexibility [24]. Reports of successful treatment with voriconazole monotherapy have been published [53]. The Infectious Disease Society of America (IDSA) recommends triazoles as preferred agents for the treatment of invasive aspergillosis. Echinocandins are recommended as salvage therapy, either alone or in combination, but not as primary treatment [62].

12.2.2 Mucormycosis

Mucormycosis is another acute fulminating, visual- and life-threatening opportunistic fungal infection. It is classified into different forms based on the organ systems involved, the most common clinical presentation of which is rhino-orbital-cerebral infection (ROCM). In a review of 175 patients of sino-orbital mucormycosis, males were more commonly affected (68.5%), and the overall mean age was 43 years. The overall survival rate was 59.5% [80]. The initial symptoms are rather nonspecific. Patients usually present with acute sinusitis—fever, nasal congestion, rhinorrhea, ocular pain, facial pain, and headache. OAS represents an emergency as it signifies neuromuscular infarction and a threat to cavernous sinus extension. The following red flags have been proposed in DM patients to facilitate early recognition, testing, and intervention: cranial nerve palsy, diplopia, sinus pain, proptosis, periorbital swelling, OAS, and palatal ulcer [16].

Mucormycosis is caused by fungi belonging to the class *Zygomycetes* and the order *Mucorales*, which comprise *Rhizopus*, *Mucor*, *Rhizomucor*, *Lichtheimia* (*Absidia*), *Apophysomyces*, *Cunninghamella*, *Saksenaea*, *Cokeromyces*, *Actinomucor*, *Mortierella*, and *Syncephalastrum* [65, 76]. These organisms are ubiquitous in the environment, particularly in soil and decaying organic matter. The first four genera are the most commonly reported pathogens in humans [43], and *Rhizopus arrhizus* (formerly *Rhizopus oryzae*) accounts for 90% of ROCM.

Poorly controlled DM, with or without diabetic ketoacidosis (DKA), is the leading predisposing factor for mucormycosis globally, especially in Asian and African countries. In a meta-analysis of 851 cases, DM is reported as the commonest underlying condition and an independent risk for ROCM (odds ratio 2.49), with an overall mortality of 46% [28]. Other risk factors include prolonged neutropenia, hematological malignancies, other malignancies, allogeneic bone marrow transplantation, solid organ transplantation, corticosteroids and other immunosuppressive agents, open wounds, burns, illicit intravenous drug use, chronic malnutrition, AIDS, liver disease, chronic kidney disease, and post-pulmonary tuberculosis [5, 70, 71, 76]. Iron overload and deferoxamine treatment for iron chelation are other specific risk factors, because some fungi like *Rhizopus* can bind to deferoxamine which supplies the organism with extra iron for its growth [18, 27]. Hematological malignancies and transplantation are more prevalent risk factors among patients in Western countries [76].

Like aspergillosis, mucormycosis usually begins in the paranasal sinuses through inhalation of spores into the oral and nasal cavities. These fungal hyphae are angioinvasive and cause necrotizing vasculitis and thrombosis, resulting in extensive infarction and necrosis of host tissues (hence the name "black fungus" because it turns tissues black). The disease can spread to the orbit by direct extension, via hematogenous route or via nasolacrimal duct. Intracranial extension may give rise to grave conditions like cavernous sinus thrombosis, sagittal sinus thrombosis, carotid artery occlusion, cerebral infarction, cerebral aneurysm, and brain abscesses.

Because clinical diagnosis has a low sensitivity and specificity, laboratory testing remains an invaluable tool. Direct microscopy of specimens obtained from the nasal cavity and paranasal sinuses show broad ribbon-like nonseptate or pauci-septate hyphae forming right-angle branching. Culture in Sabouraud's dextrose agar shows typical findings of cottony white or grayish black colonies. Histopathology by hematoxylin and eosin (H&E), PAS, or GMS stains can demonstrate the characteristic fungal hyphae. It is indispensable by showing necrotizing vasculitis with invasion of vessel walls by fungal hyphae. Alternative techniques for tissue diagnosis include immunohistochemistry, PCR, and in situ hybridization [22, 76].

The management of ROCM requires early diagnosis and high index of suspicion. Due to its rapid progression and destructive nature, empirical antifungal therapy should be started once the diagnosis is considered. A delay of even 6 days in initiating treatment is associated with a doubling of 30-day mortality from 35% to 66%. Antifungal therapy consists of systemic conventional or liposomal amphotericin B or combination therapy with amphotericin B and posaconazole or caspofungin. Isavuconazole can be used as salvage therapy. Reversal of predisposing risk factors if possible and control of systemic conditions like hyperglycemia and DKA are essential.

The global guidelines for diagnosis and management of mucormycosis in 2019 by the European Confederation of Medical Mycology (ECMM) and Mycoses Study Group Education and Research Consortium (MSGERC) recommends an early surgical intervention in addition to systemic antifungal treatment [15]. Surgical debridement of infected and necrotic tissue, with drainage of infected parental sinuses should be performed. It reduces the fungal load in the tissue and allows for better penetration of intravenous drugs.

Medical management alone with antifungal is ineffective because extensive vascular thrombosis and ischemic necrosis prevent entry of antifungal in adequate concentrations.

Some centers advocate aggressive surgical debridement of sinuses with orbital exenteration. However, there are reports of success with a more conservative approach with limited or no surgical intervention in the orbit [22]. There remains a lack of consensus regarding the indications for exenteration. A retrospective study concluded that there was no added survival benefit. Some series have even found exenteration to be detrimental because it allows for further dissemination of the infection [52].

Various treatment modalities have been employed to avoid orbital exenteration [63]. Frozen section monitoring of the surgical margin has been utilized with success. Drug-soaked packing of the affected orbit and sinuses and direct irrigation with amphotericin B via percutaneous catheters might enhance direct drug delivery to the infected tissues. Hirabayashi et al. have reported a successful case managed with retrobulbar injections of amphotericin B [25]. Hyperbaric oxygen therapy has been tried to improve survival rate through several mechanisms such as promoting the fungicidal effect of neutrophils and macrophages.

In a review of 145 patients by Yohai et al., the following factors were associated with a lower survival rate: delayed diagnosis and treatment, hemiparesis or hemiplegia, bilateral sinus involvement, leukemia, renal disease, and treatment with deferoxamine [89].

12.2.2.1 COVID-19-Associated Mucormycosis (CAM)

The coronavirus disease 2019 (COVID-19) first documented in Wuhan, China, has rapidly become a global public health crisis. COVID-19 is caused by a novel coronavirus SARS-CoV-2. As of this writing, 181 million confirmed COVID-19 cases were reported worldwide, with more than 3.9 million deaths [84]. Patients with COVID-19 are at increased risk of a wide range of secondary bacterial and fungal infections which complicate their clinical course. Fungal infections are more likely to develop during the middle and later stages of COVID-19 infection. The mortality rate is higher among COVID-19 patients with secondary fungal infections (53% vs. 31%).

Ismaiel et al. in Egypt have reported a threefold rise in the incidence of acute invasive fungal rhinosinusitis in 2020 compared to those of the previous 3 years. Sixty-two percent of these patients suffered from COVID-19. The most common organisms were *Rhizopus arrhizus*, *Aspergillus fumigatus*, and *Absidia mucor* [27]. In India, there was an explosion of cases [20], with an estimated number of cases of over 4000 in May 2021 [57]. Patel et al. conducted a nationwide, retrospective multicenter study across India between September and December 2020. They found a 2.1-fold increase in mucormycosis cases when compared with the corresponding study period in 2019. Among the total 287 patients with mucormycosis, 65.2% had CAM [61].

Multiple factors may contribute to the vulnerability of COVID-19 patients to secondary fungal infections:

- Hypoxia due to acute respiratory distress syndrome (ARDS), hyperglycemia (corticosteroid-induced or pre-existing DM), and acidosis facilitate the germination of fungal spores.
- SARS-CoV-2 can infect the beta cells of the pancreas with the possibility of causing hyperglycemia.
- Iron overload. The binding of iron to ferritin and transferrin is reduced in acidosis.
- Shared pre-existing comorbid risk factors for COVID-19 and invasive fungal rhinosinusitis. DM is an independent risk factor for both COVID-19 and mucormycosis.
- Hypoxia may exacerbate the tissue infarction caused by angioinvasion of fungal hyphae.
- SARS-CoV-2 also induces endothelialitis and microvascular thrombosis in the pulmonary and extrapulmonary vascular beds [32].
- Damage to the lung tissues by SARS-CoV-2 puts the patients vulnerable to develop invasive fungal infections [5].
- Immune dysregulation with decreased number of CD4+ and CD8+ T lymphocytes, overexpression of inflammatory cytokines, and reduced phagocytic activity of white blood cells.
- Widespread and inappropriate use of corticosteroids.
- Liberal and empirical use of broad-spectrum antibiotics may suppress normal bacterial flora allowing fungi to colonize.
- ICU admission, long duration of hospital stay, mechanical ventilation.

Ashour et al. published a radiological case series of acute invasive fungal rhino-orbital-cerebral sinusitis (AIFS) patients. At least six out of the eight cases were mucormycosis. Symptoms of fungal sinusitis started 12–35 days after the COVID-19 diagnosis. There was moderate to severe mucosal thickening of variable sinuses. Their cases illustrated that the imaging findings associated with COVID-19 infection were not different from those reported in non-COVID-19 cases. However, these patients had numerous features commonly identified at an aggressive late stage. These included panophthalmitis, orbital compartment syndrome, optic nerve infiltration, osteonecrosis of the hard palate, and nasal septum. Intracranial complications included perineural spread along the trigeminal nerve, meningeal infiltration, cavernous sinus thrombosis, vasculitis/thrombosis of the cavernous segment of the internal carotid artery, mycotic aneurysm, cerebral abscess, and cerebral infarction.

Their mortality and long-term morbidity were 37.5% and 100%, respectively [2].

Mucormycosis can develop during the course of COVID-19 or during the recovery phase.

Werthman-Ehrenreich first reported a 33-year-old woman with concurrent new onset DKA, COVID-19, ROCM, and orbital compartment syndrome. She presented with cough, shortness of breath, and vomiting followed by altered mental status. An emergent lateral canthotomy was performed due to raised intraocular pressure. MRI of the brain revealed evidence of cerebral infarction which later evolved to bifrontal brain abscesses. The patient succumbed on day 26 [83].

Another 24-year-old obese woman who presented with facial pain, facial numbness, and lid swelling was similarly diagnosed with new onset DKA, rhino-orbital mucormycosis, and COVID-19. Fungal culture revealed *Lichtheimia* (*Absidia*). There was a rapid progression of eschar on her face over a few days. She died of septic shock and multi-organ failure eventually [82].

Karimi-Galougahi et al. reported a 61-year-old female with good past health who was hospitalized with COVID-19 for 2 weeks. She was treated with remdesivir, interferon-alpha, and corticosteroid during hospitalization. She did not require mechanical ventilation. One week later she developed symptoms of invasive mucormycosis including facial pain, facial numbness, and visual loss. On examination, there was an eschar over the nasal, malar, and periorbital regions on top of the typical signs of OAS. Blood glucose levels were elevated. CT and MRI showed acute maxillary and ethmoid sinusitis and intraorbital fat involvement. Unfortunately she required orbital exenteration despite treatment with insulin, systemic antifungals, and endoscopic debridement. This is a case of new-onset DM and immunosuppression induced by systemic corticosteroids [32].

Another 60-year-old male, long-standing DM patient received meropenem, oseltamivir, methylprednisolone, dexamethasone, and tocilizumab for the treatment of COVID-19. Rhino-orbital mucormycosis started on the right side on day 10. On the next day, the left eye appeared fixed, and the left pupil was dilated and nonreactive to light, with the authors suggesting that it was either due to the spread of infection or COVID-19 coagulopathy. He was treated with amphotericin B and enoxaparine. This man unfortunately died on day 6 [47].

Sen et al. presented a case series of six consecutive patients managed at their centers in India over 4.5 months. Their mean age was 60.5 (range: 46.2–73.9) years. All patients were male with DM, and two of them were newly diagnosed. Three had DKA during hospitalization for COVID-19. All but one received systemic corticosteroid treatment for COVID-19 and developed symptoms of rhino-orbital mucormycosis after recovering from COVID-19, with a time lag of 15.6 ± 9.6 days (range: 3–42 days) from the diagnosis of COVID-19. Intracranial extension was common and visual recovery was poor. Two underwent orbital exenteration, and all six patients were alive at their last follow-up [70].

Bayram et al. evaluated 11 patients from Turkey over 9 months [4]. Their mean age was 73.1 (range: 61–88) years. Nine were male, eight had uncontrolled DM, and 63.6% developed OAS. Three had cerebral involvement. All patients had received corticosteroids for the treatment of ARDS. The mean time interval between diagnosis of COVID-19 and mucormycosis was 14.4 ± 4.3 days. Despite treatment with intravenous and retrobulbar/intravitreal liposomal amphotericin B and radical surgical debridement, the mortality was 63.6% with a mean duration of follow-up of 51.2 (range: 15–153) days.

Singh et al. conducted a systematic review of case reports and case series published up to May 13, 2021. They found a total of 101 cases of mucormycosis in COVID-19 patients have been reported. Most cases (81.2%) were from India. DM was present in 80% of cases (DKA 14.9%). Corticosteroids were given for COVID-19 in 76.3% of cases. Mucormycosis was predominantly seen in males (78.9%), both in people who were active (59.4%) or recovered (40.6%) from COVID-19. Mucormycosis involving the nose and sinuses (88.9%) was most common followed by rhino-orbital (56.7%) and ROCM (22.2%). Mortality was noted in 30.7% of cases [75].

These case examples and systematic review highlight the importance of considering mycotic co-infection in COVID-19 patients. Given the rapid upsurge in the incidence of CAM, the Pan American Health Organization/World Health Organization has issued an alert and guidance to its member states to prepare for this devastating crisis [57]. In fact, diagnostic and management challenges of CAM are even greater than those of mucormycosis without COVID-19, given the critical conditions that many patients are suffering with ARDS, hemodynamic instability, and multi-organ dysfunction. These preclude timely diagnostic imaging, testing, and surgical debridement.

12.2.3 Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus (HZO) refers to herpes zoster affecting the ophthalmic branch of the trigeminal nerve, which accounts for 10–20% of overall herpes zoster occurrence [44]. HZO develops after the reactivation of latent varicella zoster virus (VZV) infection in the trigeminal ganglion. Most patients belong to the older age group, over the age of 50, when VZV-specific cell-mediated immunity declines. During the pre-antiviral era, 50% of HZO patients developed ocular complications [23], for example, blepharitis, keratoconjunctivitis, anterior uveitis, and scleritis. Furthermore, it may give rise to acute phthisis bulbi, central retinal artery

occlusion, acute retinal necrosis, cataract, or secondary glaucoma. Ophthalmoplegia with involvement of the oculomotor nerve, trochlear nerve, or abducens nerve has been documented in 3.5% and 9.8% of HZO cases in the Mayo Clinic series and the Moorfields Eye Hospital series, respectively [46, 85]. OAS is a rare but serious vision-threatening complication of HZO.

Multiple mechanisms have been proposed in the pathogenesis of OAS secondary to HZO. Different pathogenic mechanisms may be associated with different prognoses:

1. In many reported cases, HZO-induced optic neuritis in immunocompetent patients. It points towards an immune-mediated mechanism of damage. The immune response is both humoral and cell-mediated.
2. Naumann et al. described chronic inflammatory cell infiltration along the long posterior ciliary nerves and vessels in 21 enucleated eyes affected by HZO. Ocular ischemia due to extensive inflammation around the posterior ciliary nerves and vessels has been postulated to contribute to optic nerve dysfunction [51].
3. Orbital soft tissue edema or myositis produces a compressive effect on the surrounding cranial nerves.
4. Direct viral cytopathic effect caused by dissemination of VZV from trigeminal nerve to the neighboring cranial nerves, due to their close proximity at the orbital apex, superior orbital fissure, or cavernous sinus.
5. Demyelination of the cranial nerves with perivascular monocytic infiltrates of the vessels supplying these nerves [37].

A literature search for articles published in English from 1997 to 2020, and review of these cases showed that the mean age of patients was 67.4 years (range: 29–84 years). In addition, 48% were male (Table 12.1). Nine of these previously reported cases had backgrounds of immunocompromised state. One had chronic lymphocytic leukemia for 19 years treated with pulse chemotherapy [11]. Saxena et al. reported a 29-year-old patient newly diagnosed with human immunodeficiency virus (HIV) infection. HIV was suspected due to her atypical age, severity of presentation, and the presence of soft exudates in the retina. Her ocular motility and visual acuity improved by the end of the fourth week after treatment. The authors attributed her favorable outcome to the prompt initiation of highly active antiretroviral therapy (HAART) and judicious use of systemic corticosteroids with rapid tapering over 10 days [69]. Another patient had a history of multiple myeloma and had recently received a course of chemotherapy. Despite treatment with intravenous acyclovir and oral steroids, he made a minimal recovery at 8 months. The authors suspected ischemic vasculitis to be the cause of irreversible damage [19]. Another six patients had diabetes mellitus (Table 12.1).

The diagnosis of OAS secondary to HZO is primarily based on clinical assessment. Patients typically present with rash, swelling of eyelids, visual loss, periorbital pain, and headache. Systemic symptoms like fever, anorexia, nausea, vomiting, malaise, and dizziness may occur [38, 45, 48]. On examination, periocular edema, conjunctival injection, chemosis, ptosis, proptosis, reduced visual acuity, complete ophthalmoplegia, reduced sensation in the territory of the ophthalmic division of the trigeminal nerve, diminished corneal sensation, anisocoria, and relative afferent pupillary defect may be observed. Swollen optic disc may be found [19, 81]. Intraocular pressure can be elevated [19, 29, 77]. Ophthalmoplegia and optic nerve involvement usually manifest within the first 2 weeks following the appearance of herpetic skin eruptions [30, 38]. By definition, visual acuity was always impaired, from 0.4 to no perception of light (Table 12.1).

Crusted and vesiculopustular skin eruptions in the dermatome of the ophthalmic nerve (upper eyelid, forehead, and tip and side of the nose) are almost always present. Dermatomal involvement can be minimal as compared to the ocular manifestations. It highlights the fact that the severity of cutaneous involvement may not correlate well with that of ophthalmic involvement [30]. Even a single lesion in the territory of the nasociliary nerve (Hutchinson's sign—lesions at the tip, side, or root of the nose) should alert the clinicians owing to its strong prediction of ocular inflammation and corneal denervation.

CT scan of the orbit shows exophthalmos, soft tissue swelling, and myositis with enlargement of the extraocular muscles [19, 48]. Unlike bacterial and fungal causes of OAS, there is no paranasal sinus involvement.

The characteristic MRI findings were first described by Krasnianski et al. and Shirato et al. [34, 73]. Contrast-enhanced MRI with gadolinium and fat suppression sequences demonstrate exophthalmos, enhancing soft tissue swelling of periorbital tissues [1, 38], orbital myositis with swollen extraocular muscles [1, 9, 29, 30, 34, 38, 59, 69, 77, 78, 81], and retrobulbar fat stranding causing crowding at the orbital apex [29, 33, 69]. It is very common to detect enhancement of the retrobulbar optic nerve sheath [9, 29, 30, 33, 35, 38, 54, 59, 67, 78, 81] as well as the optic nerve [9, 34, 69, 77, 81]. Prominent superior ophthalmic veins can occasionally be present [1, 29].

Paraskevas et al. reported an interesting case with increased T2 signal intensity along the spinal trigeminal tract and nucleus within the medulla oblongata and pons, suggesting an anterograde transsynaptic spread of the virus with high neurotropism [59]. Xiao et al. mentioned another patient with concurrent T2 lesions in the ipsilateral temporo-occipital lobe and cerebellar hemisphere with dural enhancement, suggestive of meningoencephalitis [86]. Other associated intracranial involvements can sometimes be

Table 12.1 Reported cases of OAS secondary to HZO

	Gender/age	Comorbidities	Treatment	Ptosis/ocular motility recovery	Visual recovery
Chang-Godinich et al. [11]	F/72	Chronic lymphocytic leukemia	Oral acyclovir for several days followed by IV acyclovir for 6 days (for rash). Oral acyclovir for 3 months, oral prednisolone with tapering for 8 weeks	2 mm residual ptosis, mild adduction, and elevation deficits after 8 weeks of treatment	VA 0.1–0.8 after 8 weeks of treatment
Krasnianski et al. [34]	F/67	–	IV acyclovir for 10 days, IV prednisolone then oral taper	–	VA 0.3–0.6 within 2 weeks
Shin et al. [72]	M/70	–	IV acyclovir for 3 days. IM dexamethasone for 10 days followed by oral prednisolone tapered over 4 weeks	Ptosis and ophthalmoplegia recovered except adduction 6 months after the onset of herpes zoster	–
Dhingra et al. [19]	M/63	Multiple myeloma recently completed a course of chemotherapy	IV acyclovir followed by oral, stopped within 2 weeks. Oral prednisolone tapered over 2 months	Complete ptosis, minimal ocular movement 8 months after presentation	VA 0.1 to HM 8 months after presentation; disc pale
Shirato et al. [73]	M/71	Colonic carcinoma	Oral prednisolone at the 22nd day after the onset of periocular pain	Ptosis and abduction palsy after 291 day	0.06 after the 22nd day, did not improve during the 10 month follow-up period; optic atrophy
Saxena et al. [69]	F/29	HIV infection	HAART, oral acyclovir. Oral prednisolone 5 days later. By the tenth day, steroids were tapered over the next 10 days HAART and acyclovir were continued	Ocular motility and ptosis improved at the end of 4 weeks	VA 0.03–0.8 at the end of 4 weeks
Ugarte et al. [77]	F/80	Migraine, HT, hypercholesterolemia	Oral acyclovir for 1 week (for rash). Ten days later, oral acyclovir and prednisolone (with tapering) for 2 months	Ocular motility: near complete recovery 6 months later	VA HM to 0.67 6 months later
Kurimoto et al. [35]	F/81	–	IV vidarabine and betamethasone. Vidarabine and IV prednisolone about 17 days later, followed by tapering	Ptosis had recovered by 11 weeks after the start of treatment, limited abduction at 20 weeks	VA 0.4–1.0 at 12 weeks after onset
Arda et al. [1]	M/75	HT	Oral fluocortolone switched to oral valacyclovir and then switched to IV acyclovir. Tapering dose of oral prednisolone after acute symptoms improved	Partial improvement in ptosis and ocular motility at the end of 5 month follow-up period	HM to CF from 1.5 months (did not significantly improve because of cataract and choroidal detachment)
Paraskevas et al. [59]	F/67	–	Oral acyclovir for 1 week (for HZO). About 4 weeks later, IV acyclovir for 10 days, IVMP for 5 days	Slow saccades 5 months later	VA 0.2 to marked improvement
Merino-Iglesias et al. [48]	M/61	–	IV acyclovir for 7 days followed by oral antiviral. Oral methylprednisolone for 7 days then tapered over 10 weeks	Ocular motility was completely restored	VA CF from 1 month to 1.0 after 1 year
Ugurlu et al. [78]	F/49	No chronic illness	Oral brivudine (for HZO). IV acyclovir and oral prednisolone and then oral acyclovir and prednisolone both tapered over 3 months	Complete recovery of extraocular motility	VA 0.1–0.67 at 5 months after presentation
Lee et al. [38]	M/78	DM, chronic obstructive pulmonary disease	IV acyclovir for 15 days, oral prednisolone for 4 days followed by monthly taper over 12 weeks	Limitation of abduction and paralysis of the upper eyelid at 180 days	VA 0.05–0.2

Table 12.1 (continued)

	Gender/age	Comorbidities	Treatment	Ptosis/ocular motility recovery	Visual recovery
Xiao et al. [86]	F/65	(Immunocompetent)	IV ganciclovir. IV dexamethasone. Oral prednisolone tapered over 6 weeks	Persistent ophthalmoplegia 3 months later	Persistent blindness 3 months later
Kalamkar et al. [30]	M/65	–	IVMP for 3 days followed by oral steroid tapered over 2 months. Oral acyclovir	Limited abduction at 6 month follow-up	Light perception (no improvement) at 6 month follow-up; optic atrophy
Verhaeghe et al. [81]	M/80	Bilateral cataract surgery, myocardial infarction, atrial fibrillation, corneal foreign body (removed)	Oral acyclovir for 1 week (for keratitis), followed by IV acyclovir for 14 days. IVMP for 15 days after 7 days of IV acyclovir. Then oral valacyclovir and prednisolone, tapered over 2 months	Ptosis had resolved and ocular motility had improved at 5 months	VA CF to 0.4 at 5 months; optic disc pale
Chandrasekharan et al. [9]	F/60	HT, DM	IVMP for 3 days followed by oral prednisolone tapered over 4 weeks. Oral acyclovir	Mild ptosis. -1 limitation of adduction, elevation, and depression	HM to 0.5 at 3 months; optic disc pallor
Lim et al. [45]	F/77	HT	Oral acyclovir for 2 months. Oral prednisolone tapered over 2 months	Full extraocular movements at 2 months Partial ptosis	Light perception at 2 months (remained poor due to extensive vascularization and scarring of the cornea)
Lim et al. [45]	M/65	DM	Oral acyclovir for 10 days	Mild ptosis and full eye movements at 6 weeks	VA 0.033–0.25 at 6 weeks (worsening of nuclear sclerosis)
Othman et al. [55]	F/59	HT, DM, asthma	Oral acyclovir followed by IV acyclovir and oral prednisolone for 2 weeks, then oral acyclovir for 12 weeks and oral prednisolone tapered over 6 weeks	Full ocular motility at 6 weeks later	Light perception to 0.16 (hyphema) 6 weeks later
Jun et al. [29]	M/67	HT, DM, hyperlipidemia, ischemic heart disease	Oral acyclovir (for HZO) followed by IV acyclovir for 22 days, followed by oral valacyclovir for 4 weeks	Complete ophthalmoplegia 9 months later	No perception of light 9 months later; optic atrophy
Kocaoğlu et al. [33]	M/67	HT, DM	Oral valacyclovir. Pulse prednisolone for 5 days followed by oral prednisolone tapered over 4 months	Ptosis and ophthalmoplegia regressed at 2 months after diagnosis of OAS	VA 0.2–0.4 at 2 months after diagnosis of OAS (permanent); temporal disc pallor
Ruiz-Arranz et al. [67]	F/84	Hypothyroidism, multinodular goiter, asthma, pulmonary hypertension, nocturnal apnea syndrome, congenital dyserythropoietic hemolytic anemia type II, bilateral pseudophakia, age-related macular degeneration	Oral acyclovir (for rash) Oral valacyclovir IV acyclovir and IVMP for 10 days, followed by prednisolone tapered over 10 weeks and oral valacyclovir	Slight abduction limitation	VA 0.05–0.2; slight papillary pallor

CF counting fingers, *DM* diabetes mellitus, *HAART* highly active antiretroviral therapy, *HM* hand movements, *HT* hypertension, *IV* intravenous, *IVMP* intravenous methylprednisolone, *VA* visual acuity

detected including cavernous sinus involvement [29, 35, 67], extension to Meckel's cave [67], diffusion abnormalities in the frontal and frontoparietal regions [1], and transverse sinus thrombosis [33].

Laboratory tests including complete blood count with differential, erythrocyte sedimentation rate, and C-reactive protein are usually normal [9, 30, 69, 77]. Cerebrospinal fluid analysis may reveal lymphocytic pleocytosis and elevated protein level [9, 29, 35, 59, 86]. VZV DNA by polymerase chain reaction can be positive [29]. Positive IgG antibodies against VZV in the blood or CSF were reported in three cases [35, 55, 59].

Visual evoked potentials have been performed in several patients. They were either not recordable [31, 69, 73] or with reduced amplitude and delayed latency [34].

Optimal therapy for OAS secondary to HZO has not been studied with a randomized controlled trial, and there is no standard regimen. In most reported cases, a core combination of systemic corticosteroids and systemic antivirals, either oral or intravenous, was employed (Table 12.1). For the best results, antiviral treatment should be started within 72 h of the onset of rash. Options for antivirals include acyclovir, valacyclovir, and famciclovir. Systemic corticosteroids are used to mitigate the inflammatory response to VZV and are usually given in the form of intravenous methylprednisolone or oral prednisolone. Duration of corticosteroid treatment varies in literature from 2 weeks to 6 months.

As stated in the case reports, there were variable improvements in ptosis, ocular motility, and visual function. As discussed, different pathogenic mechanisms involved may affect the prognosis. Orbital myositis may cause temporary compression on the structures at the orbital apex and carry a better outcome as the congestion resolves. On the other hand, occlusive vasculitis may cause permanent damage and irreversible visual loss [19]. From Table 12.1, we can appreciate that 15 patients (68%, one missing data) showed some recovery of visual acuity, but a complete resolution was rather uncommon (8.7%) [35, 48]. Overall, complete or near resolution of ophthalmoplegia secondary to HZO has been reported to occur in 65% of cases and may take between 2 weeks and 1.5 years to achieve (mean: 4.4 months) [68].

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