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CASE REPORT

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Case report of unilateral retrobulbar hematoma associated with von Willebrand disease in a Doberman Pinscher dog

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Abstract

A 5-year-old Doberman Pinscher dog was presented with sudden onset left-sided periocular bleeding following third eyelid gland replacement surgery. Left-sided exophthalmos and 360-degrees subconjunctival hemorrhage were present. The ophthalmic examination revealed blindness with absent direct and consensual pupillary light reflexes. A superficial exposure ulcerative keratitis due to exophthalmos was also present. Computed tomography (CT) revealed a large left-sided retrobulbar mass lesion surrounding the optic nerve, compatible with a retrobulbar hematoma. Due to absence of orbital fractures and no history of trauma, a coagulopathy was strongly suspected. The buccal mucosal bleeding time (BMBT) was prolonged (>4 minutes) consistent with a primary hemostatic defect in the absence of thrombocytopenia. Von Willebrand factor antigens levels were decreased (24%- Normal Range: 50%-150%). Surgical drainage of the retrobulbar hematoma was performed uneventfully thirty minutes after subcutaneous injection of desmopressine acetate, Minirin® (1 µg/kg, SC). Von Willebrand disease type I gene mutation was confirmed by PCR amplification of the DNA encoding von Willebrand factor. This case report demonstrates that hemostatic disorders, including von Willebrand Disease (vWD), are a risk factor for orbital bleeding following surgical trauma. Retrobulbar hematoma should be considered as a differential diagnosis in any dog with exophthalmos.

KEYWORDS

dog, exophthalmos, ophthalmology, orbital disease, primary hemostatic disorder, thrombocytopathia

Key Clinical Message

Although rarely reported, isolated ophthalmic manifestation of type 1 vWD should be considered as differential diagnosis for extraocular and intraocular hemorrhage.

1 | CASE PRESENTATION

1.1 | Case history

A five-year-old entire male Doberman Pinscher dog was presented for assessment of acute onset left-sided periocular

bleeding following a Morgan pocket surgical technique to address an ipsilateral nictitating membrane (NM) gland prolapse. At the first postoperative control (Day 14), a severe subconjunctival bleeding was present in the left eye (OS). The referring veterinarian performed a ventral trans-conjunctival debridement, prescribed systemic antibiotics (amoxicillin and clavulanic acid: Clavubactin®, Le Vet Pharma, Oudewater, Holland: 12.5 mg/kg q12h PO) as well as topical ophthalmic antibiotic therapy in the OS (tobramycine: Tobrex collyre®, q3h), however the bleeding deteriorated. The dog had no history of trauma or systemic disease prior to surgery. Vaccination and fleas and ticks preventative medicine were up to date.

1.2 | General clinical examination

Upon physical examination, no evidence of trauma was present. The dog was slightly lethargic and reluctant to open the jaw due to pain. The remainder of the physical examination was unremarkable.

1.3 | Ophthalmic examination

The left eye failed the cotton ball test and had absent menace response. Direct (OS) and indirect pupillary light reflexes (OS to OD) were absent. Palpebral reflexes were present bilaterally. Distant and close ophthalmic examination revealed OS exophthalmos associated with ipsilateral third eyelid protrusion. The OS exophthalmos was painful, non-pulsating, non-axial (lateral and dorsal deviation) and associated with subconjunctival hemorrhage and hemorrhagic ocular discharge (Figure 1). The retropulsion of the globe (OS) was not possible. The Schirmer tear test 1 (Dina strip Schirmer-Plus, Dina-Hitex, Czech Republic) was 15 mm/min in the right eye (OD) and was not evaluated in OS due to the presence of periocular hemorrhage.

Biomicroscopic examination (Kowa SL17 slit lamp, Kowa, Düsseldorf, Germany) revealed a superficial axial ulcerative keratitis on OS (Figure 1), and the examination of anterior segments OU was unremarkable. Indirect binocular ophthalmoscopy (Heine Omega 500, Herrsching, Germany; Volk 2.2, Panretinal lens, Mentor, USA) was unremarkable in OD and was not possible in OS. The intraocular pressure (IOP) assessed by rebound tonometry (Tonovet, Icare, Vantaa, Finland) was mildly elevated on OS (27 mm Hg) and within the normal range on OD (15 mm Hg).

2 | DIFFERENTIAL DIAGNOSIS

The differential diagnosis for subconjunctival hemorrhage included local causes with macroscopic (traumatic and surgical) or microangiopathic (vasculitides) vascular injuries then coagulopathies represented by primary and secondary hemostatic disorders. Primary hemostatic disorders include thrombocytopenic states and inherited (including vWD) or acquired thrombocytopathies (ie, uremic states). Secondary hemostatic disorders are mainly represented by disseminated intravascular coagulation, end-stage liver failure, or rodenticide intoxication.[1]

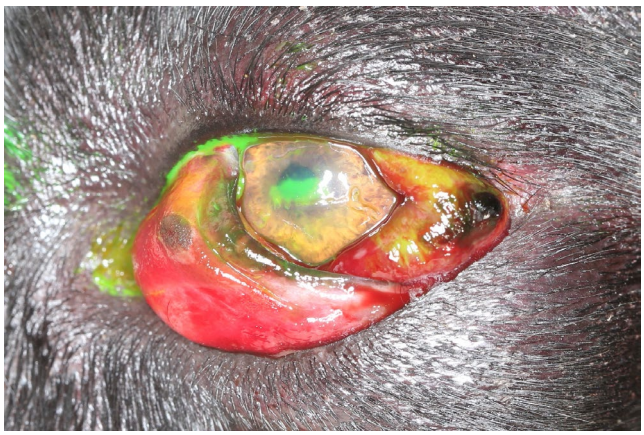

FIGURE 1 OS ophthalmic examination revealed an exophthalmos with subconjunctival hemorrhage and a superficial axial keratitis

Considering the anamnesis and ophthalmic examination, a trauma or hemostatic defect was suspected; an orbital cellulitis, a retrobulbar abscess, or a primary orbital tumor was considered less likely.

3 | INVESTIGATIONS

3.1 | Complementary examinations

Baseline blood testing, including a complete blood count with manual platelet estimation and a biochemistry panel, was unremarkable. This excluded thrombocytopenia as a cause for the bleeding tendency. Considering the absence of thrombocytopenia, a thrombocytopathia was suspected instead.

A coagulation profile including a prothrombin time (PT) at 11 seconds (reference interval: 11-17 seconds), and an activated partial thromboplastin time (aPPT) at 107 seconds (reference interval: 71-102 seconds) did not suggest a significant alteration of extrinsic or intrinsic clotting pathways, respectively. The buccal mucosal bleeding time (BMBT), performed with dedicated Surgicutt®, was greater than 4 minutes and suggested a primary hemostatic defect. The potential causes included the inherited von Willebrand Disease (vWD) or cyclic thrombasthenias, though Doberman Pinscher is overrepresented for the first disorder. Evaluation of von Willebrand factor (vWF) by ELISA confirmed the suspicion of vWD (24% - reference interval: 50%-150%).

Computed tomography scan (16 Slice CT, General Electric Revolution ACT) was performed under general anesthesia, induced with intravenous injection of propofol 4 mg/kg (Propovet multidose®, Zoetis) and ketamine 3 mg/kg (Anesketin® 100 mg/mL, Dechra), and maintained with isoflurane after intubation. CT revealed a large left-sided lobulated heterogeneous retrobulbar soft tissue attenuating (45-50HU) and partially peripherally enhancing mass (about 6.9 × 4.3 × 2.3 cm), with irregular margins. The mass extended from the level of the left pterygoid muscles caudally to the level of the left globe rostrally (Figure 2), involving most of the retrobulbar space. A marked mass effect was noted, associated with lateral displacement and compression of the left zygomatic salivary gland, obliteration of the intraconal and extraconal fat, and severe left-sided exophthalmos (Figure 3). The mass lesion surrounded the left optic nerve and globe, associated with marked thickening of the conjunctiva. Moderate thickening of the left eyelids and periorbital subcutaneous tissue was also noted. The left ophthalmic venous plexus and associated dorsal and ventral external ophthalmic and deep facial veins, embedded in the mass, were markedly reduced in size and ill-defined compared to the contralateral ones (Figures 2D and 3). Moderate left-sided medial retropharyngeal lymphadenomegaly was present. Given the history, clinical signs, and CT findings of a large heterogeneous soft tissue attenuating peripherally enhancing retrobulbar mass, a retrobulbar hematoma/hemorrhage was considered the most likely diagnosis. An abscess, orbital cellulitis, and granuloma were considered less likely although could not be completely excluded. A neoplastic process was considered unlikely given the lack of enhancement of the center of the mass and the acute onset of clinical signs. As there were no other concurrent CT abnormalities suggesting trauma and because this was not reported by the owners, a coagulopathy was strongly suspected. Clinical examination, CT findings, BMBT, and bloodwork results suggested a thrombocytopathia leading to retrobulbar and subconjunctival hemorrhage. vWD was confirmed with a vWF ELISA assay.

4 | TREATMENT

Surgical management of the retrobulbar hematoma causing compression of the optic nerve was decided as an emergency, pending on the vWF antigen test results. Thirty minutes after a subcutaneous (SC) injection of desmopressin acetate (DDAVP: Minirin® 1µg/kg), a drainage of the retrobulbar hematoma was performed by a transoral approach without any immediate complication. A 1-cm long incision through the oral submucosa and mucosa behind the last left upper molar teeth was performed with a #15-scalpel blade, then a pair of closed straight mosquito hemostats was inserted through the pterygopalatine fossa, gently opened and removed, and finally blood clots were removed. The incision was not closed,

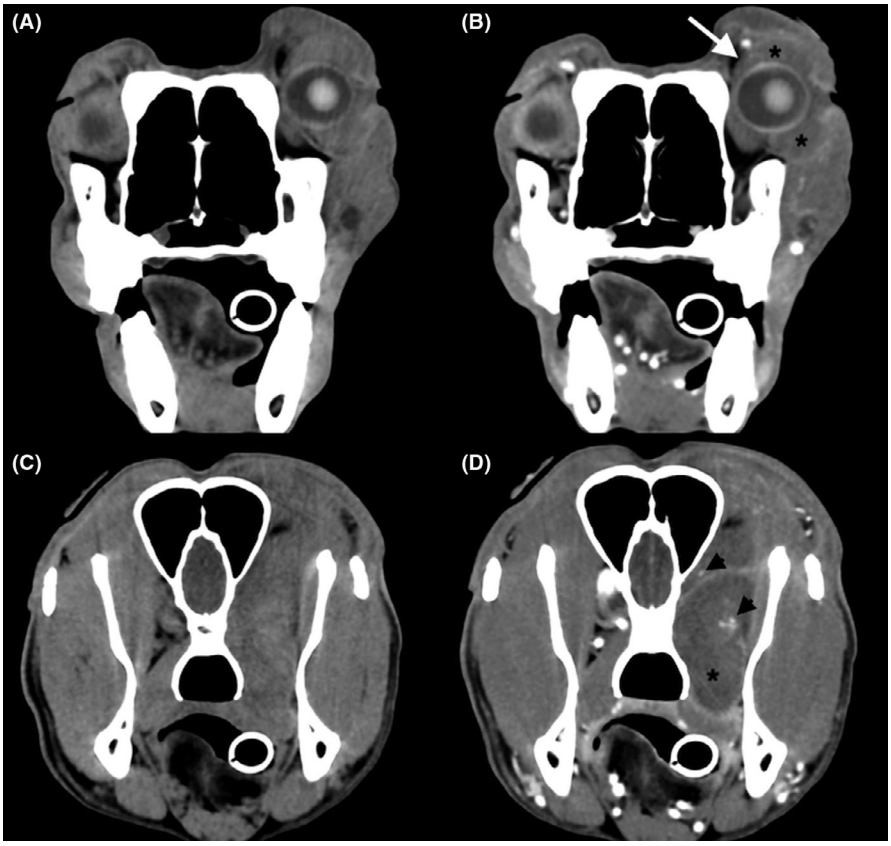

FIGURE 2 Transverse pre- (A, C) and post-contrast (B, D) CT images at the level of the globes (A, B) and of the ophthalmic venous plexuses (C, D), showing a large heterogeneous partially rim enhancing soft tissue attenuating mass (black asterisks) extending from the left conjunctiva to the left pterygoid muscles within the retrobulbar space. Note the marked left-sided exophthalmos (white arrow) and the severe reduction in size of the left dorsal and ventral external ophthalmic and deep facial veins (black arrow heads)

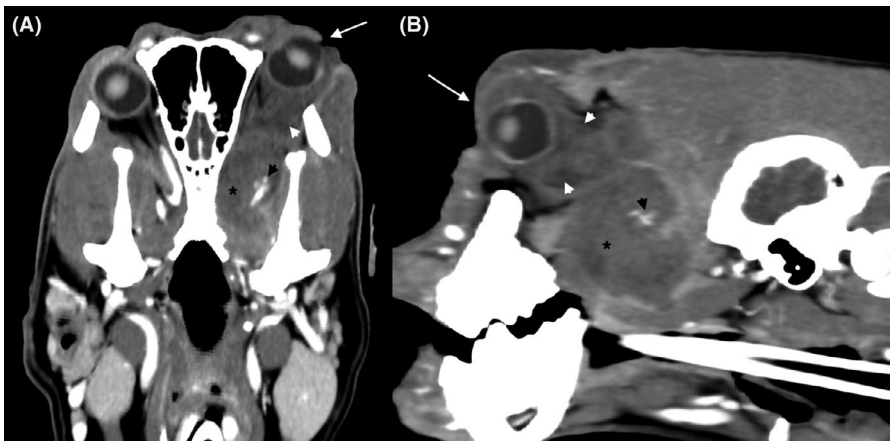

FIGURE 3 Dorsal (A) and parasagittal oblique (B) post-contrast CT images, showing the extent of the large lobulated partially rim enhancing soft tissue attenuating mass within the left retrobulbar space (black asterisks). Note the associated left-sided exophthalmos (white arrow) and obliteration of the retrobulbar fat (white arrowheads). There was an abrupt interruption in the visualization of the ventral external ophthalmic vein and severe thinning of the dorsal external ophthalmic vein (black arrowheads)

but allowed to heal by secondary intention. At the end of the surgery, a temporary nictitating membrane flap to protect the cornea was sutured to the dorsolateral conjunctival fornix, using Nylon 6/0 (Vetsuture non-absorbable monofilament). Even if the nictitating membrane was swollen, this did not create excessive tension on the lid suture.

5 | OUTCOME AND FOLLOW-UP

The dog was hospitalized after surgery. A second subcutaneous injection of desmopressin acetate (Minirin®: 1 µg/kg) was administered 120 minutes after the end of surgery. Morphine chlorhydrate 50mg (Morphine Lavoisier®: 0.2 mg/kg q6h), oral treatment of amoxicillin and clavulanic acid (Clavubactin® : 12.5 mg/kg q12h), and local OS drops of tobramycine (Tobrex collyre® q2h) were initiated. No further bleeding was seen during hospitalization. The dog started eating spontaneously by 24 h after surgery and was discharged from the hospital after 48 h of treatment. Only oral amoxicillin and clavulanic acid and topical tobramycine were continued at home at the same dosage. The temporary nictitating membrane flap was removed after 7 days. The left eye was in normal position in the orbit but blind, the ulcerative keratitis was healed. Indirect binocular ophthalmoscopy was possible on OS and was unremarkable. IOP assessed by rebound tonometry was within normal limits on OS (17 mmHg) at this recheck.

The owners declined subsequent rechecks because of financial constraints. Finally, 4 weeks after the initial presentation, the dog presented with a new episode of spontaneous bleeding with epistaxis and was euthanized by the referring veterinarian. A post-mortem PCR testing was performed and confirmed positivity for von Willebrand disease type I gene mutation (the causal mutation is a G > A transversion in the last nucleotide of exon 43 encoding the vWF) by amplification of the DNA encoding von Willebrand factor (Antagene®, La tour de Salvagny, 69890, France). The dog carried two copies of the mutant gene (mutated homozygous).

6 | DISCUSSION

To the author's knowledge, this is the first case report describing clinical and imaging findings of severe retrobulbar hemorrhage and exophthalmos occurring in a dog following routine third eyelid surgery. The hemorrhage led to exophthalmos, blindness, and corneal ulceration. An investigation into hemostatic disorders revealed that this hemorrhage was due to vWD. Very little data are published on this topic in the veterinary literature. Indeed, few reports described retrobulbar hematoma as the consequence of trauma,[2] maxillary nerve block,[3] or coagulation disorder: fibrinogen deficiency [4] or brodifacoum toxicosis.[5] So far, to the authors' knowledge, only one abstract has reported retrobulbar hemorrhage in a dog secondary to inherited vWD.[6]

Acute retrobulbar hemorrhage is a serious ophthalmic emergency due to an increasing accumulation of blood in the enclosed retrobulbar space, compression of the optic nerve, and subsequent compartment syndrome. This condition usually occurs because of orbital trauma, vasculitis, or coagulopathy, and exophthalmos is a common manifestation of this condition.[7] In humans, retrobulbar hematoma usually results from an arterial rupture of the infraorbital artery or the anterior or posterior ethmoidal arteries.[7] This condition remains rare, as 74% of cases occur after trauma, while 26% occur after an initial ocular surgical procedure to address another issue.[8]

The globe and orbital contents (fat, extraocular muscles, vessels, nerves, and lacrimal gland) are constrained in a

confined space without capacity to expand. In this setting, an acute increase of the intraorbital pressure can result in an acute increase of the intraocular pressure with subsequent compression of the optic nerve and its vascular supply. This can lead to permanent vision loss if prompt management is not performed. Orbital compartment syndrome (OCS) is the name of this pathological process in humans.[7,9]

Retrobulbar hemorrhage is essentially a clinical diagnosis but the orbit cannot be visualized directly and advanced diagnostic imaging procedures (10mHZ ultrasonography, CT, and Magnetic resonance imaging (MRI)) are needed to confirm the diagnosis and reveal the cause and extension of the disease. However, their use can delay surgical management and cause permanent vision loss.[10] In our clinical case, a CT was performed to exclude any evidence of trauma. Given its speed of execution (about 15 minutes), CT is a good imaging tool in an emergency setting to further assess soft tissue and bone damages and their extension. If bleeding disorders are suspected, additional laboratory tests should be performed.[4]

In humans, retrobulbar hemorrhage is responsible for blindness in 22% of cases and only 51% of patients show complete visual recovery despite early management.[8] The presence of blindness and/or reduced extraocular motion at the time of diagnosis is a negative prognosis factor.[8] Most of the time, surgical decompression is necessary, ideally within the first 120 minutes after the start of hemorrhage in humans.[10] In dogs, the most widely documented surgical approach is surgical drainage behind the last upper molar.[11] In our case, the visual prognosis was very poor, as the surgical correction was performed late after the appearance of hemorrhage. The aim of the surgical drainage was to relieve the pain induced by the compression in the orbit, while controlling bleeding during surgery in view of the main hypothesis of vWD. The degree of exophthalmos often increases temporarily after drainage [2]; therefore, a temporary nictitating membrane flap was performed to protect the cornea until the swelling decreased. Regarding the topical use of tobramycin without microbial culture, the medication was already initiated by the referring veterinarian and therefore continued until the corneal ulcer had healed.

vWD is the most common primary, inherited bleeding disorder in humans and dogs.[1] Type 1, defined by a low plasma concentration but normal function of vWF (<50% of reference range values), is by far the most common form in dogs (95% of cases).[12] The defect has been reported in more than 70 breeds and affects more than half of the Doberman Pinschers population.[13] Inheritance of the disease is described in most breeds as an autosomal recessive trait.[14] vWD should be suspected in any dog showing a combination of bleeding tendencies manifested by a prolonged BMBT, especially after surgery or trauma and that has a normal platelet counts, PT, and aPTT.[1] Laboratory confirmation of vWD is partly based on results of vWF antigen assay. This test measures the amount of vWF in a blood sample, but this method is not specific for the diagnosis of vWD. DNA testing for vWD type 1 gene, available for the Doberman Pinscher, is an accurate test to confirm the disease.[1]

Treatment of vWD is based on normalizing vWF levels in case of bleeding or before a surgical procedure. Administration of DDAVP, a synthetic analogue of the neurohypophyseal hormone arginine vasopressin, can temporarily increase the vWF plasma concentration. Despite this modest increase in plasma vWF concentration, administration of DDAVP to Doberman Pinschers with type 1 vWD only results in a transient improvement of hemostatic function.[14] Cryoprecipitate or fresh-frozen plasma should be used intraoperatively if significant bleeding occurs during surgery of dogs with vWD.[1]

The ocular manifestations due to primary hemostatic defect include both extraocular and intraocular bleeding, such as retrobulbar,[4] subconjunctival[15] or retinal hemorrhage,[16] hyphema, and iridal petechiae.[16] Their consequences may lead to optic nerve compression, retinal detachment, and blindness. A study in dogs has found a significant association between thrombocytopenia and ocular lesions (most of them are hemorrhagic in nature), and the severity of these lesions is inversely correlated with the platelet count.[16] However, among these primary hemostatic disorder, ocular manifestations of vWD are very rare both in humans and dogs. Only a few cases of intraocular bleeding (vitreous, retinal and/or subretinal hemorrhages) due to vWD type 1 have been reported in humans.[17-19] In the veterinary literature, only two cases have been reported, one of cerebral and conjunctival hemorrhages associated with von Willebrand syndrome (acquired vWF deficiency) secondary to angiostrongylosis in a young Golden Retriever [15] and the other one of retrobulbar hemorrhage in a dog suffering from inherited vWD.[6]

It could be presumed that extraocular and more probably intraocular bleedings associated with type 1 vWD may have a non-negligible frequency in dogs though the condition may remain underdiagnosed in those dogs. Ophthalmologists can play an important role in the recognition of the disease and a multidisciplinary approach is mandatory for optimal management of these patients. In breeds at risk of type 1 vWD or other primary hemostatic disorder, a BMBT should be considered before a periocular surgery to prevent any postoperative hemorrhage, which could be difficult to manage in the context of an enucleation. In the current case, the vWF antigen assay and the genetic test could have been performed prior to the third eyelid gland surgery in order to investigate if von Willebrand disease was present given its prevalence in the Doberman pinscher. Third eyelid gland replacement is considered an elective surgery; therefore, it could have been performed after the test results were available. If vWD is present, it should be discussed with owner whether the surgery should be performed at all.

7 | TAKE HOME MESSAGES

This case report demonstrates that any patient with a retrobulbar hematoma without an obvious local (traumatic or mechanic) etiology should have full hematology, platelets count, and a full clotting profile evaluated. Isolated ophthalmic manifestation of type 1 vWD is extremely rare but should be considered as a differential diagnosis of any extraocular and intraocular hemorrhage.

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CONFLICT OF INTEREST

None declared.

AUTHORS CONTRIBUTIONS

JBB: involved in main work and manuscript writing. ASP: involved in manuscript revision. AD: served as a ECVDI specialist, involved in CT images reading and interpretation, manuscript revision. TB: served as a ECVIM specialist, and involved in manuscript revision. OB: served as a Ophthalmology DESV specialist, in charge of the patient, and approved the final version for submission.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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