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Case report

Vasculitic central retinal vein occlusion: The presenting sign of seronegative rheumatoid arthritis

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ABSTRACT

Purpose: To report the case of a patient who presented with a vasculitic central retinal vein occlusion (CRVO), which was the result of an undiagnosed systemic inflammatory condition, seronegative rheumatoid arthritis (RA).

Observations: The patient presented with reduced vision in the left eye and polyarthralgia. Fundoscopic examination revealed a central retinal vein occlusion (CRVO) with concurrent evidence of vasculitis. Work-up for polyarthralgia included comprehensive serologic testing for connective tissue disease, including Vectra® disease activity (DA) testing. Results of these studies confirmed the diagnosis of seronegative rheumatoid arthritis (RA). Systemic steroid therapy was initiated with subsequent anatomic and visual improvement.

Conclusions and importance: We hypothesize that the systemic inflammation—a hallmark of RA—led to the development of a vasculitic CRVO and, thus, the retinal manifestations served as the disease marker that prompted thorough work-up of the patient's disease, even in the face of initial seronegativity. This case serves as a reminder that, in the setting of CRVO and polyarthralgia, systemic inflammatory conditions must be considered as the underlying etiology. Further, this case report highlights our evolving understanding of the role that serologic markers play in the diagnosis and monitoring of RA.

1. Introduction

Rheumatoid arthritis (RA) is estimated to affect 0.8% of the world's population, making it the most common inflammatory arthritis [1]. It is characterized by a painful, persistent, and often symmetrical polyarthritis that primarily involves the synovial tissues. Additionally, RA can be categorized and broadly divided into two categories based on serology: seropositive RA and seronegative RA. Approximately 40% of seropositive RA patients experience extra-articular involvement of multiple organ systems, including the eyes [2]. Less is known about seronegative RA and its extra-articular features, but generally speaking seronegative RA is felt to be less aggressive, with fewer joint erosions and better response to treatment than seropositive RA [3]. The ophthalmic sequelae of RA vary widely and range from relatively benign findings, such as keratoconjunctivitis sicca and episcleritis, to serious vision-threatening conditions, including anterior scleritis, necrotizing scleritis, scleromalacia perforans, peripheral ulcerative keratitis and retinal vasculitis secondary to posterior scleritis [4].

1.1. Case report

Personal identifying information was removed from this report because informed consent to publish such information was not obtained. Our patient presented, in the sixth decade of life, with acute painless vision loss in the left eye that had progressed over two weeks. In addition, the patient had noticed new onset floaters. The patient had no past ocular, medical, surgical, or pertinent family history, was not taking any medications and at presentation (as well as on subsequent visits) had a normal blood pressure. Further questioning did reveal that the patient had been experiencing progressive joint stiffness of the wrists and hands for several months; these symptoms were most prominent in the morning and seemed to improve as the day progressed. The involved joints were mildly edematous and tender to the touch at the metacarpophalangeal joints of both hands, suggesting the presence of active synovitis. Despite the progressive nature of this pain, the patient had not sought medical attention and had not taken any

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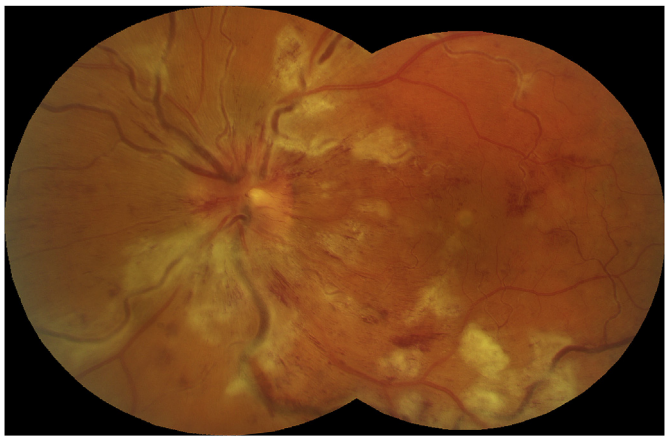

Fig. 1. Widefield color fundus photograph shows dilated and tortuous veins with scattered flame-shaped hemorrhages, cotton-wool spots and perivascular exudation.

medication to manage the pain. In an attempt to uncover a possible unifying etiology for the combination of polyarthralgia and decreased vision in the left eye, the patient was specifically asked about a history of hypertension, hyperlipidemia, hypercoagulable states, immunocompromised states and autoimmune disease; all of which the patient denied.

On ophthalmic examination, the patient's Snellen visual acuity (BCVA) was 20/20 in the right eye (OD) and count fingers (CF) at 2 feet in the left eye (OS). Intraocular pressures were 15 mm Hg OD and 16 mm Hg OS. Anterior segment examination was unremarkable. Importantly, no cell or flare was detected in the anterior chamber. Dilated fundus exam of the left eye showed vitreous cell, dilated and tortuous vessels with perivascular exudation, scattered flame-shaped hemorrhages and significant macular edema—all consistent with the diagnosis of a central retinal vein occlusion (CRVO) (Fig. 1). In the early phase, widefield fluorescein angiography (FA) demonstrated multiple venous filling defects with associated stretches of capillary non-perfusion (Fig. 2A). In the late phase (Fig. 2B), widefield fluorescein angiography was positive for venous staining and showed mild perivenous leakage. Spectral-domain optical coherence tomography (SD-OCT) detected extensive intraretinal fluid (between the outer nuclear layer and the ellipsoid zone), scattered intraretinal fluid in the other layers and mild vitritis (Fig. 3A). Examination of the OD was unremarkable. The patient was started on frequent difluprednate 0.05% drops in the OS, and a broad workup for inflammation and vaso-occlusive disease was initiated in conjunction with the Rheumatology service.

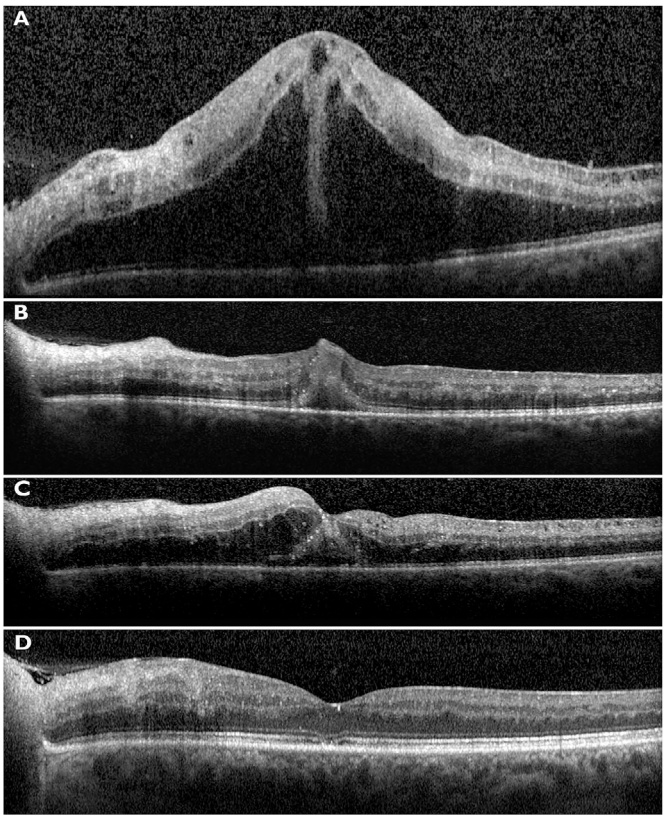

Fig. 3. **(A)** Spectral-domain optical coherence tomography (SD-OCT) at the time of presentation showed significant macular edema and vitreous cell; **(B)** On day three of the initial topical steroid therapy, SD-OCT showed marked improvement of the intraretinal fluid; **(C)** On day ten, the macular edema recurred despite continued topical therapy. Intravitreal ranibizumab was administered at this time. **(D)** At 3.5 months of monthly ranibizumab treatment, the patient's visual acuity improved to 20/30 and there was a resolution of the macular edema.

At three days' follow-up, the patient's VA OS had improved to 20/80 in the left eye, and there was marked improvement of the intraretinal fluid on SD-OCT without any steroid mediated intraocular pressure increase (Fig. 3B). Based on this response, a sub-Tenon injection of triamcinolone acetonide was used to supplement the topical therapy. Surprisingly, however, the initial work-up for occlusive vascular disease was largely uninformative: aside from a homogenously-positive anti-nuclear antibody (ANA; Titer 1:80) and a mildly elevated Erythrocyte Sedimentation Rate (ESR; 29 mm/h). Other antibodies such as rheumatoid factor (RF), anti-

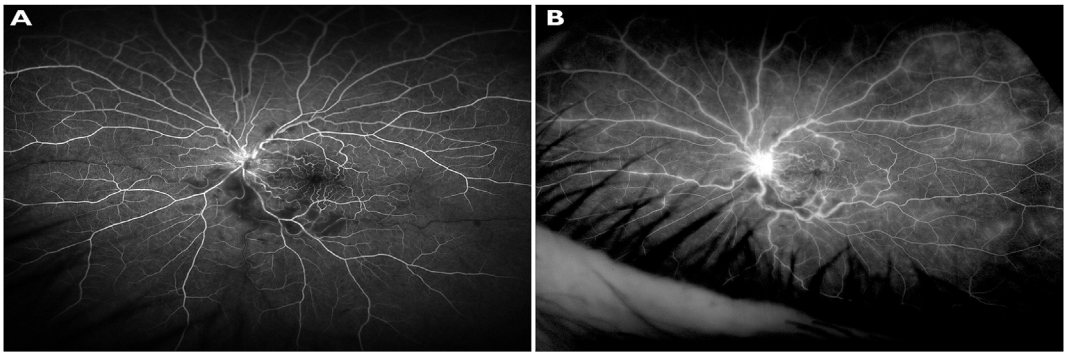

Fig. 2. **(A)** Early phase widefield fluorescein angiography showed capillary non-perfusion. **(B)** Late phase widefield fluorescein angiography showed staining of the vessel wall and perivascular leakage.

citrullinated protein antibody (ACPA) and other common infectious, inflammatory, hypercoaguable and autoimmune markers were all negative (see Table 1). Previously performed magnetic resonance imaging (MRI) of the hands and wrists did show bony erosions at the metacarpophalangeal (MCP) joints, a diagnostic finding for advanced RA; however, the serologic testing for RA was negative.

Although the combination of the patient's symptomatology, negative RF/anti-ACPA status and imaging studies established the diagnosis of seronegative rheumatoid. A Vectra® disease activity (DA) assay (Crescendo Biosciences, South San Francisco, CA) was ordered by the collaborating rheumatologist to confirm the diagnosis of RA and to assess the level of disease activity. The Vectra® DA assay objectively measures the levels of 12 serologic markers to stratify an RA patient's disease activity into 3 groups: low, moderate and high. The test showed a Vectra® DA Score of 52, which is consistent with a high level of disease activity. Accordingly, the patient was started on intravenous methylprednisolone sodium succinate therapy for 3 days and was then transitioned to oral prednisone. In addition, the rheumatologist started the patient on a weekly dose of 15 mg methotrexate sodium with supplemental folic acid.

At ten days' follow-up, the patient's VA OS had improved to 20/60. There was concurrent improvement of the retinal tortuosity on clinical examination, however a slight increase in the intraretinal fluid was noted on SD-OCT (Fig. 3C). Consequently, anti-vascular endothelial growth factor (VEGF) therapy was initiated. Ranibizumab was administered, and the macular edema improved. At 3.5 months the patient's BCVA was 20/30 with marked improvement of the edema after monthly injections of ranibizumab (Fig. 3D).

Table 1
Serologic testing for occlusive vascular disease.

Markers of Autoimmune Disease
*Anti-Nuclear Antibody (ANA)**
Rheumatoid Factor
Anti-Cyclic Citrullinated Peptide (ACPA)
Anti-Histone Antibody
Scleroderma Antibody (SCL 70)
Sjögren SS A Antibody
Sjögren SS B Antibody
Anti-Neutrophil Cytoplasmic Antibody (ANCA)
Extractable Nuclear Antigens (ENA)
Ribonucleoprotien (RNP) Antibody
Smith Antibody
Anti-Double Stranded DNA
Human Leukocyte Antigen (HLA)-B27
Markers of Hypercoagulable States
Antithrombin
Antiphospholipid antibody
Activated Partial Thromboplastin Time (aPTT)
International Normalized Ratio (INR)
Anti Cardiolipin Antibody (IgM, IgG, IgA)
Protein C
Protein S
Factor V Leiden
Prothrombin 20210
Markers of Inflammation
C reactive Protein (CRP)
Erythrocyte Sedimentation Rate (ESR)*
Complement Factor 3 (C3)
Complement Factor 4 (C4)
Human Leukocyte Antigen B27 (HLA − B27)
Markers of Infection
B. Burgdorferi Ab Screen
Venereal Disease Research Laboratory (VDRL)
Human Immunodeficiency Virus (HIV -1 and HIV 2)
QuantiFERON ®- TB test

Serologic testing for occlusive vascular disease was performed to elucidate possible etiologic factors which may have contributed to our patient's CRVO. Of these markers Antinuclear Antibody (ANA) tested homogenously positive with a titer of 1:80 and Erythrocyte Sedimentation Rate (ESR) was mildly elevated at 29 mm/h; the remaining markers were negative. Although Table 1 does not represent an exhaustive list of markers for occlusive vascular disease, the patient's history and physical exam findings helped to direct the appropriate laboratory testing.

2. Discussion

In this case report, we present a patient who suffered a vasculitic CRVO as a presenting sign of seronegative RA. Based on the American Rheumatism Association's 1987 Criteria, a positive rheumatoid factor was a central component of the diagnosis of RA [5]. In 2010, a new RA classification criteria was introduced, which intended to identify patients with early RA in order to allow the initiation of disease-modifying anti-rheumatic drugs (DMARDs) earlier in the disease course [6]. This classification requires a more detailed assessment of joint involvement and an expansion of biomarkers. This revised rubric opened the door for seronegative RA as an official diagnosis [7].

Until recently, there was no objective serologic testing capable of comprehensively assessing disease activity in seronegative RA patients [8]. Certain newer biomarker assays have sought to fill this gap. The Vectra® DA test determines the plasma levels of the following 12 biomarkers: vascular cell adhesion molecule 1 (VCAM-1), vascular endothelial growth factor A (VEGF-A), tumor necrosis factor receptor-type 1 (TNF-R1), matrix metalloproteinase-3 (MMP-3), leptin, serum amyloid A (SAA), epidermal growth factor (EGF), interleukin 6 (IL-6), matrix metalloproteinase-1 (MMP-1), human cartilage glycoprotein 39 (YKL-40), resistin, and C-reactive protein (CRP) [8]. The test then distills the disparate levels of these biomarkers to a single numeric value that corresponds to disease activity and the associated risk of joint damage progression [9].

Retinal vasculitis is a well-known complication of systemic inflammatory diseases, such as RA [10]. It is felt that cell mediated inflammation, immune complex mediated inflammation and autoantibody mediated inflammation all play a role in the development of vasculitis in RA [11]. Inflammation, in any of these forms, can induce vascular intimal proliferation. This intimal proliferation disrupts laminar flow within blood vessels, predisposing them to thrombus formation which can lead to local ischemia [12]. Further research suggests a link between the systemic markers of inflammation (CRP and ESR), which are elevated in RA and the increased risk of atherosclerotic plaque formation in RA patients; suggesting another possible mechanism of thrombus formation and vascular occlusion [13]. Yet despite this evidence, the precise pathophysiology which underlies the mechanism of retinal vasculitis and RA remains unclear.

Regardless of the pathophysiology, a vasculitic CRVO is a rare ocular complication and an unusual presenting sign of RA. In this case, successfully identifying retinal vasculitis was of paramount importance in determining the root cause for our patient's CRVO and polyarthalgia. Retinal vasculitis is defined as vascular leakage and/or staining of the vessel walls on fluorescein angiography, with or without the clinical appearance of fluffy white perivascular infiltrates and commonly includes the presence of inflammatory cells in the vitreous body or aqueous humor [14]. Based on the above criteria, our patient certainly met the definition of retinal vasculitis, which is a well-known causative agent of CRVO. To the best of our knowledge, we present here the first report of a vasculitic CRVO in a patient with seronegative RA, which was definitively diagnosed with MRI imaging and confirmed with Vectra® DA testing.

Interestingly, our patient's seronegative status—in combination with clear radiographic evidence of RA and a high Vectra® DA score—support the notion that mechanisms of joint damage and vasculitis which are not related to RF or anti-ACPA are likely involved. Our patient's specific testing showed significant

Table 2
Summary of Vectra® DA assay.

Disease Activity Markers	Result (Units)	RA Percentile (Reference Range)
Adhesion Molecules		
Vascular Cell Adhesion Molecule 1 (VCAM-1)	**0.51** (μg/mL)	**32%** (0.35–1.1)
Growth Factors		
Epidermal Growth Factor (EGF)	**230** (pg/mL)	**81%** (21–380)
Vascular Endothelial Growth Factor A (VEGF-A)	**240** (pg/mL)	**46%** (83–780)
Cytokine-related Proteins		
Interleukin 6 (IL-6)	**100** (pg/mL)	**97%** (2.2–100)
Tumor Necrosis Factor Receptor-Type 1 (TNF-R1)	**1.4** (ng/mL)	**11%** (1.1–4.5)
Matrix Metalloproteinases		
Matrix Metalloproteinase-1 (MMP-1)	**11** (ng/mL)	**55%** (3.1–39)
Matrix Metalloproteinase-3 (MMP-3)	**38** (ng/mL)	**68%** (9.2–130)
Skeletal-related Proteins		
Human Cartilage Glycoprotein 39 (YKL-40)	**99** (ng/mL)	**59%** (26–440)
Hormones		
Leptin	**4.2** (ng/mL)	**21%** (1.0–45)
Resistin	**5.7** (ng/mL)	**21%** (3.6–19)
Acute Phase Proteins		
Serum Amyloid A (SAA)	**2.5** (μg/mL)	**33%** (0.64–100)
C-Reactive Protein (CRP)	**16** (mg/L)	**81%** (0.24–77)
Composite Vectra® DA Score	**52**	

Table 2 is a comprehensive summary of Vectra DA® Assay. The patient's composite score was 52, which was considered high disease activity. In addition, you will find not only the results for our patient, but also how these results compare to a reference range that was experimentally determined.

elevations of both interleukin 6 (IL-6) and CRP (See Table 2); because these biomarkers are known to be proinflammatory they likely reflect the presence of active inflammation, which may have promoted the formation of central retinal vein vasculitis, ultimately resulting in a CRVO. Current research is underway to more clearly define the various “serotypes” of RA and the genetic and environmental influences which contribute to this heterogenous disease [15].

3. Conclusions

We report a patient who was diagnosed with seronegative RA with vasculitic CRVO as the presenting sign. Although the classic RA biomarkers were negative, the patient was eventually diagnosed with seronegative RA using MRI imaging of the hands. This diagnosis was supported by Vectra® DA testing, which showed a high level of disease activity and helped to direct the proper management—including appropriate therapy for the patient's vision loss. Newer biomarker assays, such as the Vectra® DA test, should be considered in patients with retinal vasculitis and arthritis in the appropriate clinical situations.

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