History
A 1.5-year-old 29.5-kg spayed female Labrador Retriever was evaluated for a 4-month history of diffuse nonpruritic plaques on the caudoventral aspect of the abdomen. The dog had a history of an ear infection at 6 months of age that resolved with a 7-day course of topical treatment with a gentamicin-mometasone furoate-clotrimazole otic suspension (Mometamax) but had no other history of skin disease or relevant medical concerns. The lesions on the caudoventral aspect of the abdomen had developed over the course of a few weeks, and there was no recent prior history of topical or systemic drug administration. Following their initial discovery, the lesions did not appear to have been progressive. Results of clinicalopathologic testing performed by the referring veterinarian were unremarkable. Punch biopsies were performed, and specimens were sent to a commercial laboratory for histologic examination. The histologic appearance was consistent with low-grade or grade II mast cell tumors, and the patient was subsequently referred to a veterinary oncologist for further work-up. Given that the clinical presentation of diffuse nonpruritic plaques would be an atypical manifestation of low-grade mast cell tumors, which tend to be nodular, the oncologist recommended a dermatology consult.

Clinical and Gross Findings
On referral, physical examination revealed numerous, diffuse, multifocal to coalescing, irregular, raised, pale-pink papules and plaques of various sizes (0.2 to 4 cm in diameter) on the caudoventral aspect of the abdomen and in the inguinal area, extending down the medial aspects of the thighs bilaterally (Figure 1). The dog did not appear pruritic, and the remainder of the physical examination, including palpation of the peripheral lymph nodes, was within normal limits. Results of cytology examination of impression smears of the skin lesions obtained with acetate tape were unremarkable. Owing to the lack of concurrent systemic signs, abdominal ultrasonography and other diagnostic imaging were not pursued.

Histopathologic Findings
Paraffin-embedded tissue blocks were obtained from the referring veterinarian, and additional sections were cut. A total of 6 sections of the punch biopsy specimens were stained with H&E stain and examined. All sections contained numerous well-differentiated mast cells arranged in sheets and rows with low numbers of eosinophils within the dermis and extending into the panniculus (Figure 2). The mast cells contained lightly to deeply staining basophilic intracytoplasmic granules, a central oval nucleus with a finely stippled chromatin pattern, and a small indistinct nucleolus; cells displayed minimal anisokaryosis and anisocytosis. The mitotic count was variable, with 3 mitotic figures/2.73 mm² in the most mitotically active areas. The subcutis was
edematous with patchy infiltrates of eosinophils, macrophages, lymphocytes, and plasma cells. The blood vessels were reactive.

**Morphologic Diagnosis and Case Summary**

Morphologic diagnosis: multifocal cutaneous mast cell proliferation.

Case summary: cutaneous mastocytosis in a young Labrador Retriever.

**Comments**

Cutaneous mastocytosis is characterized by proliferation of nonneoplastic mast cells in the skin. The World Health Organization recognizes 3 clinical manifestations of the disease: maculopapular mastocytosis (also termed urticaria pigmentosa), diffuse cutaneous mastocytosis, and solitary mastocytoma.

To date, cutaneous mastocytosis has been described in humans, dogs, cats, cows, and horses. In humans, urticaria pigmentosa is the most common presentation of cutaneous mastocytosis and is characterized by numerous macules, papules, or plaques appearing in childhood and resolving by adolescence. Pruritus is variable. Adult-onset mastocytosis is less common, often has a more chronic course, and is more frequently associated with systemic signs.

Although solitary and multifocal mast cell tumors are relatively common in dogs, cutaneous mastocytosis and urticaria pigmentosa-like disease are very rare, with publications limited to a handful of case reports. The histopathologic appearance of low-grade mast cell tumors and all 3 clinical manifestations of cutaneous mastocytosis are similar, consisting of nonencapsulated, poorly demarcated, perivascular to diffuse proliferations of well-differentiated mast cells in rows or sheets extending from the superficial to deep dermis but sparing the epidermis; scattered eosinophils are commonly seen. The cytologic, histopathologic, and immunohistochemical findings in cutaneous mastocytosis are indistinguishable from those associated with low-grade mast cell tumor. A diagnosis, therefore, is made by relating diagnostic findings to the clinical presentation. In dogs, low-grade mast cell tumors present as solitary or occasionally multiple dermal nodules, but the clinical presentation of cutaneous mastocytosis in dogs includes nonpigmented, pink, and erythematous macules, papules, or plaques. Although some dogs have low numbers of large nodular lesions with occasional ulceration, the diffuse maculopapular appearance is more typical as was seen in the present case. The number of lesions and lesion size reportedly are highly variable, and pruritus is present in some but not all cases. Lethargy has been reported in one case, and regurgitation and coughing were reported in another. In some cases, manual scratching or rubbing of lesions leads to erythema or urticaria (known as a positive Darier sign) as mast cell degranulation is triggered.

Similar to children with urticaria pigmentosa, dogs with cutaneous mastocytosis appear to be young, with all reported cases being under 2 years of age at the time of lesion onset. Three of the 7 cases described to date, including the dog in the present case, were Labrador Retrievers or their crosses, suggesting this breed may be predisposed. That being said, because the current case number is low, no definitive conclusions can be drawn about breed predilections.

Treatment for urticaria pigmentosa-like disease is mostly focused on symptomatic relief. The most commonly prescribed treatments include H1- and H2-antihistamines to reduce pruritus, urticaria, and gastric acid release. Lesions and clinical signs
resolved spontaneously without treatment in 1 previously reported dog, and 2 dogs had complete resolution of clinical signs and lesions with the use of H1- and H2-antihistamines (chlorpheniramine and cimetidine). One dog had improvement of pruritus but persistent lesions with cetirizine and famotidine, and in another dog, pruritus and lesions were refractory to antihistamines, glucocorticoids, and cyclosporine. In that dog, the pruritus responded to lokivetmbut the lesions persisted. The dog of the present report showed marked improvement but incomplete resolution of lesions with cetirizine (1 mg/kg, PO, q 24 h) and famotidine (0.6 mg/kg, PO, q 12 h). The lesions improved gradually over the course of 4 months but did not improve after that. At 6 months, owing to a lack of continued improvement, the cetirizine and famotidine were discontinued, leading to a minor relapse of clinical signs, characterized as development of a small number of new maculopapular eruptions. Both H1- and H2-antihistamines were reinitiated, halting disease progression. Unfortunately, 11 months following initial presentation, the patient was euthanized because of septic peritonitis secondary to foreign body ingestion and subsequent small intestinal perforation.

Mutations in the c-kit gene at exons 8 through 11 and 17 appear to play a role in some cases of cutaneous mastocytosis in humans. The c-kit gene is a proto-oncogene that encodes KIT type III receptor tyrosine kinase. KIT type III receptor tyrosine kinase is found on mast cells and is activated by binding stem cell factor. Activation leads to differentiation, proliferation, and survival of mast cells. Gain of function mutations to the c-kit gene on exons 8 and 11 have been implicated in the development of mast cell tumors in dogs; however, some canine mast cell tumors develop without a c-kit mutation. The importance of c-kit mutations in the pathogenesis of cutaneous mastocytosis in dogs is unknown. A mutation at exon 11 was found in 1 case, whereas no mutations were identified at exons 8 or 11 in 2 other cases, making it difficult to interpret the importance of c-kit mutations in canine cutaneous mastocytosis. Evaluation for c-kit mutations was not performed in the present case.

The present case highlights the importance of interpreting histopathologic findings in conjunction with clinical presentation to make an accurate clinical diagnosis. It also highlights the importance of clinicians providing pathologists with a complete history, including signalment and physical examination findings, to allow for formulation of a complete list of differential diagnoses. The most important differential diagnosis for this case was multicentric low-grade mast cell tumors. Cutaneous mast cell tumors usually present as solitary or multiple nodules with occasional ulceration that show progressive growth and are more common in middle-aged to older dogs. By contrast, cutaneous mastocytosis typically occurs in young patients and presents as variably pruritic, multifocal to diffuse papules and plaques that are nonprogressive. Response to antihistamine therapy is supportive of a diagnosis of cutaneous mastocytosis but is not seen in all cases. The prognosis for dogs with cutaneous mastocytosis appears to be good, but more information is needed to further characterize this disease.

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References