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Smoking and Chronic Obstructive Pulmonary Disease: Key Contributors to Central Retinal Vein Occlusion in an Elderly Patient

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Statistical Analysis C
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Patient: Female, 70-year-old
Final Diagnosis: Central retinal vein occlusion (CRVO) and chronic obstructive pulmonary disease (COPD)
Symptoms: Poor visual acuity
Clinical Procedure: —
Specialty: Ophthalmology

Objective: Rare coexistence of disease or pathology

Background: Central retinal vein occlusion (CRVO) is associated with cardiovascular risk factors, but hypercoagulability, endothelial dysfunction, and stasis of blood present in patients with chronic obstructive pulmonary disease (COPD) may also play a role in its pathogenesis. This report describes the case of a 70-year-old woman who presented with reduced vision in the right eye due to CRVO.

Case Report: A 70-year-old woman with a history of smoking presented with decreased vision in the right eye. Except for well-controlled hyperlipidemia, she lacked the classic CRVO risk factors. The workup showed elevated polyclonal free light chains (FLCs), elevated Beta-2 microglobulin (β2M), and anemia. A thorough history-taking revealed involuntary weight loss, morning headaches, fatigue, a productive morning cough with white sputum, and shortness of breath over the past 3 months. Clinical ophthalmological examination, multimodal imaging, extensive laboratory workup, and clinical workup were performed and the results were consistent with CRVO. After pulmonary examination, spirometry, and thorax imaging, she was diagnosed with COPD.

Conclusions: COPD can be a potential underlying condition in patients presenting with CRVO that cannot be attributed to other etiologies, particularly if they have a past medical history suggestive of COPD. An emphasis should be placed on inquiries regarding the main symptoms of COPD: shortness of breath, morning cough, and sputum production. A further pulmonary examination may be beneficial in patients with CRVO and smoking history, given that early diagnosis of COPD prolongs survival.

Keywords: Retina • Retinal Vein Occlusion • Smoking

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Introduction

Central retinal vein occlusion is one of the main causes of sudden, painless vision loss in adults, with a prevalence rate of 0.8 per 1000 [1,2]. Primary risk factors include age, systemic arterial hypertension, hyperlipidemia, diabetes mellitus, and open-angle glaucoma [1,3]. Additional risk factors include smoking, optic disc drusen or edema, and various hypercoagulable conditions such as polycythemia, multiple myeloma, cryoglobulinemia, Waldenström macroglobulinemia, antiphospholipid syndrome, factor V Leiden, activated protein C resistance, hyperhomocysteinemia, and deficiencies in protein C, protein S, or antithrombin III, as well as prothrombin mutations. Other contributing factors may include infections like syphilis and HIV, systemic conditions such as sarcoidosis, vasculitis, sickle cell disease, and Black race. Certain medications (eg, oral contraceptives, diuretics), abnormal platelet function, orbital disorders, and, rarely, migraines have also been implicated [1]. Moreover, a meta-analysis has shown a 69.1% increased risk of myocardial infarction in patients with CRVO, which may elucidate its complex pathogenesis [4]. The exact pathogenesis of CRVO remains poorly understood, but 3 hallmarks of thrombosis – venous stasis, endothelial damage, and hypercoagulability – play a role; therefore, any condition that increases those factors may precipitate a CRVO [1]. Furthermore, inflammation is believed to play an important role through cytokine overproduction and the resulting endothelial dysfunction [4-6]. Higher intraocular levels of inflammatory mediators, including cytokines (e.g., IL-8, IL-6, and CCL2), metalloproteinase, and neutrophil elastase (eg, lipocalin-2), have been observed in CRVO patients [5]. In addition, higher levels of C3, C5, and complement factor H (CFH) have been found in blood and aqueous humor of patients with CRVO, suggesting activation of the complement system, which is an important part of innate immunity, thereby supporting the importance of inflammatory pathways in the pathogenesis of CRVO [5]. Chronic inflammation is a hallmark of chronic obstructive pulmonary disease (COPD), an inflammatory respiratory condition characterized by persistent respiratory symptoms and airflow limitation caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) [7]. Timely diagnosis and early management are crucial, as they slow the disease progression and thus prolong survival [7]. To the best of our knowledge, COPD as a possible cause of CRVO has not been studied yet [8,9]. This report describes the case of a 70-year-old woman with a history of smoking presenting with reduced vision in the right eye due to central retinal vein occlusion (CRVO), who was additionally diagnosed with COPD during the extensive diagnostic workup.

Case Report

A 70-year-old woman presented to our department with decreased vision in the right eye. She had a history of well-controlled hyperlipidemia and smoking. At the first presentation, her best corrected visual acuity (BCVA) was 20/40 and 20/32 in her right and left eyes, respectively. Intraocular pressure was normal. She identified 6/11 Ishihara color plates in her right eye and 9/11 in her left eye. Her pupils were normal, and there was no relative afferent pupillary defect. The anterior segment was unremarkable. Fundus examination of the right eye revealed a round area of atrophy in the macula, tortuosity, and dilatation of retinal veins associated with flame-shaped hemorrhages in all 4 quadrants of the retina and blurred optic disc margins (**Figure 1**). Peripapillary atrophy was present in her left eye. Optical coherence tomography showed no macular edema, but confirmed the presence of optic disc edema (**Figure 1**). Fluorescein angiography demonstrated delayed filling of the dilated and tortuous retinal veins (**Figure 1**). Based on the clinical examination and multimodal imaging, she was diagnosed with a CRVO in the right eye.

Over a period of 3 months, she noticed an additional visual decrease in the right eye and was sent back for re-evaluation. Her visual acuity was 20/63 and 20/32 in the right and left eye, respectively. Intraocular pressure was normal. Her pupils were normal, and there was no relative afferent pupillary defect. She identified 6/11 Ishihara color plates in her right eye and 9/11 in her left eye. The anterior segment was normal. Fundus examination revealed worsening, with more flame-shaped hemorrhages around the optic disc and more blot hemorrhages in all 4 quadrants of the retina, with increased optic disc edema. There was no change in the clinical examination results of the left eye. Goldmann's perimetry showed a concentrically narrowed visual field and an enlarged blind spot in her right eye. Optical coherence tomography of the optic nerve and macula in the right eye demonstrated marked optic nerve head edema extending temporally into the macula, where there was also atrophy of the retinal layers. The unusual presentation led to further investigation into her past medical history and diagnostic workup. A review of her medical history revealed that she had involuntarily lost weight (3.2 kg) over the past 3 months, and she had occasional morning headaches and fatigue. In the past 4 months, she had noticed a productive morning cough with white sputum and shortness of breath. She had no known allergies. Her family history was non-contributory. She has been smoking 20 cigarettes per day for 50 years. Her blood pressure was within normal limits. Subsequent magnetic resonance imaging (MRI) with gadolinium contrast excluded a focal lesion. Initial blood work showed an elevated sedimentation rate (SR) (92) while CRP remained in the normal range. The lipid profile was within normal limits, proving the hyperlipidemia was very well controlled. ANA, ANCA, and anticoagulant assays were within normal limits. A hematological workup revealed normocytic anemia (Hb 100 g/L, MCV 98 fl), and a differential white blood cell count showed a decrease in lymphocytes (0.60×10^9, 14.9%). Serum-free light chain analysis

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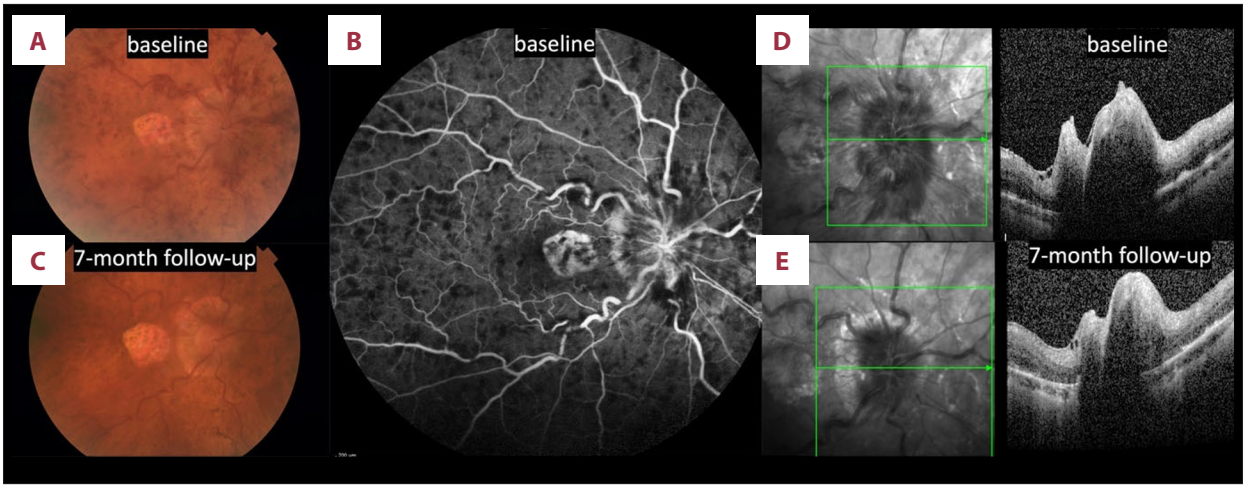

Figure 1. Multimodal imaging of a patient with central retinal vein occlusion in the right eye. Color fundus photograph at baseline (A) shows extensive hemorrhages in all 4 quadrants, dilated and tortuous veins, and optic disc edema, which are hallmarks of central retinal vein occlusion (CRVO). Due to preexisting macular atrophy, seen as atrophic areal in the macula, there is no macular edema. Fluorescein angiography at baseline (B) demonstrates delayed filling of the dilated and tortuous retinal veins, hypofluorescent dots represent retinal hemorrhages, dye leakage from the capillaries of the optic disc, and staining of the disc in late phases is consistent with optic disc edema. Color fundus 7 months after initial diagnosis (4 months after chronic obstructive pulmonary disease [COPD] treatment) (C) shows marked improvement, with only a few remaining hemorrhages and markedly reduced optic disc edema. Spectral domain optical coherence tomography (OCT) of the optic disc at baseline shows marked optic disc edema at baseline (D) and its resolution 7 months after initial diagnosis (4 months after COPD treatment) (E).

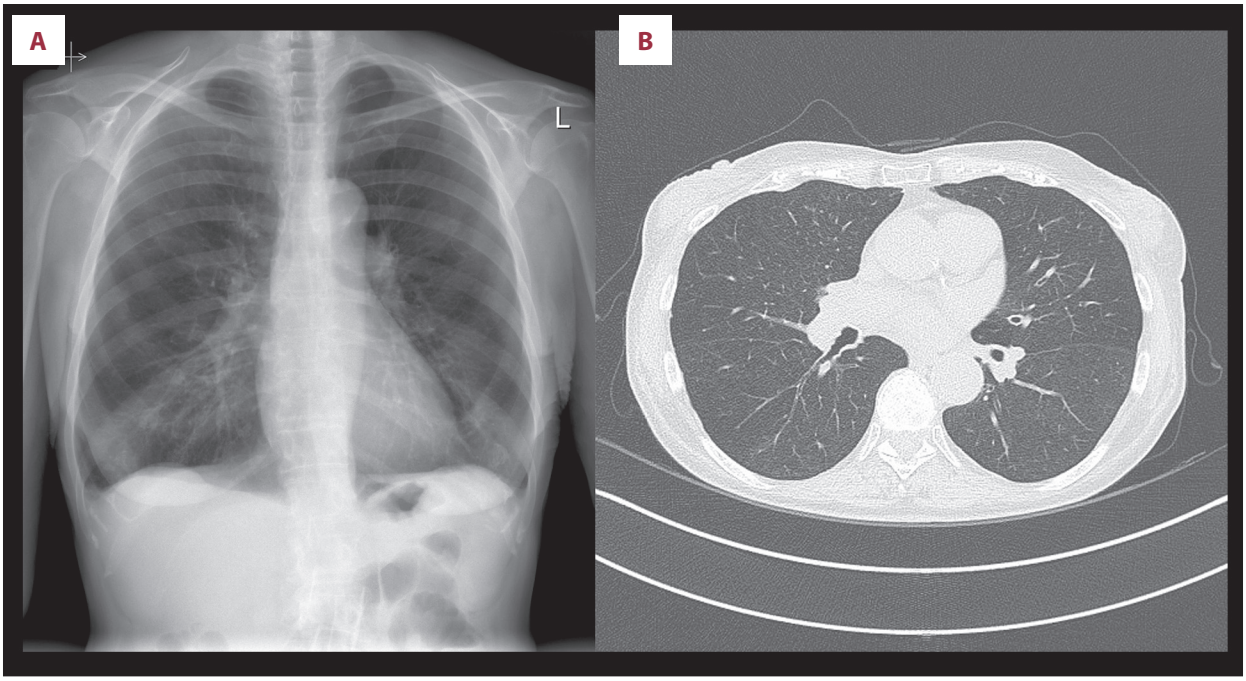

Figure 2. Thorax imaging of a patient with newly diagnosed COPD. A chest radiograph (A) and chest high-resolution computed tomography (B) revealing centrilobular emphysema.

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showed elevated free light chains: lambda (38 mg/L), kappa (47 mg/L). Beta 2 microglobulin was also elevated (4.53 mg/L), and serum potassium and LDH were in the normal range.

She was evaluated by a pulmonologist. On physical examination, prolonged expiration and wheezing on forced exhalation were noted. Heart and abdominal examinations were within normal limits. A chest radiograph was obtained and was suspicious of emphysema (**Figure 2**). Spirometry demonstrated airflow obstruction with a FEV1 54% and the FEV1: FVC ratio 51%. There was no significant FEV1 reversibility after the bronchodilatation test. Chest high-resolution computed tomography (HRCT) revealed centrilobular emphysema (**Figure 2**). Bronchoscopy was indicated as the patient had a chronic cough with mucopurulent sputum and a history of smoking. *Haemophilus influenzae* and *Streptococcus pneumoniae* were isolated from bronchoalveolar lavage fluid (BALF). She was diagnosed with COPD. Her initial treatment consisted of salmeterol with fluticasone 25/250, tiotropium bromide, and levofloxacin 500 mg. Smoking cessation was strongly encouraged. On the next follow-up visit, 7 months since the first presentation and 4 months after the initiation of the treatment for COPD, the patient described improvement in visual acuity (BCVA in the right has Furthermore, improved from 20/63 to 20/30). On funduscopic examination, only a few remaining hemorrhages with a markedly reduced optic disc edema were noted (**Figure 1**).

Discussion

We describe an unusual presentation of CRVO and hypothesize about its possible association with COPD. To the best of our knowledge, COPD as a possible cause of CRVO has not been studied yet. Except for well-controlled hyperlipidemia, our patient lacked the classic CRVO risk factors of hypertension, diabetes mellitus, atherosclerosis; thus, other possible underlying conditions were considered. Given the elevated SR and the presence of normocytic anemia, an extensive laboratory workup was performed to exclude a possible underlying hematological condition, such as myeloproliferative disorders (eg, polycythemia vera, Waldenström's macroglobulinemia), acquired hypercoagulable states (eg, hyperhomocysteinemia), or hereditary thrombophilic conditions (eg, protein C or S deficiency, antithrombin deficiency) [1]. The workup showed elevated polyclonal free light chains (FLCs), elevated Beta-2 microglobulin (β2M), and anemia. Elevated FLCs have been described in various autoimmune and inflammatory conditions, including COPD. In our patient, chronic bacterial colonization of the airway presented a possible stimulus for the adaptive immune system and subsequent production of antibodies, leading to an overproduction of FLCs, which were consequently elevated [10]. β2M is major histocompatibility complex-associated polypeptide. Its role as a biomarker in several neoplastic, inflammatory, and infectious conditions is well established. Research has shown that patients with higher levels of FLCs and β2M exhibit a higher prevalence of emphysema, which was also seen in our patient [10,11]. Our patient's anemia could have been a consequence of the systemic inflammation seen in COPD and thus classified as anemia of chronic disease, which was shown to be the most common type of anemia seen in COPD patients, with a prevalence ranging from 7.5% to 33% [12]. Since the laboratory workup and her past medical history, including morning cough with sputum production, shortness of breath, weight loss, and fatigue, were indicative of an underlying respiratory condition, she was referred to a pulmonologist. Subsequent diagnostic procedures suggested the diagnosis of COPD. Although the exact pathophysiological mechanism of CRVO is not known, Virchow's triad of hypercoagulability, endothelial dysfunction, and stasis of blood is believed to be crucial in its pathogenesis [10]. Endothelial dysfunction is characterized by reduced vasodilatation capacity, enhanced blood coagulation, and increased platelet activation, resulting in a higher risk of thrombotic events [13]. Smoking and COPD-related chronic inflammation seen in our patient have both been shown to induce endothelial dysfunction [13]. Endothelin-1 (ET-1) is a potent vasoconstricting peptide produced by endothelial cells, whose role in the pathogenesis of retinal vein occlusion has been confirmed, and it is crucial for regulation of retinal blood flow. Increased levels of ET-1 cause constriction of retinal veins, increasing retinal venous pressure, which in turn leads to venous occlusion [14,15]. Since smoking and COPD have both been shown to increase ET-1 levels and induce endothelial dysfunction, we hypothesize that they played an important role in the pathogenesis of the CRVO in our patient [14,15]. Although COPD is not a traditional risk factor for CRVO, we believe it could have had affected the course of the disease of our patient. Nevertheless, limitations of this article are that it is a single case report, and the improvement observed in our patient may also reflect the natural course of the disease, in which one-third of older patients improve without treatment, one-third remain stable, and one-third experience deterioration. However, the improvement is usually seen in patients younger than 50 years, while our patient was 70. Advanced age and a history of smoking may have contributed to the development of CRVO in this patient. Although her condition initially worsened within the first 3 months following diagnosis, consistent with the natural course, as approximately one-third of patients experience deterioration, it subsequently improved with the initiation of COPD treatment. This improvement coincided with the use of fluticasone (a steroid medication), which could have also contributed to the reduction of optic disc edema and hyperemia. Given that our patient had preexisting macular atrophy, treatment with intravitreal anti-VEGF or a dexamethasone implant, which is used in CRVO patients who develop macular edema, was not indicated, as there was no macular edema [1].

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Conclusions

COPD can be an underlying condition in patients presenting with CRVO that cannot be attributed to other etiologies, particularly if they have a past medical history suggestive of COPD. An emphasis should be placed on inquiries regarding the main symptoms of COPD: shortness of breath, morning cough, and sputum production. Since smoking is a known risk factor for both CRVO and COPD, a further examination consisting of pulmonary auscultation and chest X-ray may be of benefit in patients presenting with CRVO and a history of smoking, given that early diagnosis of COPD prolongs survival. Further research of the complex relationship between CRVO and COPD is warranted.

Department and Institution Where Work Was Done

The Department of Ophthalmology, University Medical Centre Ljubljana, Ljubljana, Slovenia.

Patient Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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