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Case Report

Severe anemia and neutrophilic leukocytosis resembling Sweet's syndrome in a dog

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Abstract

Sweet's syndrome is a rare inflammatory condition characterized by the presence of neutrophilic infiltrate of the skin. We describe a case of severe anemia and neutrophilia with post-mortem findings resembling Sweet's syndrome in a five-years-old female Labrador Retriever with bilateral epistaxis, hematemesis, hyporexia, pale oral mucosa, and fever. Laboratory analysis evidenced severe unresponsive anemia, thrombocytopenia, and leukocytosis. Biochemistry showed hypoalbuminemia and increased ALT and SAP activities. The patient was transfused and received doxycycline and prednisone for one week without improvement. Two further blood transfusions were administered. Bone marrow analysis showed a mild erythroid hypoplasia, granulocytic hyperplasia, myeloid to erythroid ratio of 6.01:1 (reference: 0.9:1 – 1.76:1) without dysplasia, mild megakaryocytic hyperplasia, and increased iron stores. Macrophages were slightly increased in number with erythrophagocytosis, and immune-mediated anemia was considered. Immunosuppressive treatment was prescribed to reduce red blood cell destruction, but no improvement after one week was observed, and euthanasia was performed. Necroscopic findings resembled those described for the systemic form of Sweet's Syndrome. Bone marrow histopathology showed remarkably increased granulopoiesis and destruction of platelets and erythrocytes. Sweet's syndrome is frequently associated with hematologic malignancy or drug exposure. Leukemia was excluded after bone marrow analysis because no increase in blast population was seen as well as no signs of dysplasia. Previous treatment could be related to the development of Sweet's syndrome, which might be the primary event. Although rare, this syndrome should be considered in the differential diagnosis of dermatosis and leukocytosis when infectious agents are not identified.

Keywords: anemia; blood transfusion; malignancy; neutrophilic dermatosis.

Introduction

Sweet's syndrome (SS), also known as febrile neutrophilic dermatosis, is an inflammatory condition characterized by the presence of a neutrophilic infiltrate in the upper dermis of the patients. The disease can spread as a multisystemic disorder, which includes extracutaneous sites (18). It is considered a rare condition (12), however, there are several reports in humans (4, 12, 16, 19). However, there are few reports in dogs (1, 3, 6, 9, 11). This report describes a case of severe anemia and febrile neutrophilic leukocytosis resembling SS in a dog with systemic manifestations.

Case description

A five-year-old female and intact Labrador Retriever was presented to a veterinary clinic with a five-day history of bilateral epistaxis, one episode of hematemesis, and hyporexia. The owner denied the presence of ticks. Even intact,

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it never manifested signals of oestrus. At the physical examination, the dog showed extreme thinness (body condition score: 2/9; muscle mass score: 0/3), pale mucous membranes, petechiae in the skin, and fever.

A complete blood count (CBC) and serum biochemistry profile were carried out. Abnormalities found included normocytic normochromic anemia (1.19 x 10^6 erythrocytes/mm^3 – reference values: 5.5-8.5 x $10^6/mm^3$; hematocrit 11.3% - reference: 37-55%; hemoglobin 2.7 g/dl – reference: 12.0-18.0) with metarubricytes (5%), moderate polychromasia; thrombocytopenia (58,000 platelets/mm^3 – reference: 200,000-500,000/mm^3); neutrophilic leukocytosis (32,800 leukocytes/mm^3 – reference: 6,000-17,000/mm^3) with regenerative left shift (25,256 segmented neutrophil/mm^3 – reference: 3,000-11,500/mm^3; 1,968 band neutrophil/mm^3 – reference: 0-300/mm^3). Table 1 presents the sequence of complete blood counts according to the days since the first presentation. Figure 1 shows the evolution of erythrocyte counts according to time, and Figure 2 shows leukocyte and neutrophil counts. Serum biochemistry showed slight increases of alanine aminotransferase (ALT) and serum alkaline phosphatase (SAP) activities (137 IU/l; reference 17-95 IU/l) and (171 IU/l; reference 7-115 IU/l), respectively, elevated blood ureic nitrogen (BUN) concentration (218 mg/dl; reference 9-26 mg/dl) and hypoalbuminemia (1.5 g/dl; reference 3.0-4.0 g/dl).

The presumptive diagnosis was piroplasmosis. The therapy was instituted with 1 mg/kg omeprazole each (q) 24 h; 0.22 mg/kg ondansetron q 8 h; 1.5 mg/kg prednisolone q 12 h, 5 mg/kg doxycycline q 12 h, and two doses of 5 mg/kg imidocarb hydrochloride subcutaneously with a 14-day interval. A blood transfusion was performed on the day of admission.

Three days after blood transfusion (day 5), the dog had a mild increase in erythrocyte count, 1.81 x $10^6/\mu l$; hematocrit 14.8%; hemoglobin 4.1 g/dl – and in platelet count (130,000/mm^3). Signs of regeneration were present. The number of total leukocytes decreased to 22,100/mm^3. The abdominal ultrasonography showed an enlarged and hyperechogenic liver and microsplenia with decreased echogenicity.

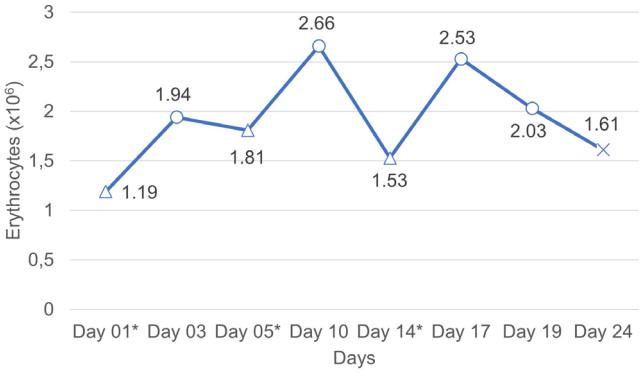

Figure 1. Erythrocyte counts (x10^6) in a five-year-old Labrador Retriever with a syndrome that resembles Sweet's Syndrome. ▲ represents the blood transfusion's time. X represents the day of euthanasia.

Table 1. Complete blood counts of a five-year-old Labrador Retriever with a syndrome resembling Sweet's Syndrome from the first day until the last.

Complete blood count	Day 1	Day 3	Day 5	Day 10	Day 14	Day 17	Day 19	Day 24
Erythrogram								
Erythrocytes (x10^6 µL)	1.19	1.94	1.81	2.66	1.53	2.53	2.03	1.61
Hemoglobin (g/dL)	2.7	4.3	4.1	6.2	3.7	5.9	4.5	3.7
Hematocrit (%)	11.3	15.8	14.8	19.8	10.8	16.3	13.6	11.6
MCV (fL)	95	81.4	81.9	74.5	71.2	64.5	67.0	72.2
MCHC (%)	23.9	27.2	27.7	31.3	34.2	36.0	33.0	31.8
RDW (%)	-	-	22.1	18.4	17.4	16.9	16.4	17.6
PP (g/dL)	-	-	5.8	5.8	6.8	8.0	7.0	6.6
Platelets (/µL)	58,000	48,000	130,000	345,000	120,000	121,000	341,000	198,000
Reticulocytes (/µL)				2,470				
Leucogram								
Total leukocytes (/µL)	32,800	17,300	22,100	21,400	74,900	81,100	55,900	45,700
Band neutrophils (/µL)	1,968	692	0	214	1,498	0	0	0
Neutrophils (/µL)	25,256	13,494	16,575	19,046	65,912	73,801	45,838	42,216
Lymphocytes (/µL)	4,264	1,038	3,536	642	2,247	1,622	4,472	914
Monocytes (/µL)	1,312	2,076	1,989	1,498	5,243	5,677	5,590	4,570

MCV: Mean corpuscular volume; MCHC: Mean corpuscular hemoglobin concentration; RDW: red cell distribution width; PP: plasmatic protein.

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The patient received a second transfusion of whole blood on the following day. Four days after the second transfusion (day 10), a new CBC showed anemia (2.66 x 10^6/µl) and improved platelet count (345,000/mm^3). Neutrophilic leukocytosis was present (21,400/mm^3), but with lymphopenia (642/mm^3) and monocytosis (1,498/mm^3), with the presence of activated monocytes. A reticulocyte count was performed two days after the last CBC with an absolute value of 2,470/µl (0.038%).

Another CBC was requested on day 14. A new decrease in erythrocytes (1.53 x 10^6/µl), hemoglobin (3.7 mg/dl), hematocrit (10.8%), and platelets count (120,000/mm^3) was detected. Leukocytosis significantly increased (74,900/mm^3) due to left shift neutrophilia – 65,912 neutrophils/mm^3; 1498 band neutrophils/mm^3 – and monocytosis (5,243/mm^3). Due to the non-improvement of the condition and weight loss, 12.5 mg/kg amoxicillin + potassium clavulanate q 12 h was added to the treatment. On day 15, a third blood transfusion was performed.

On day 17, two days after the last blood transfusion, anemia had a mild increase, and a worsening was detected in neutrophilic leukocytosis. On day 18 after the admission, doxycycline was discontinued, and 10 mg/kg amikacin q 12 h was prescribed. Another CBC was performed on day 19 with a new decrease in erythrocytes count (2.03 x 10^6/µl), hemoglobin (4.5 g/dl), and hematocrit (13.6%). The number of leukocytes decreased but was still high – 55,900 leukocytes/mm^3 and 45,838 neutrophils/mm^3. Monocytosis (5,590/mm^3). Activated monocytes were also observed. To rule out the possibility of a corticosteroid-unresponsive immune-mediated hemolytic anemia, 2 mg/kg azathioprine q 24 h was started on day 21 and ferrous sulfate, supplemented at day 23. One application of 2 mg/kg nandrolone decanoate was also performed to stimulate red blood cells production.

A bone marrow analysis was performed to evaluate bone marrow response or a possible primary bone marrow malignancy. Bone marrow cytology showed myeloid hyperplasia with mild megakaryocytic hyperplasia, mild erythroid hypoplasia with increased iron stores, mild increase in macrophages, some containing phagocytized erythrocytes. Myeloid to erythroid ratio was markedly increased (6.01:1, reference values (0.9:1 – 1.76:1) (10), and no significant signs of dysplasia of any lineage were observed. Figure 3 shows an image of the bone marrow cytology.

On day 24, a new CBC detected worsening in anemia – erythrocytes: 1.61 x 10^6/µl; hemoglobin: 3.7 g/dl; hematocrit: 11.6% -, mild thrombocytopenia (198,000 platelets/mm^3) and a mild decrease in the of leukocyte count – 45,700/mm^3, with 42,216 neutrophils/mm^3 and 4,570 monocytes/mm^3. Macroplatelets and activated monocytes were observed. Due to the failure to respond to the treatment, the owner requested euthanasia.

Necroscopic examination showed fibrine deposits inside the pericardium, suggesting pericarditis; in the myocardium, whitish areas were present, compatible with infarction; the spleen edges were rounded with one infarction area; the bone marrow was homogeneously white; multiple petechiae were found in the cranial lobe of the left lung, who was armed, heavy and brilliant; an irregular and circumscribed increase of volume in mesenteric lymph node, measuring 7.5 x 5 x 0.3 cm; the liver had rounded edges, with accentuation of the lobular pattern; in the kidney, 2 mm diameter nodules were found in the capsular and the cutting surface, either homogeneously whitish. The renal cortico-medullary region had wedge-shaped red and white infarction areas. Figure 4 shows the necropsy findings.

Microscopically, the bone marrow had myeloid and megakaryocytic bi-lineage hyperplasia, small amount of adipocytes and a great amount of myeloid precursors (neutrophils and eosinophils); extramedullary erythropoiesis was observed in spleen; multifocal acute and subacute infarction in kidneys associated to leukocytostasis, which were also observed in the heart; the lungs had moderate to accentuated diffuse leukocytostasis, with hemorrhage and foamy

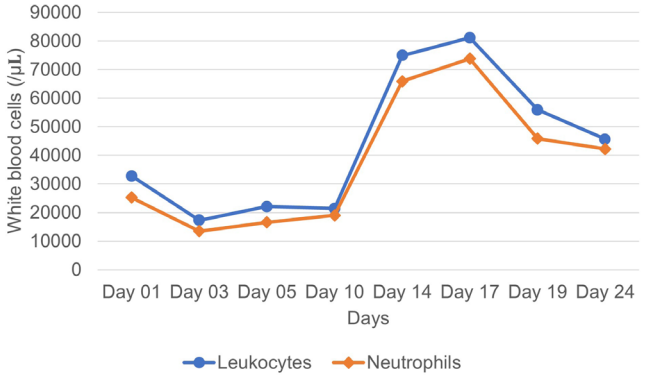

Figure 2. Number of circulating leukocytes (blue line) and neutrophils (orange line) in a five-year-old Labrador Retriever with a syndrome that resembles Sweet's Syndrome.

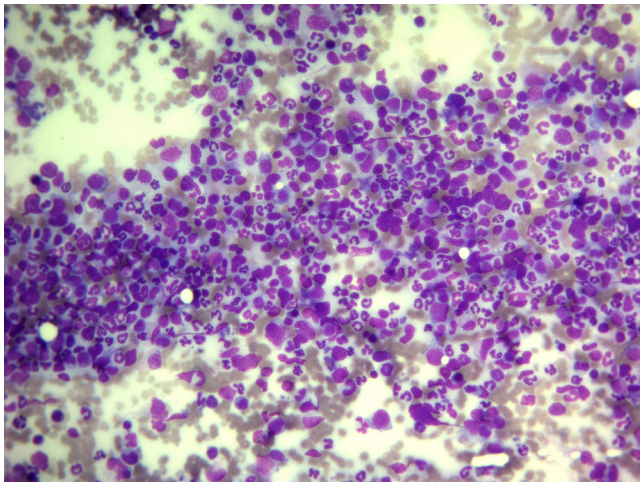

Figure 3. Bone marrow cytology of a five-year-old female dog. Representative field showing myeloid hyperplasia. Diff quick stain, x200 objective.

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Figure 4. Necropsy findings of a five-year-old female dog. **A-** The femoral bone marrow is diffusely whitish. **B-** Liver presenting an increase in size (hepatomegaly). **C-** Hydropericardium. **D-** Kidney, cut surface. Multiple renal infarcts are observed.

macrophages inside the alveoli; a great amount of fibrine with degenerated neutrophils, compatible with thrombus was found in mesenterium; the liver presented multifocal areas with hepatocytes and vacuolized cytoplasm (glucose). Histopathological findings are pointed in Figure 5.

Discussion

The changes observed resemble the systemic form of SS. It was not possible to determine the primary event. However, it triggered the exaggerated production of neutrophils by the bone marrow, which destroyed platelets and erythrocytes, filled the microcirculation vessels of different organs, causing leukocytostasis and, sometimes, endothelial injuries, vasculitis, and renal and cardiac infarction areas. The excess of neutrophils filled the entire bone marrow, which could not produce new erythrocytes because of the lack of space (benign myelophtysis), compatible with myeloid hyperplasia.

A small number of SS cases are described in dogs, with ages ranging from 10 months to seven years (2, 3, 6, 9, 11, 13, 17). Many different breeds were related to the diagnosis, and one article reported SS in three Labrador Retriever dogs (2), the same breed as in this report.

Although it is impossible to determine a single causal event, the patient in this report was treated with many drugs. The occurrence of SS is frequently associated with drug exposure, like granulocyte colony-stimulating factor, tretinoin, sulfamethoxazole + trimethoprim, azathioprine (18), carprofen, amoxicillin + clavulanate, doxycycline, metronidazole and vaccination (2). Three of them were prescribed to the patient – azathioprine, amoxicillin + clavulanate, and doxycycline. Another subset of this condition is related to a malignant response to neoplasms, like a paraneoplastic accompaniment (15, 18), which was not found in this case.

SS is mainly characterized by miscellaneous skin alterations. Clinically, humans present fever, asymmetrically distributed erythematous skin lesions (papules, nodules, plaques), neutrophilia, and pain in different areas, such as joints, head, and muscles (5). The main clinical signs described in dogs included fever, generalized erythema, nodules, coalescing papules, plaques, macules, edema, and pruritus (2).

In our patient, we observed a multisystemic manifestation resembling SS, with fever and changes in different organs, e.g., bone marrow, spleen, kidneys, heart, and lungs. Extracutaneous signs are frequently reported in other cases of febrile neutrophilic dermatosis. Disorders in bones, brain, lungs, eyes, liver, intestine, and heart are described in humans (5, 15) In more severe cases, it can even become an emergency (4, 5, 12). The extracutaneous manifestations reported

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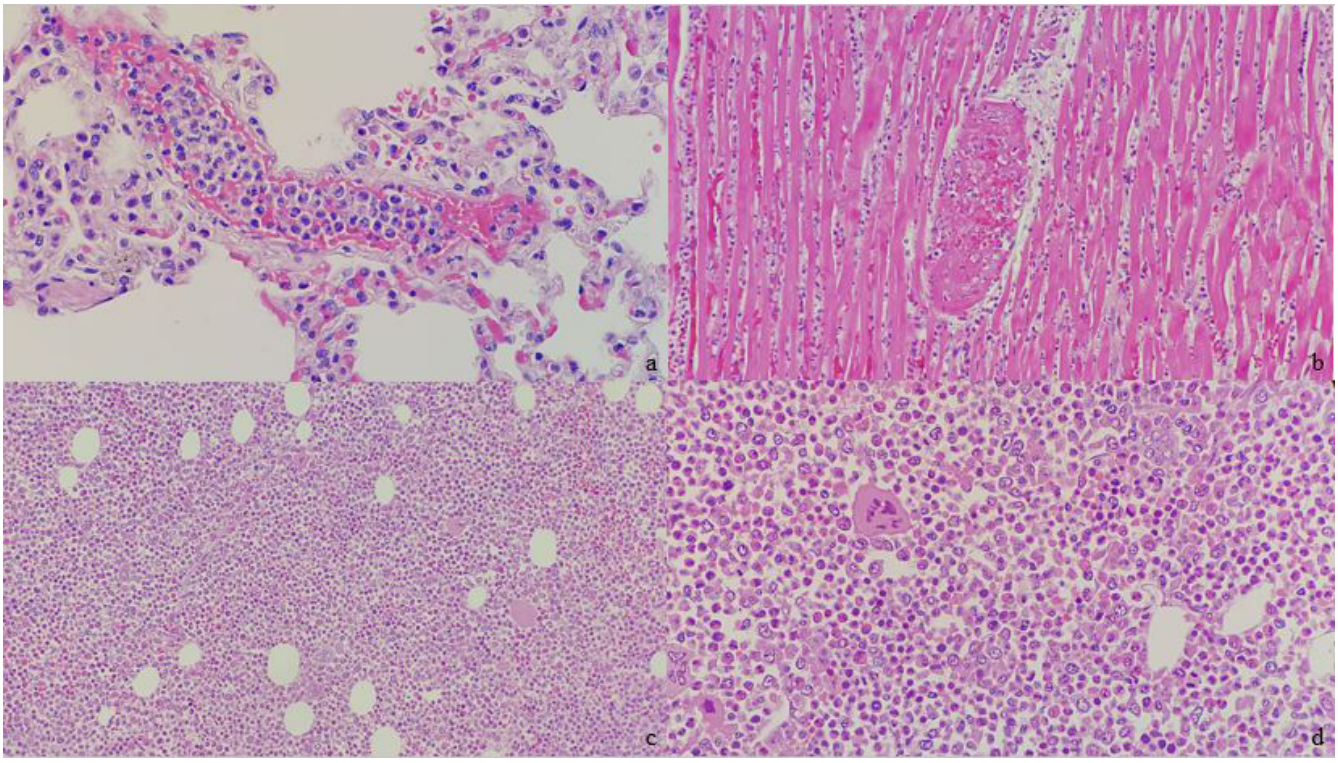

Figure 5. Histopathological findings of a five-year-old female dog. **A-** Lung. The pulmonary capillaries and vessels are filled with numerous neutrophils. **B-** A severe neutrophilic infiltration is observed within the myocardium. In the center, a fibrin thrombus is observed within a blood vessel. **C-** The bone marrow is densely cellular. **D-** The bone marrow is predominantly constituted of myeloid precursor cells. H&E, x40 objective.

in dogs were gastrointestinal disease, lymphadenopathy, ptyalism, polyuria, polydipsia, hindlimb weakness, lameness, jaundice, and anemia (2, 3, 9, 11).

The dog reported here presented severe non-responsive anemia. This disorder is uncommon in dogs presenting SS. Three other dogs with anemia and SS were described, two with immune-mediated hemolytic anemia (13, 14) and another with signs of immune-mediated arthritic, hepatic inflammation, nephropathy and which could not discard leptospirosis and leishmaniasis (9). In the case reported, however, criteria for immune-mediated hemolytic anemia (i.e., spherocytes, bilirubinuria, jaundice, hemoglobinemia, hemoglobinuria, and/or erythrocyte ghosts (7) were absent, and the patient did not even respond to the immunosuppressive therapy. On the other hand, the neutrophilia observed here is a more common finding and is described as mild or severe (1, 9, 11, 13, 17). The bone marrow findings, compatible with anemia of inflammation, could also partly explain the severity of anemia.

The pathogenesis of SS is unclear and probably has different factors, e.g., drug hypersensitivity, infections, inflammatory conditions, malignancy, and immune-mediated (15). Some authors claim that interleukin (IL)-1 activates the infiltration of neutrophils in these conditions (18). Other cytokines like granulocyte-colony stimulating factor, granulocyte macrophage colony-stimulating factor, IL-3, IL-6, IL-8, and gamma interferon (IFN)-ɣ seems to have some participation in etiology. Leukotatic mechanisms, autoantibodies, leukocyte antigen serotypes, and immune complexes also were associated with SS in humans (4, 5).

An exacerbated production of neutrophils by bone marrow triggered the SS. The histopathological findings in this dog were similar to those described in a poodle from another report (11). Among the malignancy-associated SS cases, the most reported in humans in acute myeloid leukemia, related to paraneoplastic syndromes or secondary to drugs used against the neoplasia. These cases are associated with pro-inflammatory cytokines, which can affect neutrophil function (8). The dog's bone marrow reported here presented a complete and staggered granulocytic series, which allowed us to rule out the possibility of myeloid leukemia.

Immunosuppression usually is the gold standard therapy for sterile neutrophilic disease. Glucocorticoids are the first-choice drugs, but other agents are recommended, like azathioprine, cyclosporine, chlorambucil, and mycophenolate mofetil (4, 9, 15, 18). Unfortunately, the dog in this report failed in response to therapy.

Sweet's syndrome is a rare condition in dogs but should be considered in severe leukocytosis and skin lesions without an infectious agent.

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Conflict of Interest

The authors declare no competing interests.

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