Goitrous hypothyroidism associated with treatment with trimethoprim-sulfamethoxazole in a young dog

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**Case Description**—A 16-week-old female Boxer that had been treated for 5 weeks with trimethoprim-sulfamethoxazole and chloramphenicol because of aspiration pneumonia was evaluated for bilaterally symmetric masses in the subcutaneous tissues of the ventral neck, in the region of the larynx.

**Clinical Findings**—Fine-needle aspirates were obtained from the neck masses; cytologic examination revealed well-differentiated thyroid epithelial tissue. A blood sample was collected for serum biochemical and thyroid function analyses. Mild hyperphosphatemia, severe hypercholesterolemia, mild hyperkalemia, and a mild increase in creatine kinase activity were identified. Serum concentration of total thyroxine was less than the lower reference limit, and that of thyroid-stimulating hormone was greater than the upper reference limit. Findings were consistent with a diagnosis of clinical hypothyroidism in a skeletally immature dog.

**Treatment and Outcome**—Treatment with trimethoprim-sulfamethoxazole was discontinued. The dog was reevaluated 3 weeks later, at which time the neck masses were markedly decreased in size. Serum concentrations of cholesterol and potassium were lower; serum concentrations of total thyroxine and thyroid-stimulating hormone were near or within respective reference ranges. Age-appropriate increases in serum phosphorus concentration and serum alkaline phosphatase activity were also detected.

**Clinical Relevance**—To the authors’ knowledge, this is the first report of antimicrobial-induced goiter in a dog. Cytologic examination of fine-needle aspirates and interpretation of data from serum biochemical and thyroid function analyses were needed to obtain a definitive diagnosis. Practitioners should include goiter among the differential diagnoses for ventral neck swellings in young dogs receiving potentiated sulfonamide antimicrobials. (J Am Vet Med Assoc 2008;232:1181–1185)

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**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>T-SMX</td>
<td>Trimethoprim-sulfamethoxazole</td>
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<tr>
<td>CK</td>
<td>Creatine kinase</td>
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<tr>
<td>TT₄</td>
<td>Total thyroxine</td>
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<tr>
<td>TSH</td>
<td>Thyroid-stimulating hormone</td>
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<td>ALP</td>
<td>Alkaline phosphatase</td>
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<td>TMS</td>
<td>Trimethoprim-sulfadiazine</td>
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<tr>
<td>HPTA</td>
<td>Hypothalamic-pituitary-thyroid axis</td>
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<td>TRH</td>
<td>Thyrotropin-releasing hormone</td>
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<tr>
<td>fT₄</td>
<td>Free thyroxine</td>
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A 10.7-kg (23.5-lb) 16-week-old sexually intact female Boxer was examined at a private veterinary clinic (Arapahoe Animal Hospital) for administration of routine vaccinations, reevaluation of aspiration pneumonia, and evaluation of newly identified swellings in the neck of the dog. Aspiration pneumonia had been diagnosed 5 weeks earlier on the basis of the findings of physical examination (tachypnea, fever, and mucoid nasal discharge) and thoracic radiograph analysis (patchy alveolar pattern in the ventral aspects of the cranial lobes of the lungs). Treatment with theophylline (14 mg/kg [6.7 mg/lb], PO, q 12 h), hydrocrodine (0.7 mg/kg [0.3 mg/lb], PO, q 24 h), chloramphenicol (20 mg/kg [9.1 mg/lb], PO, q 8 h), and T-SMX (30 mg/kg [13.6 mg/lb], PO, q 12 h) had been initiated. During the subsequent 5 weeks, in which chloramphenicol and T-SMX were continuously administered, all clinical signs of pneumonia gradually resolved. At reevaluation, the dog was bright, alert, responsive, and normothermic (38.2°C [100.8°F]). Physical examination detected 2 bilaterally symmetric, 3 × 3 × 3-cm, firm, and freely moveable subcutaneous masses within the jugular grooves, in the region of the larynx. The remaining physical examination findings were unremarkable. Fine-needle aspirates of the masses were obtained. Two slides were prepared from the aspirates and submitted to the Clinical Pathology Service at Colorado State University for cytologic evaluation.

For cytologic evaluation, slides were stained with a modified Wright-Giemsa stain. Microscopic analysis revealed the preparations were of moderate cellularity; each slide, nucleated cells predominantly consisted of a uniform population of minimally pleomorphic epithelial cells that were often grouped in small clusters (Figure 1).
Cells were polygonal to cuboidal in shape, with distinct cellular borders and detectable intercellular junctions. Cell nuclei were round, positioned slightly eccentrically, and contained evenly dispersed chromatin. Many cells contained granules and clumps of dark blue-to-gray intracytoplasmic pigment, which were interpreted to be tyrosine granules. Small numbers of disrupted cells were evident as free nuclei dispersed throughout the background of the specimen. The cytologic interpretation was thyroid epithelial tissue, with a tentative diagnosis of thyroid gland hyperplasia (goiter). Given the considerable cytomorphologic overlap between cytologically normal thyroid tissue, hyperplastic (goitrous) tissue, and neoplastic thyroid nodules, primary thyroid neoplasia and cytologically normal thyroid tissue were considered less likely differential diagnoses.

Because reduced thyroid function with compensatory goitrous enlargement was suspected, a blood sample was collected and submitted for serum biochemical and thyroid function analysis. At that time, serum biochemical abnormalities included mild hyperphosphatemia (6.8 mg/dL; reference range, 2.1 to 6.0 mg/dL), severe hypercholesterolemia (179 mg/dL; reference range, 130.0 to 300.0 mg/dL), a mild increase in CK activity (340 IU/L; reference range, 50 to 275 IU/L), and mild hyperkalemia (5.4 mEq/L; reference range, 3.5 to 5.2 mEq/L). Values of other serum biochemical analytes were within their respective reference ranges. Results of the thyroid function analysis revealed a low serum TT4 concentration (<0.4 µg/dL; reference range, 1.2 to 3.1 µg/dL) and high serum TSH concentration (7.10 ng/mL; reference range, 0.03 to 0.40 ng/mL).

On the basis of all available information, a diagnosis of sulfonamide-induced goitrous hypothyroidism was made, and treatment with T-SMX was immediately discontinued. Administration of chloramphenicol at the original dosage was continued for an additional 10 days without complication. Other causes of hypothyroidism (lymphocytic thyroiditis, idiopathic thyroid gland atrophy, hypothyroidism attributable to reduced secretion of TSH by the pituitary, or hypothyroidism secondary to concurrent illness) were considered less likely on the basis of the young age of the dog and lack of concurrent disease.

Three weeks after treatment with T-SMX was discontinued, the dog was reevaluated. Physical examination revealed the neck masses had decreased to approximately a third of their original size; no other physical abnormalities were detected. At that time, another blood sample was collected and submitted for serum biochemical and thyroid function analysis. Serum biochemical abnormalities included moderate hyperphosphatemia (8.8 mg/dL), mild hypercholesterolemia (317 mg/dL), mildly increased serum ALP activity (220 U/L; reference range, 20 to 142 U/L), and mild hypochloremia (107 mEq/L; reference range, 108 to 120 mEq/L). Values for other serum biochemical analytes were within their respective reference ranges. The second thyroid function analysis detected a mild increase in serum TT4 concentration (5.7 µg/dL) and an unremarkable serum TSH concentration (0.13 ng/mL). The diagnosis of sulfonamide-induced, goitrous hypothyroidism was confirmed on the basis of progressive resolution of the neck masses and decrease of the thyroid hormone values toward reference ranges after treatment with T-SMX was discontinued. Given the clinical response to cessation of treatment, surgical biopsy of the masses was deemed unnecessary.

Discussion

Potentiated sulfonamides are commonly used in veterinary medicine to treat a wide variety of bacterial infections. Two formulations are available: the proprietary compound (TMS®) and a generic form (T-SMX). Other than cost, these compounds are generally considered to be equivalent. The reported adverse effects of potentiated sulfonamides are numerous, varied, and id-
iodosyncratic and dose dependent in nature. Iodosyncratic reactions include gastrointestinal tract disorders, sterile polyarthritis, blood dyscrasias, hepatotoxicosis, fever, and skin eruptions. Apparent dose-dependent reactions include keratoconjunctivitis sicca, anemia, and impaired function of the thyroid gland.

To the authors’ knowledge, the dog described here is the first in which clinically evident goitrous hypothyroidism secondary to treatment with a potentiated sulfonamide antimicrobial has been reported. In contrast to the single report of an adult dog with sulfonamide-associated goitrous changes, in which only microscopic abnormalities were identified, the dog described here had macroscopically evident neck masses and supporting biochemical, hormonal, and cytopathologic data.

Adequate synthesis of thyroid hormones requires a functional HPTA and an appropriate amount of dietary iodine. When both factors exist, the hypothalamus synthesizes and secretes TRH, which stimulates the pituitary to synthesize TSH. Release of TSH stimulates follicular cells of the thyroid gland to generate the hormones triiodothyronine and T4 via a series of enzyme-mediated biochemical alterations to thyroglobulin, a scaffold protein secreted by thyroid follicular cells. The enzyme thyroid peroxidase, which catalyzes 2 important reactions in the biosynthesis of thyroid hormones, is an important component of this process. In turn, the 2 thyroid hormones provide negative feedback to the hypothalamus, which decreases the secretion of TRH.

Goiter is the clinical term for the nonneoplastic, noninflammatory enlargement of the thyroid gland secondary to insufficient synthesis of thyroid hormones. When thyroid hormones are deficient, negative feedback to the hypothalamus decreases, which results in compensatory increased secretion of TRH and TSH. When the HPTA is functioning, this increase can result in hyperplasia and hypertrophy of thyroid follicular cells and macroscopic (goitrous) enlargement of the thyroid gland. Pathophysiologically, goiter develops via many of the mechanisms that cause hypothyroidism, although in contrast to typical (nongoitrous) hypothyroidism, the development of goiter requires a functional HPTA. Three conditions can result in the development of goiter: exposure to substances that interfere with the synthesis of thyroid hormones (thyrotoxic or goitrogenic compounds), intake of abnormal amounts of dietary iodine (excess or deficiency), and congenital defects in the synthesis of thyroid hormones (congenital goiter).

Sulfonamides are believed to interfere with the biosynthesis of thyroid hormones through the reversible, dose-dependent, and duration-dependent inhibition of thyroid peroxidase. The disruption in hormone synthesis results in decreased serum concentrations of triiodothyronine and T4, reduced feedback to the hypothalamus, and increased growth of the thyroid gland. Humans are relatively insensitive to the thyrotoxic effects of potentiated sulfonamides; however, the goitrogenic effect of these compounds has been reported in rats, mice, and neonatal pigs. In addition to sulfonamides, several other drugs, including glucocorticoids, phenobarbital, propanolol, caprofen, and potassium bromide, can affect serum concentrations of thyroid hormones in dogs. None of these compounds were administered to the dog reported here. Moreover, the remaining therapeutic agents administered to this dog (chloramphenicol, hydrocortone, and theophylline) do not affect thyroid function, nor do they cause the biochemical alterations detected here.

Published reports regarding the impact of orally administered potentiated sulfonamides on thyroid function in dogs are somewhat contradictory, although the lack of agreement appears to reflect the apparent dose-dependent nature of the toxic effects. In 1 report, T-SMX administered to healthy dogs at a dosage of 15 mg/kg (6.8 mg/lb) every 12 hours for 4 weeks had no apparent effect on thyroid function. In 2 other reports, dosages of 14.1 to 16 mg/kg (6.4 to 7.3 mg/lb) and 26.5 to 31.3 mg/kg (12 to 14.2 mg/lb) every 12 hours for 3 and 6 weeks, respectively, resulted in low serum TT4 concentrations. Similar decreases in serum TT4 concentration were detected when T-SMX was administered to dogs with pyoderma at 30 mg/kg every 12 hours for 6 weeks. In addition to the effects of T-SMX on concentrations of circulating thyroid hormones, there are 2 reports in which the authors describe clinically evident hypothyroidism in dogs treated with T-SMX. In those reports, the hypothyroid condition resolved after treatment with sulfonamides was discontinued, although in some dogs, resolution required up to 12 weeks. In the dog reported here, serum concentrations of TT4 and TSH were within respective reference ranges 3 weeks after treatment with T-SMX was discontinued.

Most reported cases of goiter in dogs are congenital in origin, although dietary (iodine-deficient and iodine-excess) and drug-induced goiter have also been described. In 2 reports of dogs with congenital goiter, a nonsense mutation in the gene for thyroid peroxidase was identified. In the single previous report of drug-induced goiter, an adult dog treated with TMS (24.8 mg/kg [11.3 mg/lb], PO, q 12 h) because of bacterial pneumonia for 18 weeks subsequently developed clinical signs consistent with hypothyroidism. Serum TT4 concentration was undetectable, and response to a TSH stimulation test was negative. Histologic evaluation of a biopsy specimen obtained from an apparently unenlarged thyroid gland revealed histopathologic characteristics consistent with a diagnosis of diffuse hyperplastic goiter. Seven days after treatment with TMS was discontinued, serum TT4 concentration was within the reference range.

In the dog reported here, several biochemical abnormalities appeared to result from treatment with T-SMX, including effects attributable to the drug and those attributable to secondary hypothyroidism. The mild hyperkalemia appeared to reflect both because trimethoprim is a known direct inducer of potassium retention (due to inhibition of the amilorde-sensitive Na+ channel and inhibition of K+ secretion in the distal portion of the nephron), and experimentally induced hypothyroidism causes resting and exercise-induced serum potassium concentrations to increase in dogs. Hypercholesterolemia, which has been identified in 73% of hypothyroid dogs, has been attributed to reduced activities of hepatic and lipoprotein lipase. Additionally, elevations in serum CK activity have been reported in dogs and humans with hypothyroidism. In humans, these increases

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resolve with thyroid hormone supplementation. In the dog reported here, the restoration of serum potassium and cholesterol concentrations and serum CK activity to near or within respective reference ranges after treatment with T-SMX was discontinued supports the hypothesis that these abnormalities were attributable to drug-induced hypothyroidism.

In young, growing dogs, hyperphosphatemia and increases in ALP activity are common and expected findings that have been attributed to high circulating concentrations of growth hormone and high rates of osteogenic activity. Respectively. In the dog reported here, the minimal increase in serum phosphorus concentration and unremarkable serum ALP activity detected during the goitrous hypothyroid phase were inappropriate given the young age of the dog and may have indicated that hypothyroidism was retarding growth of the dog. Experimentally induced hypothyroidism in young dogs can result in defective bone remodeling and, similar to the results for the dog reported here, values of serum ALP activity and serum phosphorus concentration that are significantly lower than values in euthyroid dogs. The dog reported here, the increases in serum ALP activity and serum phosphorus concentration that were detected after thyroid function was restored supported the hypothesis that these were hypothyroid-induced abnormalities.

Hypothyroidism is diagnosed in dogs through evaluation of data obtained from patient history, physical examination, and hematologic assays (including evaluation of serum concentrations of T4 [free and total] and TSH). When each analyte is evaluated separately as a predictor of hypothyroidism, serum fT4 concentration is generally considered to be the most sensitive and specific predictor while serum TSH concentration is considered to be the least sensitive and specific. However, when a TSH assay is used in combination with a TT4 assay and the results are interpreted serially (ie, a positive result for both tests is required to conclude that a dog has hypothyroidism), the specificity of the results of this combination is comparable to results of the TT4 assay alone or to the serial interpretation of results from TT4 and TSH assays, all of which approach 100%. The development of goitrous masses in the dog reported here was unusual, particularly in light of the minimal serum phosphorus concentration and unremarkable serum ALP activity detected in euthyroid dogs.

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The dog reported here, whose hypothyroidism was confirmed by the restoration of serum TSH concentration to within the reference range after treatment with T-SMX, was the only dog in which similar dosages of T-SMX were discontinued made that possibility unlikely. Rather, we speculate that the development of the goitrous masses was largely attributable to the young age of the dog and consequent high demand for thyroid hormones.

On the basis of these findings, we concluded that goiter should be included in the list of differential diagnoses for ventral neck swellings in young dogs treated with potentiated sulfonamide antimicrobials.

References

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Selected abstract for JAVMA readers from the American Journal of Veterinary Research

Determination of reference intervals for plasma biochemical values in clinically normal adult domestic shorthair cats by use of a dry-slide biochemical analyzer
Brice S. Reynolds et al

Objective—To establish reference intervals of plasma biochemical values in healthy adult domestic shorthair (DSH) cats by use of controlled conditions.

Animals—95 healthy client-owned cats.

Procedures—Food was withheld from the cats overnight. All blood samples were obtained on the same day, at the same location, and by the same investigator. Blood samples were collected from a cephalic vein into lithium heparin tubes. After centrifugation of blood samples, plasma supernatants were harvested and stored at −20°C until assayed for total proteins, albumin, creatinine, urea, glucose, calcium, phosphates, sodium, chloride, potassium, and CO₂ concentrations and alkaline phosphatase and alanine aminotransferase activities.

Results—Reference intervals in healthy adult DSH cats were 65 to 85 g/L for total proteins, 27 to 39 g/L for albumin, 89 to 207 µmol/L for creatinine, 6.6 to 11.3 mmol/L for urea, 4.1 to 8.2 mmol/L for glucose, 2.4 to 2.9 mmol/L for calcium, 1.1 to 2.1 mmol/L for phosphates, 153 to 161 mmol/L for sodium, 120 to 127 mmol/L for chloride, 3.3 to 4.2 mmol/L for potassium, 15 to 21 mmol/L for CO₂, 32 to 147 U/L for alkaline phosphatase, and 34 to 123 U/L for alanine aminotransferase.

Conclusions and Clinical Relevance—This study provided reference intervals for plasma analytes in adult DSH cats. The influence of potential confounding factors was minimized through use of controlled preanalytic and analytic conditions. However, these results cannot be extrapolated to other feline breeds or used to interpret results from other biochemical analyzers. (Am J Vet Res 2008;69:471–477)