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What Is Your Neurologic Diagnosis?

A 1-year-old 21-kg (46.2-lb) spayed female mixed-breed dog was evaluated at the Auburn University Small Animal Teaching Hospital because of a history of polyuria and polydipsia (each of 2 months' duration) and mentation change, ataxia, and depressed appetite (each of 1 month's duration). Prior to evaluation, the referring veterinarian had performed a thyroid hormone assessment, urinalysis, and water deprivation test. Serum total thyroxine concentration (0.5 ng/dL; reference interval, 1.0 to 4.0 ng/dL) and free thyroxine concentration (7.0 ng/dL; reference interval, 8.0 to 40 ng/dL) were low, and levothyroxine (400 µg, PO, q 12 h) was prescribed. The water deprivation test result indicated central diabetes insipidus as the cause of polyuria and polydipsia, and the dog was treated intraocularly with a nasal formulation of 0.01% desmopressin acetate (100 µg/mL). Analysis of a urine sample revealed specific gravity of 1.005, pH of 5.0, and no evidence of protein. Additionally, several small cutaneous masses were detected, and fine-needle aspirate specimens were obtained by the referring veterinarian. Cytologic evaluation of those specimens yielded a tentative diagnosis of benign histiocytomas.

Neurologic examination

Observation

Mental	Alert		Depressed	X	Disoriented		Stupor		Coma		
Posture	Normal	X	Head tilt		Tremor		Falling				
Gait	Normal		Ataxia	X	Pelvic limbs		All 4	X	Circling		
Paresis	Pelvic limbs		Tetra		Hemi		Mono				
Other	The dog had become aggressive toward the owner and was aggressive toward examiners.										

Key: 4 = Exaggerated, clonus; 3 = Exaggerated; 2 = Normal; 1 = Diminished; 0 = None; NE = Not evaluated.

Postural reactions

	LF	RF	LR	RR
Wheelbarrow	2	2		
Hopping	2	2	2	2
Ext postural thrust			2	2
Proprioceptive pos	2	2	2	2
Hemistand/walk	2	2	2	2
Placing–tactile	2	2		
Placing–visual	2	2		

Spinal reflexes

	LF	RF	LR	RR
Quadriceps			2	2
Extensor carpi	2	2		
Flexion	2	2	2	2
Crossed extensor	2	2	2	2
Perineal			2	2
Patella			2	2

Cranial nerves

	L	R
II, VII–Vision menace	1	1
II, III–Pupils resting	3	3
Stim L	2	2
Stim R	2	1
II–Fundus	2	2
III, IV, VI–Strabismus, resting	2	2
III, IV, VI, VIII–Strabismus, position	2	2

	L	R
VIII–Nystagmus, resting	2	2
VIII–Nystagmus, change	2	2
V–Sensation	2	1
VII–Facial mm	2	1
V, VII–Palpebral flex	2	2
IX, X–Gag	2	2
XII–Tongue	2	2

Comments CN

Mydriasis was observed bilaterally. There was reduced vision and menace response and decreased consensual pupillary light response of the right eye. Facial sensation in areas innervated by the right maxillary branch of the trigeminal nerve was decreased.

Sensation (Locate and describe abnormal)

Hyperesthesia	2	
Superficial pain	2	
Cutaneous reflex	2	
Deep pain	2	

What is the problem? Where is the lesion? What are the most probable causes of this problem? What is your plan to establish a diagnosis? Please turn the page.

Assessment

Anatomic diagnosis

Problem	Rule out location
Dull mental state with occasional aggressive outbursts	Cerebrum, diencephalon, midbrain, or pontomedullary region
Bilateral mydriasis with abnormal vision and menace response of the right eye	Left cerebrum, right cerebellum, or diencephalon
Facial sensation decreased in areas innervated by right maxillary branch of the trigeminal nerve	Pontomedullary region, central vestibular area, or right or left forebrain

Likely location of 1 lesion

Diencephalic syndrome with possible pontomedullary involvement

Etiologic diagnosis—The differential diagnoses for a 1- to 2-month history of polyuria and polydipsia, change in mentation, ataxia, and depressed appetite in a young dog included infectious or inflammatory diseases (eg, bacterial, protozoal, fungal, or immune-mediated) or neoplasia (histiocytoma, lymphoma, carcinoma, or other). The initial diagnostic plan included a CBC, serum biochemical panel, and assessment of titers of serum antibodies against canine distemper virus, tick-borne disease agents, and protozoal disease agents. These test findings were to be used to differentiate between systemic and localized disease. Given the dog's diagnoses of hypothyroidism and diabetes insipidus at such a young age, a pituitary lesion was first on the differential diagnosis list. Planned diagnostic imaging included thoracic radiography and MRI of the brain.

Diagnostic test findings—Results of the CBC and serum biochemical panel revealed no clinically important abnormalities. The dog was seronegative for the infectious diseases assessed. Three-view thoracic radiography revealed no notable abnormalities.

The dog was anesthetized and underwent MRI of the brain. T2-weighted, T1-weighted, fluid attenuated inversion recovery, T2*-gradient echo, and postcontrast T1-weighted images revealed a 2.3-cm-diameter mass dorsal to the pituitary fossa that was isointense (compared with gray matter) on T2-weighted images and hypointense (compared with surrounding brain tissue) on T1-weighted images. After IV administration of contrast medium, images revealed a moderate, mostly uniform enhancement of the mass with well-defined margins **(Figure 1)**. The mass appeared to extend into or originate from the pituitary fossa. In addition, the left frontal sinus contained a mass with similar signal characteristics and enhancement. The left frontal sinus was trephined and the mass within the sinus cavity was removed but clean margins could not be confirmed. Impression smears of the mass and tissue samples were preserved in formalin and submitted for cytologic and histologic examination, respectively.

In the impression smears, the predominant nucleated cells were large round cells with a round nucleus and a moderate amount of light blue cytoplasm that often contained a few crisp, clear vacuoles. The nuclei of these cells had a finely stippled chromatin pattern with 1 or 2 prominent nucleoli. A few binucleated cells and mitotic figures were seen. The cytologic findings were interpreted as a malignant round cell tumor with moderate lymphocytic inflammation. The appearance of the neoplastic cells was suggestive of transmissible venereal tumor (TVT). Differential diagnoses that would be considered less likely included histiocytic sarcoma, agranular mast cell tumor, amelanotic melanoma, or atypical lymphoma. Fine-needle aspirates were obtained from the subcutaneous masses previously aspirated by the referring veterinarian, and the cytologic findings were similar to those for the excised mass.

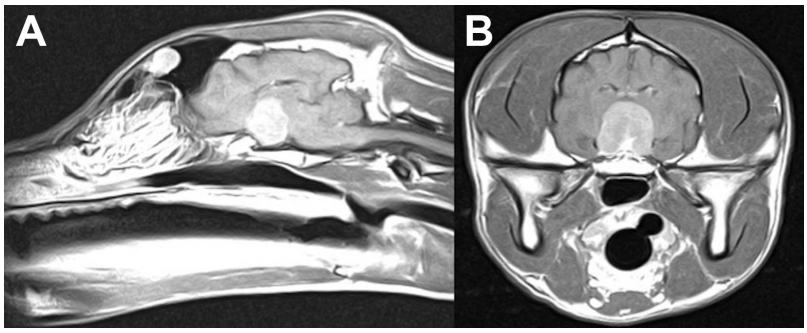

Figure 1—Sagittal (A) and transverse (B) postcontrast MRI images obtained from a 1-year-old dog that was evaluated because of a history of polyuria and polydipsia (2 months' duration) and mentation change, ataxia, and depressed appetite (1 month's duration). The images were obtained before treatment. Notice the approximately 2.3-cm-diameter mass that apparently originates from the region of the pituitary fossa and appears as an intra-axial mass. There is also a small contrast-enhanced mass in the frontal sinus. The frontal sinus mass was subsequently removed, and chemotherapy was instituted.

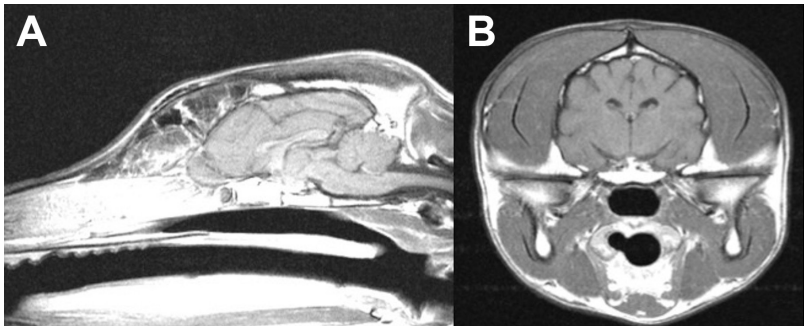

Figure 2—Sagittal (A) and transverse (B) post-contrast MRI images obtained from the dog in Figure 1 after treatment. These images were obtained 40 days after the original MRI images and following 4 treatments with vincristine. There is evidence of resolution of the intra-axial mass.

Microscopic examination of the fixed tissue samples revealed tumor cells separated into numerous tightly packed nests by a delicate fibrovascular stroma. Individual tumor cells had large, round, granular to vesicular central nuclei and moderate amounts of lightly eosinophilic, finely vacuolated cytoplasm. Mitotic activity was moderate to high with a mean mitotic rate of approximately 5 mitoses/hpf (400X). Immunocytochemically, the tumor cells were strongly positive for vimentin and were negative for CD79a, CD3, CD18, α1 anti-trypsin, and S-100; the cells failed to stain metachromatically with toluidine blue stain. The mass was infiltrated by large numbers of small, well-differentiated, CD3-positive T lymphocytes.

On the basis of the cytologic, histologic, and immunohistochemical findings, the top differential diagnoses for the dog of the present report were histiocytic sarcoma (HCS) and TVT. For this dog, a presumptive diagnosis of TVT was made. The TVT neoplastic cells have large nuclei, scant cytoplasm, a high mitotic index, and cellular monotony. Histiocytic sarcomas can have a similar appearance but in general do not have the same degree of cellular monotony. In addition, presence of the mass in the sinus cavity would be more unlikely for histiocytic sarcoma.

For canids with TVT, chemotherapy with vincristine (0.7 mg/m^2, IV, weekly including 2 treatments after resolution of lesions) has a very high cure rate.[1-3] Vincristine treatment was elected for this dog, the first dose of which was administered in the hospital; following the dog's discharge from the hospital (4 days after surgery), the referring veterinarian administered subsequent doses on a weekly basis. Oral administration of tramadol was instituted for postoperative pain control. The dog continued to receive levothyroxine and desmopressin at home.

One week after the first vincristine treatment, the owners reported the dog's mentation had changed from extreme lethargy back to its normal active state. Following the dog's fourth weekly vincristine injection, the dog was returned for reexamination and MRI of the head to determine the effect of treatment. A CBC revealed leukopenia (4,440 WBCs/µL [reference interval, 6,000 to 17,000 WBCs/µL]) with neutropenia (667 neutrophils/µL [reference interval, 3,000 to 11,400 neutrophils/µL]), most likely attributed to the vincristine chemotherapy. A serum biochemical panel revealed no clinically important abnormalities. The dog was anesthetized and underwent MRI of the head, which revealed thickening of the mucosal lining of the left frontal sinus, likely attributable to the surgical procedure. No other evidence of the sinus mass was observed. In addition, the previously observed large contrast-enhancing mass dorsal to the pituitary fossa was no longer present **(Figure 2)**. These findings indicated that vincristine therapy had effectively resulted in regression of the pituitary tumor and possible prevention of recurrence of the frontal sinus tumor. Furthermore, the small cutaneous nodules were no longer palpable.

Comments

Transmissible venereal tumors most commonly appear as genital ulcerative proliferations; however, they may metastasize on rare occasions. Extragenital cases are more uncommon.[4,5,6] In the case described in the present report, it was presumed that the dog became infected by sniffing the genitalia of a dog with TVT. The tumor cells reached the sinus mucosa, either by direct contact or through aerosolization. From there, the affected cells likely spread to cutaneous tissue via a hematogenous route and proliferated because of an impaired host immune system. By means of that hematogenous mechanism, the cells would have been able to penetrate the blood-brain barrier and proliferate within the brain parenchyma at the level of the pituitary gland. It is interesting to note this particular dog had no gross vaginal nor perianal lesions and had been spayed before its adoption from a local humane society. The initial diagnosis of benign histiocytomas within the skin may have been a misinterpreted cytologic evaluation.

In a telephone conversation with the owners approximately 10 years after the original diagnosis and treatment, the dog was reported to be doing well, had had no seizures or visual or behavioral issues, and had been kept indoors with constant interaction with the family, including young children. The only residual issue had been the need to continue treatment with desmopressin for diabetes insipidus.

References

1. Das U, Das AK. Review of canine transmissible venereal sarcoma. *Vet Res Commun* 2000;24:545–556.

2. Hantrakul S, Klangkaew N, Kunakornsawat S, et al. Clinical pharmacokinetics and effects of vincristine sulfate in dogs with transmissible venereal tumor (TVT). *J Vet Med Sci* 2014;76:1549–1553.
3. Vermooten MI. Canine transmissible venereal tumor (TVT): a review. *J S Afr Vet Assoc* 1987;58:147–150.
4. Boscos CM, Tontis DK, Samartzi FC. Cutaneous involvement of TVT in dogs: a report of two cases. *Canine Pract* 1999;24:6–10.
5. Papazoglou LG, Koutinas AF, Plevraki AG, et al. Primary intranasal transmissible venereal tumor in the dog: a retrospective study of six spontaneous cases. *J Vet Med A Physiol Pathol Clin Med* 2001;48:391–400.
6. Rani RU. Pazhanivel N. Rare cases of primary canine extragenital transmissible venereal tumours. *Int J Adv Vet Sci Tech* 2015;4:149–152.

This report was submitted by Jennifer J. Rich, DVM; Katie L. Simon, BS; Elizabeth A. Spangler, DVM, PhD; and Andy Shores, DVM, PhD; from the Veterinary Specialty Center and College of Veterinary Medicine, Mississippi State University, Mississippi State, MS 39762 (Rich, Simon, Shores); and College of Veterinary Medicine, Auburn University, Auburn, AL 36849 (Spangler).

Address correspondence to Ms. Simon (kls370@msstate.edu).

This feature is published in coordination with the American College of Veterinary Internal Medicine on behalf of the specialty of neurology. Contributors to this feature should contact Dr. Helen L. Simons (800-248-2862, ext 6692) for case submission forms. Submissions will be sent to Dr. Karen Kline, DVM, DACVIM, for her review, except when Dr. Kline is an author.