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Histopathologic Findings in Canine Pituitary Glands

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Abstract

To optimize the histologic evaluation of hypophysectomy specimens, sections of 207 canine pituitary glands (196 postmortem, 11 hypophysectomy specimens) were reviewed. Adenohypophyseal proliferation was the most common (n = 79) lesion. Proliferative lesions were sparsely to densely granulated; the granules were usually basophilic to chromophobic and periodic acid-Schiff-positive. Adenohypophyseal proliferation was classified as hyperplasia (n = 40) if ≤2 mm diameter with intact reticulin network, as microadenoma (n = 22) for 1–5 mm homogeneous nodules with lost reticulin network, or as macroadenoma (n = 17) for larger tumors. Craniopharyngeal duct cysts were common incidental lesions and the only lesion in 15 dogs. Uncommon diagnoses included lymphoma (n = 4), hemorrhagic necrosis (n = 4), metastatic carcinoma (n = 3), hypophysitis (n = 3), ependymoma (n = 2), craniopharyngioma (n = 2), and 1 case each of metastatic melanoma, pituicytoma, gliomatosis, germ cell tumor, meningioma, and atrophy. The pituitary histologic diagnosis was associated with hyperadrenocorticism (HAC; $P < .001$) and adrenocortical histologic diagnosis ($P = .025$). Both HAC and adrenocortical hyperplasia showed a positive trend with the degree of adenohypophyseal proliferation. The association of adrenocortical hyperplasia with HAC was not significant ($P = .077$). Dogs with adenohypophyseal proliferations were older than dogs with normal pituitary glands ($P < .05$). Brachycephalic breeds were overrepresented among dogs with pituitary macroadenoma or craniopharyngeal duct cysts, but the association was not statistically significant ($P = .076$). Adenohypophyseal hyperplasia was more common than adenoma among postmortem specimens, but was unexpected in >80% of cases. Pituitary macroadenoma was the most common diagnosis in hypophysectomy specimens.

Keywords

adenohypophyseal hyperplasia, dogs, hyperadrenocorticism, pituitary adenoma, pituitary-dependent hypercortisolism, transsphenoidal hypophysectomy

The pituitary gland is capable of diverse responses to injury; however, in most species, the most common lesion is proliferation.[14,28] When functional, adenohypophyseal proliferations can result in dysfunction of secondary endocrine glands. Indeed, corticotroph adenoma is considered the most common cause of spontaneous canine hypercortisolism.[26] Until recently, the medical and surgical treatment of canine pituitary-dependent hypercortisolism (PDH) has been aimed mainly at the adrenal gland,[3,11,15,23] and histologic evaluation of canine pituitary glands has been predominantly a postmortem endeavor. In contrast, pituitary adenectomy or hypophysectomy is a mainstay in the treatment of human PDH (Cushing's disease) and other pituitary diseases, and surgical pathology is an important part of diagnosis and management.[2,4,5,22,24,27,29–31]

With improved imaging, microsurgical techniques, and postoperative care, transsphenoidal hypophysectomy has become a viable treatment option for canine pituitary disease, yet surgical pathology has been a minor component of most publications.[9,16,17,21,25] The main goal of this study was to classify canine pituitary lesions in archived case materials as the basis for development of a standardized approach to histologic evaluation of transsphenoidal hypophysectomy specimens. In addition to

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Table 1. Antibodies, Reagents, and Procedures for Immunohistochemistry.[a]

Antibody (Code or Clone)	Dilution	Incubation (min.)[b]	HIER Antigen Retrieval	Detection System	Antibody Source
Adrenocorticotrophic hormone (ab75683)	1:16 000	45	Target Retrieval Solution,[c] pH 6.0	EnVision+ HRP-labeled polymer anti-rabbit[c]	AbCam
Growth hormone (PA1-85518-T16000)	1:20 000	45	Diva Decloaker, pH 6.2	EnVision+ HRP-labeled polymer anti-rabbit[c]	Thermo Fisher Scientific
Melanocyte stimulating hormone (MZ1111-0050)	1:500	60	Reveal Decloaker, pH 6.0	Rabbit-on-canine HRP polymer[d]	Enzo Life Sciences
Prolactin (A0569-T300)	1:300	45	None	EnVision+ HRP-labeled polymer anti-rabbit[c]	Dako Agilent Pathology Solutions

Abbreviations: HIER, heat-induced epitope retrieval; HRP, horseradish peroxidase.
[a]The chromogen for all markers was 3, 3' diaminobenzidine (Betazoid DAB Chromogen Kit).[d]
[b]All incubations were performed at room temperature.
[c]Dako Agilent Pathology Solutions.
[d]Biocare Medical.

evaluating the prevalence and nature of adenohypophyseal proliferations and other pituitary lesions, the primary study objectives were to evaluate the association between (1) pituitary histologic diagnosis and a clinical diagnosis of hyperadrenocorticism, (2) pituitary histologic diagnosis and histologic evidence of adrenocortical hyperplasia, and (3) adrenocortical hyperplasia and a clinical diagnosis of hyperadrenocorticism. The secondary objectives were to investigate whether age, breed (brachycephalic vs nonbrachycephalic), or sex of dogs was associated with pituitary histologic diagnosis, adrenocortical hyperplasia, or hyperadrenocorticism.

Materials and Methods

Records of the Indiana Animal Disease Diagnostic Laboratory from July 2007 through August 2015 were retrieved for all dogs in which the pituitary gland had been examined histologically. Cases were included if histologic sections or paraffin blocks of suitable quality (adequate sample size without severe autolysis or tissue artifact) were available. Signalment, history, clinical impression, and gross and histologic findings were tabulated from submission forms and pathology reports. All pituitary sections were reviewed by 2 authors (MAM, ALV) at a double-headed microscope and classified[14,28] independently from the original pathology report into one or more of the following categories: histologically normal, adenohypophyseal proliferation (hyperplasia, microadenoma, or macroadenoma), craniopharyngeal duct cysts, or miscellaneous lesions (other pituitary neoplasms, secondary neoplasia, hypophysitis, atrophy, etc). Proliferative adenohypophyseal cells were categorized as basophilic, chromophobic, or acidophilic based on tinctorial characteristics of the cytoplasmic granules in hematoxylin and eosin-stained (HE) sections. Periodic acid-Schiff (PAS) and Gordon and Sweet's reticulin histochemistry, and immunohistochemistry (IHC, Table 1) for adrenocorticotrophic hormone (ACTH), growth hormone (GH), melanocyte stimulating hormone (MSH), or prolactin were used for selected cases when authorized by the referring veterinarian or as part of development of an IHC panel for evaluation of hypophysectomy specimens of pituitary adenoma. For trophic hormone IHC, neutral buffered formalin-fixed (1–2 days), paraffin-embedded sections of normal canine pituitary gland (with pars nervosa, pars intermedia, and pars distalis) were used to standardize each test. The final IHC protocol used the primary antibody dilution, antigen retrieval method, and detection system that produced the best signal-to-noise ratio in the targeted cells. Normal canine pituitary gland was the positive control tissue. Adenohypophyseal proliferations in which the cells expressed ACTH, but not other trophic hormones, were classified as corticotroph hyperplasia or adenoma. Lesions in which the cells expressed MSH and ACTH were classified as melanotroph hyperplasia or adenoma. Lesions in which the cells expressed ACTH and GH were classified as plurihormonal. Adenohypophyseal nodular proliferations were classified as hyperplasia if $\leq$2 mm in diameter, with expanded but intact reticulin network; as microadenoma if homogeneous (one cell type) and 1–5 mm in diameter with loss of the reticulin network; and as macroadenoma if homogeneous and >5 mm in diameter with loss of the reticulin network (because adenomas >5 mm in diameter enlarge the canine pituitary gland).[14,19] However, the diameter of proliferative lesions could not be measured in histologic sections of the hypophysectomy specimens, so classification as macroadenoma in those cases was based on pituitary dimensions >1 cm in magnetic resonance (MR) images. For nodular proliferations >1 mm in diameter, maintenance of the reticulin network was the criterion used to distinguish between hyperplasia and microadenoma. Adenohypophyseal hyperplasia, microadenoma, and macroadenoma were mutually exclusive classifications. Thus, a pituitary gland with both hyperplasia and microadenoma was categorized as microadenoma, and a gland with microadenoma and macroadenoma was categorized as macroadenoma. Mucin-filled structures lined by pseudostratified columnar epithelium with ciliated cells and goblet cells were classified as craniopharyngeal duct cysts if at least 1 mm in diameter. The categories of

Table 2. Descriptive Statistics of 207 Dogs With Pituitary Histologic Diagnoses.

Diagnosis[a]	Histologically normal	Adenohypophyseal hyperplasia	Pituitary microadenoma	Pituitary macroadenoma	Miscellaneous[b]	Craniopharyngeal duct cysts
Number (%)	92 (44)	40 (19)	22 (11)	17 (8)	21 (10)	15 (7)
Median age (range)	7.0 (0–15.0)	10.0 (2.0–16.0)[c]	11.5 (8.0–17.0)[c]	10.0 (5.0–13.0)[c]	8.0 (3.0–15.5)	9.0 (2.0–14.0)
Brachycephalic breed, n (%)						
Yes	11 (44)	3 (12)	0 (0)	4 (16)	3 (12)	4 (16)
No	81 (45)	37 (20)	22 (12)	13 (7)	18 (10)	11 (6)
Sex, n (%)						
Male	38 (41)	19 (21)	12 (13)	9 (10)	9 (10)	5 (5)
Female	54 (47)	21 (18)	10 (9)	8 (7)	12 (10)	10 (9)

[a]See Materials and Methods for diagnostic criteria.
[b]Miscellaneous included neoplasms other than pituitary adenoma, inflammation, or degeneration.
[c]Significantly different from "Histologically normal" ($P < .05$).

craniopharyngeal duct cysts and miscellaneous lesions were not considered mutually exclusive.

For all dogs that had been patients of Purdue University Veterinary Teaching Hospital (PUVTH), medical records were reviewed for evidence of hyperadrenocorticism (HAC), defined as the presence of $\geq$3 of the following clinical signs: polyuria, polydipsia, polyphagia, abdominal distension, alopecia, or hypertension. A confirmed diagnosis of HAC was made in dogs with both clinical signs of HAC and a positive endocrine test, for example, failure to suppress cortisol concentrations to <1.9 μg/dL at 8 hours on the low-dose dexamethasone suppression (LDDS), or a post-ACTH serum cortisol >17 μg/dL. The dogs were categorized as HAC not suspected, HAC suspected but not confirmed, or HAC confirmed.[6,26] For cases with adenohypophyseal proliferation, available histologic sections of adrenal gland were reviewed for adrenocortical proliferation, which was classified as within normal limits, hyperplasia, adenoma, or carcinoma.[14,28] For data analysis, the adrenocortical histologic variable was dichotomized into hyperplasia versus other classifications. Eleven cases were non-PUVTH transsphenoidal hypophysectomy specimens (surgery by author TJO); all 11 dogs had been evaluated for PDH by one or more of the following tests: urinary cortisol to creatinine ratio, LDDS, ACTH-stimulation test, basal ACTH concentration, or high-dose dexamethasone suppression (HDDS).[6,8,26]

Fisher's exact tests were used to evaluate the bivariate correlation between pituitary histologic diagnosis, a clinical diagnosis of hyperadrenocorticism, and a histologic diagnosis of adrenocortical hyperplasia. The age distribution was compared across the classifications of pituitary histologic diagnosis and clinical diagnosis of HAC using Kruskal-Wallis tests, followed by the pairwise comparisons with a significant result. Mann-Whitney *U* test was used to compare age distribution between a histologic diagnosis of adrenocortical hyperplasia and other adrenocortical diagnoses. The association of breed (brachycephalic vs nonbrachycephalic) and sex with pituitary histologic diagnosis, clinical diagnosis of HAC, or histologic diagnosis of adrenocortical hyperplasia was evaluated by Fisher's exact test. Significance was set at $P < .05$ for all statistical analyses.

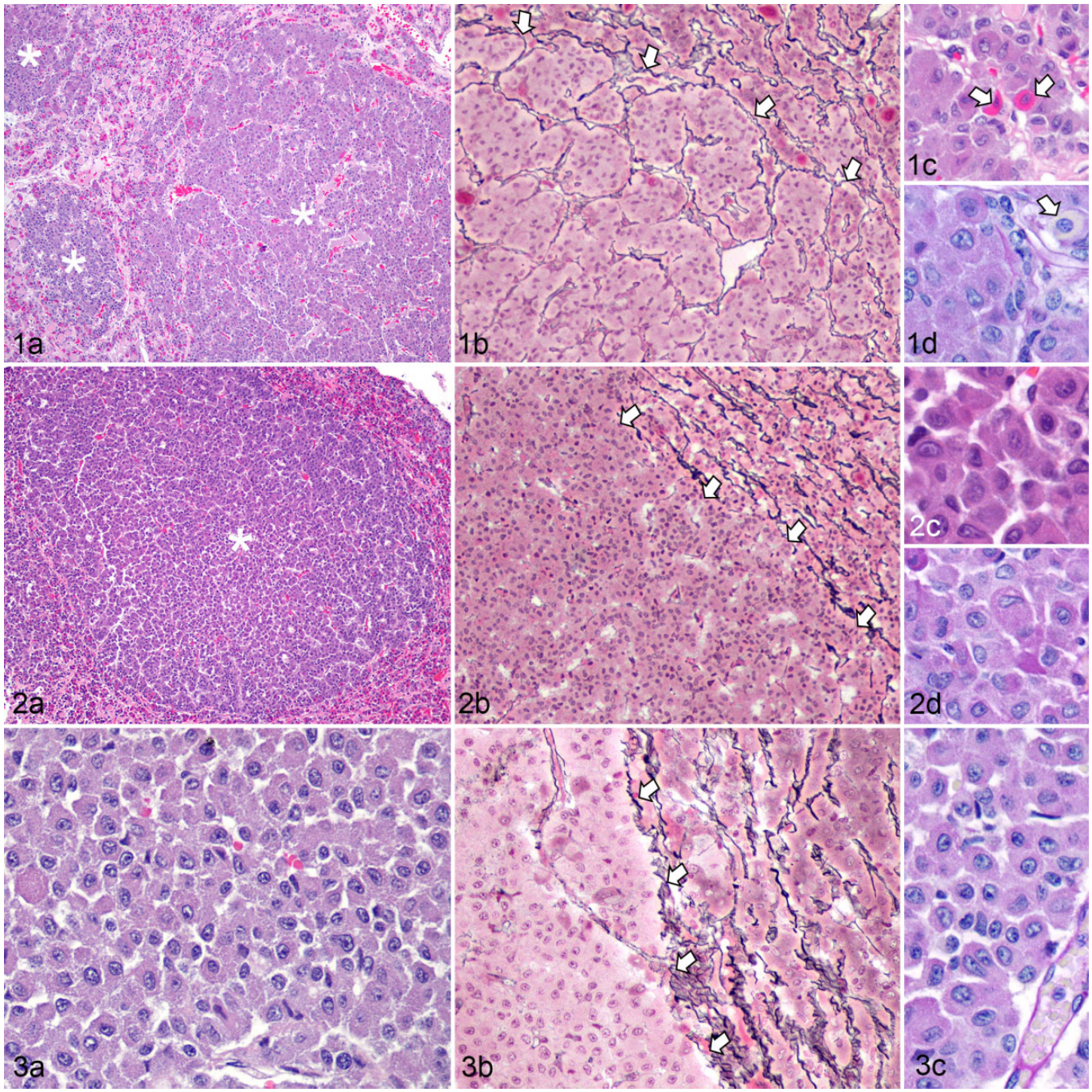
Results

Of the 234 archived canine pituitary specimens, 207 met the inclusion criteria. Of these pituitary glands, 196 were collected at autopsy and 11 were transsphenoidal hypophysectomy specimens. The histologic diagnoses are compared with signalment of the dogs in Table 2. In 92 (44%) dogs, the pituitary gland was histologically normal. Adenohypophyseal proliferation (hyperplasia, microadenoma, or macroadenoma) was the most common pituitary lesion, found in 79 (38%) dogs. Among dogs with adenohypophyseal proliferation, 36 (46%) had been considered histologically unremarkable on initial postmortem examination.

Adenohypophyseal proliferative lesions were classified as hyperplasia in 40 dogs (all examined postmortem), including 27 (60%) for which pituitary lesions were not recorded in the original histopathology report. Hyperplastic nodules (Fig. 1) typically appeared as multiple microscopic aggregates of hypertrophied cells with ample densely granulated basophilic cytoplasm; the cytoplasmic granules were PAS-positive and immunolabelled for ACTH. Most hyperplastic nodules contained a few scattered acidophils. The largest hyperplastic nodule was 2 mm in diameter (ie, larger than the smaller microadenomas), but was classified as hyperplasia rather than neoplasia because the reticulin network was expanded rather than disrupted, and because rare acidophils were scattered among the basophils.

Adenohypophyseal proliferations were classified as microadenoma in 22 pituitary glands (all examined postmortem), including 9 (41%) that had been considered unremarkable on the original examination. Microadenomas (Fig. 2) appeared as 1 or more homogeneous nodules of basophilic to chromophobic cells with exclusion of acidophils. The hypertrophied cells had densely granulated cytoplasm, and the granules were PAS- and ACTH-positive. Ten microadenomas were accompanied by 1 or more hyperplastic nodules. Mitotic figures were noted in only 1 microadenoma (1 per ten 400× fields).

Adenohypophyseal proliferations were classified as macroadenoma in 17 dogs. Of these, 10 were in hypophysectomy specimens, 4 were postmortem cases from PUVTH, and 3 were



Figures 1–3. Adenohypophyseal hyperplasia. a. The hyperplastic nodules (asterisks) are up to 1.3 mm in diameter and are composed of basophilic cells. Hematoxylin and eosin (HE). b. In the hyperplastic nodule (arrows), hypertrophied cells enlarge the acini, but the reticulin fiber network is intact. Nonproliferative adenohypophysis is in the upper right. Gordon and Sweet's reticulin stain. c. A few acidophils (arrows) are scattered among the basophils in the center of a hyperplastic nodule. HE. d. The hyperplastic corticotrophs have PAS-positive granules. An acidophil (arrow) in this hyperplastic nodule is PAS-negative. Periodic acid-Schiff (PAS). **Fig. 2.** Microadenoma, pituitary gland, dog. a. The microadenoma (asterisk) is 1.1 mm in diameter and consists of coalescing nests of basophilic cells. HE. b. In the microadenoma (arrows), the reticulin fiber network is lost. Nonproliferative adenohypophysis is in the upper right. Gordon and Sweet's reticulin. c. The adenoma consists of a homogeneous population of densely granulated cells. HE. d. The cytoplasmic granules are PAS-positive. PAS. **Fig. 3.** Macroadenoma, pituitary gland, dog. a. The adenoma consists of a sheet of basophilic cells. HE. b. The reticulin fiber network is lost in the adenoma (arrows). Nonproliferative adenohypophysis is compressed to the right. Gordon and Sweet's reticulin. c. The adenoma consists of a homogeneous population of densely granulated cells. The cytoplasmic granules are PAS-positive. PAS.

postmortem specimens from other clinics. One macroadenoma, a hypophysectomy specimen, was composed of pale acidophilic and sparsely granulated cells that immunolabeled for ACTH and for GH, and negative for MSH and prolactin; that dog had no evidence of hyperadrenocorticism or hypersomatotropism. One dog with PDH and a macroadenoma diagnosed by MR imaging alone was treated with the somatostatin analog pasireotide instead of hypophysectomy. Autopsy of this dog revealed severe pan-adenohypophyseal atrophy with no evidence of neoplastic tissue in histologic sections of pituitary gland. The remaining macroadenomas were composed of chromophobic to pale basophilic cells with sparsely to densely granulated cytoplasm (Fig. 3). Minimal to moderate nuclear atypia was noted in 4 cases, but mitotic figures were rare (0-1 per ten 400× fields) with the exception of 1 case with a mitotic index of 7. Necrosis with cholesterol granulomas and neutrophilic inflammation was observed in or adjacent to some macroadenomas.

Miscellaneous lesions included neoplasms other than pituitary adenoma, hypophysitis, and degeneration. Other pituitary, sellar, or secondary neoplasms were diagnosed in 16 dogs. One dog had a 2-mm-diameter pituicytoma in the pars nervosa. A suprasellar germ cell tumor (Fig. 4) was diagnosed in a 4-year-old dog. Craniopharyngioma was diagnosed in 2 dogs: 1 postmortem case (Fig. 5) and 1 hypophysectomy case. Secondary neoplasms included 3 metastatic carcinomas (urothelial carcinoma; Fig. 6), nasal carcinoma, and carcinoma of unknown origin), 4 lymphomas (each part of multicentric lymphoma; Fig. 7), 1 metastatic oral melanoma, local extension of 2 ependymomas, and 1 case each of oligodendroglial gliomatosis and meningioma.

Inflammatory or degenerative pituitary lesions were found in 8 dogs. Hypophysitis, diagnosed in 3 dogs, included 1 case each of systemic blastomycosis (Fig. 8), idiopathic granulomatous meningoencephalitis (GME), and idiopathic lymphocytic hypophysitis (Fig. 9). Hemorrhage and necrosis of unknown cause was the sole diagnosis in 4 dogs. Adenohypophyseal atrophy was diagnosed in 1 dog with bilateral adrenocortical carcinoma.

Craniopharyngeal duct cysts were diagnosed in 32 dogs, and were the sole pituitary lesion in 15. These cysts typically appeared in the pars intermedia as uni- to multilocular mucin-filled cysts, 1–5 mm in diameter, and lined by pseudostratified columnar epithelium with ciliated cells and goblet cells (Fig. 10). The cysts were not associated with clinical disease in any dog.

The frequency count (joint distribution) of pituitary histologic diagnosis by HAC clinical diagnosis in 129 dogs is summarized in Table 3. Medical records were reviewed for 118 PUVTH patients and for all 11 hypophysectomy cases. The pituitary histologic diagnosis was significantly ($P < .001$) associated with HAC. Overall, HAC was not suspected in 100, suspected but not confirmed in 18, and confirmed in 11 dogs. There was a positive trend between adenohypophyseal proliferation and HAC with increasing percentage of dogs with confirmed HAC as the degree of adenohypophyseal proliferation increased. Only 1 dog with a histologically normal pituitary gland had a confirmed diagnosis of HAC; this dog had adrenocortical nodular hyperplasia of unknown cause. Of the 3 PUVTH macroadenoma cases, HAC had not been suspected in 1, was suspected but not confirmed in 1, and was confirmed in 1 dog. Of the 11 hypophysectomy specimens (10 of which had pituitary macroadenoma), PDH had been confirmed in 6. Hyperadrenocorticism was not suspected in any of the PUVTH dogs with other pituitary neoplasms or nonproliferative pituitary lesions.

Adrenal gland sections from 35 dogs that had adenohypophyseal hyperplasia were classified histologically as within normal limits in 18 (51%) dogs, adrenocortical hyperplasia in 14 (40%), adrenocortical adenoma in 2 (accompanied by adrenocortical hyperplasia in 1 case), and adrenocortical carcinoma in 1 (3%). Adrenal sections from 21 dogs with pituitary microadenoma were classified as within normal limits in 5 (24%) dogs, adrenocortical hyperplasia in 12 (57%), adrenocortical adenoma in 2 (10%), and adrenocortical carcinoma in 2 (10%). All 4 pituitary macroadenoma cases in which adrenal gland was evaluated histologically had adrenocortical hyperplasia. The data suggested a significant ($P = .025$) monotonic association between adenohypophyseal proliferation and adrenocortical hyperplasia, in which 40% of dogs with adenohypophyseal hyperplasia, 57% of dogs with pituitary microadenoma, and 100% of dogs with pituitary macroadenoma had adrenocortical hyperplasia (Fig. 11). Dogs with adrenocortical hyperplasia or neoplasia were 5.7 times more likely to be suspected of having or confirmed to have HAC ($P = .035$), but the association between adrenocortical hyperplasia and HAC was not significant ($P = .077$).

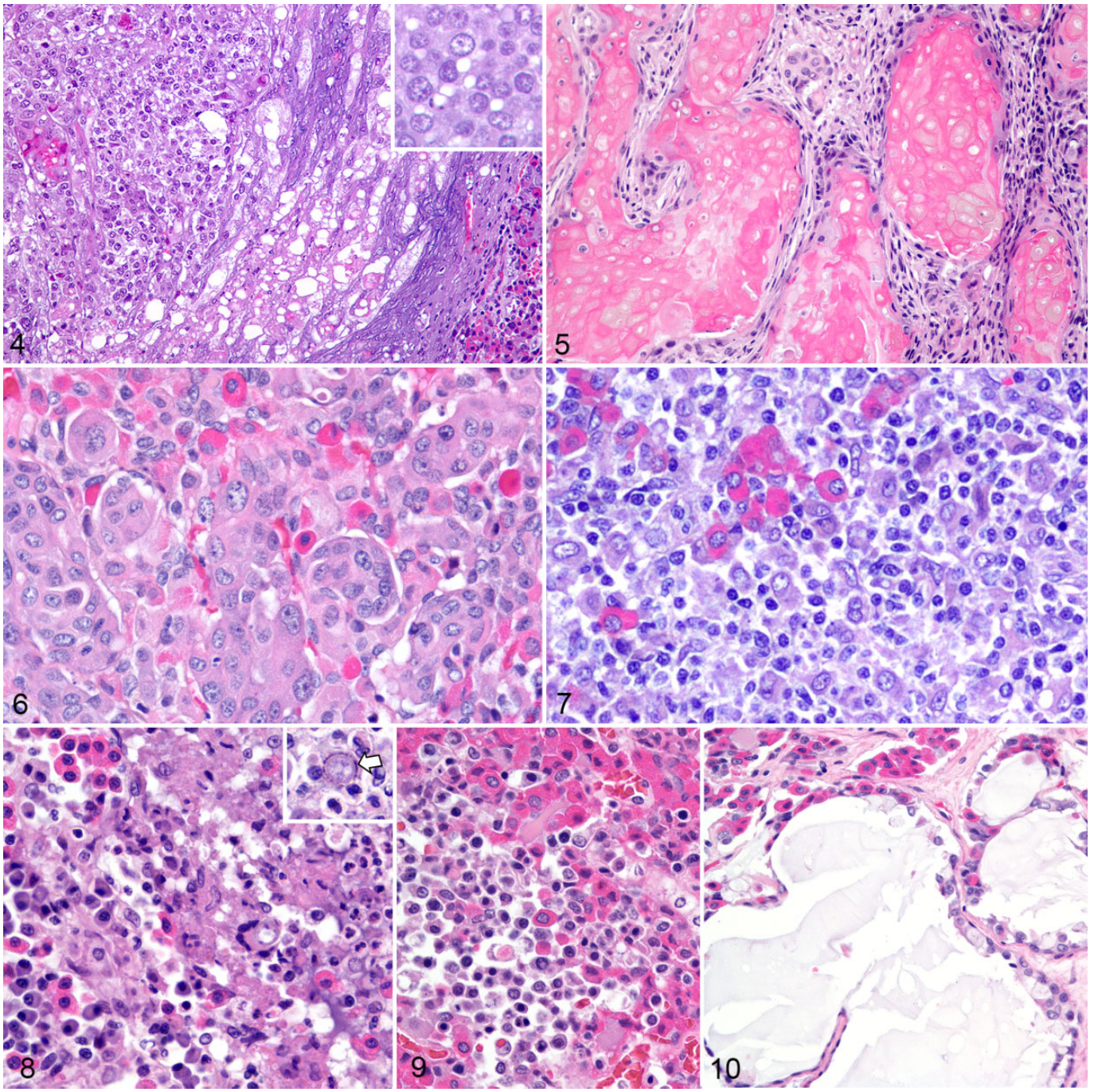
The age of dogs in the study ranged from 1 day to 17 years old with a median age of 9 years old. Age was significantly ($P < .001$) associated with pituitary histologic diagnosis (Table 2). Dogs with adenohypophyseal proliferation (hyperplasia or adenoma) were older than dogs in which the pituitary gland was within normal limits ($P < .05$). Age was also significantly associated with a diagnosis of HAC ($P = .026$), but not with adrenocortical hyperplasia ($P = .715$).

Brachycephalic breeds comprised 25 (12%) of the 207 dogs (Table 2). These were over-represented among dogs with pituitary macroadenoma or craniopharyngeal duct cysts, but the difference was not statistically significant ($P = .076$). There was no apparent association of brachycephalic phenotype with HAC ($P = .279$) or with adrenocortical hyperplasia ($P = .492$).

There were 115 female (81 spayed) and 92 male (59 castrated) dogs in the study (Table 2). No association of sex with pituitary histologic diagnosis ($P = .747$) or a clinical diagnosis of HAC ($P = .601$) was apparent, but sex was associated with adrenal histopathology ($P = .038$). The data suggested that male dogs were more likely to have a histologic diagnosis of adrenocortical hyperplasia.

Discussion

Greater than 50% of the archived canine pituitary glands had histologic changes. Adenohypophyseal proliferation was the most common lesion and occurred in older dogs without sex



Figures. 4–10. Suprasellar germ cell tumor, pituitary fossa, dog. The germ cell component is in the upper left; lipid-laden hepatoid cells in the middle, and compressed adenohypophysis in the bottom right. *Inset:* Detail of the seminoma-like germ cells. Hematoxylin and eosin (HE). **Fig. 5.** Craniopharyngioma, pituitary fossa, dog. The neoplastic tissue consists of coalescing nests of squamous epithelial cells in fibrous stroma. Anucleate, heavily keratinized "ghost" cells are in the center of the nests. HE. **Fig. 6.** Metastatic urothelial carcinoma, pituitary fossa, dog. The neoplastic urothelial cells form solid nests in the pars distalis. HE. **Fig. 7.** Multicentric lymphoma, pituitary gland, dog. The neoplastic lymphocytes are smaller than the basophils, acidophils, and chromophobes of the pars distalis. HE. **Fig. 8.** Systemic blastomycosis, pituitary gland, dog. Granulomatous inflammation with macrophages and neutrophils surrounded by lymphocytes and plasma cells. Inset: Detail of yeast of *Blastomyces dermatitidis*. HE. **Fig. 9.** Idiopathic hypophysitis, pituitary gland, dog. Lymphocytes and plasma cells infiltrate the pars distalis. HE. **Fig. 10.** Craniopharyngeal duct cyst, pituitary gland, dog. A multilocular cyst is lined by respiratory epithelium and filled with mucus. HE.

predilection. Brachycephalic dogs may have been more likely to have pituitary macroadenoma, which warrants further investigation. Hyperplastic nodules were more common than pituitary adenomas in the postmortem specimens and were composed of basophilic to chromophobic cells with acidophils lightly interspersed, whereas adenomas were a homogeneous

Table 3. Histologic Diagnosis in Canine Pituitary Glands with Clinical Diagnosis of Hyperadrenocorticism (n = 129).

Pituitary Histologic Diagnosis	HAC Not Suspected[a]	HAC Suspected[a]	HAC Confirmed[a]	Total
Within normal limits	43 (80%)	10 (19%)	1 (2%)	54 (100%)
Adenohypophyseal hyperplasia	19 (83%)	3 (13%)	1 (4%)	23 (100%)
Microadenoma	13 (68%)	4 (21%)	2 (11%)	19 (100%)
Macroadenoma	6 (43%)	1 (7%)	7 (50%)	14 (100%)
Miscellaneous[b]	10 (100%)	0 (0%)	0 (0%)	10 (100%)
Craniopharyngeal duct cysts[c]	9 (100%)	0 (0%)	0 (0%)	9 (100%)

Abbreviation: HAC, hyperadrenocorticism.
[a]See Materials and Methods for HAC diagnosis in 118 Purdue Veterinary Teaching Hospital dogs and 11 dogs treated by hypophysectomy.
[b]Miscellaneous diagnoses included other neoplasms (6 dogs) and inflammatory or degenerative lesions (4 dogs).
[c]This diagnosis was made in cases in which cysts ≥1 mm diameter were the sole pituitary lesion.

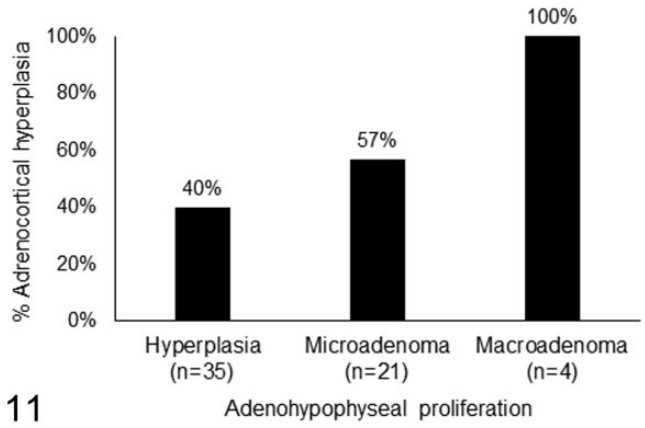


Figure 11. The association of adrenocortical hyperplasia with adenohypophyseal proliferation. The percentage of dogs with adrenocortical hyperplasia increased as the degree of adenohypophyseal proliferation increased from hyperplasia through microadenoma to macroadenoma.

proliferation of a single cell type. As in human pathology,[2,4] reticulin histochemistry highlighted the expansion of the reticulin network in adenohypophyseal hyperplasia versus its disruption in adenoma, and was particularly useful in distinguishing hyperplastic nodules that approached or exceeded 1 mm in diameter from small microadenomas. This distinction of hyperplasia from adenoma was particularly useful in hypophysectomy fragments, in which the diameter of a lesion was not apparent. Microadenomas were usually composed of densely granulated basophilic cells, whereas macroadenoma, the most common diagnosis in hypophysectomy specimens, tended to be less well granulated and more chromophobic.

In a 1967 review,[10] 61 of 67 previously reported canine pituitary neoplasms had been classified as basophil (23), chromophobe (20), acidophil (4), or unspecified, mixed or pars intermedia (14) adenomas. In the same article, 26 newly reported adenomas were classified with a broad histochemical panel as 20 chromophobe adenomas and 6 pars intermedia adenomas. The authors concluded that most canine pituitary adenomas were composed of chromophobic cells, and in contrast to previous reports, they had not encountered a canine basophil adenoma in their collective experience.

Although tinctorial classification of pituitary adenomas has been succeeded by immunohistochemistry for trophic hormone expression,[14,28,31] the term "chromophobe adenoma" has lingered in veterinary medicine as the expected appearance of corticotroph adenoma, perhaps because larger adenomas can be sparsely granulated and chromophobic. However, many nonneoplastic corticotrophs, those in hyperplastic nodules or microadenomas, and even many of those in macroadenomas in the current study were densely granulated and at least faintly basophilic with HE. Furthermore, neoplastic cells in hypophysectomy specimens of 46 canine pituitary adenomas, although described as chromophobic, often had fine basophilic granules.[20]

Human corticotroph microadenomas are typically composed of densely granulated cells; the granules are basophilic or amphophilic, PAS-positive, and strongly immunoreactive for ACTH.[31] In contrast, macroadenomas can be sparsely granulated and chromophobic.[2,4] In human chromophobic tumors, PAS-reactivity of the granules and immunoreactivity for ACTH are weaker, but still helpful in identifying the cells as corticotrophs.[2,29] However, canine melanotroph adenomas are also sparsely to densely granulated with weak to strong PAS and ACTH reactivity, so IHC for MSH is needed in a canine pituitary panel to distinguish melanotroph from corticotroph adenoma.

As in other studies,[10,14,28] adenohypophyseal hyperplasia and adenoma were the most common canine pituitary diagnoses, and other pituitary or sellar neoplasms (germ cell tumor, craniopharyngioma, secondary neoplasms, granular cell tumor, and pituicytoma) were rare. Corticotroph carcinoma with systemic metastasis has been reported in a dog,[13] but pituitary carcinoma of any type is exceedingly rare in any species,[4,14,29] and was not observed in the current study.

Only 3 cases of hypophysitis were recorded in the current study, and in 2 cases, inflammation was part of meningoencephalitis or systemic inflammation, in keeping with the literature.[28] Lymphocytic hypophysitis, seemingly primary, was observed in only 1 dog. Lymphocytic hypophysitis was diagnosed in a hypophysectomy specimen from a dog with diabetes insipidus and a pituitary mass.[18] Two postmortem cases of lymphocytic hypophysitis were accompanied by adrenalitis in 1 dog[1] and adrenocortical atrophy in the other.[32] Craniopharyngeal duct cysts were relatively common but seemingly incidental lesions of the pars intermedia in this and in other canine[14,20,28] or human[2,4] case series.

Though results of this study may not reflect the prevalence of pituitary disease in the general canine population, 35% of postmortem cases in which the pituitary gland was examined had adenohypophyseal proliferation, and 15% had pituitary adenoma. The prevalence of pituitary adenoma has been estimated at 14% in human postmortem studies.[12] Lactotroph adenoma is the most common (and often incidental) human pituitary adenoma encountered postmortem; however, lactotroph adenomas are usually treated medically and are rare among surgical specimens.[4,5,29,31] In most surgical case series, somatotroph adenomas and corticotroph adenomas each account for up to 15% of human pituitary adenomas.[4,29,31] Melanotroph adenomas are generally absent in human case series, but relatively common in dogs.[14,28]

In another canine study,[10] HAC was diagnosed in 14/20 dogs with chromophobe adenoma of the pars distalis and in 2/6 dogs with pars intermedia adenoma.

In the current study, HAC was confirmed in only a small proportion of the cases of adenohypophyseal proliferation, but was increasingly common with increasing degree of adenohypophyseal proliferation from no proliferation through hyperplasia, microadenoma, and macroadenoma. In elderly humans, corticotroph hyperplasia is also seldom associated with HAC, but in a few cases was the only adenohypophyseal lesion in patients with Cushing's disease.[30]

At autopsy of 318 laboratory beagles 6–17 years of age,[7] 10% had pituitary adenoma, and 17% had adrenocortical neoplasia. Approximately half those dogs with adenohypophyseal or adrenocortical neoplasia had pathologic or clinical features of HAC. In the current study, all 6 of the postmortem cases with confirmed HAC had adrenocortical hyperplasia or neoplasia.

Hyperplastic nodules or small microadenomas can be missed in the plane of section on histologic examination of pituitary specimens.[2,30] This could explain the absence of pituitary lesions in the current study in a dog with adrenocortical nodular hyperplasia and confirmed HAC. It is also possible that adrenocortical nodular hyperplasia, as opposed to diffuse adrenocortical hyperplasia, could be difficult to distinguish from a small adrenocortical adenoma.[8] Nevertheless, in the current study, the prevalence of adrenocortical hyperplasia increased with the increase in degree of adenohypophyseal proliferation from hyperplasia through microadenoma to macroadenoma.

In summary, adenohypophyseal proliferation was the most common canine pituitary lesion in this retrospective study. Hyperplastic nodules and adenomas were typically composed of basophilic to chromophobic cells with PAS-positive granules, consistent with origin from corticotrophs or melanotrophs. Reticulin histochemistry was used to accentuate the loss of the reticulin network in adenoma versus its preservation in hyperplasia, and this facilitated recognition of adenoma in fragmented hypophysectomy specimens. In postmortem specimens, a diagnosis of hyperplasia or microadenoma was more common, but pituitary macroadenoma was the most common diagnosis in biopsy specimens. Dogs with a histologic classification of adenohypophyseal proliferation were older and were more likely to have a clinical diagnosis of HAC or PDH. The association between adenohypophyseal proliferation and hyperadrenocorticism underscores the importance of distinguishing among hyperplasia, microadenoma, and macroadenoma.

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