Review article

Orbital manifestations in patients with acquired immunodeficiency syndrome

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Abstract

Introduction: The orbital manifestations of acquired immunodeficiency syndrome (AIDS) are uncommon. **Objective:** To provide a review of orbital manifestations of AIDS, the predisposing factors, investigations, treatment and outcome. **Materials and methods:** Meticulous and systematic literature search of Pubmed to identify manuscripts describing orbital manifestations of AIDS was done and the articles were reviewed. The keywords used in the search were "orbit and AIDS", "HIV positive and orbit", "orbit manifestations in AIDS", "orbital disease and AIDS" and "orbital infections and AIDS". The orbital involvement in AIDS may present with opportunistic infections from organisms like fungi, viruses, bacteria and protozoa or with malignancies like Kaposi's sarcoma, squamous cell carcinoma, smooth muscle cell tumors and lymphoma. The predisposing factors for orbital involvement in AIDS are low $CD4^+$ cell count and the immunosuppressive states like diabetes, diabetic ketoacidosis, intravenous drug abuse and neutropenia. A patient may present with fever, headache, nausea, vomiting, decreased vision, ocular pain, and, in cases of mass formation, there is periorbital swelling, axial proptosis, globe displacement and swollen optic disc. Radiologically, mass formation, orbital bony destruction, and spread of disease to contiguous structures including the central nervous system may be seen. The medical management includes therapy for infection and HIV-1 protease inhibitors (highly active antiretroviral therapy) to suppress HIV-1 replication. For tumors, radical surgery including debulking followed by postoperative radiotherapy is generally needed. **Conclusion:** Orbital involvements with AIDS in any form, infective or malignancy, causes significant morbidity and mortality and should be diagnosed and managed as early as possible.

Keywords: Orbit and AIDS, HIV positive and orbit, orbit manifestations in AIDS, orbital disease and AIDS, orbital infections and AIDS

Introduction

The incidence of AIDS is rising, but orbital manifestations from this disease are infrequently discussed. The orbital area is vital not only as an important function of sight is involved but also that it is placed near the central nervous system (Kleinschmidt-DeMasters BK, 2002). Additionally, the incidence of AIDS associated neoplasms is high (Orem et al, 2004). Orbital involvement with AIDS in any form, infective or malignant, causes significant morbidity and mortality (Kronish et al, 1996; Thomas, 2003). In this review article, the orbital manifestations in AIDS are discussed.

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The orbital involvement in AIDS predominantly takes place in the form of infection or malignancy. Generally, these infections are opportunistic. Among these, fungal infections with aspergillus or rhizopus fungus (Kronish et al, 1996) are commonly found in AIDS patients. Other forms of infections are those from viruses like herpes simplex II, herpes zoster, cytomegalovirus, adenovirus and hepatitis C virus (Johnson et al, 1999; Shayegani et al, 1996; Collaco et al, 2000); bacteria like Pneumocystis carinii, Mycobacterium avium, Mycobacterium tuberculosis; fungus like Cryptococcus (Johnson et al, 1999); and protozoa like toxoplasma (Suankratay et al, 2005).

Opportunistic infections frequently involve the anterior and posterior segments of the eye, but, rarely, also involve the orbit of patients with human immunodeficiency virus (HIV) infection (Kronish et al, 1996). Predominant opportunistic orbital infections are found with organisms including Propionibacterium acnes, Pseudomonas aeruginosa, Staphylococcus aureus, Rhizopus arrhizus, Toxoplasma gondii, and Pneumocystis carinii (Kronish et al, 1996).

Tuberculosis is the most common systemic disease which occurs concurrently with various forms of orbital involvements in AIDS patients (Lewallen et al, 1994). The most peculiar pattern of orbital infections in AIDS patients is involvement of several contiguous structures like paransal sinuses and CNS extensions and this happens very commonly with fungi, e.g., aspergillus and rhizopus (Thomas, 2003). Thus AIDS is also a risk factor for central nervous system aspergillosis (Kleinschmidt-DeMasters BK, 2002).

The common types of malignancies which invade the orbit in patients with AIDS are Kaposi sarcoma, squamous cell carcinoma, smooth muscle cell tumors and lymphoma (Karp & Broder, 1991; Safai et al, 1985; Harnley et al, 1988; Than-Trong et al, 1999). Among the lymphomas involving the orbit in AIDS patients, Non-Hodgkin lymphoma followed by Burkitt's lymphoma and large cell immunoblastic type (Reifler et al, 1994) are the commoner ones. Non-Hodgkin lymphoma can present in the form of acute retinitis and proptosis in patients of AIDS (Matzkin et al, 1994), while Burkitt's lymphoma can present as an orbital mass (Reifler et al, 1994).

Predisposing factors

In AIDS patients, the predisposing factors for orbital infection, especially fungal infections, are immuno-suppressive states which may be diabetes (Lee et al, 1996 & Maurriello et al, 1995), diabetic ketoacidosis, intravenous drug abuse, or neutropenia (Evangelo et al, 2006). Notably, the use of protease-inhibitor-based antiretroviral regimes can also precipitate diabetic ketoacidosis (Maurriello et al, 1995 & Evangelo et al, 2006), which further aggravates immuno-suppression and opportunistic infections with fungi including rhino-orbital zygomycosis (Lee et al, 1996 & Evangelo et al, 2006). A state of ketoacidosis in HIV-infected patients can also be induced with the use of pentamidine, which has been seen to cause an increase in the frequency of zygomycosis in HIV-infected patients (Evangelo et al, 2006). Therefore, laboratory studies should attempt to essentially rule out acidosis (Evangelo et al, 2006).

The other risk factors for orbital involvement with AIDS include marijuana smoking (Johnson et al, 1999), homosexuality (Johnson et al, 1999), promiscuity (Johnson et al, 1999), alchohol abuse (Maurriello et al, 1995), steroid therapy (Maurriello et al, 1995), advanced age (Maurriello et al, 1995), Epstein Barr virus infection (Suankratay et al, 2005) and intravenous drug abuse (Reifler et al, 1994). The $CD4^+$ cell count in patients with orbital infection has uniformly been found to be low (Johnson, 1999).

Rhino-orbital zygomycosis has rarely been reported in patients having exclusively HIV infection. Rather, zygomycosis has been seen usually in patients having accompanying predisposing conditions, as mentioned above (Evangelo et al, 2006).

Reifler et al, found that patients affected with orbital lymphoma are uniformly young adult males with a history of homosexuality and/or intravenous drug abuse (Reifler et al, 1994). Immunosuppression also acts as a predisposing factor to the development of smooth muscle tumors (Pritzker et al, 1970). The risk factors for the manifestation of multifocal, smooth muscle tumors in patient with AIDS are HPV infection (Suankratay et al, 2005) and EBV infection (Suankratay et al, 2005). The CD4 cell count in AIDS patients having multifocal, smooth muscle tumors is as low as < 200 cells/µl (Suankratay et al, 2005).

Epidemiology

The patients of AIDS with sino-orbital infection are young patients having the mean age of 34.0 years (Johnson et al, 1999), while the patients with opportunistic infections of the orbit in AIDS had a mean age of 33.8 years (Kronish et al, 1996). However, no gender predisposition has been noted (Johnson et al, 1999). Mansour found that the incidence of periocular involvement, for example of adnexal affections, in AIDS patients is as low as 6 % (Mansour, 1993). In developing countries, the incidence of AIDS-associated neoplasm is high (Orem et al, 2004). In AIDS-infected individuals, squamous cell carcinoma of the conjunctiva and multifocal, smooth-muscle tumors can involve the orbit in even young patients (Suankratay et al, 2005); Tulvatana & Tirakunwichcha, 2006).

In patients of AIDS, squamous cell carcinoma of the conjunctiva is more aggressive, presents at an early age, is multifocal and is complicated by intraocular penetration (Tulvatana & Tirakunwichcha, 2006). There is also an increased incidence of multifocal, smooth-muscle tumors in children with AIDS (Suankratay et al, 2005). Smooth muscle tumors are the second most common tumors in children with AIDS (Suankratay et al, 2005).

Pathology

Infections in AIDS are commonly opportunistic infections affecting imunocompromised patients, (Evangelo et al, 2006) and these individuals have a low $CD4^+$ cell counts (Rosenberg & Fauci, 1992; Germain, 1998). Selective loss of the critical component of the immune system, i.e., T-helper ($CD4^+$) lymphocytes, leads to low $CD4^+$ cell counts, though there is little evidence that T-cell mediated defects per se are critical for host susceptibility to fungal infections (Weng et al, 1998). In addition to a lowered helper-inducer T cell count (less than 10), a lowered WBC count (1.3) is also noticed in patients with AIDS (Adler et al, 1997). In AIDS patient with varicella zoster infection, serologic testing disclosed a CD^4 lymphocytes count of as low as 20 cells/mm^3 , and additionally, an antinuclear antibody of 1:2,560 (Shayegani et al, 1996). Positive auto-antibodies probably represent HIV-induced polyclonal B-lymphocyte activation (Cassini et al, 1991).

In patients with diabetic ketoacidosis, the fungistatic serum activity of transferrin which reduces the free iron available to the fungus for growth is disrupted (Sutcliffe et al, 1980; Artis et al, 1982). Despite this, the fungi are still able to grow as they have ketoreductase by which they can use ketone bodies in their metabolism (Yeung et al, 2001).

Macrophages form the front line of defense by rapidly killing the fungus spores when they first contact tissue. A selective defect in phagocytic killing predisposes these patients to fungal infections, and this in fact under scores the importance of oxidative killing as a measure of the human host defense against infection with fungi (Adler et al, 1997) in HIV-positive patients.

Additionally, the vicious cycle of arterial invasion by the fungus and consequent occlusion causes tissue hypoxia and necrosis and the resultant local acidosis leads to further extension of the infection (Pelton et al, 2001). In AIDS patient, rhizopus invasion can cause massive infarction of the optic chiasma and necrosis of the optic nerve due to an occlusive vasculitis (Lee et al, 1996). Invasive aspergillosis, like mucormycosis, is characterized by a rapidly progressive, fulminant, gangrenous process caused by fungal vascular invasion along with coagulative necrosis of vessels resulting in mycotic thrombosis (Brandwein, 1993). Vascular invasion by fungi can also lead to distant adverse effects from direct extension or hematogenous spread of the fungus to the orbit, brain or cavernous sinus. Its angioinvasive quality can result in tissue necrosis beyond the area of direct physical extension (Brandwein, 1993).

In non-Hodgkin's lymphoma (NHL), there is neoplastic spread directly along the scleral canal of the ciliary nerve. There is also massive necrosis involving the retina, retinal pigment epithelium, choroid, and optic nerve. Resultantly, several solid retinal pigment epithelial detachments can be seen. Immunophenotyping of the orbital tumor may disclose positive staining for Leu 4 (T cells, 30 %) and Leu 14 (B cells, 60 %). Immunostaining for light and heavy chains is however precluded by tumor necrosis (Matzkin et al, 1994). Reifler et al, (1994) found that the morphology of the histopathologic specimen in their case of NHL was consistent with a high-grade, small non-cleaved cell NHL, and flow cytometry revealed an atypical immunophenotype for Burkitt's lymphoma in that CD20 and immunoglobulin light chain antigens were not expressed. In patients with multifocal, smooth muscle tumors, a low $CD4^+$ cell count less than 200 cells/mL has been found (Suankratay et al, 2005).

Clinical features

In AIDS patients, there is characteristically infection of several contiguous structures with the same organism along with associated infections. A number of cases of zygomycosis (infection with Mucorales and Entomophthorales) in HIV-infected patients have been reported (Evangelo et al, 2006; Nagy-Agren, 1995). The association between AIDS and sino-orbital aspergillosis has been described by several authors (Kronsh et al, 1996; Vitale et al, 1992; Cahill et al, 1994; Teh et al, 1995; Meyer et al, 1994). Aspergillus flavus and Aspergillus fumigatus are the usual causative organism of sino-orbital aspergillosis in patients of AIDS (Johnson et al, 1999; Rudwan & Sheikh, 1976) and aspergillosis is very invasive and fulminant in them (Johnson et al, 1999; Khoo & Denning, 1994; McGill et al, 1980).

The patients with sino-orbital aspergillosis already have seropositivity for HIV for as long as 3 to 10 years (mean duration, 6.4 years) (Johnson et al, 1999). Treatment with protease-inhibitors- based antiretroviral regimes (Evangelo et al, 2006), the CD^{4+} count less than 0.050×10^6/L (Johnson et al, 1999) and later stages of AIDS are risk factors for fungal sinusitis. When a HIV positive neutropenic patient develops persistent fever of unknown origin, symptoms of rhinitis, sinusitis, cutaneous finding over the nose, palate or on the gingival region (Talbot et al, 1991), then infection of the orbit or nearby structures can be suspected.

In AIDS patients, the aspergillus infection primarily involves one or more paranasal sinuses, but as the disease progresses, the fungus may secondarily invade the orbit. In cases of sino-orbital aspergillosis, the presenting complaints include fever, headache, nausea, vomiting, decreased vision and pain in the eye (Johnson et al, 1999; Maurriello et al, 1995), though the visual acuity of the involved eye is not very diminished (Johnson et al, 1999). In cases of mass formation, a pressure effect leads

to diminution of vision, chemosis, periorbital swelling, axial proptosis (which may be as much as 5 mm), afferent pupillary defect, restriction of ocular motility (Johnson et al, 1999), retro-orbital pain, decreased vision (Adler et al, 1997) along with displacement of the globe (Adler et al, 1997) and a swollen optic disc (Johnson et al, 1999). Fundus examination in affected patients may show cotton wool spots (Johnson et al, 1999). Due to an angio-invasiveness of aspergillus, there is an interruption of blood supply to sensory nerves, and the patients may complain of nasal obstruction and rhinorrhea, and an extensive bony destruction may be present, even in the initial stages of the disease, though notably it may be without much symptomatology.

The endogenous aspergillus in HIV-positive patients may penetrate the posterior wall of the eye and may also infiltrate adjacent orbital structures. In the cases of aspergillus endophthalmitis, the necessity of enucleation has to be considered if the sclera gets involved (Peterson, et al, 1997).

As there is a lack of host inflammatory response in aspergillus infection, there are minimal external inflammatory signs (Johnson, 1999; Maurriello et al, 1995) and clinical signs of sinusitis such as facial swelling or proptosis may appear only in advanced stages of the disease (Adler et al, 1997). Aspergillosis is rarely fatal except in the severely immuno-suppressed patient and survival in these patients has been found to be more dependent on return of immuno-competence than on any other factor (Adler et al, 1997). Even after debulking and systemic and local treatment with antifungal agents, there is recurrence of abscesses implying that these cases thus have poor prognosis (Johnson et al, 1999). In patients of AIDS with sino-orbital aspergillosis, the cause of death is an intracranial extension of the disease (Johnson et al, 1999).

Rhinorbital mucormycosis progresses very rapidly in patients with AIDS (Lee et al, 1996). There is an extensive invasion of rhizopus into the orbits and paranasal sinuses. The fundus examination shows a patent retinal vasculature, without disc pallor or hyperemia, and an absence of macular whitening or edema (Lee et al, 1996). The rhizopus may also invade the base of the brain, extending from the optic chiasma to the pontine medullary junction (Lee et al, 1996). This causes infarction at the optic chiasma leading to sudden blindness in the affected patient (Lee et al, 1996).

Orbital involvement in patients of AIDS can also be subsequent to ocular affection with AIDS associated ocular diseases like recurrent varicella zoster, herpes zoster ophthalmicus and cytomegalovirus retinitis (Johnson et al, 1999). A lymphoma, bacterial orbital cellulitis, orbital cellulitis due to toxoplasma, panophthalmitis, orbital infection with P carnii, or sino-orbital aspergillosis (Mansour, 1993) may present in the form of an orbital mass in HIV-positive patients.

The optic nerve infestation with toxoplasma can cause an ischemic central retinal vein occlusion which may also lead to orbital inflammation. This orbital inflammation may subsequently present as lid swelling, conjunctival swelling, axial proptosis and ocular motility restriction (Lee et al, 2006).

Propionobacterium acne or Pseudomonas aeruginosa can cause orbital infections presenting in the form of orbital cellulites with subperiosteal abscess and Staphylococcus aureus can cause orbital cellulitis and panophthalmitis in HIV-positive patients. Ikoona et al, (2003) found purulent conjunctivitis and palpebral molluscum contigiosum as common ocular findings in AIDS patients.

Ocular and orbital TB is relatively rare in AIDS patients and can occur even at CD4+ cell counts greater than 200 cells/µl. It can have varied presentations ranging from superficial

involvements like conjunctival TB to severe, sight-threatening complications (Babu et al, 2006).

Patients with AIDS have an increased risk of developing orbital neoplasms such as Kaposi sarcoma, squamous cell carcinoma, smooth muscle cell tumors and lymphoma (Karp & Border, 1991; Safai et al, 1985; Harnley et al, 1988). In non-HIV infected patients, squamous cell carcinoma affects middle-aged to elderly male patients. Additionally, the tumor is more prevalent in males. On the other hand, in patient with AIDS, squamous cell carcinoma presents at a young age, with a mean age of approximately 35 to 40 years (Tulvatana & Tirakunwichcha, 2006; Timm et al, 2004; Kaimbo et al, 1998). In patient with AIDS, squamous cell carcinoma is more aggressive than usual, multifocal and presents with clinical features like redness of eyes, rapid deterioration and loss of vision, multiple whitish masses at the lower bulbar conjunctiva along with intraocular penetration (Tulvatana & Tirakunwichcha, 2006). Additionally, it requires exenteration at an early age (Tulvatana & Tirakunwichcha, 2006; Masanganise & Magava, 2001). In one patient, squamous cell carcinoma was multifocal and two separate whitish masses on the bulbar conjunctiva were seen adjacent to the infero-medial limbus (Tulvatana & Tirakunwichcha, 2006). The carcinoma in this patient had also invaded the anterior chamber, and anterior surface of the iris of this patient was filled with tumor cells containing keratin pearls (Tulvatana & Tirakunwichcha, 2006). Tulvatana et al found that their patients with multifocal, squamous cell carcinoma had had AIDS for about three years on average, before this carcinoma had manifested (Tulvatana & Tirakunwichcha, 2006).

Characteristically, the smooth muscle tumors in patients with AIDS are multifocal (Suankratay et al, 2005), involve the central nervous system (Suankratay et al, 2005), are common in children (McLain et al, 1995; Cohen, 2000; Thorley-Lawson & Gross, 2004) and occur at very unusual sites that are often not observed in immuno-competent individuals (Suankratay et al, 2005) having smooth muscle tumors. The patients with multifocal, smooth muscle tumors in AIDS usually have a concurrent gastrointestinal, respiratory tract, central nervous system, laryngeal, adrenal gland and hepatic involvement (Suankratay et al, 2005). Some of these patients do not survive for more than one year, while some who were followed-up for two years did not have any remission during this period (Suankratay et al, 2005).

Orbital Kaposi's sarcoma in an AIDS patient is known to have an incessant progression and a fatal outcome despite the patient being given intensive chemotherapy (Collaco et al, 2000).

Orbital lymphoma may present with marked proptosis and distortion of the globe (Lim et al, 1997; Desia et al, 1992).

Non-Hodgkin lymphoma is more common in patients with the acquired immune deficiency syndrome (AIDS). The incidence of non-Hodgkin lymphoma in the AIDS population has been increasing as the life expectancy of these patients has increased. Orbital non-Hodgkin lymphoma, intraocular NHL, and those concurrent with primary central nervous system NHL have rarely been reported in patients with AIDS (Matzkin et al, 1994). Co-existent intraocular and orbital NHL is exceptionally unusual (Matzkin et al, 1994).

Associated infections and diseases

Associated infections are very common in patients having orbital involvement with AIDS, and this particularly results due to a state of immunosuppression. In patients with AIDS, associated ocular infection from other viruses like herpes simplex virus II, varicella zoster virus, cytomegalo virus and adenovirus have been found (Shayegani et al, 1996). Along with aspergillus sinus infection, authors have also

observed associated xanthomonas maltophilia infection (Adler et al, 1997).

Previous AIDS-related ocular disease like recurrent varicella zoster can cause orbital affection with AIDS in their subsequent course (Lee et al, 1996). Previous AIDS-related systemic diseases like Pneumocystis carinii pneumonia, Mycobacterium avium-intracellulare complex, cryptococcal meningitis, systemic lymphoma and hepatitis C can later be followed by orbital affection in different ways (Johnson et al, 1999). Patients with orbital TB very commonly have concurrent pulmonary TB (Babu et al, 2006).

The AIDS patient with multifocal, smooth muscle carcinoma can have associated infections with mycobacterium gordonae, Pneumocystis jirovecii, and/or mycobacterium tuberculosis. These associated infections can result in further orbital involvement with organisms like cryptococcus, toxoplasma, hepatitis B virus and cytomegalo virus (Suankratay, et al, 2005).

In patients with orbital Kaposi's sarcoma, systemic examination may reveal other lesions suggestive of disseminated mucocutaneous Kaposi's sarcoma, oral candidiasis, membranous esophagitis and granulomatous hepatitis (Collaco et al, 2000).

Imaging studies

Radiological findings predominantly are in the form of a mass, orbital bony destruction, and involvement of contiguous structures in patients with AIDS having infective orbital disease., Computed tomography findings in those having sino-orbital aspergillosis included heterogeneous, enhancing, sino-orbital masses with bony destruction involving neighboring sinuses like the ethmoid and sphenoid sinus, the brain (Johnson et al, 1999), and calcifications. Invasive aspergillosis presented in the form of complete opacification of the sinuses with extension to the contiguous structures (Adler et al, 1997) on CT scan. MRI may exhibit soft tissue-enhancing masses, which are hypo intense on T1- and T2- weighted images (Johnson et al, 1999).

Patients with rhino-orbital zygomycosis and mucormycosis (rhizopus infection) may show fluid collection and opacification of affected paranasal sinuses and signs of orbital cellulites on MRI of the brain (Lee et al, 1996; Evangelo et al, 2006).

The MRI scan of the head and orbit in patients having orbital inflammation in AIDS showed inflammatory changes in the extraocular muscles and orbital fat (Lee et al, 2006).

Radiological findings in patients with tumors show involvement of periorbital structures spread to contiguous areas, CNS involvement, and systemic spread. Patients having squamous cell carcinoma may show a slight thickening of the involved eyelid (Tulvatana & Tirakunwichcha, 2006) in the CT scan. In patients having multifocal, smooth muscle tumors, the MRI may show CNS involvement in the form of an enhancing epidural mass at the neural foramina of the involved spinal nerves and at the regions of the brain involved (Suankratay et al, 2005). Similarly, Suankratay et al (2005) have seen enhancing suprarenal masses in patients with renal involvement.

In orbital lymphoma, the orbital CT scan shows extraocular muscle involvement (Reifler et al, 1994) while the thoracic CT-scan shows a mediastinal lymph node enlargement which can reach to be as large as 18 cm in diameter (Johnson et al, 1999; Than-Trong et al, 1999).

Diagnosis

Clinically, the diagnosis of AIDS in the orbit can be established by the mere presence of diseases like Kaposi's sarcoma or mycobacterium avium complex (Lee et al, 1996). The infections commonly found in AIDS patients have been described above, and their presence can also help in reaching the diagnosis of AIDS (Adler et al, 1997).

The laboratory tests show a lowered CD^4 T-lymphocyte count, which is usually below 200 cells/ml (Lee et al, 1996). Analysis of cerebrospinal fluid should be done if the infection is suspected to be in the central nervous system (Lee et al, 1996). Aspergillus infection is difficult to diagnose due to the lack of a host-inflammatory response (Adler et al, 1997). The lavage of the paranasal sinuses can be used to grow cultures for fungi like A fumigatus, which are common in patients of AIDS (Adler et al, 1997). Infective tissue can also be obtained by surgical excision or debulking of the sino-orbital mass, and tissue thus obtained can be cultured and examined histopathologically. Johnson et al (1999) noticed that fungal cultures in their patients yielded Aspergillus fumigatus, and they noticed superimposed secondary bacterial infections in three of their patients. The confirmatory test for fungal infection is, however, sinus biopsy, which may show large amounts of broad, aseptate, ribbon-like hyphae (Evangelo et al, 2006).

In cases of death, multiple granulomata of the optic nerve (Lee et al, 1996) may show the fungal organisms on autopsy.

Tumor tissue specimens of smooth muscle tumors can be subjected for immuno-histochemical analysis, in situ hybridization, and real-time quantitative PCR (Suankratay et al, 2005; Tulvatana & Tirakunwichcha, 2006) for diagnosing EBV infection. The plasma and serum samples can also be tested by real time quantitative polymerase chain reaction and serologic analysis (Suankratay et al, 2005) for diagnosing EBV infection.

Orbital lymphoma involving the orbit can be diagnosed by orbital biopsy (Reifler et al, 1994). Extensive involvement of the abdomen by the disease process also aids in reaching the diagnosis of a lymphoma (Reifler et al, 1994).

For diagnosing Non-Hodgkin's lymphoma in their patients, Matzkin et al performed an orbital biopsy, followed by enucleation of the eye and studied the material by light microscopy. Further immunophenotyping of the tissue obtained by orbital biopsy also was performed by these researchers (Matzkin et al, 1994). In Non-Hodgkin's lymphoma, extraocular muscle involvement can be documented by computed tomography and subsequently confirmed by orbital biopsy (Reifler et al, 1994).

Kaposi's sarcoma is diagnosed by an eyelid incisional biopsy (Collaco et al, 2000). Ultrasonography and computed axial tomographic scans are used to document orbital involvement in these patients (Collaco et al, 2000).

Medical management

When fungal sinusitis is suspected, prophylactic antifungal chemotherapy is initiated. Medical treatment consists of oral fluconazole and amoxicillin and on non-response, treatment with amphotericin B in low doses (0.3 mg/kg/d) followed by high doses (2.7 mg/kg/d) is used (Adler et al, 1997). In patients of rhino-orbital zygomycosis with a HIV-positive status, prolonged antifungal regime of liposomal amphotericin B at a dose of 4 mg/kg daily for 4 weeks, followed by deoxycholate amphotericin B 0.5 mg/kg twice a week for 6 months, has been given (Evangelo et al, 2006). Antifungal therapy varies from use of a single agent (amphotericin B) as the first line drug (Abramowicz, 1994), to treatment with multiple combinations (of amphotericin B, flucytosine, rifampin) (Yu et al, 1980). Other newer antifungal medications that offer promise include itraconazole, liposomal amphotericin B, miconazole, and fluconazole. Invasive rhizopus infection is treated with intravenous amphotericin B (Lee et al, 1996). The antifungal therapy is administered along with antiretroviral therapy including indinavir, stavudine and lamivudine (Evangelo et al, 2006).

A new class of compounds, i.e., HIV-1 protease inhibitors, have been found to suppress HIV-1

replication and reduce HIV disease progression; and thus these compounds reduce the mortality in patients with AIDS when used in combination with reverse transcriptase inhibitors. These new drug combinations that include potent protease inhibitor agents are called "highly active antiretroviral therapy (HAART)". These data clarify that combination therapy with protease inhibitors may improve the longevity and survival in patients of AIDS.

Immunologic stimulation has also been attempted in this disease by the use of granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) in an attempt to raise the absolute neutrophil count and host resistance (Denning & Stevens, 1990; Abramowicz, 1992).

Patients of multifocal, smooth muscle tumors associated with HIV infection are treated with drugs like zidovudine, didanosine, stavudine, lamivudine, nevirapine and efavirenz (Suankratay et al, 2005). In these patients, the concurrent infections like tuberculosis and cryptococcus are treated with the respective medications (Suankratay et al, 2005). The orbital lymphomas in AIDS are treated with chemotherapy (Than-Throng et al, 1999).

Surgical management

As aspergillus is an angioinvasive fungus, it causes tissue necrosis both by infarction as well as by direct involvement (Adler et al, 1997). This perpetuates an anaerobic environment suitable for fungal growth and limits the penetration of systemic antifungal agents by hematogenous routes. Thus, complete removal of the dead tissue is necessary for cure of infection. Although endoscopic techniques provide a good sinus view, these may not permit complete removal of the dead tissue. Thus, in a patient with an extensive invasive disease, an external approach should be used for carrying out controlled removal of the orbital soft tissue and bone. In these patients, intravenous amphotericin B, at a dose of 25 to 35 mg/d, is administered along with local intracavitary irrigation with amphotericin B (1mg/ml) for delivering the antifungal agents to the marginal tissues. It is concluded that in patients of AIDS, in addition to giving antifungal medications, effective treatment entails removal of the whole of the devascularised tissue in order to permit penetration of the antifungal agents into the tissue.

In aggressive cases, more radical surgical measures involving excision of more tissue need to be adopted. For example, in patients of rhino-orbital zygomycosis, orbital exenteration plus maxillary oesteotomy was performed by Evangelo et al (Evangelo et al, 2006). Operative findings in patients with fungal infection show a thickened, necrotic mucosa and necrotic periosteum (Adler et al, 1997). Thus, the repeat surgeries, if needed, are generally more extensive with operations on several contiguous nasal sinuses, debridement of the orbit, followed by post-operative placement of nasal, lacrimal and frontal sinus irrigating tubes by combined otolaryngology and ophthalmology teams (Adler et al, 1997). In these surgeries, complete evacuation of the necrotic tissue is done, and debridement of the periorbita is done, while every attempt is made to preserve the orbit (Adler et al, 1997). In such patients, postoperatively, local wound care along with daily local irrigation of the sinuses with amphotericin B (5mg/50mL of normal saline) is required (Adler et al, 1997).

The limitation of orbital exenteration is that it does not guarantee complete cure if an embolus of infective tissue has already travelled to distant regions like the central nervous system via an arterial supply (Adler et al, 1997).

The surgical measures are the mainstay of treatment of carcinomas in AIDS-infected individuals. In AIDS-infected individuals, due to the rapid progress and aggressive nature of

the squamous cell carcinoma, the patient requires an early exenteration (Tulvatana & Tirakunwichcha, 2006). In AIDS patients with multifocal, smooth muscle tumors, surgical removal of the tumor followed by postoperative radiotherapy is done (Suankratay et al, 2005).

Outcome

Orbital involvement with AIDS in any form - infective or malignant - causes significant morbidity and mortality (Kronish et al, 1996; Thomas, 2003).

From 1991 to 2003, only about 15 AIDS patients having orbital mycoses have been reported, and the prognosis was generally poor in these patients, with resolution or improvement of the orbital mycotic infection in just six of the 15 patients (Thomas, 2003).

The factors which lead to a good prognosis are focal lesions, a limited form of the infection, lack of spread to intracranial structures, achieving complete debridement of infected tissue, and combined use of amphotericin B intravenously and in the form of local irrigation in fungal infecions. Generally these patients require radical surgeries like orbital exenteration along with a prolonged amphotericin B regime and antiretroviral medicines (Evangelo et al, 2006).

Mylonakis E et al found that aspergillus infection in HIV-infected patients is usually fatal (Mylonakis et al, 1997). However, Mylonakis et al (1997) & Barry et al (1999) state that in the event that an early diagnosis of aspergillus is made clinically and radiologically, prompt and aggressive antifungal therapy along with surgery can cure aspergillus infection in HIV patients and avoid a dismal prognosis. When endogenous aspergillus infection of the orbit causes scleral involvement, enucleation has to be considered (Peterson et al, 1997).

The factors which lead to a bad prognosis in AIDS patients are intracranial extension of infection, rhizopus infection, recurrence of infection, massive involvement of tissues, presence of other systemic diseases and spread of infection or embolus via an arterial supply to distant areas, specifically the central nervous system. In the event of an intracranial extension, specifically because it is refractory to aggressive therapy, the usual result is death of the patient (Johnson et al, 1999).

Invasive rhizopus infection in AIDS has a very fulminant course, and it rapidly progresses to result in the death of the patient (Lee et al, 1996). The patients may also die of other systemic diseases. AIDS patients with aspergillus infection of the paranasal sinuses and orbit, even when treated with surgical and antifungal medical treatments, may die of respiratory complications, despite the absence of a concurrent intracranial involvement (Adler et al, 1997).

In patients of AIDS with sino-orbital aspergillosis, the lack of a host-inflammatory response may result in a delayed diagnosis, and, consequently, the massive involvement results in a a high mortality (Pritzker et al, 1970). In some cases, despite continuous antifungal treatment accompanied with surgical debridement, the patient may not survive for more than six weeks after surgery, even when, surprisingly, clinical evidence of intracranial or orbital aspergillosis is absent (Adler et al, 1997).

Patients with orbital involvement in AIDS may have complete loss of vision (Kronish et al, 1996). Orbital exenteration does not guarantee complete cure if an embolus of infective tissue has already traveled to the central nervous system via an arterial supply (Adler et al, 1997). The mortality is also increased if there is recurrence and/or intracranial extension (Johnson et al, 1999) of the disease (Kronish et al, 1996).

Orbital Kaposi's sarcoma in AIDS has a continuous progression and a fatal outcome despite intensive chemotherapy (Collaco et al, 2000).

Complete removal of unifocal, smooth muscle tumors followed by HAART can lead to total remission (Suankratay et al, 2005). In patients with multifocal, smooth muscle tumors in AIDS, surgical removal of the tumor followed by postoperative radiotherapy is done (Suankratay et al, 2005). The prognosis for patients with smooth muscle tumors in AIDS depends on the location, size and mitotic activity of the tumors (Suankratay et al, 2005). According to Suankratay C et al, (2005) smooth muscle tumors are extremely refractory to treatment and even complete removal, adjuvant radiotherapy, or chemotherapy may not prove to be an effective treatment for these patients. Improvement of the immune status might improve the outcome of EBV-associated smooth muscle tumors in patients with AIDS.

In AIDS-infected individuals with squamous cell carcinoma, due to the rapid progress, rapid spread and aggressive nature of the carcinoma, the patient requires early exenteration and visual outcome is obviously poor (Tulvatana & Tirakunwichcha, 2006). Thang Trong et al (1999) found that the orbital lymphomas regress completely with use of chemotherapy and no recurrence may be found even after 21 months of follow-up.

Conclusion

The orbital infections in AIDS are varied and generally opportunistic infections; and these characteristically have a massive spread involving several structures including spread to contiguous organs. Due to the thin bony margins of orbit and paranasal sinuses, the patient can present with involvement of several contiguous structures including spread to the central nervous system. Thus, specific microbiological diagnostic techniques should be used to reach a correct and an early diagnosis.

Fungal infections are very common in patients with AIDS. Mucormycosis is an opportunistic infection that can progress swiftly in AIDS patients, especially if the patient has diabetes (Lee et al, 1996). Fulminant invasive aspergillosis is very common in patients with AIDS (Adler et al, 1997). Aspergillosis of the orbit and neighbouring areas follows a more destructive course in AIDS patients than in an otherwise normal individual. Success in treatment is determined by promptness in initiation of the treatment, complete removal of necrotic tissue, effective antifungal medications, and, most importantly, improvement in the immune status of the patient (Adler et al, 1997). Antifungal agents have to be used both systemically and locally, for irrigation; and surgical debridement along with orbital exenteration is the modality of treatment,which has to be adopted. No single medical or surgical measure can treat the disease completely and these measures have to supplement each other (Adler et al, 1997). Prognosis however remains poor due to the widespread involvement and tissue necrosis.

Treatment with a protease-inhibitor-based anti-retroviral drug regime can lead to orbtal fungal infections in patients with AIDS especially if the patients have underlying systemic diseases like diabetes or diabetic ketoacidosis. Hence, in such patients, a close watch for orbital infection should be kept (Evangelo et al, 2006).

Though exenteration was considered as the radical treatment for invasive fungi like aspergillus and rhizopus, recently, more conservative treatment involving the exclusive removal of the infected tissue is being advocated in order to save the eye and prevent impairment of vision. This is especially because even exenteration is not considered the complete treatment as it might have been preceded by an embolic spread of the infected tissue into the central nervous system via an arterial supply (Adler et al, 1997).

The common forms of orbital tumor in patients of AIDS are squamous cell carcinoma, smooth

muscle cell tumor, lymphomas, and Kaposi sarcoma. These tumors characteristically occur at an early age, are more aggressive, are complicated by intraocular penetration, very easily spread to the CNS and require an early exenteration.

Immunocompromised individuals have an increased likelihood for more severe and atypical presentations in orbital AIDS. This highlights the need for an increased index of suspicion for HIV infection particularly also because ocular or orbital disease may be the first manifestation of this life-threatening disease. As the opportunistic infections of the orbit with bacterial, fungal and parasitic organisms are associated with a high ocular morbidity and mortality rate, these should be cognized as a serious complication of systemic HIV infection (Kronish et al, 1996).

Because of the underlying chronic and progressive immune dysfunction, the ocular symptoms, signs and clinical course are often atypical and severe, and patients require protracted medical therapy.

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