IgG4-related Hashimoto's thyroiditis – A new variant of a well known disease

Tireoidite de Hashimoto associada a IgG4 – Uma nova variante de uma doença bem conhecida

Henrique Vara Luiz[1], Diogo Gonçalves[2], Tiago Nunes da Silva[1], Isabel Nascimento[3], Ana Ribeiro[4], Manuela Mafra[4], Isabel Manita[1], Jorge Portugal[1]

[1] Department of Endocrinology and Diabetology, Hospital Garcia de Orta, Almada, Portugal
[2] Department of Anatomic Pathology, Hospital Garcia de Orta, Almada, Portugal
[3] Department of General Surgery, Hospital Garcia de Orta, Almada, Portugal
[4] Department of Anatomic Pathology, Centro Hospitalar de Lisboa Central, Lisboa, Portugal

SUMMARY

Hashimoto's thyroiditis (HT) has been characterized for many years as a well-defined clinicopathologic entity, but is now considered a heterogeneous disease. IgG4-related HT is a new subtype characterized by thyroid inflammation rich in IgG4-positive plasma cells and marked fibrosis. It may be part of the systemic IgG4-related disease. We report a case of a 56-year-old Portuguese man who presented with a one-month history of progressive neck swelling and dysphagia. Laboratory testing revealed increased inflammatory parameters, subclinical hypothyroidism and very high levels of thyroid autoantibodies. Cervical ultrasound (US) demonstrated an enlarged and heterogeneous thyroid gland and two hypoechoic nodules. US-guided fine needle aspiration cytology was consistent with lymphocytic thyroiditis. The patient was submitted to total thyroidectomy and microscopic examination identified typical findings of HT, marked fibrosis limited within the thyroid capsule and lymphoplasmacytic infiltration, with > 50 IgG4-positive plasma cells per high-power field and an IgG4/IgG ratio of > 40%. After surgery, serum IgG4 concentration was high-normal. Symptoms relief and reduction in laboratory inflammatory parameters were noticed. Thyroid function is controlled with levothyroxine. To our knowledge we report the first case of IgG4-related HT in a non-Asian patient. We also perform a review of the literature regarding IgG4-related disease and IgG4-related HT. Our case highlights this new variant of the well known HT, and helps physicians in recognizing its main clinical features, allowing for proper diagnosis and treatment. Arq Bras Endocrinol Metab. 2014;58(8):862-8

Correspondence to:
Henrique Vara Luiz
Department of Endocrinology and Diabetology,
Hospital Garcia de Orta
Av. Torrado da Silva
2801-951 – Almada, Portugal
hvaraluiz@gmail.com

Received on Feb/13/2014
Accepted on Mar/3/2014

DOI: 10.1590/0004-2730000003283

SUMÁRIO

A tireoidite de Hashimoto (TH) foi caracterizada durante muitos anos como uma entidade clinicopatológica bem definida, mas é atualmente considerada uma patologia heterogênea. A TH associada a IgG4 apresenta-se como um novo subtipo, sendo caracterizada por inflamação da tireoide com numerosos plasmócitos IgG4-positivos e fibrose extensa. É possível que pertença ao espectro da doença sistêmica associada a IgG4. Relatamos o caso de um homem português de 56 anos que se apresentou com aumento progressivo do volume cervical e disfagia, com um mês de evolução. A avaliação laboratorial revelou elevação dos parâmetros inflamatórios, hipotireoidismo subclínico e níveis muito elevados de autoanticorpos tireoidianos. Por ultrassonografia cervical demonstrou-se tireoide aumentada, heterogênea, com dois nódulos hipoecoicos. Foi realizada citologia aspirativa com agulha fina guiada por ultrassom, compatível com tireoidite linfocítica. O doente foi submetido à tireoidectomia total e o exame histológico revelou achados típicos de TH, extensa fibrose localizada dentro da cápsula tireoidiana e infiltrado linfoplasmocitário, com > 50 plasmócitos IgG4-positivos por campo de grande ampliação e uma relação IgG4/IgG > 40%. Após cirurgia, a concentração sérica de IgG4 encontrava-se no limite superior do normal. Ocorreu melhoria sintomática e redução dos parâmetros inflamatórios. A função tireoidiana foi controlada com levotiroxina. Relatamos o primeiro caso de TH associada a IgG4 num indivíduo não asiático. Além disso, realizamos uma revisão da literatura sobre doença associada a IgG4 e TH associada a IgG4. Este caso destaca uma nova variante da TH e permite aos médicos reconhecerem suas principais características clínicas, proporcionando diagnóstico e tratamento adequados. Arq Bras Endocrinol Metab. 2014;58(8):862-8

INTRODUCTION

Hashimoto's thyroiditis (HT) was first reported in 1912 by Hakaru Hashimoto, who described four patients with a chronic disorder of the thyroid gland (1). It is the most common cause of hypothyroidism in areas of the world where dietary iodine is sufficient and is defined by the presence of goiter and serum thyroid autoantibodies (2). Typical histological features of HT include lymphoplasmacytic infiltration, lymphoid follicles with germinal center formation and the presence of large follicular cells with abundant granular eosinophilic cytoplasm (oxyphilic cells). For many years, it has been characterized as a well-defined clinicopathologic entity. However, HT is now considered a heterogeneous and poorly understood disease, with several subtypes, presentation forms, pathogenesis and outcomes.

IgG4-related HT is a new subtype, first recognized by Li and cols. in 2009 (3) and characterized by thyroid inflammation rich in IgG4-positive plasma cells and marked fibrosis. It may be part of the systemic IgG4-related disease. There are few articles about this topic, all of them from Japan.

We report, to our knowledge, the first case of IgG4-related HT in a non-Asian patient, and perform a review of the related literature.

CASE REPORT

A 56-year-old Portuguese man presented to the outpatient clinic with a one-month history of progressive neck swelling and dysphagia. No symptoms of thyroid dysfunction were noticed. His past medical history was unremarkable. He had Portuguese descent and no relevant family diseases. The patient had good general condition and nutritional status and presented with diffuse neck swelling (Figure 1A). Cervical palpation identified an enlarged, hard and painless thyroid gland. He had no palpable adenopathies. His respiratory and abdominal exams were normal. No other changes were found on physical examination.

Laboratory testing revealed a normal hemoglobin level of 15.1 g/dL (normal, 14-18), a normal white blood cell count of 10.4 X 10^3/µL (normal, 4-11) and an elevated platelet count of 521 X 10^3/µL (normal, 150-450). Increased erythrocyte sedimentation rate (ESR) of 81 mm/h (normal, < 31) and C-reactive protein of 8.2 mg/dL (normal, < 1) were found, with an elevated thyroid-stimulating hormone (TSH) of 19 mIU/L (normal, 0.1-4) and a normal free thyroxine (FT_4) of 0.99 ng/dL (normal, 0.93-1.7). Very high thyroid peroxidase and thyroglobulin antibodies were noticed, with levels of > 600 IU/mL (normal, < 35) and > 4000 IU/mL (normal, < 40), respectively.

Cervical ultrasound (US) demonstrated an enlarged and heterogeneous thyroid gland, both lobes with maximal dimension > 10 cm and two hypoechoic nodules with 3.2 and 2.2 cm located on the isthmus and right lobe, respectively (Figure 1B). Cervical computed tomography (CT) showed a thyroid gland with increased dimensions and a substernal component, producing a mass effect on the trachea with tracheal shift to the right and slightly reducing its caliber, with no visible adenopathies (Figure 2). US-guided fine needle aspiration cytology was performed and the material removed from both nodules was consistent with lymphocytic thyroiditis.

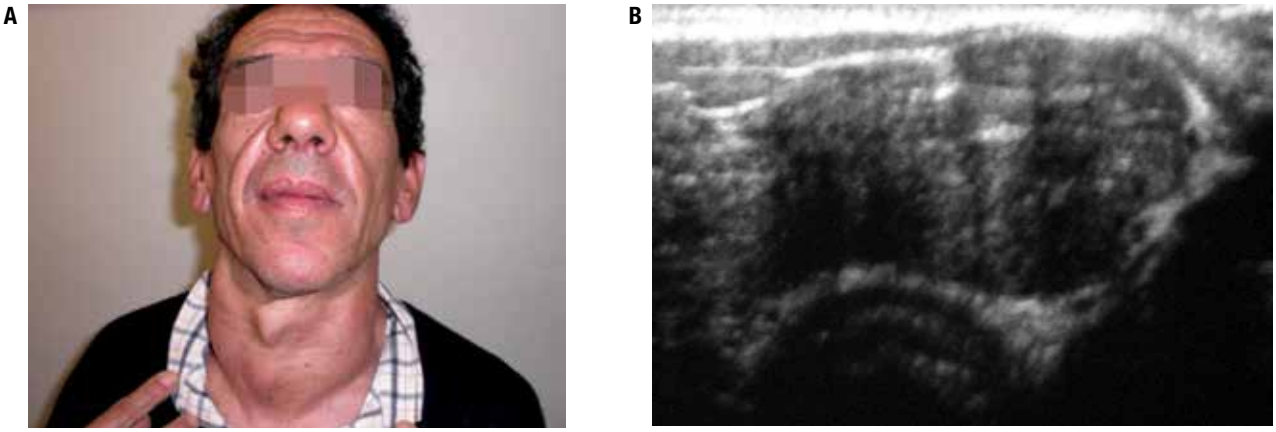

Figure 1. (**A**) Initial presentation of the patient with diffuse neck swelling. (**B**) Cervical ultrasound image showing a hypoechoic nodule with 3.2 cm of maximal dimension located on the thyroid isthmus.

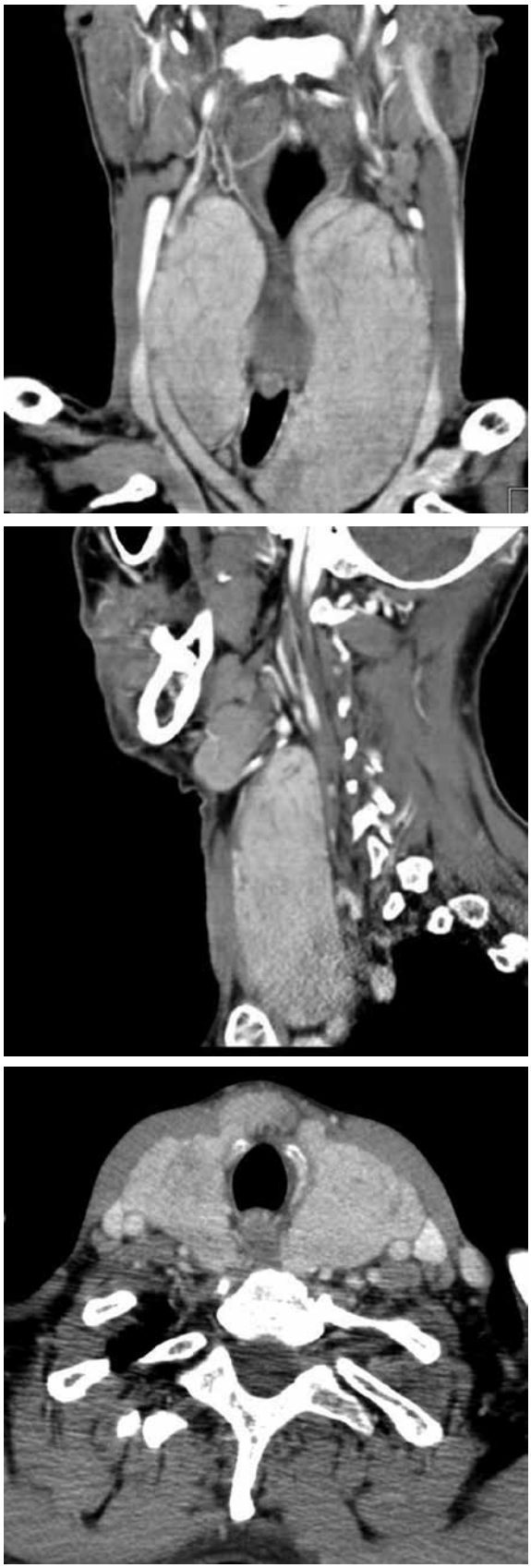

Figure 2. (**A**, **B**, **C**) Cervical computed tomography images showing a thyroid gland with increased dimensions and a substernal component, producing a mass effect on the trachea.

The patient was submitted to total thyroidectomy. Due to the size of the gland and the presence of fibrosis, the surgical procedure was complex and time-consuming, with difficulties in mobilizing the thyroid gland. Surgeons have identified and preserved the recurrent laryngeal nerve and the parathyroid glands and had no other complications. Macroscopic findings showed a thyroid gland with a weight of 284 g (right lobe 10 x 6 x 4.5 cm and left lobe 12 x 6 x 6 cm) and a hard consistency. Microscopic examination identified lymphoplasmacytic infiltration, lymphoid follicles with germinal centers, oxyphilic cells, focal squamous metaplasia, atrophic follicles and marked fibrosis limited within the thyroid capsule. Immunostaining for IgG4 (mouse monoclonal, HP6025, 1:40; GeneTex, Irvine, USA) and IgG (rabbit polyclonal, NCL-IgGp, 1:2500; Novocastra, Newcastle, UK) was performed on a Ventana BenchMark ULTRA with Ultra DAB Detection Kit. Tonsil tissue served as a positive control. Five high-power field (HPF) were counted and > 50 IgG4-positive plasma cells per HPF were found (Figure 3). The calculated IgG4/IgG ratio was > 40% (Figure 4).

One month after surgery, serum IgG4 concentration was high-normal, 187 and 165 mg/dL (normal, 3-201). Symptoms relief and reduction in laboratory inflammatory parameters, with an ESR of 20 mm/h, were noticed. Thyroid function is controlled with levothyroxine 137 µg/day (TSH 2.9 mIU/L, FT_4 1.2 ng/dL, thyroid peroxidase antibodies > 600 IU/mL and thyroglobulin antibodies > 4000 IU/mL) and the patient is normocalcemic and has a normal parathyroid hormone level. The remaining basal pituitary function is unremarkable, including normal levels of follicle-stimulating hormone, luteinizing hormone, growth hormone, insulin-like growth factor 1, prolactin, adrenocorticotropic hormone and cortisol.

DISCUSSION

IgG4-related disease was first proposed in relation to autoimmune pancreatitis (AIP) by Hamano and cols. in 2001 (4). Since then, it has been identified in virtually every tissue and is now considered a single condition that comprises multiple manifestations. Most patients are middle aged and elderly men and the disease usually presents subacutely, as a generalized entity or involving a single organ. Clinical findings are dependent on the location of involved tissues and often include forming mass lesions, mimicking malignancies,

infections and other autoimmune-mediated disorders. Organ failure may occur. Fever, constitutional symptoms and elevation in laboratory inflammatory parameters are unusual (5-7).

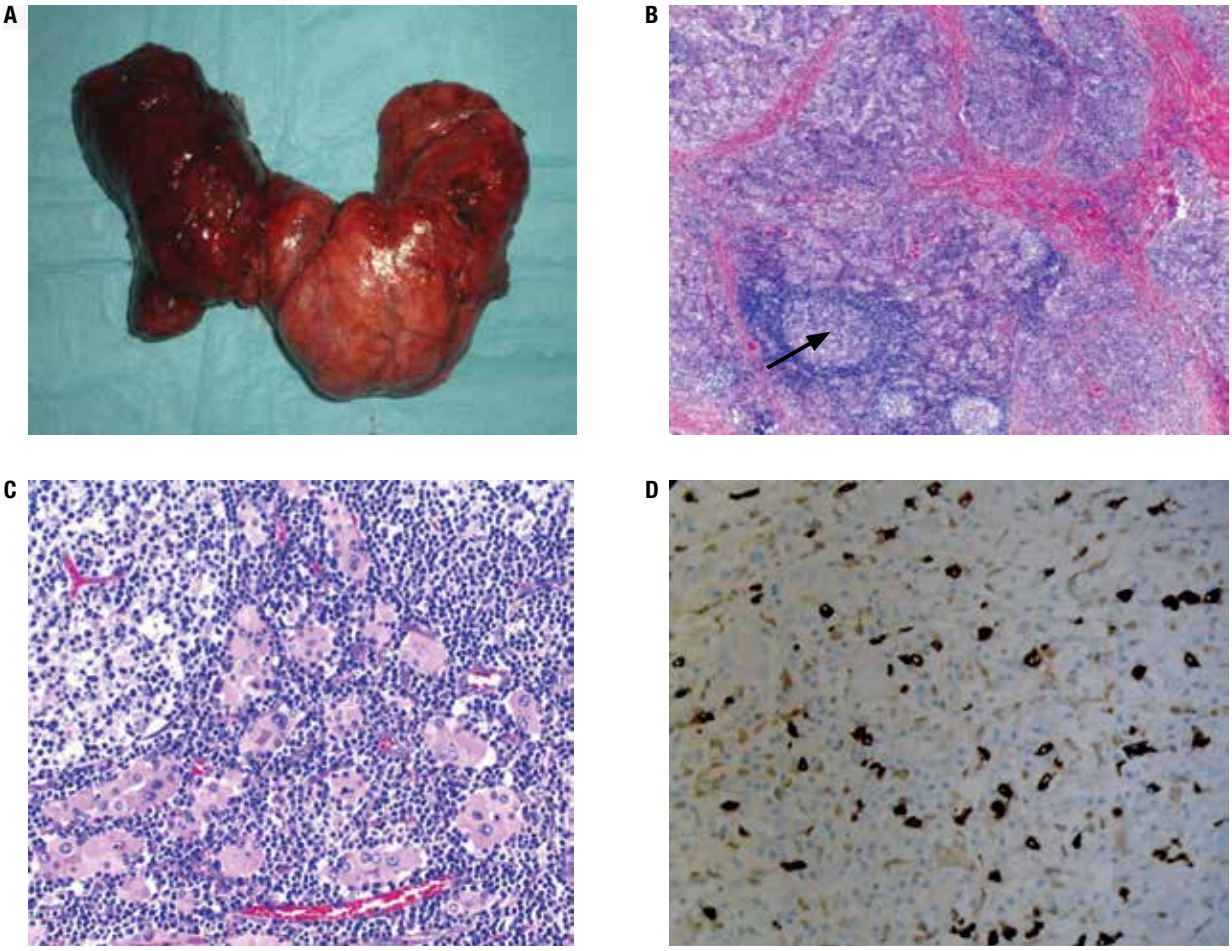

Figure 3. Postoperative histopathological analysis of the thyroid gland. (**A**) Macroscopic findings revealing a large thyroid gland with a hard consistency. (**B**) An inflammatory infiltrate is seen, along with lymphoid follicles with germinal centers (*black arrow*) and marked fibrosis (hematoxylin and eosin, 40X). (**C**) Lymphoplasmacytic infiltration is found and atrophic follicles with oxyphilic cells predominate (hematoxylin and eosin, 200X). (**D**) Increased number of IgG4-positive plasma cells are seen, with > 50 cells per high-power field (IgG4 immunostaining, 400X).

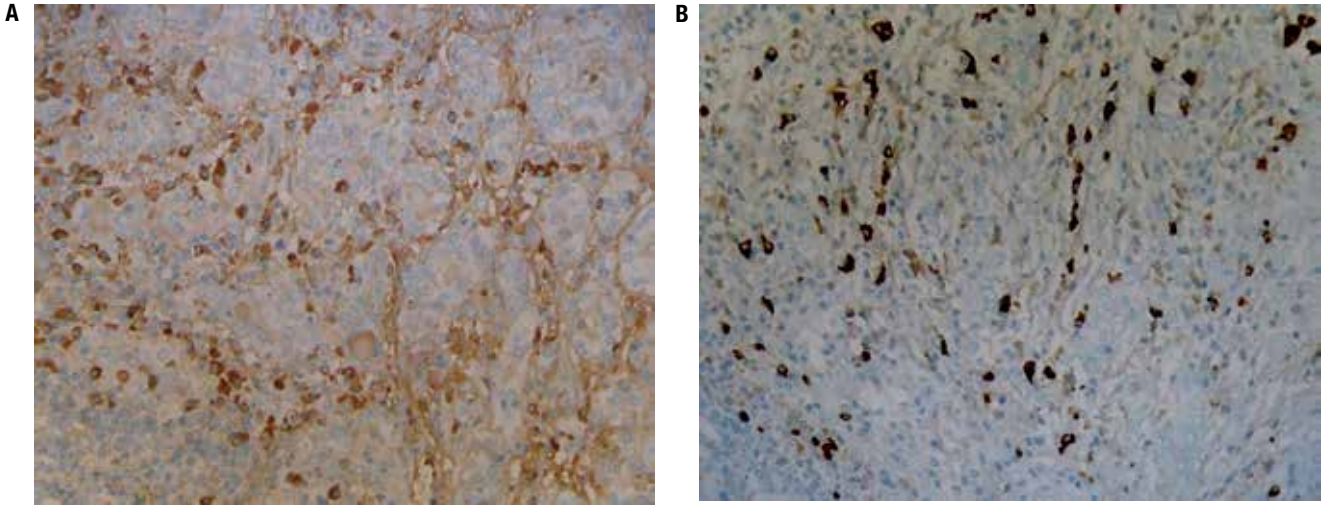

Figure 4. Immunohistochemistry of IgG and IgG4. (**A**) Numerous IgG-positive plasma cells are found (IgG immunostaining, 400X). (**B**) An increased proportion of these cells are IgG4-positive, with an IgG4/IgG ratio of > 40% (IgG4 immunostaining, 400X).

This condition is reported in the literature by different names: IgG4-related disease, IgG4-associated disease, IgG4-related systemic disease, IgG4-related sclerosing disease, IgG4-related systemic sclerosing disease, IgG4-related autoimmune disease, hyper-IgG4 disease, IgG4-positive multiorgan lymphoproliferative syndrome, systemic IgG4-related plasmacytic syndrome and IgG4 syndrome. Some groups reached a consensus to refer it as IgG4-related disease (5,8).

Diagnostic criteria have been proposed by some authors (5,9), but are not universally established. They include, independently of the affected organ, histological features such as a dense lymphoplasmacytic infiltrate, storiform-type fibrosis and obliterative phlebitis, along with the demonstration of an increased population of IgG4-positive plasma cells. Cheuk and Chan considered that the diagnosis requires an increase in the absolute number of IgG4-positive cells of > 50 per HPF and a raised IgG4-positive/IgG-positive ratio of > 40% (10). At least three HPFs should be used to calculate the average results. Deshpande and cols. stated that histological data are the mainstay for diagnosis, since both elevated numbers of IgG4-positive plasma cells and IgG4/IgG ratios have been described in other inflammatory conditions and malignancies (11). A high serum IgG4 concentration is often present but approximately 20-30% of patients with classic histopathological and immunochemical findings of the disease have normal serum levels (12). Therefore, it is not mandatory for the diagnosis of IgG4-related conditions.

A preoperative suspicion is of greater significance because these patients can be treated with glucocorticoids with the avoidance of surgery. Although they usually respond well to steroids, relapse can occur following therapy reduction or withdrawal. Some groups suggested therapeutic regimens (13). A major determinant of treatment effectiveness is the degree of fibrosis and patients in whom fibrosis is well established are less likely to respond to glucocorticoids (7).

Our patient seems to have a single involvement of the thyroid gland and he presented with the classic diagnostic features of IgG4-related disease, namely: lymphoplasmacytic infiltrate, fibrosis and an increased number of IgG4-positive plasma cells.

Despite striking histopathological similarities among involved organ, subtle tissue variations are noticed (8). Organ-specific diagnostic criteria have been suggested for some of the IgG4-related conditions, but little is known about the thyroid gland.

Patients with IgG4-related disease that included AIP have hypothyroidism in 27% of cases (14) and that finding led investigators to search for a relationship between HT and that systemic disease.

In 2009, Li and cols. first described a unique subtype of HT, known as IgG4-related HT, which was referred by those authors as IgG4 thyroiditis. They classified HT cases in two groups, IgG4 thyroiditis and non-IgG4 thyroiditis, based on IgG4 immunohistochemistry, using the cut-off > 20 cells per HPF and > 30% IgG4/IgG ratio. The IgG4 thyroiditis group presented with severe lymphoplasmacytic infiltration, dense fibrosis, marked follicular cell degeneration, oxyphilic change and lymphoid follicle formation, resembling IgG4-related disease, and a relationship with this systemic entity was proposed (3). The same group in 2010 demonstrated that the IgG4 thyroiditis group was associated with male gender, rapid progress requiring surgery, more subclinical hypothyroidism, higher levels of thyroid autoantibodies and more diffuse low echogenicity on US, when compared with the non-IgG4 thyroiditis group (15). In 2012 these authors studied 105 patients with HT and, using the same cut-off, 28 cases (27%) were classified as IgG4 thyroiditis (16).

Our patient shows all the typical characteristics of IgG4-related HT. The presentation form, with neck swelling of rapid growing in a male patient, subclinical hypothyroidism, high levels of thyroid autoantibodies and low echogenicity on US, suggested the diagnosis, which was confirmed based on histological data and immunohistochemistry of IgG and IgG4. Since this condition seems to be more common than previously thought, we suggest performing the immunostaining in a case presenting with these typical clinical features and with lymphoplasmacytic infiltration and marked fibrosis.

When a preoperative suspicion of IgG4-related HT is present, glucocorticoid therapy may improve local symptoms and clinical outcomes. If the initial complaints recur despite steroid therapy, surgical treatment is required (17). However, as these patients usually present with a rapidly progressing neck swelling, surgery is often the first choice for treatment. Before surgical intervention serum IgG4 is often elevated but, after total thyroidectomy, levels usually exhibit a significant reduction and return to normal, indicating that the major origin of IgG4 is the thyroid gland (16). In our case, serum IgG4 was not performed preoperatively but a normal level one month after total thyroidec-

tomy may suggest that it is decreasing and no other organ is involved besides the thyroid gland. The patient is asymptomatic, has normal laboratory inflammatory parameters and his thyroid function is controlled with levothyroxine.

IgG4-related HT also shares some features with the fibrous variant of HT, which accounts for 10-13% of HT cases. Its diagnostic criteria were defined by Katz and Vickery in 1974 and included a marked fibrous replacement of more than one-third of the thyroid parenchyma and changes typical of HT in the remaining tissue (18). However, these conditions do not overlap completely. Li and cols. identified 14% of patients in the IgG4 thyroiditis group as having only mild fibrosis in the stroma, whereas 38% in the non-IgG4 thyroiditis group were found to meet the diagnostic criteria for the fibrous variant of HT. Some authors found that the IgG4 thyroiditis group was significantly associated with the presence of a predominant interfollicular pattern of fibrosis, while the fibrosis in the non-IgG4 thyroiditis group was mainly interlobular (19).

In addition to IgG4-related HT, IgG4-related disease of the thyroid gland may include Riedel's thyroiditis (RT), but this is still to be confirmed (15,20). RT is a rare condition, first recognized in 1896 by Bernhard Riedel (21). At the Mayo Clinic, 37 cases of RT were diagnosed in a series of 56,700 thyroidectomies performed between 1920 and 1984, giving an incidence of 0.06% (22). The diagnostic criteria of this entity were established by Woolner and cols. in 1957, based on histological data (23). They have been modified and include: a fibroinflammatory process involving all or a portion of the thyroid gland, the presence of fibrous extension beyond the thyroid capsule into adjacent anatomic structures, infiltration of inflammatory cells without giant cells, lymphoid follicles, oncocytes or granulomas, evidence of occlusive phlebitis and absence of a neoplasm (24).

Some characteristics can help distinguishing IgG4-related HT and RT. The absence of extensive fibrosis beyond the thyroid capsule is still the most reliable evidence to confirm a diagnosis of IgG4-related HT. Furthermore, when IgG4-related disease occurs in a systemic pattern, the thyroid involvement may present as RT, since IgG4-related HT is organ-specific. In fact, none of the patients in the IgG4 thyroiditis group reported by Li and cols. showed involvement of other organs (19). Therefore, in a patient with confirmed IgG4-related HT and no additional signs and symptoms, we consider that it is not mandatory to discard general IgG4-related disease. In addition, obliterative phlebitis is not present in any subtype of HT (16,24). Based on these features, our case is better defined as IgG4-related HT than as RT.

A relatively rapid growth in size of the thyroid gland should also lead to include lymphoma and other types of thyroid cancer in the differential diagnosis. Preexisting HT is a risk factor for primary thyroid lymphoma (25).

Besides the thyroid gland, other endocrine organs can be involved in the spectrum of IgG4-related disease including the pituitary gland. More than 20 cases of IgG4-related hypophysitis have been described, all but one with pituitary insufficiency (26).

In conclusion, we report the first case of IgG4-related HT in a non-Asian patient, a Portuguese male presenting with a neck swelling of rapid growing and dysphagia, subclinical hypothyroidism, high levels of thyroid autoantibodies and low echogenicity on US. The presentation form and the additional histological data with lymphoplasmacytic infiltration and marked fibrosis were in agreement with the previous articles about IgG4-related HT, and led us to perform immunostaining for IgG and IgG4. The diagnosis was then confirmed. Our case highlights this new variant of the well known HT, and helps physicians in recognizing its main clinical features, allowing for proper diagnosis and treatment.

Acknowledgements: we thank Sérgio Lameiras for the assistance in preparing the manuscript.

Disclosure: no potential conflict of interest relevant to this article was reported.

REFERENCES

1. Hashimoto H. Zur kenntnis der lymphömatosen veränderung der schilddrüse (Struma lymphomatosa). Archiv für Klinische Chirurgie. 1912;97:219-48.
2. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med. 2003;348(26):2646-55.
3. Li Y, Bai Y, Liu Z, Ozaki T, Taniguchi E, Mori I, et al. Immunohistochemistry of IgG4 can help subclassify Hashimoto's autoimmune thyroiditis. Pathol Int. 2009;59(9):636-41.
4. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344(10):732-8.
5. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol. 2012;22(1):1-14.
6. Divatia M, Kim SA, Ro JY. IgG4-related sclerosing disease, an emerging entity: a review of a multi-system disease. Yonsei Med J. 2012;53(1):15-34.

7. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012;366(6):539-51.
8. Stone JH, Khosroshahi A, Deshpande V, Chan JK, Heathcote JG, Aalberse R, et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis Rheum. 2012;64(10):3061-7.
9. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012;22(1):21-30.
10. Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. Adv Anat Pathol. 2010;17(5):303-32.
11. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25(9):1181-92.
12. Sah RP, Chari ST. Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. Curr Opin Rheumatol. 2011;23(1):108-13.
13. Kamisawa T, Okazaki K, Kawa S, Shimosegawa T, Tanaka M; Research Committee for Intractable Pancreatic Disease and Japan Pancreas Society. Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP. J Gastroenterol. 2010;45(5):471-7.
14. Komatsu K, Hamano H, Ochi Y, Takayama M, Muraki T, Yoshizawa K, et al. High prevalence of hypothyroidism in patients with autoimmune pancreatitis. Dig Dis Sci. 2005;50(6):1052-7.
15. Li Y, Nishihara E, Hirokawa M, Taniguchi E, Miyauchi A, Kakudo K. Distinct clinical, serological, and sonographic characteristics of Hashimoto's thyroiditis based with and without IgG4-positive plasma cells. J Clin Endocrinol Metab. 2010;95(3):1309-17.
16. Kakudo K, Li Y, Taniguchi E, Mori I, Ozaki T, Nishihara E, et al. IgG4-related disease of the thyroid glands. Endocr J. 2012;59(4):273-81.
17. Kakudo K, Li Y, Hirokawa M, Ozaki T. Diagnosis of Hashimoto's thyroiditis and IgG4-related sclerosing disease. Pathol Int. 2011;61(4):175-83.
18. Katz SM, Vickery AL Jr. The fibrous variant of Hashimoto's thyroiditis. Hum Pathol. 1974;5(2):161-70.
19. Li Y, Zhou G, Ozaki T, Nishihara E, Matsuzuka F, Bai Y, et al. Distinct histopathological features of Hashimoto's thyroiditis with respect to IgG4-related disease. Mod Pathol. 2012;25(8):1086-97.
20. Pusztaszeri M, Triponez F, Pache JC, Bongiovanni M. Riedel's thyroiditis with increased IgG4 plasma cells: evidence for an underlying IgG4-related sclerosing disease? Thyroid. 2012;22(9):964-8.
21. Riedel B. Die chronische, zur bildung eisenharter tumoren führende entzündung der schilddrüse. Ver Deutsch Ges Chirurg. 1896;25:101-5.
22. Hay ID. Thyroiditis: a clinical update. Mayo Clin Proc. 1985;60(12):836-43.
23. Woolner LB, McConahey WM, Beahrs OH. Invasive fibrous thyroiditis (Riedel's struma). J Clin Endocrinol Metab. 1957;17(2):201-20.
24. Papi G, LiVolsi VA. Current concepts on Riedel thyroiditis. Am J Clin Pathol. 2004;121:S50-63.
25. Ahmed R, Al-Shaikh S, Akhtar M. Hashimoto thyroiditis: a century later. Adv Anat Pathol. 2012;19(3):181-6.
26. Hattori Y, Tahara S, Ishii Y, Kitamura T, Inomoto C, Osamura RY, et al. A case of IgG4-related hypophysitis without pituitary insufficiency. J Clin Endocrinol Metab. 2013;98(5):1808-11.