European Journal of Ophthalmology / Vol. 18 no. 4, 2008 / pp. 567-571

Primary intraocular lymphoma: Another great masquerader

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PURPOSE. *To describe diverse and atypical presentations of the most common masquerader in neoplastic masquerade syndromes.*
METHODS. *Retrospective interventional case series. The authors identified three patients who presented with atypical and diagnostically challenging masquerading manifestations. These patients were eventually found to have primary intraocular lymphoma (PIOL). Their case histories, presenting signs and symptoms, diagnostic tests, and treatments are described.*
RESULTS. *Patient 1 masqueraded as viral retinitis and branch retinal vein occlusion but was resistant to 5 weeks of oral and intravenous acyclovir. Patient 2 presented with choroidal infiltrates and vision loss. This patient had had breast carcinoma for the last 25 years and secondary metastasis was suspected. Patient 3 had chronic uveo-retinitis and a chronic Propionibacterium acnes infection was suspected. All three patients were diagnosed with PIOL.*
CONCLUSIONS. *PIOL is an aggressive masquerader and not only presents clinical diagnostic difficulties but also requires expert tissue handling and analysis, so that early diagnosis can be made and therapy can be instituted. (Eur J Ophthalmol 2008; 18: 567-71)*

KEY WORDS. *Neoplastic masquerades, PIOL, Intraocular lymphoma, Ocular masquerades*

Accepted: January 4, 2008

INTRODUCTION

Primary intraocular lymphoma (PIOL) is a high-grade malignant non-Hodgkin's lymphoma, arising in the retina with secondary involvement of the choroid and occasionally the optic nerve. It is now the most common "masquerader" according to a recent large series investigating the neoplastic masquerade syndromes (1). PIOL is considered to be a subtype of the primary central nervous system lymphoma (PCNSL). The vast majority of PIOL is of B cell origin and can be subdivided as diffuse large B cell lymphomas (DLBCL), according to the updated World Health Organization (WHO) Lymphoma Classification (2).
An inexplicable increase in the incidence of PCNSL has been reported over the past two decades in both immunosuppressed and immunocompetent patients (3), which can partly be accounted for by an increase in incidence of human immunodeficiency virus infection (4). Although PIOL typically presents with bilateral uveitis that is unresponsive to steroid therapy, it can manifest with a diverse spectrum of ophthalmic presentations which elude early diagnosis and result in a delay in the institution of appropriate therapy. We describe herein a case series of three patients with PIOL who presented with atypical and diagnostically challenging masquerading manifestations.

METHODS

The records of patients with recalcitrant uveitis and vasculitis between 2004 and 2006 were evaluated and we found three patients with a diagnosis of PIOL. Their presenting complaints, past medical history, review of systems, ocular findings on examination, diagnostic tests, and serologic investigations are shown.
This study was approved by the Institutional Review

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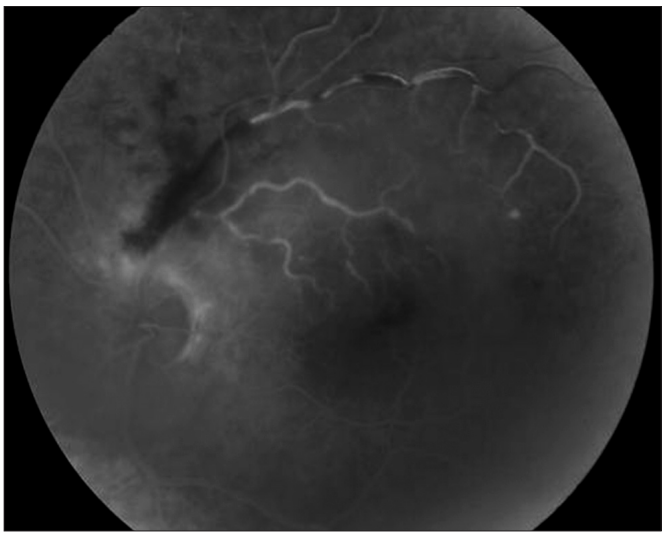

Fig. 1 - *Fluorescein angiogram demonstrating a branch vein occlusion with active superotemporal arteriolar vasculitis.*

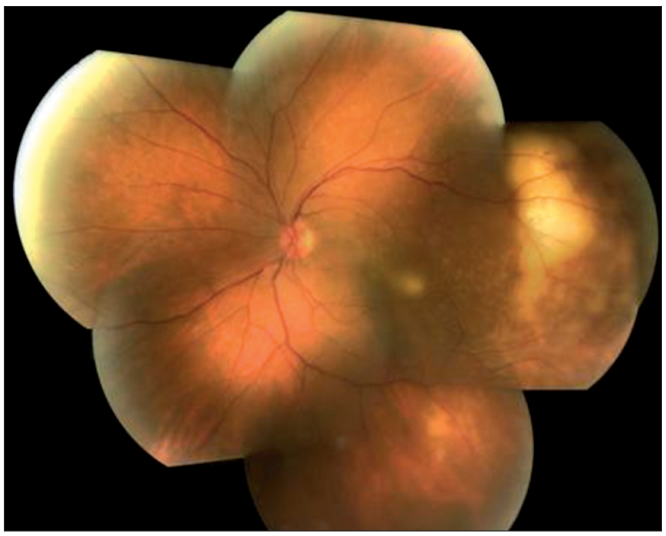

Fig. 2 - *Temporal, inferior, and submacular choroidal infiltrates.*

Board of Massachusetts Eye and Ear Infirmary and was carried out in accordance with the Declaration of Helsinki.

Case 1

A 51-year-old man presented with sudden visual loss in his left eye. He was diagnosed with neuroretinitis, presumed to be viral in origin, and commenced on systemic acyclovir. After 2 weeks of treatment, he was referred to the Massachusetts Eye Research and Surgery Institute for a second opinion. He had no significant medical or family history and review of systems was noncontributory.

At presentation his visual acuities were 20/20 in the right eye (OD) and 20/25 in the left (OS). His left fundus demonstrated a superotemporal branch retinal vein occlusion (Fig. 1). A fluorescein angiogram was performed which confirmed the examination finding and also revealed active superotemporal arteriolar vasculitis (Fig. 1). Investigative serologies were performed. Treatment was continued with high dose intravenous acyclovir (1000 mg tid), but the patient continued to deteriorate with a symptomatic increase in floaters and an associated decrease in visual acuity to 20/30 OS. Laboratory work-up revealed elevated serum homocysteine levels and increased antithrombin III activity. The patient was also found to be heterozygous for a factor V Leiden mutation. In lieu of these positive markers for hypercoagulability and vaso-occlusion in the retina, we recommended anticoagulation with Coumadin. Hematology consultation was sought and aspirin therapy was commenced along with B complex vitamins and folic acid. Three weeks post presentation, a repeat fluorescein angiogram was performed which demonstrated an increase in retinitis and infarction. Due to the worsening of inflammation and lack of response to intravenous acyclovir, a diagnostic vitrectomy was performed. The vitrectomy sample was negative by polymerase chain reaction (PCR) for HSV1 and 2, toxoplasmosis, and tuberculosis. Cytology demonstrated nonspecific chronic inflammatory cells suggestive of an immune process. PCR testing for monoclonal gene rearrangements of immunoglobulin heavy (IgH) chains was positive, indicative of a primary intraocular lymphoma. A systemic workup was performed which did not reveal any evidence of PCNSL.

Case 2

A 64-year-old woman was referred to Massachusetts Eye Research and Surgery Institute for uveitis evaluation. She complained of rapidly progressive vision loss in the left eye associated with multiple floaters, color changes, and photopsia. Her past medical history was remarkable for breast cancer (treated with surgery, chemotherapy, and radiation 20 years earlier) and cigarette smoking. She was not on any treatment at the time of referral.

At presentation her visual acuities were 20/25 OD and counting fingers at 2 feet in OS. Slit lamp examination disclosed keratic precipitates bilaterally and with anterior

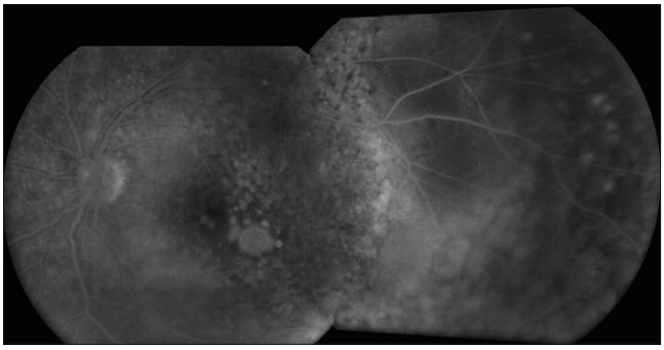

Fig. 3 - *Mottled hyperfluorescence in late phase fluorescein angiogram with areas of multiple focal leakage in the temporal periphery.*

chamber inflammation of 1+ cell and flare OD and 3+ OS. Fundus examination was unremarkable in OD. Her OS fundus demonstrated a 2+ vitritis with multiple confluent yellowish subretinal lesions in the macular and peripheral temporal area (Fig. 2). Fluorescein angiogram was performed and disclosed early hypofluorescence of the subretinal lesions with late hyperfluorescence. No retinal vasculitis or abnormal leakage was observed (Fig. 3). Extensive investigative serologies were performed and the patient was commenced on prednisolone acetate 1% every hour bilaterally. Two weeks later serologies disclosed a positive ANA screen at 1:320 titer and elevated interleukin (IL)-2 receptor and IL-6 levels. Despite treatment her vision and posterior inflammation did not improve and in the absence of a clear diagnosis, a diagnostic vitrectomy was performed. Vitreous specimens were sent for cytology, PCR for IgH gene rearrangements, PCR for herpes virus, and IL-10 and IL-6 determination.

PCR for herpes virus was negative and cytology disclosed nonspecific chronic inflammatory cells and was interpreted as inconclusive. IL-10 was greatly increased at 2134 pg/mL with an IL-6 level of 31 pg/mL. Molecular diagnostic testing disclosed clonal rearrangement of IgH gene products. A diagnosis of PIOL was made and a systemic workup was performed which included lumbar puncture, magnetic resonance imaging, and positron emission tomography. A lung nodule was discovered and a subsequent biopsy was positive for systemic lymphoma.

Case 3

A 46-year-old man was referred to Massachusetts Eye Research and Surgery Institute with blurry vision and ocular pain in his left eye of 1 year duration. He had a previous diagnosis of idiopathic recurrent uveitis and secondary glaucoma. The patient was on corticosteroids and ocular hypotensives but continued to have recurrent attacks of inflammation with elevation of intraocular pressures. His past ocular history was significant for left cataract extraction with a PCIOL implant. Review of symptoms was noncontributory.

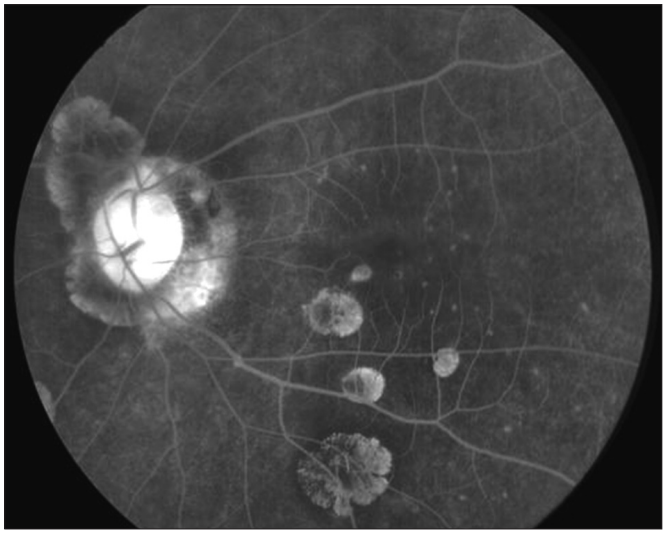

Fig. 4 - *Peripapillary atrophy, large areas of chorioretinal atrophy, and scattered retinal infiltrates.*

Presenting visual acuities were 20/20 OD and 20/100 OS with intraocular pressures of 14 and 45 mmHg respectively. The anterior segment examination revealed 1+ cell and flare in the left eye. The posterior segment demonstrated multiple areas of chorioretinal atrophy with retinal infiltrates at the posterior pole (Fig. 4). A fluorescein angiogram confirmed the examination findings. Uveitis secondary to chronic *Propionibacterium acnes* infection was suspected as the patient had undergone a cataract extraction prior to the onset of his uveitis. The patient's intraocular pressure was controlled with oral acetazolamide and serologies were drawn. An urgent diagnostic vitrectomy was performed and intravitreal amikacin and vancomycin were instilled. Postoperatively there was no resolution of the posterior uveitis. Serologies were noncontributory.

Vitreous cell cytomorphology demonstrated rare inflammatory cells with markedly elevated levels of IL-10 (241 pg/mL) and IL-6 (20 pg/mL). The IL-10 to IL-6 ratio was 12:1. Sampling for evaluation of PCR gene re-arrangement for immunoglobulin heavy chains was not per-

formed. The patient's recalcitrant uveitis coupled with his atypical examination findings and corroborative evidence of an elevated vitreous IL-10: IL-6 ratio is highly suspicious for intraocular lymphoma. A repeat vitreous biopsy for molecular analysis along with an investigative survey for evidence of systemic lymphoma with imaging studies and lumbar puncture in collaboration with a neuro-oncologist is planned for this patient.

DISCUSSION

Our case series represents diverse and atypical presentations of the most common masquerader in neoplastic masquerade syndromes.

Case 1 masqueraded as a viral retinitis, but with a poor response to treatment and with a progressive increase in retinal vasculitis an atypical infective etiology needed to be ruled out. Vitreous sampling was negative for toxoplasmosis and tuberculosis, but polymerase chain reaction for monoclonal rearrangement of IgH chains was positive, indicative of a PIOL.

Case 2 presented with a 2+ vitritis with multiple confluent yellowish subretinal lesions in the macular and peripheral temporal area. In a background of breast carcinoma, this presentation was strongly suggestive clinically of choroidal metastases. On vitreous sampling, however, the IL-10: IL6 ratio was significantly raised with molecular diagnostic testing indicative of a diagnosis of PIOL.

Case 3 masqueraded as a chronic uveo-retinitis, possibly secondary to chronic *P acnes* infection. Therapeutic vitrectomy was performed, but cytokine analysis was strongly indicative of a PIOL. Further investigation is warranted in this case to establish the diagnosis and assess any possible systemic involvement.

Classically, anterior segment findings in the form of corneal precipitates, anterior flare, and pseudohypopyon occur in 43% of patients presenting with PIOL (5). In the posterior segment vitreous cells and haze are present in the majority of cases with the classic fundus lesion being a flat creamy orange-yellow subretinal mass which may be singular, multiple, discrete, or confluent (6).

The clinical suspicion of PIOL can be diagnostically supported with ancillary testing in the form of ultrasonography, fluorescein angiography, and high resolution neuroimaging of the central nervous system. Multiple yellow-orange subretinal lesions, with the corresponding "leopard skin" appearance on fluorescein angiography, are considered pathognomic for PIOL.

Cytologic studies of vitreous biopsies, however, remain the gold standard for the morphologic diagnosis of PIOL. Specimens require experience both in their preparation as well as in the cytomorphologic interpretation. Close communication between clinician and pathologist is essential to allow for optimal processing of these biopsies. False negative diagnoses are not uncommon and multiple specimens may be required before a definitive diagnosis of PIOL can be made (7). Hence, the clinical and morphologic diagnosis is often delayed.

In addition to cytomorphology, adjunctive supportive diagnostic investigations are indicated including determination of cytokine concentrations in the vitreous fluid, particularly the IL-10: IL-6 ratio, which is elevated in this disease. IL-10 can be produced by lymphoma cells and patients with nonmalignant intraocular inflammation have elevated IL-6 levels in the vitreous. A ratio of greater than 1.0 has been strongly associated with PIOL (8). Polymerase chain reaction examining for monoclonal rearrangements of immunoglobulin heavy (IgH) chains provides strong evidence for the diagnosis of PIOL as these do not occur at any significant frequency in normal B or T cell differentiation.

The treatment recommendations for PIOL with or without CNS disease remain controversial. Standard protocols of isolated radiotherapy with traditional chemotherapeutic regimes are ineffective for the adequate long-term treatment of PCNSL/PIOL. Recent innovations in treatment include multi-agent primary chemotherapy which was designed to reduce radiation-associated cognitive defects that can occur in up to 40% of patients over the age of 50 years (9). Other alternative therapies that require further assessment include intravitreal methotrexate or rituximab. Trofosfamide has been administered in patients with recurrent PIOL/PCNSL, and may offer an alternative treatment option with a very favorable side effect profile. Unfortunately, the prognosis of PIOL is very poor, with the majority of cases developing central nervous system disease within 2 years. The mean survival has increased to over 3 years with newer therapies (10).

This aggressive masquerader not only presents clinical diagnostic difficulties, but expert tissue handling and analysis is essential so that an early diagnosis can be made and therapy instituted.

None of the authors has proprietary interest in the publication of this article.

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REFERENCES

1. Rothova A, Ooijman F, Kerkhoff F, et al. Uveitis masquerade syndromes. Ophthalmology 2001; 108: 386-99.
2. Jaffe ES, Harris NL, Stein H, et al. World Health Organisation Classification of Tumours. Tumours of Haematopoietic and Lymphoid Tissues. Pathology and Genetics. Lyon: IARC, 2001.
3. Corn BW, Donahue BR, Rosenstock JG, et al. Performance status and age as independent predictors of survival among AIDS patients with primary CNS lymphoma: a multivariate analysis of a multi-institutional experience. Cancer J Sci Am 1997; 3: 52-6.
4. Eby NL, Grufferman S, Flannelly CM, et al. Increasing incidence of primary brain lymphoma in the US. Cancer 1988; 62: 2461-5.
5. Cassoux N, Merle-Beral H, Leblond V, et al. Ocular and central nervous system lymphoma: clinical features and diagnosis. Ocul Immunol Inflamm 2000; 8: 243-50.
6. Peterson K, Gordon KB, Heinneman MH, et al. The clinical spectrum of ocular lymphoma. Cancer 1993; 72: 843-9.
7. Coupland SE, Bechrakis NE, Anastassiou G, et al. Evaluation of vitrectomy specimens and chorioretinal biopsies in the diagnosis of primary intraocular lymphoma in patients with masquerade syndrome. Graefes Arch Clin Exp Ophthalmol 2003; 241: 860-70.
8. Levy-Clarke GA, Chan CC, Nussenblatt RB. Diagnosis and management of primary intraocular lymphoma. Hematol Oncol Clin North Am 2005; 19: 739-49.
9. Freilich RJ, Delattre JY, Monjour A, et al. Chemotherapy without radiation therapy as initial treatment for primary CNS lymphoma in older patients. Neurology 1996; 46: 435-9.
10. Jahnke K, Bechrakis NE, Coupland SE, et al. Treatment of primary intraocular lymphoma with oral trofosfamide: report of two cases and review of the literature. Graefes Arch Clin Exp Ophthalmol 2004; 242: 771-6.