

Ophthalmic Manifestations in Human Immunodeficiency Virus Infection in Singapore

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Abstract

The paper retrospectively reviews the spectrum of ophthalmic manifestations in human immunodeficiency virus (HIV) infection in Singapore between May 1995 and October 1996. One hundred and eighteen patients were examined for ocular abnormalities. Criteria for examination were 1) visual complaints, 2) absolute CD4 count of less than 50 cells/ul, 3) patients with acquired immunodeficiency syndrome-defining illness or 4) any relevant systemic illnesses which may have ocular involvement. Only 25 patients (21.2%) had visual symptoms. Eighteen patients (15.3%) had abnormalities associated with microvasculature. Forty-four patients (37.3%) had opportunistic infection involving the eye of which 37 were that of cytomegalovirus retinitis (CMVR). Seven patients (5.9%) had neuro-ophthalmic disorders. One patient presented with proptosis due to orbital lymphoma. Four patients (3.4%) had episcleritis and 3 patients (2.5%) had symptomatic dry eyes. It is still not known if episcleritis and dry eyes are associated with HIV infection or are coincidental. Fifty-one patients (43.2%) had no ocular pathology and remained so throughout the period of study. Nine patients (7.4%) had more than one pathology. The major cause of visual loss was due to ocular infections, with CMVR being most prevalent. Recognising the ophthalmic signs in HIV patients will facilitate early diagnosis. Prompt treatment of eye involvement can prevent or delay blindness, which is psychologically and functionally important to these patients.

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Introduction

The first case of human immunodeficiency virus (HIV) infection in Singapore was detected in 1985. Since then we have seen an increase in the number of infected individuals. The cumulative number of infected individuals at the end of 1996 was 558. In 1996 the total number of HIV notifications was 139, compared to 111 in 1995.

Primary HIV infection results in a disease entity called acute sero-conversion illness, which begins 3 to 6 weeks after infection. A clinically quiescent state follows which can be interrupted by episodes of symptomatic illness related to HIV infection. When CD4 count falls to between 500 and 200 cells/ul, mucocutaneous infections such as herpes zoster, molluscum contagiosum and bacterial folliculitis begin to appear. Most of the local patients present late when CD4 counts are below 200 cells/ul. At such an advanced stage of HIV infection, opportunistic infections such as *Pneumocystis carinii*

pneumonia, tuberculosis, cerebral toxoplasmosis, and malignancies such as high grade B cell lymphoma and Kaposi's sarcoma are common presenting conditions.

Epidemiological studies in Singapore show that 25% of acquired immunodeficiency syndrome (AIDS) individuals in Singapore are affected by cytomegalovirus retinitis (CMVR).¹ However, there is limited information of other ocular involvement in our local population. This study aims to review the ophthalmic manifestations of HIV infection in Singapore.

Materials and Methods

This is a retrospective study of all patients referred to the Ophthalmology Clinic at the Department of Infectious Diseases of Tan Tock Seng Hospital, Singapore between May 1995 and October 1996. Criteria for referral included 1) visual complaints, 2) CD4 counts less than 50 cells/ul, 3) patients with AIDS-defining illnesses and 4) patients with relevant systemic illnesses such as

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CMV colitis and cryptococcal meningitis. Data were collected from case records. Parameters looked at consisted of patients' age, sex, race, zidovudine and cotrimoxazole prophylaxis, visual complaints, ophthalmological findings, and latest CD4 counts, which may not coincide with the time of referral or ocular examination. The reason is because the majority of patients who were referred for eye examination were in the advanced stage of HIV infection and CD4 counts were generally below 200 cells/ul. Further CD4 measurements were of little value and were thus rarely performed.

Results

A total of 118 HIV-infected patients were seen over an 18-month period. The ocular findings are classified into 4 groups (Table I): 1) ocular infections, 2) HIV-related microangiopathy, 3) neuro-ophthalmic signs and 4) neoplasms. Patients with episcleritis and symptomatic dry eyes were also seen. It remains to be determined if these conditions are related to HIV infection.

Forty-four patients (37.3%) had ocular infections involving the eye. Eighteen patients (15.3%) had cotton-wool spots in the retina. Seven patients (5.9%) had neuro-ophthalmic signs. Four patients (3.4%) had episcleritis and 3 patients (2.5%) had symptomatic dry eyes. One patient (0.8%) had high-grade lymphoma with orbital involvement. Fifty-one patients (43.2%) had no ophthalmic pathology on initial examination and during subsequent follow-up over the study period. Ten patients (8.4%) had more than one pathology.

The mean CD4 count of the patients was 69 cells/ul

TABLE I: BREAKDOWN OF THE INCIDENCE OF DIFFERENT EYE DISORDER SEEN IN HIV-INFECTED PATIENTS DURING THE STUDY PERIOD

Group	Subgroup	Number	Total
HIV related microangiopathy		18	18
Opportunistic infections	CMVR	37	43
	Herpes simplex	1	
	Orbital cellulitis	1	
	PORN	3	
	Acute retinal necrosis	1	
Neuro-ophthalmic signs	Papilloedema	4	7
	Optic neuritis	1	
	Bell's palsy	1	
	Others	1	
Neoplasms	Lymphoma	1	1
Others	Episcleritis	4	8
	Symptomatic dry eyes	3	
	Syphilitic chorioretinitis	1	
No ophthalmic abnormality		51	51

CMVR: cytomegalovirus retinitis; PORN: progressive outer retinal necrosis

(range 2 to 588 cells/ul). Thirty of the 118 patients (25.4%) had CD4 counts greater than 50 cells/ul. Of these 30 patients, 8 had CMVR, 4 had cotton-wool spots in the retina, 2 had dry eyes, 1 had acute retinal necrosis, 1 had lymphoma, 1 had herpes simplex keratitis and 12 had no ocular pathology.

Ocular infections formed the major group of disorders among these patients (44/118 or 37.3%). All of them were opportunistic eye infections except for one patient who had syphilitic chorioretinitis. The most common infection was CMVR (37/44 or 84.1%). Of the 37 cases of CMVR seen, only 10 patients (27.0%) had visual symptoms. Their mean CD4 counts was 51 cells/ul (range 4 to 359 cells/ul). Eight of them (21.6%) had CD4 count greater than 50 cells/ul. However, this may not be a true reflection of the counts at the onset of CMVR because the CD4 measurements were not done at the time of diagnosis of CMVR. All new cases were treated with intravenous ganciclovir unless there were contraindications such as neutropenia from zidovudine therapy. In these cases, intravenous foscarnet was used. All patients were kept on maintenance dose of ganciclovir or foscarnet for life. For non-responders or cases of reactivation, the patients were either re-induced, changed to foscarnet or treated with intravitreal ganciclovir. One patient received intraocular ganciclovir implant.

Other opportunistic infections were considerably less common. One patient complained of unilateral red eye which on examination turned out to be herpes simplex keratitis. His latest CD4 count was 67 cells/ul.

During the study period, 3 patients were diagnosed to have progressive outer retinal necrosis (PORN). Ophthalmological examination revealed multi-focal deep retinal lesions and cotton-wool spots. Cutaneous zoster was observed in 1 patient. One patient had myelitis, bilateral optic neuritis and neuroretinitis, while the other two had retrobulbar neuritis, myelitis and meningitis.

One patient had a clinical picture of bilateral acute retinal necrosis. He presented with blurring of vision in the left eye and photophobia in the right eye. He also had a history of two episodes of herpes zoster. The first occurred several weeks prior to his eye symptoms, he was still recovering from the second episode when he was referred. The CD4 count was 20 cells/ul. The patient was treated with intravenous acyclovir but the condition continued to progress resulting in bilateral retinal detachment. He refused surgery for the detachments.

One patient presented with syphilitic chorioretinitis. At the time of presentation he also had a maculo-papular rash affecting the soles, as well as widespread excoriations and post-inflammatory hyper-pigmentation. Visual acuity was 6/9 in the right eye and counting fingers in the left eye. Ophthalmological examination revealed bilateral panuveitis. Funduscopy showed bilateral vitritis,

perivascular sheathing and optic disc hyperaemia. Venereal disease reagent laboratory reaction was positive in the serum (1:512) and cerebrospinal fluid (1:32). A diagnosis of secondary neuro-syphilis was therefore made. This patient was treated with ziduvodine, intravenous crystalline penicillin and oral prednisolone (starting one week after penicillin).

Abnormalities in microvasculature can involve various organs in HIV patients. In the eye, this is manifested as cotton-wool spots, haemorrhages and microaneurysms in the retina. In this study, 18 patients had cotton-wool spots in the retina. All these patients were asymptomatic. Their CD4 counts ranged from 5 to 208 cells/ul with a mean of 46 cell/ul. Two of these patients had concomitant CMVR in the fellow eye and 1 had papilloedema secondary to cerebral toxoplasmosis.

Seven patients presented with neuro-ophthalmic abnormalities. Four of them had papilloedema, three secondary to cryptococcal meningitis and the other due to intracranial toxoplasmosis. There was a patient with syphilitic optic neuritis, which is the same patient with syphilitic chorioretinitis described earlier. Another patient had Bell's palsy. Onset, however, was several years prior to diagnosis of HIV infection. It was uncertain whether this was secondary to early HIV infection. One patient had VII and VIII cranial nerves palsy, left internuclear ophthalmoplegia, and cerebellar nystagmus due to HIV encephalopathy.

One patient presented with a fungating sternal mass, vesicular lesions of the right eyelid, proptosis and orbital cellulitis. Fine needle aspiration biopsy of the sternum confirmed the diagnosis of malignant B cell lymphoma. Computed tomographic (CT) scan of the orbit showed a soft tissue mass in the ethmoidal sinuses with destruction of the medial wall of the orbit causing bowing of the right medial rectus muscle. There were also obstructive sinusitis and orbital cellulitis. This patient was treated with chemotherapy but without much improvement.

Discussion

HIV infection can affect the eye in many ways. Ocular manifestations are seen in up to 70% of AIDS patients.² Occasionally, ocular involvement may be the first presentation in patients with HIV infection. In the study, the major cause of visual loss was due to ocular infections, with CMVR being most common. Recognising the ophthalmic signs in HIV patients will facilitate early diagnosis and prompt treatment of the eye involvement. The prevention or delay of blindness is psychologically and functionally important to these patients during their terminal stages.

The most prevalent ocular infection is that of CMVR and various theories have been postulated to account for this observation. Studies have revealed the occurrence

of both CMV and HIV in retinal lesions. On the basis of *in-vitro* studies that demonstrated enhancement of CMV replication by the HIV virus, it has been suggested that co-infection of retinal cells by both viruses may be a factor that contributes to the frequency and severity of CMV infection.³ Yet others believe that the primary event is ischaemia of the retina as a result of microvascular changes secondary to the disease. This ischaemia results in disruption of the retinal vasculature, providing the virus access to the retina.³

Current research involves identifying patients at risk of CMVR. Hansen et al⁴ describes a technique which employed polymerase chain reaction to quantify CMV DNA load in the serum so as to predict the risk of developing CMVR. Recent studies have also indicated that CMVR does not develop unless the CD4 count is less than 50 cells/ul.⁵ Our study showed that 30% of patients had CD4 counts over 50 cells/ul. However, because counts in this study were taken from the last recorded value which were not performed at the time of diagnosis of CMVR, it could not be correlated with the incidence of CMVR.

Other posterior segment infections are less common. To date there is little literature on the epidemiology. In this review other infections included PORN, syphilitic chorioretinitis and acute retinal necrosis. Toxoplasmosis and histoplasmosis were not encountered.

PORN was first described by Forster et al⁶ in 1990. They described two patients with AIDS who manifested deep retinal lesions, which progressed rapidly to result in large areas of retinal necrosis. Inflammation in the anterior chamber and vitreous was absent or minimal. Both these patients had herpes zoster at the time of presentation. Response to intravenous acyclovir was dismal, and both eventually were complicated by retinal detachment. Herpes virus was demonstrated in both patients. Since then the number of cases reported have increased. Engstrom et al⁷ described 38 patients with this syndrome in 1993. In their series, 67% of patients had a history of cutaneous zoster. They found that this syndrome was the second most common opportunistic infection among North American patients with AIDS. In contrast, only three cases were seen in this series.

Syphilis is an uncommon infection in patients with AIDS. In 7 separate reviews on 235 patients, no patient had ocular syphilis.⁸⁻¹⁴ However, occasional cases have been reported.¹⁵ Features of ocular syphilis include uveitis, optic neuritis and retinitis. In addition, they also have dermatological and neurological signs of secondary syphilis. Recent reports of syphilis in HIV-infected individuals show that the course of the disease is accelerated and more severe, frequently affecting the central nervous system.¹⁶ Response to standard therapy is poor.¹⁷ All patients with syphilis are at risk of HIV infection and

vice versa. Hence, all patients with syphilis should be screened for HIV antibodies. Treatment in such cases should be aggressive. Tamesis and Foster¹⁸ suggested that all such patients be admitted to hospital and recommended cerebrospinal fluid examination. Treatment of ocular syphilis in HIV-infected individuals should follow the standard regimen for neurosyphilis, i.e. 12 to 24 MU/day of aqueous crystal penicillin G intravenously for at least 10 days, followed by 2.4 MU/week of benzathine penicillin G intramuscularly for three weeks.

Multifocal choroiditis is an alarming although non-specific sign. It is seen in patients with disseminated infection caused by *Pneumocystis carinii*, *Cryptococcus neoformans*, *Mycobacterium avium* intracellulare, candida or *Histoplasma capsulatum*,^{19,20} all of which are life-threatening if not treated. Hence, it is important that such a patient be worked up thoroughly and given appropriate systemic treatment.

Anterior segment infections could also be seen. In this study, singular cases of lid infection with herpes simplex virus type 1, herpes simplex keratitis, and orbital cellulitis secondary to obstructive sinusitis were observed. In the literature, CMV²¹ and microsporidia²² have also been reported to cause keratitis in HIV-infected individuals.

AIDS-related retinal microvasculopathy was first reported in 1982.²³ This retinopathy consists of cotton-wool spots, microaneurysms and haemorrhages. Recently, pathological documentation of AIDS vasculopathy has been described.²⁴ These include perivasculitis of retinal vessels, acellular and hypocellular capillaries and venules, thickened basal lamina, endothelial cell proliferation, swollen endothelial cells and degenerating pericytes. Conjunctival vascular abnormalities have also been described since 1987.²⁵ These changes include capillary dilatation, blood column disruption and sludging.

Retinal cotton wool spots are the most common ocular manifestation in AIDS. Figures of 40% to 60% have been quoted.²⁶ Freeman et al²⁶ studied the prevalence and significance of these findings in HIV-infected individuals and AIDS patients. Their results show that these findings are seen in symptomatic HIV-infected individuals and almost half of AIDS patients on initial ophthalmological examination. However, they are almost never seen in asymptomatic HIV-infected individuals. They are also associated with a lower CD4 to CD8 ratio. Hence, when seen in HIV-infected individuals, it indicates a more advanced disease.

Since the advent of AIDS, two types of neoplasms have shown an increase in incidence. They are Kaposi's sarcoma and B cell lymphoma. Altogether about 25% of AIDS patients develop cancer during HIV infection.²⁷ The most accredited pathogenesis of oncogenesis in HIV-infected individuals is the production of multiple

growth factors by the HIV-infected lymphocytes (in Kaposi's sarcoma) or the dysregulation of B cells caused by T cell destruction.²⁸

Kaposi's sarcoma has been reported in 30% of AIDS patients, mostly in male individuals.²⁹ Holland et al³⁰ reported that 20% of patients with Kaposi's sarcoma have ocular involvement. Eighty per cent of them affecting the ocular adnexa and eyelids, and 20% affecting the conjunctiva. These lesions can give rise to problems that include ocular irritation, recurrent haemorrhage, infection, trichiasis, visual obstruction and cosmetic disfigurement. In addition, they can be life-threatening if not treated.

Kaposi's sarcoma may have an infectious origin.³¹ HIV itself has been implicated in the pathogenesis. Transgenic mice bearing the HIV-1 transactivator (TAT) gene under the influence of the virus regulatory region (HIV-LTR) have been observed to develop Kaposi's sarcoma.³² Recent studies have also implicated a human gamma-herpes virus-like agent, this being demonstrated in tumour endothelial cells by polymerase chain reaction.³³ Researchers have also postulated a hormonal relationship as these tumours are found predominantly in males.

The incidence of B cell lymphoma has also risen since the start of the AIDS epidemic. In the eye, these can be either primary or secondary tumours. Primary B cell lymphoma of the eye (reticulum cell sarcoma) has been reported by Schanzer.³⁴ The patient in this paper presented with bilateral anterior and posterior chamber activity, peripapillary infiltrates, optic disc swelling, flame-shaped haemorrhages and yellowish-white retinochoroidal lesions. Diagnosis was established by cytologic examination of the vitreous fluid.

Our patient presented with spread of lymphoma to the orbits giving rise to proptosis and resultant obstructive sinusitis. AIDS-associated lymphomas can be divided into three groups: 1) large cell lymphomas, 2) Burkitt's-like lymphoma and 3) primary central nervous system lymphoma, which are expansions of Epstein-Barr virus-immortalised B cells.³⁵ All of these can spread either by direct invasion or indirectly by haematogenous route to the orbit.

Neuro-ophthalmic signs in HIV-infected individuals occur as a result of CNS pathology. This can result from infection or tumour. Mansour³⁶ published a study of 177 patients with AIDS or AIDS-related complex who underwent eye examination in one centre from January 1984 to May 1989. In this study, 12 patients (6.8%) had positive CNS findings which is comparable to 6% in this review.

Ormerod et al³⁷ evaluated the neuro-ophthalmic findings in AIDS patients with progressive multifocal leukoencephalopathy (PML). PML is a progressive de-

myelinating brain disorder caused by the JC virus, a papovavirus (named by the initials of the patient from whose brain the virus was first cultivated). It can cause a variety of cerebral or brain stem disorders depending on the pattern of focal or multi-focal demyelination of the CNS. Neurologic dysfunction begins insidiously and progresses rapidly. The disease is markedly asymmetrical. PML comprises 10% of cerebral radiologic lesions occurring in AIDS patients.

In this study, there was no patient with PML. However, there were 4 patients with CNS infection resulting in papilloedema. Two patients had long standing Bell's palsy. Bell's palsy has been considered as one of the possible complications of HIV infection, mainly seen in the early stages. Mastroianni et al³⁸ reported 3 HIV-infected patients with Bell's palsy between 1986 and 1992 in an Italian study.

There were also 4 patients with episcleritis and 3 with symptomatic dry eyes. Whether this is due to an immunologic disorder associated with HIV infection or merely coincidental is still not known.

Conclusion

The incidence of HIV infection is increasing in Singapore. The ophthalmologic manifestations are protean and early diagnosis can lead to decrease morbidity and improved quality of life. Furthermore, ophthalmic manifestations may be the first presentation of HIV infection and thus their early recognition can lead to early diagnosis. It is therefore essential that all ophthalmologists be familiar with the many different manifestations of this disease.

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