Review Article

Systemic complications of intravitreal bevacizumab: a case report and literature review

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ABSTRACT

Background: Systemic complications of intravitreal bevacizumab (IVB) injections have been previously reported. We aimed to summarize the systemic complications reported in online primary studies. Moreover, we describe a patient experiencing simultaneous renal and cutaneous drug-induced adverse effects, with exacerbation of chronic renal insufficiency and granulomatous skin lesions, after receiving several IVB injections to manage bilateral ischemic branch retinal vein occlusion (BRVO).

Case Presentation: A 69-year-old Hispanic diabetic man with chronic renal insufficiency due to polyclonal gammopathy received several IVB injections to treat bilateral ischemic BRVO. One week after the sixth injection, the patient developed acute-on-chronic renal failure and multiple rounded maculopapular, erythematous, and ulcerated skin lesions. Renal and skin biopsy specimens revealed granulomatous drug-induced responses in both organs, and granulomatous diseases of infectious and oncological sources were ruled out. We performed an electronic search of the PubMed/MEDLINE database with no language or time restrictions using the keywords "intravitreal bevacizumab" or "intravitreal Avastin" combined with "systemic side effects," "systemic complications," or "systemic adverse," or "systemic adverse event." The search yielded 147 articles published over almost two decades. After screening and assessment, we selected and summarized 40 primary studies that mentioned IVB-related systemic complications.

Conclusions: IVB-induced systemic complications, such as arteriothrombotic events, venous thrombotic events, and hypertension, are rare but potentially serious. Care should be taken when administering multiple doses of intravitreal IVB to patients with pre-existing kidney dysfunction. Bevacizumab-related toxicity must be considered in cases of sudden deterioration of renal function and / or unexpected granulomatous skin lesions in oncologic or chronically polymedicated patients.

KEYWORDS

state of the art reviews, case study, avastin, intravitreal injection, chronic renal insufficiency, drug side effect, drug toxicity

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How to cite this article: Gramajo AL, Aucar ME, Laborie MV, Schlottmann PG, Luna JD. Systemic complications of intravitreal bevacizumab: a case report and literature review. Med Hypothesis Discov Innov Optom. 2023 Summer; 4(2): 63-75. DOI: https://doi.org/10.51329/mehdioptometry175

Received: 10 March 2023; Accepted: 07 June 2023

INTRODUCTION

Intravitreal bevacizumab (IVB) is effective for the treatment of a broad spectrum of common retinal pathologies [1-3], such as exudative age-related macular degeneration (ARMD), macular edema secondary to retinal vein occlusion, diabetic macular edema, proliferative diabetic retinopathy, and myopic choroidal neovascularization. It is also used as an adjunct therapy before vitrectomy for neovascular intraocular conditions [4-7].

IVB is administered in amounts approximately 150-fold less than those of the systemically administered doses. However, intravitreal injections of an anti-vascular endothelial growth factor (VEGF) can lead to systemic absorption and a decrease in serum free VEGF production [8, 9]. Although intravitreal anti-VEGF injections are usually administered monthly when both eyes are treated, they can be used more frequently; thus, their systemic levels and inhibition of systemic free VEGF may be higher [10].

Intravitreal bevacizumab and aflibercept have higher potencies than ranibizumab, with longer ocular half-lives, greater systemic absorption, and more prolonged decreases in serum VEGF levels [11]. Systemic adverse events after intravitreal anti-VEGFs are uncommon and can include hypertension [12], non-ocular hemorrhage, higher risk of hemorrhagic stroke [13], arteriothrombotic events [2, 14], venous thrombotic events [2, 14, 15], and even death [14]. However, renal [16, 17] and dermatological [18, 19] IVB-related toxicities are rare.

In this narrative review, we summarize the systemic complications of IVB injections reported in primary online studies of various designs. Moreover, we describe a patient with simultaneous renal and cutaneous drug-induced adverse reactions consisting of exacerbation of chronic renal insufficiency and development of granulomatous skin lesions after receiving several IVB injections to manage bilateral ischemic branch retinal vein occlusion (BRVO).

CASE PRESENTATION

We performed an electronic search of the PubMed/MEDLINE database with no language or time restriction using the keywords “intravitreal bevacizumab” or “intravitreal Avastin” combined with “systemic side effect,” “systemic complication,” “systemic adverse,” or “systemic adverse event” to include online primary studies that reported systemic adverse events after IVB injection.

The search yielded 147 articles published over almost two decades. We screened the titles and abstracts of 147 articles with various study designs and selected 57 papers. The full texts of these 57 papers were retrieved and assessed, and 17 studies were excluded because they did not report, or had not encountered, IVB-related systemic adverse events by the end of the study period. Ultimately, 40 papers fulfilled our criteria, and we summarize all these reported IVB-related systemic complications in Table 1.

We now present a case of systemic complications attributable to IVB injections from our ophthalmology clinic. A 69-year-old Hispanic man consulted our clinic in October 2018 with decreased visual acuity in his left eye (OS). The patient’s systemic medical history included diabetes, which was managed without insulin, arterial hypertension of 10 years’ duration, and chronic renal insufficiency due to polyclonal gammopathy with increased immunoglobulin (Ig) G and beta 2-microglobulin levels. At his initial encounter with us, he had received prior IVB injections for the treatment of macular edema due to BRVO: three in the right eye (OD), and one in the OS.

His best-corrected distance visual acuity (BCDVA) was 20 / 50 OD and 20 / 200 OS, as obtained using the Original Series Sloan Letter ETDRS chart (Precision Vision, Illinois, USA). Funduscopic examination using the Vantage Plus Binocular Indirect Ophthalmoscope (Keeler Instruments Inc., Broomall, PA, USA) with a + 20 D non-contact lens (Volk Optical, Mentor, OH, USA) revealed a hemi-retinal ischemic vein occlusion in the OS and a BRVO in the OD (Figure 1A, B).

Fundus fluorescein angiography (FFA) performed using a VISUCAM Lite Digital Fundus Camera (Carl Zeiss Meditec, Inc., Dublin, CA, USA) showed marked macular and peripheral retinal ischemia with areas of capillary non-perfusion in both eyes (OU) and evidence of leakage from neovascularization of the optic disc (NVD) and elsewhere in the retina (NVE) in the OS and NVE in the OD (Figure 1C, D). After obtaining informed patient consent, IVB 1.25 mg (Avastin; Genentech Inc., South San Francisco, CA, USA) was injected in the OS using a 30-gauge needle, 4.0 mm posterior to the limbus.

In December 2018, the patient returned for consultation because of blurred vision in the OS. Ophthalmological examination revealed a mild vitreous hemorrhage; thus, another injection of IVB 1.25 mg was administered. One week after the last IVB injection, the patient presented with significant deterioration of renal function with nephrotic-range proteinuria and microalbuminuria, prompting a renal ultrasound and kidney puncture biopsy. Simultaneously, multiple rounded, maculopapular, erythematous, indurated lesions appeared on his upper extremities, shoulders, and upper back. The lesions were biopsied a few days later.

Table 1. Summary of the reported systemic complications of intravitreal bevacizumab

Author (Year)	Specifications of study	Systemic complications of intravitreal bevacizumab
Johari et al. (2022) [20]	A prospective cross-sectional study including 118 patients (74 [62.7%] with DME and 44 [37.3%] with retinal vein occlusion) who received their first IVB injection.	Systemic complications were facial erythema one day after IVB injection (n = 1, 0.8%), facial erythema one month after IVB injection (n = 1, 0.8%), and myocardial infarction one month after IVB injection (n = 2, 1.7%).
Fam and Finger (2020) [18]	A 52-year-old man with subfoveal choroidal melanoma was treated with plaque brachytherapy. The patient received IVB injections for macular edema, retinal detachment, and delayed radiation retinopathy.	Three days after his eighth IVB injection, the patient developed signs of a delayed cutaneous cell-mediated drug hypersensitivity reaction: pruritus, skin rash, and progressive exacerbation. IVB was discontinued and treatment switched to periodic intravitreal aflibercept. He had no recurrent cutaneous hypersensitivity reactions.
Balci et al. (2020) [1]	Retrospective review of 270 patients with nARMD treated with IVB.	Short-term increase in systemic arterial blood pressure.
Weinstein et al. (2020) [21]	A retrospective cohort study of 2102 consecutive patients with nARMD treated with IVB injections over 4 years.	Significantly higher rates of acute coronary syndrome and stroke after the first IVB injection was found within 2 years versus 2 years before injection, and these complications were more likely in those aged > 80 years and with < 6 injections. However, other thromboembolic events had no statistically significant differences within 2 years after IVB injections versus 2 years before injection.
Touzani et al. (2019) [16]	Case report of a 72-year-old man who received monthly IVB injections for neovascular glaucoma in the previous 6 months.	The patient developed asymptomatic acute kidney injury associated with creatininemia and albuminuria without hematuria. A renal biopsy specimen showed two obsolescent glomeruli with complete glomerulosclerosis, eight glomeruli with thickened capillary walls, and evidence of renal microangiopathy. The only positive finding in immunofluorescence was a sparse endothelial positivity for C3 in arterioles. Endothelial cell irregularities and focal loss of fenestrations were detected on electron microscopy with subendothelial space expansion. The findings were compatible with endothelial injury. Four months after cessation of IVB, serum creatinine level was reduced, and albuminuria normalized, confirming IVB-induced renal microangiopathy. One year after IVB cessation, there was a further reduction in serum creatinine level, and the urinary albumin-creatinine ratio reached 3.3 mg / g.
Kunzmann et al. (2019) [22]	Case report of a six-week-old girl with Incontinentia Pigmenti receiving IVB injection for left eye retinopathy with impending tractional detachment.	Immediate onset of abdominal symptoms after IVB injection, abdominal distension, and bloody stools were consistent with acute necrotizing enterocolitis. The diagnosis was confirmed with a pathological examination of resected intestine. One year later, the child had normal feeding with adequate weight gain.
Lekha et al. (2017) [23]	Evaluation of the long-term safety and efficacy of IVB injections in a noncomparative, retrospective interventional case series that included 15 eyes of 10 patients with CNV secondary to angioid streaks who received monthly IVB injections until stabilization of the lesion.	In a mean follow-up of 57.33 months (range: 25 – 100), one patient developed two thromboembolic events.
Schauwvlieghe et al. (2016) [24]	Primary or recurrent sub- or juxtafoveal CNV secondary to nARMD in 161 patients treated with monthly 1.25 mg IVB injections during one year.	The occurrences of serious adverse events and adverse events were 34 and 256 in the bevacizumab group, with one death due to a serious adverse event. However, there was no significant difference compared with the adverse event rate of the ranibizumab group. Adverse events by the MedDRA system organ class in patients treated with IVB were cardiac disorder (n = 4), infection (n = 4), nervous system disorder (n = 3), injury or procedural complication (n = 5), benign or malignant neoplasm (n = 2), surgical or medical procedure (n = 13), gastrointestinal disorder (n = 2), and any other system organ class (n = 18).
Berg et al. (2015) [15]	A multicenter, randomized, noninferiority clinical trial comparing the efficacy and safety of IVB versus ranibizumab for the treatment of nARMD.	At one year, of the 213 IVB-treated patients with nARMD, 4 died and 37 had ≥ 1 serious systemic adverse event. The IVB group had significantly fewer arteriothrombotic, nonfatal myocardial infarction, and cardiac events than the ranibizumab group. However, the number of patients with a history of myocardial infarction in the ranibizumab group was significantly greater. Other serious adverse events, gastrointestinal disorders, and venous thrombotic events were similar and infrequent with both anti-VEGF treatments.

Continued Table 1. Summary of the reported systemic complications of intravitreal bevacizumab

Author (Year)	Specifications of study	Systemic complications of intravitreal bevacizumab
Krebs et al. (2013) [25]	Comparing IVB versus ranibizumab for treating nARMD in a prospective randomized parallel group multicenter clinical trial; 154 patients received IVB.	Overall, the total number of adverse events or number of adverse events in any of the subgroups was comparable. Frequency of adverse events at one year in IVB-treated patients: death (n = 3), heart attack (n = 3), stroke (n = 1), mesenteric artery occlusion (n = 1), arrhythmia (n = 1), nervous system disorders (n = 2), infection (n = 3), injury or procedural complication (n = 2), benign or malignant neoplasm (n = 1), surgical or medical procedure (n = 1), and any other system organ class (n = 3).
Kodjikian et al. (2013) [2]	A multicenter, double-masked, prospective, noninferiority, randomized trial for comparing efficacy and safety of IVB versus ranibizumab intravitreal injections to manage nARMD.	The proportion of patients with serious systemic adverse events was comparable between the two groups. In the IVB group, 30 patients (12.2%) had at least one serious systemic adverse event, and 2 (0.8%) had died (not related to IVB injection). Other adverse events were arteriothrombotic events (myocardial infarction [n = 1, 0.4%]), venous thrombotic events (pulmonary embolism [n = 1, 0.4%]), and hypertension (n = 1, 0.4%). Adverse events based on the MedDRA system organ class: cardiac disorders (n = 2, 0.8%), infections and infestations (n = 4, 1.6%), nervous system disorders (n = 3, 1.2%), injury, poisoning, and procedural complications (n = 4, 1.6%), neoplasms (benign, malignant, and unspecified) (n = 1, 0.4%), surgical and medical procedures (n = 5, 2.0%), gastrointestinal disorders (n = 3, 1.2%), and any other system organ class (n = 10, 4.1%).
Chakravarthy (2013) [26]	In a multicenter, non-inferiority randomized clinical trial, patients with active, treatment naive nARMD were randomly assigned to intravitreal IVB (1.25 mg) or ranibizumab (0.5 mg) injections in continuous (monthly) or discontinuous (as needed) regimens, with monthly review.	Serious systemic adverse events among IVB-treated group (n = 96) within two years: death by any cause (n = 15, 5%), arterial thrombotic event (n = 10, 3%) (non-fatal myocardial infarction [n = 4, 1%], non-fatal stroke [n = 3, 1%], death from vascular causes [n = 4, 1%]), arterial thrombotic event or heart failure (n = 12, 4%) (heart failure [n = 2, 1%]), venous thrombotic event (n = 4, 1%) (deep vein thrombosis [n = 1, < 1%], pulmonary embolism [n = 3, 1%]), hospital admission for angina (n = 3, 1%), hospital admission for non-ocular hemorrhage (n = 1, < 1%), transient ischemic attack (n = 1, < 1%), any serious systemic event excluding non-vascular deaths (n = 19, 6%), any serious systemic event including non-vascular deaths (n = 28, 9%), and ≥ 1 serious systemic event (n = 80, 27%). Frequency of adverse effects based on MedDRA system organ class among IVB treated group (n = 254) within two years: cardiac disorders (n = 19, 6%), gastrointestinal disorders (n = 9, 3%), general disorders and administration site conditions (n = 16, 5%), infections and infestations (n = 12, 4%), injury, poisoning, and procedural complications (n = 10, 3%), neoplasms (benign, malignant, and unspecified; including cysts and polyps) (n = 14, 5%), nervous system disorders (n = 8, 3%), respiratory, thoracic, and mediastinal disorders (n = 7, 2%), surgical and medical procedures (n = 14, 5%), vascular disorders (n = 6, 2%), and other (n = 14, 5%).
Besozzi et al. (2013) [27]	Case report of a 54-year-old man treated with IVB for CNV-induced vision loss in context of angioid streaks due to pseudoxanthoma elasticum.	The patient developed acute stroke three days after injection of second dose of IVB.
Chakravarthy et al. (2012) [28]	Multicenter, noninferiority factorial clinical trial comparing the efficacy and safety of ranibizumab versus IVB in treating nARMD.	At one year, there was no significant difference between the two drugs in the proportions experiencing a serious systemic adverse event. Serious systemic adverse events among IVB-treated group (n = 294) at one year: 5 (1.7%) had died, which was comparable with the ranibizumab-treated group. Fewer patients treated with IVB (0.7%) had an arteriothrombotic event or heart failure than with ranibizumab, with no significant difference between them. One or more serious systemic adverse events occurred in 12.5% (n = 37) and were comparable with the ranibizumab-treated group. Cardiac disorders and surgical or medical procedures were comparable between the two drugs.

Continued Table 1. Summary of the reported systemic complications of intravitreal bevacizumab

Author (Year)	Specifications of study	Systemic complications of intravitreal bevacizumab
Sharma (2012) [3]	A retrospective chart review for comparison of serious ocular or systemic adverse effects of IVB and ranibizumab in treating various eye diseases.	Arterial thromboembolic events within one month of injection among 222 IVB-treated patients were two myocardial infarctions and one transient ischemic attack, with a higher incidence in the IVB group, yet the confidence interval was wide.
Martin et al. (2012) [14]	A multicenter, randomized trial investigating the efficacy of ranibizumab and bevacizumab when administered monthly or as needed in treating patients with nARMD.	At two years, 36 (6.1%) of 586 IVB-treated patients had died, 29 (5.0%) developed arteriothrombotic events, and 10 (1.7%) developed venous thrombotic events; results were not significantly different from those of the ranibizumab treatment group. One or more serious systemic adverse events were recorded in 234 (39.9%) IVB-treated patients and were significantly more frequent than in the ranibizumab treatment group. Considering only events occurring in year 2, 131 (24.4%) of 536 IVB-treated patients experienced a systemic serious adverse event. The risk ratio within two years for all systemic serious adverse events was 1.30. The proportion of events was higher among IVB-treated patients for each of the MedDRA system organ classes except for gastrointestinal disorders, such as hemorrhage, hernia, nausea, or vomiting, which occurred in 28 (4.8%).
Micieli et al. (2011) [29]	Case report of a 64-year-old man with bilateral nARMD who had a history of 13 IVB injections in the right eye (last injection was 16 days prior) and seven IVB injections followed by six ranibizumab injections in the left eye (last injection was 2 weeks prior).	Third cranial nerve palsy.
Martin et al. (2011) [30]	A multicenter, single-blind, noninferiority clinical trial comparing the efficacy and safety of ranibizumab or IVB on a monthly or as-needed schedule in managing nARMD.	At one year, 4 of 286 patients (1.4%) in the IVB-monthly group and 11 of 300 patients (3.7%) in the IVB-as-needed group had died. Frequencies of serious systemic adverse events in the IVB-monthly group (n = 286) and the IVB-as-needed group (n = 300) were: arteriothrombotic event 6 (2.1%) and 8 (2.7%) (nonfatal myocardial infarction 2 [0.7%] and 1 [0.3%], nonfatal stroke 2 [0.7%] and 2 [0.7%], death from vascular causes 2 [0.7%] and 5 [1.7%]), venous thrombotic event 4 (1.4%) and 1 (0.3%), transient ischemic attack 0 (0.0%) and 3 (1.0%), hypertension 2 (0.7%) and 0 (0.0%), ≥ 1 serious systemic event 64 (22.4%) and 77 (25.7%), MedDRA system organ class (cardiac disorder 16 [5.6%] and 13 [4.3%], infection 11 [3.8%], and 18 [6.0%], nervous system disorder 9 [3.1%] and 9 [3.0%], benign or malignant neoplasm 5 [1.7%] and 9 [3.0%], surgical or medical procedure 6 [2.1%] and 8 [2.7%], gastrointestinal disorder 6 [2.1%] and 9 [3.0%], any other system organ class 26 [9.1%] and 28 [9.3%]), respectively.
Luu et al. (2010) [31]	A retrospective study of 231 eyes of 210 patients treated with IVB (1.25 mg / 0.05 mL) for CNV secondary to nARMD.	At one year, one patient (0.4%) had a cerebrovascular accident; yet, no other systemic adverse events including myocardial infarction, peripheral vascular disease, or transient ischemic attacks were reported.
Yohendran et al. (2010) [32]	Case report of a 40-year-old man who received two doses of IVB injection for macular edema due to branch retinal vein occlusion.	The patient developed transient erectile dysfunction three days after the first IVB injection and gradually returned to normal within one week. After the second IVB injection, he reported a reduced, but not absent, effect on his erectile function.
Cakmak et al. (2010) [33]	Case report of a 64-year-old man with right-eye nARMD treated with IVB (1.25 mg / 0.05 mL) after a complaint of reduced vision for 15 days.	The patient developed binocular horizontal diplopia one week after IVB injection and was diagnosed with sixth cranial nerve palsy.
Tufail et al. (2010) [34]	A prospective, double blind, multicenter, randomized controlled clinical trial on the efficacy and safety of IVB (1.25 mg / 0.05 mL) for treating 65 patients with nARMD.	At 54 weeks, one (2%) patient had died of a vascular cause. Severe adverse events were reported in three patients treated with IVB; two patients with myocardial infarctions and one with atrial fibrillation.
Petrou et al (2010) [35]	A report of two cases with early loss of pregnancy after IVB injection.	A 29-year-old woman with well-controlled type 1 diabetes received an IVB (1.25 mg) injection for left eye inferior vitreous hemorrhage. Although she was unaware, an ultrasound confirmed a 5-week pregnancy, and one week after the IVB injection, she experienced an early loss of pregnancy. A 25-year-old healthy myopic woman received IVB (1.25 mg) injection for subfoveal CNV. Although she was unaware, an ultrasound confirmed a 4-week pregnancy, and 10 days after the IVB injection, she experienced an early loss of pregnancy.

Continued Table 1. Summary of the reported systemic complications of intravitreal bevacizumab

Author (Year)	Specifications of study	Systemic complications of intravitreal bevacizumab
Curtis et al. (2010) [36]	A retrospective cohort study comparing outcomes of 146 942 patients treated for ARMD in one year among four groups: patients who received PDT (the active control group), pegaptanib octasodium, ranibizumab, or IVB treatment groups.	The one-year cumulative incidence of adverse events in the IVB group (n = 38 718): all-cause mortality 1324 (4.4%), incident myocardial infarction 378 (1.2%), bleeding 1719 (5.5%), and incident stroke 659 (2.1%). The hazard of mortality or myocardial infarction was not significantly different between IVB use and other treatments. The differences across treatment groups for bleeding events or stroke were not significantly different.
Potter et al. (2010) [37]	A randomized, double-masked, controlled trial including 36 patients with nARMD comparing outcomes of IVB plus PDT using a light dose of either 25 J / cm^2 or 12 J / cm^2 or IVB plus sham PDT.	A 95-year-old patient had died due to a stroke that occurred the same day as a hip fracture, 93 days after the second IVB injection. These events were not attributable to either treatment. No additional serious adverse events were observed.
Byeon et al. (2009) [38]	Case report of a 71-year-old man with hypertension and decreased vision in his left eye due to pigment epithelial detachment with macular edema who received an IVB (1.25 mg / 0.05 mL) injection.	Transient global amnesia following IVB injection that lasted three hours.
Roth et al. (2009) [17]	A retrospective, consecutive chart review of patients who received at least 1 IVB injection of 1.25 mg for nARMD (93.9%), diabetic retinopathy, or retinal vein occlusions.	Of 812 patients, 319 received IVB only and reported the following systemic adverse events: myocardial infarction (n = 6, 1.9%), congestive heart failure (n = 9, 2.8%), angina (n = 10, 3.1%), hypertension (n = 18, 5.6%), seizure (n = 3, 0.94%), cerebrovascular accident (n = 7, 2.2%), renal disorders (n = 6, 1.9%), gastrointestinal bleeding (n = 5, 1.6%), and death (n = 7, 2.2%).
Kaiser et al. (2009) [39]	A retrospective case series reporting outcomes of 1196 patients with CNV due to nARMD treated with PDT and IVB.	Nonocular serious adverse events were reported in 22 patients within 11 to 435 days after IVB injection and 42 to 423 days after PDT but were judged by Registry Oversight Board as unrelated to either treatment. These events were: myocardial infarction (n = 4), unknown cause of death (n = 3), respiratory failure (n = 3), transient ischemic attack (n = 3), cerebrovascular accident (n = 1), renal failure (n = 1), renal cell carcinoma (n = 1), colon cancer (n = 1), gastrointestinal hemorrhage (n = 1), hepatic cirrhosis (n = 1), accidental fall (n = 1), hip osteoarthritis (n = 1), and hip dislocation (n = 1). Eleven of these patients died due to myocardial infarction (n = 2), respiratory failure (n = 3), unknown cause of death (n = 3), gastrointestinal hemorrhage (n = 1), subarachnoid hemorrhage from an accidental fall (n = 1), and hepatic cirrhosis (n = 1). Of 22 events, eight were cardiovascular (four of which had a temporal relationship to treatment).
Soheilian et al. (2009) [40]	A randomized three-arm trial comparing the results of IVB alone (n = 50 eyes) or combined intravitreal triamcinolone acetonide and IVB (n = 50 eyes) with macular laser photocoagulation (n = 50 eyes) as a primary treatment of DME.	Although no significant increase in blood pressure or thromboembolic events were detected for up to 36 weeks, four patients (n = 5 eyes) had died during the trial (two in the combined intravitreal triamcinolone acetonide and IVB group and two in the laser group).
Amselem et al. (2009) [19]	Case report of a 61-year-old woman with left-eye CNV secondary to pathological myopia received two IVB (2.5 mg) injections.	Six days after the first IVB (2.5 mg) injection, she developed multiple scattered, erythematous papules, especially over the head and trunk. Her skin-punch biopsy revealed a hyperkeratotic follicular infundibulum with an inflammatory cell infiltration of the dermis. She received a second IVB injection (2.5 mg) two months after the initial presentation due to deterioration of vision. Recurrence of the papulopustular reaction on the forehead was documented five days after the IVB injection.
Fong et al. (2008) [41]	A retrospective review of 109 patients with treatment-naive nARMD who received a variable-frequency regimen of IVB.	Two patients had died. One was an 87-year-old woman with hypertension who died of myocardial infarction six weeks after her third IVB injection, and the second was an 88-year-old woman with unremarkable past medical history who died two months after her third IVB injection due to an upper respiratory tract infection. However, there is no suggestive evidence in this paper to prove that these deaths were relevant to IVB treatment.

Continued Table 1. Summary of the reported systemic complications of intravitreal bevacizumab

Author (Year)	Specifications of study	Systemic complications of intravitreal bevacizumab
Wong et al. (2008) [42]	A retrospective review of all consecutive patients (186 patients, 203 eyes) who received IVB injection for nARMD, DME, retinal vascular occlusion, neovascular glaucoma, and five other indications.	Systemic adverse events were worsened: hypertension (n = 2, 1%), headache (n = 2, 1%), and nausea and vomiting (n = 1, 0.5%).
Wu et al. (2008) [43]	An open-label, uncontrolled, multicenter interventional case series reviewed 4303 IVB injections in 1310 eyes with various posterior segment indications.	Up to one-year post IVB injection, 18 (1.5%) of patients had systemic adverse events, including seven (0.59%) with an acute elevation of blood pressure, six (0.5%) with cerebrovascular accidents, five (0.4%) with myocardial infarctions, two (0.17%) with iliac artery aneurysms, two (0.17%) with toe amputations, and five (0.4%) had died.
Shima et al. (2008) [44]	A retrospective review of the systemic and ocular complications among 707 patients with 1300 IVB injections within two months after treatment for managing macular edema or intraocular neovascularization.	Of 707 patients, eight (1.13%) developed systemic complications: menstrual irregularities (n = 3), elevation of systolic blood pressure (n = 2), cerebral infarction (n = 1), diffuse pruritic rash (n = 1), and facial erythema (n = 1).
Scott et al. (2007) [45]	A phase II randomized clinical trial on efficacy and safety of IVB injection in treating eyes with DME.	Among the 107 patients with at least one IVB injection, two developed a myocardial infarction and one congestive heart failure. One myocardial infarction was fatal and occurred in a 78-year-old man 73 days after the second injection of IVB (1.25 mg), and one was a nonfatal myocardial infarction that occurred in a 69-year-old man five days after the first IVB (2.5 mg) injection; both had a history of coronary artery bypass surgery. The congestive heart failure occurred in a 56-year-old woman 40 days after the second IVB (1.25 mg) injection who had a history of three similar episodes. Three IVB-treated patients experienced an elevation of blood pressure; one had a history of hypertension. Other reported adverse events in IVB-treated patients were death due to pancreatic cancer (n = 1), peripheral vascular disease (n = 1), syncope (n = 1), worsening of renal function (n = 3), and anemia (n = 4).
Park and Guy (2007) [46]	Case report of a 62-year-old man with nARMD and decreased vision who received three IVB injections in his right eye within a six-month period.	Five days after the third IVB injection he developed binocular horizontal diplopia, which was diagnosed as an isolated sixth cranial nerve palsy. He had experienced a remarkable improvement one month later.
Rodrigues et al. (2007) [47]	Case report of a healthy nulliparous 35-year-old woman who received IVB (2.5 mg / 0.1 mL) injection for disc neovascularization secondary to branch retinal vein occlusion.	Two weeks after the IVB injection, she reported metrorrhagia for ten days unrelated to her menstrual cycle. Systemic and gynecological work-up was unremarkable. The metrorrhagia was managed successfully.
Moshfeghi et al. (2006) [48]	An open-label, single-center, uncontrolled study for evaluation of the safety, efficacy, and durability of IVB injection in managing subfoveal CNV in patients with nARMD.	Over 24 weeks, hypertension was the only adverse event identified; 10 of the 18 patients required either adjustment or initiation of antihypertensives. Only one patient required an adjustment to antihypertensive medication between 12 and 24 weeks of follow-up.
Fung et al. (2006) [49]	An internet-based survey with 61 centers to find possible adverse events associated with IVB injection. During the first month of data collection, 61 centers with 4576 patients reported 6090 IVB injections. Overall, 5228 patients with 7113 IVB injections were reported by 70 centers from 12 countries.	Possible systemic adverse events after IVB injections were a mild increase in blood pressure (n = 15, 0.21%), transient ischemic attack (n = 1, 0.01%), cerebrovascular accident (n = 5, 0.07%), and deep venous thrombosis (n = 1, 0.01%). The transient ischemic attack occurred one day after IVB injection in a patient with uncontrolled hyperlipidemia, and after resolving, the patient received at least one additional IVB injection without another event. Four patients with cerebrovascular accidents were reported between 1 and 10 days after IVB injection, and most required hospitalization without subsequent disability, and one had died (this patient was at high risk due to pre-existing atrial fibrillation with mural thrombosis). The fifth patient with a cerebrovascular accident had no major subsequent impairment. One deep vein thrombosis recurred in a patient with a history of deep vein thrombosis. There were two reported deaths (0.03%): one died of pneumonia three weeks after an IVB injection, and the second died of a cerebrovascular accident, as mentioned earlier.

Continued Table 1. Summary of the reported systemic complications of intravitreal bevacizumab

Author (Year)	Specifications of study	Systemic complications of intravitreal bevacizumab
Spaide et al. (2006) [50]	A retrospective review of patients with CNV secondary to ARMD who received IVB injection with three-month follow-up.	During the study period, two patients died: one due to metastatic breast cancer after a long illness and another due to myocardial infarction. The second patient was a smoker with emphysema and had no improvement after the first IVB injection, thus declined additional injections and died three months after his solitary IVB injection. Three patients reported systemic events. One patient had a nonfatal myocardial infarction one month after the third IVB injection. One patient with a history of transient ischemic attack voluntarily stopped his anticoagulant treatment due to concern of bleeding from the IVB injection; he developed another probable transient ischemic attack and restarted his anticoagulant. He had no residual deficit, and his neurologist raised the possibility that he never had a transient ischemic attack but rather a seizure antecedent to the IVB injection. One patient reported transient numbness of the lips, and the internist correlated the symptoms to a transient ischemic attack. Neither had a residual deficit, and both were cleared for further IVB injection by their internists.

Abbreviations: IVB, intravitreal bevacizumab; DME, diabetic macular edema; nARMD, neovascular age-related macular degeneration; mg / g, milligram per gram; CNV, choroidal neovascularization; n, numbers; MedDRA system organ classes, Medical Dictionary for Regulatory Activities system; anti-VEGF, anti-vascular endothelial growth factors; PDT, photodynamic therapy; J / cm2, Joules per square centimeter.

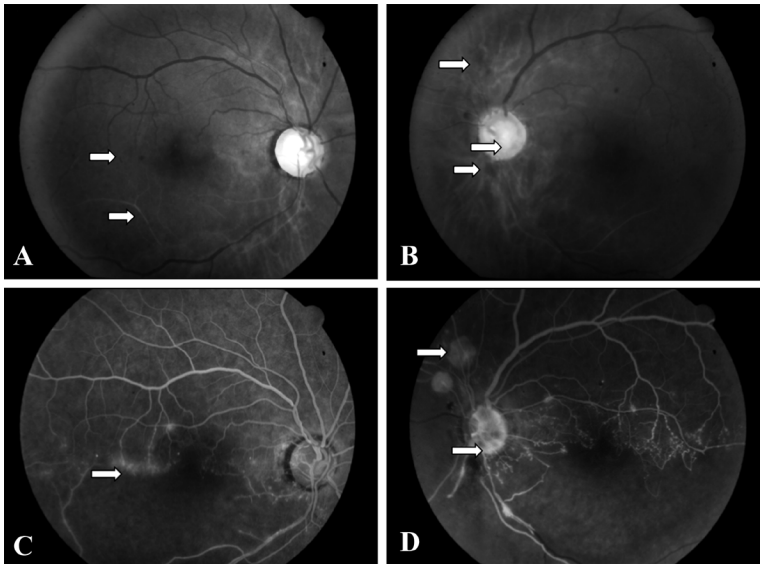

Figure 1. (A) Fundus photograph of the right eye (OD) showing inferotemporal ischemic branch retinal vein occlusion with ghost vessels (white arrows). (B) Fundus photograph of the left eye (OS) showing hemi-retinal ischemic retinal vein occlusion. Note the presence of neovascularization of the optic disc (NVD) and elsewhere in the retina (NVE) (white arrows). (C) Arteriovenous phase fluorescein angiogram (VISUCAM Lite Digital Fundus Camera, Carl Zeiss Meditec, Inc., Dublin, CA, USA), OD, showing an inferior non-perfusion area with evidence of leakage from NVE and collateral vessels in the superior macula. (D) Arteriovenous phase fundus fluorescein angiogram, OS, demonstrating a large inferior non-perfusion area with evidence of leakage from NVE and NVD (white arrows).

His laboratory results were as follows: serum creatinine level, 6.86 mg / dL (range, 0.7 to 1.3 mg / dL); serum C-reactive protein level, 5.77 mg / dL (normal, < 0.9 mg / dL); serum beta 2-microglobulin level, 11.2 mg / L (range, 1.1 to 2.4 mg / L); proteinuria, 816 mg / 24 h (normal, < 150 mg / 24 h); and creatinine clearance, 15 mL / min (range, 80 to 120 mL / min).

The patient began hemodialysis with plasma ultrafiltration. A renal biopsy specimen revealed a cylinder of kidney tissue containing glomeruli and tubules. A blood vessel surrounded by granulomatous reaction (histiocytes and lymphocytes) was observed, with a reduced lumen size (Figure 2A). The tubular portions showed reaction to both light chains of Ig, as well as to IgA and IgM, ruling out nephropathy due to underlying oncological disease.

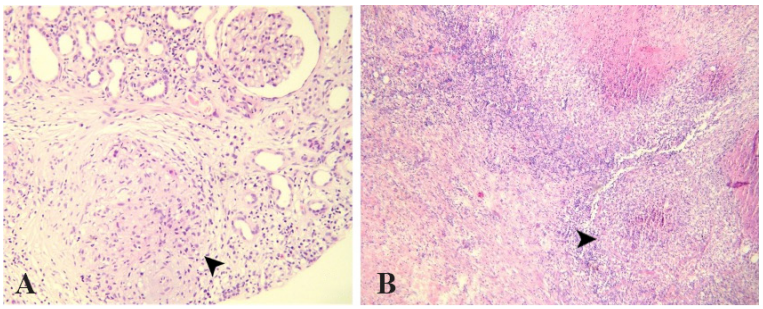

Figure 2. (A) Hematoxylin-eosin (H&E staining with original magnification × 4) stained core cylinder of renal tissue showing glomeruli and tubules with an adjacent blood vessel featuring a peripheral rim of epithelioid histiocytes and lymphocytes, indicating granulomatous reaction, reducing the size of its lumen (black arrowhead). (B) Subcutaneous tissue (H&E staining with original magnification × 10) with features of granulomatous panniculitis consisting of multiple granulomas with central non-caseating subcutaneous fat necrosis replacing the adipose tissue. Granulomas consist of epithelioid histiocytes, multinucleated giant cells, and a lymphocyte crown. The necrotic center shows neutrophilic polymorphonuclear cells.

Skin biopsy specimens showed epidermal hyperplasia and, toward the center of the field, an active ulcer bed with numerous congested vessels and a mixed lymphocytic and neutrophilic inflammatory infiltrate. The center of the lesion featured a necrotic area with neutrophilic polymorphonuclear cells (Figure 2B). The presence of mycoses and acid-fast bacteria was excluded by specific staining of both tissue specimens. Having ruled out infectious factors, a granulomatous cutaneous drug eruption was considered. After three months of dialysis, the patient was hospitalized for a stroke, which led to his death.

This submission received Institutional Review Board approval from the Oulton-Romagosa Joint Committee on Clinical Investigation (CIEIS OULTON-Romagosa). A detailed explanation of the proposed intervention (IVB injection) was provided to the patient, and informed consent was obtained.

DISCUSSION

There are many reports of systemic adverse events after IVB injection that were mere coincidences or were judged attributable to treatment [1-3, 14-50] (Table 1). Our patient developed a significant deterioration of renal function with maculopapular skin lesions one week after the last IVB injection.

The reported dermatological adverse events after IVB injection have included facial erythema [20, 44]; delayed cell-mediated drug hypersensitivity reactions with pruritus, skin rashes, and progressive exacerbation [18]; multiple scattered, erythematous papules, especially over the head and trunk [19]; and diffuse pruritic rash [44]. Likewise, renal adverse events following IVB injection have included acute kidney injury associated with creatininemia and albuminuria without hematuria [16], associated renal disorders [17], renal failure [39], and worsening of renal function [45]. To the best of our knowledge, our patient is the first to experience simultaneous renal and dermatological adverse events after IVB injection, which were confirmed by pathological examination.

Recently, safety concerns have arisen regarding renal or cutaneous adverse effects associated with systemic anti-VEGF therapies [51, 52]. However, studies associating the intravitreal administration of VEGF inhibitors with these complications are inconclusive. Although patients who receive systemic anti-VEGF agents are frequently under close laboratory monitoring, patients receiving intravitreal anti-VEGF injections are not frequently monitored; hence, worsening renal condition could be underreported, as mentioned by Shye et al. [53]. Moreover, many candidates for intravitreal anti-VEGF therapy have diabetes and are prone to pre-existing chronic kidney disease (CKD) [8]. Thus, an increase in proteinuria could be attributed to the disease process itself rather than to treatment-related adverse effects. We believe that the incidence of adverse events with intravitreal anti-VEGF could escalate if patients have pre-existing CKD, as VEGF receptors are present in mesangial endothelial cells and peritubular capillaries, thereby affecting glomerular function [54].

Kameda et al. [8] reported that the intravitreal administration of anti-VEGF agents is unlikely to deteriorate renal function in patients with diabetes and CKD. In contrast, Bagheri et al. [55] found that although IVB was relatively safe in diabetic patients with pre-existing proteinuria, 45% of the patients with diabetic nephropathy showed increased albuminuria after VEGF blockade by IVB injection [55]. We believe that further long-term studies of patients with abnormal but similar renal function and the same number of IVB injections, along with monitoring of renal function, could reveal robust evidence on the effect of IVB in patients with significant worsening of kidney function.

Not only did our patient develop renal failure one week after the last of a series of IVB applications, but according to the renal biopsy result, he presented specifically with interstitial granulomatous changes previously described in the presence of drug toxicity [56], and the coexistence of infectious diseases compatible with these lesions was ruled out [57]. Additionally, our patient developed multiple rounded maculopapular, erythematous, ulcerated skin lesions on the trunk and upper limbs seven days after the last IVB injection, as described in previous papers [18-20, 44], concurrent with the decompensation of renal function.

After intravitreal injection, anti-VEGF agents are measurable in the systemic circulation despite the presence of the blood-ocular barrier [58]. We must consider that in patients with diabetic macular edema, the blood-retinal barrier is often disrupted [59], likely enhancing systemic absorption. Bevacizumab, in notable contrast to ranibizumab, includes the Fc component of the antibody, which delays movement of the full antibody into the systemic circulation [60]. Given that bevacizumab has a longer systemic half-life [61] and higher mean peak concentration than ranibizumab [11], it can induce substantially longer-lasting systemic VEGF inhibition [61, 62].

In this narrative review, we have summarized the systemic complications of IVB injections reported by clinicians across various study designs. Moreover, we presented, for the first time, a patient with simultaneous, pathologically confirmed renal and dermatological adverse events after IVB injection. In patients with pre-existing renal pathology who require treatment with IVB, consultation with a nephrologist is recommended. Early identification of a drug-related renal insult is crucial to avoid further tissue damage, because repeated injections are generally required. Despite the rare simultaneous presentation of renal and cutaneous complications of IVB injection in our patient, our report is only of a single case, and stronger evidence to prove this causal relationship is necessary. Further large-scale clinical trials are needed, with detailed clinical evaluations and grouping patients with similar renal function, the same number of injections, the same anti-VEGF inhibitor, and other factors. Longer postoperative follow-up is needed to discover subtle systemic side effects of IVB injection, such as a reduction in kidney function, or the safety of IVB in patients with impaired kidney function.

CONCLUSIONS

IVB-induced systemic complications, such as arteriothrombotic events, venous thrombotic events, and hypertension, are rare but potentially serious. To our knowledge, this is the first report describing simultaneous renal and cutaneous adverse events after IVB injections. Care should be taken when administering multiple doses of intravitreal IVB to patients with pre-existing kidney dysfunction. Bevacizumab-related toxicity must be considered in cases of sudden deterioration of renal function and / or unexpected granulomatous skin lesions in oncologic or chronically polymedicated patients. Further studies are required to understand the relationships among intravitreal anti-VEGF inhibitors, renal dysfunction, and skin involvement. However, because we found no other explanation of these sudden changes in the kidneys and skin of our patient, we believe that this case provides further evidence that IVB can have systemic manifestations in renal and cutaneous tissues.

ETHICAL DECLARATIONS

Ethical approval: This submission received Institutional Review Board approval from the Oulton-Romagosa Joint Committee on Clinical Investigation (CIEIS OULTON-Romagosa). A detailed explanation of the proposed intervention (IVB injection) was provided to the patient, and informed consent was obtained.
Conflict of interests: None.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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