“Acute onset tetraplegia associated with immune-mediated thrombocytopenia and suspected secondary intraspinal hemorrhage in a dog”

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Abstract
Neurologic manifestations of immune-mediated thrombocytopenia are uncommon, and limited reports exist in human and veterinary medicine. This report documents acute onset of tetraplegia in a dog with immune-mediated thrombocytopenia and suspected secondary intraspinal hemorrhage with subsequent recovery of neurologic function following treatment.

Keywords
hematology, immune-mediated disease, intraspinal hemorrhage, neurology, veterinary

1 INTRODUCTION

Immune-mediated thrombocytopenia (ITP) is a common cause of severe thrombocytopenia in dogs. The immune-mediated destruction of platelets can be primary or secondary. A definitive diagnosis of ITP is made by detecting antiplatelet antibodies on the surface of platelets; however, assays are not readily available and do not differentiate between primary and secondary ITP. A diagnosis of primary ITP is typically made when no underlying cause for the immune-mediated destruction is found. Secondary ITP can occur as a result of certain medications, infections, and neoplasia. In both primary and secondary ITP, antiplatelet antibodies adhere to platelet surface antigens, stimulating Fc receptor–mediated phagocytosis of the circulating platelets by macrophages. Reported prognostic indicators for ITP in dogs have included the presence of melena and an increased BUN concentration. A recent report documented an increased risk of relapse if a blood transfusion was needed.

The mainstay of treatment for ITP is immunosuppression, and standard of care in both humans and animals involves glucocorticoids. However, only approximately two-thirds of human patients achieve a complete or partial response with corticosteroids alone, and a high proportion of patients relapse or require alternative therapies due to the adverse side effects of steroids. Adjunctive immunomodulatory medications include cyclosporine, azathioprine, mycophenolate, and leflunomide. Survival rates of 94% and 90% have been reported in dogs treated with cyclosporine and mycophenolate, respectively, in addition to glucocorticoid therapy. Other immunotherapies including vincristine (VINC) and intravenous immunoglobulin (IVIG) have been evaluated in both people and animals. The use of VINC or IVIG in addition to prednisone has been shown to shorten the time to platelet count recovery when compared to treatment with prednisone alone, in dogs with ITP. More recently, thrombopoietin receptor (TPO-R) agonists have been investigated in dogs with refractory and severe ITP, with favorable results.

Common presenting clinical signs in dogs with ITP include petechia, ecchymoses, gingival bleeding, melena, hematemesis, hematochezia, epistaxis, hematuria, hyphema, and scleral hemorrhage. Spontaneous hemorrhage usually does not occur until the platelet count decreases to less than 30 000-50 000/uL. Overall reported short-term survival...
rates range from 74% to 97% with a rate of recurrence of 26%-58%. A more recent study reports survival rates of 89.6% with a relapse rate of 31%. Neurologic manifestations of ITP are uncommon, and there are limited reports in human and veterinary medicine. To the authors knowledge, this is the first case report in the veterinary literature describing a presentation of tetraplegia associated with presumed primary ITP in a dog.

2 | CASE SUMMARY

A 10 year-old female spayed Havanese weighing 4.8 kg was referred for continued evaluation of acute onset of nonambulatory tetraplegia. The dog had been previously healthy, with the exception of left forelimb lameness 1 month prior to presentation that resolved with the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), as well as hypotrichosis and pigmented changes to the skin that were noted 2 months prior to presentation, and had since resolved. The dog was heard vocalizing the night prior to presentation and was found nonambulatory by the owner. On physical examination to the primary veterinarian, the dog was quiet but responsive with a heart rate of 136/min and normal respiratory rate and effort. A grade II-III/VI left apical systolic murmur was audible on thoracic auscultation. Mucous membranes were pink with a normal capillary refill time (CRT). The dog was laterally recumbent with absent motor and severely decreased pain sensation in all four limbs. A chemistry panel performed in the clinic was unremarkable, and a complete blood count (CBC) showed a marked thrombocytopenia (platelet count 0 × 10^9 cells/L [0k/uL]); reference interval (RI) 1.86-5.45 × 10^9 cells/L [186000-545 000/uL]). The dog was referred to the authors’ hospital for evaluation.

Upon presentation to the authors’ hospital (day one), vital signs were normal. Neurologic assessment revealed nonambulatory tetraplegia with severely decreased pain sensation in all four limbs. Conscious proprioception was absent, and no cervical or spinal pain was appreciated. Cranial nerves were within normal limits. Spinal reflexes were normal in all four limbs. These findings were consistent with a cervical myelopathy (C1-C6). Small areas of petechiation and ecchymoses were noted along the ventral abdomen and inguinal area. A minimum database was performed and revealed the following: packed cell volume (PCV) 0.49 (49%; RI 0.383-0.565 [38.3%-56.5%]), total plasma protein (TPP) 52 g/L (5.2 g/dL; RI 50-72 g/L [5.0-7.2 g/dL]), lactate 1.46 mmol/L (RI, 0-2.0 mmol/L), and blood glucose (BG) was 5.6 mmol/L (101 mg/dL;RI 3.8-5.8 mmol/L [68-104 mg/dL]). Systolic blood pressure (SBP) as measured by Doppler ultrasonography (Doppler flow detector model 811-B, Parks Medical Electronics) was normal at 140 mmHg. A blood smear was evaluated in the clinic and confirmed the presence of severe thrombocytopenia (0-1 PLT per high power field [RI, 10-20 PLT per high power field]). Additional diagnostics included thoracic radiographs, which were unremarkable, and an echocardiogram which revealed myxomatous degeneration of the mitral and tricuspid valves, moderate tricuspid regurgitation, and trace pulmonic insufficiency. An abdominal ultrasound revealed a slightly hyperechoic liver, suggestive of a mild chronic hepatopathy. A rapid point-of-care qualitative assay for tick-borne disease (SNAP 4DX(IDEXX)) was negative. A comprehensive vector disease panel was submitted to an external laboratory (Vector Borne Disease Diagnostics). A CBC was submitted to an external laboratory(IDEXX Labs, Animal Medical Center) and confirmed a severe thrombocytopenia (Table 1). Magnetic resonance imaging (MRI) was not pursued on initial presentation in favor of further stabilization of the dog’s clinical status. Treatment for suspected ITP was initiated, and the dog was administered corticosteroids (dexamethasone SP [Dexium SP, Bimeda] 0.2 mg/kg IV q 24) and doxycycline (Doxy 100,

TABLE 1 Selected CBC values and blood smear findings in a dog with acute tetraplegia secondary to immune-mediated thrombocytopenia

| Parameters                      | Day 1               | Day 2               | Day 3               |
|---------------------------------|---------------------|---------------------|---------------------|
| Hematocrit (%)                  | 0.448 (44.8%)       | 0.393 (39.3%)       | 0.379 (37.9%)       |
| White blood cell count (x 10^9  |
| cells/L [k/uL])                | 10.6 (10 600)       | 16.7 (16 700)       | 19.9 (19 900)       |
| Neutrophil count (x 10^9        |
| cells/L [k/uL])                | 8.724 (8724)        | 14.429 (14 429)     | 16.318 (16 318)     |
| Platelet count (x 10^9 cells/L  |
| [k/uL])                        | < 10.0 (<10 000)    | < 10.0 (<10 000)    | 14.0 (14 000)       |
| Platelet estimate – blood smear |
| (x 10^9 cells/L [k/uL])        | 10.0 (<10 000)      | No platelet number estimate; extremely rare platelets observed | No platelet estimate; markedly decreased platelet count |
| Other blood smear findings      | No significant      | Normal erythrocyte morphology, mild neutrophilia, lymphopenia, monocytes consistent with stress/glucocorticoid response | Mild nonregenerative/pre-regenerative anemia, mild neutrophilia, monocytes consistent with nonspecific inflammation |
Fresenius Kabi; 10 mg/kg IV q 24). Additional treatments included maropitant (Cerenia, Zoetis; 1 mg/kg IV q 24), pantoprazole (Pantoprazole sodium, AuroMedics Pharma LLC; 1 mg/kg IV q 24), isotonic crystalloid fluid therapy (Vetivex, Dechra Veterinary Products) with 20 mEq/L potassium chloride supplementation (at 11 mL/hr), and metoclopramide (Metoclopramide, Hospira Inc; continuous rate infusion [CRI] at 1 mg/kg/day IV).

On day two, vital signs were within normal limits. Neurologic status was unchanged. Repeat CBC revealed a persistent severe thrombocytopenia (Table 1). A pathologist review (PR) confirmed a markedly decreased PLT count with only extremely rare platelets observed (Table 1). Magnetic resonance imaging (ESAOTE Vet-MR Grande 0.25 Tesla. Sequences included transverse and sagittal T1, T1 + contrast, T2, and FLAIR weighted image series, as well as sagittal STIR and transverse T2* weighted image series) of the cervical spine was performed with contrast (Magnevist [gadopentetate dimeglumine 0.5 mmol/mL]; Bayer HealthCare LLC.) under general anesthesia. The dog was premedicated with fentanyl (Fentanyl citrate injection, USP, West-Ward; 5 mcg/kg IV) and midazolam (Midazolam injection, USP, Akorn, Inc; 0.2 mg/kg IV). Anesthesia was induced using propofol (PropoFlo, Zoetis; 6 mg/kg IV) and maintained with gas inhalant (isoflurane [Isoflurane, USP, Patterson Veterinary]). Additional treatments included a fentanyl(Fentanyl citrate injection, USP, West-Ward) CRI (1.25-2.5 mcg/kg/hr IV) and dobutamine (Dobutamine injection, USP, Hospira) CRI (1.25-5 mcg/kg/min IV). The MRI demonstrated a crescentic accumulation of material within the left dorsolateral aspect of the spinal canal along the entire length of C3, causing mild-to-moderate displacement and compression of the spinal cord. The material was T1 hyperintense (to cerebrospinal fluid), T2 hyperintense, and did not suppress on FLAIR (fluid-attenuated inversion recovery)- or STIR (short tau inversion recovery)- weighted images. The material did not demonstrate susceptibility artifact on T2* but did demonstrate mild peripheral contrast enhancement. Intramedullary hyperintensity was present from approximately mid-C2 to the cranial aspect of C5 (Figure 1). Findings were most suggestive of intraspinal hemorrhage (ISH). Surgical decompression was not pursued in favor of medical management, given the increased risk of life threatening hemorrhage. The dog recovered uneventfully from anesthesia. Given the persistent thrombocytopenia, cyclosporine (Atopica, Novartis Animal Health; 5 mg/kg PO q 12) was added to the treatment plan.

On day three, the dogs’ vital signs remained within normal limits, and neurologic status remained unchanged. Progressive bruising along the hind limbs was noted, along with peripheral limb edema. A CBC revealed a neutrophilia and marginally improved but persistent thrombocytopenia, confirmed with a PR (Table 1). Previous treatments were continued as before with the exception of an increased dexamethasone dose (0.25 mg/kg IV q 24) and the addition of buprenorphine (Buprenorphine HCL injection, Par Pharmaceutical; 0.01 mg/kg IV q 8) for discomfort associated with the edema. Vincristine (Vincristine sulfate injection, USP, Hospira; 0.02 mg/kg IV) and human intravenous immunoglobulin (Gammagard Liquid, Baxalta; IVIG; 0.5 g/kg over 4 hours) were also administered. On day four, vital signs remained within normal limits, and neurologic status was unchanged. The CBC revealed improvement in the thrombocytopenia (Table 1), and the PR showed a nonregenerative or pre-regenerative anemia. The aforementioned treatments were continued. On day five, the dog was able to sit in sternal recumbency with no assistance. Thrombocytopenia remained resolved on the CBC (Table 1). The dog was transitioned to oral corticosteroids (prednisone [PREDNISONE, Qualitest Pharmaceuticals] 1 mg/kg PO q 12) and doxycycline (Doxycycline hyclate, Puracap Caribe; 10 mg/kg PO q 24). All previous IV treatments

| Day 4 | Day 5 | Day 6 | Reference interval |
|------|------|------|-------------------|
| 0.355 (35.5%) | 0.329 (32.9%) | 0.33 (33%) | 0.383-0.565 (38.3%-56.5%) |
| 13.8 (13 800) | 22.0 (22 000) | 16.4 (16 400) | 4.9-17.6 (4.900-17 600) |
| 10.626 (10 626) | 18.480 (18 480) | 13.776 (13 776) | 2.94-12.67 (2940-12 670) |
| 64.0 (64 000) | 144.0 (1 44 000) | 205.0 (2 05 000) | 143-448 (1 43 000-4 48 000) |
| 60-80.0 (60-80 000) | No platelet estimate; adequate platelet numbers | No platelet estimate; adequate platelet numbers | 186-545 (1 86000-5 45 000) |
| Mild nonregenerative or pre-regenerative anemia, adequate white cell density | Mild nonregenerative or pre-regenerative anemia, inflammatory leukogram | Mild nonregenerative/pre-regenerative anemia, inflammatory leukogram | Not applicable |
were continued, and IV fluids were tapered. On day six, the dogs’ neurologic status was further improved with nonambulatory tetraparesis and improved pain sensation. The dog was able to bear a small amount of weight in the left forelimb and hind limb with support. The CBC revealed continued resolution of the thrombocytopenia (Table 1). The dog was discharged from the hospital with oral prednisone (1 mg/kg PO q 12), cyclosporine (Atopica 5 mg/kg PO q 12), doxycycline (10 mg/kg PO q 24), gabapentin (Gabapentin oral solution, Amneal Pharmaceuticals: 10 mg/kg PO q 12), and omeprazole (Omeprazole compounded liquid, Best Pet RX Pharmacy; 1 mg/kg PO q 24).

The results of the comprehensive vector disease panel were available after discharge and revealed a positive result for anaplasma on a rapid point-of-care qualitative assay (Snap 4DX test), with a negative anaplasma polymerase chain reactivity (PCR) result. Immunofluorescence assay (IFA) for bartonella revealed weakly positive titers for *Bartonella vinsonii* (1:64), *Bartonella henselae* (1:128), and *Bartonella koehlerae* (1:128). Polymerase chain reaction (PCR) for bartonella was negative on this panel. In light of these results, enrofloxacin (Enrofloxacin compounded liquid, Best Pet RX Pharmacy) was recommended for 6 weeks (10 mg/kg PO q 24), and a repeat PCR was recommended thereafter.

The dog began hydrotherapy and physical therapy at a rehabilitation center and continued to make neurologic improvements. Approximately five weeks after discharge, the dog was fully ambulatory with only mild generalized ataxia. Regular monitoring of bloodwork revealed a persistently normal PLT count.

3 | DISCUSSION

This is the first case report in the veterinary literature describing tetraplegia likely caused by ITP in a dog. Tetraplegia is defined as paralysis of all four limbs, and commonly reported causes in dogs include intervertebral disk disease, trauma, ischemia from fibrocartilaginous embolism, and spondylo-myelopathy. Other less commonly reported causes include lower motor neuron diseases (tick paralysis, botulism, and polyradiculoneuritis), neoplasia, and inflammatory or infectious diseases. The prognosis is variable and depends upon the underlying cause, and the severity of spinal cord compression. While ITP has not been documented as a cause of tetraplegia in animals, neurologic manifestations of the disease in the form of seizures have been observed at the authors’ hospital. Guever et al reported a case of thrombocytopenia in
a dog presenting for progressive ambulatory tetraparesis over a six-week period prior to the onset of nonambulatory tetra-
paresis. The PLT count of the dog at the time was $3 \times 10^9$
cells/L (3000/ul), and a diagnosis of presumed primary ITP
was made. Unfortunately, that dog was euthanized despite
normalization of PLT count within 48 hours of starting im-
munosuppressive treatment, due to progressive neurologic
decline and loss of motor and nociception. Immune-me-
diated thrombocytopenia (previously known as idiopathic
thrombocytopenic purpura or immune thrombocytopenic
purpura) has been associated with neurologic manifesta-
tions in children. The incidence of intracranial hemorrhage caus-
ing mortality in children with acute ITP is estimated to be 0.2
to 1%. Intracranial hemorrhage and intraspinal hemorrhage
have been reported in association with neonatal alloimmune
thrombocytopenia secondary to maternal anti-human plate-
let antigen antibody formation. Intraspinal hemorrhage in
humans has also been described in association with trauma,
lumbar puncture, spinal surgery, coagulopathy, tumors, and
vascular malformations as well as of spontaneous, unknown
etiologies. Clinical signs in people include lower back pain,
with or without a radiculopathy. Rarely, paraplegia or tetra-
plegia has been described, depending on the site and severity
of spinal cord compression.

Intraspinal hemorrhage can be further categorized as
spinal epidural hemorrhage, spinal subdural hemorrhage,
spinal subarachnoid hemorrhage, and intramedullary hem-
orrhage. Extramedullary intraspinal hemorrhage has been
reported to occur in dogs spontaneously or due to interverte-
bral disk herniation, coagulopathies, hemophilia, and snake
envenomation. Intramedullary intraspinal hemorrhage has
been described in dogs experiencing myelomalacia, sponta-
neous bleeding, or vascular malformations, causing a variety
of clinical signs. Intraspinal hemorrhage has a character-
stic appearance on MRI depending on its age, as reported
by Braun et al. In the dog reported here, the presence of
both T1 and T2 hyperintensity with the absence of sus-
cceptibility artifact on the T2*-weighted images and the lack of
suppression on FLAIR-weighted images is most compat-
ible with ISH in the late subacute phase, based upon human
reports, and is similar to prior descriptions in dogs. The
clinical progression described in the dog reported here, how-
ever, was more consistent with an acute process. There are
additional descriptions of ISH in humans where both T1 and
T2 hyperintensity are reported within the peracute and acute
time frames, which is consistent with the dog reported here.
The presumptive ISH in this case demonstrated peripheral
contrast enhancement, which has previously been reported
in humans and dogs. The variability of MRI findings
in people with ISH and the lack of consistency among the
limited reports in the veterinary literature, combined with the
presence of severe thrombocytopenia and the absence of any
other findings, led the authors to consider ISH secondary to
ITP as the most likely diagnosis in this case. The additional
intramedullary changes observed on MRI may represent con-
current intramedullary hemorrhage, edema, myelitis, or some
combination thereof. Unfortunately, the poor spatial resolu-
tion of the low-field MRI study limited further characteri-
zation of the presumed hemorrhage as epidural, subdural, or
subarachnoid.

When considering a diagnosis of primary ITP in dogs,
underlying causes for secondary ITP must be ruled out.
Infectious agents that have been associated with ITP in vet-
erinary patients include rickettsial, protozoal, nematodal, and
viral diseases, and thrombocytopenia secondary to vector-
borne disease (ehrlichiosis, babesiosis, and Rocky Mountain
spotted fever) has been well documented in veterinary medi-
cine. Positive results of serologic tests for rick-
ettsial tick-borne infections in endemic areas can be difficult
to interpret as they can indicate prior exposure rather than
an active infection. The drug reported here tested positive for
anaplasma on a rapid point-of-care qualitative assay (Snap
4DX test) and negative on the PCR, which indicates previous
exposure but not active infection. The dog also tested weakly
positive for bartonella on IFA, which is consistent with previ-
ous exposure but not active infection. The Center for Disease
Control (CDC) recommends culture or tissue PCR for the de-
finitive diagnosis of Bartonella. The decision to treat the
dog empirically with enrofloxacin was made because the dog
was receiving immunosuppressive therapy and the implica-
tions of not treating bartonella could have been detrimental;
however, the authors considered vector-borne disease to be
an unlikely inciting cause of ITP in this case.

Drug-induced thrombocytopenia has been demonstrated
in veterinary medicine with sulfad-based antibiotics. The
pathogenesis is not well understood, both metabolic and
immunologic mechanisms are thought to be involved. There
are reports in human medicine of sensitization leading to
drug-induced ITP secondary to NSAID drugs (meloxicam and
naproxen) as well as acetaminophen. Though there are no reports of ITP secondary to NSAID drug administra-
tion in veterinary patients, the dog in this report did receive a
course of meloxicam one month prior to the development of
thrombocytopenia.

Treatment with immunosuppressive doses of glucocortic-
oids is standard of care for human and veterinary patients
with ITP. Most patients treated with glucocorticoids exhibit
platelet count recovery within 1-15 days after beginning
treatment. However, a high proportion of patients will not
respond to steroids alone. Intravenous immunoglobulin was
first demonstrated to be effective in treatment of ITP in chil-
dren in the 1980s and is now considered standard of care. Vincristine has also been utilized in conjunction with
corticosteroids for the treatment of ITP in human medicine. In
particular, it has been used in patients with refractory ITP that had failed standard therapeutic options with one study stating 87% rate of complete response. Rozanski et al described a shortening of platelet recovery time when vincristine and IVIG were used to treat ITP in dogs, when compared to the use of corticosteroids alone. The dog described in the current report received both human IVIG and vincristine in short succession of each other; therefore, the specific efficacy of either treatment cannot be evaluated. Newer therapies emerging in human and veterinary medicine include thrombopoietin receptor (TPO-R) antagonists which stimulate megakaryocytes and increase platelets in the peripheral blood circulation. Initial results appear promising; however, further studies are needed before these medications are used routinely in veterinary patients.

This report documents an unusual presentation of ITP that has not previously been reported in the veterinary literature. The authors suggest that ITP should be considered as a differential diagnosis in dogs presenting with tetraplegia, until a CBC has been performed to confirm a normal PLT count. Fortunately, as demonstrated here, with time and supportive care, the prognosis can be favorable.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

JSL, TJB, BL: involved in patient management, diagnosis, and treatment. JSL, TJB: wrote the manuscript. TJB, ASY, JSL, TJB, BL: involved in patient management, diagnosis, care, the prognosis can be favorable. Fortunately, as demonstrated here, with time and supportive care, the prognosis can be favorable.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

JSL, TJB, BL: involved in patient management, diagnosis, and treatment. JSL, TJB: wrote the manuscript. TJB, ASY, BL: provided editing and review of the manuscript.

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