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Case Report

Intravitreal Anti Vascular Endothelial Growth Factor-Driven Deterioration in Proteinuria, Renal Function, and Hypertension in the Context of Diabetic Nephropathy: A Case Report (Case Report)

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Abstract

Background: Diabetic retinopathy and nephropathy are microvascular complications of diabetes mellitus that often occur concomitantly. Anti vascular endothelial growth factor (VEGF) therapy is the mainstay of treatment for proliferative diabetic retinopathy and although oral and intravenous anti-VEGF therapies have been linked with adverse renal outcomes and hypertension, such associations with intravitreal anti-VEGF agents are less well established. **Case Description:** A case is presented of worsening hypertension, proteinuria, and renal function of a 62-year-old patient with presumed diabetic nephropathy who was referred to renal services with declining proteinuria and edema after being commenced on intravitreal anti-VEGF. **Discussion:** Intravitreal anti-VEGF agents have a significant amount of systemic absorption and cases of worsening proteinuria, hypertension, and estimated glomerular filtration rate have been previously reported. There is a significant clinical overlap with the natural history of diabetic nephropathy and the epidemiology of this association is poorly understood. It is not clear what modifiable factors exist to minimize the development of this syndrome of worsening proteinuria, hypertension, and renal function. **Conclusion:** A heightened awareness of the potential for intravitreal anti-VEGF agents to lead to worsening proteinuria, hypertension, and renal function is required. Further study is needed to understand the potential modifiable factors to mitigate the adverse effects of these agents that have a key role in treating diabetic retinopathy.

Key words: Diabetes, hypertension, nephropathy, retinopathy, vascular endothelial growth factor

Introduction

Diabetes mellitus is associated with significant macrovascular and microvascular systemic complications, and patients frequently exhibit coexistent vascular disease in multiple territories.[1] Diabetic retinopathy is the most common complication of diabetes mellitus. Hyperglycemia-induced microvascular damage results in retinal ischemia/hypoxia, leading to the upregulation of angiogenesis signaling protein vascular endothelial growth factor (VEGF), and consequent pathological neo-vascularization.[2] The mainstay of therapy in patients with proliferative diabetic retinopathy and macular edema is intravitreal anti-VEGF which targets the inappropriate blood vessel proliferation which threatens sight.[2]

The adverse systemic effects of oral and intravenous anti-VEGF agents have been well established in their widespread use in oncology as anti-neoplastic agents; this includes new or worsening proteinuria, renal dysfunction, and hypertension.[3] The association with intravitreal anti-VEGF agents and these adverse effects is less well established but has been previously described.[4-6] Considering the established clinical association between diabetic retinopathy and nephropathy, and therefore the widespread use of anti-VEGF agents in a population already vulnerable to kidney insults, the exploration of this relationship deserves further consideration.

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Case Report

A 62-year-old female, with a medical history of hypothyroidism, hypertension, and type 2 diabetes mellitus, was referred to renal services due to significant peripheral edema, nephrotic range proteinuria (urinary protein creatinine ratio 373 mg/mmol) with relatively preserved renal function (estimated glomerular filtration rate [eGFR] 92.3 ml/min), and serum albumin (35 g/L). She had been diagnosed with diabetes mellitus 6 months previously after severe non-proliferative retinopathy in both eyes and macular edema of the left eye had been noted during a routine eye examination. The extent of her eye disease suggested her diabetes mellitus had been present for a significant time, and her hemoglobin A1c (HBA1c) was 93 mmol/mol at time of diagnosis. She was hypertensive at 176/87 mmHg. Her medications included levothyroxine, metformin, furosemide, and ramipril.

A glomerulopathy screen confirmed negative/normal antinuclear antibody, antineutrophil cytoplasmic antibodies, anti-phospholipase A2 receptor antibody, rheumatoid factor, complement factors, blood-borne virus serology, and no evidence of elevated immunoglobulin or serum paraprotein. A renal ultrasound revealed right kidney 13 cm, left kidney 12.4 cm with no hydronephrosis nor calculi, and normal cortical thickness and echogenicity bilaterally.

Diabetic nephropathy was felt the most likely underlying reason for her proteinuria and her ramipril was uptitrated, furosemide increased for control of peripheral edema, and amlodipine added for blood pressure control. At this point, her HBA1c had improved to 56 mmol/mol.

On return visits to the renal clinic, her peripheral edema continued to deteriorate. An N-terminal pro-brain natriuretic peptide level was undertaken and found elevated at 1256 pg/ml. She, therefore, underwent echocardiography which revealed an estimated ejection fraction of 60–65% with undilated ventricles, Grade II diastolic dysfunction, mild-moderate left atrial dilatation, and estimated mild pulmonary hypertension (37 mmHg). Her hypertension remained poorly controlled. At this stage, her bisoprolol was uptitrated further, amlodipine stopped and canagliflozin commenced.

Her diuretic requirements improved with the introduction of canagliflozin but her blood pressure remained elevated and doxazosin was added to her antihypertensive regime. Her eGFR showed significant decline over 20 months, but stabilized at an eGFR ~20 ml/min.

Her case notes were re-reviewed given the difficulty controlling her peripheral edema and hypertension. It was noted that 6 months before her referral to renal services, she had been commenced on ranibizumab (Lucentis) injections, a humanized monoclonal antibody to VEGF, by ophthalmology due to the appearances of her ocular examination, which had not appeared on her primary care repeat prescription.

The patient's proteinuria and eGFR are displayed graphically in Figures 1 and 2. She continues to receive anti-VEGF therapy. Over the graphically displayed period, she received nine ranibizumab injections and 17 aflibercept (a soluble decoy receptor that binds to VEGF) injections to her left eye and seven ranibizumab injections and 16 aflibercept injections to her right eye.

Discussion

In this case, the progression of hypertension and peripheral edema coinciding with the initiation of intravitreal VEGF inhibition, led to the suspicion of VEGF blockade exacerbating existing proteinuric chronic kidney disease. The clinical overlap between diabetic nephropathy and adverse renal outcomes from anti-VEGF therapy is considerable and presents a diagnostic challenge given the widespread use of these agents in this patient population.

The use of systemic anti-VEGF agents in oncology settings has been clearly associated with adverse renal outcomes including new or worsening proteinuria, decline in GFR, and irreversible glomerular injury with a variety of pathologies reported on kidney biopsy (focal segmental glomerulosclerosis, minimal change, and membranous).[3] The amount of proteinuria appears linked with the duration of the anti-VEGF therapy.[3] In addition, these agents have been associated with worsening hypertension and thrombotic microangiopathy, and increased cardiovascular-associated mortality.[5]

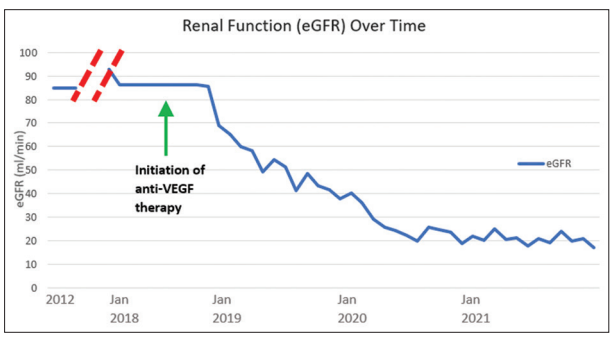

Figure 1: Case patient's trend in renal function using chronic kidney disease-EPI estimated glomerular filtration rate. Baseline renal function in 2012 before regular blood testing from 2018 onwards. Timing of anti vascular endothelial growth factor therapy indication on graph with arrow

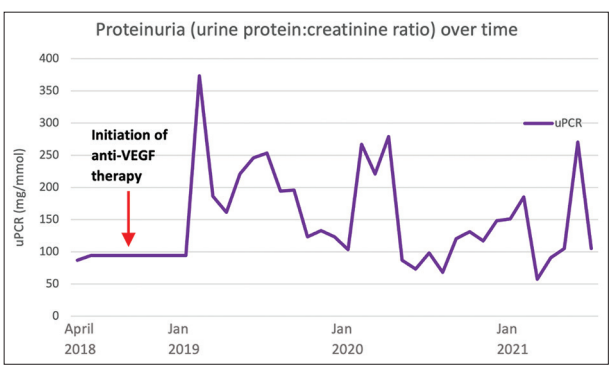

Figure 2: Trend in case patient's level of proteinuria over time. Arrow indicates timing of commencement of anti vascular endothelial growth factor therapy

VEGF signaling plays an important role in the maintenance of the healthy structure of the kidney podocyte through organization of the actin cytoskeleton.[3,5] Disruption of this signaling can lead a loss of endothelial fenestrations, podocyte effacement, and the clinical presentation of nephrotic syndrome.[2,5] VEGF signaling is also required for the functioning of the renal endothelium and is involved in nitric oxide production and vasodilation. Inhibition of this signaling results in an increase in potent vasoconstrictor endothelin-1 and inhibition of nitric oxide production.[3,5] Endothelial dysfunction results in hypertension, thrombotic microangiopathy, and dysregulation of the clotting cascade.[3] Declining renal function is related to these underlying pathological mechanisms driving glomerular disease and hypertension.

Although intravitreal anti-VEGF therapy has not previously been associated with these systemic adverse effects, several case reports have described the clinical syndrome of worsening proteinuria, hypertension, and renal function following its initiation, and many have correlated with renal biopsy pathology reports.[4-6] This has included case reports of patients with no diagnosis of diabetes mellitus/diabetic nephropathy.[6] Withdrawal of intravitreal anti-VEGF treatment has been associated with improvement in renal function and proteinuria.[6] Shye *et al.* estimated a 14% risk of worsening of hypertension and 14–45% risk of proteinuria worsening through analysis of available limited data, which compares to an estimated risk of 23.6% of worsening hypertension and 21–63% of worsening proteinuria for intravenous agents.[5]

However, population studies have thus far failed to find a significant relationship between intravitreal anti-VEGF therapy and the development of these adverse outcomes. Glassman *et al* (2018)[7] undertook a randomized clinical trial comparing intravitreal anti-VEGF agents without control and did not find a significant worsening of category measurement of proteinuria nor hypertension for 660 participants over a 2-year follow-up period. O'Neil *et al.* (2019)[8] did not find a significant association with intravitreal anti-VEGF exposure and declining eGFR or worsening albuminuria in 85 patients over a 2.5-year follow-up period, although acknowledged a longer follow-up of more participants was likely required to power a study designed to capture low-frequency systemic events. Therefore, the true incidence of glomerular disease due to intravitreal VEGF inhibition is unknown, and there is a need for further epidemiologic study to determine this and the subgroups of patients that are at particular risk. This requires transparent recording of medication administration out with a patient's primary care prescription record.

Intravitreal anti-VEGF agents are typically given on a monthly basis. The drug levels with intravitreal injection are 100–200 times lower than with systemic therapy.[5] Nonetheless, ophthalmic administration of anti-VEGF agents can result in detectable serum levels which are high enough to suppress more than 50% of intravascular VEGF levels.[9] Injection in one eye can have therapeutic benefits for the other given the systemic absorption.[4] The modulating factors for the variation in systemic absorption of VEGF inhibitors are unknown. The association between number of anti-VEGF injections and development of adverse effects has not been demonstrated. Ranibizumab has a shorter half-life and lower systemic absorption compared with the other anti-VEGF and possibly associated with less severe VEGF inhibition.[9] Confirmation of VEGF inhibition/measurement of drug levels has not featured in studies assessing adverse outcomes of intravitreal anti-VEGF, which is possibly a contributor to the conflicting results of studies.

Further study of the optimal dosage and frequency of these injections to minimize the development of systemic complications is required, as complete withdrawal of these agents may not be possible due to the lack of alternative options for preserving sight. Focal laser as an adjuvant treatment can significantly reduce the frequency of anti-VEGF injections.[2] Increasing evidence that other inflammatory pathways and retinal neurodegeneration are implicated as independent pathogenesis pathways in diabetic retinopathy may provide alternative therapeutic avenues.[2]

Conclusion and Clinical Significance

The clinical syndrome of anti-VEGF-induced worsening eGFR, proteinuria, and hypertension overlaps with the natural progression of diabetic nephropathy, and this clinical presentation represents significant diagnostic challenge. Given the widespread use of these agents in patients with diabetic retinopathy who have concomitant nephropathy, there needs to be a heighted awareness to changes in proteinuria and blood pressure after the initiation of these treatments. Epidemiological research is required to assess the prevalence of adverse reactions to anti-VEGF in this vulnerable patient group. Anti-VEGF agents are often necessary to maintain sight, and therefore, quality of life for patients and identification of patient factors which increase susceptibility for adverse renal events and hypertension are welcomed to develop strategies for renal protection, and help patients make informed choices regarding the risks of these therapies.

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