Clinical features of secondary retinal vasculitis

Aspectos clínicos de vasculitis retinianas secundarias

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Abstract

Secondary retinal vasculitis are unusual ocular manifestations of several autoimmune diseases, such as granulomatosis with polyangiitis, Behcet disease, sarcoidosis, systemic lupus erythematosus, and multiple sclerosis, among others. As a consequence of systemic repercussions, the correct diagnosis is of greater importance. The most frequent ophthalmological symptoms are blurry vision and floaters. In some cases, highly suggestive ophthalmological signs of certain diseases might be presented, such as retinal periphlebitis also known as "candle wax drippings" image of sarcoidosis and the hypophion in Behcet disease. Systemic manifestations are essential for a correct diagnosis; therefore, main features of the frequently involved diseases shall be identified.


Resumen

Las vasculitis retinianas secundarias son manifestaciones oculares poco frecuentes de diversas enfermedades con componente autoinmunológico, como granulomatosis con poliangitis, enfermedad de Behcet, sarcoidosis, lupus eritematoso sistémico y esclerosis múltiple, entre otras. Debido a las repercusiones sistémicas el diagnóstico correcto es de mayor importancia. Los síntomas oftalmológicos más frecuentes son visión borrosa y miodesopsias. En algunos casos se observan signos oftalmológicos altamente sugestivos de ciertas enfermedades como la imagen de periflebitis retiniana en «gota de cera» de la sarcoidosis y el hipopion en la enfermedad de Behcet. Las manifestaciones sistémicas son esenciales para el diagnóstico por lo cual se deben reconocer las principales características de las enfermedades frecuentemente involucradas.

The term retinal vasculitis refers to the inflammation of retinal arteries or veins of autoimmune, infectious, neoplastic, pharmacological, or idiopathic etiology (Table 1). Primary vasculitis refers to a retinal vasculitis with exclusive involvement of retinal vasculature without evidence of associated systemic disease; while secondary vasculitis is a vasculitis associated with a systemic disease.

Secondary vasculitis can cause blurred vision and floaters, occasionally scotomas, and some cases may be asymptomatic. The characteristic ophthalmological sign is vascular sheathing (perivasculitis); meaning the perivascular accumulation of inflammatory granulomatous material that gives an impression of “candle wax drippings.” Vasculitis may be occlusive (Fig. 1), with data of retinal ischemia, punctate hemorrhages, and cotton wool spots. Chronic changes comprise arteriovenous shunts, cystic macular edema, or choroidal neovascularization.

In all cases, infectious etiologies such as tuberculosis, syphilis, and currently, Lyme disease and “cat scratch disease” should be ruled out. After excluding these diagnoses, the possibility of vasculitis of probable autoimmune origin will be considered, which, as already mentioned, can be primary or secondary.

Within the spectrum of secondary retinal vasculitis, the diseases listed below should be ruled out.

### Systemic Lupus Erythematosus

Multisystemic autoimmune disease, it may affect any organ and connective tissue, it presents with remissions and relapses.

### Epidemiology

It is more common in Africans and Asians; the main complications occur in Caucasians, the highest prevalence is in Italy, Spain, and in the Afro-Caribbean population of the United Kingdom. The age of presentation is from late adolescence to 40 years of age, and it is 9 times more common in women associated with HLA-A1, B8, and DR3.

### Systemic manifestations

Multisystemic affection is highly variable. Non-erosive arthritis may occur, predominantly in proximal metacarpophalangeal and interphalangeal joints, wrists and knees; mucocutaneous disease (occurring as malar rash, discoid rash, photosensitivity, or painless oral ulcers); hematological disorders: cytopenias and/or thrombophilia; renal alterations manifested by proteinuria and urinary casts; and central nervous system disease: cognitive dysfunction, organic brain syndrome, delirium, psychosis, seizures, headache, chorea, and peripheral neuropathy. The classic triad of hematological alterations, mucocutaneous disease, and malar rash in women of reproductive age should rule out this diagnosis.

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**Table 1. Causes of secondary retinal vasculitis by etiology**

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Associated with neurological diseases</th>
<th>Associated with neoplasms</th>
<th>Autoimmune</th>
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</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>Multiple sclerosis</td>
<td>Paraneoplastic</td>
<td>Sarcoidosis</td>
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<tr>
<td>Syphilis</td>
<td>Lyme’s disease</td>
<td>Ocular lymphoma</td>
<td>Behcet’s disease</td>
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<tr>
<td>Cat-scratch disease</td>
<td>Susac’s syndrome</td>
<td>Leukemia</td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Toxoplasmosis</td>
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<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Acute retinal necrosis</td>
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</tbody>
</table>

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**Figure 1. Retinal photography with occlusive vasculopathy of the inferior temporal arcade.**
Ocular manifestations

They occur in up to 33% of cases and the most frequent is keratoconjunctivitis sicca. Ocular manifestations may arise as orbital, scleral and episcleral alteration, corneal epitheliopathy, peripheral ulcerative keratitis, choroidopathy, or lupus retinopathy (cotton wool spots, perivascular hard exudates, retinal hemorrhages, and vascular tortuosity). In 29% of cases, vasculitis may occur with cotton wool spots with or without hemorrhage, which is considered a sign of disease activity. Another form is occlusive arteriolar vasculitis, which may be bilateral and has been associated with central nervous system involvement. The resulting ischemia favors neovascularization, vitreous hemorrhage, and eventually tractional retinal detachment.

Diagnosis

For diagnosis, 4 of the following 11 criteria are required: malar rash, discoid rash, photosensitivity, oral ulcers, non-erosive arthritis, serositis, and renal dysfunction, neurological disorders such as psychosis or epileptic seizures, hematological disorders, immunological disorders (anti-DNA, anti-S, and false positive venereal disease research laboratory), and presence of antinuclear antibodies.

Treatment

Corticosteroids are the most effective short-term therapy for systemic lupus erythematosus. Due to the frequent association of ocular alterations with central nervous system alterations, the use of intravenous corticosteroids at high doses has been recommended to prevent morbidity and mortality. Periocular steroids can also be used in unilateral or asymmetric disease. Because prolonged use of corticosteroids at high doses is associated with an important number of ocular complications such as glaucoma (5-19%) and cataract, immunosuppressants should be used for long-term therapy; the use of intravenous bolus of methotrexate, azathioprine, mycophenolate mofetil, cyclosporin A, and cyclophosphamide has been reported. The prognosis is bad for long-term function and the probability of survival varies according to the degree of organic involvement, especially renal and central nervous system. Anticoagulants and acetylsalicylic acid can be added when there are positive antiphospholipid antibodies due to the increased risk of occlusive vasculopathy, and they are also used to stabilize retinal disease and prevent vascular events. The use of antimalarials such as chloroquine or hydroxychloroquine has been described since they are very effective in reducing future reactivations with fewer side effects compared to alkylating agents; however, macular damage may occur due to the use of these drugs. There are reports describing the use of biological agents such as rituximab in the management of these patients. The patients with lupus should not undergo refractive surgery since there is a risk of post-operative ectasia, a fact that has been demonstrated when studying the changes in the biomechanical properties of the cornea.

Multiple sclerosis (MS)

Chronic demyelinating disease of the central nervous system characterized by episodes of optic neuritis, eye movement alterations, and multiple associated systemic neurological symptoms. It affects several structures of the eye.

Epidemiology

It presents in young adults between 20 and 40 years, affecting more women than men with a 3.5:1 ratio and a prevalence of 1.5 per 100,000 in the Mexican population. It has been described that 1% of cases can develop intraocular inflammation.

Systemic manifestations

They are caused by the demyelinating process; the symptoms vary since the location and intensity of each flare can be different. Paresthesias, spasticity, sexual, urinary, and intestinal dysfunction have been described. Trigeminal neuralgia, facial myokymia, constitutional symptoms, depression, and transverse myelitis have also been reported. There is a well-established association between the increase in body temperature, due to intrinsic or extrinsic factors, and the severity of symptoms; this is known as Uhthoff’s phenomenon.

Ocular manifestations

About 50% of patients with MS and ocular inflammation have optic neuritis. The most frequently reported type of uveitis is the intermediate, described in up to 78% of cases: in 12.5% of affected eyes, vasculitis may be observed, mainly with venous involvement and anterior uveitis is seen only in 10%. It has been reported that 15% of intermediate uveitis are associated with...
MS. Internuclear ophthalmoplegia and nystagmus have also been described. The complications associated with vasculitis are vascular obstructions, retinal neovascularization, and vitreous hemorrhage. In retinal fluorangiography, periphlebitis, areas of focal retinal ischemia due to retinal arterioles non-perfusion, and hyperfluorescent arteriolar walls may be observed.

**Diagnosis**

The diagnosis is clinical, confirmed by the presence of areas of periventricular demyelination observed by magnetic resonance imaging (T2/gadolinium). McDonald criteria are used for diagnosis (Table 2).  

**Treatment**

Intravenous bolus of corticosteroids for acute episodes of the disease is a therapeutic alternative. Interferon, classically used for MS with central nervous system involvement, has also been described in recent years for ocular involvement, however, there are no studies proving its effectiveness.

**Behcet’s disease**

Chronic multisystem inflammatory disease characterized by three recurrent manifestations: oral ulcers, genital ulcers, and uveitis.

**Epidemiology**

It is more frequent in Japanese and inhabitants of the eastern areas of the Mediterranean Basin, affects men and women equally, predominantly young adults; it has been described that in males its evolution is more aggressive. It has been associated with histocompatibility antigens HLA DR5 and B51, which implies an immunogenic predisposition. The estimated prevalence is of 0.33 cases per 100,000.

**Systemic manifestations**

Recurrent oral ulcers, with three or more episodes per year (first manifestation of the disease), ulcers with a yellowish necrotic base that heal in 1-2 weeks without scarring. Genital ulcers are also painful; they occur in 80% of cases, their appearance is similar to oral ulcers with the difference that they leave a scar. In female, the involvement of the vulva may be subclinical; in male, the scrotum is usually affected. Dermal changes include folliculitis (80%), erythema nodosum which is more common in female, affects mainly legs, can also be painful (50%); and the acneiform eruptions are more frequent in male, occurring mainly in chest and extremities. Arthritis is observed in up to 60% of patients, is more common in knees, ankles, wrists, and elbows. It is asymmetric, non-deforming and can affect one or several joints.

Aneurysms of the pulmonary artery may occur; this complication is fatal and usually affects male. Venous involvement is more common, presenting as a superficial thrombophlebitis, although it can affect medium-sized veins. The clinical manifestations depend on the site involved. The gastrointestinal tract (esophagus and ileocecal region) and the genitourinary tract (sterile urethritis, epididymitis, and neurogenic bladder) can also be affected. Renal (nephritis and glomerulonephritis) and cardiac involvement (coronary vasculitis, pericarditis, and myocarditis) have been reported.

Neurological manifestations occur in late stages of the disease; they are usually located in the parenchyma or in the brain stem, commonly affecting memory or behavior. Less common manifestations are infarction secondary to vasculitis or thrombosis, meningoencephalitis or demyelination.

**Ocular manifestations**

They occur in up to 70-80% of patients. Ocular involvement is bilateral in 78.1% of patients. In 10-15%
of the cases, systemic disease is diagnosed based on the ocular disease, although in most cases, oral or genital ulcers occur 3-4 years before. Anterior uveitis (48%) typically presents with hypopyon that moves around in accordance with the patient's head position (26%); the hypopyon appears and disappears quickly without leaving sequelae. Pain, conjunctival hyperemia, and photophobia may occur. In the posterior pole, the characteristic lesion is retinal vasculitis, which affects both arteries and veins. Retinal hemorrhages, edema, exudates, and infiltrates are observed, as well as papillitis. Vasculitis can cause thrombosis with subsequent retinal ischemia; retinal vein branch obstruction may also be found (68%). Panuveitis is the most common presentation form. In severe cases, retinal neovascularization and neovascular glaucoma may be found.

Recurrent inflammatory episodes eventually cause retinal and papillary atrophy.

**Diagnosis**

It is clinical and according to the international criteria for Behcet’s disease, three points are required for diagnosis (Table 3). The differential diagnoses of Behcet's disease with ocular and systemic manifestations are syphilis, systemic lupus erythematosus, HIV, and herpes, mainly in immunosuppressed patients.

**Treatment**

The purpose of treatment is to suppress inflammation, reduce the frequency and severity of relapses, and limit retinal involvement. It must be aggressive when there is ocular involvement to avoid serious visual complications. The European league against rheumatism described new treatment guidelines. Systemic anti-inflammatory treatment with corticosteroids can be used for treating acute episodes, but for chronic use, systemic immunosuppressants such as cyclosporine are required. Similarly, periocular steroid injections may be used. Biological agents have recently been used to prevent visual loss in severe cases of uveitis secondary to Behcet’s disease; however, there are no controlled clinical studies. Anti-tumor necrosis factor-alpha monoclonal antibody, infliximab (5 mg/kg infusion), has shown good results in patients with Behcet’s uveitis resistant to conventional treatment, severe flares or at high risk of visual loss. Interferon alpha is effective in 90% of cases.

**Prognosis**

The prognosis for visual loss (>0.1) in 5-10 years is from 21% to 10% in men and 30% to 17% in women. Young men have a worse visual prognosis. The incidence of visual loss of 20/200 or worse is 0.09 per year.

**Sarcoidosis**

It is a multisystemic inflammatory disease of unknown etiology that manifests with non-caseating granulomas predominantly in lungs and lymphatic nodules.

**Epidemiology**

It can appear at any age, but it affects mainly patients from 20 to 39 years of age. The highest incidence is in Europe, with 5-40 cases per 100,000. Systemic vasculitis in sarcoidosis may be responsible for 1.4% of cases of retinal vasculitis.

**Systemic manifestations**

Asymptomatic disease may occur in up to 5% of cases. Pulmonary manifestations (exertional dyspnea, cough, and chest pain) occur in 50% of cases. Löfgren’s syndrome (polyarthralgia, bilateral hilar adenopathy, and fever) is more commonly observed in Scandinavian
patients than in African-Americans or Japanese. The most frequent dermatological manifestations are erythema nodosum, lupus pernio, and violaceous rash on the cheeks and nose. Cardiac involvement is characterized by ventricular tachyarrhythmias in 15% of patients. Bone and cardiovascular involvement, as well as lymphocytic meningitis and cranial nerve palsy, have been reported less frequently.

**Ocular manifestations**

Eye involvement occurs in up to 60% of patients with systemic sarcoidosis. Affection of the lacrimal gland is found in a third of the patients, occurring as palpable painless edema, which can cause keratitis sicca. If the orbital cavity is affected, the most common manifestation is proptosis.

Bilateral granulomatous anterior uveitis is the most common presentation. In 25-30% of patients, posterior pole manifestations are vitreous opacities (snowballs/string of pearls), macular edema, choroidal granulomas, optic nerve granuloma (Fig. 2), and retinal neovascularization. Retinal vasculitis in the form of periphlebitis is characteristic of the disease (8.7%). In some cases, it has the appearance of “candle wax drippings,” but commonly only sheathing is observed. In 38% of ocular sarcoidosis cases, systemic sarcoidosis can be diagnosed, mainly in women older than 60 years with chronic uveitis. Bilateral ocular disease has been reported in up to 84% of cases with panuveitis (Fig. 2).

**Diagnosis**

Currently, there are precise criteria for ocular sarcoidosis resulting from the first “International Workshop on Ocular Sarcoidosis” (Tables 4 and 5). There are diagnostic tests for signs of ocular sarcoidosis as follows:

- Negative tuberculin test in a previously vaccinated patient or with a previous positive test.
- Elevated levels of angiotensin-converting enzyme or serum lysozyme.
- Chest X-ray with bilateral hilar infiltrates.
- Liver enzymes alteration.
- Positive chest computed tomography in a patient with negative radiography.

In patients without non-caseating granulomas or in whom the chest radiograph is negative (Table 6) and

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<thead>
<tr>
<th>Table 4. Diagnosis of ocular sarcoidosis according to the “International Workshop on Ocular Sarcoidosis”</th>
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<tbody>
<tr>
<td><strong>Definitive diagnosis of ocular sarcoidosis</strong></td>
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<tr>
<td>Presumed ocular sarcoidosis</td>
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<tr>
<td>Probable ocular sarcoidosis</td>
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<tr>
<td>Possible ocular sarcoidosis</td>
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<tr>
<th>Table 5. Signs of ocular sarcoidosis</th>
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<tr>
<td>Small retrokeratic or mutton-fat precipitates, iris with Koepp and Busacca nodules</td>
</tr>
<tr>
<td>Trabecular meshwork nodules or tent-shaped anterior synchiae</td>
</tr>
<tr>
<td>Snowball or string of pearls type vitreous opacities</td>
</tr>
<tr>
<td>Multiple peripheral chorioretinal lesions (active or atrophic)</td>
</tr>
<tr>
<td>Nodular or segmented periphlebitis with “candle wax drippings” and/or retinal macroaneurysms in inflamed eyes</td>
</tr>
<tr>
<td>Optic disc nodules, granuloma or solitary choroidal nodule</td>
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<tr>
<td>Bilateral involvement</td>
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![Figure 2. Choroidal nodule (A) and optic nerve nodule (B) in ocular sarcoidosis.](image)
sarcoidosis is suspected, chest computed tomography can be performed (Table 7).  

### Treatment

Corticosteroids are the basis of treatment, with administration of oral prednisone 1 mg/kg/day. When there is ocular involvement, periorcular steroids can be used. Immunosuppressive agents such as methotrexate, cyclophosphamide, and azathioprine may be used. Recent studies use antimycobacterial therapy (levofloxacin, ethambutol, azithromycin, and rifampicin) for the treatment of ocular and cutaneous sarcoidosis, with good results.

### Prognosis

When there is ocular involvement, after 10 years, 54% of patients maintain their visual acuity and 4.6% have a vision acuity worse than 20/100 in both eyes; 51% require oral steroids for the treatment of uveitis and 11% require the use of immunosuppressants. At the time of ocular involvement, 37% of the cases have lung disease. Frequent eye complications include posterior synechiae, cataract, and glaucoma; other complications are posterior pole changes and peripapillary and subfoveal choroidal neovascularization. In systemic disease, 30-50% of the cases improve without treatment in a period of 3 years; about 20% of patients with pulmonary disorders will have permanent lung damage. The total mortality rate for sarcoidosis is 5%. The causes of death are pulmonary hemorrhage, heart failure, and pulmonary fibrosis.

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### Conflicts of interest

The authors declare no conflicts of interest.

### References

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