NOTE *Internal Medicine*

Generalized Alopecia with Vasculitis-Like Changes in a Dog with Babesiosis

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ABSTRACT. A locally bred, 12-year-old, intact female Satsuma dog presented with generalized alopecia. Erythema, crusts and desquamation were observed primarily on the truck. Papules and erosions were present in the pinnae, and there were multiple areas of skin necrosis on the right forelimb. The cutaneous lesions had not responded to treatment with systemic antibiotics and prednisolone. The dog also had progressive anemia. *Babesia gibsoni* was detected in the blood, and the dog was treated with antiprotozoal agents. The skin lesions and anemia improved, but relapsed after the treatment was discontinued. Histopathological examination of skin biopsies revealed findings suggestive of early leukocytoclastic vasculitis or ischemic vasculopathy.
KEY WORDS: alopecia, Babesia, canine.

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Cutaneous vasculitis is a pathological condition resulting from inflammation of the vascular wall and perivascular connective tissue. Cutaneous vasculitis can be primary, but usually occurs secondary to infection, neoplasia, immune-mediated disease or adverse response to drugs [1]. There are a few reports that describe the pathologic features of multifocal necrotizing arteritis associated with babesiosis in dogs [8], but there are no detailed histopathological reports in the literature of cutaneous vasculitis associated with Babesia infection. In this report, we describe the clinical symptoms and the histopathological features of skin lesions in a dog infected with *Babesia gibsoni.*

A locally bred, 12-year-old, intact female Satsuma dog was referred to the Kagoshima University Veterinary Teaching Hospital for evaluation of skin lesions. The owner reported that the dog's weight had decreased from 13 kg to 9.5 kg. Cutaneous symptoms had begun 2 months prior to presentation with papules, alopecia and mild pruritus of the pinnae and muzzle. These gradually spread from the face to the neck and abdomen and finally to the whole body. The dog had been treated with prednisolone (2 mg/kg/day) and cephalexin (25 mg/kg twice daily) for approximately 1 month, but did not respond to the treatment. The owner stopped all medications a few days before the first visit to our hospital.

On physical examination, the dog was underweight with a body temperature of 38.0°C and slightly pale mucous membranes. There was generalized alopecia, and the remaining hairs on the back were easily epilated with mild traction (Fig. 1A). Mild erythema, crusts and desquamation were observed, primarily on the trunk (Fig. 1A and 1B). Alopecia, papules, erosions and crusts were found in the pinnae (Fig. 1C). Multiple pruritic areas of cutaneous necrosis were present on the cranial aspect of the right forelimb (Fig. 1D). There were also erosions on the cranial aspect of the left forelimb. Repeated skin scrapings were negative for ectoparasites and fungal elements. Direct impression smears prepared from the trunk and pinnae revealed neither bacterial infection nor *Malassezia* overgrowth.

A complete blood count revealed leukocytosis ($32.2 \times 10^3/\mu l$) with neutrophilia and regenerative anemia (red blood cells $2.59 \times 10^6/\mu l$, hematocrit 21%, hemoglobin 5.9 g/d*l*, mean cell volume 74.9 fl and mean cell hemoglobin concentration 30.4 g/d*l*) with polychromasia and anisocytosis. No intraerythrocytic parasites were detected in the blood smear. The Coombs' test was not conducted, because the dog had been receiving prednisolone. Hematuria and hemoglobinuria were not reported. Platelet count was within the normal range ($284 \times 10^3/\mu l$). Serum chemistry analysis revealed slightly elevated concentrations of alkaline phosphatase (260 U/*l*) and blood urea nitrogen (38.3 mg/d*l*). C-reactive protein (0.65 mg/d*l*) was within the normal range. Since the clinical signs did not suggest Cushing's syndrome or hypothyroidism, the serum concentrations of thyroid hormone and cortisol were not determined. Abdominal ultrasound findings were normal, except for enlarged, hypoechoic ovaries.

Although a definitive diagnosis was not yet established, we suspected based on the skin lesions, and the polychromatic erythrocytes and anisocytosis, that this dog had an immune-mediated skin disease with concurrent immune-mediated hemolytic anemia. We restarted the prednisolone and cephalexin prescribed by the previous veterinarian

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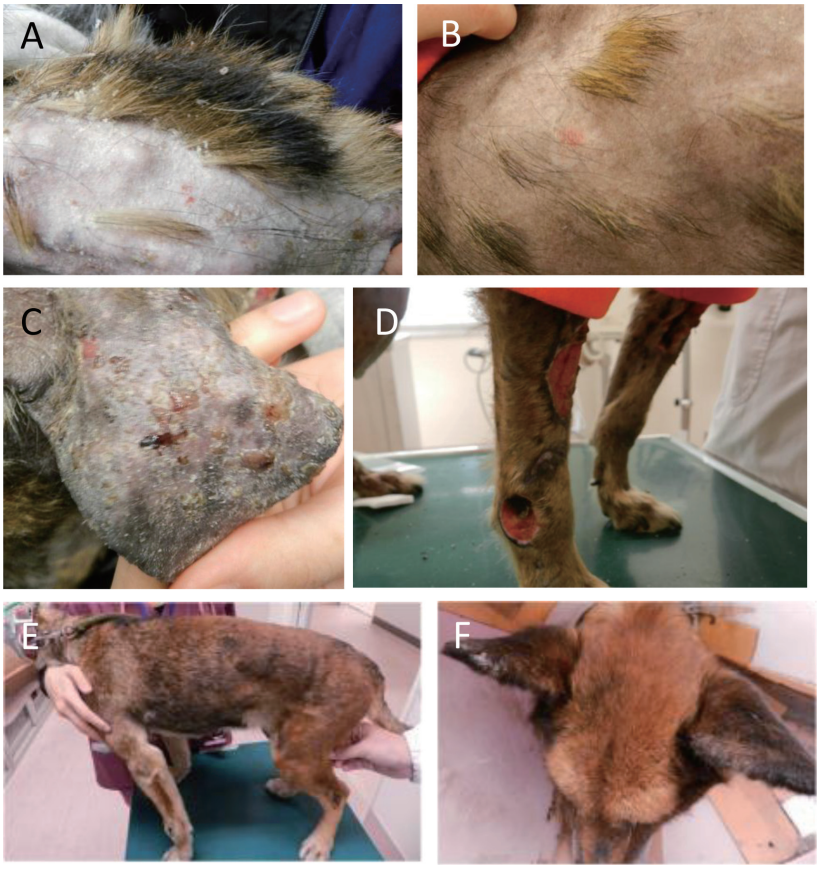

Fig. 1. A–D: Appearance of the dog on initial presentation. A: Alopecia, scales and desquamation in the lumbar area. B: Alopecia and erythema on the trunk. C: Erosion and crusts in the pinnae. D: Cutaneous necrosis on the right forelimb. E, F: Appearance during remission after approximately 2 months of antiprotozoal therapy. E: Alopecia and other skin lesions on the trunk are improved, and the hair color changed from light brown to dark brown. F: Erosion and crusts disappear in the pinnae.

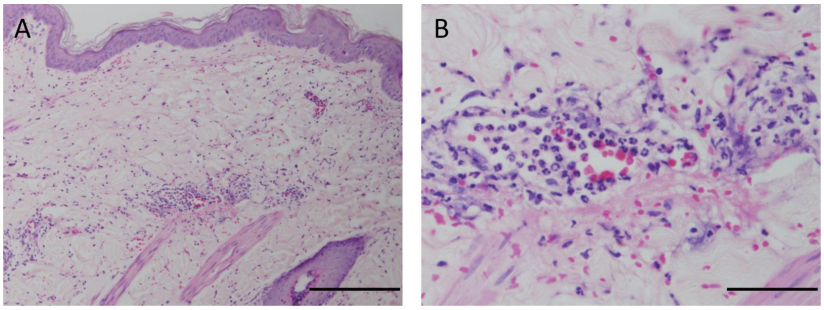

Fig. 2. Histopathological sections of affected skin. A: Lower magnification showing perivascular infiltration of inflammatory cells in the middle portion of dermis. Edema and intense extravasation are seen in the superficial dermis. B: Higher magnification of A showing infiltration of neutrophils into the vessel walls and perivascular area, and fibrin deposition adjacent to the blood vessels.

(prednisolone 2 mg/kg/day and cephalexin 25 mg/kg twice daily). We also prescribed digestive enzymes and an adequate amount of food to improve malnutrition, because the dog had lost weight in spite of a good appetite,

The dog gained weight 7 days after the first visit. Trypsin-like-immunoactivity was within the normal range (29.9 *n*g/m*l*; reference 9.2–46.3 *n*g/m*l*), and iron-deficiency anemia was ruled out by a high serum iron value (322 μg/d*l*; refer-

ence 50–173 μg/d*l*). However, at a second examination 14 days after the first visit, the clinical signs had considerably worsened. The alopecia continued to spread over the whole body, the region of necrosis on the right forelimb had worsened, the anemia had progressed (red blood cells $1.45 \times 10^6/\mu l$, hematocrit 16% and hemoglobin 4.0 g/d*l*), and the platelet count had markedly decreased ($57 \times 10^3/\mu l$). At this time, Babesia-like organisms were found on a blood smear. *B. gibsoni* was detected in a peripheral blood sample by polymerase chain reaction [2, 5]. Thus, we made a tentative diagnosis of babesiosis. A blood transfusion was performed, and the prednisolone dose was tapered. Atovaquon (13.3 mg/kg PO three times daily) and azithromycin (10 mg/kg PO once daily) were given for 9 days [3], after which the treatment was changed to a combination therapy (clindamycin 25 mg/kg PO twice daily, doxycycline 5 mg/kg PO twice daily and metronidazole 25 mg/kg PO twice daily) as described previously [7].

Twenty-one days after beginning the antiprotozoal treatment, the anemia had improved (hematocrit 36%), and the platelet count had returned to normal ($465 \times 10^3/\mu l$). Systemic cutaneous symptoms had also improved dramatically (Fig. 1E and 1F). We stopped the antiprotozoal medications after approximately 100 days of therapy. Two months later, the patient relapsed with desquamation and alopecia on the pinnae and forelimbs. Leukocytosis ($43.2 \times 10^3/\mu l$) and anemia (red blood cells $448 \times 10^4/\mu l$ and hematocrit 29%) also recurred. Babesia-like organisms were not detected on a blood smear. Platelet count remained within the normal range ($354 \times 10^3/\mu l$). C-reactive protein was elevated this time (7.8 mg/d*l*). Skin biopsy samples were collected from areas of erythema and desquamation on the trunk. Histological examination revealed mild to moderate hyperkeratosis and epidermal acanthosis, as well as perivascular infiltration of neutrophils with mild edema and marked extravasation in the upper to middle portion of the dermis (Fig. 2A). Neutrophilic perivascular infiltration of small vessels, excessive extravasation and fibrin deposition were also observed in the middle portion of the dermis (Fig. 2B). Fibrinoid degeneration in the vessel walls was not seen in the histological sections examined. Large vessels in the deep dermis or subcutis were not affected. Mild perivascular and interstitial infiltrations of eosinophils and lymphocytes were also observed. Periodic acid-Schiff and gram staining revealed no fungi or bacteria. No mite infestation was detected. These histopathologic findings suggested an early leukocytoclastic vasculitis or ischemic vasculopathy. Based on the clinicopathologic and histopathologic findings, we made the diagnosis of cutaneous vasculitis associated with babesiosis and restarted antiprotozoal treatment with clindamycin (25 mg/kg PO twice daily) and doxycycline (5 mg/kg PO twice daily). Metronidazole was not administered, because of owner noncompliance. The dog's skin condition again improved.

Gross cutaneous lesions that have been reported in dogs infected with *B.canis* include cutaneous hemorrhagic macules, urticaria and necrosis of the extremities (as was also present in this case) [4]. The systemic alopecia, desquamation, papules, crusts and scales seen in this case have not been previously reported. Cutaneous vasculitis associated with babesiosis is thought to be mediated by immune complexes, which adhere to blood vessel walls and activate inflammatory cells. The activated inflammatory cells then release free radicals or histamine, which promote inflammatory cell infiltration and vascular permeability. These reactions eventually damage the perivascular tissue [6]. In the previous report [4], skin biopsies were taken from only two dogs, and histopathological examination revealed a mixed perivascular inflammatory infiltrate in one case. Skin biopsy was not performed on initial presentation in this case, but histopathologic findings during the relapse suggested early leukocytoclastic vasculitis or ischemic vasculopathy, in which marked fibrinoid degeneration of the vessel walls may not be prominent. There were no histopathologic findings indicative of endocrine alopecia. In this patient, the alopecia was thought to be associated with ischemic changes in the skin. Improvement of skin lesions coincided with remission of the babesiosis during treatment with antiprotozoal agents, and the relapse and improvement after stopping and restarting the medication also suggest that the skin lesions were associated with babesiosis. To date, the course of treatment for cutaneous babesiosis has not been reported. In a case of suspected cutaneous vasculitis/vasculopathy, one should consider chronic babesiosis as a differential diagnosis in endemic areas.

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