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Toxoplasmosis as a cause of subacute thyroiditis in dogs (La toxoplasmosis como causa de tiroiditis subaguda en el perro)

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Resúmen
La tiroiditis subaguda es causada por la acción de agentes infecciosos. Clínicamente se observa bocio, disfonía y disfagia. Respecto a la función tiroidea, puede haber hipertirotoxinemia debida a la ruptura de folículos, en tanto que la concentración de TSH se mantiene normal y la captación de yodo está disminuída. El objetivo del presente trabajo fue investigar si la toxoplasmosis en perros puede afectar la morfología y función tiroidea. Se estudiaron 8 perros con toxoplasmosis comprobada (título de anticuerpos por aglutinación directa [AD] > 1/128). La palpación tiroidea impresionó bocio, confirmado por ecografía de la glándula. La medición de TSH fue normal, en tanto que la tiroxina resultó normal en 4 casos, elevada en 3 y disminuída en un caso, sin signos de tirotoxicosis ni de hipotiroidismo respectivamente. Los perros fueron tratados con clindanmicina (12,5 mg/kg oral cada 12 hs) por 30 días, siendo reevaluada la función y morfología tiroidea. En los 8 casos hubo remisión de los signos tiroideos y normalización de la tiroxina, al igual que la signología clínica. Se halló una correlación positiva entre título de anticuerpos AD y el volúmen tiroideo (r = 0,78, p<0,0002) y la tiroxina (r = 0,77, p<0,002). A los 6 meses del tratamiento, 2 casos evolucionaron hacia el hipotiroidismo, pese a haber estado eutiroideos durante el período agudo de la toxoplasmosis, siendo su causa la tiroiditis autoinmune de aparición ulterior (anticuerpo antitiroglobulina >160 %). Se concluye que la toxoplasmosis afecta la morfología tiroidea pudiéndose alterar su funcionamiento y desencadenar tiroiditis autoinmune en individuos predispuestos.
Palabras Clave: bocio | tiroiditis | toxoplasmosis | tiroides.

Abstract
Subacute thyroiditis is caused by the action of infectious agents Clinically, goitre, dysphonia and dysphagia can be observed. Hyperthyroxinemia may be present, while thyrotropine (TSH) concentration stays normal and iodine uptake is reduced frequently. The objective of the present work was to investigate if toxoplasmosis in dogs can affect thyroid morphology and function. The study was conducted on eight dogs with proven high *T. gondii* titres (Direct aglutination <1/128). Goitre was confirmed by ultrasound of the gland. TSH measurement was normal, and thyroxine resulted normal in four cases, high in three and low in one case. The dogs were treated with clindamycin (12.5 mg/kg/twice a day PO) for 30 days. Positive correlations were found between the titre of antibodies and the thyroid volume (r = 0.78, P< 0.0002) and thyroxine (r = 0.77, P< 0.002). After six months treatment, two cases developed hypothyroidism due to autoimmune thyroiditis (thyroglobulin antibody >160%) in spite of being euthyroid during the acute period of toxoplasmosis. In conclusion, toxoplasmosis affects the thyroid morphology, being

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able to alter its function with the development of autoimmune thyroiditis in susceptible individuals.

Keywords*:* goitre | thyroiditis | toxoplasmosis | thyroids.

INTRODUCTION

Inflammation of the thyroid tissue is called thyroiditis. According to its aetiology, thyroiditis can be classified into autoimmune (autoimmune thyroiditis) and non autoimmune (including acute, subacute and chronic thyroiditis). In human each of these types can be characterized by its clinical development and the aetiological agents it is caused by (Reed Larsen et al., 1998). Subacute thyroiditis (ST) usually presents the following clinical signs: sudden mild to moderate pain in the upper and ventral third of the neck, corresponding to the laryngopharyngeal and tracheal area, dysphagia, dysphonia, and occasionally a cough, the latter also of sudden occurrence.

A study of the thyroid function reveals a normal or slightly low concentration of thyrotropine (TSH), normal or slightly high levels of thyroxine (T_4), caused by the rupture or loss of thyroid follicles, thus depleting any reserve of hormones stored in the colloid of the thyroid follicles. Iodine up-take is frequently reduced (hypocaptating), whereas on ultrasound there is an enhancement of the gland volume with mainly hypoechogenic images due to the inflammation (Reed Larsen et al., 1998). There are not report about subacute thyroiditis (not autoimmune) in dogs.

Systemic viral infections or post vaccination reactions have been described as causes of ST.

But the effects in thyroid function following natural infestation by the protozoa *Toxoplasma gondii* (*T. gondii*) and *Neospora caninum* have not been described in dogs. Stahl and Kaneda (1998a, b) describe that thyroid dysfunction occurs in mice experimentally infected with *Toxoplasma gondii*. Toxoplasmosis is a frequent infestation in dogs which are or have been occasionally fed on bovine raw meat (carry the oocysts) or in dogs which live with or near cats and are used to eating their faeces. Neuromuscular signs, such as ataxia, muscle atrophy or even paresis and convulsions, are typical of the acute phase of the disease (Taboada and Merchant, 1997). The diagnosis of this pathology is usually performed by the titre of antibodies against *T. gondii.*

The purpose of the present study was to investigate whether the thyroid gland in dogs infected by *T. gondii* might be affected, both in its morphology and in its function and if such a disorder was permanent, transitory or if it might appear later, as an after-effect of toxoplasmosis.

MATERIALS AND METHODS

Study population

The study was conducted on eight dogs weighing (median and range) 24 kg (18 -30 kg), 5 male and 3 female, which were derived to Endocrinology Unit from the Clinical Area of the School Hospital of the Veterinary School (UBA) with previous

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diagnostic of toxoplasmosis. he dogs did not have received any treatment previously.

The serological study for the diagnosis of toxoplasmosis (methodology developed by Instituto de Zoonosis "L. Pasteur", Buenos Aires, Arg.) was performed by the measurement of the titre of antibodies against *T. gondii* by direct agglutination method (DA, normal less than 1/54) with mercaptoethanol, which indicates current infection, and by indirect immunofluorescence (IIF, normal less than 1/128), which shows past infection or previous contact with protozoa. Should the result be negative with DA, the test would be repeated in 15 days, and a second negative result would refute the disease. The titre was repeated post treatment (30 days), and once more after 6 months of treatment (in this measurement the result is expressed as < 1/54 in normal cases and with the exact value in those cases above that value).

The thyroid area was palpated and findings suggested both enlarged thyroid glands (goitre) and a tense glandular consistency in every case (Castillo & Mazzini, 1998)

Biochemical-endocrine studies

TSH concentration (ng/mL) was measured by IRMA (immunoradiometric assay) methodology, using the specific canine kit (cTSH – IRMA, DPC). The free fraction of T_4 was measured (FT_4; ng/dL) by the equilibrium of dialysis method. Both studies were conducted at the time of the toxoplasmosis diagnosis (basal), after 30 days (2^{nd} measurement) and six months post treatment (3^{rd} measurement). Only the cases with values below or above the normal reference range were subject to this last measurement.

The antithyroglobulin antibody (Tg Ab) was determined by the ELISA method (Oxford) at the same time as the hormones. Its values are expressed as below or above 150 % (with or without present Tg Ab). A value >150% shows autoimmune thyroiditis.

Image Studies

(a) Ultrasound: a 7.5 mHz transducer was used, with longitudinal (assessment of longitudinal diameters and width) and transverse (assessment of thickness) exploration. With these three measures, the total thyroid volume was calculated (TTV, cm^3) according to the Rezzónico formula (Rezzónico et al., 1994), where:

Thyroid volume = left lobe volume (LL) + right lobe volume (RL)
Volume of each lobe = longitudinal diameter X transverse diameter X thickness X 0.523=
where 0.523 = correction of the thyroid ellipsoid model (3.14/6), and the size for each lobe are expressed as cm^3 .
The ultrasound was performed: basal time, 30 days and 6 month post-treatment by the same operator. The reference range of total thyroid volume by dogs ≥ 20 kg is 0.8 cc to 1.8 cc (values obtained from the Endocrinology and Imagenology Units of the School Hospital of Veterinary-UBA). The 6- month results are only expressed if they are above or below the reference range (showing goitre and thyroid atrophy

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respectively).

(b) Thyroid scintigraphy: it was conducted in gamma camera using pertechnetate 99 (^{99}Tc) as radiotracer, measuring the tracer activity 15 minutes after the subcutaneous injection of 15 mCi. The scintigraphy was performed at the time of diagnosis and at the end of the treatment

Toxoplasmosis treatment
Dogs were treated with clindamycin in 12.5 mg/kg oral doses every 12 h during 30 days was prescribed.

If there were either an increase or decrease in T_4 by cause the illness, not antithyroid drugs nor levothryroxine would be prescribed in order to evaluated if the changes observed in the thyroid status are caused by *T. gondii* and resolving with clyndamycin. Although treatment with glucocorticoids are usually advised due to their anti-inflammatory effect (Reed Larsen et al., 1998), these were not prescribed to avoid their immunosuppressive effect.

Statistical analysis

The results are expressed in medians and ranges (Me; x-x). The mean difference was made by the Mann-Whitney test for non paired samples with a significance level of $P< 0.05$. The Spearman correlation analysis (r, $P < 0.05$) was used to establish whether there were correlations between the titre of antibodies by DA and the total thyroid volume, the concentration of FT_4 and the concentration of TSH. The confronted data was basal and 30-day post treatment. The statistical program used was GraphPad InStat, 3.05 version.

RESULTS
Serology for T. gondii *and biochemical-endocrine studies (Table 1)*

TABLE 1. *Titre of DA, total thyroid volume (TTV), FT_4, TSH and Tg Ab in dogs with toxoplasmosis. Pretreatment, 30-days and 6-months post treatment.*

	Pretreatment	30-day post treatment		6-month post treatment
Titre DA	1/500 (1/200 -1/645)	1/92 (1/56 - 1/120)	**	all < 1/128
TTV (cm^3)	3.40 (2.80 - 4.30)	1.25 (0.90 - 1.80)	**	all < 1.000.
FT_4 (pmol/L)	2.50 (0.60 - 4.33)	1.54 (0.86 - 2.10)	*	50^a – 0.37^b
TSH (ng/mL)	0.25 (0.05 - 1.20)	1.00 (0.08 - 0.40)	ns	0.90^a – 1.20^b

Reference values: Titre DA : < 1/128; TTV: 0.70 – 1.20 cm^3 ; FT_4: 0.86 – 3.10; TSH: 0.02 – 0.40; Tg Ab: < 150%.
$^{**}P < 0.0001$; $^{*}P < 0.03$, ns (non significant) Mann-Whitney test. Values expressed in medians and ranges. N = 8 dogs. Values "a" and "b" are the two cases with development of hypothyroidism and AIT.

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The titre of antibodies by DA was high in all eight studied cases, supporting the diagnosis of acute phase toxoplasmosis. Thirty days post treatment, the titre by DA was found within the reference range in all cases ($P< 0.0001$), whereas by IIF it was >1/300, showing past exposure (data not shown). After six months post treatment, the titre by DA continued normal in all studied cases, while by IIF the titre remained high in six cases, but not presenting clinical signs. TSH concentration was normal in every case for the basal and second measurements, without significant differences between both determinations. In the 6-month post treatment measurement, the value was found high in two cases. The initial concentration of FT_4 was found above the normal range in three cases, normal in four and low in one, although the TSH was normal in this last case. After 30 days, thyroxine values returned to the reference range in the eight cases ($P< 0.03$). In the 3rd determination, two cases presented concentrations of FT_4 below the minimum corresponding to high TSH, thus these dogs developed hypothyroidism. These two cases had high Tg Ab, acquired after having finished the treatment, and had consequently developed autoimmune thyroiditis (AIT). The remaining cases presented normal Tg Ab in the three determinations.

Positive and significant correlations were found between the titre of antibodies by DA and the TTV ($r = 0.78$; $P< 0.0002$) and between DA and FT_4 ($r = 0.77$; $P< 0.002$) (Fig. 1a and b). No correlation was found with the TSH or with the titre of Tg Ab.

Images

Ultrasound: an increase in the thyroid volume was confirmed in the eight studied cases (goitre); this increase was assessed by determining the thyroid total volume (TTV) (Table 1). The gland was mainly hypoechogenic, but strongly hyperechogenic in the periphery igs. (Figs a1) . After 30 days of treatment, the TTV had reached normal values ($P< 0.0001$) below 1.20 mL for the size and weight of the studied dogd Figs. a2). After 6 months, the TTV was unchanged in six cases, and increased in the two dogs with autoimmune thyroiditis and hypothyroidism.

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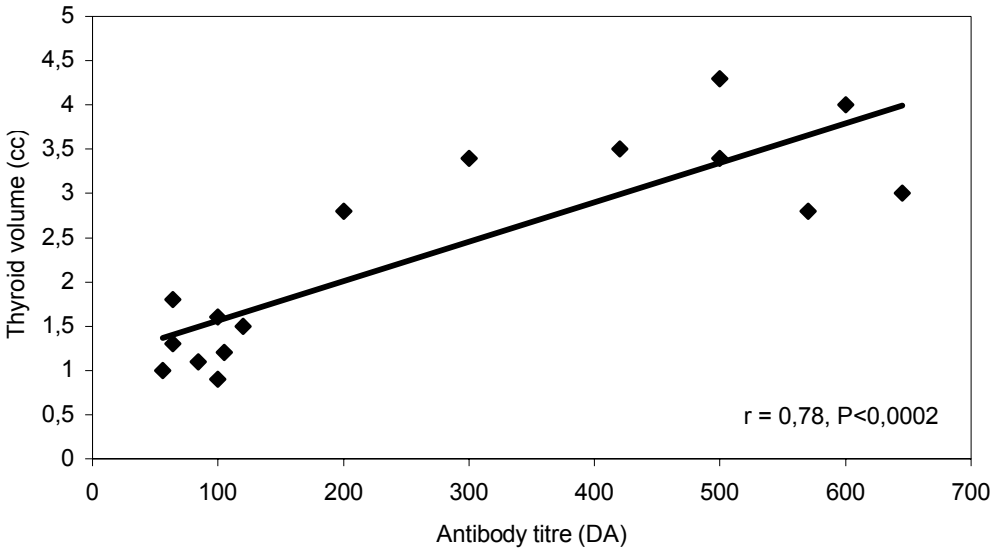

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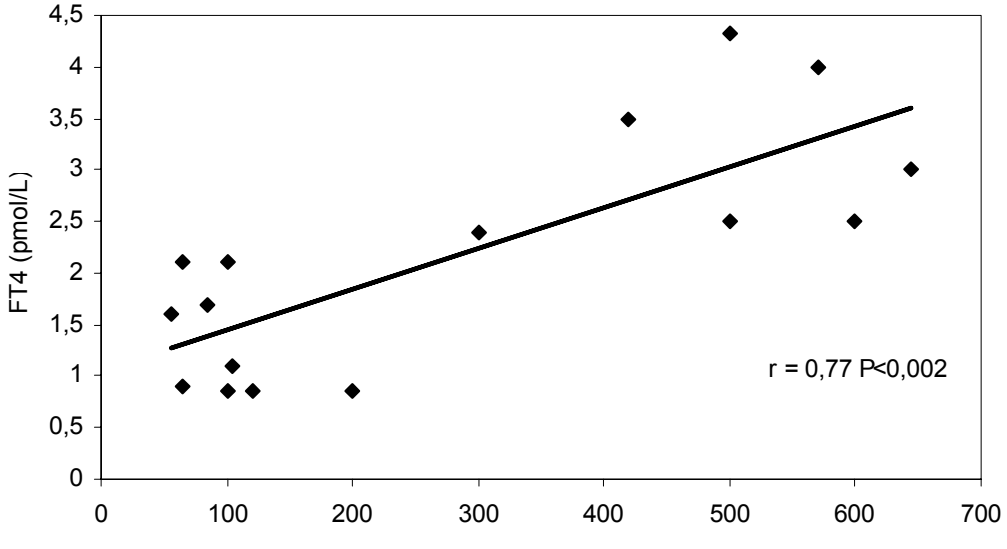

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Fig. 1. Correlation between the titre of antibodies by DA, the thyroid volume (1a) and the concentration of free thyroxine (1b) Spearman correlation, n= 8 dogs, correlated data: basal and 30-day post treatment (16 total data for each studied variable).

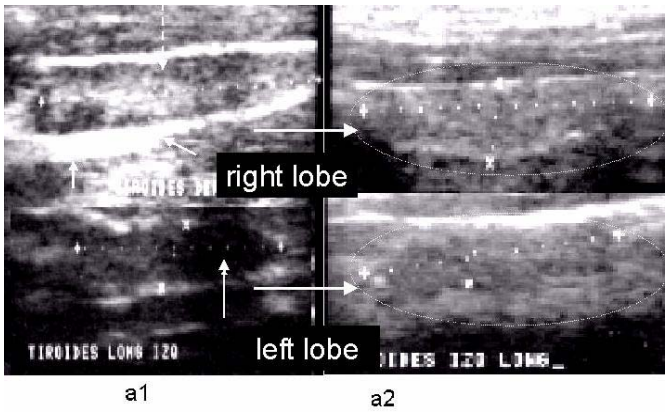

Fig. 2. Thyroid ultrasound, pre (a1) and post (a2) treatment of toxoplasmosis. Note in 2a the large hypoechogenic image (arrow in dotted line) in the right lobe and the strong hyperechogenic halo (white, indicated by the arrow) as well as the nodular area (arrow in dotted line) surrounded by hypoechoic areas in the left lobe. In Fig. 2b, the change in echogenicity is observed (normal for the thyroid gland) as well as the reduction in the size of both lobes (transducer of 7.5 mHz).

Scintigraphy

The first study reported an irregular distribution of the radiotracer with an increase in ^{99}Tc hypocaptating areas (Fig. 3, pre-treatment). The reassessment performed after 30 days shows a uniform uptake of the radioisotope (Fig. 3, pos-treatment). It showed normalisation of the radiotracer uptake at the same time with the improvement in the thyroid volume (thyroid functionality and morphology). All cases were euthyroid during the period under study.

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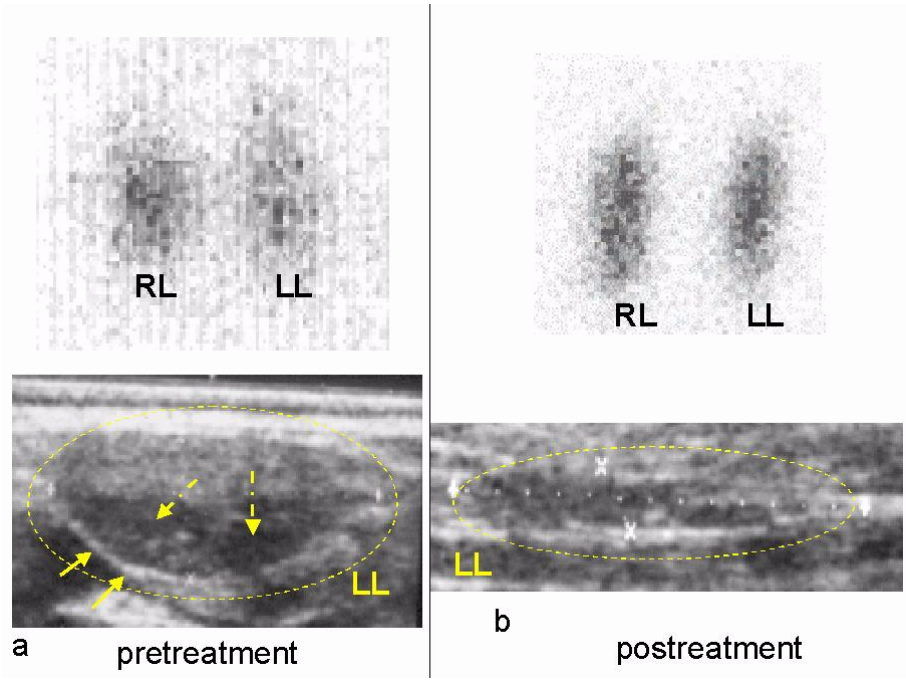

Fig. 3. Scintigraphy in gamma camera and thyroid ultrasound of the same dog, pre and post treatment of toxoplasmosis. In the image pre-treatment, both hypocaptating lobes can be noted, typical of subacute thyroiditis, corresponding with its highly enhanced left lobe (into the circle) and with prevalence of hypoechoic areas (dotted arrows) and with strong hyperechogenic areas (white halo, see line arrow). In the pos-treatment , the thyroid scintigraphy is normal (uniform distribution of radiotracer ^{99}Tc), and so is the left lobe ultrasound image, since it reduced its size and presents uniform echogenicity.

DISCUSSION

Toxoplasmosis is common in dogs, presenting neuromuscular clinical signs in its acute phase, both affecting the nervous system and causing myositis (Taboada and Merchant, 1997). Being a pathology provoked by an infectious agent of intracellular location, the immunologic response is mainly cell mediated (Sher and Coffman, 1992; Taboada and Merchant, 1997), triggering via the TCD8 lymphocyte (cytotoxicity) as well as the TCD4 (Aliberti et al., 2002; Fux et al., 2003; Sher and Coffman, 1992). The production of interleukin 12 (IL-12) by the macrophage activates the T helper 1 (Th1) lymphocyte which participates in the cell mediated immunity. In turn, the Th1 releases gamma interferon (Inf-γ) and IL-10, contributing to this type of response (Araujo and Slifer, 2003; Fux et al., 2003; Sher and Coffman, 1992). Both IL-12 and Inf-γ are released during the acute phase of toxoplasmosis (Aliberti et al., 2002; Araujo and Slifer, 2003). The release of other interleukins, such as IL-6 as well as tumour necrosis factor alpha (TNF-α) is also described. These cytokines have been claimed to affect thyroid glands, causing a reduced gland function (Karp and Atkinson, 1997; Kawakami et al., 1990).

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Histopathological and immunohistolabelling studies must be conducted to prove that the protozoan directly damages the thyroid gland, as it does with muscle and nervous system.

In this case, the thyrocyte may behave as an antigen-presenting cell (as it does in other circumstances) and develop an autoimmune response. The presence of goitre and ultrasound aspect of the thyroid gland, suggest that it is being affected by the action of toxoplasma either directly or indirectly by the cytokines. This concept is reinforced by the fact that, by the end of the specific treatment with clindamycin, the thyroid gland recovers its normal values and echographic aspect as well as by the strong correlation between the titre of DA and the TTV.

As regards the glandular function, it would be affected during the acute phase, as show from the thyroxine values obtained in 4 cases. Furthermore, the correlation between the titre of DA and thyroxine suggest that the *T. gondii* can affect the function and morphology of the gland. It is evident that the higher the titre of DA, the more compromised the thyroid gland. As it was previously described, in 4 cases (50%) there were no modifications in the TSH and thyroxine concentrations, even though the latter was found in the higher limits. This observation differs from what was reported by Stahl and Kaneda (1998a, b), who described a decrease of thyroxine in mice experimentally infected with *T. gondii*. This event is attributed to a hypothalamus dysfunction (not pituitary or thyroid) with alterations in the secretion of thyrotropine releasing hormone (TRH) caused by the hypofunction of the thyroid axis. On the contrary, our findings in dogs show that TSH tends to be normal or in the higher limit. In this case, the thyroid axis would not be hypofunctioning, at least in a natural infection.

It is worth mentioning that only three dogs presented increased FT_4, perhaps because of the rupture of follicles with hormone release from the thyroid colloid into the systemic circulation. This process is typical of acute and subacute thyroiditis in humans as a result of the noxa and the inflammatory cytokines on the thyroid epithelium (Reed Larsen et al., 1998). The fact that the TSH concentration was constant, even when the T_4 increased, clearly shows that there is not a glandular hyperfunction, as in hyperthyroidism. In these cases, hyperthyroxinemia is transitory, returning to normal values once the thyroid follicle is repaired. The reduction in thyroxine observed in one case can be attributed to the suppressing effects of the thyroid function by the cytokines, particularly INF-γ and IL-12 (Kawakami et al., 1990)

In spite of the hypothyroxinemia present, the TSH did not increase its concentration in serum over its normal values, as it is to be expected in hypothyroids.

This condition is transitory, as well as the hyperthyroxinemia cases described, with T_4 turning to normal values once the basal disease is treated.

This shows that it is thes gland which is affected in contrast to observed by Stahl and Kaneda (1998).

Hypocaptation of ^{99}Tc in the scintography reinforces this concept. The higher or lower damage in the thyrocyte and in its function might be due to the intra-

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thyrocyte protozoal load, the severity of the immune and inflammatory reaction or a combination of both effects. It is possible that the highest immunological and inflammatory response causes follicular damage. If the titre of antibodies by DA and the correlation with the TTV are taken into account, the animals with higher titres presented hyperthyroxinemia and higher thyroid volume (Fig.1a-b). Another possibility would be that the toxoplasma affects the gland directly, as it does on the muscle, causing the loss and rupture of the follicles and triggering the autoimmune response on the thyrocyte.

A histological and immunohistochemical or PCR (polymerase chain reaction) (Feng and Milhausen, 1999) examination would be necessary to confirm the presence of intrathyroid *T. gondii*.

The occurrence of autoimmune thyroiditis and hypothyroidism in 2 cases would elements (viruses, bacteria, chemicals) is considered to be the cause of AIT by affecting the gland and altering the major histocompatability complex (Paul and Seder, 1994; Sher et al., 2003; Simon et al., 1986) in individuals susceptible to the pathology. The affected thyrocyte can also behave as an antigen-presenting cell, exposing *T. gondii* antigens to the action of cytotoxic T and TCD4 lymphocytes with the subsequent immune response (Sher et al., 2003; Simon et al., 1986)

Another element that should be taken into account is the thyroid inflammation in the development of the AIT, since the inflammatory process with tissue rupture exposes intracellular antigens which, not being recognized by T lymphocytes, trigger immune response (Davies et al., 1991; Karp and Atkinson, 1997; Paul and Seder, 1994). Because of the presence of intrathyroid toxoplasma or as a result of the inflammatory mechanisms which allow the exposure of intracellular antigens or due to the effect of the combination of both actions, susceptible individuals will develop autoimmune thyroiditis some time after the diagnosis of toxoplasmosis and regardless of its cure (Davies, et al,, 1991; Karp and Atkinson, 1997). It is thus important to consider this fact in order to conduct a proper follow-up in the medium and long terms.

We conclude that *T. gondii* can directly or indirectly affects the thyroid morphology and its function. Even if in most cases damage is transitory and disappears once the basal disease is treated, some cases might evolve into AIT and hypothyroidism. A follow-up of the thyroid function and morphology should be conducted in the medium and long terms.

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