Masquerade syndromes are classically defined as entities which emulate inflammatory conditions but which are in fact due to a neoplastic process. It is the term used for any malignant process that simulates benign disease.

The term masquerade syndrome was first used in ophthalmology in 1967 by Theodore in connection with a case of conjunctival carcinoma mimicking chronic conjunctivitis. Presently in ophthalmology, malignant intraocular processes that present as chronic uveitis are termed as ‘masqueraders’. A wide variety of conditions can produce cells in the intraocular space, resulting in what appears to be “uveitis.” Neoplastic masquerade syndromes may account for just 2%-3% of all patients seen in tertiary uveitis referral clinics. In a large series of 853 cases by Grange et al, only 21 cases (2.5%) were diagnosed with neoplastic masquerade syndromes. Recognition of such an entity requires detailed clinical evaluation as well as extensive laboratory investigations. However, early diagnosis has impact over survival of patient.

Other disorders such as retinal degenerations and intraocular foreign body can also masquerade as a uveitis, and, again, misdiagnosis frequently leads to inappropriate therapy. These are not malignant disorders and termed ‘non malignant masquerades’ (Table 1).

Neoplastic Masquerade Syndromes

Lymphoid Malignancies

Primary Intraocular Lymphoma (PIOL)

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 with or without concomitant CNS involvement. PIOL is a subtype of Primary Central Nervous System Lymphomas (PCNSL). The PCNSL comprises approximately 5% of all primary CNS malignancies and 1% to 2% of all malignant lymphomas. PIOL can manifest along with cerebral disease but can also precede this or occur during the course of PCNSL. The predominant histological appearance is of a diffuse, large B-cell lymphoma. Only 2% are T-lymphocyte lymphomas.

PIOL/PCNSL is frequently associated with immunosuppression especially HIV infection. 95% of HIV-positive patients with PIOL/PCNSL have evidence of antibodies to Epstein-Barr virus (EBV) compared to only 20% of immunocompetent patients.

Table 1: Masquerading conditions

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5% of all primary CNS malignancies and 1% to 2% of all malignant lymphomas. PIOL can manifest along with cerebral disease but can also precede this or occur during the course of PCNSL. The predominant histological appearance is of a diffuse, large B-cell lymphoma. Only 2% are T-lymphocyte lymphomas.

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Although PCNSL mainly affects patients in their fifth to seventh decade of life, it also occurs, in rare instances, in young. PIOL may be either unilateral or bilateral on initial presentation; however, the vast majority of patients will ultimately develop a bilateral manifestation. Intracranial lymphoma develops in 60-85% of patients with initial ocular disease, usually within the first 2 years of diagnosis. In turn, approximately 15-25% of patients with PCNSL will develop ocular disease.

The site of origin of PCNSL is unknown since it is held that neither CNS nor eye contain lymphatic tissue. It is postulated that lymphoma cells arise in a site external to CNS or eye but are able to grow unabated in these immunologically sequestered locations.

Clinical features and findings

When occurring prior to CNS disease, PIOL frequently presents as bilateral idiopathic steroid-resistant chronic uveitis, possibly with accompanying vitritis. Patient complains of decreased vision and floaters. Examination reveals a variable degree of vitritis with the variable presence of anterior chamber cells. Sites of ocular involvement can include the vitreous, retina, subretinal pigment epithelium (sub-RPE).

On examination of retina, it classically reveals creamy yellow subretinal infiltrates with overlying RPE detachments (Figure 1). The lesions vary in thickness from about 1 mm to 2 mm. They can look like discrete white lesions from acute retinal necrosis, toxoplasmosis, frosted branch angiitis, or retinal arteriolar obstruction with coexisting multifocal chorioretinal scars and retinal vasculitis. Marked vitritis causes hazy media in many cases obscuring fundus details (Figure 2).

The frequency of anterior segment involvement reported in the literature varies. Slit lamp findings include mild anterior inflammation with cells, flare and keratic precipitates. Pseudohypopyon has been reported. Iris or angle neovascularisation with secondary glaucoma has been described.

Most patients are mistakenly diagnosed as a case of autoimmune uveitis and treated with anti-inflammatory medication. This can improve the vitreous cellular infiltration, but the effect is not long lasting and the uveitis often becomes resistant to therapy. High index of suspicion is required in such cases.

Involvement of the CNS by tumor cells causes nonspecific symptoms and signs with the most frequent single symptom being “behavioral change”. CNS lesions are most commonly found in the periventricular regions, and as a result the most common presenting features of PCNSL are personality alterations and changes in alertness. Other features are raised intracranial pressure, hemiparesis, cerebellar signs, seizures and cranial nerve palsies.

Diagnostic testing

Ultrasonography shows choroidal thickening, vitreous debris, elevated chorioretinal lesions, and serous retinal detachment.

Fluorescein angiography shows hypofluorescent areas due to blockage from a sub-RPE tumor mass or from RPE clumping.

Tissue diagnosis is the definitive method for establishing the presence of PIOL. Vitreous sample is obtained by either aspiration or by vitrectomy. With newer techniques vitrectomy is most commonly used for cytological confirmation of diagnosis. The immunohistology, immunophenotyping with flow cytometry and molecular genetic analysis support the diagnosis made on the biopsy material. Vitreous aspirates in PIOL are mildly to moderately cellular, and comprise mature inflammatory
Ocular Malignancies

Cells such as macrophages, small lymphocytes with scattered large atypical lymphocytes. The neoplastic cells are usually pleomorphic showing hyperchromatic nuclei with irregular contours and prominent, sometimes multiple, nucleoli (Figure 3). The cytoplasmic rim is usually narrow or absent. The neoplastic cells are usually positive for B cell antigens, such as CD20, CD79α or PAX-5. These additional diagnostic verifications are based on the fact that PIOL is comprised of monoclonal B lymphocytes in most cases.

Because recognition of malignant lymphocytes in the vitreous can be difficult, a negative finding should be followed by a chorioretinal biopsy if doubt persists.

If the diagnosis of intraocular lymphoma is established first, an extensive search for CNS involvement must be undertaken, as 60% to 85% of patients with intraocular lymphoma will eventually develop intracranial involvement and it is CNS disease which leads to the high morbidity and mortality. Neuroimaging shows multiple, diffuse, periventricular lesions with contrast enhancement. Cerebrospinal fluid analysis may reveal lymphoma cells. CSF from lumbar puncture may lead to a diagnosis of PIOL and obviate the need for the higher morbidity procedure of vitreous biopsy. Lymphoma cells have been identified in the CSF of 25% of patients with known MRI lesions. If lymphoma cells are found in the CSF, then no other diagnostic procedures are necessary to achieve a tissue diagnosis.

Treatment

PIOL has an unfavorable prognosis. Because of rarity of the disease, published treatment studies are all small, non-randomized and frequently retrospective. Best treatment has not yet been established.

Local irradiation with doses up to 45Gy has been used. Radiation therapy when used alone leads to early CNS progression. Radiotherapy-associated ocular complications have been reported in several series.

Classical chemotherapy regimes that are effective against systemic lymphomas are invariably ineffective in PIOL. Intravenous high-dose Methotrexate and high-dose Ara-C have both been used alone or in combination with other chemotherapeutic agents with reasonable success. Intravitreal Methotrexate has been used to treat both isolated and recurrent ocular lymphoma. Local chemotherapy with intravitreal injection of methotrexate has been advocated at the dose of 400 μg. Intravitreal Methotrexate, unfortunately, does not treat CNS disease.

The current consensus on treating PIOL with concurrent CNS disease is systemic high-dose Methotrexate-based chemotherapy with radiotherapy to the globes.

Primary Uveal Lymphoma

The primary uveal lymphomas are the least common of the intraocular lymphomas. As primary uveal lymphomas are generally clinically indolent, they have previously been misnamed “reactive lymphoid hyperplasia” and “uveal pseudotumours”. However, the demonstration of monoclonality amongst infiltrating lymphocyte populations and immunophenotyping led to their redefinition as low-grade B-cell NHL.

On ultrasonography, the choroid is diffusely thickened with low reflectivity and lacks choroidal or scleral excavation. Low-dose irradiation is considered the treatment of choice, although resolution has been achieved with moderately high doses of systemic corticosteroids.

Secondary to Systemic Lymphoma

Secondary intraocular lymphomas are systemic lymphomas that have metastasized to structures within the eye. Secondary intraocular lymphomas tend to involve the uveal tract, in contrast to PIOL. Secondary intraocular lymphomas are invariably of non-Hodgkin’s type, with Hodgkin’s lymphoma presenting intraocularly being exceptional.

Secondary intraocular lymphoma typically occurs in older patients, although it can occur in young children. Most patients have a known history of systemic lymphoma although intraocular disease may be the initial presentation. Systemic lymphomas hematogenously spread to the choroid, to the subretinal space, into the vitreous, and occasionally into the anterior chamber. These entities often present with vitritis and creamy subretinal infiltrates of variable size, number, and extent. Involvement is usually bilateral. Patient may have features of retinal vasculitis or diffuse choroiditis.

Treatment is not established in these cases and carried on lines of systemic disease.
Leukemia

Patients with leukemia may have retinal findings, including intraretinal hemorrhages, cotton-wool spots, white-centered hemorrhages, Roth spots, microaneurysms, and peripheral neovascularization. In rare instances, leukemic cells may invade the vitreous cavity. If the choroids is involved, exudative retinal detachment may be present and is angiographically similar to Vogt-Koyanagi-Harada (VKH) syndrome. Leukemia may also present with a hypopyon or hyphema, iris heterochromia, or gray-yellow pseudo hypopyon. The presence of malignant leukaemic cells may be confirmed by vitrectomy or aspiration of anterior chamber pseudohypopyon.

Uveal Lymphoid Proliferations

The uveal tract may be a site for lymphoid proliferations that can mimic chronic uveitis. These can range from benign reactive uveal lymphoid hyperplasia to frank lymphomas. Differentiation from posterior scleritis and uveal effusion syndrome is important. Biopsy specimens demonstrate mature lymphocytes and plasma cells, quite different from the specimens seen with PCNSL. Therapy with corticosteroids, radiation, or both has been used with variable results. Systemic and periocular corticosteroid therapy can result in rapid regression of the lesions, as can external-beam radiation.

Nonlymphoid Malignancies

Uveal melanoma

Malignant melanoma of the uveal tract is the most common primary intraocular tumour in adults. Approximately 5% of patients with uveal melanoma present with ocular inflammation, including episcleritis, anterior or posterior uveitis, endophthalmitis, or panophthalmitis. Most tumors that present in this fashion are epithelioid cell or mixed cell choroidal melanomas. Ultrasonography is useful in diagnosing these atypical cases because of the characteristic low internal reflectivity of these lesions. Other imaging modalities such as CT, MRI and CT/PET have been used for diagnostic purposes in uveal melanoma. Treatment is for the primary tumour once diagnosed. Various treatment modalities include brachytherapy, proton beam radiotherapy, transpupillary thermotherapy, trans-scleral local resection and enucleation.

Retinoblastoma

Approximately 1%-3% of retinoblastomas may present with the appearance of inflammation, most due to the relatively rare variant of diffuse infiltrating retinoblastoma. Patients are usually between age 4 and 6 years at presentation. These cases can be diagnostically confusing because of the limited visibility of the fundus and the lack of calcification on radiography or ultrasonography. Patients may have conjunctival chemosis, pseudohypopyon, and vitritis. The pseudohypopyon typically shifts with changes in head position and is usually white as opposed to the yellowish color of inflammatory hypopyon (Figure 4). Diagnostic aspiration of the aqueous humor may be required, but there is a significant risk of tumor spread through the needle tract.

Juvenile xanthogranuloma

Juvenile xanthogranuloma is a histiocytic process affecting mainly the skin and eyes, and, in rare instances, viscera. Patients usually present before age of one year with characteristic skin lesions that are reddish yellow. Histologic investigation shows large histiocytes with foamy cytoplasm and Touton giant cells. Ocular lesions can involve the iris, from which spontaneous hyphema may occur. Iris biopsy if taken shows fewer foamy histiocytes and fewer Touton giant cells than a skin biopsy. Intraocular lesions may respond to topical, periocular, or systemic corticosteroid therapy. Resistant cases may require local resection, radiation, or immunomodulatory therapy.

Metastatic Tumors

Metastatic tumours are the commonest intraocular malignancy in adults, but these rarely mimic intraocular inflammation. Most patients with metastatic ocular lesions are systemically ill with advanced disease. However, approximately one-third of patients have no history of primary cancer at the time of ocular diagnosis. The uveal tract is most commonly affected, but retinal metastases are extremely rare. Metastatic lesions may rarely be mistaken for intraocular inflammation that mimic uveitis. Patients with renal and lung carcinomas have the highest frequency of presenting with eye symptoms as the initial
Complaint. Lung metastases are most common in men and breast metastases are the most common in women. Usually, intraocular metastases are solid, posterior, amelanotic, choroidal tumors that can simulate a benign intraocular inflammation. Anterior uveal metastasis may present with cells in the aqueous humor, iris nodules, rubeosis iridis, and elevated IOP. Anterior chamber paracentesis may help confirm the diagnosis.

Retinal metastases are extremely rare. Primary cancers metastatic to the retina include cutaneous melanoma (the most common), followed by lung, gastrointestinal, and breast cancer. Metastatic melanoma often produces brown spherules in the retina, whereas other metastatic cancers are white to yellow and result in perivascular sheathing, simulating a retinal vasculitis or necrotizing retinitis.

Paraneoplastic syndromes
Paraneoplastic syndromes may cause intraocular inflammation with an autoimmune retinopathy and masquerade as a uveitis

Cancer-associated retinopathy (CAR) is a paraneoplastic syndrome that was initially described in three patients with oat cell carcinoma of the lung but has now been reported with a number of malignant conditions. Patients usually have loss of vision, and although the fundus can appear normal early in the course of the disease, vascular sheathing, disturbances of the RPE, and optic disc pallor may ensue.

Histologic studies show destruction of the photoreceptors. Retinal autoantibodies have been identified in patients with CAR suggesting the retinal destruction may be immune mediated. Patients respond favorably to corticosteroid therapy.

Other Nonmalignant conditions
A number of nonmalignant conditions can masquerade as idiopathic uveitis. An intraocular foreign body may elicit an anterior or a posterior uveitis. Patients with uniconal uveitis should be questioned about possible antecedent trauma. Gonioscopic examination should be performed to rule out a foreign body in the angle.

A number of retinal diseases can masquerade as ocular inflammatory disease. Retinal detachment can sometimes produce enough intraocular inflammation to be misdiagnosed as a uveitis, and myopic degeneration can produce cream-colored atrophic lesions that may be confused with a focal choroiditis. Retinal degenerations, such as retinitis pigmentosa may have a number of signs consistent with underlying inflammatory disease. Vitreous cells, posterior subcapsular cataract, and cystoid macular edema may occur.

Finally, uveitis may occur after vaccination and has also been associated with a vast number of medications. Topical prostaglandin analogues can lead to inflammatory response. Drugs like Rifabutin are known to cause ocular inflammatory response with hypopyon uveitis.

Conclusion
Clinician should keep in mind a possibility that in a small sub group of patients, uveitis not responding to conventional treatment may have underlying malignancy presenting with Masquerade syndrome. PIOL forms the commonest type of malignant masquerade syndrome encountered in clinical practice. However other causes like systemic lymphoma, intraocular melanoma, and metastasis from distant primary can be present. Through search and detailed evaluation can have positive impact on treatment and outcome.

References