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BEHCET'S DISEASE PRESENTING WITH CENTRAL RETINAL VEIN OCCLUSION AND COEXISTENT HOMOZYGOUS MTHFR A1298C MUTATION: A CASE REPORT AND LITERATURE REVIEW

Ophthalmology

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ABSTRACT

Purpose: To report unusual case of central retinal vein occlusion (CRVO) as the first manifestation of Behcet's disease (BD) with coexistent hyperhomocysteinemia (Hcy) and homozygous MTHFR A1298C mutation.in a young male, and to provide a literature review regarding the role of Hcy and MTHFR mutations as risk factors for retinal vein occlusion (RVO) in BD patients.

Methods: We are reporting a case of CRVO as the first manifestation of BD with coexistent Hcy and homozygous MTHFR A1298C mutation.in a young male. A search was conducted in the Medline/pubmed database using keywords "CRVO, Behcet's disease, Hyperhomocysteinemia, homocysteine, MTHFR". Full texts of 38 original articles directly related to the aim of the review were used.

Results: A 30 year old male was found to have BD few months after presenting with Right CRVO. A lab work-up was carried for investigations of thrombophilia and possible coexisting autoimmune disorders, as possible causes for CRVO. Lab results revealed the presence of homozygous mutation of MTHFR A1298C subtype with Hcy, which was strongly suggestive of thrombotic pathophysiology for CRVO in our patient. Later the patient reported an episode of diarrhea with abdominal pain which appeared to be caused by stage 3 ciliac disease. Afterwords he started to have recurrent frequent episodes of painful oral ulcers, with an episode of genital ulceration and folliculitis like lesions on his back and shoulders. A diagnosis of BD was made and previous right CRVO was attributed to retinal vasculitis in the context of BD. The patient was well controlled on IV solumedrol followed by oral prednisolone and oral cyclosporine, which was later replaced by azathioprine 150mg. After a whole year of stabilization tapering of oral prednisolone was continued and by reaching a dose of 2.5 mg the patient had recurrence of right macular edema (ME) with signs of impending left CRVO, which was controlled again by raising oral prednisolone to 80 mg and azathioprine to 200mg. This led to right ME regression and left eye stabilization. While tapering again oral prednisolone and reaching a dose of 12,5 mg, impendig left CRVO progressed to CRVO with ME and right ME recurred. IV solumedrol was started again followed by oral prednisolone, azathioprine 200 mg with the add of infliximab. Both eyes became stable with total regression of ME. 6 months later, recurrent left ME was noticed and treated with suprachoroidal triamcinolone acetonide injection (SCTA). One week post SCTA, left ME regressed and remained stable through 1 month follow up.

Conclusion: CRVO can be the first presentation of BD in young patients. Associated homozygous MTHFR A1298C mutation and Hcy are possible risk factors for hypercoagulability state causing thrombotic complications in these patients

KEYWORDS

"CRVO, Behcet's disease, Hyperhomocysteinemia, homocysteine, MTHFR"

INTRODUCTION:

Central retinal vein occlusion (CRVO) is one of the most common vision-threatening retinal vascular diseases. It affects 4.67 million people with a prevalence of 0.13% worldwide. Retinal vein occlusion (RVO) has a clear increasing trend by age (0.26% in individuals aged 30–39 year versus 1.23 % in those aged 60–69 years and 3.38 in those older than 80 years) [1].

While arterial hypertension, diabetes mellitus, smoking, hyperlipidemia and open angle glaucoma have been well-known risk factors for RVO especially in elderly patients [2], the pathogenesis and risk factors in young patients with none of the previous factors are still unclear. Many retrospective studies of these young patients revealed the association of RVO with factors predisposing to thrombophilia including hyperhomocysteinemia (Hcy) [2-5] and inflammatory diseases associated with occlusive periphlebitis such as Behcet Disease (BD) [2,5].

The potential role of Hcy and MTHFR mutation as a risk factor for retinal vascular occlusion has earned concern in clinical research in the last decade [4, 6-8]. Many studies suggested the role of Hcy as an independent factor in the pathogenesis of RVO [9].

A recent evidence demonstrated that serum levels of homocystein are increased and correlated with ocular involvement in BD patients [10,11] with a potential role of the polymorphisms of the MTHFR C677T gene as the underlying variant for the demonstrated hyper-homocysteinaemia [12,13].

The vast majority of studies investigated MTHFR C677T variant while only few of them studied the other A1298C variant with contradictory results [4, 6-8].

We are reporting a case of unilateral CRVO as the first manifestation of BD with coexistent homozygous MTHFR A1298C mutation.

METHODS AND RESULTS

Case Report:

A 30-year-old man was referred to our tertiary retina and uveitis clinic at Al Mouwassat University Hospital with a 5-month history of sudden painless deterioration of visual acuity in his right eye without redness or floaters. He was then diagnosed to have right CRVO with diffuse macular edema (ME) and was treated with three consecutive intra-vitreal bevacizumab injections (IVB) 1 month apart, followed by one intravitreal injection of Triamcinolone with reported improvement in Snellen best corrected visual acuity (BCVA) to 0,8 within 1 week of each injection.

He was an ex-smoker with no previous history of drug abuse, alcohol consumption or sexually transmitted infections. His past medical history was unremarkable with no other systemic complaints and no history of diabetes mellitus, hypertension, deep vein thrombosis or use of any medication.

His ocular examination revealed a BCVA of counting fingers at 2 meters in the right eye and 1.0 in the left eye. Anterior segment examination was unremarkable with clear cornea, quiet anterior chamber and no vitreal haze in both eyes. Intraocular pressure was 17 mmHg and 14 mmHg in the right and left eye respectively. Right fundus exam showed generalized engorgement and tortuosity of retinal veins with mild intra-retinal hemorrhages scattered in the posterior pole and mid periphery in all four quadrants with blurred inferior and medial borders of the optic disk. Left fundus exam revealed normal optic disk with cup to disk ratio of 0.2, normal appearing retina and retinal blood vessels (Fig 1). Spectral domain optical coherence tomography (OCT) showed marked right diffuse ME with large intra-retinal cysts and presence of subretinal fluid (Fig 2). OCT of left macula was within normal limits (WNL).

OCT angiography (OCTA) images of right macula showed enlarged, irregular foveal avascular zone (FAZ) due to presence of superior area

of non-perfusion at the level of superficial capillary plexus (SCP), and reduced capillary density with scattered small areas of capillary non perfusion causing irregular FAZ at the level of deep capillary plexus (DCP). OCTA images of left eye showed normal superficial and deep capillary plexus (Fig 3).

Fluorescein Angiography (FA) of right eye showed delayed arterio-venous transit time, late leakage and staining of retinal veins with areas of capillary non-perfusion (Figure 4).

An extensive hematologic and biochemical lab work was carried on to investigate the presence of a 'hypercoagulable state' or autoimmune disorder, which can predispose to CRVO in our young patient. The results revealed mild hyperhomocysteinemia (21 micro mol/L), decreased vitamin B12 plasma level (182 pg/ml) and decreased vitamin D level. All other tests were WNL and pathergy test was negative. Electrical cardiogram ECG showed sinus_regular rhythm with an inverted T wave on III lead. Lung functions and chest x-ray were WNL. Carotid doppler echogram showed atherosclerotic changes in the internal carotid artery without clinically significant hemodynamic stenosis in either side. Echocardiogram showed a prolapse of the anterior leaflet of the mitral valve and mild regurgitation with EF of 60%.

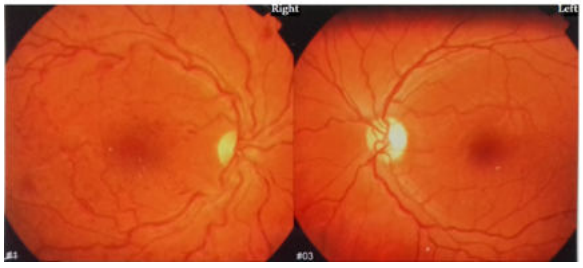


Figure (1): colored fundus photo of right eye shows generalized engorgement and tortuosity of retinal veins, mild intra-retinal hemorrhages scattered in posterior pole and mid periphery in all four quadrants and blurred inferior and medial borders of the optic disk. Colored fundus photo of left eye WNL

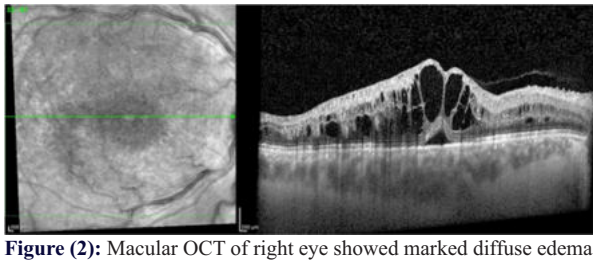


Figure (2): Macular OCT of right eye showed marked diffuse edema with large intra-retinal cysts and presence of subretinal fluid.

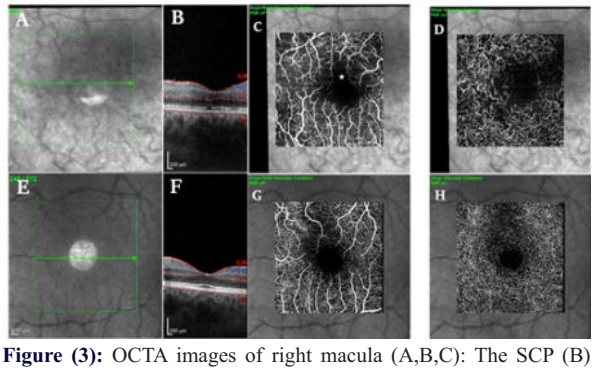
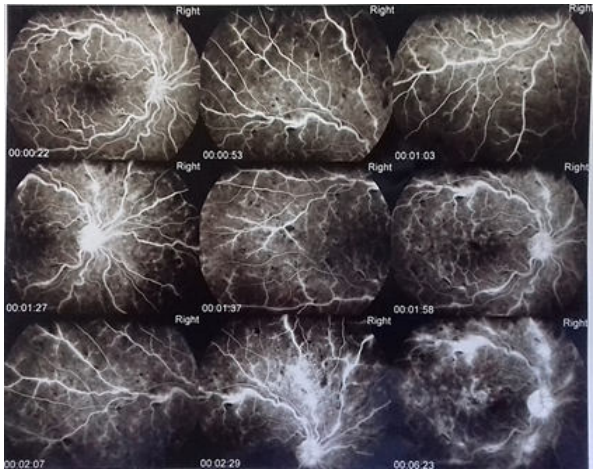


Figure (3): OCTA images of right macula (A,B,C): The SCP (B) showed enlarged and irregular FAZ due to superior area of capillary non perfusion. The DCP (C) showed reduced capillary density with scattered small areas of capillary non-perfusion causing irregular FAZ at the level of DCP. OCTA images of left eye (D, E, F) showed normal SCP and DCP.

A complete thrombotic genetic testing revealed a A1298C subtype homozygous mutation for the gene encoding methylenetetrahydrofolate reductase (MTHFR). A prescription of systemic vitamin B12, vitamin D and aspirin was started and IVB was done. One week later right BCVA improved to 0.2 with total regression of ME documented by OCT. 34-days post- injection the patient complained of new decrease in visual acuity. Examination revealed decreased BCVA to 0.05 secondary to recurrent right ME. This new episode of visual deterioration was accompanied with mucous diarrhea with occasional blood and peri-umbilical abdominal pain that increased after eating. Upper endoscopy showed ulcerative gastritis, bulbar duodenitis with aphthous-like ulcerations and villous atrophy. Gastric biopsies showed hemorrhages, ulcerations and mild inflammatory infiltrate with absence of Helicobacter Pylori. Duodenal biopsies showed shortening and widening of the intestinal villous, crypts hyperplasia and severe inflammatory infiltrate with increased intraepithelial T lymphocytes (IEL) which was consistent with stage 3B ciliac disease according to Modified Marsh-Oberhuber classification.

Further laboratory tests showed weak positivity of Anti Deamidated Gliadin IgG and negative anti transglutaminase IgA. The patient continued to use the prescription of aspirin, vitamins D, B9, B12 with gluten-free diet and IVB injections administered on as needed basis. After each bevacizumab injection anatomical but not functional improvement was encountered. Later the patient reported recurrent frequent episodes of painful oral ulcers, an episode of genital ulceration and folliculitis like lesions on his back and shoulders. A diagnosis of Behcet's Disease was made and right CRVO was attributed to retinal vasculitis in the context of BD . IV Solumedrol 1 g daily was given for 3 days followed by oral prednisolone (initial dose 80 mg with gradual tapering) and cyclosporin 200 mg daily for 3 months after excluding Crohn Disease. An impressive improvement in right ME was noticed as it completely disappeared with no recurrences in spite of stopping IVB injections and right BCVA went back to 0.3 and remained stable. Due to difficulties in availability of cyclosporine the patient was then transferred to azathioprine 150 mg daily with a maintenance dose of 10 mg prednisone.



Figure(4): Fluorescein Angiography of the right eye showing dilatation and tortuosity of retinal veins, small areas of capillary non-perfusion, late staining and marked peri-venular late leakage. Late diffuse vascular leakage in the macula and late staining of the optic nerve head are also seen.

Being stable for a whole year the rheumatologist started tapering oral prednisolone. At the dose of 2.5mg the patient had recurrent macular edema in the right eye and engorgement and tortuosity of retinal veins with mild retinal hemorrhages and no ME or vitreal haze in his left eye (impending left CRVO). His BCVA was 0.3 and 1.0 in the in the right and left eye respectively, FA of the left eye showed delayed arteriovenous transit time, congested and tortuous retinal veins with mild late staining and peri-vascular leakage. Prednisolone dose was raised again to 80 mg and azathioprine 200 mg continued. Complete regression of right ME and stabilization of left eye with no progression to CRVO was noticed at 1 week follow up, and BCVA remained stable in both eyes. As BCVA and fundus exam findings remained the same for another 3 weeks of follow up, prednisolone was gradually tapered over a period of 5 months to reach a dose of 12.5 mg, when the patient complained of a new decrease in visual acuity of his left eye. His BCVA was 0.5 and 0.6 in the in the right and left eye respectively, fundus examination showed completely regressed ME and with no signs of inflammatory CRVO in the right eye, with increased engorgement and

tortuosity of left retinal veins and scattered intraretinal hemorrhages in all four quadrants of left fundus with no vitreous haze or vascular sheathing. FA of left fundus showed congested and tortuous retinal veins and mild diffuse retinal hemorrhages in the early phase, and mild late staining of retinal veins and peri-venular leakage in late phase (Fig 5) This was diagnosed as inflammatory left CRVO secondary to BD. IV solumedrol 1 g daily was started for 3 days followed by oral prednisolone (initial dose 80 mg which was tapered gradually), azathioprine 200 mg was continued, and infliximab was added. The patient remained stable over the next 5 months while tapering prednisolone and continuing azathioprine and infliximab, with no macular edema in both eyes. At 6 months post left CRVO, recurrent ME in the left eye was noticed and treated with suprachoroidal triamcinolone acetonide injection (SCTA). One week post SCTA, left BCVA went up to 0.8 as ME regressed and remained stable for 1 month follow up (Figure 6)

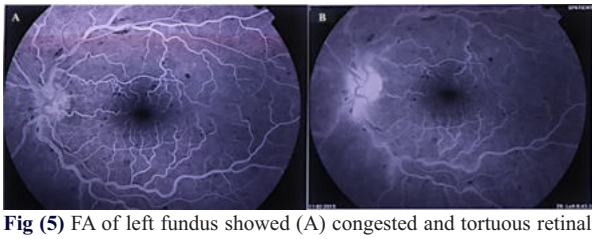


Fig (5) FA of left fundus showed (A) congested and tortuous retinal veins and mild diffuse retinal hemorrhages in the early phase, and (B) mild late staining of retinal veins and peri-venular leakage in late phase

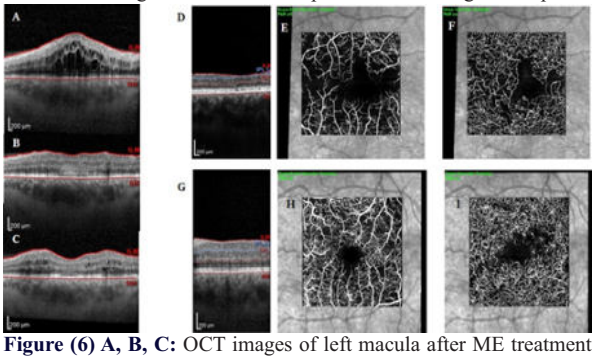


Figure (6) A, B, C: OCT images of left macula after ME treatment with SCTA: marked macular edema before injection (A), regression of ME at 1 week (B) and 1 month (C) post injection.: D, E, F: OCTA images of the right macula showing atrophic retina(D), markedly enlarged and irregular FAZ in both SCP (E) and DCP (F), G,H,I: OCTA images of the left eye showing mildly irregular FAZ in the SCP (H) and reduced vascular density and enlarged as well as irregular FAZ in the DCP (I).

A search was conducted in the Medline/pubmed database using keywords "CRVO, Behcet's disease, Hyperhomocysteinemia, homocysteine, MTHFR". Full texts of 38 original articles directly related to the aim of the review were used.

Literature Review And Case Discussion:

We are reporting a case of unilateral CRVO as the first sign of BD in a young otherwise healthy male. The diagnoses of BD was established few months after CRVO. At first presentation with right CRVO, because of patient's young age and absence of history of risk factors predisposing to CRVO, we carried investigations for thrombophilia and autoimmune disorders as possible causes for CRVO. His laboratory work-up revealed the presence of homozygous mutation of MTHFR A1298C subtype with hyperhomocysteinemia (Hcy) and this was strongly suggestive of thrombotic pathophysiology for CRVO in our patient.

Homocysteine is an intermediate amino acid product in the metabolism of methionine, in which the latter is catabolized to produce cysteine. Homocysteine may be metabolized further either through irreversible trans-sulfuration to cystathionine and cysteine or remethylated to form methionine again through the enzyme Methylene-Tetrahydro-Folate Reductase (MTHFR) with important role of vitamins B6, B9 and B12 as cofactors [4, 14]. Homocysteine levels become elevated due to genetic, nutritional and disease related processes, most often occurring in combination with each other. Hyc is graded as mild: 15- 30 µmol/L (prevalence of <10%), moderate/intermediate: 31-100 µmol/L (prevalence of <1%) and severe: > 100 µmol/L (prevalence of <0.02%) based on concentrations measured during fasting [14].

Hyc causes a cascade of cytokine activation, lipid peroxidation, impaired vasomotor regulation, vascular endothelial injury, prothrombotic surface, atherothrombogenesis, thrombo-embolism, and therefore systemic and retinal vascular occlusive disease [14].Suggested mechanisms of Hcy in promoting such a clotting cascade are the inactivation of protein C, activation of coagulation factor V, and inhibition of thrombomodulin. Similarly, increased levels of circulating endothelin-1 (ET-1), which is a potent vasoconstrictor peptide, promote retinal capillary ischemia and occlusion and represent a marker of vascular endothelial dysfunction [9, 14]. It is via these mechanisms that Hyc has been shown to be an independent risk factor for atherosclerotic vascular disease including myocardial infarction, cerebrovascular events and retinal vascular occlusive disease [15].

The most common genetic cause of Hcy is mutation in the gene encoding MTHFR enzyme, which can raise homocysteine levels by up to 25% [16]. This mutation is located on chromosome 1 with up to 33 rare mutations associated with severe enzyme deficiencies. The most common being studied are the C677T (cytosine to thymine mutation at nucleotide 677) and A1298C (Adenosine to cytosine mutation at nucleotide 1298) which reduces the activity of MTHFR by 40-50% and 35% respectively [14].

There have been conflicting reports as to whether this genetic mutation in isolation conveys a raised homocysteine to a level where it causes vascular occlusive disease including retinal vein occlusion [4, 6-8]. However, a more dramatic rise in homocysteine levels is seen when this genetic defect occurs in combination with vitamin deficiency [16]. A recent meta-analysis of 42 case-control studies showed a significant association between total plasma homocysteinemia (tHcy) and the risk of RVO (a 1 µmol/L increase in tHcy level was associated with an OR of 1.14) with no evidence of a significant association between the MTHFR C677T genotype and RVO in any genetic model tested [7]. Li et al [4] found some evidence that tHcy is associated with an increased risk of RVO, but they did not find evidence to suggest an association between homozygosity for the MTHFR C677T genotype and RVO. Ghaznavi et al [8] revealed a similar result for the other A1298C homozygous mutation. This latter study demonstrated that Hcy but not homozygosity for MTHFR A1298C polymorphism is a significant risk factor for RVO in the Iranian population.

BD is a chronic, relapsing, multisystemic autoinflammatory disorder of unknown etiology characterized by relapsing episodes of oral and genital ulcers, skin lesions, and ocular lesions.[17, 18] Despite the international concern and the copious researches on BD, no pathognomonic laboratory finding or diagnostic test has yet been validated and the diagnosis of the disease remains a clinical decision and it often takes several years to establish a definitive diagnosis after the appearance of initial manifestations. Over 15 different sets of criteria for the diagnosis of BD have been proposed but the most commonly used are the criteria of the International Study Group (ISG) which were created in 1990 [19] and the Japanese criteria that were revised by the Behcet's Disease Research Committee of Japan in 2003 [20], which were created in order to avoid BD over diagnosis and the latest of which is the International Criteria for Behcet's Disease (ICBD) which was created in 2006 and revised in 2011 [21].

Thus BD is a very complex entity which is highly variable in its clinical phenotypes and clinical course. The initial manifestations and the combination of clinical symptoms are very heterogeneous between patients, even within the same ethnic group. [22].

Mucocutaneous manifestations are markers of BD, and their recognition may allow diagnosis and treatment. Oral ulcers are present in almost all cases. These lesions are the initial manifestation in 47-86% of the patients and precede subsequent ones in an average of 7-8 years [18].

Gastrointestinal (GI) manifestations of BD occur in about 3-40% with lower frequency in the Middle East, and they usually occur 4.5-6 years after the onset of oral ulcers. Although ileocecal involvement is most commonly described, BD may involve any segment of the alimentary tract and the various GI organs. The stomach is thought to be the least involved segment [18, 23].

Ocular involvement in BD is frequent (30-70%) and is an important cause of morbidity. The highest prevalence rate of the disease has been reported from Turkey and Japan. The mean age at onset of uveitis is between 20 and 30 years in male and 30 years in female patients [24, 25]. Ocular manifestations are usually bilateral in 85% of cases and typically occur 2 -4 years after the onset of the disease. It may be the presenting manifestation of the disease in 10–20% of cases [18, 24].

Uveitis may be anterior, intermediate, posterior or panuveitis. Anterior uveitis is always non granulomatous, sometimes associated with hypopion. Posterior involvement may include the presence of vitritis, retinal vasculitis, mainly venous and often occlusive, macular edema, and/or foci of necrotizing retinitis. Male patients with younger age at onset and severe lesions at presentation are at higher risk of severe visual loss over time [18, 25]. The 10-year risk of developing severe visual loss of 6/60 or worse was 13% and ischemic maculopathy secondary to RVO was attributed to half the cases of irreversible severe visual loss [23].

Retinal vasculitis is common among patients with ocular BD. In one multi-center study, 22% of eyes with ocular BD had retinal vasculitis [26]. Retinal vasculitis in BD most commonly manifests as vitritis with diffuse vascular leakage on FA due to inflammatory hyperpermeability. This may be accompanied by capillary non perfusion secondary to occlusive vasculitis resulting in neovascularizations. Both retinal arteries and veins can be involved, though venous involvement is more common [27]. RVO with intraretinal hemorrhages and ME are frequently seen. RVO and ischemic retinal vasculitis have been reported in 28% and 21% of ocular BD patients respectively, while CRVO reported in 0.4-4% and artery occlusions in 1% of patients are less common presentations [28, 29].

The pathophysiology of vascular thrombosis in BD is not well understood. Endothelial dysfunction due to inflammation is considered to be an important factor of thrombosis. However, endothelial injury itself cannot clearly account for the hypercoagulable status of BD, because other vasculitis syndromes do not show the same tendency towards thrombosis. Some studies have shown that Hcy might be an independent and correctable risk factor for thrombosis in BD [10-13].

A systematic review and meta-analysis [30] studying the association between Hcy and hypercoagulability state and thrombotic complications in patients with BD, showed that Hcy levels are significantly higher in patients with thrombosis compared with patients not having thrombotic events. This association suggested that the presence of Hcy should be evaluated in patients with BD presenting with thrombosis [30].

Recent evidences suggest that Hcy thought to induce proinflammatory cytokines during the course of BD. Serum Hcy and ET-1 levels have been found to be increased and correlated with the ocular involvement and the inflammatory activity of the disease [10, 13, 24, 25, 27, 31, 32]. Yesilova Z et al [33] showed in their study that increased catabolism of folate and vitamin B12 due to chronic inflammation and moderately increased tHcy concentrations related with deficiency of these cofactors and immunosuppressive drug administration, might be potential threats of vascular disease in BD Similarly, Feki M et al [34] has shown that plasma Hcy levels and the prevalence of Hcy are higher in BD patients, and that Hcy was related to male gender, disease severity and uveitis, but not to deep venous thrombosis, arthritis, or neurological disease. [34]. They hypothesized that this Hcy may be caused by the combination of the genetic defect of MTHFR mutation and inadequate folate intake, thus this elevation of Hcy could be corrected with folic acid supplements. [34].

Stoimenis et al.[35] suggested that BD might not constitute a single disease and that patients who present with vessel thrombosis, coexistent thrombophilic factors and MTHFR mutation, and some BD features, for instance oral aphthosis and HLA-B51 positivity, may actually suffer from a distinct entity. They proposed that all patients with BD who manifest thrombotic events should be assessed for thrombophilia testing, so that their optimal management can be appropriately weighed.

However, there is not enough evidence supporting that, treatment of Hcy could be efficacious in the course of BD associated thrombosis. Houman MH et al [36] found in their small randomized controlled trial in BD patients with Hcy and ocular involvement, a significantly lower number of uveitis attacks in patients treated with folic acid, which suggested its potential benefit in reducing Hcy levels in these patients.
Management of Behçet's syndrome/disease is guided by European League Against Rheumatism EULAR recommendations [37] which state that any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regimen such as azathioprine, cyclosporine-A, interferon-alpha or monoclonal anti-TNF antibodies. Systemic glucocorticoids should be used only in combination with azathioprine or other systemic immunosuppressives. Patients presenting with an initial or recurrent episode of acute sight threatening uveitis should be treated with high-dose glucocorticoids, infliximab or interferon-alpha. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment [37].

SCTA has earned concern in the last years as a novel therapeutic approach that offers great promise for highly chorioretinal bioavailability with improved safety in the treatment of non-infectious uveitis [38]. ME in non-infectious uveitis represents the main actual and the most studied indication for SCTA, as phase 3 studies showed a significant visual and anatomical improvement of associated ME with limited side effects [38].

In conclusion BD represents a highly heterogenous complex entity, and our case demonstrates unusual CRVO presenting manifestation of BD, which emphasizes the importance of careful evaluation of the medical history and meticulous physical examination on every visit following idiopathic CRVO in young patients to detect concomitant systemic manifestations.

Homozygous MTHFR A1298C mutation and associated Hcy are risk factors for hypercoagulability state causing thrombotic complications in BD patients. It is beneficial to assess patients with BD for Hcy and thrombophilia, as the treatment of Hcy could be efficacious in the course of BD associated thrombosis.

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