Hypertension and Neuroimaging Changes After Bevacizumab for Retinopathy of Prematurity

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abstract

Bevacizumab is a human monoclonal immunoglobulin G1 antibody to vascular endothelial growth factor indicated in several adult diseases. Emerging literature and expert opinion support the off-label use of intravitreal bevacizumab in the treatment of retinopathy of prematurity (ROP), a common disease process seen in premature neonates. One of the most common side effects of systemic therapy in adults is hypertension; however, this has not been well described in infants receiving bevacizumab for ROP. In this report, we review a case of a former 25-week premature infant treated for stage 3 ROP with administration of intravitreal bevacizumab. The immediate posttreatment course was uncomplicated; however, at 10 days posttreatment, he developed new-onset systemic hypertension. In addition, neuroimaging revealed new areas of vasogenic edema, which improved over time. To the best of our knowledge and after a review of the literature, neither of these effects has been described in neonates after intravitreal bevacizumab for ROP.

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PRESENTATION

The patient is a male infant born at 25 4/7 weeks' gestational age via cesarean delivery secondary to breech presentation in the setting of preterm labor with a birth weight of 750 g. The hospital course was complicated by bronchopulmonary dysplasia and grade IV intraventricular hemorrhage with subsequent posthemorrhagic hydrocephalus. Serial eye examinations for retinopathy of prematurity (ROP) screening began at 6 weeks of life. In the initial examination, immature retinas were noted in zone 1, with bilateral progression to stage 3, zone 1, and plus disease at 34 6/7 weeks' corrected gestational age (CGA).

The parents were counseled on treatment options by pediatric ophthalmology and elected to proceed with bilateral intravitreal bevacizumab under appropriate sedation at 34 6/7

weeks' CGA. The procedure was well tolerated without complication, and the infant had an uneventful immediate postprocedure course.

The next day, he was electively intubated and underwent a planned removal of a ventriculosubgaleal shunt, with placement of a ventriculoperitoneal shunt. He subsequently developed and was treated for *Klebsiella* pneumonia and returned to his baseline respiratory support of nasal cannula at 36 4/7 weeks' CGA.

Within 10 days of bevacizumab administration, at 36 2/7 weeks' CGA, he developed persistently elevated blood pressures (>95th percentile for age), measured by cuff and arterial monitoring. Previous measurements were within normal range, and there was no history of renal or cardiac disease. Results of a nephrology

workup for new-onset hypertension were negative and included evaluation of kidney function indices, such as creatinine levels, a urinalysis, a renal ultrasound, and urine output. An echocardiogram revealed normal cardiac structure and function, without any indirect evidence of pulmonary hypertension. Blood pressure control was difficult to achieve and ultimately required enteral clonidine, labetalol, and isradipine.

At that time, a cranial ultrasound revealed a new left-sided intraparenchymal hemorrhage (Figs 1 and Figs 2). A subsequent MRI revealed abnormal increased T2 signaling and diffusion and vasogenic edema in both parieto-occipital subcortical regions. Similar changes were observed in bilateral frontal subcortical white matter. Additionally, multifocal cortico-subcortical hemorrhages were seen in the left parieto-occipital region (Figs 3 and 4).

Post hypertensive crisis, another MRI at 38 6/7 weeks' CGA revealed interval improvement of the abnormal increased T2 signaling and vasogenic edema in both bilateral
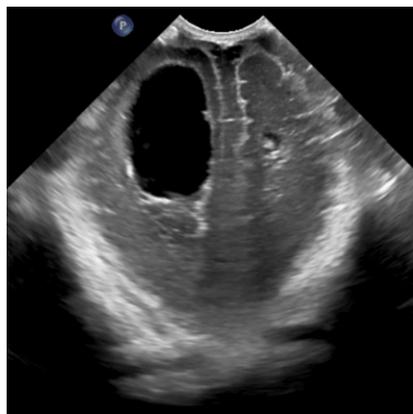

FIGURE 2
Cranial ultrasound obtained on day of life 76. The coronal cranial ultrasound image obtained on day of life 76 (36 3/7 CGA), 11 days after treatment with bevacizumab, reveals a left-sided parieto-occipital cortical hemorrhage (arrow).

parieto-occipital and frontal subcortical regions (Fig 5).

The infant clinically improved, and oral antihypertensives were weaned. Isradipine was used for 16 days and was discontinued

after adequate blood pressure control was achieved. He was discharged from the hospital at 39 6/7 weeks' CGA on full feeds by mouth and supplemental oxygen via nasal cannula. His home antihypertensive regimen included clonidine and labetalol.

DISCUSSION

Bevacizumab is a monoclonal antibody to vascular endothelial growth factor (VEGF) that was first approved in the early 2000s as a systemic treatment of adult metastatic colon cancer.[1] Its proposed mechanism of action involves inhibition of new vessel growth, regression of tumor vessels, and alteration of tumor blood flow.[2] Given the effect on angiogenesis, its use expanded to intravitreal administration for adult eye conditions, including macular degeneration and diabetic retinopathy, in the mid-2000s.[1,3]

FIGURE 1
Cranial ultrasound obtained on day of life 63. The coronal cranial ultrasound image obtained on day of life 63 (34 4/7 CGA), before administration of bevacizumab, reveals no evidence of a left-sided parieto-occipital cortical hemorrhage.
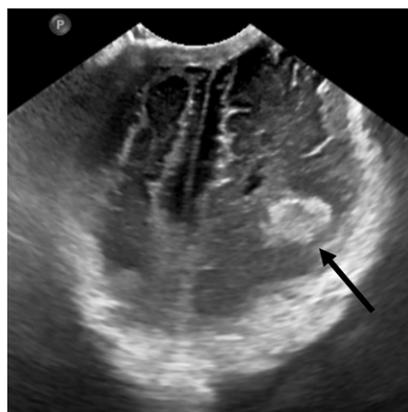

FIGURE 3
Axial T2 imaging and ADC map from day of life 79. A brain MRI was obtained on day of life 79 (36 6/7 CGA). A, Axial T2-weighted image and, B, axial diffusion ADC map reveal abnormal increased T2 signal and increased diffusion, revealing vasogenic edema in both parieto-occipital subcortical regions (black arrows). Similar changes are also seen in both frontal subcortical white matter (white arrows). ADC, apparent diffusion coefficient.
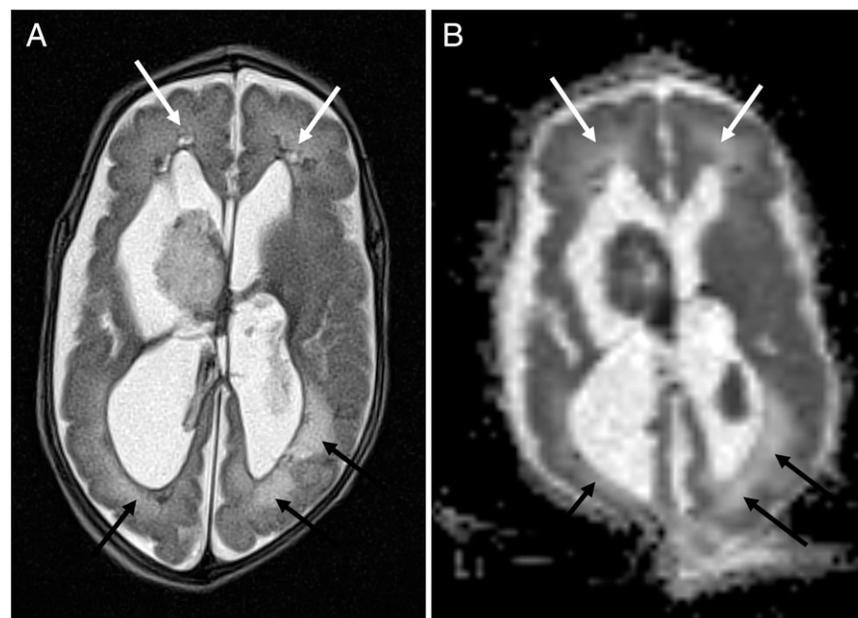
FIGURE 4
Axial SWI imaging obtained on day of life 79. A brain MRI was obtained on day of life 79 (36 6/7 CGA). The axial SWI-weighted image reveals multiple cortico-subcortical hemorrhage foci (on the left) in the parieto-occipital region (white arrows). The star represents artifacts related to a VP shunt catheter (on the right). SWI, susceptibility-weighted imaging; VP, ventriculoperitoneal.
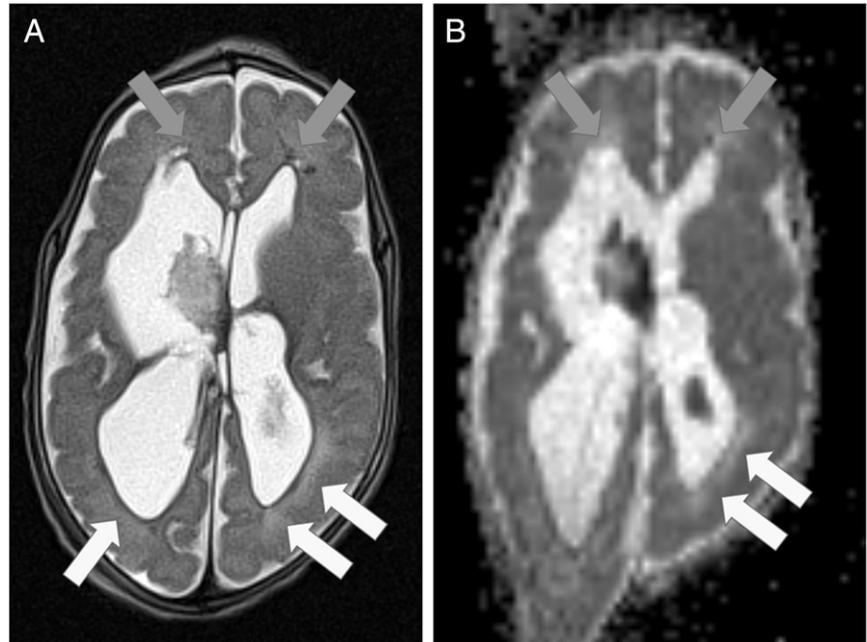

FIGURE 5
Brain MRI with axial T2-weighted image and diffusion ADC map. A, Axial T2-weighted image and, B, axial diffusion ADC map reveal interval improvement of abnormal increased T2 signal and improvement of vasogenic edema in both parieto-occipital (white arrows) and frontal subcortical regions (gray arrows). ADC, apparent diffusion coefficient.

ROP, characterized by abnormal and incomplete vascularization of the retina, occurs in premature infants and can lead to retinal detachment and blindness in the absence of appropriate treatment. In the United States, nearly 70% of high-risk infants are diagnosed with ROP, with the incidence and severity increasing with decreasing birth weight and gestational age.[4] Treatments for advanced stages of ROP include laser photocoagulation and intravitreal bevacizumab, and surgical intervention is reserved for the most severe cases with retinal detachment.[5]

The use of intravitreal bevacizumab in the premature infant population increased in the mid-2000s with the first multicenter randomized controlled trial, Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP).[6,7] Although bevacizumab is currently not approved by the Food and Drug Administration for treatment of ROP, the joint policy statement by the American Academy of Pediatrics Section on Ophthalmology, the American Academy of Ophthalmology, the American Association for Pediatric Ophthalmology and Strabismus, and the American Association of Certified Orthoptists states that "consideration may be given to treatment of infants with zone 1, stage 3+ ROP," which is based on the findings of the BEAT-ROP trial.[8]

Although the efficacy of bevacizumab treatment was described in the BEAT-ROP study, the study was not powered to assess the safety of anti-VEGF therapy in neonates.[8,9] At this time, data describing long-term effects and neurodevelopmental outcomes are conflicting and unclear.[10–13] Studies of serum bevacizumab levels indicate continued detection up to 60 days after intravitreal administration, and suppression of serum VEGF levels is seen up to 8 weeks after treatment.[11,14] It is unknown at this point what effects, if any, decreased systemic VEGF levels have on brain development or other organ systems.[11,14]

In the adult literature, multiple adverse effects from systemic administration of bevacizumab are reported, the most common being hypertension, in addition to more severe but less common complications, such as bowel perforation and arterial thrombosis.[1,15–17] Hypertension can be seen in up to 35% of adult patients who receive systemic bevacizumab, with nearly 15% requiring multiple antihypertensive agents for severe-range blood pressure levels.[16] Potential etiologies include the presence of preexisting conditions (ie, increased age, elevated BMI, underlying hypertensive disease), interaction with other medications, and genetic predisposition.[15,17,18] Although the specific mechanism for the development of bevacizumab-induced hypertension is not well

understood, it is thought to involve impaired nitric oxide signaling, leading to subsequent endothelial dysfunction and increased vascular resistance.[19,20]

Although the majority of the literature involves bevacizumab-induced hypertension secondary to systemic therapy, it has also been reported after intravitreal administration. Rasier et al[20] described the pattern of hypertension in patients who were normotensive and hypertensive after receiving intravitreal bevacizumab. In the group with preexisting hypertension, statistically significant elevations above baseline blood pressure levels were seen at weeks 1, 3, and 6 after treatment.[20] Statistically significant elevations occurred at week 3 after treatment in the previously normotensive group.[20] Our patient demonstrated hypertension consistent with this time frame, with the first occurrence at 10 days post treatment and persistent findings lasting through week 4 post treatment.

One of the rare complications (incidence of <0.5%) with administration of systemic bevacizumab is the development of posterior reversible encephalopathy syndrome (PRES), which typically appears within the half-life of bevacizumab (~20 days) but can occur anywhere from 16 hours to 1 year after drug administration.[1] This syndrome is characterized by clinical findings, such as headache, encephalopathy, and seizures, in addition to radiographic findings, including white matter changes and vasogenic edema on MRI.[1,21] Small petechial hemorrhages; larger, more typical focal hematomas; and sulcal-based subarachnoid hemorrhages can also be seen.[22] In >90% of patients, the vasogenic edema associated with PRES is seen in a distinctive parieto-occipital or posterior frontal distribution.[23,24] The hallmark of PRES is the reversibility of these

abnormal neuroimaging findings once the offending agent has been removed or the underlying condition has been resolved.[23–25] Although clinical symptoms were not seen, the age of the patient makes some of these difficult to elicit. The patient did, however, demonstrate the classic pattern of vasogenic edema and reversibility on follow-up imaging, making PRES a likely diagnosis.

Although PRES can be precipitated by acute medical illness and immunosuppressive or chemotherapy agents,[1,26] adult literature reveals that 70% to 80% of cases follow moderate to severe hypertensive crises, a known side effect of bevacizumab.[21,26] The association between PRES and bevacizumab administration is not well understood at this point. It is unclear if it is the drug itself that is the trigger or if induced hypertension precipitates the development of PRES. One proposed mechanism is endothelial dysregulation and subsequent disruption of the blood-brain barrier, leading to autoregulatory failure.[1] Although more commonly described in the setting of systemic bevacizumab administration, PRES has also been described in the adult population after intravitreal administration for treatment of age-related maculopathy.[1,26–28]

In the pediatric population, PRES typically occurs in older children, and is rarely seen in children <1 year of age. Sparse case reports exist, including one of a 10-month-old infant with predisposing factors of hyponatremia and syndrome of inappropriate antidiuretic hormone[29]; one of a 5-week-old infant, formerly 36 weeks' gestation, after a bilateral inguinal hernia repair[30]; and one of a 3-month-old infant with history of obstructive sleep apnea and laryngomalacia who developed PRES after laryngoscopy and bronchoscopy procedures.[31] To our knowledge, no case reports of

PRES after intravitreal administration of bevacizumab for ROP exist.

CONCLUSIONS

Our patient developed not only significant hypertension after intravitreal administration of bevacizumab but also vasogenic edema and white matter changes seen on MRI. These changes were noted in a pattern of distribution and with the characteristic reversibility that is consistent with PRES. Although white matter changes can be seen in association with intraventricular hemorrhage, the pattern and timing of the MRI findings in association with a hypertensive crisis are consistent with the adult literature for a diagnosis of PRES.[1,27]

Our patient's presentation of hypertension and neuroimaging changes after administration of bevacizumab for ROP raises several questions related to the side effects and overall systemic effects of this drug in neonates, which should be considered with its evolving use.[8] Given the current lack of literature, and in light of the patient case discussed above, a high index of suspicion for the development of adverse effects, and perhaps a longer monitoring period for the development of hypertension, may be prudent in the care these patients until further studies regarding long-term safety and effects of bevacizumab in neonates can be completed.

ABBREVIATIONS

BEAT-ROP: Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity
CGA: corrected gestational age
PRES: posterior reversible encephalopathy syndrome
ROP: retinopathy of prematurity
VEGF: vascular endothelial growth factor

TWITTY et al

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