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CASE REPORT

Companion or pet animals

Severe thrombocytopenia due to subinvolution of placental sites in a Maltese terrier

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Abstract

A 2-year 6-month, primiparous, female, entire Maltese terrier presented 4 weeks after whelping with an acute history of lethargy and vulval haemorrhage. It was found to be anaemic and severely thrombocytopenic, which raised the concern about thrombocytopenia being the primary cause of the profuse haemorrhage. The dog received a packed red blood cell transfusion that resulted in the improvement of the anaemia. The platelet count normalised without a specific intervention. Abdominal ultrasound revealed changes consistent with subinvolution of placental sites. An ovariohysterectomy was performed and the dog recovered uneventfully. This case has shown unusually severe thrombocytopenia secondary to haemorrhage, which should be considered a differential diagnosis for severe thrombocytopenia in dogs.

BACKGROUND

Postpartum haemorrhage (PPH) is a major cause of maternal death in humans and accounts for 50% worldwide.[1] Retained placenta is the main cause of PPH in people, although this is much less common in dogs, likely due to the different placenta type. Persistent PPH is a rare occurrence in dogs[2] and tends to be accompanied with uterine ulceration, or a coagulopathy.[3] Subinvolution of placental sites (SIPS) is the delay of the normal uterine involution process during the postpartum period. SIPS can cause persistent haemorrhage, and tends to occur in primiparous bitches of less than 2.5 years of age.[4] The rate of incidence is suspected to be 10%–20% of postpartum bitches.[4] Most cases of SIPS are self-limiting, and affected animals may only have mild haemorrhagic vulval discharge. However, more severe, life-threatening metrorrhagia may require blood transfusion and/or immediate surgery.[3]

CASE PRESENTATION

A 2-year 6-month, female, intact Maltese terrier presented with a 2-day history of lethargy and vulval haemorrhage. The patient whelped 4 weeks before presentation and produced five healthy puppies. It initially had haemorrhagic vulval discharge for 24 hours after whelping, but this resolved without intervention. The owners reported her to be generally healthy with no prior medical problems. It was up to date with annual vaccinations, was regularly administered flea and worm prevention and had no travel history.

On presentation, the patient was quiet, but alert and responsive. Mucous membranes were pale. Cardiac auscultation revealed a new left apical systolic grade III/VI murmur. A single pinpoint round red spot (suspected area of petechiae) was present over her caudal mammary glands. The mammary glands were enlarged with galactorrhoea, but no abnormalities were present on palpation. No melaena was noted on rectal examination. A moderate amount of metrorrhagia was present. Heart rate was 162 beats per minute and pulses were hyperdynamic and synchronous. Respiratory rate was 72 breaths per minute and noninvasive blood pressure was 170 mmHg. The rest of the physical examination was unremarkable.

INVESTIGATIONS

Packed cell volume (PCV) was found to be 10% with total solids (TS) of 40 g/L (reference ranges 37%–55% and 54–75 g/L, respectively). A blood gas analyser (ABL800 FLEX; Radiometer) revealed hyperlactatemia (5.3 mmol/L; reference range <2.5 mmol/L). A complete blood count (ADVIA 2120i; Siemens Healthineers) showed a severe regenerative anaemia (RBC 1.25 × 10^{12}/L; reference range 5.5–8.5, reticulocyte count 230 × $10^{2}/\mu$l, 18.4%; reference range ≤1.0%, reticulocyte haemoglobin 23.2 pg), a mature neutrophilia (19.66 × 10^{9}/L; reference range 3–11.5) and a marked thrombocytopenia (13 × 10^{9}/L; reference range 150–900). Blood smear evaluation by clinical pathology resident under supervision of a board-certified clinical pathologist confirmed the presence of severe thrombocytopenia and absence of platelet clumps. Manual platelet count confirmed the automated estimate and the platelets present were frequently macroplatelets. An in-saline agglutination test (ISAT) showed a weak positive result. Serum biochemistry (AU680; Beckman Coulter) revealed hypoproteinaemia (albumin 16.8 g/L, reference range

26.3–38.2; globulin 19.4 g/L, reference range 23.4–42.2), hypocalcaemia (1.91 mmol/L, reference range 2.18–2.79) and a mild increase in urea (17.5 mmol/L, reference range 3.1–10.1). The patient was tested for vector-borne diseases (*Ehrlichia canis*, *Ehrlichia ewingii*, *Borrelia burgdorferi*, *Anaplasma phagocytophilum*, *Anaplasma platys* and *Dirofilaria immitis*) and was found to be negative for all four diseases (SNAP 4Dx Plus Test; IDEXX). It also tested negative for *Angiostrongylus vasorum* antigen (Angio Detect Test; IDEXX).

The patient was DEA 1.1 positive (Quick Test; Alvedia) and a transfusion of 8.6 ml/kg DEA 1.1 positive packed red blood cells was administered over the course of 4 hours due to poor pulse quality, tachycardia and anaemia. DEA positive packed red blood cells were administered due to the presence of severe anaemia. A transfusion of fresh whole blood would have been a suitable alternative due to the benefit of increasing circulating platelet numbers; however, this was not available at the time. An improvement in cardiovascular status was noted, and the posttransfusion PCV and TS were 20% and 48 g/L, respectively. Tranexamic acid (Tranexamic Acid; Bowmed Ibisqus, 10 mg/kg IV TID) was administered in case of a coagulopathic aetiology and to improve clot strength. A 5-day course of cabergoline (Galastop; Ceva, 5 mg/kg SID PO) was administered to halt the galactorrhoea.

Once the patient's condition stabilised, further investigations included thoracic radiographs and abdominal ultrasonography. Radiographs did not reveal any abnormalities. Abdominal ultrasonography demonstrated uterine lumen distension. The left uterine horn was distended, up to 14-mm diameter, with a large volume of heterogeneous, predominantly hyperechoic avascular luminal content consistent with haemorrhage or haematometra. The right uterine horn was filled with anechoic luminal content of an uncertain aetiology, and was dilated up to 12-mm diameter. The uterine wall was intermittently irregularly focally circumferentially thickened in both horns—up to 6–7 mm thick and 10–20 mm long. There were strong mural Doppler signal in these regions, likely representing sites of previous placental attachment (Figure 1). The uterine wall was up to 1–2 mm thick in the interposed regions. The uterine body region had diffuse irregular mural thickening, with poor definition of the uterine lumen. Both ovaries were considered normal in size. A small amount of peritoneal fluid was present and was sampled by abdominocentesis. Analysis was consistent with a transudate with a total protein of 0 g/dl and found to be acellular on cytology.

LEARNING POINTS/TAKE HOME MESSAGES

- Subinvolution of placental sites should be considered as a potential cause for life-threatening haemorrhage.
- Haemorrhage can, in rare cases, cause a severe thrombocytopenia (platelet count of <30,000/μl) and should be considered as a cause before diagnosing immune-mediated disease.
- Further studies into severe thrombocytopenia due to haemorrhage are warranted.

TREATMENT

Twenty-four hours following admission, the volume of metrorrhagia was decreasing and a repeat complete blood count showed resolution of the thrombocytopenia, suspected to be due to a strong bone marrow platelet regenerative response (platelets estimated to be >580 × 10^9/L). The cause for the decrease in the volume of metrorrhagia is unclear and could be coincidental. Another hypothesis is that the recovery of platelet count that was documented before ovariohysterectomy could have improved haemostasis. The anaemia was improved (RBC 2.31 × 10^{12}/L) and PCV was 17%. Vaginal examination under general anaesthetic was unremarkable. An ovariohysterectomy was performed and ovaries and uterus submitted for histological examination. The uterus and uterine horns appeared to be macroscopically normal although fluid filled.

OUTCOME AND FOLLOW-UP

Histological examination revealed uterus lined by a hyperplastic epithelium with dilated, mucous-containing glands, congested vessels and trophoblasts within the endometrium

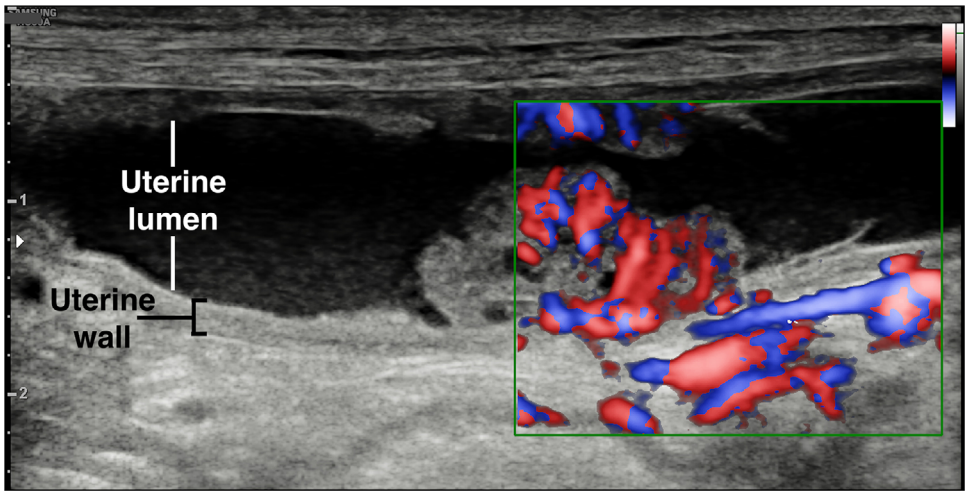

FIGURE 1 Longitudinal ultrasonographic image of the right uterine horn, with directional power Doppler display (green box). Note the hypervascular, focal florid thickening of the uterine wall protruding into the uterine lumen, which is distended with hypoechoic material

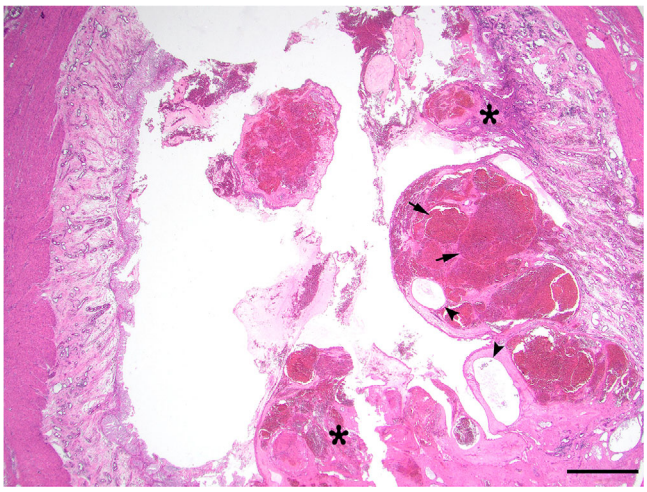

FIGURE 2 Histopathology of the uterus: the endometrium is expanded by congested vessels (arrows), dilated glands containing mucus (arrowheads), which form a florid proliferation that narrows the lumen and cellular debris (asterisk) in a dog diagnosed with subinvolution of placental sites (×1.25; bar = 1 mm)

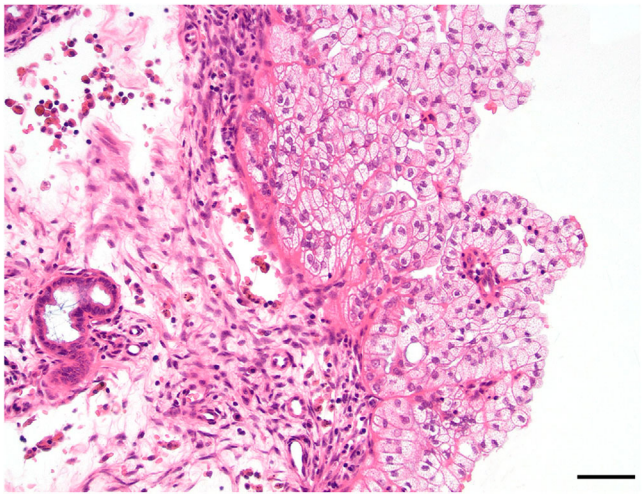

FIGURE 3 Histopathology of the uterus: the lining epithelium is multifocally hyperplastic and cells are expanded by intracytoplasmic clear vacuoles (microvesiculation) (×200; bar = 50 μm)

(Figure 2). Epithelial cells were expanded by intracytoplasmic clear vacuoles (microvesiculation, Figure 3). All these histological findings were consistent with a diagnosis of SIPS. The ovaries contained follicles in various stages of development and occasional corpora haemorrhagica and corpora lutea, with no evidence of neoplasia.

The patient recovered well from general anaesthetic. PCV decreased to 16% following surgery, but 24 hours later was 24% and the patient was discharged 2 days after surgery. Up until the time of writing this report, 6 months later, the patient was alive and remained asymptomatic.

DISCUSSION

The case described here is unusual due to severe metrorrhagia causing marked anaemia and thrombocytopenia. The severity of thrombocytopenia on initial presentation raised concerns of a primary haemostatic disorder, such as immune-mediated thrombocytopenia (IMTP) causing, or contributing to, the development of metrorrhagia. However, it became evident that the thrombocytopenia was due to a consumptive process and the platelet count normalised without any specific intervention.

Thrombocytopenia can occur due to a wide range of aetiologies; broadly categorised into platelet loss, destruction, decreased production or sequestration.[5] The most common cause is reported to be infections or inflammatory (34.9%), followed by neoplasia (28.01%), miscellaneous (25.5%) and immune mediated (5.6%).[6] The miscellaneous category includes nephropathy, hepatopathy, intoxication and others. Thrombocytopenia due to consumption and external platelet loss is not a commonly reported occurrence in dogs, especially when the platelet count is as low as in this case. Most commonly, a severe thrombocytopenia (platelet counts $\leq$30,000/μl) is caused by immune-mediated disease.[7] In a case series of dogs with rodenticide toxicity,[8] the median platelet count was 112,000/μl and only five dogs (8.06%) were found to have platelet counts $\leq$200,000/μl. Pintar et al. (2003) have reported a rate of thrombocytopenia of 97% in nontraumatic haemoabdomen, with a median platelet count of 40,000/μl and a lowest platelet count of 4000/μl.[9] In humans, platelet changes during PPH is minimal, with one study showing a mean platelet count to be within normal range in groups of women with severe and nonsevere anaemia due to PPH.[10] Another human study reported the lowest platelet count to be 26×10^9/L in women with PPH, with only eight of 347 cases with a platelet count $\leq 75 \times 10^9$/L, and with the largest fall in platelet count when compared to a prehaemorrhage count of 257×10^9/L.[11]

Initial haematology showed the presence of a weak positive ISAT, which is commonly seen in immune-mediated haemolytic anaemia (IMHA). However, due to lack of other signs of IMHA on blood smear or blood work (i.e., hyperbilirubinemia, spherocytosis, ghost cells and haemoglobinemia),[12] the significance of a positive ISAT in this case was unclear. False-positive results are frequently seen with ISATs, suspected to be due to low saline-to-blood ratios; a ratio of 49:1 has been shown to have a high specificity (97%) for IMHA, whereas a ratio of 1:1 has a specificity of 29%.[13] Moreover, additional investigations did not reveal potential triggers for an immune-mediated process and the patient did not receive immunosuppressive drugs that could have treated IMHA.

PPH is the most common cause of postpartum death in humans,[1] although secondary PPH (defined as significant haemorrhage from the genital tract 24 hours to 42 days postpartum) is very rare with a reported incidence of 0.23%.[14] The most common cause of secondary PPH in humans is retained placenta (30.0%), which is rare in dogs, with SIPS occurring in only 13.3% of cases.[14] The incidence of PPH in dogs has not been reported in the literature,[15] but is noted to be rare.[2] The incidence of SIPS in dogs has not been documented,[16] but a case series has found 20/95 postpartum bitches to have SIPS.[17] Other differentials for PPH include coagulopathies, metritis, proestrus, vaginitis, trauma, retained or mummified fetus and neoplasia.[3,18,19] While the primary aetiology of SIPS is unknown, histology findings are characterised by cytotrophoblasts within the endometrium, which would normally degenerate after parturition, and which prevent endometrial blood vessels from developing thromboses.[4] It has been speculated that the underlying cause could be oestrogen-induced

capillary fragility, failure of normal endometrial blood vessel thrombus formation or bacterial infection of the placental sites.[20] The normal time for uterine involution in the dog has been reported to be 12–15 weeks.[20,21] In normal bitches, mild metrorrhagia can be present for 1–6 weeks postpartum, whereas cases of SIPS demonstrate a persistent discharge for up to 8 weeks or, in some cases, until the next proestrus.[3,4] As SIPS is normally a self-limiting condition, treatment is rarely required. Several methods of medical management in more severe cases have been reported, but with limited success.[16–18,22] Surgical treatment is usually ovariohysterectomy, but hysterolaparatomy with curettage of selected sites has also been reported.[23]

An underlying disorder causing a predisposition to haemorrhage and thrombocytopenia seemed unlikely in this case based on the history and response to treatment. A limitation of this case is the lack of further investigations into coagulopathies. Evaluating activated clotting time, prothrombin time and partial thromboplastin time would have provided information about deficits within the coagulation cascade. These were not pursued as a consumptive coagulopathy and/or a disorder of primary haemostasis were suspected, which would result in increased clotting times. Thromboelastography could have been used to assess clot formation, strength and lysis.[24] However, results can be affected by low haematocrit,[25] as well as by severe thrombocytopenia due to decreased clot strength and rigidity,[26] so may not have been accurate in this case.

This case report has shown the importance of considering SIPS as a potential cause for life-threatening haemorrhage. In addition, it has highlighted the lack of literature and research investigating severe thrombocytopenia due to haemorrhage. Further studies are warranted, especially as IMTP is a diagnosis of exclusion and currently is strongly associated with a platelet count of <30,000/μl.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

ETHICS STATEMENT

No ethical approval was necessary. Permission to report the case was provided by the owner of the patient.

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