

Case Report Rapport de cas

Urticaria pigmentosa-like disease in a dog

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Abstract — Urticaria pigmentosa is a rare dermatologic syndrome in humans, cats, and dogs. This report documents a case of canine urticaria pigmentosa-like disease with unusual features and no C-kit mutation.

Résumé — **Maladie s'apparentant à l'urticaire pigmentaire chez un chien.** L'urticaire pigmentaire est un syndrome dermatologique rare chez les humains, les chats et les chiens. Ce rapport documente un cas canin s'apparentant à l'urticaire pigmentaire comportant des caractéristiques inhabituelles et l'absence de mutation C-kit.

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Mastocytosis consists of a proliferation of mast cells affecting the bone marrow, liver, spleen, lymph nodes, gastrointestinal tract, and skin in humans, cats, and dogs. In humans, the most common forms of mastocytosis are cutaneous mastocytosis and indolent systemic mastocytosis, both of which have a good prognosis. Cutaneous mastocytosis can be categorized into 3 clinical patterns: urticaria pigmentosa (UP), diffuse cutaneous mastocytosis, and mastocytoma of the skin (1). Urticaria pigmentosa presents as hyperpigmented macules, papules, or nodules at any location but generally sparing the palms, soles, face, and scalp. In some human patients, mild trauma or friction can cause urtication and erythema to develop around lesions: the “Darier sign” (1). Treatment is directed at controlling the clinical signs of histamine release including pruritus and gastric hypersecretion. Concurrent use of H1 and H2 antihistamines has been reported to provide improvement in the signs and symptoms of UP (1).

In dogs, solitary or multifocal mast cell tumors are common, but other forms of mastocytosis, such as UP, are rare (2–5). Urticaria pigmentosa in dogs can present as small papules that can progress to erythematous plaques. Lesions tend to develop on the head, neck, trunk, perineum, and legs. Spontaneous regression has been noted in younger dogs (6,7).

In humans, mutations of C-kit have been noted in adult onset cases of UP (1,2). C-kit is a proto-oncogene which encodes a transmembrane KIT type III receptor, tyrosine kinase, which can

be found on mast cells, hematopoietic stem cells, melanocytes, and germ cells. It is activated by binding of stem cell factor (SCF) to the second and third immunoglobulin-like domains of KIT, which leads to protein kinase activity (8–10). Activated KIT is needed for differentiation, proliferation, chemotaxis, activation, and survival of mast cells by decreasing apoptosis and increasing cellular proliferation via PI3K/Akt, Jak/Stat, Src, and Ras pathways (9–12). A gain of function mutation at exon 8 or 11 in the juxtamembrane domain leads to survival, proliferation, and oncogenic transformation in canine mast cell tumors; however, some mast cell tumors can develop without a C-kit mutation (9–11,13). C-kit mutations were not evaluated in the canine UP-like reported cases (4,5).

In this article, we describe a variant of UP-like disease in a dog characterized by transient pruritus, which was successfully controlled with a combination of H1 and H2 antihistamines. Skin biopsies were evaluated for C-kit gene mutations at exon 8 and 11.

Case description

A 3-year-old, neutered male Labrador retriever mixed breed dog was presented to the dermatology service with a 9-month history of pruritic diffuse small, non-pigmented papules. Initial lesions were noted on the ventral abdomen after an episode of flea infestation, which was controlled with a monthly topical (K9 Advantix II; Bayer Health Care Animal Health, Shawnee, Kansas, USA) and oral flea medication (Comfortis; Elanco, Greenfield, Indiana, USA). This treatment eliminated the fleas but the lesions did not improve. There was a subsequent spread of papules from the abdomen to the chest and the anterior thigh with persistent pruritus. The patient developed a mild cough that, at times, caused him to gag and regurgitate. The primary veterinarian initially treated the dog with cefpodoxime (Zoetis, Madison, New Jersey, USA) and hydroxyzine pamoate (unknown manufacturer) with no response. Subsequently, the dog was started on a strict food trial of Hill's Science Diet z/d for both the regurgitation and dermatological problems, but there was no improvement in pruritus or resolution of the

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Figure 1. Abdomen of dog with UP-like disease. Small raised papules that became mildly erythematous after manipulation.

papules. The owner treated the patient with diphenhydramine (unknown manufacturer), which controlled the pruritus. After 2 mo, the diphenhydramine was discontinued without a return of pruritus. During this time, the small papules, coughing, and regurgitation remained unchanged.

On presentation, dermatological examination revealed approximately 100 small non-pigmented papules, 2 to 4 mm in diameter, mostly on the abdomen, with some on the chest and anterior thigh (Figure 1). Palpation of the papules resulted in mild erythema of the skin within a few minutes; a positive Darier sign. Cytologic preparations of crusted papules showed normal epithelial cells.

The only abnormalities demonstrated on complete blood (cell) count (CBC), serum chemistry, and total thyroxine level (T4) (Idexx Laboratories; Lenexa, Kansas, USA) were a mild thrombocytopenia of $111 \times 10^3/\mu\text{L}$ [reference interval (RI): 164 to $510 \times 10^3/\mu\text{L}$] with clumping of platelets, lymphopenia of $900/\mu\text{L}$ (RI: 1000 to $4800/\mu\text{L}$), and an eosinophilia of $2510/\mu\text{L}$ (RI: 100 to $1250/\mu\text{L}$). Three skin biopsy samples (6-mm punch) from the right side of the abdomen were taken for histopathology, which revealed a dense proliferation of mature mast cells in the upper dermis extending to the dermo-epidermal junction with a mixed cell population of eosinophils, lymphocytes, and neutrophils. The mast cells had a low mitotic index and minimal pleomorphism (Figure 2). Based on the clinical lesions, positive Darier sign, and supporting histopathology, a diagnosis of UP-like disease was confirmed.

The day after the biopsy the owner reported that the dog appeared to be in pain and its abdominal skin was inflamed. A general physical examination was normal, but dermatological examination demonstrated moderate erythema of the right side of the abdomen. The papules adjacent to the recent biopsies were erythematous and were enlarged to twice their original size.

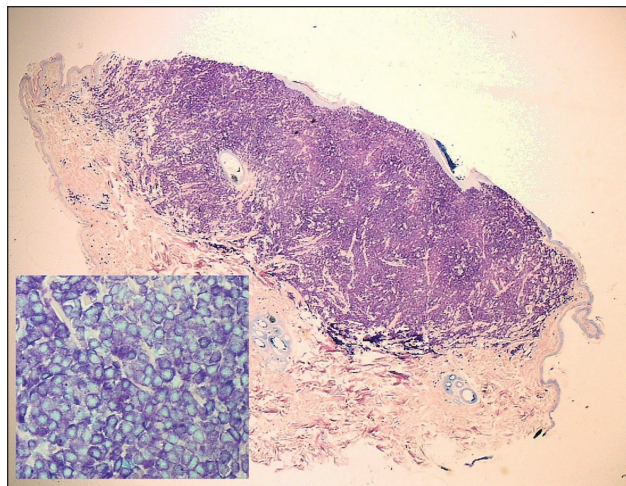


Figure 2. Giemsa-stained section showing area of sheet-like proliferation of uniform cells in the upper dermis. Giemsa, 40 $\times$. The cells show ample cytoplasm containing purple-stained granules characteristic of mast cells. Giemsa, 200 $\times$.

A 3-cm area of serous exudate with erythema was noted adjacent to the scrotum, and a 3-cm area of petechiae was present on the right side of the abdomen near the biopsy sites. The left side of the abdomen remained unchanged. The dog had been wearing an E-collar and T-shirt in order to reduce the likelihood of self-induced trauma lesions.

The next day the dog developed vomiting, diarrhea, hematochezia, and lethargy. Based on a positive SNAP canine pancreatic lipase immunoreactivity test (Idexx Laboratories) and abdominal radiographs, a diagnosis of pancreatitis was made and the dog was started on a home-cooked diet of boiled chicken and rice. At this point the patient's therapy consisted of diphenhydramine, 2.2 mg/kg body weight (BW), PO, q8 to 12h, tramadol, 2.9 mg/kg BW, PO, q8 to 12h, and famotidine, 0.9 mg/kg BW, PO, q24h.

At the 2-week reevaluation, the skin lesions had returned to their original appearance as non-pigmented papules. No new lesions were noted, and coughing and regurgitation were unchanged. An abdominal ultrasound was normal, and chest radiographs demonstrated a mild bronchial interstitial pattern. An internal medicine specialist recommended that no further diagnostic testing be done unless the cough worsened. Additional polymerase chain reaction testing (Idexx Laboratories) of the biopsy samples demonstrated no C-kit mutation at either exon 8 or 11. Treatment was given to counteract the symptoms of mast cell degranulation, including diphenhydramine, 2.2 mg/kg BW, q8 to 12h, and famotidine, 0.9 mg/kg BW, q24h; the tramadol was discontinued.

At the 12-week reevaluation, the skin lesions remained stable. The cough had significantly worsened, and the dog was regurgitating up to 3 times per day. An evaluation of his coughing and regurgitation by an internal medicine specialist was recommended, but the owner declined. General blood work (CBC, serum chemistry, and T4) (Idexx Laboratories) was relatively unchanged; the only abnormality noted was eosinophilia of $2120/\mu\text{L}$. For convenience, the antihistamine was changed to

second-generation H1 antihistamine, cetirizine, (1 mg/kg BW, q24h, PO) (unknown manufacturer), and the famotidine (0.9 mg/kg BW, q24h, PO) (unknown manufacturer) was continued.

At 20 wk the owner stated that the patient's general health was stable, and the skin lesions were unchanged. The dog's coughing and regurgitating persisted but were improving.

Discussion

The published literature on canine urticaria pigmentosa-like disease in dogs describes 3 patients (4,5). The most notable similarities are the clinical and histopathologic features of the non-pigmented papular lesions. Only one of the reports described the histopathologic findings (4), but there were many similarities to the present case. Each had a non-encapsulated, poorly demarcated dense infiltrate of well-differentiated mast cells in rows or sheets. Scattered eosinophils were noted (4); however, a mixed inflammation of eosinophils, neutrophils, and lymphocytes was seen in the present case.

There were several differences in the current case compared with the 3 published cases. In the published cases of UP-like disease the symptoms started in dogs less than 1 y of age (4,5), whereas in the current case the lesions did not start until the patient was middle-aged, a presentation often seen in human adult UP (1). In the 3 published cases in dogs, the lesions were non-pigmented papules to nodules, but the size of the lesions varied greatly from 1 to 5 cm (4,5), much larger than those of the current case. Previous cases (4,5) also had fewer lesions (1 to 10 papules or nodules) in contrast to the numerous lesions of the current case.

In 2 of the 3 previously reported canine patients (4,5), lesions urticated with trauma as seen in the current case. Pruritus, which was transient in the current case, was seen in only 1 previous case and was consistent until the lesions resolved spontaneously (4,5). Only 1 previously reported case (4) showed eosinophilia, which was consistently seen in the present case. The other 2 documented cases showed no abnormalities of blood chemistries (5).

Respiratory symptoms, especially coughing, were not described in the literature (4,5); however, it is unknown if the coughing was related to UP-like disease or an unrelated disease as the owners declined further workup and diagnosis.

Unlike the previously reported cases, the dog herein showed clinical evidence of mast cell degranulation, specifically, petechiae, vomiting, diarrhea, and hematochezia after the initial trauma of the biopsy (4,5,14,15). Mast cell degranulation causes release of the intracytoplasmic granules which contain biogenic amines (histamine), granule enzymes (acid hydrolases, cathepsin G, chymase, tryptase, carboxypeptidase) and proteoglycan (heparin, chondroitin sulfate) which have systemic effects (15,16). Increase in plasma histamine concentrations from mast cell degranulation can lead to gastric acid hyperacidity and gastrointestinal ulceration, increase in gastrointestinal motility and capillary permeability, promoting intravascular thrombosis and mucosal ulceration by binding to H2 receptors of gastromucosal parietal cells (1,15,17). These lead to vomiting, diarrhea, and hematochezia (15,17). Increase in plasma histamine concen-

tration gives rise to pruritus and inflammation by binding to H1 receptors (1,15,16). Inflammation can also be created by local release of mast cell granule contents, which lead to recruitment of cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-4, IL-5, IL-6, IL-13, Chemokine (C-C motif) ligand (CCL)3, CCL4, IL-3 and granulocyte monocyte colony-stimulating factor (GM-CSF) (15,16). Petechia, bruising, and prolonged hemorrhage can be related to release of proteoglycans, specifically heparin (1,15,16,17).

Treatment response was also different than in previous reports. Two of the previous dogs had a good to excellent response to oral glucocorticoids and H1 and H2 blockers, specifically complete resolution of lesions with only an occasional new lesion (5). In one dog there was spontaneous resolution (4). In the current case, resolution of lesions was not achieved; however, oral glucocorticoids were never administered per the owner's request. Stability of the lesions was achieved with H1 and H2 blockers.

A unique finding of the current case is the absence of C-kit mutation at exons 8 and 11. This absence may explain why this dog did not show malignant transformation, as seen in humans (9–11,18).

Despite the differences in the published cases of canine UP-like disease, there are many similarities to human adult-onset UP. The dog presented with numerous small papules on his abdomen, chest, and anterior thighs. There were no lesions on the paws, head, muzzle, or pinnae. Human UP lesions are localized to the trunk and limbs, generally sparing the palms, soles, face, and scalp (1,19). Darier sign, seen in the current case, is generally present in human UP. The lesions appear stable until they are traumatized or subjected to frictional stress (1). As in human cases, treatment with H1 and H2 blockers appeared to improve or cure the lesions.

Some clinical features in this case differed from those of human UP. In contrast to the usual human situation, this dog's lesions, and all reported canine lesions, were non-pigmented (1,4,5). The dog in this case did not have a C-kit mutation, which is generally found in UP of human adults, but is not commonly seen in UP of children (1,2).

As in human medicine, a diagnosis of urticaria pigmentosa or "UP-like" disease rests on a compatible clinical picture supplemented by confirmatory histopathology (19). Both elements were present in the current case.

A differential diagnosis for a canine patient with multiple papules or nodules which display proliferation of mast cells on histopathology would be indicative of mast cell tumor. Mast cell tumors most commonly present as a single cutaneous mass on the trunk, extremities or head/neck, occasionally with ulceration and satellite nodules (6,20). Multicentric mast cell tumors occur but these cases do not show the large number of papules seen in the current case (6). The lesions in the current case were indolent and stable unless traumatized, unlike malignant neoplasms, which generally show progressive growth (20). A diagnosis of mast cell tumor would not be consistent with the clinical picture of the current patient, a young dog with 50 to 100 papules, and with none of the histologic features of malignant mastocytic diseases (6,20). In the current case, the

clinical and the histopathologic findings were also consistent at multiple independent sites.

The combination of the patient's clinical presentation of hundreds of uniform, stable papules and the uniform microscopic findings of proliferation of benign-appearing mast cells led to the diagnosis of UP-like disease. This case report documents a rare dermatological presentation, UP-like disease in a canine patient, which has many features that differ from those of the 3 cases reported in dogs but many similarities to human UP. The lack of C-kit mutation at exon 8 and 11 is a unique finding and might account for the clinical course seen in this case. CVJ

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