LETTERS TO THE EDITOR

Idiopathic keratoconus in a patient with congenital rubella syndrome

EDITOR.—Keratoconus is very rarely found in patients with congenital rubella syndrome (CRS). The only known aetiology of keratoconus associated with CRS is eye rubbing.¹ We report here a patient with CRS who developed idiopathic keratoconus.

CASE REPORT

A 24 year old woman with CRS was examined for progressive visual blurring of 2 years' duration in her left eye. The diagnosis of CRS was based on the maternal history of rash and fever in the first trimester of pregnancy, cataract, and microphthalmia in the right eye, bilateral rubella retinopathy, nystagmus, deafness, congenital heart disease.

Available medical records dated from the time she was 1 year old. At that time, extracapsular cataract surgery was performed in the right eye. She had esotropia in the right eye and poor fixation. Apart from pigmentary changes in the fundus, the left eye was normal. A follow up examination when she was 15 documented nystagmus, esotropia, and microphthalmia in her right eye, and bilateral rubella retinopathy. Visual acuity was RE light perception; LE 6/9 (with $-4.0 -1.0 \times 180$). Two other examinations at the ages of 18 and 21 gave similar results.

On present examination, visual acuity with spectacles was LE 6/60. Retinoscopy revealed high, irregular myopic astigmatism with scissoring of the red reflex. Central keratometry showed irregular mires which could not be superimposed; 4 dioptre irregular astigmatism was found. A conical reflection on the nasal cornea was obtained by shining a penlight from the temporal side (Rizzuti's sign). Bulging of the lower eyelid on downgaze was also observed (Munson's sign). Slit lamp examination revealed an inferiorly located ectatic protrusion of the central cornea with reticular anterior stromal scars. As a result, the diagnosis of mild keratoconus was made. Treatment with a Softperm contact lens was successful and visual acuity was again LE 6/9. All other ocular findings were the same as in earlier observations.

The patient attended a special school for the deaf and dumb, learning sign language and to read and write. There was no history of eye rubbing or atopy, or a family history of keratoconus. Serum total IgE (34 IU/ml) and blood eosinophils (1.1%) were normal.

COMMENT

Congenital rubella produces a spectrum of ocular and systemic abnormalities. Infection during the first trimester of pregnancy is more serious, with the virus disrupting organogenesis and differentiation. Many fetal tissues are susceptible to infection leading to the abnormalities found in the CRS—deafness, cardiac malformations, bone and dental abnormalities, ocular malformations, and mental retardation.

"Salt and pepper" retinopathy is the most common ocular disorder; other ocular manifestations include microphthalmia, strabismus, congenital cataract, transient corneal

leucoma, iris atrophy and hypoplasia, and glaucoma.² Keratoconus and hydrops have been reported in patients with CRS with a history of mental retardation and eye rubbing.¹

The microtrauma associated with eye rubbing is generally thought to be the aetiological link between keratoconus and associated systemic and ocular diseases.³⁻⁵ All four patients with keratoconus and CRS described by Boger *et al*¹ were retarded and vigorously rubbed and poked their eyes. These authors postulated that keratoconus and acute corneal hydrops probably resulted from chronic traumatising mannerisms common in other mentally retarded patients⁶ and is not specific to congenital rubella. Thus far, this is the only known aetiology of keratoconus associated with CRS.

In the case presented here the keratoconus appeared to be idiopathic. Indeed, there was no history of eye rubbing or atopy, or family history of keratoconus. To the best of our knowledge, this report is unique in as far as idiopathic keratoconus has never been associated with CRS. It is likely that in this case there is no such association but merely an overlap of two uncommon conditions^{6,7} occurring in the same person. An association between idiopathic keratoconus and CRS may be determined only after other confirmatory cases have been reported in the literature.

ANTONIO PINNA
FRANCESCO CARTA

*Institute of Ophthalmology, University of Sassari,
Sassari, Italy*

Correspondence to: Dr Antonio Pinna, Istituto di Clinica Oculistica, Università degli Studi di Sassari, Viale San Pietro 43 A, 07100 Sassari, Italy.
Accepted for publication 21 April 1998

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Pseudouveitis as a manifestation of hyperlipidaemia

EDITOR.—We report a case of unilateral anterior pseudouveitis in a diabetic retinopathic eye, as a manifestation of hyperlipidaemia. High levels of lipids were detected in the aqueous humour and the anterior flare resolved only after successful control of diabetes and hyperlipidaemia was obtained.

CASE REPORT

A 44 year old man was referred for anterior uveitis not responsive to a 5 day topical steroid

therapy. His past medical history was significant for non-insulin dependent diabetes mellitus, systemic hypertension, hyperlipidaemia, and obesity.

At presentation, the patient complained of pain and redness in his left eye. Visual acuity was 20/25 in the right eye and light perception in the left eye. Examination of the right eye disclosed only mild diabetic retinopathy. Slit lamp examination of the left eye showed hyperaemia of the conjunctiva, and an intense milky flare obstructing the view of the iris and the fundus (Fig 1). It was difficult to detect the presence of cells in the anterior chamber because of the flare. There were neither keratic precipitates nor hypopyon or iris neovascularisation. Intraocular pressures in both eyes were within normal limits. B-scan ultrasonography was unremarkable.

Results of laboratory tests showed hyperglycaemia (24 mmol/l), a twofold increase in normal cholesterol levels (15 mmol/l), and a 22-fold increase in normal triglyceride levels (38 mmol/l). Results of laboratory examination including HLA typing, angiotensin converting enzyme, serologies for herpes simplex virus (HSV) and lues, purified protein derivative (PPD) skin test, and chest and sacroiliac x rays, were not contributory. A β and pre- β lipoproteinaemia pattern was established by serum electrophoresis. Analysis of the aqueous humour of the left eye disclosed no cells, and high levels of proteins (32 g/l), cholesterol (3.4 mmol/l), and triglycerides (4.9 mmol/l).

Visual acuity recovered at 20/50 and the flare resolved after lipidaemia and diabetes had been controlled by oral fibrates and insulin, respectively. Fundus examination of the left eye showed mild diabetic retinopathy including microaneurysms, hard exudates, and many paravascular retinal haemorrhages. Six weeks later, fundus examination of the left eye showed evidence of central retinal venous occlusion (CRVO).

COMMENT

Although clinical presentation including pain, perilimbal conjunctival hyperaemia, and anterior chamber flare, was consistent with acute anterior uveitis, many features favoured a strong relation between the metabolic disorders and the occurrence of the flare. These clues included the milky appearance of the flare, the results of the anterior chamber paracentesis, the lack of response to topical

Figure 1 Slit lamp photograph of the left eye showing an intense milky flare in the anterior chamber.

steroids, and the resolution of the flare only after the control of hyperlipidaemia.

To our knowledge, only one case of pseudoendophthalmitis related to hyperlipidaemia has been published.¹ Both eyes were involved in a patient with bilateral proliferative diabetic retinopathy. Blood-aqueous barrier breakdown has been demonstrated in diabetic patients, especially those presenting with diabetic retinopathy,² and in patients with CRVO.³ In the present case, an underlying mild diabetic retinopathy was diagnosed in both eyes. The unilateral leakage of lipids in the anterior chamber may be related to ipsilateral blood-aqueous barrier breakdown following an undiagnosed partial vein occlusion or an episode of transient iridocyclitis rapidly cured by topical steroid therapy.

THANH HOANG-XUAN
DANIELE HANNOUCHE
HERVÉ ROBIN
MARGOT VAN DER DONK
JEAN-FRANÇOIS KOROBELNIK
Department of Ophthalmology,
Bichat-Claude Bernard Hospital,
Paris, France

Correspondence to: Thanh Hoang-Xuan, MD,
Department of Ophthalmology, Bichat-Claude
Bernard Hospital, 46, rue Henri Huchard, 75018
Paris, France.

Accepted for publication 15 April 1998

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Detection of anticytomegalovirus antibody synthesis in the anterior chamber in Vogt-Koyanagi-Harada syndrome

EDITOR.—Vogt-Koyanagi-Harada (VKH) syndrome has long been suspected to be the consequence of autoimmunity or hypersensitivity against melanocytes. Nevertheless, to date no certain aetiological factors has been reported.

CASE REPORT

A previously healthy 30 year old Portuguese woman was admitted complaining of progressive visual loss in both eyes, over 2 weeks, associated with headaches and pain on eye movements and meningismus. Symptoms appeared 24 hours after the beginning of a flu-like syndrome. The patient had no past history of ocular trauma or surgery. On examination, the visual acuity was 20/100 in both eyes. Slit-lamp examination revealed 2+ cells in both anterior chambers with non-granulomatous keratic precipitates. Intraocular pressure was 10 mm Hg in both eyes. There were 1+ cells in the anterior vitreous of both eyes. Fundus examination revealed a bilateral papilloedema and the fluorescein angiography showed focal areas of leakage at the level of the retinal pigment epithelium and staining of the optic disc (Fig 1A, B).

The initial clinical examination revealed an erythrocyte sedimentation rate of 10 mm in the first hour (normal range 1-12), a white blood count of 4.2 g/l (normal range 4-11 g/l) with a normal differential count. Chest x ray was normal. A lumbar puncture showed a

lymphocytic pleocytosis (proteins 0.37 g/l, white cells 77×10⁶/l, lymphocytes 96%), without oligoclonal bands on electrophoresis. A magnetic resonance cerebral scan was normal. Suspecting a herpetic infection, aciclovir (900 mg/8 hours), topical steroids, and prednisone (1 mg/kg) were administered on the day of admission.

Further investigations revealed that serology (cytomegalovirus (CMV), Epstein-Barr virus, herpes simplex I/II, varicella zoster virus, rubella virus, toxoplasmosis, *Borrelia burgdorferi*, *Treponema pallidum*, and HIV) was positive for anti-CMV IgM (ratio: 0.7, normal 0.6) and IgG (521 units of IgG antibody anti-CMV per ml (UA/ml), normal 15) and early CMV antigen was detected in the urine. An anterior chamber tap was performed (the day of admission, before starting antiviral and anti-inflammatory therapy); results were positive for a local production of anti-CMV immunoglobulins; the Goldmann-Witmer coefficient was 4.47 for CMV, 0.56 for herpes simplex virus, and not calculable for varicella zoster virus and for Epstein-Barr virus. Viral serologies in the cerebrospinal fluid were negative. Tests for sarcoidosis and for connective tissue disorders were negative. Immunoglobulin electrophoresis, quantitative immunoglobulin levels, PPD skin test, CD4-CD8 lymphocytes count, C3-C4, and CH50 examination were within the normal range.

Based on the clinical findings, by the positive CMV serology, the presence of early CMV antigen in the urine and by the result of the anterior chamber tap an acute CMV infection was diagnosed; aciclovir was discontinued after 4 days, and we administered the more specific drug foscarnet (180 mg/kg) for 21 days. Topical steroids and oral prednisone (1 mg/kg) were also continued for 1 month at tapering doses. After 3 weeks of treatment, visual acuity returned to 20/20 in both eyes. Papilloedema disappeared in both eyes. Two months later, viral titres revealed a decrease in CMV IgM (ratio: 0.5) and an increase of the CMV IgG to 707 U/ml. Early CMV Ag was no longer detectable in the urine.

After 3 months, the patient developed poliosis of her eyelashes, eyebrows, and scalp hair. A vitiligo appeared. Fundus examination revealed a diffuse depigmentation affecting both posterior segments, and areas of chorioretinal atrophy (Dalen-Fuchs nodules) in the periphery of both fundi (Fig 2A, B). Tests seeking to establish a hearing loss were unremarkable. HLA typing was positive for the HLA-DRB1*0701/08. On the basis of the clinical evolution, the presence of integumentary manifestations and the results of the cerebrospinal tap a VKH syndrome was diagnosed.

COMMENT

VKH syndrome is a bilateral panuveitis associated with vitiligo, poliosis, auditory signs and neurological manifestations (cerebrospinal fluid lymphocytic pleocytosis, meningoencephalitis, hemiparesis). Typically, the presence of these features is variable and might depend on the race of the patient. Clinically, this syndrome is characterised by a prodromal stage (headache, fever) and followed by a panuveitis with retinal oedema and/or multiple retinal serous detachments. After several weeks of evolution, a depigmentation of the integuments and choroid appear. Moreover, most of the patients relapse and develop a chronic recurrent phase of the disease. VKH syndrome has a predilection for darkly pigmented races (Asian, Hispanics, American

and Asian indians) and is uncommon in whites.¹ Our patient was Portuguese and had these clinical features. Most patients are in their second to fourth decade of life at onset of the disease; nevertheless, VKH syndrome has also been reported in children and young adults.¹

To date no certain aetiological factors has been reported, but taking into account that this illness affects various organs (skin, eye, central nervous system) a common aetiological factor seems to be involved in the pathogenesis. Among the hypotheses that have been formulated, the role of genetic constitution is important. Ohno first discovered, among the Japanese population, a link between VKH syndrome and HLA-DR4/Dw53.² Other authors have reported the presence of antiretinal antibodies directed against photoreceptors and Müller cells in the sera of patients with a VKH syndrome.³ Moreover, other studies have demonstrated the presence of a close relation between melanocytes and the presence of lymphocytes directed against these cells. These findings tend to suggest the presence of an autoimmune response and/or hypersensitivity against melanocytes, leading to the development of an inflammation affecting the uvea, the skin, and the meninges resulting from a break of tolerance to self antigens. However, the initiating factor responsible of the autoimmune process is still unknown.

Autoimmune disorders are characterised by the breaking of immunological tolerance to self antigens after the activation of lymphocytes. The exact mechanism by which there is a loss of tolerance to self antigens is mostly unknown. Viruses have been implicated, as triggers, of this mechanism together with other mechanisms such as the presence of a genetic predisposition or through the activation of the cytokine network.

The induction and the development of the autoimmune process may be explained by the exposition of ocular tissue antigens to the immune system after a break of the blood-retinal barrier. It is conceivable that a tissue damage, by infectious agents, may render foreign some non-immunogenic ocular antigens.

Figure 1 Late phase of the fluorescein angiogram, right eye (A) and left eye (B). Focal areas of leakage at the level of the retinal pigment epithelium (arrows) and staining of the optic disc.

Figure 2 Colour picture of right eye (A) and left eye (B). Diffuse depigmentation affecting both posterior segments, and areas of chorioretinal atrophy (Dalen-Fuchs nodules) in the periphery of both fundi.

Another mechanism by which micro-organisms can induce ocular autoimmunity is by the presence of homology between some sequences of their proteins and the sequence of uveitogenic determinants of ocular antigens. Recently, it has been shown that there is an amino acid sequence homology between certain bacterial antigens and some autoantigens and between sequences in retinal S-antigen and protein from yeast histone H3 and *Escherichia coli*, as well as with certain viral peptides.⁴⁻⁶ This similarity between self and

foreign antigens called "molecular mimicry", may induce a cross reaction with one or more self antigens sharing determinants with the foreign agents; this suggests that infectious agents can act as a trigger of organ specific autoimmunity in predisposed individuals.⁷ Among presumed triggers that could initiate the immune process, viruses may play a role in the pathogenesis of VKH syndrome. Indeed, various authors have reported the presence of Epstein-Barr virus genome in the cerebrospinal fluid or in the vitreous of patients with

VKH syndrome,⁸⁻⁹ although it is difficult to establish the exact role of ubiquitous viruses in specific diseases.¹⁰ Our patient had an anti-CMV antibody synthesis in the anterior chamber and an acute CMV infection.

This case illustrates the possible implication of CMV in the aetiology of VKH syndrome; nevertheless, other known or unknown viruses may be involved in the pathogenesis of this syndrome in predisposed individuals.

Presented at the Fourth International Symposium on Uveitis, October 1997, Yokohama, Japan.

EDOARDO BAGLIVO
BÉATRICE ROSSILLION
PHILIPPE DE GOTTRAU
PETER LEUENBERGER

Department of Ophthalmology, Geneva University
Hospital Switzerland

Correspondence to: Dr Edoardo Baglivo, Clinique d'Ophtalmologie, Hôpital Cantonal Universitaire, Rue Alcide-Jentzer, 22, CH-1205 Genève.

Accepted for publication 21 April 1998

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Bilateral small retinal infiltrates during rickettsial infection

EDITOR,—Rickettsiae may cause heterogeneous retinal manifestations, the most characteristic of which are vascular lesions, periphlebitis, retinal haemorrhages and oedema, central retinal thrombosis, and papilloedema.¹⁻⁵ We present the first case in which rickettsiae led to small retinal white infiltrates.

CASE REPORT

A previously healthy 25 year old woman had a fever up to 40°C of unknown origin during a trip to Queensland, Australia in August. Five days after the onset of fever a generalised maculopapular rash and a black lesion on the forefoot (eschar) were visible, without a known history of a tick bite. The patient was transferred to our hospital with the signs of general illness. Extensive examination for infectious disease including eye examination was initiated.

Visual acuity was 20/25 in both eyes. Slit lamp examination revealed bilateral conjunctival hyperaemia. Moderate inflammation of

the vitreous in both eyes was visible. Fundus examination disclosed bilateral small white infiltrates within the neurosensory retina, practically without involvement of the choroid, mainly in the posterior pole (Fig 1). In the right eye, a tiny well defined haemorrhage near the temporal inferior artery was seen. Fluorescein angiography of both eyes showed punctuate hypofluorescence corresponding to the white infiltrates (Fig 2), staining of the optic discs, but no signs of vasculitis. Indocyanine green (ICG) angiogram, visual field examination, and colour tests were unremarkable in both eyes.

Results of the following laboratory tests were pathologic: erythrocyte sedimentation rate (86 mm in the first hour), platelets (135 g/l), CRP (15 mg/dl), GOT (165 U/l), GPT (127 U/l), GGT (49 U/l), and LDH (527 U/l). Abdominal ultrasound sonography revealed an enlarged spleen (160 mm). The main serological finding was a definite increase of the Weil-Felix reaction from 1:160 (OX19, OX2), 1:40 (OX K) to 1:1280 (OX 19, OX2) and 1:160 (OX K) within 1 week. Serology for brucella, salmonella, *Yersinia enterocolica*, *Listeria monocytogenes*, *Mycoplasma pneumoniae*, *Francisella tularensis*, *Mycobacterium tuberculosis*, *Coxiella burnetii*, *Borrelia burgdorferi*, *Treponema pallidum*, hepatitis (A, B, C), HIV, rubella virus, rubella virus, Epstein-Barr virus, cytomegalovirus, herpes simplex I and II, *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus*, toxoplasmosis, and chlamydia were all negative.

During antibiotic treatment with doxycycline 200 mg once daily for 14 days and clarithromycin 500 mg twice daily for 5 days, all symptoms subsided and the Weil-Felix reaction decreased to 1:640 (OX 19, OX2) and 1:80 (OX K). The visual acuity increased to 25/20 in both eyes. Four weeks after this treatment all laboratory tests were normal. Oph-

thalmic re-examination and angiography 3 weeks after initial presentation revealed improvement; 3 weeks later there was a complete resolution of retinal dots, and 6 months later findings were normal with no chorioretinal scars.

COMMENT

Based on patient history, clinical signs, and serology we concluded that the illness presented was associated with rickettsiae. Within the genus *Rickettsia*, small obligate intracellular bacteria, three groups of antigenically related organisms are known: spotted fever, typhus, and scrub typhus.^{6,7} Travel history, incubation time, and the marked titre increase of OX19 and OX2 indicate that the infectious agent was of the spotted fever group, most likely *Rickettsia australis* which occurs in Queensland, Australia. This rickettsia causes the Queensland tick typhus and its most prevalent vector is ixodic tick (*Ixodes holocyclus*, *Ixodes tasmani*).⁸ A bite by *Ixodes tasmani* may have been overlooked in the case presented, as, contrary to *Ixodes holocyclus*, the former is less apparent during feeding.⁸ Additional tests to specify the infectious agent unfortunately did not reveal any further clarification.

In general, rickettsiae invade endothelial cells, resulting in destruction of smooth muscle fibres, thrombosis, and extravasation of blood into the tissues.¹⁻⁹ The papilloedema, also observed in our patient, is supposedly based on microvessel destruction.¹ Further, rickettsiae may cause round cell infiltration in perivascular spaces in lungs, kidneys, brain, and adrenals.^{6,9} This is the first report to demonstrate small retinal infiltrates. The differential diagnosis of the ocular findings included many diseases which were excluded by serology. The complete resolution without any residual scars and normal ICG angiograms practically excluded chorioretinitis. Further, this retinitis did not meet the fluorescence-angiographic criteria of white dot syndrome, since no hyperfluorescence was observed. In conclusion, rickettsiae may lead to white dots in the retina and, thus, should be considered in the differential diagnosis.

JULIUS R LUKAS
STEFAN EGGER

Department of Ophthalmology and Optometry,
University Hospital Vienna, Austria

BERNHARD PARSCHALK

Department of General Medicine I, Section of Infectious
Diseases, University Hospital Vienna, Austria

MICHAEL STUR

Department of Ophthalmology and Optometry,
University Hospital Vienna, Austria

Correspondence to: J R Lukas, Department of Ophthalmology and Optometry, University of Vienna, A-1090 Vienna, Währinger Gürtel 18-20, Austria.

Accepted for publication 15 April 1998

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Progressive outer retinal necrosis in a patient with cutaneous non-Hodgkin's T cell lymphoma (Sézary syndrome)

EDITOR.—The progressive retinal outer necrosis syndrome (PORN) is a recognised variant of necrotising herpetic retinopathy, presumably caused by the varicella zoster virus.^{1,2} The syndrome is characterised by minimal intraocular inflammation, rapidly spreading multifocal deep retinal lesions without vascular involvement (until late in the disease), bilateral involvement in the majority of the cases, and poor visual prognosis irrespective of treatment.² So far, the majority of the described cases were related to HIV disease. We present a HIV seronegative immunocompromised patient with normal CD4 counts, who developed PORN and responded well to aciclovir.

CASE REPORT

A 29 year old man with cutaneous non-Hodgkin's T cell lymphoma (Sézary syndrome) for 4 years, developed a progressive loss of vision of his right eye within 5 days. Five weeks previously, he had had a thoracic zoster that responded well to orally administered aciclovir (5 × 800 mg per day). On admission, the visual acuity of the right eye was 0.4 and a central subcapsular posterior cataract was present. Intraocular cells were absent, and remained absent thereafter. Extensive central and peripheral oedematous and white necrotic lesions, including the macula were observed with sparing of the perivascular region (Fig 1). Slight optic oedema and a few scattered retinal haemorrhages were also found. The left eye exhibited no abnormalities. A diagnostic aqueous tap was performed and intravenous aciclovir, 10 mg/kg body weight three times per day, was immediately initiated. Treatment with chlorambucil 4 mg and prednisone 22.5 mg daily for the non-Hodgkin's lymphoma was continued. CD4 counts were normal (390×10⁶/l, reference range 350–1500×10⁶/l), CD8 counts, however, were low (14.8×10⁶/l) resulting in high CD4/CD8 ratio (26, reference range 1.1–2.5). Microparticle enzyme immunoassay (IMX 8B3220, Abbott, CA, USA) demonstrated HIV seronegativity.

Figure 1 Posterior pole of patient's right eye showing multifocal infiltrates 3 days after starting intravenous aciclovir treatment (10 mg/kg body weight).

Figure 1 Fundus photograph of the left eye demonstrating multiple white spots in the posterior pole which were mainly confined to the neuroretina without any involvement of the choroid.

Figure 2 In the fluorescein angiogram these neuroretinal infiltrates blocked the background fluorescence throughout the whole phase of dye transit. (left eye, mid-phase, scanning laser ophthalmoscope).

Figure 2 Fundus photograph of patient's right eye 2.5 weeks after initiation of intravenously administered aciclovir showing optic atrophy, resolution of infiltrates, and attenuation of vessels. Poor contrast quality is caused by associated cataract; the vitreous was clear.

After 3 days, resolution of the peripheral lesions started but progression into the posterior pole occurred. Fluorescein angiography disclosed retinal necrotic lesions with perivascular sparing and areas of resolution with arteriolar attenuation. Because of the development of phlebitis along the cannula intravenously administered aciclovir was temporarily switched to oral aciclovir (5×800 mg per day) from day 8 until day 13. Nevertheless, resolution of the necrotic lesions continued, resulting in opaque chorioretinal scarring and optic atrophy by the end of the second week (Fig 2). After a month patient was discharged with a maintenance therapy (5×800 mg aciclovir orally per day). Visual acuity in the right eye stabilised at 0.2 for the following 11 months; however, the patient developed a mature cataract, leading to light perception only. Retinal detachment did not occur (shown by ultrasound biomicroscopy) and the left eye re-

mained uninvolved until his death (due to respiratory failure) at 18 months' follow up.

Aqueous humour analysis revealed low Goldmann-Witmer coefficients (<3.0) and no DNA of varicella zoster virus (VZV), herpes simplex virus, and cytomegalovirus (polymerase chain reaction negative) was detected. High serum IgG levels (1:8192) against VZV might have contributed to the low Goldmann-Witmer coefficients.

COMMENT

Our patient was immunocompromised by the cutaneous non-Hodgkin's lymphoma and the accompanying therapy, but in contrast with AIDS patients CD4 counts were, albeit low, within the normal limits. Characteristically for the Sézary syndrome however, the CD4/CD8 ratio was elevated due to low counts of CD8 cells. Compared with HIV seropositive patients or AIDS patients with PORN,² our patient responded well to aciclovir treatment. Furthermore, notwithstanding the optic atrophy, he retained useful visual acuity and retinal detachment did not develop. As suggested earlier, the degree¹ and probably the type of immune deficiency might be responsible for the differences in clinical picture, and therapy outcome.

Five cases with PORN in HIV seronegative, but otherwise immunocompromised, individuals were reported. In contrast with our patient, none of these cases displayed all typical features of PORN as described originally in AIDS patients¹: two patients had moderate or pronounced intraocular inflammation,^{3,4} and the third patient showed ophthalmological lesions resembling bilateral acute retinal necrosis syndrome.⁵ Two other cases were only briefly mentioned but not described.⁴ Recently, PORN was described in a HIV sero-

negative patient following bone marrow transplantation with poor visual outcome despite preventive antiviral treatment; however, this patient had low CD4 counts.⁶

Our case demonstrates that PORN may develop in HIV seronegative, immunocompromised patients with normal CD4 but low CD8 counts.

Sponsors/grants: none.

FEY LIENG NJOO
ANIKI ROTHOVA

ALLEGONDA VAN DER LELIJ

F C Donders Institute, Department of Ophthalmology,
University Hospital Utrecht, Utrecht, Netherlands

Correspondence to: F L Njoo, MD, F C Donders
Institute, Department of Ophthalmology, University
Hospital Utrecht, PO Box 85500, 3508 GA
Utrecht, Netherlands.

Accepted for publication 21 April 1998

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