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Exceptional Case

EXCEPTIONAL CASE

Three patients with injection of intravitreal vascular endothelial growth factor inhibitors and subsequent exacerbation of chronic proteinuria and hypertension

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ABSTRACT

Vascular endothelial growth factor (VEGF) receptor inhibition is a commonly used tool to prevent vascular proliferation in tumors and retinal diseases. The antiangiogenic effects of these drugs have made them potent adjunct therapies when given systemically for malignancies. They are also useful tools to ameliorate diminishing eyesight in retinopathy. Hypertension and proteinuria have been observed in systemic VEGF inhibitor therapy, with rarer presentations involving nephrotic-range proteinuria due to glomerulopathies. Pharmacokinetic studies have shown detectable blood levels of anti-VEGF inhibitors up to 30 days postintravitreal injection. Animal studies have also demonstrated binding of VEGF inhibitors in simian glomeruli 1 week after a single intravitreal injection. We report three patients who received intravitreal bevacizumab and/or aflibercept with worsening hypertension, proteinuria and renal injury. Data regarding emerging evidence of VEGF inhibitor nephrotoxicity after intravitreal injections are also presented. The clinical data and the existing literature are reviewed to support the hypothesis that intravitreal anti-VEGF agents may be unrecognized nephrotoxins. These agents are given to vulnerable patients with diabetes, hypertension and preexisting nephropathy and proteinuria. This case series is reported to spur further study of the systemic effects of intravitreal VEGF inhibitors.

Keywords: angiogenesis, diabetes mellitus, diabetic nephropathy, hypertension, proteinuria, VEGF

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INTRODUCTION

Vascular endothelial growth factor (VEGF) inhibitors started to make an entrance in clinical use in the late 1990s as novel anti-neoplastic agents. Bevacizumab (Avastin®; Genentech, South San Francisco, CA, USA), the first agent of its class on the market, is a humanized anti-VEGF monoclonal antibody. It is currently indicated for non–small cell lung cancer, renal cell carcinoma, breast cancer, ovarian cancer, glioblastoma multiforme (GBM) and other malignancies [1–6]. Its side-effect profile as a systemic agent has been extensively studied and includes hypertension, proteinuria, thrombotic microangiopathy (TMA), renal injury and in some cases frank glomerular disease with nephrotic-range proteinuria [7–9].

Bevacizumab inhibits angiogenesis by direct binding of VEGF-A, which in turn disrupts signaling of VEGF receptors 1 and 2. VEGF receptors are predominately expressed on vascular endothelial cells. VEGF activity is also required in a paracrine manner as a trophic signal by the renal podocytes that line the glomerular basement membrane [10, 11]. Pathological VEGF signaling has been implicated in proteinuria due to preeclampsia and diabetic nephropathy (DN) and induced by mammalian target of rapamycin (mTOR) inhibitors like sirolimus and everolimus [12–14].

Because VEGF is a crucial regulator of angiogenesis, it has become an attractive target for treating ophthalmic diseases caused by inappropriate blood vessel proliferation. Bevacizumab is given through the intravitreal route as an 'off-label' treatment for the management of intraocular neovascular, edematous and proliferative disorders [15, 16]. Systemic administration of bevacizumab and related anti-VEGF agents is known to cause hypertension and proteinuria in a variable manner [17, 18]. The relationship between intravitreal anti-VEGF agents and systemic hypertension has not been well established due to conflicting study results [19–23]. Furthermore, the effects of intravitreal anti-VEGF injections on proteinuria and renal function have not been directly studied.

Given the extensive use of intravitreal anti-VEGF agents in diabetics with retinopathy and concomitant nephropathy, special attention needs to be focused on changes in proteinuria and blood pressure after these injections are administered. New studies show that anti-VEGF agents are absorbed systemically [24], actively suppressing VEGF activity *in vivo* [24]. There are also additional studies showing anti-VEGF agents binding to and disrupting the glomerular basement membranes of simian glomeruli 1 week after intravitreal injection [25]. A more positive effect is the 'fellow eye effect' that has been observed after intravitreal injection with anti-VEGF agents. The effect is that an injection of anti-VEGF agent in one eye ameliorates diabetic retinopathy in the contralateral eye [26].

An earlier study by Avery *et al.* [27] showed evidence of systemic absorption in patients with age-related macular degeneration (AMD). A more recent publication by the same group reproduced these results in patients with diabetic macular edema and central retinal vein occlusion [27]. The elegant pharmacodynamic studies showed serum concentrations as high as 0.1–0.2 nmol/L, which is comparable with data published by the US Food and Drug Administration (FDA). These levels were near or above the 50% inhibitory concentrations (IC50) of bevacizumab, aflibercept and ranibizumab as reported by Avery *et al.* [24]. Both studies noted that ranibizumab had the lowest level of drug absorption after intravitreal injection and caused the least amount of systemic VEGF inhibition [24, 26–28]. These same findings were validated by Rogers *et al.* [29], who analyzed the participants in the Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) trial. Rogers *et al.* also confirmed less systemic VEGF inhibition after intravitreal ranibizumab relative to intravitreal bevacizumab or intravitreal aflibercept.

Given the aforementioned evidence, we began inquiring about recent intravitreal exposures to anti-VEGF agents in our clinic visits with patients with chronic kidney disease (CKD). We looked for any changes in proteinuria, hypertension control or renal function in diabetic patients who were initiated on these agents. We quickly noted two diabetic patients who developed rapidly worsening proteinuria after initiation of bevacizumab injections. A third patient developed refractory hypertension after initiation of bevacizumab injections that persisted when she was switched to aflibercept. We present these three cases to examine the unexplored question of whether there are systemic effects of intravitreal injections of VEGF inhibitors.

CASE REPORTS

Patient 1

The first patient is a 54-year-old Hispanic female with poorly controlled diabetes mellitus with a hemoglobin A1C of >10 since diagnosis in 2011. She was treated with oral agents and insulin shortly after diagnosis, given her poor glycemic control. She initially did not have overt DN, but gradually started developing albuminuria and renal function decline. Her serum creatinine first started rising to 123.79 μmol/L (1.4–1.6 mg/dL) over 2014–15 and her proteinuria rose from 1000 μg albumin/mg creatinine (1000 μg albumin/mg creatinine = 1 g albumin/g creatinine) to 2000–3000 μg albumin/mg creatinine. Her hyperglycemia remained persistent in spite of her medication regimen. She began to take nonsteroidal anti-inflammatory drugs (NSAIDs) a few times a month, but as her renal function declined, she was instructed to stop NSAID use in 2016–17. Urine protein:creatinine ratios were not obtained in the Kaiser Permanente (KP) system, so trends of albumin:creatinine ratio (ACR) were followed at the University of California Los Angeles Health System.

She was examined in KP's ophthalmology clinic and was noted to have worsening glaucoma and proliferative DN. She started treatment with bevacizumab every 4 weeks as needed in January 2016. She required a monthly dose of 1.25 mg of bevacizumab over the next 13 months in either one or both eyes over a total of 10 separate visits, with the indication of proliferative diabetic retinopathy (DR). Thus the full dose administered was 12.5 mg of bevacizumab over 10 injections during this period. A notable increase in the slope of proteinuria was noted, with an increase in ACR to 4000 μg/mg and ultimately to 7000 μg/mg (see Figure 1 for trends of renal function decline and worsening proteinuria in this patient). The patient's blood pressure did not rise beyond her usual range of 140–150 mmHg and, as such, it was not plotted.

It was noted that her renal function seemed to worsen more rapidly in the year after bevacizumab was started. A full serological workup was performed, but was unrevealing. Due to the more rapid than expected decline in renal function, a renal biopsy was performed. The biopsy showed nodular diabetic glomerulosclerosis and hypertensive nephrosclerosis without any histological features suggestive of other glomerular disease. The timing of proteinuria exacerbation corresponded with the first few months after starting intravitreal bevacizumab injections. The mechanism of renal function decline may be due to worsening proteinuria and acute tubular necrosis. Given the severity of the patient's DR, a change to a less potent agent, like

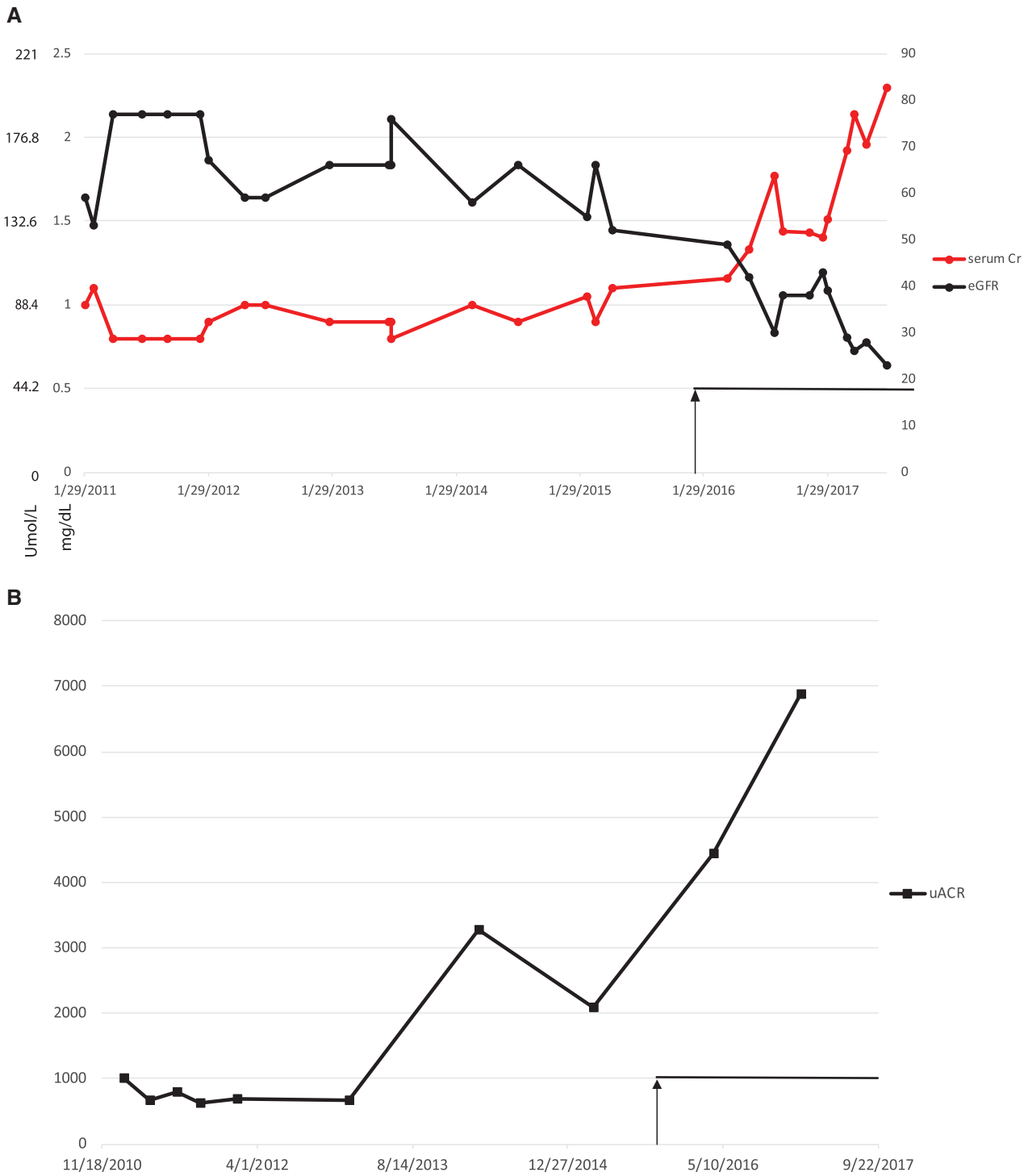

FIGURE 1: Changes in proteinuria and renal function in a diabetic (Patient 1) treated with bevacizumab. (**A**) Serum creatinine (μmol/L and mg/dL) and eGFR (by Cockroft–Gault, non-African American, in mL/min versus date). (**B**) ACR (μg albumin/mg creatinine) (equivalent to 0.001 g/g creatinine) versus date. Black arrow and line shows the period of bevacizumab injections (10 injections of 1.25 mg; total = 12.5 mg).

ranibizumab, was not immediately feasible. The patient was managed with renin–angiotensin–aldosterone system (RAAS) blockade with plans to add a non-dihydropyridine calcium channel blocker (i.e. verapamil or diltiazem) for proteinuria control, with continuing attempts to optimize hypertensive control.

Patient 2

The second patient is a 53-year-old Asian male with a history of type 2 diabetes mellitus that was diagnosed in 2010. His medical history also includes hyperlipidemia, severe uncontrolled hypertension and advanced renal disease with Stage 4 CKD just

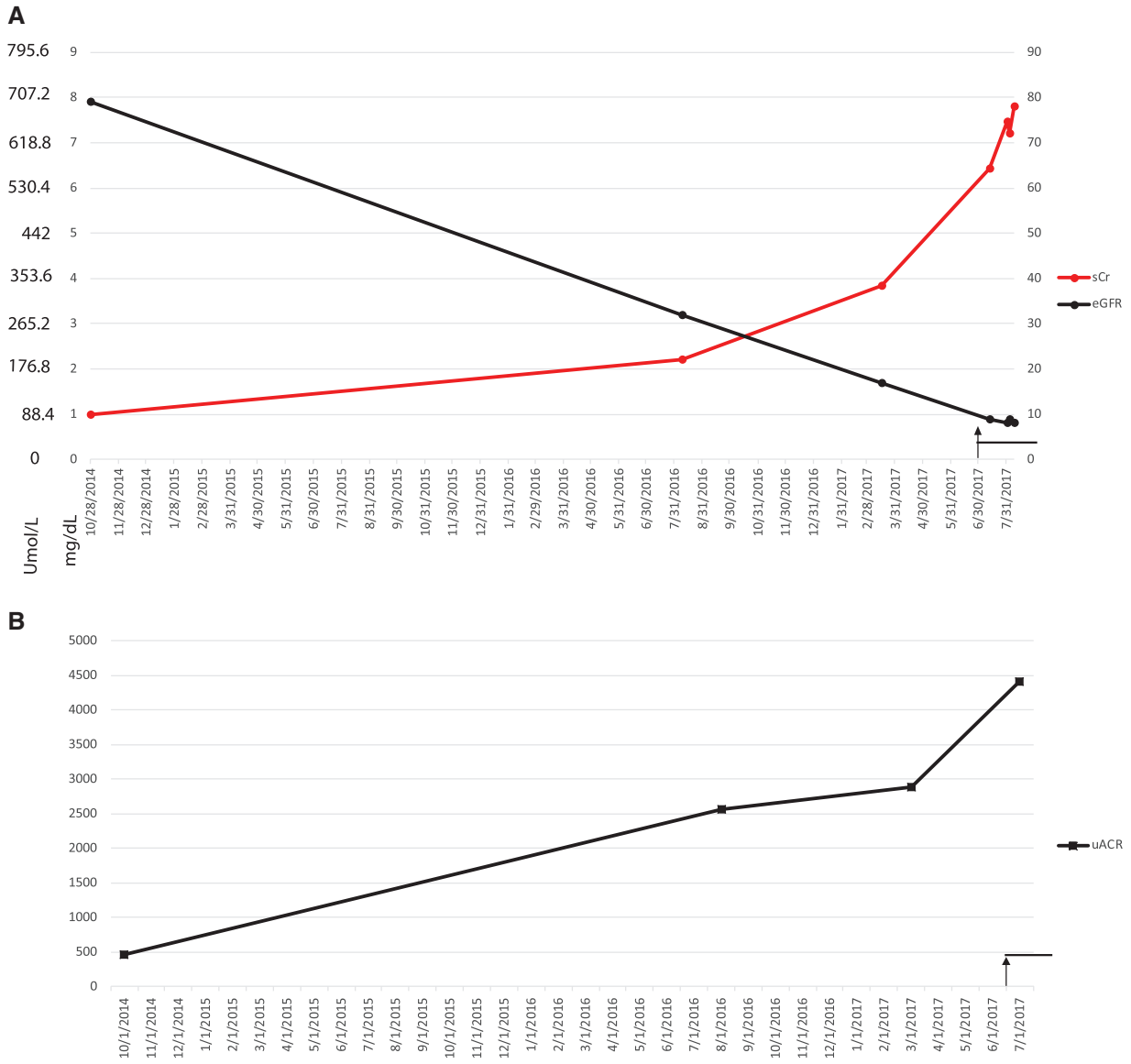

FIGURE 2: Changes in proteinuria and renal function in a diabetic (Patient 2) treated with bevacizumab. (**A**) Serum creatinine (μmol/L and mg/dL) and eGFR (by Cockroft–Gault, non–African American, in mL/min versus date). (**B**) ACR (μg albumin/mg creatinine) (equivalent to 0.001 g/g creatinine) versus date. Black arrow and line show the period of bevacizumab injections (four injections of 1.25 mg; total = 6.25mg).

before the need for intravitreal anti-VEGF therapy was noted. He had poor compliance with his prescribed diabetic diet. His hemoglobin A1C ranged between 10% and 11% at the time of initial diagnosis and remained consistency high for years afterwards. He was on oral agents for his diabetes mellitus since he declined insulin therapy despite elevated blood sugar levels and had a history of NSAID use earlier in his history that likely contributed to his CKD progression. As his renal function declined, he reduced his NSAID usage significantly and would only use NSAIDs during infrequent gout flares. His metformin was stopped in March 2017 and changed to a sulfonylurea due to his declining renal function.

He had an estimated glomerular filtration rate (eGFR) of 17 mL/min at the initiation of bevacizumab injections on 1 July 2017. He had a nearly linear decline in eGFR (mL/min) as measured by the Cockroft–Gault equation. His proteinuria had been stable at 2800–3000 μg albuminuria/mg creatinine (= 2.8 g albumin/g creatinine), but after starting bevacizumab injections for proliferative DR his ACR increased to 4500 μg albumin/mg creatinine.

Within the first 2 months of initiating therapy he received four injections of 1.25 mg of bevacizumab at an interval of every 2 weeks alternating between each eye. His injections were planned so that he waited at least 1 month between injections in the same eye. The total dose delivered over these four injections was 5 mg, and within that short interval, his renal function deteriorated to the extent of needing renal replacement therapy (hemodialysis).

His renal function had already been declining prior to anti-VEGF therapy, but after starting therapy his creatinine rose from a baseline of 338 μmol/L (3.83 mg/dL) to 688.8 μmol/L (7.79 mg/dL). His blood pressure at baseline was 180–200 mmHg systolic (SBP) and 100–120 mmHg diastolic (DBP). There was no discernible change in the SBP or DBP, though his blood pressure was already severely elevated. The increase in urine protein

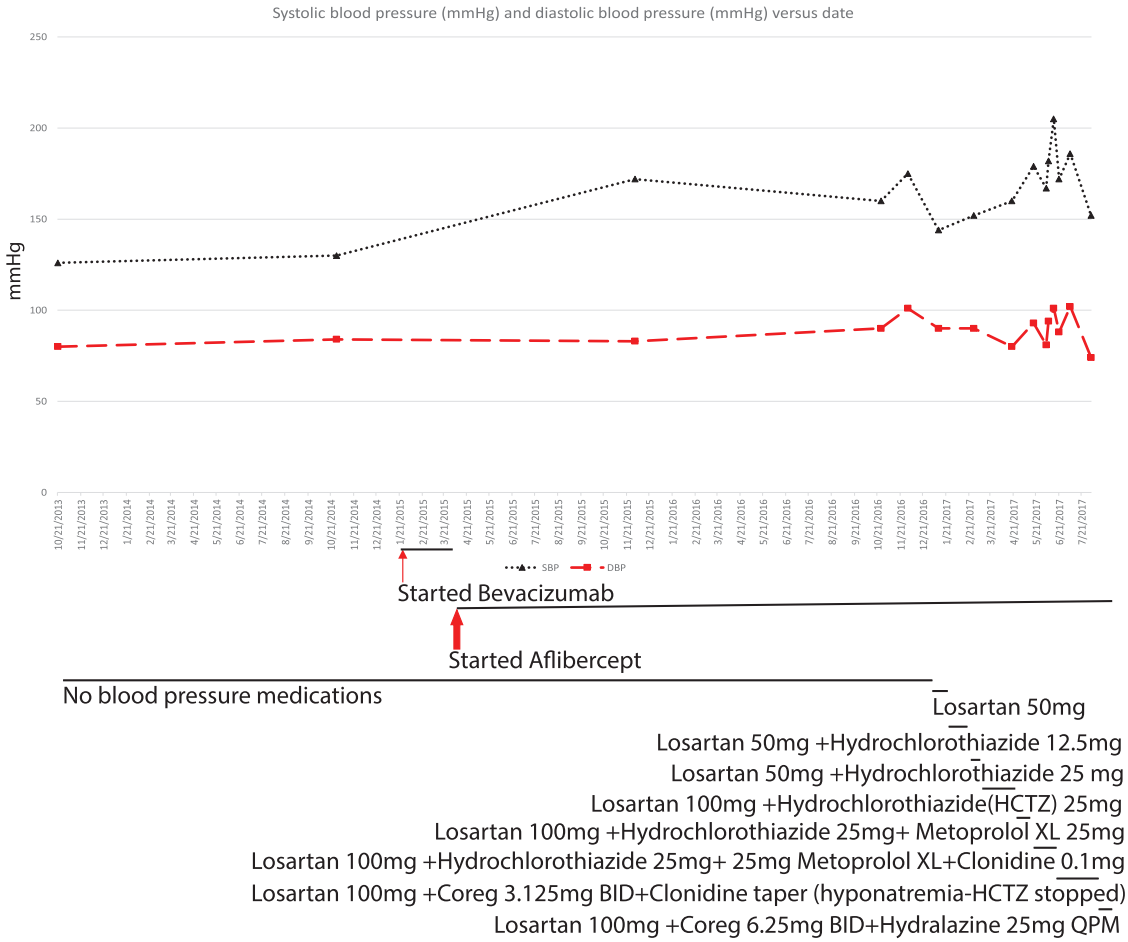

FIGURE 3: Blood pressure changes in Patient 3 with AMD treated with bevacizumab followed by aflibercept. BID, twice a day; HCTZ, hydrochlorothiazide; QPM, every evening; XL, extended release. Black lines show the period of medication administration. Thin arrow = time of bevacizumab injection (one 1.25-mg injection of bevacizumab); thick arrow = period of aflibercept injections (16 injections of 2 mg aflibercept; total = 32 mg).

from baseline to higher levels after the anti-VEGF injections and renal function trends are depicted in Figure 2.

Patient 3

The third patient presented is a nondiabetic, 65-year-old female who was diagnosed with AMD. She had normal renal function at 56.59 μmol/L (0.64 mg/dL) with no measurable proteinuria. She started bevacizumab in January 2015 and continued receiving anti-VEGF injections every 4–6 weeks. After one dose of bevacizumab (1.25 mg) she was switched to aflibercept because of the need for a stronger antiproliferative agent. Initially the patient only met the criteria for prehypertension, with an SBP within the 130–140 mmHg range and normal DBP. However, we noticed her blood pressure began to rise from her recorded baseline after initiating injections. She was monitored until July 2016, when her SBP was routinely 170–200 mmHg and antihypertensive therapy was initiated. Thus she received 1.25 mg of bevacizumab and 16 injections of 2 mg aflibercept in the period between January 2015 and July 2016, for a total dose of 32 mg of aflibercept.

Despite multidrug regimens, her SBP rarely dropped below 150 mmHg. Her secondary hypertension workup for renal artery stenosis and hyperaldosteronism was negative. She had a borderline elevated urine cortisol test, but it was too low to be diagnostic of hypercortisolemia, and the lack of weight loss, potassium wasting or finding of an abdominal mass did not suggest another endocrine cause for the observed hypertension. (Refer to Figure 3 for blood pressure trends and antihypertensive regimens needed to control increasingly resistant hypertension in this patient.) A recommendation was made to change the patient to ranibizumab if possible. Some difficulties arose from the ophthalmology perspective, however, given the severity of her macular degeneration (MD) and the lower potency of ranibizumab. The plan of care was to work to optimize this patient's blood pressure management with the goal of minimizing anti-VEGF intravitreal injections as able and to switch to a lower potency agent, like ranibizumab, when clinically feasible.

DISCUSSION

The observations presented above are not sufficient to establish a firm link between intravitreal anti-VEGF therapies and worsening of hypertension, proteinuria and/or renal function, although the timing observed suggests a correlation between beginning treatment with intravitreal injections of anti-VEGF agents and worsening of the aforementioned parameters. This is of interest given the established links between intravenous VEGF treatment and worsening of hypertension [12], proteinuria and glomerular disease [30].

Table 1. Cases of intravitreal injections of VEGF inhibitors resulting in glomerular disease or hypertension

Reference	Anti-VEGF agent	Proteinuria	Renal biopsy	Treatment	Age (years)	Gender	DR	N	UC HTN
[31]	Bevacizumab, ranibizumab	2.2–2.4 g/g Cr UPC	Case 1 MGN, Case 2 AKI, Inc Prot and TMA	Case 1: WD, Case 2: MMF, Px	52, 67	2M	No (MD)	2	No
[32]	Bevacizumab	NR	No, decreased eGFR no biopsy	No immunosuppression	NR	NR	Yes	3	No
[33]	Ranibizumab, bevacizumab	Inc	No, decreased eGFR no biopsy	HD started	51, 68	1F, 1M	Yes	2	No
[34]	Not specified	NR	No, decreased eGFR no biopsy	No immunosuppression	NR	NR	Yes	1	No
[35]	Bevacizumab	8.6 g/g Cr UPC	MGN	No immunosupression, WD	74	M	Yes	1	No
[36]	Ranibizumab	9.4 g/g Cr UPC	Class IV DN	No immunosuppresion	56	M	Yes	1	No
[37]	Ranibizumab	NR	TMA	WD	77	F	No (MD)	1	No
[38]	Bevacizumab	11 g/g Cr UPC	MCD	High-dose prednisone	54	M	Yes	1	No
[39]	Bevacizumab	4.2 g/g Cr UPC	MCD	High-dose prednisone, mizoribine	16	F	Yes	1	No
Unpub	Bevacizumab	34 g/g Cr UPC	MCD	High-dose prednisone	82	F	Yes	1	No
Case 1	Bevacizumab	6890 μg/mg ACR	DN	No immunosupression	54	F	Yes	1	No
Case 2	Bevacizumab	4416 μg/mg ACR	No	No immunosupression, HD started	53	M	Yes	1	Yes, BL
Case 3	Bevacizumab then aflibercept	None	No	No immunosupression, WD	65	F	No (MD)	1	Yes, new

AKI, acute kidney injury; BL, high blood pressure at baseline; F, female; HTN, hypertension; Inc, increased; M, male; MCD, minimal change disease; MGN, membranous glomerulonephritis; MMF, mycophenolate mofetil; NR, not reported; Prot, protein; Px, plasma exchange; UC, uncontrolled; Unpub, unpublished; UPC, urine protein:creatinine ratio; WD, withdrawal of agent.

Reports of glomerular disease [30] and worsening hypertension have also been noted in patients using intravitreal anti-VEGF injections [21, 22]. Pharmacokinetic and pharmacodynamic studies prove that intravitreal anti-VEGF drugs are absorbed and remain detectable in the blood for >1 month post-injection [24]. Other studies show that a week after intravitreal anti-VEGF agents are injected these agents can be detected binding to simian glomeruli, causing pathological changes in the glomerular basement membrane [25]. Thus it is not completely surprising that patients receiving intravitreal anti-VEGF injections display the same phenotypes of systemically treated patients. This is because intravitreal injections of bevacizumab, aflibercept and even ranibizumab are absorbed to varying degrees.

There have been nine other reports encompassing 13 patients who demonstrated renal failure, hypertension and glomerulopathies after intravitreal anti-VEGF injections [31–39]. This is postulated to occur through disruption of VEGF and downstream receptor tyrosine kinase signaling, leading to protein kinase C activation and dysregulation of nitric oxide (NO) generation [40, 41]. Refer to Table 1 for the 17 cases of hypertension and proteinuria, of which 13 are reported in the literature [31–39], 1 previously historic, unpublished report that we reference and the 3 cases reported in this series. Also see Figure 4 for the molecular physiology of VEGF signaling.

The cases we present show a variety of phenotypes. Patient 1 showed worsening proteinuria and possible worsening of renal function with a biopsy showing only DN and hypertensive nephrosclerosis. Patient 2 showed only an increase in proteinuria at a data point observed days after bevacizumab injection, with worsening of severe Stage 4 CKD. Patient 3 showed only uncontrolled, resistant hypertension after starting ongoing bevacizumab and then aflibercept injections for MD. None of these phenotypes would surprise an experienced oncologist who has been treating patients with adjuvant anti-VEGF medications as systemic chemotherapy. The concern is that many patients who are receiving intravitreal anti-VEGF therapy also have diabetes, hypertension, proteinuria and CKD at baseline.

Avery *et al.* helped provide evidence of systemic absorption of anti-VEGF agents injected through the intravitreal route. This was demonstrated first in AMD patients in 2014 [24], then more recently in patients with central retinal vein occlusion and in patients with diabetic macular edema [27]. Avery *et al.* [26] also raised concerns about systemic side effects, and a meta-analysis in 2016 reported a possibly increased risk of cerebrovascular accidents in patients exposed to high levels of intravitreal VEGF inhibitors [28].

The recommendations on management of worsening proteinuria observed after intravitreal anti-VEGF injections remain limited given the very limited data on this subject. It is reasonable to consider decreasing the dose or switching to a less potent agent such as ranibizumab. This is due to the decreased systemic absorption and less severe systemic VEGF inhibition seen with ranibizumab [24, 26, 27]. Withdrawal of therapy may not be a suitable option if a patient's eyesight is rapidly deteriorating, but it is an option in the most extreme cases of worsening proteinuria or renal function decline. Improving hypertensive control and RAAS blockade are reasonable adjunctive steps.

It is important to note that ranibizumab was linked to one case of TMA [37], as well as several other cases of renal function decline and proteinuria [31, 33, 36]. While ranibizumab represents a compromise as a less potent and less systemically absorbed anti-VEGF agent, it is not free from potential side effects [42]. Other less potent agents, such as pegaptanib, may offer better safety and fewer systemic side effects than the aforementioned agents, but are yet to be widely tested [43, 44]. Future investigations include prospectively confirming and

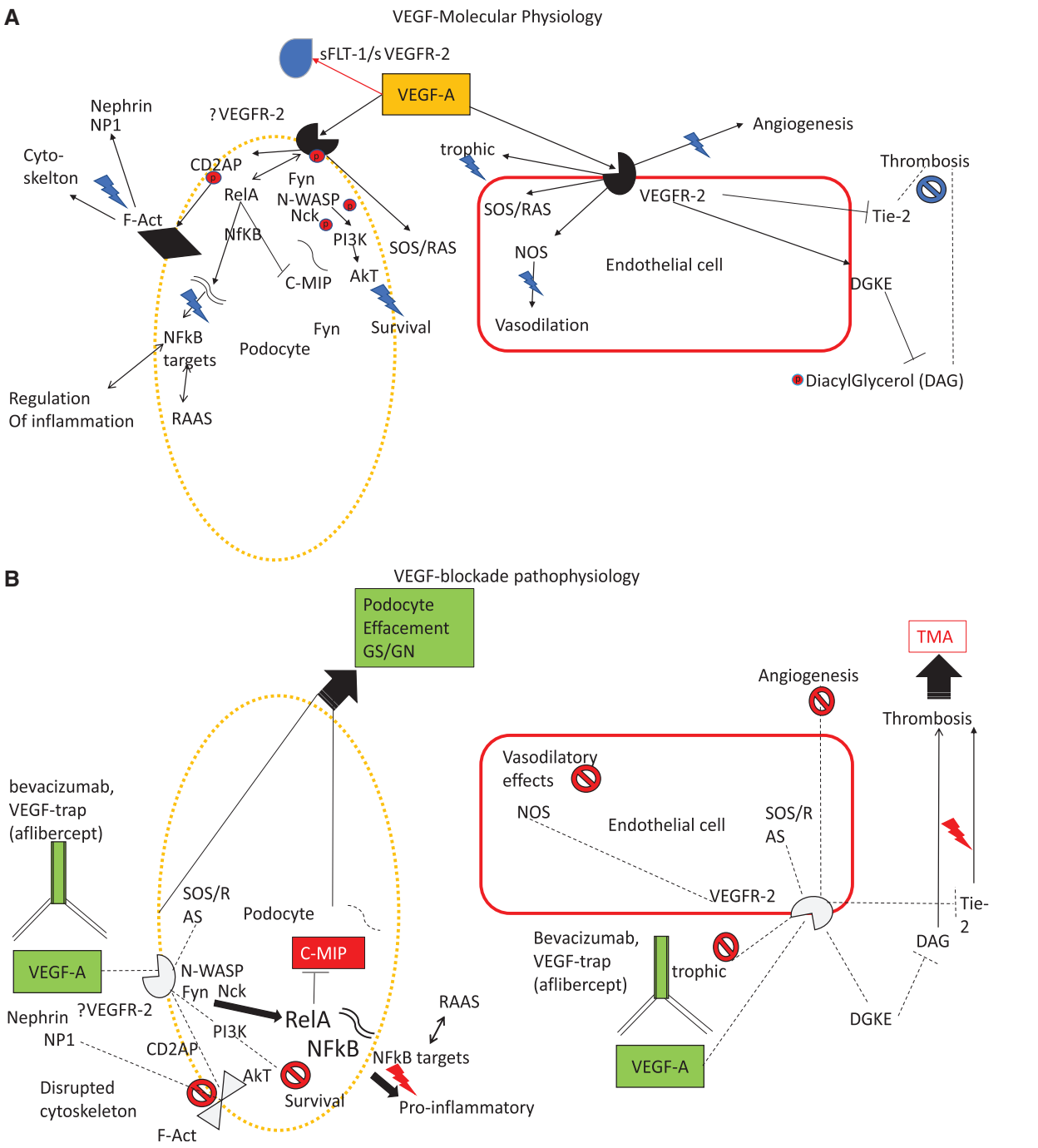

FIGURE 4: Molecular physiology of VEGF signaling in podocytes and endothelial cells and renal pathophysiology that ensues with VEGF blockade. (**A**) Molecular physiology and (**B**) pathophysiology with VEGF blockade. VEGF-A signaling to renal podocytes maybe paracrine or mediated through VEGF-2 receptors. Akt, protein kinase B (PKB); CD2AP, CD2-associated protein; C-MIP, C-Maf-inducing protein; DAG, diacyl glycerol; DGKE, diglyceride kinase epsilon; F-Act, F-actin; Fyn, proto-oncogene tyrosine-protein kinase fyn; GN, glomerulonephritis; GS, glomerulosclerosis; Nck, NCK tyrosine kinase; NFkB, nuclear factor kappa light chain enhancer of activated B cells; NP1, neuronal pentraxin 1; N-WASP, Neural Wiskott–Aldrich syndrome protein; PI3K, phosphatidylinositol-4, 5-bisphosphate 3-kinase; RAS, rat sarcoma protein; Red P, phosphoryl group; RelA, v-rel avian reticuloendotheliosis viral oncogene homolog A; SOS, son of sevenless; sVEG2R, soluble VEGF receptor 2; VEGF-A, VEGF receptor A; VEGFR2, VEGF receptor 2; Tie2, tyrosine-protein kinase receptor TIE-2. Twin nucleic acid strands = messenger RNA.

quantifying the changes in proteinuria after intravitreal injections of anti-VEGF inhibitors. Given the different pharmacodynamic profiles of the various anti-VEGF agents, it is expected that each drug may have different effects on hypertension, proteinuria and CKD progression after intravitreal administration.

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AUTHORS' CONTRIBUTIONS

R.M.H. wrote the manuscript. E.A.L., H.H. and U.S. cowrote the manuscript. P.N.Y., J.W. and S.B. edited the manuscript. N.A. produced the figures and was a research volunteer. M.G. is the senior author for this case series.

CONFLICT OF INTEREST STATEMENT

None declared. This work does not contain human subject research material.

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