Autoimmunity Reviews 16 (2017) 237–243

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Characterization of isolated retinal vasculitis. Analysis of a cohort from a single center and literature review☆

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ARTICLE INFO

Article history:
Received 24 October 2016
Accepted 6 November 2016
Available online 27 January 2017

ABSTRACT

Introduction: Isolated retinal vasculitis (IRV) is an inflammatory condition of unknown etiology confined to the retinal vessels. In contrast to secondary retinal vasculitis (RV), IRV has not been well characterized.
Objective: To describe and characterize isolated forms of RV.
Methods: We performed a retrospective review (2006–2016) of IRV patients from a multidisciplinary Uveitis Unit. RV diagnosis was based on funduscopic and fluorescein angiography findings. To distinguish between secondary RV and IRV, evaluations included clinical assessment, several inflammatory, autoimmune and microbiological laboratory markers, and a chest radiography. Ophthalmological features at disease onset, therapeutic interventions, ocular relapses, visual outcomes and laboratory findings were recorded. Our cases were subsequently compared with those from a literature review.
Results: Among 192 patients with RV, 11 (5.7%) were diagnosed with IRV. Seven patients with initially presumed IRV were reclassified as secondary after further evaluation. IRV generally affected adult women. Bilateral ocular involvement and retinal phlebitis were common findings. 72% of patients presented with visual loss, which was severe in 27%. Treatments used included systemic glucocorticoids (82%), additional immunosuppressive agents (27%), intravitreal therapy (37%), panretinal photocoagulation (37%) and pars plana vitrectomy (26%). The annual relapse rate was 0.46. Although final visual acuity was considered good in 86%, 45% experienced worsening and only 27% improved.
Conclusions: IRV is a rare sight-threatening condition. Despite intensive local and systemic immunosuppressive treatment, visual improvement is observed in only 27% of cases. When IRV is suspected, a differential diagnosis excluding a systemic disease is always warranted. A multidisciplinary approach and a guided clinical, laboratory and imaging evaluation have proven to be useful to distinguish retinal single-organ vasculitis from secondary forms of RV.

Contents

Abbreviations: BCVA, best corrected visual acuity; IRV, isolated retinal vasculitis; RV, retinal vasculitis; MRI, magnetic resonance imaging; SRV, secondary retinal vasculitis; SUN, Standardization of Uveitis Nomenclature.

☆ Supported by the Ministerio de Economía y Competitividad (SAF 14/57708-R), co-funded by Fondo Europeo de Desarrollo Regional (FEDER), Unión Europea, Una manera de hacer Europa.

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http://dx.doi.org/10.1016/j.autrev.2017.01.006
1568-9972/

1. Introduction

Retinal vasculitis (RV) is defined by an inflammatory condition of the retinal vessels leading to vascular leakage, occlusion or rupture. The term "retinal vasculitis" generates controversy between ophthalmologists and other medical specialists [1]. While systemic vasculitis is frequently identified through histopathological demonstration of vascular inflammation [2,3], and given that a biopsy proving vessel wall inflammation in the retina is not feasible, an ophthalmologist recognizes RV based on the presence of perivascular infiltrates in the retina at funduscopic examination, which are subsequently confirmed by fluorescein angiography [1]. Of note, different non-vasculitic conditions may produce vascular abnormalities apparently indistinguishable with ophthalmological examination from those produced by vasculitic lesions (e.g. diseases producing endothelial damage, endoluminal immune-complex deposition, endovascular thrombosis or perivascular inflammation). Because resolving this diagnostic conundrum is not possible, several authors have suggested the term "retinal vasculopathy" be used instead to refer to visual and funduscopic changes suggestive of RV [4–9]. Along the present study, in agreement with the previous ophthalmological publications, we will use the term of "isolated retinal vasculitis".

RV, which is considered part of a posterior uveitis [10], occurs more frequently associated with or as part of other diseases (secondary RV [SRV]), such as infectious processes (e.g. human herpes viruses, *Toxoplasma gondii* and *Mycobacterium tuberculosis*), neoplastic disorders (e.g. ocular lymphoma, acute leukemia and paraneoplastic syndromes secondary to solid tumors), or systemic autoimmune or inflammatory diseases (e.g. Behçet's disease, sarcoidosis, systemic vasculitides, systemic lupus erythematosus, Crohn's disease, rheumatoid arthritis and multiple sclerosis), as well as ocular syndromes (e.g. pars planitis, Birdshot choroidopathy, Vogt-Koyanagi-Harada disease, Fuchs uveitis syndrome and IRVAN [idiopathic RV, aneurysms, and neuroretinitis] syndrome) [1]. Less often, RV may also occur in an isolated fashion, which is known as primary, idiopathic, isolated or single-organ vasculitis [3,11–13].

The initial diagnosis of isolated RV (IRV) should be conditional pending evaluation for secondary etiologies and other diseases that may mimic RV. In addition, there is also the concern that a condition that may initially appear to be IRV may later evolve to a generalized disease [11,14]. IRV outcomes have been sporadically reported with inconsistent results, varying from benign (with significant visual recovery) [15,16] to severe permanent visual loss [11,12]. Although SRV series have been widely reported, studies of IRV are scarce [11,12,15–18].

In our multidisciplinary Uveitis Unit, among all cases with RV, those initially considered to be isolated or undetermined, undergo a predefined diagnostic protocol that supports or refutes the diagnosis of single-organ vasculitis. In this study, we describe and characterize clinical, ophthalmological and therapeutic interventions, as well as visual outcomes in all patients diagnosed with IRV in our center. Other case series published in the literature were also reviewed.

2. Material and methods

We reviewed medical records of all patients diagnosed with RV in our multidisciplinary Uveitis Unit (Departments of Ophthalmology and Autoimmune Diseases, Hospital Clínic, Barcelona) from January 2006 to June 2016. The diagnosis of RV was based on funduscopic and fluorescein angiography findings, as previously described [1].

In RV patients in whom an associated disease was initially suspected (by clinical and/or ophthalmological findings), diagnostic tests were performed according to the primary suspected disease, and these patients were subsequently excluded from the study. In patients in whom an isolated or undefined vasculitis was initially considered (by clinical and ophthalmological findings, without having other features suggesting a possible association), a diagnostic work-up protocol coordinated by specialists in Ophthalmology, Autoimmune Diseases and Infectious Diseases was used in order to definitively rule out a systemic disease. This work-up protocol included: 1) Clinical history, physical examination and chest radiography; 2) Laboratory tests: complete blood cell counts, C reactive protein, erythrocyte sedimentation rate, hepatic enzymes, lactate dehydrogenase, creatinine, urinalysis and proteinuria determination; 3) Autoimmune markers: antinuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor and complement levels; 4) Microbiologic studies: serologic tests for the most common infectious etiologies, such as syphilis (treponemal and VDRL tests), human immunodeficiency virus (HIV) and hepatitis C and B virus; and the QuantiFERON-TB Gold In-Tube test (an interferon-gamma release assay) and/or tuberculin skin test (specially useful for patients with a suspected tuberculosis-induced RV); 5) Other specific tests of all categories could be also requested according to disease presentation and/or ophthalmological findings, and included determination of: a) immunological tests: anti-double stranded DNA, antiphospholipid antibodies, circulating cryoglobulins, angiotensin-converting enzyme levels; b) microbiologic tests: serologies for *Toxoplasma gondii*, virus herpes family, *Bartonella henselae* (cat scratch disease) and *Borrelia burgdorferi* (Lyme disease); c) imaging tests: chest computed tomography, brain magnetic resonance imaging (MRI), large vessel MRI-angiography; d) other tests: electromyogram, biopsies in tissues suspected to be involved by any systemic vasculitis.

Although in other single-organ vasculitides [3], and in previous studies on IRV [15,17,18], systemic involvement had to be excluded beyond six months of the vasculitis diagnosis, we considered the diagnosis of IRV to be established only after the patient had been followed for a minimal period of 12 months during which features of infection, malignancy or manifestations of any systemic disease or ocular syndrome did not occur. As previously defined by Rosenbaum et al. patients with idiopathic uveitis associated with certain component of involvement of the retinal vessels were not included as RV [1,14].

Demographic, clinical and therapeutic data collected included age, sex, visual manifestations, ocular complications, systemic and local treatments, surgical procedures, ocular relapses and visual outcomes during the follow-up. Relapse was considered when visual symptoms recurred, associated with an increase in vitreous cellularity and/or retinal vascular inflammation [16,18], which was followed by restarting or intensification of immunosuppressive therapy. Glucocorticoids and additional immunosuppressive drugs were used according to therapeutic guidelines in patients with ocular inflammatory disorders [19]. Intraocular glucocorticoids (intravitreal triamcinolone or intravitreal dexamethasone implant) were usually administered as coadjuvant to oral glucocorticoids in cases with important ocular inflammation and/or macular edema [20]. Intravitreal injections of bevacizumab (an anti-