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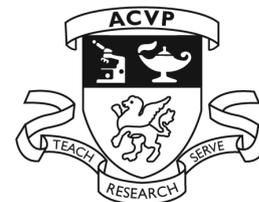
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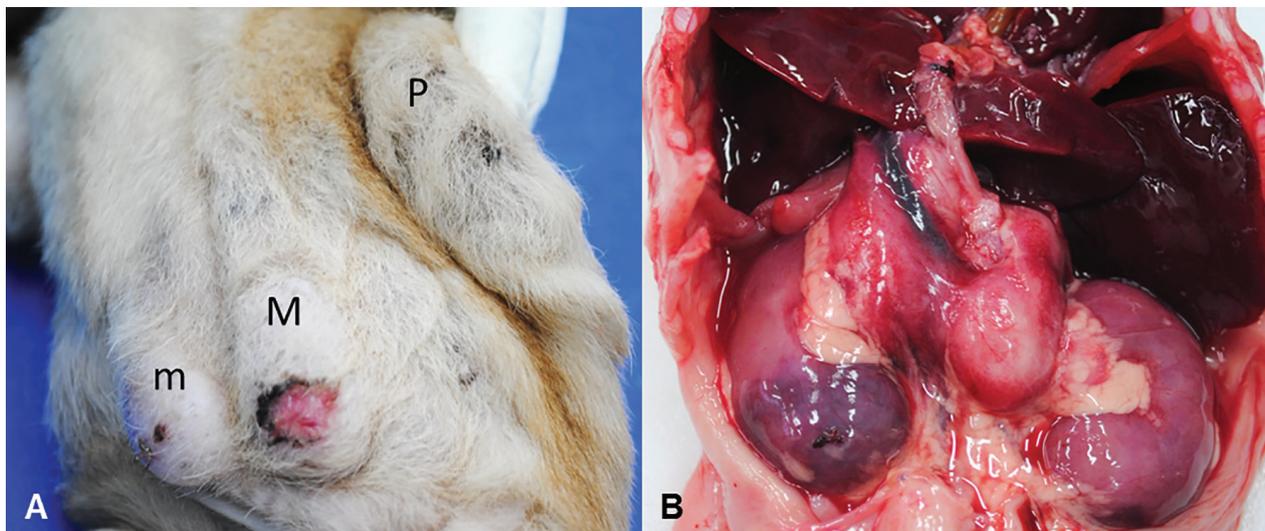
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## Pathology in Practice



**Figure 1**—Photographs of the ventrum (A) and an adrenal mass (ventral view [B]) of a female Labrador Retriever Collie-cross puppy that was born with 2 cutaneous masses on the ventral aspect of its abdomen and 2 symmetrical thickened plaques in the skin of the lumbar region. The puppy was euthanized 18 days after birth because of continued growth of the lesions and deterioration of its clinical condition. In panel A, notice a large, ulcerated mass (M), a smaller mass that had been biopsied (m), and a plaque of thickened dorsal skin (P). In panel B (obtained during necropsy), the mass has replaced both adrenal glands and is adhered to the medial surface of the right kidney and the hilus of the liver. Cranial is toward the top of both images.

### History

A female Labrador Retriever Collie-cross puppy was born with 2 cutaneous masses on the ventral aspect of its abdomen and 2 symmetrical thickened plaques in the skin of the lumbar region. All 4 lesions grew noticeably between birth and euthanasia at 18 days of age. During the first 2 weeks after birth, the puppy was reportedly bright, nursed well, and gained weight; however, its condition deteriorated during the third week, leading to euthanasia (by means of IV injection of phenobarbital solution). Eighteen months later, the puppy's sire and dam and the remaining 9 littermates were clinically normal, and neither parent had a history of a mass.

### Gross Necropsy Findings

The skin over the caudoventral portion of the abdomen contained 2 discreet soft to moderately firm masses (**Figure 1**). The larger mass (3 X 2 X 1 cm) had a raised area that was focally ulcerated. This mass was continuous with a thickened plaque within the subcutis extending 3

cm caudally and laterally. A smaller mass (2.5 X 2 X 0.8 cm) was located close to the midline, and 2 additional thickened plaques were present within the skin of the dorsum. The dorsal plaques were elliptical (5 X 6 cm) and symmetrically distributed on either side of the dorsal midline overlying the caudal rib margin. The skin over these plaques appeared darker than that in unaffected regions and had multifocal areas of crusting. The masses and plaques were confined to the skin and subcutaneous tissue and were not adhered to deeper structures.

The abdominal cavity contained a light pink, moderately firm, irregularly shaped mass that extended across the ventral midline between the medial surfaces of both kidneys; it measured 2.5 X 4.0 X 1.8 cm at its widest point to the left of midline (**Figure 1**). The cut surface of the mass was cream-colored and homogeneous except for 3 isolated red-brown areas of hemorrhage. Normal adrenal glands could not be identified grossly, and the mass was strongly adhered to the medial surface of the right kidney and focally to the hilus of the liver. The caudal third of the capsular surface and cortex of the right kidney was dark red-purple and well demarcated from the remaining red-brown tissue, suggestive of a renal infarct. Similar changes were also seen in smaller areas of the cranial pole of the right kidney and the caudal pole of the left kidney.

**Formulate differential diagnoses from the history, clinical findings, and Figure 1—then turn the page→**

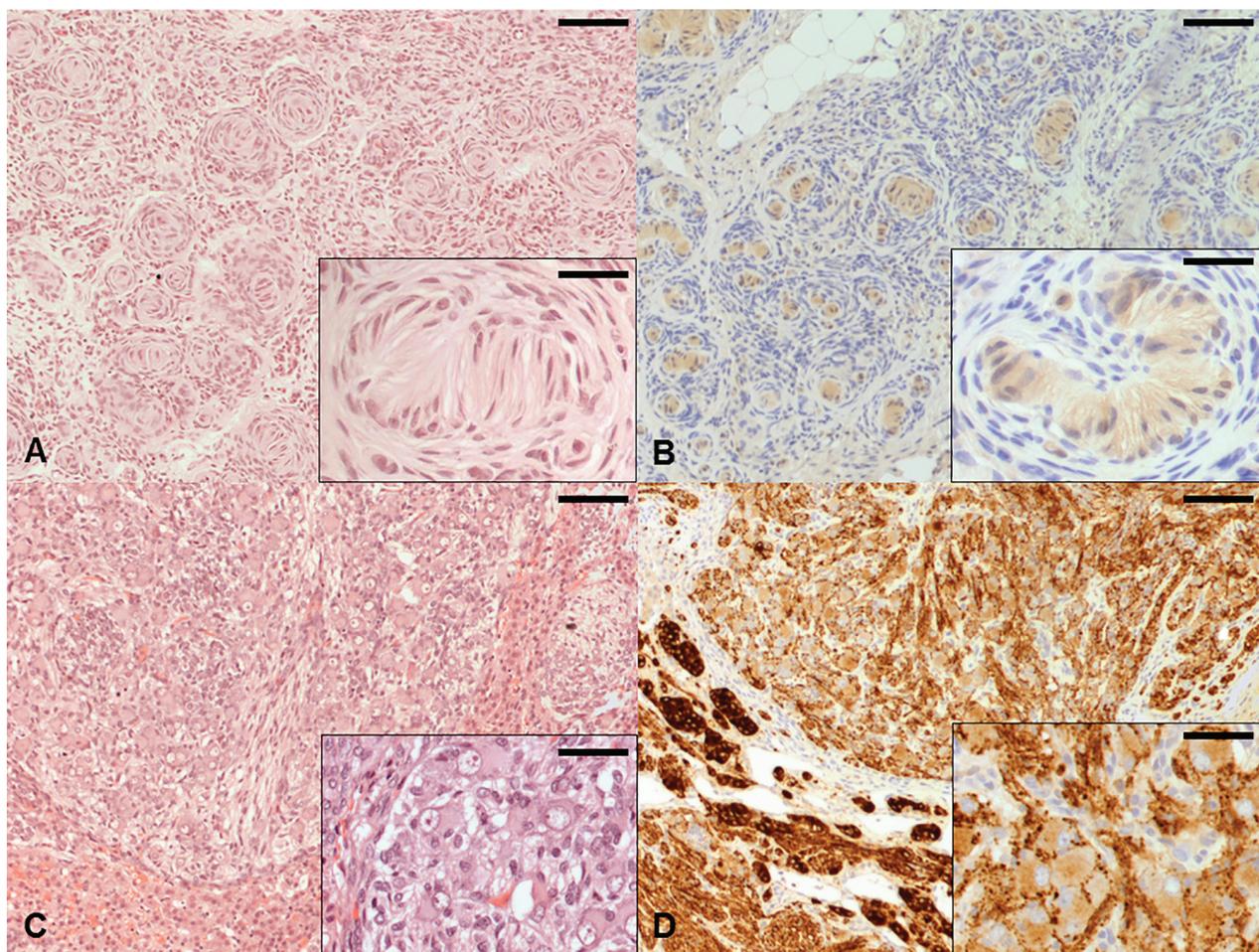
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## Histopathologic Findings

Microscopic examination of the abdominal mass revealed 2 contiguous tumors. Most of the mass was composed of a ganglioneuroma that had largely consumed both adrenal glands except for occasional small ribbons of adrenal medulla with which it was intimately associated (**Figure 2**). This mass blended with a smaller (peripheral) component that resembled diffuse neurofibroma similar to findings in the skin, and had infiltrated the right renal capsule and the mesenteric fat surrounding the hilus of the liver. The ganglioneuroma component had multifocal packets of numerous large polygonal cells

with abundant pale eosinophilic cytoplasm and eccentric vesicular nuclei. Histologically, these cells resembled ganglion cells and were immunopositive for both synaptophysin and NSE antigens but not for S100 antigen. Packets of neoplastic ganglion cells were interspersed by dense streams of wavy spindloid cells with indistinct cell borders and buckled slender nuclei. These spindle cells were immunopositive for GFAP antigen but had no immunoreactivity for S100, NSE, or synaptophysin antigens. The mass effaced both adrenal glands, and it was not possible to establish whether the mass had a uni- or bilateral origin. No cellular immune response to either the cutaneous or adrenal tumors was identified.



**Figure 2**—Photomicrographs of sections of I of the skin masses (A and B) and the adrenal mass (C and D) in the puppy in Figure 1. A—Multiple tactile structures (pseudomeissnerian corpuscles) are randomly distributed throughout the subcutis within a fibromyxomatous stroma. H&E stain; bar = 200  $\mu$ m. Inset—Higher-magnification view of a section of a pseudomeissnerian corpuscle. H&E stain; bar = 50  $\mu$ m. B—The cells of the pseudomeissnerian corpuscles have moderate diffuse cytoplasmic immunoreactivity and weak, patchy nuclear immunoreactivity for S100 antigen, consistent with a Schwann cell origin. The perineurial cell capsule is not immunopositive for this antigen. A subpopulation of the spindloid component has weak cytoplasmic immunoreactivity for S100 antigen. Immunohistochemical reaction for S100 antigen with 3,3'-diaminobenzidine (DAB) as a chromogen; bar = 200  $\mu$ m. Inset—Higher-magnification view of a section of a pseudomeissnerian corpuscle immunostained for S100 antigen. Immunohistochemical reaction for S100 antigen with 3,3'-DAB as a chromogen; bar = 50  $\mu$ m. C—In the adrenal mass, islands of neoplastic ganglion cell bodies are bordered by a thin rim of normal adrenal medulla. H&E stain; bar = 200  $\mu$ m. Inset—Higher-magnification view of neoplastic ganglion cells in the adrenal mass. H&E stain; bar = 50  $\mu$ m. D—Neoplastic neurons have strong punctate cytoplasmic immunoreactivity (mid-brown) for synaptophysin antigen. The surrounding adrenal medulla has very strong cytoplasmic immunoreactivity (dark brown) for synaptophysin antigen, and the neuromatous component has no immunoreactivity for this antigen. Immunohistochemical reaction for synaptophysin antigen with 3,3'-DAB as a chromogen; bar = 200  $\mu$ m. Inset—Higher-magnification view of neoplastic ganglion cells immunostained for synaptophysin. Immunohistochemical reaction for synaptophysin antigen with 3,3'-DAB as a chromogen; bar = 50  $\mu$ m.

## Morphologic Diagnosis and Case Summary

Morphologic diagnosis and case summary: neurofibromatosis (diffuse subtype) of haired skin and mesentery and adrenal ganglioneuroma in an 18-day-old puppy.

## Comments

In the veterinary medical literature, sporadic neurofibromas in dogs, cattle, horses, and chickens have been described.<sup>2</sup> These tumors have typically developed in the skin, peripheral and autonomic nerves, or the gastrointestinal tract.<sup>2</sup> Multicentric tumors have been encountered in adult cattle, often at slaughter,<sup>3</sup> and 2 instances of possibly familial cutaneous neurofibromatosis in calves and aged cattle have been described.<sup>4</sup> Often neurofibromas and schwannomas in animals have been described as benign peripheral nerve sheath tumors because of the perceived lack of histologic differentiation between these 2 tumor types. In a few cases, however, the same histologic features and the same nodular, plexiform, and diffuse neurofibroma subtypes in humans have been identified in veterinary species.<sup>2</sup> Diffuse neurofibromas, such as the subtype in the dog of the present report, expand the subcutis, undergo infiltrative growth, and have poor demarcation.

Sporadic neurofibromas in humans are more commonly associated with autosomal dominant or spontaneous germline mutations in the NF1 tumor-suppressor gene that lead to development of neurofibromatosis type 1 (NF1), which is also referred to as von Recklinghausen disease.<sup>5</sup> Sporadic neurofibromas are frequently associated with tumors of neural crest origin, such as adrenal ganglioneuromas and pheochromocytomas, and tumors of neuroectodermal origin, such as cerebral and optic nerve gliomas. These tumors are also associated with an increased incidence of mesenchymal tumors, such as gastrointestinal stromal tumors arising from the interstitial cells of Cajal.<sup>5</sup> Unlike previous reports<sup>2-4</sup> of neurofibroma in domestic species, the case described in the present report involved a puppy with both cutaneous neurofibromatosis and adrenal ganglioneuroma present at birth. This combination of cutaneous neurofibromas and a second tumor of neural tissue in a very young animal is highly suggestive of NF1, analogous to the human condition.

The tumor suppressor gene NF1 encodes neurofibromin, a protein that inhibits the cell cycle by inhibiting the RAS-mitogen-activated protein kinase (MAPK) pathway. To date, > 1,485 mutations have been documented to cause NF1 in humans with no particular mutation hotspot within the 350-kilobase gene.<sup>6</sup> A diagnosis of NF1 in a child or adolescent is usually made on the basis of multiple compatible clinical signs, such as so-called café au lait spots, cutaneous neurofibromas, optic glioma, and iris hamartoma.<sup>5</sup> The condition is highly heterogeneous, and

more severe cases have multiple organ involvement, with an apparent predilection for the adrenal glands and gastrointestinal tract.

Neurofibromas and ganglioneuromas are complex, mixed tumors, which is reflected by the results of immunostaining for synaptophysin, NSE, GFAP, and S100 antigens. Immunoreactivity for synaptophysin and NSE antigens is expected in the neoplastic ganglion cells in an adrenal ganglioneuroma, whereas the spindle cells that comprise the neuromatous component (generally assumed to be Schwann cells) have positive immunoreactivity for GFAP antigen but surprisingly not for S100 antigen, as was the finding in a previously reported canine case of ganglioneuroma.<sup>7</sup> Neurofibroma is a triad of Schwann cells, fibroblasts, and perineurial (or perineurial-like) cells<sup>8</sup> with the former staining weakly for S100 antigen (as in the dog of present report) and the latter 2 cell types staining only for vimentin (not performed for the dog of the present report). Meissner corpuscles are tactile receptors normally found within dermal papillae, and are formed of flattened Schwann cells in multiple stacked lamellae linked by tonofibrils to the epidermis. Pseudomeissnerian corpuscles, so named because of their morphologic similarity to Meissner corpuscles, are a feature of the diffuse variant of neurofibroma in people and dogs.<sup>2,8</sup> The cores of the pseudomeissnerian corpuscles within the skin and abdominal masses in the puppy of the present report were immunopositive for S100 antigen, a Schwann cell marker, in contrast to the perineurial capsule, which had no immunoreactivity for this antigen. Overall, NF1 in domestic species has rarely been reported, and we believe that the case described in the present report is the most convincing canine case to date.

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