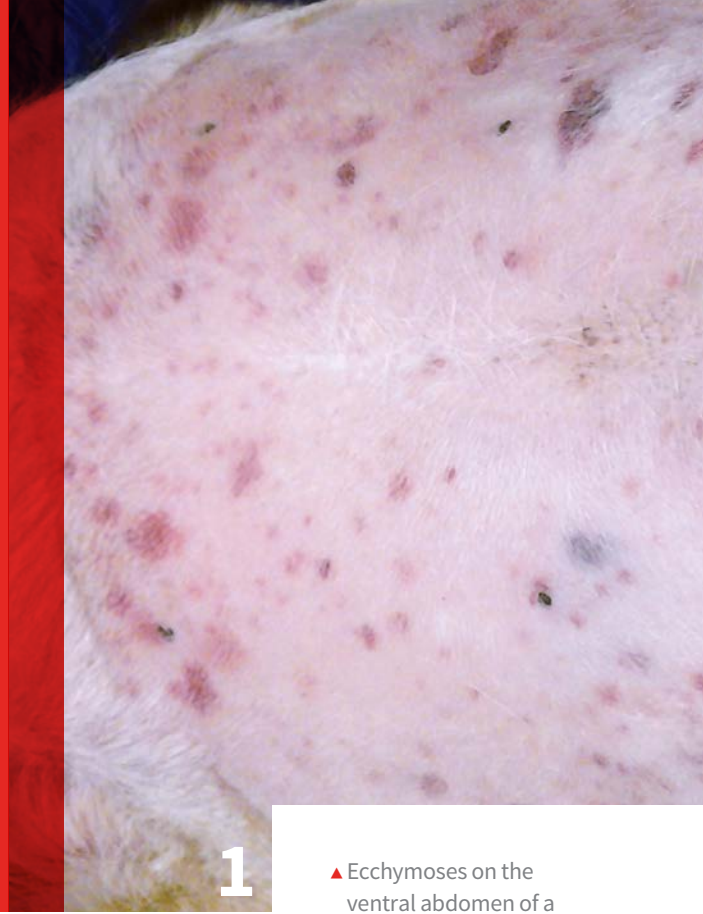


# Canine Primary (Idiopathic) Immune-Mediated Thrombocytopenia

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▲ Ecchymoses on the ventral abdomen of a patient with IMT.

## PROFILE

### Definition

- ▶ Thrombocytopenia is a deficiency of platelets in the blood.
  - Four main pathogenic mechanisms can cause thrombocytopenia:
    - Decreased platelet production
    - Platelet destruction
    - Platelet consumption
    - Abnormal platelet distribution/sequestration
- ▶ In immune-mediated thrombocytopenia (IMT), the deficiency is caused by immune-mediated destruction of platelets.
  - Platelets aid in forming blood clots.

### Signalment

- ▶ The incidence of primary IMT is high in middle-aged female dogs, cocker spaniels, Old English sheepdogs, German shepherd dogs, and poodles.<sup>1,2</sup>

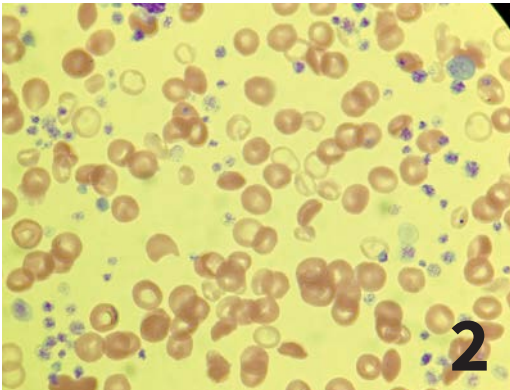
### Causes

- ▶ IMT can be primary or secondary.
  - Primary IMT is an autoimmune disorder with production of antibodies directed against normal platelet antigens.
  - Secondary IMT occurs in association with infection, drug therapy, neoplasia, poly-immune syndromes, or complication of platelet transfusion.<sup>1</sup>
    - Vaccination as a cause of secondary IMT is possible.<sup>3</sup>

### Pathophysiology

- ▶ IMT occurs when an animal's immune system produces antibodies that bind directly or indirectly to its own platelets; this leads to accelerated platelet destruction by the mononuclear phagocyte system.<sup>4,5</sup>
  - Primary IMT is usually mediated by immunoglobulin G directed against platelet

**Primary IMT is an autoimmune disorder with production of antibodies directed against normal platelet antigens.**



▲ Blood smear of a canine patient with a normal platelet count (10× magnification).

membrane glycoprotein IIb/IIIa.<sup>1</sup>

- Secondary IMT occurs when antibodies target nonself antigens adsorbed onto the surface of platelets or when immune complexes become bound to platelet surfaces.<sup>6</sup>

### History & Clinical Signs

- ▶ Travel, vaccination, medication, and tick prevention history are important in cases of thrombocytopenia to rule out causes of secondary IMT.
- ▶ Patients with IMT are often subclinically affected or are presented with clinical signs attributed to bleeding.
  - The GI tract can be a site of hemorrhage in these patients.
  - Intracavitary bleeding is uncommon.
- ▶ Systemic clinical signs are often seen only if a secondary anemia is present.
  - Some dogs without anemia will be presented for nonspecific clinical signs such as lethargy or anorexia.

### Physical Examination

- ▶ Findings can include epistaxis, gingival bleeding, petechiae and ecchymoses (**Figure 1**), bruising, hematochezia, melena, and hematuria.
- ▶ An ophthalmologic examination is recom-

mended to look for changes such as hyphema, anterior uveitis, and retinal hemorrhage.

- ▶ Clinical signs of anemia may be present.
  - This can include pale pink mucous membranes, weakness, tachycardia, bounding pulse, heart murmur, and tachypnea.

## DIAGNOSIS

### Definitive

- ▶ Diagnosis of thrombocytopenia is by manual platelet count.
- ▶ In order to diagnose primary IMT, all non-immunologic and secondary causes of IMT must be ruled out.
  - Diagnosis is confirmed when response to immunosuppressive therapy is observed.

### Differentials

- ▶ Decreased platelet production: drugs, infection, irradiation, myelonecrosis, myelofibrosis, neoplasia<sup>4</sup>
- ▶ Platelet destruction: idiopathic, drugs, infection (tick-borne disease), neoplasia, platelet transfusion, systemic immune-mediated disease (systemic lupus erythematosus)<sup>4</sup>
- ▶ Platelet consumption: blood loss, disseminated intravascular coagulation, endotoxemia, vasculitis<sup>4</sup>
- ▶ Abnormal platelet distribution or sequestration: splenomegaly, endotoxemia<sup>4</sup>

### Laboratory Findings

- ▶ Serum chemistry panel and coagulation profiles are often normal in cases of primary IMT.
- ▶ Hematuria may be evident on urinalysis.
- ▶ Cystocentesis should be avoided in patients with thrombocytopenia.
- ▶ CBC can give an automated platelet count.
  - The normal canine platelet count is  $143 \text{ to } 448 \times 10^3/\mu\text{L}$ .
    - If platelet clumping is present, a false

IMT = immune-mediated thrombocytopenia

thrombocytopenia may occur.

- All cell lines (WBCs, RBCs, platelets) should be evaluated.
  - Decreases in multiple cell lines can be associated with decreased cell production because of disease at the bone marrow level.
- A CBC with reticulocyte count should be performed to look for anemia secondary to blood loss from IMT or concurrent immune-mediated hemolytic anemia.
- Manual platelet count
  - The feathered edge and blood smear body should be scanned for an area of well-distributed platelets (**Figure 2**, previous page).
  - The number of platelets per 1000× field should be estimated.

## Many IMT patients can be treated on an outpatient basis, but it is important for owners to monitor for signs of bleeding or anemia and to avoid trauma or injury.

- At least 5 to 10 fields should be evaluated and the average number of platelets/hpf calculated.<sup>4</sup>
- The conversion factor of 1 platelet/1000× field equals 20 000 platelets/ $\mu\text{L}$  can be used to calculate the platelet count.<sup>4</sup>
- Platelet counts in cases of IMT are usually  $<50\,000/\mu\text{L}$  and often  $<10\,000/\mu\text{L}$ .
  - Megakaryocytes may be present.<sup>4,5</sup>
- With a mean platelet count of approximately  $150\,000/\mu\text{L}$ , healthy greyhounds can have lower platelet concentrations than other breeds.<sup>1,4</sup>
- Healthy Cavalier King Charles spaniels can have a hereditary macrothrombocyto-

penia, with the platelet count in affected dogs ranging from 25 000 to  $100\,000/\mu\text{L}$ .<sup>1</sup>

### Imaging

- Thoracic radiographs are recommended to evaluate for thoracic infection or neoplasia.
  - These are usually normal in animals with primary IMT.
- Abdominal ultrasonography can evaluate for the presence of abdominal bleeding, infection, or neoplasia.
  - Homogenous splenomegaly can be seen with primary IMT, especially if secondary anemia is present.
  - If diffuse splenic mottling is present, fine-needle aspiration may be recommended once the platelet count is adequate.

### Infectious Disease Testing

- Ehrlichiosis, Rocky Mountain spotted fever, anaplasmosis, histoplasmosis, leishmaniasis, and distemper have been associated with secondary IMT.<sup>4</sup>
- Tick-borne disease testing is recommended; complete panels include both polymerase chain reaction (PCR) and serology.
  - PCR is often positive early in active disease.
  - Negative PCR results do not rule out infection, and a positive serologic test does not necessarily confirm disease.
  - Serology is often positive after PCR because it takes time for antibodies to be produced.

### Advanced Testing

- The benefit of bone marrow examination in cases of suspected IMT is equivocal.
  - Normal-to-increased numbers of bone marrow megakaryocytes may not be a consistent finding.<sup>2</sup>
- Flow cytometric assays to detect antiplatelet antibodies are available but are not commonly performed in the clinical setting.
  - A positive test implicates an immune

pathogenesis but is not specific for primary IMT.

- False-negative results are possible, especially if therapy was started before testing.<sup>2,5</sup>

## TREATMENT

### Emergency Treatment

- ▶ Many IMT patients can be treated on an outpatient basis, but it is important for owners to monitor for signs of bleeding or anemia and to avoid trauma or injury.
- ▶ Patients are often hospitalized initially for monitoring or if they require a blood transfusion because of secondary anemia.
  - Although uncommon, fatal bleeding into the brain, lungs, or spinal cord is possible.
- ▶ Bleeding risk increases as platelet count decreases below 20 000/ $\mu$ L, although spontaneous bleeding typically does not occur, even with marked thrombocytopenia.<sup>6</sup>
- ▶ Platelet transfusions are usually reserved for cases of uncontrollable or life-threatening bleeding.
  - Blood or platelet transfusions do not significantly raise the platelet count but can be used in an attempt to stop life-threatening bleeding.
- ▶ Vincristine (0.5–0.7 mg/m<sup>2</sup> IV once) may have some immunosuppressant activity and may induce thrombocytosis within 7 days.<sup>2,7,8</sup>
  - A peripheral catheter should be used for administration as extravasation of vincristine can cause skin necrosis.

### Long-Term Treatment Options

- ▶ Immunosuppressive agents
  - Prednisone (1–2.2 mg/kg q12h) is the initial immunosuppressive therapy of choice for dogs with IMT; the majority of dogs will show a significantly increased platelet count within 7 days.<sup>2,7,8</sup>
    - Additional immunosuppressive medications are usually needed only if significant prednisone side effects are present.

- Azathioprine (2 mg/kg q24h, tapered to q48h after 1 week) has been described as an immunosuppressive option, but studies are lacking.
  - This medication can take more than 4 weeks to become effective.<sup>2,7,8</sup>
- Cyclosporine (5–10 mg/kg divided q12h) has been shown to be an effective immunosuppressive medication in dogs with IMT.<sup>2,8</sup>
- Mycophenolate mofetil (10 mg/kg PO q12h) has been reported to have variable response rates as an immunosuppressive medication for canine IMT in small studies.<sup>8</sup>
  - This drug can be considered in refractory cases.
- Leflunomide has shown efficacy in anecdotal reports, but studies on this immunosuppressive medication for IMT are limited.<sup>6</sup>
- ▶ Melatonin (3 mg PO q12h) has been suggested anecdotally (based on clinical response in humans) to increase platelet counts in cases of IMT.<sup>9</sup>
- ▶ Human IV immunoglobulin (0.28–1.5 g/kg IV) has been shown to significantly reduce platelet recovery time and hospitalization when combined with prednisone given slowly over 4 to 12 hours.<sup>7,10,11</sup>
  - Human IVIG should be used with caution in patients with renal dysfunction.
  - Patients should be monitored for volume overload and hypersensitivity reactions.
- ▶ Splenectomy has shown variable response rates but can be considered in refractory cases.<sup>2,8</sup>

## FOLLOW-UP

- ▶ Immunosuppressive medications are tapered slowly once the platelet count has normalized.
- ▶ Prednisone is usually tapered first as many dogs will have significant side effects from this medication.

IMT = immune-mediated thrombocytopenia, PCR = polymerase chain reaction

- If a second immunosuppressive medication is given, it is routinely tapered after the prednisone.
- Medication is generally reduced by about 25% every 3 to 4 weeks.
- Medications are usually tapered 1 medication at a time if multiple medications are given.
- The minimum duration of treatment is usually 4 to 6 months.
- The most common reason for treatment failure is an inadequate duration of therapy.
- Patients should be evaluated via a manual platelet count 1, 3, and 6 months after treatment has been discontinued and then every 6 to 12 months for life to monitor for disease relapse.
- A manual platelet count is usually performed before each medication adjustment.

**IN GENERAL****Relative Cost**

- \$\$\$\$–\$\$\$\$\$

**Prognosis**

- The prognosis for patients with primary IMT can be good with reported long-term mortality rates of 10% to 15%.<sup>2,5</sup>
- Relapse has been reported in 9% to 40% of cases.<sup>2,5,8</sup>
- Poor prognostic indicators may include melena or a high blood urea nitrogen concentration.<sup>12</sup>

**COST KEY**

\$ = up to \$100

\$\$ = \$101–\$250

\$\$\$ = \$251–\$500

\$\$\$\$ = \$501–\$1000

\$\$\$\$\$ = more than \$1000

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