Masquerade Syndromes

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Masquerade syndromes are disorders that occur with intraocular inflammation and are often misdiagnosed as a chronic idiopathic uveitis. The term "Masquerade Syndrome" was first used in 1967 to describe a case of conjunctival carcinoma that manifested as chronic conjunctivitis [22]. Today, it is used to describe disorders that stimulate chronic uveitis. Because of the nature of the underlying diseases, which often have detrimental consequences, early diagnosis and prompt treatment are critical.

We present two cases to illustrate malignancy masquerading as chronic uveitis.

Case 1

RB was a 30-year-old caucasian female who presented in August , 1984, with a six-month history of blurry vision in the right eye (RE). Her visual acuity was 1/100 RE and 20/20 LE. Slit lamp examination revealed 2+ iritis, RE. Dilated funduscopic examination of RE revealed vitritis with large cells, suspicious for malignancy, and yellow discrete lesions at the RPE with prominent pigment in the central macula (**Figure 1**). Dilated examination of the left eye only showed few drusen.

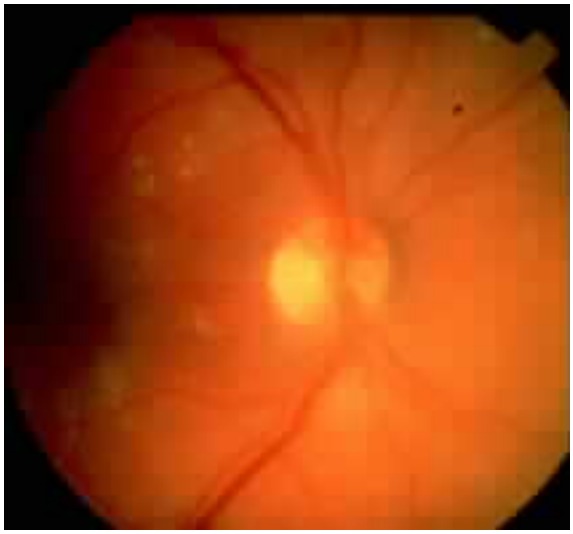

Figure 1: Vitreous haze with subretinal lesions

In September, 1984, the patient underwent pars plana vitrectomy, RE, which revealed atypical cells, suggestive of large cell lymphoma. Cranial magnetic resonance imaging (MRI) showed foci of hyperintensity in the corpus callosum, consistent with central nervous system (CNS) lymphoma. The patient was fully evaluated by an oncologist, and was treated with irradiation at the Massachusetts General Hospital (MGH). In October, 1994, the patient developed vitritis in LE. She was re-evaluated by her oncologist . The patient then received irradiation to the head and both eys. In September, 1995, her vision has returned to 20/20 RE, and 20/25 LE.

In August, 1987, the patient came back to the Infirmary, complaining of decreased vision in her RE. Her husband also stated that her personality had been "unusual" during the past several months. Her vision was 20/70 RE and 20/30 LE. There was 3+ vitritis in the RE. Repeated cranial MRI revealed recurrence of her large cell lymphoma. The patient was readmitted to the MGH Oncology Service for staging, and additional irradiation and intrathecal methotrexate.

Case 2

RF was a 62-year-old caucasian man who had a history of intermittent uveitis and ocular hypertension in his right eye since 1990. Evaluations performed by his ophthalmologist had been non-revealing. The patient required continuous topical steroids and aqueous suppressor. In November, 1993, the patient underwent uncomplicated cataract extraction and implantation of posterior chamber intraocular lens in RE. Postoperatively, the patient developed significant inflammation and intraocular pressure elevation. In February, 1994, the patient underwent pars plana vitrectomy, RE. Again, postoperatively, he developed persistent inflamamtion and intermittent elevated ocular pressure.

In June, 1995, the patient was referred I. At presentation, he had moderate panuveitis, RE, with an intraocular pressure of 28. Non-invasive uveitic laboratory evaluations were initiated. Patient was treated with diflunisal, 500 mg orally twice daily, and prednisolone, diclofenac, apraclonidine, and timolol, topically, RE. Two months later, the inflammation persisted. All evaluations were negative. Methotrexate therapy, 7.5 mg orally once weekly was initiated. During the next several months, the patient continued to have persistent iridocyclitis with elevated pressure.

In April, 1996, we performed pars plana vitrectomy in the right eye. During the surgery, we detected a brownish lesion in the ciliary body, at the 12 o'clock position, suggestive of a melanoma (**Figure 2**). Post-operatively, ultrasonography confirmed a lesion of moderate echo adherent to posterior iris, within the ciliary sulcus (**Figure 3**). A consultation was obtained from the Retina Service. The recommendation was observation of the lesion. During the next six months, the patient continued to have persistent uveitis and elevated intraocular pressure.

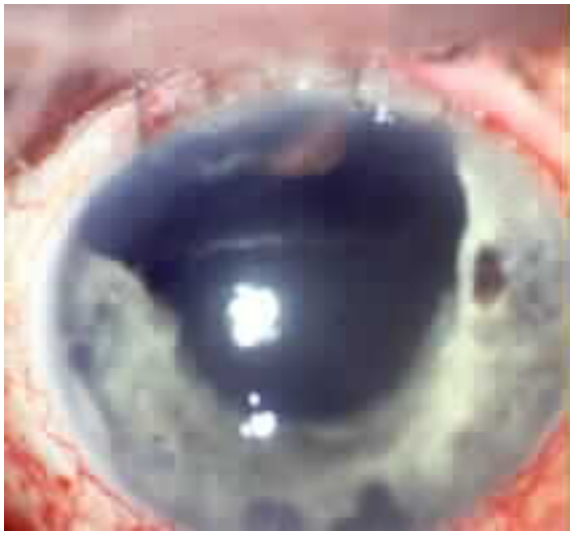

Figure 2: Superior melanotic mass

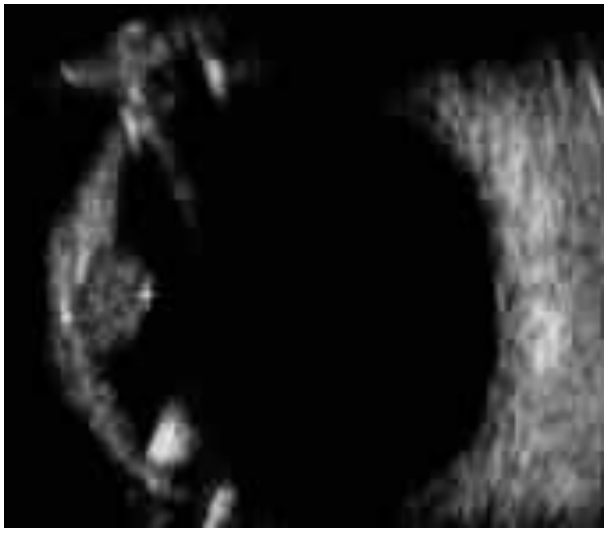

Figure 3: UTZ of Case 2 showing hyperechoic lesion in ciliary body

In November, 1996, we performed a third vitrectomy and removal of the intraocular lens implant. Continued observation of the lesion was recommended by the retina consultant. During the next six months, the patient continued to have, although diminished, uveitis on methotrexate, diflunisal, and rimexolone drops four times daily. The intraocular pressure remained elevated in the right eye, despite therapy with topical betaxolol, dorzolamide, and apraclonidine, requiring the addition of latanoprost, which intermittently controlled the pressure.

In July, 1997, retinal examination and ultrasound biomicroscopy showed that the ciliary body mass had enlarged, to approximately 7.0 x 6.0 x 4.2 mm, with extension into the limbus. Evaluation by the retinal oncologists confirmed the suspicion that the mass was probably a ciliary body melanoma. The patient elected to undergo proton beam irradiation and received a total of 70 Gy (gray) delivered in five fractions. One month after his proton beam treatment, the uveitis had dramatically improved, and the intraocular pressure had returned to normal.

There are many disorders that can manifest as uveitis. Tables 1 and 2 list several non-malignant and malignant disorders, respectively, which can present as uveitis. In this paper, we will discuss malignant disorders in more details. Readers are encouraged to learn more about the non-malignant disorders discussed elsewhere, which can also masquerade as uveitis.

Table 1. Non-malignant ocular disoders masquerading as uveitis

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Intraocular foreign body

Retinal detachment

Myopic degeneration

Pigment dispersion syndrome

Retinal degeneration

Multiple sclerosis

Intraocular infections

Drug reactions

Post-vacination

Table 2. Malignant ocular disorders masquerading as uveitis

Intraocular lymphomas

Non-Hodgkin's lymphoma of central nervous system

Systemic non-Hodgkin's lymphoma metastatic to eye

Hodgkin's lymphoma

Carcinoma metastatic to eye

Breast

Kidney

Lung

Uveal Melanoma

Iris

Ciliary body

Choroid

Paraneoplastic syndromes

Cancer-associated retinopathy

Bilateral diffuse uveal melanocytic proliferation

Childhood carcinoma

Retinoblastoma

Leukemia

Medulloepithelioma

Juvenile xanthogranuloma

Non-Hodgkin's lymphoma of the Central Nervous System

Non-Hodgkin's lymphoma (NHL) of the central nervous system (CNS) is also known as Primary CNS Lymphoma, and can arise from the brain, spinal cord, leptomeninges, or the eye, and may spread throughout the CNS [4], as illustrated in case 1 above. The incidence of CNS lymphoma has increased over the last 10 years, from 2.7 to 7.5 cases per million [11]. Such increase may be secondary to the emergence of the AIDS and other causes of immunosuppression. The median age of patients is 50 to 60 years; male is slightly predominant over female [4,11]. Ocular involvement exists in 15 to 25% of cases, and can precede detectable disease in other parts of the CNS. A study from the National Eye Institute in 1993 revealed that about two-thirds of patients with ocular disease had undiagnosed CNS disease at the time of their diagnosis [24].

Intraocular Lymphoma

Immunosuppression (e.g. being post transplantation, having AIDS) is the most common risk factor among patients with intraocular lymphoma. Typical symptoms are blurred vision and floaters; redness and pain rarely occurred. The vision is often better than the clinical symptoms. Slit lamp examination often shows mild anterior segment inflammation with aqueous cells and flare, and keratic precipitates [24]. In the vitreous, there are cells occuring in sheets, with subretinal yellow infiltrates through a hazy vitreous. Occasionally, there is hemorrhagic retinal vasculitis [5].

The diagnosis of intraocular lymphoma requires a thorough history and neurologic examination. MRI and lumbar pucture (LP) may be required. Cerebral spinal fluid (CSF) from LP should be delivered immediately to the cytology laboratory since lymphoma cells are fragile. If CSF shows no malignant cells, a completed vitrectomy can be performed to obtain vitreous specimen. Tissue culture medium enriched with 10% fetal calf serum can be added to collection chamber of vitrectomy machine to improve cell viability. Core vitreous should be obtained and taken immediately to cytology for processing 15].

Multiple vitreous specimens may be needed to detect malignant cells. In a study by Char and associates in 1988 [2], three out of 14 cases of intraocular lymphoma required more than one vitreous specimens to yield the diagnosis. Measurements of levels of various interleukins (IL) in the vitreous can also be helpful in making the diagnosis of intraocular lymphoma. Often, the ratio of IL-10 to IL-12 is elevated, in the context of atypia on vitreal biopsy. Recently, Whitcup and associates have reported elevated vitreous levels of IL-10 relative to levels of IL-6 in primary CNS lymphoma [25]. The use of corticosteroids can obscure the diagnosis, as the cells decrease in size and the viability of tumor cells diminishes.

Histopathologically, lymphoma is characterized by large and pleomorphic cells with scanty cytoplasm, and hypersegmented nuclei with prominent nucleoli. Collections of lymphomatous cells can be found between Bruch's membrane and the retinal pigment epithelium. In B-cell lymphoma, malignant cells show B-cells markers with either a kappa or lambda light chain monoclonal response [15].

The differential diagnosis of intraocular lymphoma may include: sarcoidosis, syphilis, tuberculosis, acute retinal necrosis, and CMV retinitis [15]. Thus, diagnostic tests for these entities should be performed prior or in conjunction with those for intraocular lymphoma.

Treatment of Non-Hodgkins Lymphoma of the Central Nervous System

Radiation is the first-line therapy as NHL-CNS is quite radiosensitive and responds well to 1,500 to 4,500 rads [15]. Some clinicians prefer to limit radiation therapy to the eye when there is only ocular involvements. However, there are many patients who have subclinical CNS involvement by the time intraocular lymphoma manifests. Thus, there are clinicians who will administer cranial irradiation in addition to orbital radiation, even in isolated ocular involvement [2,14,16].

Radiotherapy can also be combined with chemotherapy to achieve additional therapeutic effect. Often, placement of Omaya reservoir is required for intrathecal therapy. The use of chemotherapy before radiotherapy has been shown to decrease the incidence and degree of CNS toxicity [1]. Dahlborg and associates proposed the use of intra-arterial mannitol for blood-brain barrier disruption to enhance the effectiveness of chemotherapy. Recently, there has been report of intravitreal methotrexate as adjunct therapy [7].

Prognosis

NHL-CNS demonstrates good initial response but recurrence is common. The five-year survival rate is less than 5% [15]. Study by Hochberg and Miller shows the overall median survival time from diagnosis is 13.5 months in primary CNS lymphoma [11].

Systemic Non-Hodgkin's Lymphoma Metastatic to Eye

Such metastasis can present as anterior or posterior uveitis, or hypopyon or hyphema in an uninflamed eye [10]. In NHL-CNS, malignant cells are located between the RPE and the Bruch's membrane. In systemic NHL with ocular metastasis, the cells infiltrate the choroid and may represent ocular melanoma [8]. Ocular involvement may be the initial presentation of the disease [8].

Lymphoid Hyperplasia of the Uvea

Lymphoid hyperplasis of the uvea, also known *as inflammatory pseudotumors of the uveal tract* or *intraocular pseudotumors*, is characterized by infiltration of the uveal tract by well-differentiated small lymphocytes. There can be anterior ubveitis, vitritis, choroidal infiltrates, and iris heterochromia [12,17,18]. Extraocular extension may present as conjunctival salmon-colored lesions, or orbital masses which may cause proptosis and diplopia [17]. The condition is painless unless severe glaucoma develops.

The diagnosis is made by biopsy of extraocular extension or chorioretina. Lymphoid hyperplasia of the uvea often responds to corticosteroids and moderate dose of radiotherapy. The prognosis is favorable [12].

Uveal Melanoma

The incidence of uveal melanoma is about six per million per year, 80% in the choroid, 12% in the ciliary body, and 8% in the iris [21]. Malignant melanoma involving ciliary body yields poor prognosis compared to other uveal melanomas.

Primary choroidal melanomas can present as focal choroidal mass, which may mimic sarcoidosis, tuberculous granuloma, or posterior scleritis.

Shields and colleagues reported that secondary intraocular pressure elevation was present in 17% of eyes with ciliary body melanomas [20]. The most common mechanism of elevated intraocular pressure was pigment dispersion and tumor invasion of the angle in ciliary body

melanomas. Uveitis, as described in the second case above, is rarely associated with ciliary body melanoma.

Choroidal Metastases

Study by Ferry and Font in 1974 showed that 50% of ocular metastases are recognized before the diagnosis of underlying malignant process [6]]. Renal and lung carcinomas are most likely to manifest with ocular metastases. Breast carcinomas also frequently metastasize to the eye; however, the primary lesion is known at the time of ocular lesion in greater than 90% of cases [15].

Childhood Malignancies

Retinoblastoma is the most common intraocular malignant process in childhood. The initial presentation can be quite diverse, from tumor cells in the anterior chamber, mistaken as iritis, to leucokoria, strabismus, and uveitis of unknown etiology [3].

Cancer-Associated Retinopathy (CAR)

First described in 1976 in three patients with oat cell carcinomas of the lung [19], this paraneoplastic syndrome has now been reported with a number of malignant conditions. Patients often present with loss of vision. The fundus can appear normal early in the course of the disease. However, there may be eventual vascular sheathing, disturbances of the RPE, and optic disc pallor.

Retinal autoantibodies have been identified in patients with CAR. Such finding, together with that of the disease responding to corticosteroid therapy, suggest that the retinal destruction may be partly immune-mediated [23].

Bilateral Diffuse Uveal Melanocytic Proliferation

In 1966, Machemer first described bilateral diffuse melanocytic tumors in a patient with pancreatic carcinoma [13]. This condition can occurs in patients with carcinomas, but underlying processes are often occult. Histopathology reveals diffuse uveal tract infiltrates with benign, spindle-shaped melanocytic cells, which have foamy cytoplasm, but lack mitotic figures.

Further study by Gass and Glazer in 1991 [9] showed the presence of multiple subtle round and oval subretinal red patches that show early hyperfluorescence on fluorescein angiography; multiple, slightly elevated, pigmented, and non-pigmented uveal melanocytic tumors with evidence of diffuse thickening of the uveal tract. In addition, there may be episcleral injecition, vitritis, and exudative retinal detachment.

Summary

There are many entities that can present as chronic intraocular inflammation. In the absence of a correct diagnosis, inappropriate therapy may be prescribed, which can be dangerous. Malignancy and other diseases should be considered in cases of chronic uveitis that do not respond to aggressive medical therapy, and in all patients with undiagnosed inflamamtory eye diseases. Direct treatment of the malignancy or underlying condition may be required to control the uveitis.

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Masquerade Syndrome

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Matching Type

1. Cancer-Associated Retinopathy
2. Bilateral Diffuse Melanocytic Proliferation
3. Retinoblastoma
4. Ocular metastases
5. Masquerade Syndrome
6. Uveal Melanoma
7. Non-Hodgkins Lymphoma of the CNS
8. Intraocular lymphoma
9. Lymphoid hyperplasia of Uvea
10. Systemic Non-Hodgkins Lymphoma metastatic to the eye

A. 80% involve choroid
B. Retinal autoantibodies
C. Associated with Lung Carcinoma
D. May appear as ocular melanoma
E. Primary central nervous system lymphoma
F. Intraocular pseudotumor
G. Spindle-shaped melanocytic cells with no mitotic figures
H. Most common intraocular malignancy in children
I. Subretinal yellow infiltrates

J. Suspected in chronic uveitis not responsive to aggressive medical therapy

Answer Key:

1. B

2. G

3. H

4. C

5. J

6. A

7. E

8. I

9. F

10. D