(36)

Malignant Uveitis Masquerade Syndromes

Zespoły maskujące złośliwe zapalenia błony naczyniowej

Agnieszka Kubicka-Trząska, Bożena Romanowska-Dixon

Department of Ophthalmology, Clinic of Ophthalmology and Ocular Oncology,
Jagiellonian University, Medical College, Kraków, Poland
Head: Ass. Prof. Bożena Romanowska-Dixon, MD, PhD

Summary: The term "Masquerade Syndrome" was first used in ophthalmology in 1967 by Theodore, to describe a case of conjunctival carcinoma that manifested as chronic conjunctivitis. The Uveitis Masquerade Syndromes (UMS) are a group of various ocular diseases that may mimic chronic intraocular inflammation. Many malignant pathologies may result in an appearance masquerading as uveitis. The article reviews most common malignant conditions which may be considered masquerades such as primary intraocular lymphoma, leukemias, uveal melanoma, retinoblastoma, metastatic lesions, and paraneoplastic syndromes, among others. Diagnostic strategies, therapies, and prognosis are also reviewed.

Słowa kluczowe: zespół maskujący zapaleń błony naczyniowej, przewlekłe zapalenia wewnątrzgałkowe.
Key words: uveitis masquerade syndrome, chronic intraocular inflammation.

Mimesis is the Greek word for imitation or mimicry that represents the ability of simulation or resemblance of one organism to another or to an object in its surroundings for concealment and protection from predators. In medicine mimesis refers to the hysterical simulation of an organic disease or the imitation of one organic disease by another. In 1967 Theodore for the first time in medicine and in ophthalmology used the term "Masquerade Syndrome" to describe a case of conjunctival carcinoma that manifested as chronic conjunctivitis (1). Today, it is used to describe disorders that simulate chronic non-infectious uveitis. The diagnosis of uveitis masquerade syndromes (UMS) is difficult. Rothova et al. found a mean interval of nine months between the first ophthalmologic examination and establishing the definitive diagnosis of a masquerade syndrome. Malignant diseases took 11 months to diagnose, vs. seven months for nonmalignant conditions. The authors also reported that only 40 (5%) of 828 patients with uveitis had a masquerading condition, indicating that the UMS is relatively rare (2).

The most common malignant disorders masquerading as uveitis are presented in Table I.

Lymphomas

a. Primary intraocular lymphoma

Primary intraocular lymphoma (PIOL) is the most common neoplastic UMS involving the eye (3). PIOL is a rare extranodal non-Hodgkin B-cell lymphoma involving the retina, the subretinal space, vitreous body and the optic nerve. It is a subset of primary central nervous system lymphoma (PCNSL), which can occur either together with or independently of PCNSL (4). The diagnosis of intraocular lymphoma requires a thorough history and neurologic examination, magnetic resonance imaging (MRI) and lumbar puncture. However cytological examination of vitreal aspirates remains the gold standard for exclusion of neoplastic disease in this group of patients. The prompt, appropriate handling of specimens and review by an experienced cytopathologist are critical to the diagnosis of intraocular lymphoma (5). Malignant cells often are present in the cerebral spinal fluid at the time that ocular lymphoma is diagnosed (6). Nevertheless, multiple

Lymphomas	Primary intraocular lymphoma Systemic non-Hodgkin lymphoma metastatic to eye Hodgkin lymphoma metastatic to eye
Leukemias	
Ocular metastases	Breast Lungs Kidney
Lymphoid hyperplastic of the uvea	
Uveal melanoma	Iris Ciliary body Choroid
Childhood malignancies	Retinoblastoma Medulloepithelioma Juvenile xanthogranuloma Histiocytosis X
Paraneoplastic syndromes	Carcinoma – associated retinopathy Melanoma – associated retinopathy Bilateral diffuse uveal melanocytic proliferation

Tab. I. Malignant ocular disorders masquerading as intraocular inflammation.
Tab. I. Oczne zespoły maskujące jako złośliwe zapalenie wewnątrzgałkowe.

vitrectomies and lumbar punctures may be necessary before the correct diagnosis is made (5,7). Measurements of various interleukins (IL) levels in the vitreous can also be helpful in making the diagnosis of PIOL. Often, the ratio of IL-10 to IL-12 is elevated, in the context of atypia on vitreal biopsy (8). However Akpek et all. reported that elevation of vitreous IL-10 level is not diagnostic of PIOL (9). Recently, Whitcup and al. have reported elevated vitreous levels of IL-10 relative to levels of IL-6 in PCNSL (6). Chorioretinal biopsy increases the chance of diagnosing or excluding a PIOL involving the retina and choroid (5). PIOL usually develops in patients between the fifth and sixth life decade. The presentation of the disease is with blurred vision and floaters, but the vision is often better than the clinical symptoms. Anterior segment examination shows mild chronic anterior uveitis with hypopyon unresponsive to steroid therapy. In the vitreous, there are cells occuring in sheets, with subretinal yellow infiltrates through a hazy vitreous (Fig. 1). Occasionally, there is haemorrhagic retinal vasculitis and intermediate uveitis. The optic disc infiltration may be also seen. Bilateral but asymmetrical involvement is observed in about 80% of cases (4,6,10).

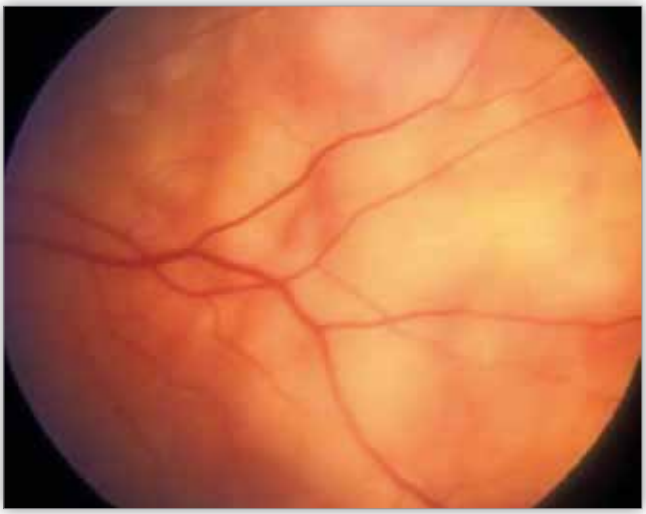

Fig. 1. Intraocular primary lymphoma masquerading as uveitis
Ryc. 1. Pierwotny chłoniak z obrazem zapalenia błony naczyniowej.

The optional therapy for PIOL has not been yet determined. It is generally believed that PIOL should be treated with a combination of systemic chemotherapy with high-dose methotrexate and radiotherapy (11). Recently intraocular methotrexate has been introduced as a therapeutic method for isolated ocular recurrences (4). Several new strategies for PIOL with CNS involvement have been reported: inrathecal therapy with methotrexate or anti CD 20 antibodies and autologous stem-cell transplantation (12). PIOL remains one of the most difficult diagnoses to establish, particularly due to its ability to mimic other diseases in the eye. The differential diagnosis of intraocular lymphoma include: sarcoidosis, syphilis, tuberculosis, acute retinal necrosis, CMV retinitis, white dot syndrome, Behçet disease, serpiginous choroidopathy (2,3,7,10,13). Thus, diagnostic tests for these entities should be performed prior or in conjunction with those for intraocular lymphoma. The prognosis is poor. The five-year survival rate is less than 5% (10).

b. Systemic non-Hodgkin lymphoma metastatic to eye

Both cutaneous or visceral T-cell lymphomas may metastize to the eye. Such metastasis can present as anterior uveitis with hypopyon or hyphema, posterior uveitis, retinal vasculitis and choroidal mass. Choroid is the primary site of ocular involvement. Ocular symptoms may be the initial presentation of the disease however most patients with ocular metastasis manifest the systemic symptoms of the disease (10).

c. Hodgkin lymphoma

Hodgkin lymphoma very rare metastases to the eye. Only a few sporadic cases of intraocular metastases in Hodgkin disease have been reported. The most common clinical presentation of the disease is uveitis and periphlebitis (10,13,14).

Leukemias

Various forms of leukemia may infiltrate the ocular tissues, causing morphologic changes masquerading as uveitis. The eye is involved most often in acute than in chronic leukemia and all ocular structures may be infiltrated by leukemic cells. Ocular involvement in leukemia can be caused by direct leukemic infiltration or indirectly due to the effects of low hematocrit, anemia, thrombocytopenia, hyperviscosity, or compromised immune status (15). The UMS in a course of leukemia is due to direct infiltration of ocular tissues by leukemic cells.

UMS associated with leukemia may precede the diagnosis or occur during the course of the disease. The choroid is the most commonly affected part of the eye (16). Pigment epitheliopathy develops secondary to choroidal infiltration and is characterized by a "leopard spot patterns". In children and young adults, acute lymphoblastic leukemia may manifest as acute unilateral anterior uveitis with massive anterior chamber cellular infiltrates which form pseudohypopyon characterized by shaggy, irregular, free-floating material that fails to settle inferiorly. Acute unilateral hypopyon may be a first sign of extramedullary relapse of leukemia (17,18). Acute papillitis with papilloedema, retinal vasculitis, vitritis, intravitreal haemorrhage, retinal infiltrates mimicking white dots, orbital and eye-lid involvemet have been also observed in leukemic patients (15,16).

Examination of the aqueous humor aspirate with the presence of malignant cells is useful in establishing the diagnosis in a case of atypical anterior uveitis with hypopyon unresponsive to steroids therapy (17). The treatment options include chemotherapy and radiotherapy to the CNS (17,19).

Ocular metastases

The uveal tract is a preferential site of ocular spread for most solid tumors. The incidence of uveal metastases among various groups of cancer patients varies from 5 to 27%. Renal, lung, breast carcinomas are most likely to manifest with ocular metastases (20). The most frequent site of intraocular metastasis is the posterior choroid, which appears the "site of choice", then the orbit, the iris and the ciliary body. Metastases within the eye may masquerade as a non-infectious anterior and posterior uveitis, choroidal effusion, retinitis or papillitis (20). About fifty percent of ocular metastases are recognized before the diagnosis of underlying malignant process. The therapy of intraocular metastases include: external beam radiotherapy (EBR), brachytherapy, transpupillary thermotherapy (TTT) and enucleation (21).

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Lymphoid Hyperplasia of the Uvea

Lymphoid hyperplasia 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. Clinical features include: anterior uveitis, vitritis, choroidal infiltrates, and iris heterochromia. Extraocular extension may present as conjunctival salmon-colored lesions, or orbital masses which may cause proptosis and diplopia (22). The results of biopsy are essential for diagnosis. Lymphoid hyperplasia of the uvea often responds to corticosteroids and moderate dose of radiotherapy. The prognosis is favorable (22).

Uveal Melanoma

Choroidal melanoma can present as focal choroidal mass, which may mimic sarcoid or tuberculous granuloma, endophthalmitis and posterior scleritis. In these cases ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) may be sufficient for correct diagnosis, however where the diagnosis cannot be established the fine needle aspiration biopsy may be indicated (23). Ciliary body melanoma with the presence of sentinel vessels may mimic the clinical manifestation of episcleritis or scleritis (Fig. 2).

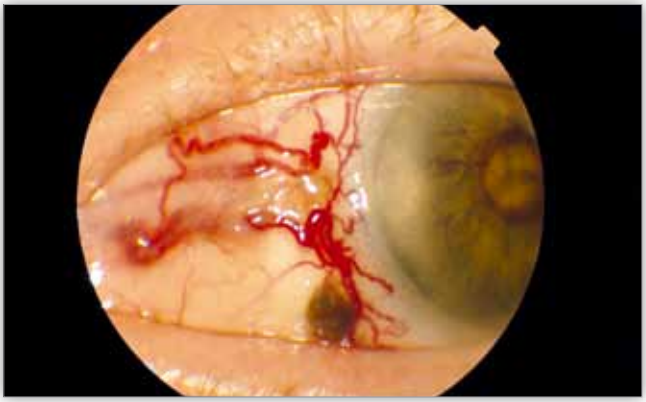

Fig. 2. Sentinel vessels in a course of ciliary body melanoma.
Ryc. 2. Poskręcane naczynia w przebiegu czerniaka ciała rzęskowego.

Secondary glaucoma as a result of pigment dispersion and tumor invasion of the anterior chamber angle may also be present. The uveitis is rarely associated with ciliary body melanoma. Slit-lamp biomicroscopy with a triple-mirror contact lens through a dilated pupil is essential for diagnosis but in the presence of opaque media high-frequency ultrasonography is useful. Fine needle-aspiration biopsy may be helpful in selected cases (23). There are three patterns of iris melanoma: ring, tapioca and diffuse. All of them may mimic anterior uveitis and can cause secondary glaucoma. Diffusely growing melanoma may give rise to ipsilateral heterochromia and may masquerade as Fuchs heterochromic uveitis (10). The documented growth of the lesion is essential for diagnosis (23).

Childhood Malignancies

Retinoblastoma is the most common malignant intraocular tumor in childhood. The initial presentation of retinoblastoma can be quite diverse, from tumor cells in the anterior chamber, masquerading as iritis, leucokoria, strabismus, secondary glaucoma and orbital inflammation mimicking orbital cellulitis. In some cases retinoblastoma may manifest as endophthalmitis (10,24). In these cases the differential diagnosis from intraocular inflammation associated with Toxocarosis may be difficult. The diagnostic methods of retinoblastoma include: ultrasonography, CT which detect the presence of calcifications and MRI. In some cases the measurement of aqueous humor lactate dehydrogenase (LDH) levels may be useful for diagnosis (25).

Medulloepithelioma is a rare, locally invasive tumor which arises from the non-pigmented ciliary epithelium. It can mimic mild anterior uveitis and for the correct diagnosis the histopathological examination is needed.

Juvenile xanthogranuloma is a self-limited skin disorder in childhood. Ocular involvement is one of the most common manifestation of the disease. Involvement of the uvea leads to uveitis or spontaneous hyphema. The presence of the iris mass which may cause an acquired heterochromia may masquerade as Fuchs heterochromic uveitis. The diagnosis is based on biopsy of an iris lesion which disclose the presence of specific Touton cells (26).

Histiocytosis X and Rosari – Dorfman disease may masquerade as anterior and intermediate uveitis. The presence of periorbital infiltrations may mimic orbital cellulitis (10).

Paraneoplastic syndromes

a. Cancer-associated retinopathy

Cancer-associated retinopathy (CAR) was first described by Sawyer in 1976 in three patients with oat cell carcinomas of the lung (27). CAR may be a first clinical sign of an underlying systemic malignancy. Presentation is with subacute loss of vision, shimmering and flickering lights. The fundus can appear normal early in the course of the disease. However, there may be eventual vascular sheathing, disturbances of the RPE, optic disc pallor and mild vitritis. Retinal autoantibodies have been identified in patients with CAR reacting against the 23kD antigen (recoverin) a component of photoreceptors (28). ERG is severely attenuated under photopic and scotopic condition, dark adaptation is abnormal. The prognosis for both vision and life is poor (28).

b. Melanoma-associated retinopathy

Melanoma-associated retinopathy (MAR) develops months to years after diagnosis of metastatic cutaneous melanoma (29). Presentation is with acute onset of night blindness with shimmering and flickering lights. Visual acuity and color vision are normal or mildly impaired. In longstanding cases RPE irregularity, arteriolar attenuation, optic disc pallor are seen. Vitritis and retinal periphlebitis may be present. Retinal autoantibodies against the bipolar cells are present in patients' serum with MAR. ERG shows marked reduction of scotopic and photopic b-wave and preservation of a-wave. The amplitude and implicit time of the b-wave are abnormal. The visual prognosis is good and most patients maintain stable vision (29).

c. Bilateral Diffuse Uveal Melanocytic Proliferation

Bilateral diffuse uveal melanocytic proliferation (BDUMP) syndrome is a rare paraneoplastic disorder characterized by bilateral diffuse infiltration of the uvea by melanocytic tumors in the presence of an associated systemic malignant neoplasm arising from ovaries, uterus or lungs (30). In half of the cases, the ocular symptoms manifest before the diagnosis of an underlying malignancy. Ocular findings in BDUMP include: multiple subtle round and oval subretinal

yellow-orange lesions, multiple, slightly elevated, pigmented, and non-pigmented uveal melanocytic tumors with evidence of diffuse thickening of the uveal tract. Episcleral injection, cataract, vitritis, and exudative retinal detachment can also be seen (30).

There are many malignant conditions that can present as a masquerading syndrome, mimicking a chronic intraocular inflammation. The ophthalmologist may be the first to recognize this malignant, life-threatening disease. Malignancy and other diseases should be considered in cases of chronic uveitis that do not respond to aggressive steroid therapy. Any patient over 50 or 60 years of age who has a first episode of uveitis deserves a closer look for malignancy. Incorrect diagnosis and therapy of the malignant UMS may have severe consequences not only for vision but also for the life of the patient.

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Reprint requests to (adres do korespondencji):
Agnieszka Kubicka-Trząska, MD, PhD
Lea Street 244/7
30-133 Kraków

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