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Clinical Manifestation and Diagnosis of a Thyroid Adenoma in a 3-year-old Horse

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ABSTRACT
Hyperthyroidism in horses is a rare disorder in young horses that causes diverse findings such as weight loss, tachypnea, aggression, change in appetite and cachexia. In this report, the clinical manifestation and methods that used in the diagnosis of thyroid adenoma are presented. It was learned that a 3-year-old male Thoroughbred horse became aggressive and had been losing weight despite an adequate diet and appetite. During the inspection, a palpable, painless and moving mass was detected caudal to the larynx, on the left side. For further diagnosis, hemogram, serum biochemistry, urine dipstick analysis and ultrasonographic examination were performed. In serum biochemistry, high HDL, LDH, triglyceride, AST, direct bilirubin, creatine kinase and fT3; low TSH, fT4 and ferritin levels were determined. Ultrasonographic examination revealed that the left thyroid tissue was 2.83 cm x 4.81 cm in size. In the microscopic examination of the aspirate, it was observed that follicles were rich in cytoplasm and surrounded by cuboidal epithelial cells of varying sizes. Dilatation was observed in some follicles, while others were small or even atrophic. As a result, high fT3 and low TSH levels were consistent with the fact that the gland was overactive, the circulating thyroid hormone level was high, and the pineal gland produced less TSH by the feedback mechanism, all of which indicated hyperthyroidism. In addition, it was concluded that thyroid adenoma can also be seen in young horses, may cause clinical symptoms, ultrasonographic examination, microscopic examination of the aspirate and comprehensive serum biochemistry analysis are sufficient for diagnosis.
Keywords: Fine needle aspiration, Serum biochemistry, Diagnosis, Ultrasound.

3 Yaşındaki Bir Atta Tiroid Adenomunun Klinik Belirtileri ve Tanısı

ÖZ
Atlarda hipertiroidizm, zayıflama, taşipne, agresyon, iştahta değişim ve kaşeksi gibi çeşitli bulgulara sebep olan, genç atlarda nadir bir bozukluktur. Bu olgu sunumunda, tiroid adenomunun klinik tablosu ve tanısında kullanılan metotlar sunuldu. 3 yaşlı erkek Safkan atın dengeli besleme ve iştaha rağmen kilo kaybettiği ve agresifleştiği öğrenildi. İnspeksiyon sırasında larinksin kaudalinde, sol tarafta, palpe edilebilir, ağrısız ve hareketli bir kitle belirlendi. Daha ileri tanı için hemogram, serum biyokimyası, idrar dipstick analizi ve ultrasonografik muayenesi yapıldı. Serum biyokimyasında HDL, LDH, trigliserit, AST, direkt bilirubin, kreatin kinaz ve fT3 düzeyleri yüksek; TSH, fT4 ve ferritin düzeyleri ise düşük bulundu. Ultrasonografik muayenede ise sol tiroid dokusu 2.83 cm x 4.81 cm boyutundaydı. Aspiratın mikroskobik muayenesinde değişken boyutlarda küboidal epitel hücreleri ile çevrelenmiş sitoplazmadan zengin foliküller gözlendi. Bazı foliküllerde dilatasyon gözlenirken bazıları küçük hatta atrofikti. Sonuç olarak elde edilen yüksek fT3 ile düşük TSH düzeyleri, bezin aşırı aktif olduğunu, dolaşımdaki tiroid hormonu seviyesinin yüksek olduğu ve epifiz bezinin feedback mekanizması ile daha az TSH ürettiği, tüm bu durumun hipertiroidizmi gösterdiği gerçeği ile uyumluydu. Ayrıca tiroid adenomunun genç atlarda da görülebileceği, klinik semptomlara sebep olabileceği, ultrasonografik muayene, ince iğne aspirasyon tekniği ile alınan aspiratın mikroskobik muayenesi ile birlikte kapsamlı serum biyokimyası analizinin tanı için yeterli olduğu kanısına varıldı.
Anahtar Kelimeler: İnce iğne aspirasyonu, Serum biyokimyası, Tanı, Ultrason.

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INTRODUCTION

Thyroid dysfunction in adult horses is rare in general and its diagnosis is difficult due to its wide variety of clinical findings (Hines, Gay, & Talcott, 1997). The reason for this difficulty is that many endogenous and exogenous factors affect thyroid function. Also, serum thyroid hormone levels vary widely and basal levels can be misleading. Thus, many euthyroid horses are diagnosed as hypothyroid. In addition to the difficulty of diagnosis, it has been reported that 750 thousand American dollars are spent annually for the treatment of thyroid disorders (Sojka, 1995). Hyperthyroidism in horses is relatively rare and there are few reported cases in the literature. Clinical findings of hyperthyroidism include weight loss, tachypnea, bad coat structure, behavioral changes, changes in appetite, and cachexia (Breuhaus, 2011). Most cases of hyperthyroidism in horses are caused by an adenoma of the thyroid gland. However, adenomas and hyperplasia are not uncommon in older horses, and most thyroid tumors do not cause changes in serum thyroid hormone levels. Therefore, enlarged thyroid glands alone are not an indication for initiating treatment of hypo- or hyperthyroidism (Costello, Firshman, Brown, Maher, & Tadros, 2019).

Since the clinical manifestations of hyperthyroidism are non-specific, it should be differentiated from other common diseases such as muscle disorders causing weight loss, gastrointestinal absorptive disorders, liver disease, cardiac disorder, dental disease and malnutrition (Tsang & Houlden, 2009). Diagnostic suspicion of hyperthyroidism can be confirmed by the presence of consistent clinical findings, persistently elevated serum thyroid elevation, fine needle aspirate or biopsy examination, ultrasonographic examination of the thyroid gland, and non-suppression of T3 and T4 levels following T3 suppression testing (Costello et al., 2019). In this report, the clinical manifestation of thyroid adenoma, which is common in elderly horses and is generally inactive and does not cause clinical symptoms, and the methods that used in the diagnosis in a 3-year-old Thoroughbred horse are presented.

CASE DESCRIPTION

A 3-year-old male Thoroughbred horse, who had been suffering from weight loss for the last 3 months despite adequate and balanced nutrition and appetite, was admitted to the Animal Hospital of Faculty of Veterinary Medicine, Harran University. In the anamnesis, it was learned that the horse did not have a previous disease history, had recently become aggressive, and the consumption of water (average 50-55 liters/day) and feed (5.5-6 kg commercial ration and 12-13 kg hay/day) had increased. The clinical examination revealed an evident muscle wasting and weak body condition score (3/9). Physical examination findings were within reference (respiratory rate: 22/minute, body temperature: 38.2 °C, capillary refill time: <3 seconds) except tachypnea (76 bpm). During the inspection, a palpable, painless and moving mass was detected caudal to the larynx, on the left side, almost between the 3rd and 6th tracheal rings (Figure 1 A, B). No swelling or palpable tissue was observed on the right side. Palpation of the trachea was painless and no abnormal sound was detected during lung auscultation. On auscultation from the right fossa paralumbalis region, caecal contraction sounds were determined to be normal. Urine dipstick (Kruuse Vet-10 Urine Strips, Denmark) analysis results were normal. No dental equilibration was needed as the horse was routinely checked.

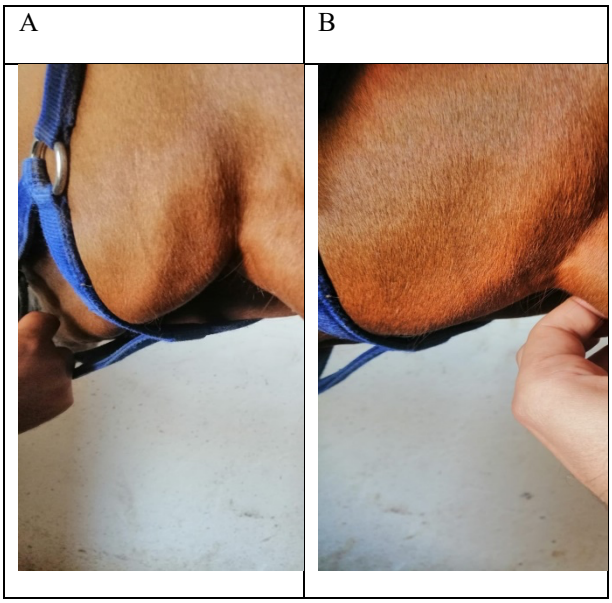

Figure 1. Appearance of the mass detected between the 3rd and 6th tracheal rings (A, B)

Serum biochemistry including hormone level measurements (from the serum samples obtained after a 5-minute centrifugation at 5000 g following a 1-hour clotting time using anticoagulant-free gel tubes) and hemogram analysis (using tubes with K_3EDTA) were performed from the venous blood sample taken with the jugular venepuncture technique with minimal patient stress. Published reports were used for reference values (Lumsden, Rowe, & Mullen, 1980), and in cases where data were not available, in-house laboratory test values were used. No remarkable abnormal results were detected in the hemogram analysis (Sysmex poch-100i, Sysmex®). In serum biochemistry analysis (Noahcali-100 Automatic Biochemistry Analyzer®), it was determined that high density lipoprotein (HDL) (46.2 mg/dL), LDH (228 U/L), triglyceride (24.6 mg/dL), AST (270 U/L), direct bilirubin (0.32 mg/L). dL), creatine kinase (134 U/L) and fT3 (7.32 pmol/L) levels were high whereas TSH (0.006 ng/mL), fT4 (8.96 pmol/L) and ferritin (0.5 mg/dL) levels were low (Table 1). Cervical, thoracic and abdominal ultrasonographic examinations (Mindray z-60®) were performed. The liver was normal in size and shape, although slightly hyperechoic. No abnormalities were observed in other abdominal organs. No abnormal bronchogram was detected in thoracic ultrasonography. In the cervical ultrasonographic examination, a focal and spherical mass with a size of 2.83 cm x 4.81 cm, consistent with the thyroid tissue, was

detected on the left side (Figure 2). The right thyroid tissue was 2.1 x 2.4 cm in size. Fine-needle aspiration from the hyperplasic thyroid gland was performed for diagnostic purposes, under the guidance of ultrasound and within the framework of the rules of asepsis and antisepsis. In the microscopic examination of the aspirate taken (Diff-Quick staining, x1000 magnification, light microscope, Olympus, BX-51®), follicles which were rich in cytoplasm surrounded by cuboidal epithelial cells of variable size were observed. Dilatation was observed in some follicles, while others were small or even atrophic. Large follicles had intraluminal papillary protrusions. The colloid structure of the small follicles had disappeared. Diffuse perifollicular hyperplasias were observed in clusters in C cells. Additionally, interstitial fibrosis was detected (Figure 3). Functional thyroid adenoma was diagnosed as a result of physical, laboratory, ultrasonographic and microscopic examinations of fine needle aspirate.

Table 1. Serum biochemistry results.

Parameters	Measured Values	Reference*
HDL↑	**46.2 mg/dL**	**19.44-24.84**
Iron	10.38 µmol/L	8.6-21.8
Potassium	4.54 mmol/L	3.5-5.5
LDH↑	**228 U/L**	**21-141**
LDL	19.2 mg/dL	46.8-54.24
Magnesium	2.2 mg/dL	2.2-2.7
Sodium	135.8 mmol/L	135-149
Phosphorous	2.80 mg/dL	0.8-1.3
Total protein	57.2 g/L	62.5-70
Triglyceride ↑	**24.6 mg/dL**	**0.18-7.74**
TSH↓	**0.006 ng/mL**	**0.02-0.97**
Amylase	3 U/L	1-144
AST↑	**270 U/L**	**80-250**
ALT	6.7 U/L	1-60
ALP	114 U/L	<250
Direct bilirubin↑	**0.32 mg/dL**	**0.04-0.16**
Total bilirubin	2.76 mg/dL	2.4-5
Calcium	2.91 mmol/L	2.5-4
Chlorine	99.5 mmol/L	90-105
Creatine kinase↑	**134 U/L**	**<50**
Creatinine	112 µmol/L	90-200
Ferritin↓	**0.5 ng/mL**	**1.19-1.85**
fT3↑	**7.32 pmol/L**	**1.7-5.2**
fT4↓	**8.96 pmol/L**	**7-47**
GGT	20 U/L	<40
Glucose	88.9 mg/dL	70-120

HDL: High density lipoprotein, LDH: Lactate dehydrogenase, LDL: Low density lipoprotein, TSH: Thyroid stimulating hormone, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, fT3: Free triiodothyronine, fT4: Free thyroxine, GGT: Gamma glutamyl transferase. *(Lumsden et al., 1980).

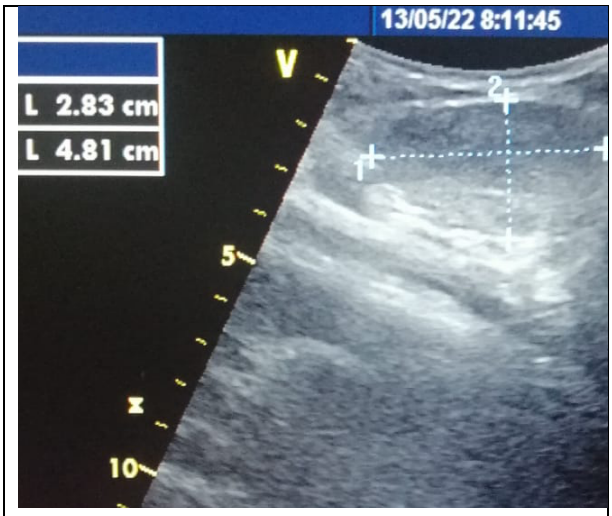

Figure 2. Ultrasonographic image of the hyperplasic thyroid gland (7.5 MHz, microconvex probe).

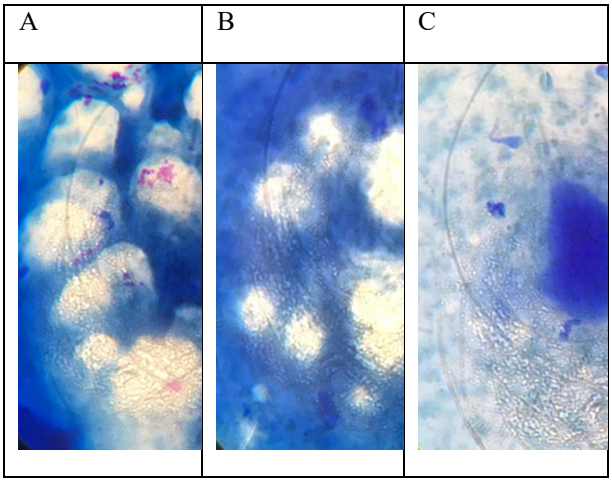

Figure 3. Microscopic image of the thyroid aspirate taken by the fine needle aspiration technique (Diff-Quick, x1000 magnification, light microscope).

(A) C-cell adenoma with small clusters and nests of tumor cells separated by fine fibrous stroma. The cells have abundant amphophilic cytoplasm. Residual follicles are still present from the original thyroid tissue.

(B) C-cell adenomas were discrete, expansile proliferations of clusters and lobules of fairly well differentiated C-cells, causing mild compression of adjacent thyroid gland follicular parenchyma.

(C) A focal proliferation of C cells is present. Contiguous nests of C cell surrounded by small follicles. High nuclear-to-cytoplasmic ratio is present in this focal proliferation.

DISCUSSION

Investigating thyroid dysfunction in horses compared to other types of animals is difficult due to the multisystemic and non-specific effects of thyroid

hormones, the low specificity of available function tests and the wide variety of extra-thyroidal factors that may cause dysfunction (Mooney & Murphy, 1995). In the previous reports, it has been reported that T4 levels are low in Thoroughbred horses at rest, and measurement of T4 level has been reported to be useful for the evaluation of thyroid function in Thoroughbred horses. In a more recent study, it was determined that thyroid hormone levels in Thoroughbred horses are lower than the reported reference values (Breuhaus, 2011; Mooney & Murphy, 1995). Although thyroid gland enlargement due to thyroid adenoma has been considered clinically insignificant in young horses until now, it can cause important clinical findings when it causes excessive thyroid hormone secretion in older horses (Tsang & Houlden, 2009).

Ultrasonographic examination of the thyroid gland is useful in evaluating the structure of the mass and evaluating the hypertrophy and atrophy of the thyroid and surrounding tissues. The normal equine thyroid gland is typically moderately echogenic and homogeneous. The thyroid gland is highly vascular and close to several large arteries and nerves. Therefore, it is important to evaluate the laryngeal function endoscopically before and after the operation in horses that will undergo thyroidectomy (Costello et al., 2019). In the present report, ultrasonographic examination revealed that the thyroid gland had a unilateral solid structure and some cystic areas, and these findings were consistent with the findings of adenomatous hyperplasia. In addition, increased echogenicity of the left thyroid lobe was interpreted as increased fibrosis. The intact capsular structure was compatible with the non-invasive neoplastic process (Tan, Davies, Crisman, Coyle, & Daniel, 2008). In the mammalian thyroid gland, the irregularly distributed cells are called parafollicular cells or C (calcitonin) cells. Abnormal proliferation of these cells can be classified as hyperplasia, adenoma and adenocarcinoma. In hyperplasic cases, the focal accumulations are smaller than the colloid-filled follicles, whereas in adenoma cases the lesions are nodular. Although the etiology of thyroid gland adenoma has not been fully elucidated, it has been reported that age, hypercalcemia, and calcitonin stimulating drugs may be effective (Capen, 2002). The characteristics of the thyroid lesion detected in the present report were unilateral, well circumscribed, and encapsulated, which were consistent with adenoma. In addition, the detected high fT3 and low TSH levels were consistent with the fact that the gland is overactive, the circulating thyroid hormone level is high, and the pineal gland produces less TSH with the feedback mechanism, all of which indicate hyperthyroidism (Tan et al., 2008).

Hypoferremia in horses may be due to two pathological conditions. These are; inflammation and iron deficiency. High ferritin level in cases of hyperthyroidism is directly related to the effect of thyroid hormones on ferritin synthesis. Low ferritin level in the present report may be associated with impaired iron utilization by erythropoietic cells along with normal hemogram findings (Kubota, Tamura, Kurabayashi, Shirakura, & Kobayashi, 1993).

Hyperbilirubinemia in horses, similar to other mammals, occurs when bilirubin formation exceeds excretion. However, unlike other domestic animals, anorexia contributes to hyperbilirubin formation in horses (Stockham, 1995). In addition, cholestasis may develop in cases of thyrotoxicosis, and the hypermetabolic state in hyperthyroidism may increase hepatic oxygen consumption without increasing hepatic blood flow. Elevated direct bilirubin levels in the present report may be associated with anorexia and increased hepatic oxygen consumption (Bal & Chawla, 2010).

In cases of hypothyroidism, HDL levels may be normal or increased. This finding is associated with a decrease in cholesteryl-ester transfer protein and hepatic lipase activities regulated by thyroid hormones (Duntas, 2002). Similarly, hypothyroidism is also associated with high triglyceride levels. In the present report, high HDL and triglyceride levels, which are detected in contrast to other reports of hyperthyroidism cases, may be related to hepatic lipase-mediated HDL2 catabolism and not yet increased CEPT-mediated cholesteryl ester transfer. In addition, high HDL level may be associated with anti-atherogenic function (Sigal et al., 2020).

Enzymes such as AST, LDH and creatine kinase, which have similar diagnostic importance in horses, are frequently used in serum biochemistry analyses and are generally used in the detection of hepatocellular diseases and muscle damage. The main sources of these enzymes are hepatocytes and skeletal or cardiac muscle fibers (Stockham, 1995). High AST, LDH and creatine kinase levels in the present report were associated with increased protein catabolism and the presence of hypermetabolic state in cases of hyperthyroidism (Ranka & Mathur, 2003).

In this report, although lack of echocardiographic examination of the heart and biopsy of hyperplasic thyroid gland can be counted as limitations, comprehensive serum biochemistry analysis along with the selected examination methods and techniques were sufficient for the diagnosis.

CONCLUSION

As a result, it was concluded that thyroid adenoma can also be seen in young horses, may cause clinical symptoms, and ultrasonographic examination, microscopic examination of the aspirate obtained by fine needle aspiration technique along with comprehensive serum biochemistry analysis are sufficient for diagnosis.

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Conflict of Interest

None.

Author Contributions
Plan, design: EG, AŞ; **Material, methods and data collection:** OÖ; **Data analysis and comments:** EG, AŞ; **Writing and corrections:** EG, AŞ, OÖ.

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