



## NOTE

Pathology

# Lymphocytic adrenal medullitis and lymphocytic thyroiditis in a laboratory beagle dog

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**ABSTRACT.** Lymphocytic adrenal medullitis characterized by inflammation and atrophy in the medulla of the bilateral adrenal glands was observed in an 18-month-old male laboratory beagle dog. It might be that the present lymphocytic adrenal medullitis is an autoimmune-mediated disease as the histological characteristics are consistent with an autoimmune pathogenesis. However, the actual cause remains unclear as the existence of serum autoantibodies against the adrenal medulla could not be confirmed. Although this dog also contracted lymphocytic thyroiditis along with serum thyroglobulin autoantibodies, indicating that the thyroiditis occurred with an autoimmune basis; the relation between the adrenal medullitis and thyroiditis is unknown.

**KEY WORDS:** autoantibody, beagle dog, lymphocytic adrenal medullitis, lymphocytic thyroiditis

There are very few reports describing adrenal medullitis in both human and veterinary medicine. Lymphocytic adrenal medullitis with a suspected autoimmune basis has been reported in 20% of the human insulin-dependent diabetes mellitus (IDDM) subjects [2]. In addition, lymphocytic inflammation of the adrenal medulla, adrenal cortex, pancreas and thyroid gland, suggestive of autoimmune polyendocrine syndrome (APS), has been reported in a mare with IDDM [3]. To our knowledge; however, there has been no report describing adrenal medullitis in dogs. We encountered an 18-month-old male laboratory beagle dog with lymphocytic adrenal medullitis, as well as lymphocytic thyroiditis. This report describes the histological characteristics of the present case and discusses the autoimmune basis as the possible pathogenesis.

This dog was purchased from Covance Research Products Inc. (Cumberland, VA, U.S.A.) at 6 months of age and orally administered distilled water from the age of 7 months to 19 months (for 52 weeks) in a background data accumulation study. The dog was housed individually in a metal cage (650 × 800 × 650 mm) in a conventional air-conditioned room at 19 to 25°C with 35 to 75% relative humidity and a 12-hr light/dark cycle. It was provided daily with 300 g of commercially available food (DS-A, Oriental Yeast, Tokyo, Japan) and allowed free access to drinking water. Moreover, it was cared for according to the principles outlined in the guides for the care and use of laboratory animals prepared by the Japanese Association for Laboratory Animal Science and our institution.

No remarkable clinical symptoms in the administration period or gross abnormalities at necropsy were noted. After the necropsy, all sampled organs and tissues were fixed in 10% phosphate-buffered formalin solution and subjected to a routine histological examination using hematoxylin and eosin (HE) stain. Frozen sections of the adrenal gland prepared from a normal beagle dog purchased from Covance Research Products Inc. were used to investigate the presence of autoantibodies against the adrenal medulla in the serum by indirect immunohistochemical staining. The serum of the present case at 16 months of age was used. The avidin-biotin-peroxidase complex (ABC) method was used with a secondary antibody (biotin conjugated affinity purified anti-dog IgG [H&L] [rabbit]; Rockland immunochemicals, Limerick, PA, U.S.A.) and a peroxidase conjugated streptavidin (Nichirei biosciences, Tokyo, Japan). Serum thyroglobulin autoantibody (TgAA) was analyzed by the enzyme-linked immunosorbent assay (ELISA), and serum levels of thyroid stimulating hormone (TSH) and total thyroxine (T4) were measured by the chemiluminescent enzyme immuno assay (CLEIA), using serum sample of the present case at 17 months of age, at IDEXX Laboratories (Tokyo, Japan).

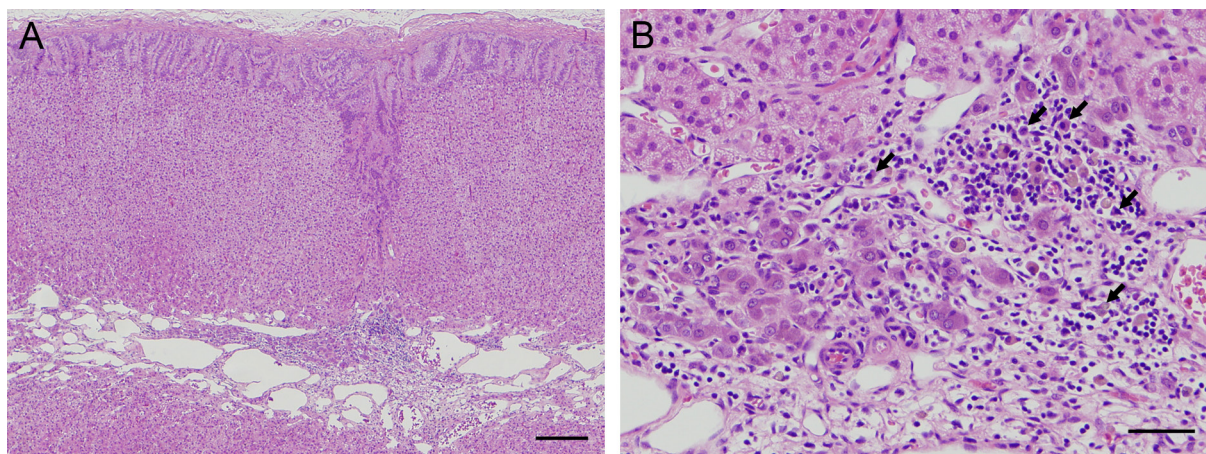
In the adrenal gland, the total bilateral weight was 912 mg, which was slightly lower than the mean value in this study (1,260.2

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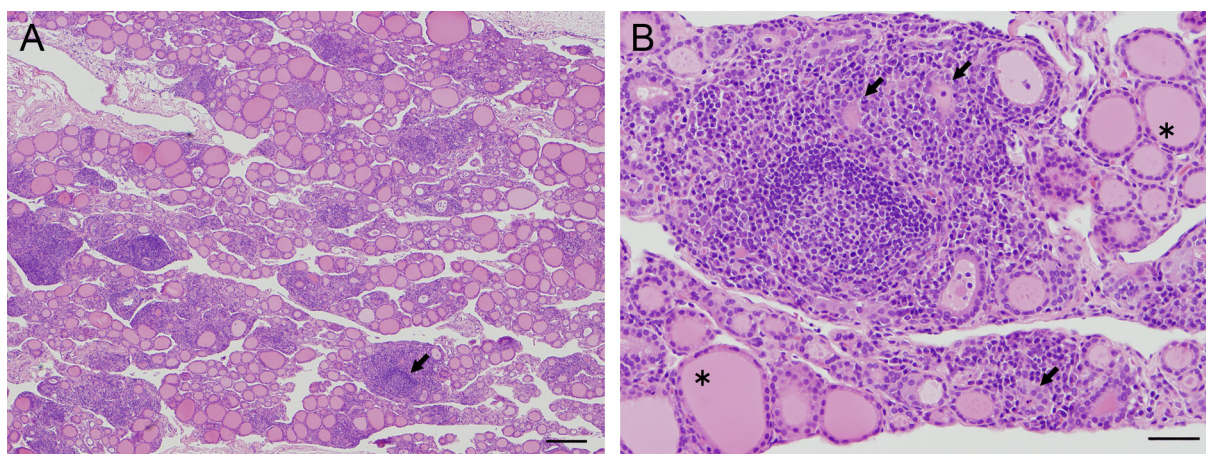
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**Fig. 1.** Adrenal gland. (A) The atrophied medulla consists of a very small number of chromaffin cells and dilated capillaries. HE. Bar, 200  $\mu$ m. (B) A small number of lymphoplasmacytes infiltrate in the medulla containing the clusters of remaining chromaffin cells including some shrunken cells (arrows). HE. Bar, 50  $\mu$ m.



**Fig. 2.** Thyroid gland. (A) A large number of lymphoplasmacytes infiltrate in the interstitium and thyroid follicles in approximately 50% of the thyroid mass. Lymph follicle with germinal center (arrow) is found. HE. Bar, 200  $\mu$ m. (B) Thyroid follicles at the inflamed area are small with a decrease in colloid (arrows), whereas those at the non-inflamed area are morphologically normal (asterisks). HE. Bar, 50  $\mu$ m.

$\pm 227.6$  mg, mean  $\pm$  SD). The cut surface revealed a narrowing of the medulla. In the histopathology, the medulla atrophied and consisted of a very small number of chromaffin cells and dilated capillaries (Fig. 1A). Although lymphocytes, plasma cells and macrophages infiltrated in the narrow medulla containing the clusters of remaining chromaffin cells including some shrunken cells (Fig. 1B), the number of inflammatory cells was very small. The adrenal cortex remained unaffected. Immunohistochemical staining using the serum of the present case against the adrenal gland tissue of the normal dog could not demonstrate the existence of autoantibodies against the adrenal medulla. In the thyroid gland, no remarkable abnormalities were observed in the organ weight or gross observation. However, in the histopathology, a large number of lymphocytes infiltrated and accumulated as well as plasma cells and macrophages in the interstitium and thyroid follicles up to approximately 50% of the thyroid mass, with lymph follicles present sporadically with germinal center (Fig. 2A). The thyroid follicles at the inflamed area were small with a decrease in colloid, whereas those at the non-inflamed area were morphologically normal (Fig. 2B). Although serum TgAA was detected (115%; positive cut-off, >10%), serum TSH or T4 level was normal (2.3  $\mu$ g/dl or 0.08 ng/ml; normal range, 0.9–4.4  $\mu$ g/dl or 0.02–0.32 ng/ml). No remarkable changes were observed in any other organs or tissues.

We diagnosed the present case as lymphocytic adrenal medullitis and lymphocytic thyroiditis. To our knowledge, this is the first report describing adrenal medullitis in dogs. Lymphocytic inflammation of the adrenal medulla suggestive of autoimmunity and high prevalence of serum autoantibody against the adrenal medulla occurred in IDDM subjects have been reported in a mare and humans [1–3, 5]. The following histological characteristics of the present adrenal medullitis were consistent with an autoimmune pathogenesis; (1) lymphocytic inflammation and atrophy (chromaffin cell depletion) were found in the medulla, (2) lymphocytes,



plasma cells and macrophages mainly infiltrated in the clusters of remaining chromaffin cells, and (3) the adrenal cortex remained unaffected. In the present case; however, the existence of serum autoantibodies against the adrenal medulla could not be confirmed, and the actual cause of the present adrenal medullitis remains unclear. Moreover, the present case was not affected with IDDM, being different from the previous cases of a mare and humans.

The detection of serum TgAA demonstrates that lymphocytic thyroiditis in the present case occurred with an autoimmune basis, and it is suggested that the present thyroiditis is in an early stage because the serum T4 and TSH levels were normal with approximately 50% of the thyroid mass showing normal histological appearance [4].

According to some reports, it is not always possible to confirm the existence of autoantibodies against the affected tissues in autoimmune mediated diseases [4, 6–8]. Autoantibodies against adrenocortical cells cannot be detected in 30% of idiopathic Addison's disease in humans, and it is suspected that a decrease in serum autoantibodies occurs with progressive destruction of the tissue [7]. Similarly, the TgAA level is not always high in the end-stage lymphocytic thyroiditis [4]. In the present case, the adrenal medulla consisted of a very small number of chromaffin cells and lymphoplasmacytic inflammatory cells, suggesting the end-stage adrenal medullitis. Therefore, it might be that serum autoantibodies against the adrenal medulla were not elevated enough to be detectable immunohistochemically at 16 months of age (one month before necropsy) due to a decrease in the serum autoantibodies along with the progressive destruction of the tissue. Ultimately, the relation between adrenal medullitis and thyroiditis still remains unknown for the following three reasons; (1) no serum autoantibodies against the adrenal medulla, (2) occasional occurrence of thyroiditis in beagle dogs and (3) no previous reports of APS involving the adrenal medulla and thyroid of dogs.

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