CASE REPORT

Bilateral BRVO in a patient with recurrent prostate cancer

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SUMMARY

Bilateral cases of branch retinal vein occlusions (BRVO) are infrequent and often related to systemic disease. A 72-year-old man with biochemical recurrence of prostate cancer was referred for decreased vision in his left eye. Fundus examination and fluorescein angiography disclosed bilateral BRVO with patches of peripheral non-perfusion and macular oedema in the left eye. A systemic work up revealed elevated fibrinogen and reduced free protein S antigen, consistent with an underlying hypercoagulable state. Cancer is a well-known cause of hypercoagulability. We report the first case of bilateral BRVO related to biochemical recurrence of prostate cancer and a proven coagulation derangement.

BACKGROUND

Retinal vein occlusion (RVO) is one of the most common causes of acquired retinal vascular abnormality in adults and a frequent cause of visual loss.^{1–3} Bilateral cases, however, are infrequent and often related to systemic disease.^{4–6} In these cases, a complete systemic work up is required.^{5–6} To date, only a few cases of RVO related to cancer have been reported, and in some, cancer therapy itself was considered to be the causative agent.^{7–11} We report the first case of bilateral branch retinal vein occlusion (BRVO) related to prostate cancer with biochemical recurrence and a proven coagulation derangement.

CASE PRESENTATION

A 72-year-old man presented with a few days of decreased vision in his left eye (OS). His medical and ocular histories included hypertension, dyslipidaemia, gout, coronary artery bypass grafting, moderate primary open-angle glaucoma controlled with latanoprost in both eyes, chronic obstructive pulmonary disease and biochemical recurrence of prostate cancer after radical prostatectomy. Biochemical recurrence with an increase in prostate-specific antigen from a stable level <0.1 to 0.2 ng/mL, was found 2 months prior to presentation to our service. The patient was awaiting commencement of radiation therapy. Best-corrected visual acuity was 20/25 in the right eye and 20/50 in the left. Applanation tonometry measured intraocular pressure was 17 mm Hg in the right eye and 16 mm Hg in the left eye. Fundus examination showed scattered haemorrhages consistent with temporal BRVO in the right eye and hemispheric BRVO with macular oedema in the left (figure 1). In the right eye, fluorescein angiography (FA)

revealed a large temporal zone of peripheral non-perfusion and inferior neovascularisation. In the left eye, FA revealed patches of peripheral non-perfusion, late leakage of the capillary meshwork in inferior hemisphere and macular hyperfluorescence (figure 2). Optical coherence tomography corroborated cystoid macula oedema in the left eye. Extensive laboratory evaluation was performed, including peripheral blood count, blood chemistry tests (ACE, lysozyme), blood coagulation work up (fibrinogen, protein S antigen, antithrombin III, partial thromboplastin time), and protein and haemoglobin electrophoresis. All laboratory work up was negative except for elevated fibrinogen and reduced free protein S antigen, which were consistent with an underlying hypercoagulable state secondary to known malignancy. The patient underwent sector pan-retinal laser photocoagulation to the non-perfused areas of the retina in the right eye and intravitreal bevacizumab injections in the left eye. The macular oedema demonstrated only a partial response to treatment at 6 months of follow-up. Aflibercept treatment was initiated and the macular oedema resolved in the left eye.

DISCUSSION

RVO is one of the most common causes of acquired retinal vascular abnormality in adults and a frequent cause of visual loss.^{1–3} Depending on the area of occlusion and amount of resulting non-perfusion, the prognosis and visual outcome are varied.

RVO constitutes the second most common retinal vascular disease after diabetic retinopathy.^{1–2} Using estimated prevalence rates and the 2008 world population, up to 16.4 million adults worldwide may be affected by RVO.¹¹ The occurrence of bilateral RVO, however, is much less common with a 0.04% incidence in a 15-year follow-up study.⁴ In the majority of cases of RVO, the pathophysiological mechanism is thought to be a combination of venous compression at arteriovenous crossings secondary to arteriosclerosis, degenerative changes within venous walls and hypercoagulability.²

Bilateral central retinal vein occlusion (CRVO) in young patients may be the first sign of a systemic disease with potentially life-threatening consequences. Since systemic causes have been associated with bilateral RVO, more extensive systemic work up may be warranted in certain cases, including patients with family history significant for vascular disease, patients under 50 years of age, or an unusual clinical appearance on presentation, namely, bilateral simultaneous vein occlusion or a

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Figure 1 (A–D) Fundus colour photography OU. Sclerosed arterioles inferiorly and temporally OD (A and B). Diffuse retinal oedema in inferior hemisphere with scattered haemorrhage OS. Note the tortuous venules with sclerosed arterioles inferiorly (C and D).

BRVO occurring at a site not associated with an arteriovenous crossing.^{3 5} In addition to the common underlying risk factors for RVO, such as age, hypertension, hyperlipidaemia, diabetes, smoking and elevated intraocular pressure, less common aetiologies should be investigated in all patients presenting with bilateral RVO.⁶ Uncommon predispositions to vein occlusion include myeloproliferative disorders, malignancy, acquired and inherited hypercoagulable states and inflammatory diseases. Myeloproliferative disorders causing RVO include polycythaemia, myeloma and Waldenström macroglobulinaemia. Hypercoagulable states include acquired conditions such as

homocysteinaemia and antiphospholipid syndrome, in addition to inherited conditions such as factor V Leiden mutation and antithrombin deficiency. Inflammatory diseases that cause RVO by occlusive periphlebitis include sarcoidosis, systemic lupus erythematosus and Behçet's disease. Thorough laboratory work up should be carried out by complete history and review of systems.⁶

Over the past few years, the role of thrombophilia in the pathogenesis of both CRVO and BRVO has been discussed.² The coagulation system is a complex cascade of reactions resulting in the conversion of fibrinogen to fibrin. This process is

Figure 2 (A–D) Fluorescein angiography OU. Note the temporal zone with peripheral non-perfusion and capillary drop-off consistent with neovascularisation in OD (A and B). OS with patches of peripheral non-perfusion, late leakage of capillary meshwork in the inferior hemisphere and macular oedema (C and D).

balanced by an anticoagulant system involving protein C, protein S and antithrombin. Any imbalance between these two systems leads to increased risk of thrombotic events.¹² In 2005, a comprehensive meta-analysis found a clear association only with antiphospholipid syndrome and a lesser relationship with factor V Leiden and mutation of the prothrombin gene.¹³ More recently, a retrospective study of 164 cases found higher levels of homocysteinaemia, anticardiolipin antibodies and inherited factor VIII in addition to lower inherited protein S in RVO compared to controls.¹⁴ In a similar mechanism, infectious and inflammatory diseases including hepatitis or cardiac graft rejection have been associated with bilateral vein occlusions.⁵

The treatment of certain urological conditions is associated with ocular manifestations, such as α -blockers (tamsulosin) and floppy iris syndrome, or phosphodiesterase 5 inhibitors (sildenafil) and colour vision changes. In the case of urological cancers, such as prostate cancer, the disease itself can have ophthalmological consequences.¹⁵ Cancer is a known cause of increased thrombotic risk due to several mechanisms.¹⁶ Ninety per cent of cancers have been associated with clotting abnormalities such as increased fibrinogen.¹⁶ Alterations in coagulability are more frequent in mucin-secreting adenocarcinomas, brain tumours, acute promyelocytic leukaemia and myeloproliferative disorders. Malignancies may also produce endothelial injury, venous stasis and blood vessel infiltration. In addition, cancer therapy itself may produce alterations in the coagulation system.¹⁶ Only a few cases of RVO related to malignancies have been reported, and

most of them are associated with haematological proliferative disorders.⁵ The association between solid organ neoplasias and retinal vascular occlusions is much less common. Moreover, the medical treatment rather than the cancer itself was thought to be the primary causative agent. Szczepanik *et al* reported a case of metastatic renal cell carcinoma treated with sorafenib, and Federici described a prostate cancer treated leuprolide acetate that was associated with RVO.^{7 8} Pathological evaluation of resected prostate cancer and blood samples of affected patients with or without hormonal chemotherapy confirm coagulation activation. Levels of increased tissue factor TF, a procoagulant protein produced by tumour cells, lead to an imbalanced activation of the coagulation system that may manifest as venous and arterial thrombosis.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- To the best of our knowledge, this is the first case of bilateral retinal vein occlusion (RVO) associated with prostate cancer and a laboratory-confirmed hypercoagulable state.
- Cases such as ours illustrate the close relationship between malignancies and retinal vascular disorders.
- Since cancer is a well-known cause of hypercoagulability, appropriate laboratory investigation should be performed in all patients with a history of malignancy and presentation with retinal vein occlusion.¹⁶ Additional laboratory work up to exclude uncommon causes of RVO should be directed by history and review of systems.
- Primary care doctors, oncologists and urologists should be aware of retinal vascular occlusion secondary to malignancies and cancer therapies. Any symptoms of vision changes should warrant prompt referral to an ophthalmologist.

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