NEOPLASTIC MASQUERADE SYNDROME

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Introduction

Neoplastic masquerade syndrome can be defined as neoplastic or proliferative lesions that cause intraocular infiltration of cells, simulating immune-mediated uveitis. The term "masquerade syndrome" is used in ophthalmology to describe conditions that are characterized by intraocular infiltration of inflammatory cells, simulating immune-mediated uveitis.[1,2] The neoplastic entities can be divided into lymphoid and non-lymphoid malignancies within either the retina or the uvea.[2,3] The lymphoid malignancies and non-lymphoid malignancies occurring in the eye are further subdivided as shown in Table 1. In this article we would discuss the relevant features of various Neoplastic Masquerade Syndromes.

	Type	**Anatomical involvement**
1.	Primary Intraocular Lymphomas	Retina and Vitreous
2.	Primary Uveal Lymphomas	Choroid and Iris
3.	Secondary Intraocular Lymphomas	Mainly choroidal involvement of systemic lymphoma
	CLASSIFICATION OF NON-LYMPHOID MALIGNANCIES OF THE EYE	
1.	Amelanotic Melanoma	
2.	Metastatic Tumor to the Choroids and Retina	
3.	Non-Neoplastic Proliferative Diseases of the Uvea, such as Juvenile Xanthogranuloma	

Lymphoid Malignancies

Primary Intraocular Lymphoma

Primary intraocular lymphoma (PIOL) is a high-grade malignant non-Hodgkin's lymphoma (NHL), arising in the retina with involvement of the vitreous and, occasionally, optic nerve. It is the most common "masquerader" according to investigators. PIOL is considered to be a subtype of the primary central nervous system lymphoma (PCNSL), and when occurring simultaneously in patients with PCNSL, the entity is named "oculocerebral lymphoma".[1,2,4]

Most PIOL are of B cell origin, and can be subtyped as diffuse large cell B cell lymphomas (DLBCL), according to the updated World Health Organization (WHO) Lymphoma Classification.1 Intraocular lymphoma of T cell type is rare, although its existence is becoming increasingly recognized. Most reported cases of intraocular T cell lymphoma, however, represent a secondary manifestation of mycosis fungoides or of a systemic T cell lymphoma in conjunction with systemic leukemia and are associated with human T cell lymphotropic virus type-1 (HTLV1) infection or with acquired immunodeficiency syndrome.[2,3,4]

Although it has been described in some young patients, PIOL typically affects those between the fifth and sixth decades. PIOL may be either unilateral or bilateral on initial presentation; however, the vast majority of patients will ultimately develop a bilateral manifestation.4 Intracranial lymphoma develops in 60-85% of patients with initial ocular disease, usually within the first 2 years of diagnosis.5 In turn, approximately 15–25% of patients with PCNSL will develop ocular disease. Systemic spread outside the CNS or ocular tissues rarely occurs. An inexplicable increase in the incidence of PCNSL has been reported over the last 15 years in both immuno competent and immuno suppressed patients.[1,3,4]

Symptoms and Signs of PIOL

PIOL when occurring prior to CNS disease, frequently presents as bilateral idiopathic steroid-resistant chronic uveitis, possibly with accompanying vitritis. Involvement of the CNS by tumor cells causes nonspecific symptoms and signs with the most frequent single symptom being "behavioral change". The most common focal neurologic signs include hemiparesis in 40-50% and cerebellar signs (eg. ataxia) in 15–40%.1

Ophthalmological Findings of PIOL

Anterior Segment

Anterior segment findings are observed in up to 43% of patients with PIOL.[3,4] Common findings include corneal precipitates, mild anterior flare, and a pseudohypopyon. Most often the posterior segment changes precede the anterior segment findings; however, occasionally, anterior segment disease can be the initial presentation of PIOL. Secondary anterior segment changes include neova scularization of the iris and irido corneal angle with possible glaucoma. In rare circumstances, PIOL can cause a mass in the iris following secondary infiltration.

- **Posterior Segment**

Vitreous cells and haze ("vitritis") are typical findings, and are present in the majority of cases. The characteristic fundus lesion is a flat creamy orange-yellow subretinal mass. These lesions may be single or multiple, discrete or confluent. The

presence of multiple subretinal pigment epithelial masses is considered by some clinicians to be pathognomic of PIOL. Rarely, PIOL presents as a single solitary intraocular mass.[3,4]

Diagnostic Techniques

The diagnosis of PIOL can be suspected on fundoscopy when the above-described "classical" retinal or subretinal infiltrates are present. Additional examinations, such as ultrasonography, fluorescein angiography, and/or high-resolution neuroimaging of the CNS, are usually performed to support the diagnosis. Fluorescein angiography provides information with regard to the location of the infiltrative process (retina versus choroid), and demonstrates any retinal pigment epithelium (RPE) disturbance. The mixed picture of hyper- and hypofluore scence on fluorescein angiography can result in a "leopardskin" appearance, considered to be highly indicative of PIOL (Figure 1a and b).[2,5] Neuroimaging studies include computed tomography scans (CT) scans, magnetic resonance imaging (MRI), and positron emission tomography (PET).

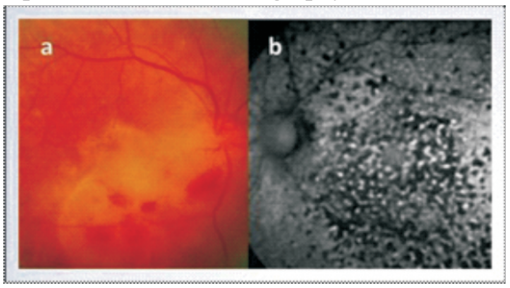

Figure 1: a- Primary Intraocular Lymphoma – Subretinal infiltrates with haemorrhages

b- "Leopard skin" appearance on fundus flourescein angiography

Cytological and Histological Diagnosis in PIOL

- **Vitreous Biopsy**

Cytological studies of vitreous biopsies remain the first line of investigation in the morphological diagnosis of PIOL.Vitreous specimens are obtained by fine needle aspiration, vitreal aspiration or via pars plana vitrectomy (PPV).[3,5,6] Vitreous aspirates in PIOL are mildly to moderately cellular, and comprise mature inflammatory cells such as macrophages, small lymphocytes with scattered large atypical lymphocytes and, possibly, fibrinous or necrotic material in the background (Figure 2). The neoplastic cells are usually pleomorphic showing hyperchromatic nuclei with irregular contours and prominent, sometimes multiple, nucleoli. The cytoplasmic rim is usually narrow or absent. Due to the fragility of neoplastic lymphocytes, a specimen may contain numerous lytic cells.The neoplastic cells are usually positive for B cell antigens, such as CD20, CD79α or PAX-5.[1,2]

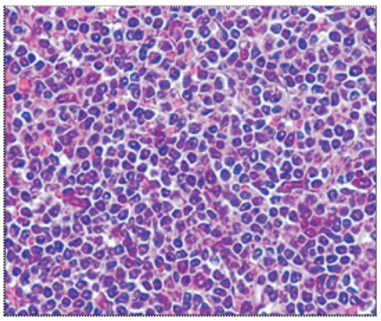

Figure 2: Histopathology of B cell lymphoma

- **Chorioretinal Biopsy**

If vitreous samples fail to demonstrate lymphoma cells, increasingly retinal and chorioretinal biopsies or subretinal aspiration are performed in patients with the subretinal infiltrates considered typical for PIOL.[5,6] Enucleation is unavoidable when a blind and painful eye develops due to secondary glaucoma and/or complete retinal detachment, and thus can lead to the diagnosis of malignant lymphoma.

- Biochemical and Molecular Analysis

In addition to cytomorphology and immunocytology, investigations such as flow cytometry, determination of cytokine concentrations, particularly interleukin-10 (IL-10), polymerase chain reaction (PCR) examining for monoclonal rearrangements of immmunoglobulin heavy (IgH) or light (IgL) chains in B cell lymphoma, or T cell receptor genes in T cell lymphoma, as well as determination of CDR3 (complementary determining regions) polymorphisms in the variable region of the immunoglobulin gene, are done[1,4,6].

Treatment of PIOL

The treatment recommendations for PIOL with or without CNS disease remain controversial. Radiotherapy alone to the eyes and CNS was the main form of treatment for PIOL/PCNSL, due to the sensitivity of lymphoma cells to radiation. Most patients usually succumbed to recurrent disease. Furthermore, ocular radiation was associated with delayed toxicity, including radiation retinopathy, optic neuropathy, dry eye, corneal epithelial defects, and loss of limbal stem cells, cataracts, and glaucoma.[1,2,3] With multimodality therapy, including a boosted radiation dose to the spinal cord and intrathecal methotrexate, vision could be improved and life prolonged. Recent innovations in treatment include multi-agent primary chemotherapy. The regimen included methotrexate and procarbazine, or vincristine, thiotepa, or both vincristine and cytarabine. Other alternative therapies that require further assessment include intravitreal methotrexate and trofosfamide.[5,6] The management of patients with intraocular lymphoma only is also controversial. Localized radiation to one or both eyes is usually performed. Promising results for PIOL were obtained with high-dose chemotherapy followed by autologous bone marrow.[6]

Primary Uveal Lymphomas

Primary uveal lymphomas are probably the rarest intraocular

lymphomas. It either arises from the choroid or iris[1,2].

1. Primary Choroidal Lymphoma

They are considered to be tumors with their origin in the choroid, due to the absence of systemic disease at the time of diagnosis, and to their unilaterality in most patients. Most primary choroidal lymphomas are low-grade and are clinically indolent. Consequently, they have been termed "pseudotumors" and "reactive lymphoid hyperplasia" of the uvea in the past and usually occur unilaterally in men in the fifth decade of life.[5-7]

Typical presenting symptoms include recurrent episodes of blurred vision, painless loss of vision as well as metamorphopsia subsequent to secondary serous detachment of the macula. The signs of primary choroidal lymphoma include the creamy choroidal infiltrates on fundus examination with low echogenicity on ophthalmic ultrasound (Figure 3). There may be an initial response to steroid therapy. Ultimately, a diffuse thickening of the uveal tract becomes obvious on fundoscopy and, in some patients, subconjunctival or episcleral extension may occur.[5,6,7]

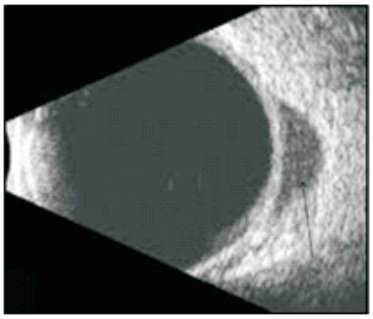

Figure 3: B scan appearance of Primary Uveal Lymphoma

On the basis of morphological features and immunopheno type, the primary choroidal lymphoma can be subtyped as "extranodal marginal zone B cell lymphomas" (EMZL) of mucosa-associated lymphoid tissue (MALT) type, according to the WHO Classification.[1,8]

Treatment of Primary Choroidal Lymphoma

Prior to any commencement of therapy in patients with primary choroidal lymphoma, a complete lymphoma "staging" investigation is essential. If no systemic disease is found, local treatment is appropriate and can include excisional biopsy of any epibulbar mass, cryotherapy, as well as low-dose irradiation in divided doses[2,4,7]. Occasional patients with primary choroidal lymphoma have been reported to have developed systemic disease following treatment. Involvement of the central nervous system by primary uveal lymphoma is exceptionally rare.

2. Primary Iridal Lymphoma

Those lymphomas occurring primarily in the iris are exceptionally rare. The typical presenting symptoms of primary iridal lymphoma include a painful eye, photophobia, and sometimes decreased vision.The clinical signs reported in the literature include uveitis of uncertain nature, nodular or diffuse iridal precipitates, iris discoloration with heterochromia and anisocoria, iridal swelling as well as hyphema or pseudohypopyon.[4,7,8] On ultrasound examination, ill-defined tumors of low reflectivity can be observed. Paracentesis from the anterior chamber and/ or iris biopsy with subsequent cytological and histological examinations respectively are the two methods employed, which usually lead to the establishment of a definitive diagnosis. Low-dose irradiation or systemic chemotherapy is the treatment of choice.

Secondary Intraocular Lymphoma or Leukemia

Leukemic involvement of the ocular tissues is the most common form of intraocular lymphomatous proliferation. At least 65% of cases of leukemia were seen to have involvement of the eye at autopsy. Ocular manifestations are rarely the first sign of disease in malignant lymphoma/leukemia, and have been reported in up to 80% of patients at some stage of their disease.[6,8] They usually occur in the choroid, and less often in the iris. Exceptionally rarely, intravascular lymphoma (also known as neoplastic angioendotheliomatosis) has also been reported to affect the eye.

Post-transplantation Lympho Proliferative Disorder

A well-known complication of solid organ transplantation is the occurrence of lymphoproliferations, such as the post-transplantation lymphoproliferative disorder (PTLD). This is considered a particular disease entity, most often caused by a chronic Epstein Barr virus (EBV) infection[6,8,9]. Some forms of PTLD undergo a malignant transformation with development of a malignant lymphoma. The risk of developing PTLD appears to be dependent upon the duration of immuno suppression. PTLD rarely affects the eye.

Non-Lymphoid Malignancies

Uveal Melanoma

Uveal melanoma is the most frequent primary intraocular tumor in white adults with an incidence of 0.7 per 100,000. These neoplasias, particularly the diffuse form, may present with clinical features suggestive of intraocular or orbital inflammation. Approximately 4.9% of patients with uveal melanoma present with symptoms such as episcleritis, anterior and/or posterior uveitis, endophthalmitis or panendophthalmitis.[10,11] The use of ocular echography has increased the diagnostic accuracy of uveal melanoma; however, unusual presentations of uveal melanoma may still perplex the clinician, masquerading as other entities.

Retinoblastoma

Retinoblastoma is the most common intra ocular tumor in childhood occurring in 1 in 17,000 to 24,000 live births and may occur either as a hereditary or as a sporadic tumor. Typically, retinoblastoma presents with leucocoria or

strabismus; in very rare cases, it may present as an inflammation. In particular, the rare variant of a diffuse infiltrating retinoblastoma, leading to conjunctival chemosis, pseudohypopyon and/or vitritis, can present with inflammatory signs.[1,9,10] Imaging studies – particularly with the presence of dystrophic calcification – are the most reliable in establishing the diagnosis; aqueous or vitreous biopsies are generally not recommended due to the considerable risk of tumor spread.

Juvenile Xanthogranuloma

Juvenile xanthogranuloma is a rare idiopathic cutaneous granulomatous disorder usually occurring in young children. The cutaneous lesions are orange-red papules or macules, predominantly occurring over the face, neck, and upper trunk. Ocular involvement usually affects the anterior segment, particularly the iris where it presents as a yellow nodule.6,8,11 Complications of iridal juvenile xanthogranuloma are recurrent hemorrhage, and possibly the development of glaucoma. Occasionally, the posterior segment is involved and can be complicated by retinal hemorrhage, detachment, and blindness.Several treatment modalities have been used, including corticosteroids, low-dose radiotherapy, and surgical excision. With uveal juvenile xanthogranuloma, however, nonsurgical therapy is recommended due to the risk of severe bleeding.[10,12]

Metastatic Tumors

Uveal Metastases

The most common metastases to the uvea are bronchial cancer in men and breast cancer in women.These may present with pale white to yellow lesions on fundoscopy under a serous detachment without involvement of the retina, superficially representing primary uveal lymphoma.[13,14]

Retinal Metastases

These are exceptionally rare.In patients where no primary malignancy is known, a vitreous aspiration or retinal biopsy may be required to establish the diagnosis.[15,16]

Points To Ponder

Primary intraocular (retinal) lymphoma is considered a subset of primary central nervous system lymphoma, with the majority of the lymphomas being high grade malignant B cell lymphomas.

Multiple yellow-orange subretinal lesions, with the corresponding "leopard skin" appearance on fluorescein angiography, are considered to be pathognomic for PIOL.

Vitreous biopsy remains the first line of investigation in PIOL diagnosis establishment.

Before commencement of treatment of all PIOL patients, extensive "staging" examinations should be performed to determine the extent of disease (i.e. CNS involvement) and to exclude a secondary ocular involvement of a previously unknown systemic lymphoma.

Although the prognosis of patients with PIOL/PCNSL is generally poor, newer therapies provide optimism in prolonging their life expectancy.

Primary choroidal lymphomas are usually low-grade B cell lymphomas of MALT type.

The majority of primary iridal lymphomas are high-grade lymphomas, either of B or of T cell type.

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