(37)

Non-malignant Uveitis Masquerade Syndromes

Zespół maskujący niezłośliwe 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 Uveitis Masquerade Syndromes (UMS) are a group of ocular diseases that mimic chronic intraocular inflammation. Many non-malignant conditions may result in an appearance mimicking an uveitis. The authors review most common non-malignant conditions which may be considered masquerades such as: retained intraocular foreign body, rhegmatogenous retinal detachment, myopic degeneration, pigment dispersion syndrome, ocular ischemic syndrome, infectious intraocular inflammation, retinitis pigmentosa, multiple sclerosis and drug and post-vaccination reactions.

Słowa klucze: zespół maskujący, przewlekłe zapalenie wewnątrzgałkowe.
Key words: masquerade syndrome, chronic intraocular inflammation.

Masquerade syndromes are disorders that occur with intraocular inflammation and are often misdiagnosed as a chronic idiopathic uveitis. Reports of masquerade syndromes are rare (1). The most common conditions that can masquerade as idiopathic uveitis are malignancies which were discussed in our paper "Malignant Uveitis Masquerade Syndromes" (submitted in "Klinika Oczna"). Among non-malignant diseases infectious endophthalmitis are the most common conditions mimicking as idiopathic intraocular inflammation (2). Other noninfectious masquerade disorders which can be misdiagnosed as uveitis include: intraocular foreign body, rhegmatogenous retinal detachment, pigment dispersion syndrome, ocular ischemic syndrome, retinitis pigmentosa, multiple sclerosis, drug and post-vaccination reactions. We discuss the common and different clinical manifestations of each masquerade disorder and its diagnosis.

Infectious intraocular inflammation

Differential diagnosis between infectious and non-infectious intraocular inflammation is the great challenge for an ophthalmologist. Unlike the other masquerade syndromes, initiating treatment with steroids in this group of intraocular inflammation can result in devastating consequences. It is one of the masquerade syndromes that should not be overlooked in any patient presenting with intraocular inflammation of unknown etiology. There are two forms of endophthalmitis masquerading as non-infectious inflammation: chronic postoperative endophthalmitis and endogenous endophthalmitis. Chronic postoperative endophthalmitis develops 4 weeks to years postoperatively and typically follows uneventful cataract extraction with a posterior chamber intraocular implant. It may rarely be precipitated by YAG-laser capsulotomy which releases the sequestrated organisms from the posterior capsule into the vitreous (3). The incidence of postoperative endophthalmitis following cataract surgery has been reported as being between 0.07% and 0.33% (4). The infection is caused most frequently by *Propionibacterium acnes* and occasionally *Staphylococcus epidermidis*. One of the signs considered to be a hallmark of the inflammation is the presence of a white plaque, usually located between the intraocular lens and the lens capsule (5). Diagnosis relies on isolation of the causative organism (4,5).

Endogenous endophthalmitis is an uncommon entity (2-8% of all forms of endophthalmitis) (6). The infection is caused by haematogenous spread of bacteria or fungi from a site of infection in the body or from contaminated intravenous catheters or needles. Potential causes include septic arthritis, urinary tract infection, endocarditis, liver abscess, infected skin wounds. Often the primary site of infection is occult. The most frequent pathogen is *Bacillus cereus* although a wide variety of organisms have been implicated including *Proprionibacterium acnes* and streptococci (4). The infecting organisms enter the uveal or retinal circulations and lodge in capillaries where they establish a septic focus. Subsequently they break through into the aqueous and vitreous. Immune compromised patients are particularly susceptible to rapid involvement of the vitreous. Both eyes are involved in about 25% of cases. The presenting symptoms and signs are similar to those of uveitis of autoimmune causes. Classically, endogenous endophthalmitis from bacteria presents more explosively than does fungal infection. Diagnosis relies on isolation of the causative microbes. The vitreous biopsy or the anterior chamber aspirate are required and in selected cases the retinal biopsy may be necessary (4).

Intraocular foreign body

Retained intraocular foreign body (IOFB) can cause various degree of intraocular inflammation. Persistent anterior or posterior uveitis is one of the most common complications associated with IOFBs. Therefore IOFB should always be considered in the differential diagnosis of chronic uveitis, specially when

the uveitis is refractory to treatment. Depending on the type of the IOFB there are three major pathophysiologic mechanisms of the eye injury: mechanical, chemical or toxic and inflammatory (2). Nonorganic and nonmagnetic substances (stone, glass, porcelain, gold, silver), cause nonspecific inflammation by mechanical irritation to the ocular tissues. The mechanical effect is essentially exudative and fibroplastic in order to isolate and encapsulate the foreign body. Metal materials (iron, copper, lead, zinc), cause the chemical damage due to electrolytic dissociation of the metal or reaction with tissue fluids, usually by oxidation. Highly toxic metal ions such as iron and cooper lead to severe damage of ocular tissues called siderosis and chalcosis, respectively. Organic materials can produce a considerable tissue-reaction of the foreign body granulomatous type. The pathologic reaction presents with a low-grade chronic inflammatory response of a fibroblastic and proliferative nature (7). An accurate and detailed history is essential for making the correct diagnosis. Complete and thorough ophthalmic examination is always required. Special tests including radiography, computed tomography (CT), ultrasonography are helpful in the detection and localization of suspected IOFB. Magnetic resonance imaging (MRI) can be useful for detection organic materials, glass or plastic IOFBs, but MRI is contraindicated for metallic IOFBs because of the risk of their intraocular movement. ERG and EOG testing have been used to assess the degree of ocular injury from metallosis (8).

Rhegmatogenous retinal detachment

Some degree of intraocular inflammation is associated with rhegmatogenous retinal detachment (RRD) which may present as anterior and/or posterior uveitis and sometimes as panuveitis (9). Usually slight flare and cells in the anterior chamber and vitreous are common in eyes with RRD. In longstanding RRD intraocular inflammation may be severe with the presence of posterior synechiae, debris in the vitreous, detachment of the ciliary body and choroid with hypotony. All cases of persistent ocular inflammation with relative hypotony and a substantial number of vitreous cells should be viewed with a high index of suspicion for a possible underlying RRD. Sometimes longstanding RRD can also present as an anterior cellular reaction with secondary elevation of intraocular pressure – Schwartz' syndrome (10). In these cases if the detachment is not detected, the patient may also be incorrectly treated for uveitis or glaucoma. Misdiagnosis can be avoided by a detailed ophthalmic history and thorough ocular examination completed with ultrasonography.

Pigment dispersion syndrome

Pigment dispersion syndrome (PDS), typically affecting young white men with myopia, is characterized by release of pigment from the pigment epithelium of the iris or ciliary body in both eyes with attendant deposition of pigment on intraocular structures such as cornea, the trabecular meshwork, the iris, the lens. The dispersion of particles into the anterior chamber can mimic the presence of inflammatory cells. Pigment particles are often seen floating in the anterior chamber especially following pupillary dilation and they may be mistaken for inflammatory cells in a course of anterior uveitis (11). Iris atrophy can mimic herpes simplex and herpes zoster uveitis (2). However in viral infection the atrophy is sectoral while in PDS the iris atrophy is localized at the midperiphery of the iris. PDS should always be suspected when the pigment deposition is in multiple location in both eyes, with midperipheral iris atrophy and heterochromia, normal or elevated intraocular pressure, keratic precipitates in a central, vertical, spindle-like pattern and heavily pigmented trabecular meshwork.

Ocular ischemic syndrome

Ocular ischemic syndrome (OIS) is a rare condition of chronic vascular insufficiency in which abnormalities may occur in both anterior and posterior segment of the eye, which may mimic intraocular inflammation. The major cause of OIS is a carotid artery stenosis or obstruction (12). Pain, red eye, anterior chamber cells and flare with extensive peripheral anterior synechiae associated with rubeosis are common manifestation of the advanced form of this disorder. Posterior segment changes include: peripheral retinal haemorrhages, peripheral microaneurysms, narrowed retinal arteries, optic disc and retinal neovascularization (13). Diagnosis can usually be made clinically, based on a detailed medical and ocular history, complete ophthalmic examination and carotid artery evaluation. Unilateral visual loss and the presence of characteristic ischemic symptoms in the eye of an elderly person are all important clues to suggest the diagnosis of OIS. Laboratory and ancillary testing including fluorescein angiography, ERG, duplex ultrasonography, carotid Doppler ultrasnography, carotid arteriography, intravenous digital substraction angiography and ophthalmodynamometry studies are helpful in establishing the definitive diagnosis of OIS (2,13).

Retinitis pigmentosa

Retinitis pigmentosa (RP) is a group of hereditary retinal degenerative diseases characterized by progressive degeneration of retinal photoreceptors with associated pigmented epithelial changes which manifest as bilateral night blindness, progressive visual field loss and abnormal electroretinogram (ERG). In some patients with RP the vitreous changes and cystoid macular edema may be the earliest findings (14). In these cases the inflammation associated with RP can masquerade as idiopathic uveitis, especially when RP occurs as an isolated case with a negative family history (50% of all cases), or in atypical cases with minimal retinopathy (2). Because the classification of RP is complicated and the clinical features associated with RP are various at different stages, any inflammation involving both eyes with subtle retinal pigmented changes or macular edema should be highly suspected as a masquerade syndrome.

Multiple sclerosis

Ocular signs and symptoms can be the first clinical manifestation of multiple sclerosis (MS). Intermediate uveitis is the form of ocular inflammation most commonly encountered in patients with MS (15). Patients with MS develop a granulomatous anterior uveitis with the presence of mutton-fat keratic precipitates, in contrast to patients with idiopathic intermediate uveitis who have minimal anterior segment inflammation (16). The periphlebitis is most frequently located at the posterior pole and there is no macular edema in contrast to idiopathic intermediate uveitis. Optic neuritis may either precede or follow the

ISSN 0023-2157 Index 362646

onset of intermediate uveitis (17). In rare cases granulomatous iridocyclitis with iris nodule formation and posterior uveitis may be present. Diagnosis of MS is based on clinical criteria including a reliable history of at least two episodes of neurologic deficit and objective clinical signs of lesions at more than one site within the CNS. An MRI, examination of the cerebrospinal fluid and evoked visual potentials are helpful in establishing the diagnosis of MS (2).

Drug and post-vaccination reactions

There are many medications; drugs and vaccines that may cause uveitis, however drug-induced uveitis is a rare event (18).

Drugs inducing intraocular inflamation include systemically, topically administrated drugs, substances injected intraocularly and some vaccines (Tab. I).

The drug can cause direct toxicity by itself or through its metabolities (19). A drug can also cause uveitis by several indirect mechanisms, mainly by stimulation of the immune system and production of antidrug antibodies. It is also possible that the drug nonspecifically stimulates the immune system acting as an adjuvant. Some drugs have a high affinity for melanin and they can also induce the release of toxic free radicals – these can induce the intraocular inflammation due to enhanced intrinsic uveitogenicity of melanin and free radicals toxicity by themselves (19). Uveitis induced by drugs is characterized most frequently by cellular infiltration in the anterior chamber and rare in the vitreous. Anterior uveitis is usually nongranulomatous. In the vitreous the cell reaction is usually mild (2). There is usually an absence of retinal or choroidal lesions. Drugs inducing uveitis by systemic routes can produce both unilateral and bilateral inflammation. Drug-induced uveitis is almost always reversible within weeks of cessation of the medication and the institution of topical treatment of the inflammation (2).

Knowledge of the clinical features of each disease, the possible masquerade syndromes, and the diagnosis as well as the differential diagnosis between an ocular inflammatory disorder and other ocular or systemic diseases is important for making a correct diagnosis.

"We see only what we look for.
We look for only what we know".
Johann Wolfgang Göthe

Praca została przedstawiona w formie wykładu na I Międzynarodowym Sympozjum i Kursie: „Postępy w diagnostyce i leczeniu zapaleń błony naczyniowej", które odbyły się w Krakowie w dniach 24-26.05.2007 r.

Medication	Type of intraocular inflammation and other clinical signs
Systemic drugs:	
Antiproteases	Anterior
Biphosphonates	Anterior, scleritis, episcleritis
Chlorpromazine	Anterior
Cidofovir	Anterior
Contraceptives	Anterior, retinal vasculitis
Diethylcarbamazine	Anterior, chorioretinitis
Ibuprofen	Anterior
Rifabutin	Anterior, vitritis, retinal vasculitis
Streptokinase	Anterior
Sulfonamides	Anterior
Topical drugs:	
Beta-blokers	Anterior
Coriticosteroids	Anterior
Latanoprost	Anterior, CMO
Mitomycin C	Anterior
Anaestetics	Anterior
Intraocular injected substances:	
Antibiotics (Amphotericin, bacitracin, tetracycline)	Anterior
Cidofovir	Anterior
Air	Anterior
Perfluorocarbons	Anterior
Silicone oil	Anterior
Vaccines:	
Influenza	Anterior
Hepatitis B	Anterior, vitritis, optic neuritis
PPD skin test	Acute multifocal placoid epitheliopathy

Tab. I. Drugs and post-vaccinations reactions.
Tab. I. Reakcja zapalna oka na leki i szczepionki.

References:

1. Rothova A, Ooijman F, Kerkhoff F, Van Der Lelij A, Lokhorst HM: *Uveitis masquerade syndrome*. Ophthalmology 2001, 108(2), 386-399.
2. Yao L, Foster S: *Nonmalignant, Noninfectious Masquerade Syndromes.* [in]: Foster & Vitale: Diagnosis and treatment of uveitis, chapter 50, 537-571, W.B. Saunders Company, Philadelphia, 2002.
3. Lundstrom M, Wejde G, Stenevi U, Thorbum W, Montan P: *Endophthalmitis after cataract surgery: a nationwide prospective study evaluating incidence in relation to incision type and location.* Ophthalmology 2007, 114(5), 866-870.
4. Samson CM, Foster CS: *Masquerade Syndromes: endophthalmitis.* [in]: Foster & Vitale: Diagnosis and treatment of uveitis, chapter 49, 528-536, W.B. Saunders Company, Philadelphia, 2002.
5. Posenauer B, Funk J: *Chronic postoperative endophthalmitis caused by Propionibacterium acnes*. Eur J Ophthalmol 1992, 2, 94-97.
6. Okada AA, Johnson RP, Liles WC, D'Amico DJ, Baker AS: *Endogenous bacterial endophthalmitis. Report of a ten-year retrospective study*. Ophthalmology 1994, 101, 832-838.
7. Waheed NK, Young LH: *Intraocular foreign body related endophthalmitis*. Int Ophthalmol Clin 2007, 47(2), 165-171.
8. De Souza S, Howcroft MJ: *Management of posterior segment intraocular foreign bodies: 14 years' experience*. Can J Ophthalmol 1999, 34(1), 23-29.
9. Ivanisevic M: *The natural history of untreated rhegmatogenous retinal detachment.* Ophthalmologica 1997, 211(2), 90-92.
10. Matsuo N, Takabatake M, Ueno H, Nakayama T, Matsuo T: *Photoreceptor outer segments in the aqueous humor in rhegmatogenous retinal detachment*. Am J Ophthalmol 1986, 101(6), 673-679.
11. Tugal-Tutkun I, Urgancioglu M: *Bilateral acute depigmentation of the iris.* Graefes Arch Clin Exp Ophthalmol 2006, 244(6), 7427-746.
12. Bennett LW: *Ocular ischemic syndrome as initial manifestation of bilateral carotid occlusive disease.* J Am Optom Assoc 1997, 68(4), 250-260.

13. Brown GC, Magargal LE: *The ocular ischemic syndrome. Clinical, fluorescein angiographic and carotid angiographic features.* Int Ophthalmol 1988, 11(4), 239-251.
14. Nagpal A, Biswas J: *Pseudouveitis – analysis of cases misdiagnosed as posterior uveitis.* Ocul Immunol Inflamm 2006, 14(1), 13-20.
15. Zein G, Berta A, Foster CS: *Multiple sclerosis-associated uveitis.* Ocul Immunol Inflamm 2004, 12(2), 137-142.
16. Nussenblatt RB, Whitcup SM, Palestine AG: *Intermediate uveitis.[in]: Uveitis. Fundamentals and Clinical Practice*. Second ed., chapter 20, pp 279-289, St.Louis, Mosby, 1996.
17. Malinowski SM, Pulido JS, Folk JC: *Long term visual outcome and complications associated with pars planitis.* Ophthalmology 1993, 100, 818-825.
18. Moorthy RS, Valluri S, Jampol LM: *Drug-induced uveitis*. Surv Ophthalmol 1998, 42, 557-570.
19. Koneru PB, Lien EJ, Koda RT: *Oculotoxicities of systemically administered drugs.* J Ocul Pharmacol 1986, 2, 385-404.

Praca włynęła do redakcji 20.12.2007 r. (1006)
Zakwalifikowano do druku 26.03.2008 r.

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

ISSN 0023-2157 Index 362646