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Type I von Willebrand Disease in a Maltese

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Abstract : A 6-year-old castrated male Maltese weighing 4.16 kg presented with a history of bleeding from the mouth after scaling and dental extraction 2 days prior. The von Willebrand factor antigen (vWf:Ag) level was 54% (reference range, 70-180%), indicating that the dog was homozygous for an inherited von Willebrand disease (vWD). The dog received whole-blood transfusion as initial treatment, consequently showing markedly improved clinical signs, and is currently in good condition. To our knowledge, this is the first reported case of type 1 vWD in a Maltese in Korea.

Key words **:** Dog, von Willebrand disease, whole-blood transfusion, von Willebrand factor antigen (vWf:Ag).

Introduction

Von Willebrand disease (vWD) is the most common hereditary coagulation abnormality disease in dogs (1). It is caused by a deficiency or abnormality in von Willebrand factor (vWf), a high-molecular-weight multimeric glycoprotein (4,8). vWf is a coagulation factor that has an essential role in pulmonary hemostatic plug formation, particularly in platelet adhesion, spreading, and vessel wall aggregation (19). vWD has been reported to have a higher prevalence in Doberman Pinschers, Airedale Terriers, Scottish Terriers, Golden Retrievers, Miniature Poodles, Yorkshire Terriers, and mixed breeds (4,12). In general, in dogs, clinical expression varies in severity from a mild bleeding tendency primarily manifested after injury to more severe forms characterized by recurrent mucosal hemorrhage and prolonged bleeding from surgery, such as excessive bleeding with tooth eruption (18). The prevalence of vWD in dogs without clinical evidence of hemorrhage is 1.43% (9), similar to the frequency reported in humans (4). vWD is usually diagnosed by measuring plasma vWf antigen (vWf:Ag) levels using antibodies against vWf in an enzyme-linked immunosorbent assay (ELISA) or by immunoelectrophoresis (5,8). However, transfusion of vWD may include administration of desamino-8-arginine vasopressin (DDAVP), a medicine that increases von Willebrand factor levels and reduces bleeding (1,8,19). However, transfusion of fresh whole-blood, fresh plasma, fresh frozen plasma, or cryoprecipitate can also supplement blood vWf levels (3,8,17). Dogs with severe vWD may require repeated transfusions to control or prevent hemorrhage (3,17).

This report first describes the diagnosis and management of a dog with vWD. Diagnosing vWD is necessary to decrease disease incidence by preventing crossbreeding of affected individuals. To our knowledge, this is the first reported case of type 1 vWD in a Maltese in Korea.

Case

A 6-year-old castrated male Maltese weighing 4.16 kg presented to our veterinary clinic with a history of bleeding from the mouth after scaling and dental extraction (molar 3, incisor 2) 2 days prior. The dog also had a history of 2 previous transfusions. The first was performed due to a right hind leg hematoma at 5 months of age; the other was performed due to prolonged bleeding following castration at 10 months of age. The causes for these episodes were not investigated at the time. No additional bleeding episodes were detected until the dog was 6 years old. No other factors such as history of recent vaccination, medications, and consumption of a vitamin K antagonist were noted. On physical examination, the dog had tachycardia (180 bpm) and was panting. The hair around the dog's mouth was blood strained, and the oral mucous membranes were pale. Blood was oozing from the gingiva, caudal to the incisors, where a hematoma had formed after incisor tooth extraction, but the gums appeared otherwise healthy (Fig 1A). No other abnormal findings were evident on physical examination. A complete blood cell count revealed normocytic hyperchromic nonregenerative anemia, with a hematocrit of 15.94% (reference range, 37-55%); a reticulocyte production index (RPI) of 0.4% (an RPI < 1 indicates a nonregenerative anemia; an RPI = 1 or 2, a slight response; an RPI > 2, a moderate response; and an RPI > 3, a marked response) (7); and moderate neutrophilic leukocytosis with a left shift (35.14×10^3/uL; reference range, 6-17×10^3/uL). Mild hypoproteinemia (5.0 g/dL; reference range, 5.4-7.4 g/dL) and mild hypoalbuminemia (2.7 g/dL; reference range, 2.9-4.2 g/dL) were also observed. A platelet count and

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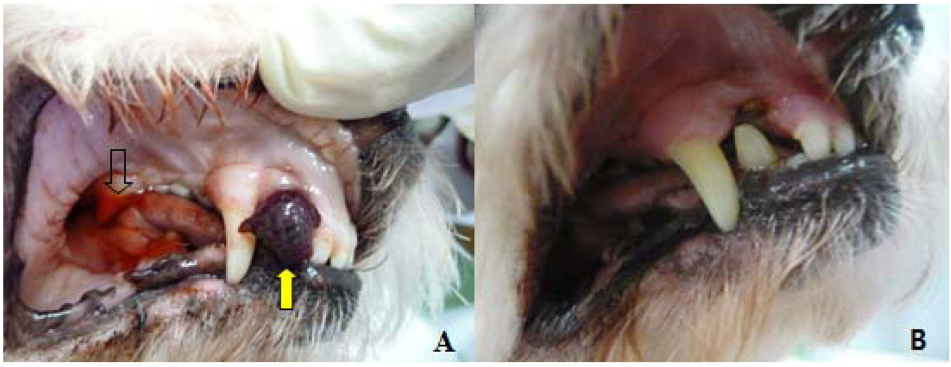

Fig 1. Clinical appearance of oral cavity with gingival hemorrhage, before and after treatment. (A) Blood oozing from the gingiva (open arrow), and hematoma after incisor tooth extraction (yellow arrow). (B) Image of gingiva 5 days after whole-blood transfusion: no evidence of gingival hemorrhage.

Table 1. Patient blood coagulation test results

Coagulation test	Result	Reference
Platelet count ($\times 10^3/u$L)	257	200-500
BMBT (min)	5.12	1.68-4.15
PT (s)	7.4	6.2-8.2
APTT (s)	17	12-18
FDP (μg/mL)	5	0-10
FVIII:C (%)	150	50-200
FIX:C (%)	81	50-150
vWf: Ag (%)	54	70-180
D-dimers (ng/dL)	0.1	0.0-0.3
AT III (%)	128	80-200

BMBT, buccal mucosal bleeding time; PT, prothrombin time; APTT, activated partial thromboplastin time; FDP, fibrin degradation products; FVIII:C, factor VIII coagulant; FIX:C, factor IX coagulant; vWf:Ag, von Willebrand factor antigen; AT III, antithrombin III.

coagulation panel including prothrombin time, activated partial thromboplastin time, fibrin degradation production, D-dimers, and anti-thrombin III were within reference ranges, but buccal mucosal bleeding time (BMBT) was mildly prolonged (Table 1). The results of a thoracic and abdominal radiographic examination were unremarkable.

The above test results led to an initial differential diagnosis of coagulopathy, including a platelet disorder such as thrombocytopathy; a congenital coagulation deficiency such as vWD and hemophilia A or B; vitamin K antagonist poisoning; or less likely, a vessel wall defect. For a definitive diagnosis, several additional diagnostic tests were employed in combination with a careful review of the case history, which included postoperation bleeding and recurrent hemorrhage from a very young age and clinical signs such as mucosal hemorrhage and hematoma after scaling and tooth extraction.

Blood was drawn into a citrated tube and submitted for von Willebrand factor antigen (vWf:Ag) assay and hemophilia A and B testing. Due to the severe anemia and continuous gingival hemorrhage, a whole-blood transfusion was administered. The dog was transfused with 137-mL fresh whole blood from a donor dog (dog erythrocyte antigen [DEA] 1.1 negative). A guideline for the amount of anticoagulant in donor blood (in mL) is as follows: body weight (kg) of patient × 80 × (desired packed cell volume [PCV] - patient PCV) divided by donor PCV (22). The gums appeared pinker, and the gingival bleeding stopped < 3 h after starting the transfusion. Shortly after transfusion, vital signs were within normal limits and hematocrit level was 21.35% (reference range, 37-55%). After the whole-blood transfusion, the dog showed markedly improved clinical signs and was in overall good condition. Five days later, there was no evidence of gingival hemorrhage (Fig 1B), the hematocrit level had increased to 31.49% (reference range, 37-55%), and the RPI had increased to 1.5% (reference range, > 1%). Blood smear features of regeneration, including anisocytosis and nucleated red cells, were observed. One month after transfusion, the hematocrit level was 39.88% (reference range, 37-55%), and we observed no evidence of gingival hemorrhage. vWf:Ag was mildly decreased, with normal factor VIII and IX coagulants in specific factor assays (Table 1). The results of the vWf:Ag assay were 54% (reference range, 70-80%). Patients with vWf antigen levels below the reference range are considered vWD carriers; thus, the dog was homozygous for inherited type 1 vWD.

This diagnosis was supported by the clinical presentation of bleeding after scaling and dental extraction and confirmed based on the results of standard vWf:Ag assay and coagulation panel, as well as normal platelet counts.

The owner has monitored the dog for recurrence of bleeding episodes manifested as epistaxis, gingival hemorrhage, hematuria, and gastrointestinal bleeding. The dog has been asymptomatic and remains in good condition.

Discussion

vWD is considered the most common inherited hemostatic disease in human and non-human animals including pigs,

rabbits, cats, horses, and cows (5,6). It was first reported in a Scottish Terrier in 1972 (15). In dogs, vWD is classified according to clinical severity, plasma vWf concentration, and type of vWf multimetric structure (1,3,6). vWD in dogs is classified into 3 types with different clinical signs and inheritance patterns (3,12,13,20). Type 1 vWD is a quantitative protein deficiency manifested by low vWf plasma concentration with a proportional reduction in vWf function. Type 2 vWD is both a quantitative and functional protein deficiency: low plasma vWf:Ag results in a disproportionate decrease in vWf function measured by collagen binding or platelet agglutination support (3,20). Type 3 vWD is a severe vWf deficiency, with no detectable plasma vWf (3,12).

In general, certain vWD types in dogs occur in specific breeds: type 1 vWD in Akitas, Bernese Mountain Dogs, Dachshunds, Doberman Pinschers, German Shepherds, Golden Retrievers, Greyhounds, Miniature Pinschers, Maltese, Welsh Corgis, Poodles, and Schnauzers, with sporadic cases reported in any breed; type 2 vWD includes German Shorthaired Pointers, German Wirehaired Pointers; and type 3 vWD includes Scottish Terriers, Shetland Sheepdogs, Austrian Shepherds, Border Collies, Cocker Spaniels, Labrador Retrievers, and Maltese (3,9). Until recently, vWD in Maltese has been reported to be types 1 and 3 (3,9). In a previous study (9,19), the vWD status of animals was classified according to vWf: Ag levels as follows: negative for vWD (> 70%), suspect for vWD (50-70%), and vWD affected (<50%). In this case, the results of the vWf:Ag assay were 54%. Thus, the vWf:Ag levels classified our case as vWD suspect. The vWf concentration in this dog was classified as type 1 vWD. A comprehensive analysis of vWD subtype classification in a previous study correlated BMBT with type 1, 5 to > 12 min; type 2, > 12 min; and type 3, > 12 min (reference, 2-4 min). The BMBT of our case was 5.12 min, similar to type 1 in this previous study (2). Dogs that are clinically affected are most likely to be the offspring of homogenous parents affected with vWD (19).

Previous studies (1,3) have shown that the most common platelet disorders are acquired rather than inherited. However, our case had recurrent hemorrhage from a very young age; mucosal hemorrhage and hematoma after tooth extraction indicated a primary hemostatic disorder, probably involving platelets. Therefore, an inherited primary hemostatic disorder was possible. In addition, the screening test findings, including a normal platelet count, normal coagulation panel, and long BMBT, were compatible with a vWD diagnosis. The definitive diagnosis was confirmed by the low plasma vWf: Ag (Table 1).

In our case, the complete blood count findings indicated normocytic hyperchromic nonregenerative anemia. On presentation, the RPI was 0.4% (reference range, > 1%) and increased to 1.4% by day 5. Anemia by acute blood loss is usually initially nonregenerative and becomes regenerative after 3-4 days (21). The dog also had neutrophilic leukocytosis with shift to the left (no toxic change). This leukogram may have been due to generalized bone marrow stimulation secondary to macrophage activation or hypoxia-induced inflammation or necrosis in organs such as the liver (7,21).

Effective management of vWD requires control of active bleeding sites; stabilization of the patient to treat blood loss, anemia, and hypovolemia; and identification and correction of the primary disease that caused or exacerbated the hemostatic defect (8,20). Initial treatment modalities include both nontransfusion and transfusion support (8,14,22). DDAVP is a synthetic vasopressin analog used in human medicine to treat a variety of hemostatic defects, including acquired platelet function defects and mild vWD (14). Previous studies (10,11,16,22) anecdotally report efficacy of plasma and cryoprecipitates to treat or prevent hemorrhage in dogs. In our case, whole-blood transfusion was selected as an initial treatment due to severe anemia and continuous gingival hemorrhage.

Diagnostic approaches to coagulation and bleeding disorders in canine patients can be challenging. To decrease the incidence and perpetuation of vWD, it is necessary to prevent affected individuals from crossbreeding.

In conclusion, to our knowledge, this is the first report of the diagnosis and successful treatment of type 1 vWD in a Maltese in Korea.

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한국내 말티즈에서 발생한 제 1형 폰 빌레브란트병 증례

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요 약 : 6살령의 중성화된 숫컷 말티즈(4.16 kg)가 2일전 스켈링과 발치를 실시한 후 지속적인 구강내 출혈로 본원에 내원하였다. 환축은 폰 빌레브란트 인자 항원 평가 결과 54% (정상 범위 70%에서 180%)였으며, 유전된 폰 빌레브란트병를 가진 동형접합체로 판정되었다. 초기 치료를 위해 신선 전혈 수혈을 실시하였다. 수혈 후 환축은 임상증상이 개선되었으며 현재까지 건강한 상태이다. 본 증례는 한국내 말티즈에서 발생한 제 1형 폰 빌레브란트병의 첫 번째 진단 보고이다.

주요어 : 개, 폰 빌레브란트병, 전혈 수혈, 폰 빌레브란트 인자항원