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Immunoglobulin G4-related thyroid disorders — diagnostic challenges and clinical outcomes

Zaburzenia tarczycy związane z immunoglobuliną G4 — wyzwanie diagnostyczne i wyniki kliniczne

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Abstract

Ig-G4 related disease (IgG4RD) is a heterogeneous disorder with multi-organ involvement recognised as a separate entity at the start of this century only. It is currently one of the hottest areas of clinical and translational research across specialties. Thyroid involvement in IgG4RD is rare, believed to occur in less than 4% of cases, may be isolated or may be associated with other organ involvement. As of today Riedel's thyroiditis, fibrosing variant of Hashimoto's thyroiditis, and few patients of Graves' orbitopathy represent the types of IgG4-related thyroid disease (IgG4RTD). This disorder is frequently confused with malignancy due to the intense sclerosis of thyroid resulting in hard texture on palpation compounded by often-associated compressive symptoms. Diagnosis involves establishing high circulating levels of IgG4 > 135 mg/dL, increased serum IgG4 to IgG ratio of > 8%, immunohistochemistry showing dense lymphoplasmacellular inflammatory infiltrate consisting of IgG4-positive plasma cells with storiform fibrosis and obliterative phlebitis, and increased IgG4 positive plasma cell > 10 cells per high-power field when at least three fields are evaluated. Glucocorticoids are the primary form of therapy in IgG4RD. However, their role in IgG4RTD needs to be evaluated. As of today levothyroxine supplementation for resulting hypothyroidism, appropriate management of Graves' disease, and surgical excision of thyroid in case of compressive symptoms remain the primary treatment options. **(Endokrynol Pol 2016; 67 (5): 520–524)**

Key words: *immunoglobulin; Hashimoto's thyroiditis; Riedel's thyroiditis; IgG4 related disease*

Streszczenie

Choroba związana z Ig-G4 (IgG4RD) jest heterogennym zaburzeniem z zajęciem wielu narządów. Jako osobna jednostka chorobowa została wyodrębniona dopiero na początku tego stulecia. Choroba ta stanowi aktualnie najgorętszy obszar badań klinicznych i translacyjnych w różnych dziedzinach medycyny. Zajęcie tarczycy w IgG4RD jest rzadkie, szacuje się, że występuje w około 4% przypadków, może być izolowane lub związane zajęciem innych narządów. Na chwilę obecną zapalenie tarczycy związane z IgG4 (IgG4RTD) reprezentują: zapalenie tarczycy Riedela, które jest włókniejącą odmianą zapalenia tarczycy w chorobie Hashimoto oraz niektórzy pacjenci z orbitopatią Gravesa. Zapalenie tarczycy związane z IgG4 jest często mylone z chorobą nowotworową ze względu na nasilone stwardnienie tarczycy, które powoduje powstanie twardej struktury wyczuwalnej w badaniu palpacyjnym z towarzyszącymi często objawami uciskowymi. Rozpoznanie choroby obejmuje: stwierdzenie wysokich stężeń krążącej IgG4 > 135 mg/dl, zwiększony stosunek w surowicy IgG4 do IgG > 8%, w badaniu immunohistochemicznym stwierdzenie gęstych nacieków zapalnych złożonych z limfocytów i IgG4 dodatnich plazmocytów , z włóknieniem i zarostowym zapaleniem żył oraz zwiększeniem liczby IgG4 dodatnich plazmocytów > 10 w polu widzenia, jeżeli oceniono minimum 3 pola. Glikokortykosteroidy stanowią leczenie pierwszego wyboru w IgG4RTD. Niemniej ich rola w IgG4RTD wymaga dalszej oceny. Na chwilę obecną podstawowe opcje terapeutyczne obejmują: suplementację lewotyroksyny we wtórnej niedoczynności tarczycy, właściwe leczenie choroby Gravesa oraz chirurgiczne usunięcie tarczycy w wypadku pojawienia się objawów uciskowych. **(Endokrynol Pol 2016; 67 (5): 520–524)**

Słowa kluczowe: *immunoglobulina; zapalenie tarczycy w chorobie Hashimoto; zapalenie tarczycy Riedla; choroba związana z IgG4*

Introduction

Immunoglobulin (Ig)-G4-related thyroid disease (IgG4RTD) is a recently recognised, yet to be fully characterised variant of thyroiditis, occurring either alone of as part of systemic IgG4-related disease (IgG4RD), having multi-organ involvement. IgG4-related disease per se as an entity was recognised only in 2001, with autoimmune pancreatitis being the prototype organ involvement [1]. Thyroid involvement in IgG4RD is rare, believed to occur in < 4% of cases [1, 2]. However, it is likely that the diagnosis is grossly under reported due

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to lack of awareness of this clinical entity. The diagnosis of IgG4RTD is a challenge in the absence of definite diagnostic criteria, compounded by a lack of availability of tests required for its diagnosis. In this review we discuss all the available literature regarding the role of IgG4 in the pathogenesis of IgG4RD, the characteristic features of IgG4RD, and the current understanding, pathophysiology, diagnosis, and management of IgG4RD focusing on IgG4RTD.

Methods

Search Strategy and Selection Criteria

References for this review were identified through searches of PubMed, Medline, and Embase for articles published up to November 2015 using the terms "IgG4-related thyroid disease" [MeSH Terms] OR "IgG4-related thyroid disorder" [MeSH Terms] OR "IgG4-related thyroid disease" [All Fields] OR "IgG4-related thyroid disorder" [All Fields] OR "IgG4-related disease" [MeSH Terms] OR "IgG4-related disorder" [MeSH Terms]. The reference lists of the articles thus identified were also searched. The search was not restricted to English-language literature.

Results

The family of Immunoglobulin-G

Representing nearly 75% of all the circulating antibodies, IgG is the commonest form of antibody in the human body [3]. Produced and secreted by plasma cells, they are an important component of the humoral immune system against a variety of foreign antigens including bacteria, viruses, and fungi. They also have an important role in the etiopathogenesis of several autoimmune disorders [3]. IgG have been further divided into four sub-classes based on subtle differences in the structure of the molecule in the hinge region, and its ability to activate and fix compliment [4]. The subclasses have been empirically named as Ig G1, G2, G3, and G4, based on their abundance in the serum [4, 5]. Ig G3 has the highest compliment activating activity followed by Ig G2 and Ig G1. Ig G4 is believed to have minimal or no compliment activating activity, along with the lowest affinity for Fc receptors on phagocytic cells. [4, 5]. It has been suggested that IgG3 along with Ig E appears earliest in the immune response, followed by Ig G2 and G1 [6]. The differential ratios of these three antibodies determine the pattern of immune response. Ig G4 is believed to appear late as a part of the humoral immune process, only on persistent antigenaemia, having a primary role in dampening down inflammation by helping to curtail FcR-mediated processes [6, 7]. The circulating half-life of Ig G4 is 21 days.

Ig-G4 related disease

IgG4RD is a heterogeneous disorder with multi-organ involvement. Its characterisation is still under evolution. IgG4RD was first proposed in relation to autoimmune pancreatitis in 2001 in Japan [8]. Since then, almost every organ in the body has been reported to be involved. Most of the literature on this disease is available from Japan (nearly 80% of all reported cases). However, this disease has subsequently been reported from almost every country in the world.

Determination of the true prevalence of IgG4RD remains a challenge, as diagnostic criteria have not yet been fully standardised, complicated by variable clinical presentation and low general awareness. The majority of data are available from Japan, where it is believed that the incidence of this disease is 0.28–1.08/100,000 population, with 336–1300 patients newly diagnosed per year, and a prevalence of around 100 cases per 1 million inhabitants [8–10]. This disease has predominantly been reported in middle-aged to elderly men, having a sub-acute presentation. In the organ involved, it usually presents as a mass lesion, which may mimic malignancy or infection. Diagnosis is often retrospective following histopathological evaluation of the resected specimen.

Organ specific IgG4RD

The pancreas was the first organ reported to be involved with IgG4RD in the form of autoimmune pancreatitis (AIP), having a prevalence of 2.2 per 100,000 population [11]. These patients usually present with epigastric pain, cholestasis, and weight loss. Eighty per cent of patients with AIP have associated biliary tract involvement, which is known as IgG4-related cholangiopathy [11].

The head and neck region is the part of the body that is perhaps most commonly involved in IgG4RD [2]. In the head and neck region, orbits are the most commonly involved organs observed in more than 50% of cases, followed by salivary glands (22%) and lacrimal glands (18.6%) [2]. Thyroid involvement is a rare manifestation of IgG4RD, believed to occur in 4% of patients [2]. Other organ systems that are involved in IgG4RD include the kidneys, blood vessels, retro-peritoneum, skin, and lungs (Table I).

Pathogenesis

The exact pathogenesis of IgG4RD is not known. It is believed that prolonged exposure to as yet undetermined antigens leads to induction of Th2-mediated immune response and upregulation of regulatory T (Treg) cells. Increased interleukin (IL)-10, IL-12, and IL-21 favour IgG4 secretion from plasma cells [12]. The source of increased circulating levels of IgG4 in these patients is believed to be primarily from the organ/organ system involved. Increased secretion of IL-10 and TGF-b from TH2 cells is responsible for increased fibrosis in the organ system involved.

Table I. *Spectrum of Ig G4-related disorders based on organ involvement*

Tabela I. *Spektrum zaburzeń zależnych od Ig G4 w oparciu o zajęcie narządu*

Organ System	Disease Phenotype
Pancreas	Autoimmune pancreatitis (AIP) 1 and 2; presents with typical features of pancreatitis; prevalence 2.2:100,000 population
Hepatobiliary	Autoimmune hepatitis & cholangiopathy (IgG4 related hepatitis & cholangiopathy); isolated hepatic or biliary involvement is uncommon in < 20% of cases; presents with typical features of cholestatic hepatitis
Ophthalmic	Most common head and neck manifestation of IgG4RD; presents typical with bilateral proptosis; close differential diagnosis include Sjögren's syndrome and thyroid associated orbitopathy which needs to be excluded; also known as orbital pseudotumour, idiopathic orbital inflammation
Salivary & Lacrimal Glands	Usually presents as bilateral swelling; needs to be differentiated from Sjögren's syndrome; Mikulicz syndrome (dacryoadenitis), Küttner's tumour (sclerosing sialo adenitis)
Renal	Presents as tubulo-interstitial nephritis; usually present with proteinuria, haematuria, hypocomplementaemia and increased serum creatinine
Mesentery	Rare manifestation; sclerosing mesenteritis, patient presents with non-specific abdominal pain, computed tomography of the abdomen is the investigation of choice for diagnosis; often associated with retroperitoneal fibrosis and renal involvement
Circulatory System	Rare; aortitis, periaortitis and aortic aneurysm; patients usually present with typical features of angina, rare manifestation; diagnosis commonly missed
Pulmonary	Rare; Usually presents with dyspnoea, cough, haemoptysis, and pleural effusion; diagnosed usually with interstitial pneumonia or pleuritis
Thyroid	Rare; < 4% of all head and neck cases of IgG4RD; Riedel's thyroiditis and fibrosing variant of Hashimoto thyroiditis are the 2 forms
Others	Retroperitoneal fibrosis (Ormond's disease), often associated with hydronephrosis due to associated ureteric compression and blockade; IgG4-related prostatitis, IgG4-related orchitis; IgG4-related cutaneous involvement

One school of thought believes that IgG4 antibodies are not pathogenic, but rather represent a down-regulatory response to another yet to be determined primary process [12, 13]. This is based on the observation that elevated serum and tissue IgG4 concentrations have been observed in a diverse set of disorders including allergic disorders, sarcoidosis, multicentric Castleman's disease, and ChurgStrauss syndrome, along with poor complement activating activity of IgG4 [14–16]. A possible role for molecular mimicry involving helicobacter pylori in the development of AIP has been suggested [12].

Diagnostic Criteria

IgG4RD diagnosis needs a high degree of clinical suspicion or the diagnosis can be easily missed because the clinical presenting features are highly non-specific and dependent primarily on the organ system involved. Usually the disease presents as a mass lesion of the involved organ system, which is usually firm to hard due to the presence of significant fibrosis. Hence the diagnosis is often confused with a malignant lesion.

A diagnostic criterion has been proposed from Japan, to aid the diagnosis [17]. This criterion is believed to be largely valid irrespective of the organ system involved. It has been suggested that in a patient with clinical suspicion, serum IgG4 should be measured first. Serum IgG4 level > 135 mg/dL is highly suggestive of IgG4RD, and should warrant further investigation for confirmation of the diagnosis [17, 18]. Among serologic tests, a serum IgG4 to IgG ratio > 8% is also highly suggestive of IgG4RD (11). Immunohistochemistry (IHC) has an important role in the diagnosis of the IgG4RD (11,17). Hence it is recommended that a biopsy of the suspected involved organ system, if possible, should always be done.

In the histopathology evaluation, dense lymphoplasmacellular inflammatory infiltrate consisting of IgG4-positive plasma cells with storiform fibrosis and obliterative phlebitis is typical for IgG4RD [18–20]. Obliterative phlebitis is defined as inflammation of the blood vessels along with obliteration of the lumen [19]. It is recommended that IgG4-positive plasma cell > 10 cells per high-power field, when at least three high-power fields have been evaluated, are diagnostic of IgG4RD [19, 20]. Also, IgG4-positive cells to IgG-positive cells in the involved tissue > 40% is also highly suggestive of IgG4RD [20].

IgG4 related thyroid disease (IgG4RTD)

IgG4RTD is one of the newest discovered organ involvement manifestations of IgG4RD. The disease is yet to be well characterised. Riedel's thyroiditis and fibrosing variant of Hashimoto's thyroiditis (FVHT) are believed to be the two predominant types of IgG4-related thyroid disease. The closest differential diagnosis is autoimmune thyroiditis and differentiating from which often remains a challenge. However, in contrast to the female preponderance of autoimmune (Hashimoto's) thyroiditis, there is no sex predilection for IgG4RTD. It is believed to occur equally among males and females [1, 2]. Recent reports have also suggested that a small fraction of Graves' disease patients also have elevated IgG4 levels with some features suggestive of IgG4TD [21, 22]. Takeshima K et al. reported that 6.4% of 109 patients with Graves' disease had elevated IgG4 titres [21]. Bozkirli E et al. observed that IgG4 levels were higher

in patients of Graves' disease with Graves' orbitopathy (GO) as compared to those without orbitopathy, and the levels correlated with clinical activity score [22].

Riedel's thyroiditis, first reported in 1896, is an inflammatory sclerosing disorder of the thyroid, having an estimated incidence of 1.06 cases per 100,000 population [23]. Classically the thyroid gland in Riedel's thyroiditis has been referred to as "cast iron struma", viz. gland as hard as iron [23]. The gland is hard to palpate; hence, it is often confused with thyroid malignancy. The gland in Riedel's thyroiditis does not usually move with swallowing or deglutition. It exerts local compressive effects resulting in constriction of the airway by invasive growth leading to respiratory distress. Patients may also develop laryngeal paralysis, hence altered voice and speech [23]. All of these features mimic malignant tumour. It is, however, important to highlight that all the histopathological features that are seen in IgG4-related disease have been observed in some patients with Riedel's thyroiditis, viz. dense lymphoplasmacellular inflammatory infiltrate consisting of IgG4-positive plasma cells with storiform fibrosis and obliterative phlebitis. A review of the literature database in Japan revealed only 10 confirmed cases of Riedel's thyroiditis over a 25-year period (1988–2012), of which only two patients had definitive evidence of IgG4RTD [24]. Hence, it is likely that Riedel's thyroiditis itself is a spectrum disorder, with a fraction of patients having features suggestive of IgGrRTD.

Fibrosing variant of Hashimoto's thyroiditis as of today is an ill-defined disorder. It has been observed that some patients with Hashimoto's thyroiditis have a firmer gland on palpation, and perhaps more rapidly progress to overt primary hypothyroidism. These patients have been observed to have very high levels of circulating anti-thyroid peroxidase antibodies and increased circulating IgG4 levels. Histopathological evaluation of the resected thyroid specimen revealed a picture similar to that seen in IgG4-related disorders. However, it is important to highlight that obliterative phlebitis, which is classically seen in IgG4-related diseases as well as Riedel's thyroiditis, is not seen in fibrosing variant of Hashimoto's thyroiditis. Also, IgA, which is specifically elevated in Riedel's thyroiditis, is not elevated in fibrosing variant of Hashimoto's thyroiditis.

A recent study from Poland revealed that as many as one-third of patients of Hashimoto's thyroiditis had increased circulating levels of IgG4 [9]. In a cohort of 53 patients with Hashimoto's thyroiditis, 32.5% had IgG4 levels > 135 IU/mL [9]. The authors observed higher circulating levels of TNFa and higher levothyroxine dose requirement for managing hypothyroidism in the subset of patients having increased IgG4 [9]. In contrast, another recent paper from Japan reported that only 6 out of 149 (4%) consecutively evaluated patients of Hashimoto's thyroiditis had elevated serum IgG4 > 135 IU/mL [24]. Levothyroxine requirement and titres of anti-TPO antibody were comparable in patients with elevated IgG4 antibody titres as compared to those having normal anti-TPO antibody titres [25]. Patients with elevated anti-TPO antibody titres were older and exhibited enlarged hypoechoic areas in the thyroid gland on ultrasonography [25]. Two out of the six patients with elevated IgG4 antibody titres had extrathyroidal involvement (eyelids and lacrimal glands) [25].

It is important to highlight that, as of today, histopathology remains the investigation of choice for diagnosis of IgG4-related thyroid disease, because serum IgG4 is elevated in only 70% of diagnosed cases. In a study from Japan evaluating thyroid tissue samples obtained from 70 patients with Hashimoto's thyroiditis managed surgically, 19 patients (27.14%) were diagnosed to have IgG4RTD based on the presence of increased IgG4-positive cells along with increased IgG4/IgG ratio on immunohistochemistry of thyroid tissue [26]. However, it is important to highlight that different studies have used slightly different immunohistochemical criteria in defining IgG4-related sclerosing disease (greater than 10, greater than 20, and greater than 30 IgG4-positive plasma cells per HPF) [27, 28]. With regards to IgG4RTD a cutoff of 20 IgG4-positive plasma cells per HPF and greater than 30% IgG4/IgG ratio has been proposed, which was also used in the above-mentioned study [26]. Hence it is likely the diagnostic criteria for IgG4RTD may undergo further subtle changes in the future once data from a larger number of patients are available from different ethnic groups.

Patients with IgG4RTD in the previously discussed study from Japan [26] were observed to be more likely male, had rapid disease progression, higher occurrence of subclinical hypothyroidism, more diffuse low echogenicity on ultrasonography, and higher level of circulating antibody titres [26]. A similar study from China retrospectively diagnosed 22.64% (12/53) of patients of Hashimoto's thyroiditis to have IgG4RTD based on the immunohistochemical evaluation of thyroid tissue [29]. In this study, no significant differences were found in the serum levels of IgG4, total IgG, and IgG4/IgG ratio in patients with IgG4-related Hashimoto's thyroiditis as compared to those with non-IgG4-related Hashimoto's thyroiditis [29]. However, serum anti-TPO antibody and anti-thyroglobulin antibody levels were significantly higher in patients with IgG4-related Hashimoto's thyroiditis group [29].

Treatment

Treatment of IgG4-related thyroid disorders is believed to be the same as patients with IgG4-related diseases. Maximum data on treatment has been obtained from

patients with autoimmune pancreatitis, which has been extrapolated and used for patients with other organ system involvement. Glucocorticoids form the mainstay for treatment of IgG4 related disease. The Japanese guidelines recommend the use of prednisolone at 0.6 mg/kg/day (usually at 30-40 mg per day) for a period of three months, which is known as the induction regimen for inducing remission, followed by a maintenance therapy of low dose prednisolone (2.5–5 mg per day) for 6–12 months, to maintain remission and prevent relapse [11]. Steroid sparing agents like methotrexate, azathioprine, mycophenolate, rituximab, cyclosporine, chlorambucil, and cyclophosphamide have been tried in the management of IgG4RD [2, 11]. However, their use in the management of IgG4RTD needs to be evaluated.

Glucocorticoids have been found to be beneficial in reducing circulating levels of IgG4 and size of pituitary, and improving pituitary function in a patient with IgG4-related infundibulo-hypophysitis [30]. However, as yet the use of glucocorticoids in the management of IgG4RTD has not been evaluated and established in terms of actual hastening the recovery and reducing the need for long-term levothyroxine supplementation, a sequel of resulting primary hypothyroidism. Glucocorticoids are not recommended in the management of Hashimoto's thyroiditis due to lack of clinical evidence [31, 32].

Conclusions

IgG4RD and IgG4RTD represent one of the hottest areas of research globally in this decade. To summarise, IgG4RTD tends to have an equal sexual predisposition as compared to a predominantly female predisposition for Hashimoto's thyroiditis. It tends to occur at an older age, with more sclerosing involvement of the gland, which can mimic malignancy. It is usually associated with high circulating titres of anti-thyroid peroxidase antibodies. Glucocorticoids may have some role in reducing the associated fibrosis and hastening recovery; this needs further evaluation. As of today, levothyroxine supplementation remains the primary modality of therapy in the case of ensuing hypothyroidism, appropriate treatment of Graves' disease/orbitopathy, and surgical excision of the gland in case of compressive symptoms.

References

1. Kawashima ST, Tagami T, Nakao K et al. Serum levels of IgG and IgG4 in Hashimoto thyroiditis. Endocrine. 2014; 45: 236-43.
2. Mulholland GB, Jeffery CC, Satija P et al. Immunoglobulin G4-related diseases in the head and neck: a systematic review. J Otolaryngol Head Neck Surg. 2015; 44: 24. doi: 10.1186/s40463-015-0071-9.
3. Junqueira, Luiz C, Jose Carneiro. Basic Histology. McGraw-Hill, 2003 ISBN 0-8385-0590-2.
4. Bonilla FA. Pharmacokinetics of immunoglobulin administered via intravenous or subcutaneous routes. Immuno Allergy Clin N Am 2008; 28: 803–819. doi: 10.1016/j.iac.2008.06.006.
5. Hashira S, Okitsu-Negishi S, Yoshino K. Placental transfer of IgG subclasses in a Japanese population. Pediatr Int 2000; 42: 337–342.
6. Collins AM, Jackson KJ. A Temporal Model of Human IgE and IgG Antibody Function. Front Immunol 2013; 4: 235.
7. Gao ZH, McAlister VC, Wright Jr. JR et al. Immunoglobulin-G subclass antidonor reactivity in transplant recipients. Liver Transplantation 2004; 10: 1055–1059.
8. Hamano H, Kawa S, Horiuchi A et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 200; 344: 732–738.
9. Popławska-Kita A, Kościuszko-Zdrodowska M, Siewko K et al. High Serum IgG4 Concentrations in Patients with Hashimoto's Thyroiditis. Int J Endocrinol 2015; 2015: 706843.
10. Umehara H, Okazaki K, Masaki Y et al. Research Program for Intractable Disease by Ministry of Health, Labor and Welfare (MHLW) Japan G4 team. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol 2012; 22: 1–14.
11. Kleger A, Seufferlein T, Wagner M et al. IgG4-related autoimmune diseases: Polymorphous presentation complicates diagnosis and treatment. Dtsch Arztebl Int 2015; 112: 128–135.
12. Zen Y, Nakanuma Y. Pathogenesis of IgG4related disease. Curr Opin Rheumatol 2011; 23: 114.
13. Fragoulis GE, Moutsopoulos HM. IgG4 syndrome: old disease, new perspective. J Rheumatol 2010; 37: 1369.
14. Mahajan VS, Mattoo H, Deshpande V et al. IgG4related disease. Annu Rev Pathol 2014; 9: 3
15. Aalberse RC, Stapel SO, Schuurman J et al. Immunoglobulin G4: an odd antibody. Clin Exp Allergy 2009; 39: 469.
16. Liu LJ, Chen M, Yu F et al. IgG subclass distribution, affinity of anti-myeloperoxidase antibodies in sera from patients with Wegener's granulomatosis and microscopic polyangiitis. Nephrology (Carlton) 2008; 13: 629.
17. Okazaki K, Umehara H. Are Classification Criteria for IgG4-RD Now Possible? The Concept of IgG4-Related Disease and Proposal of Comprehensive Diagnostic Criteria in Japan. Int J Rheumatol 2012; 2012: 357071.
18. Sah RP, Chari ST. Serologic issues in IgG4-related systemic dis- ease and autoimmune pancreatitis. Curr Opin Rheumatol 2011; 23: 108–113.
19. Masaki Y, Kurose N, Yamamoto M et al. Cutoff Values of Serum IgG4 and Histopathological IgG4+ Plasma Cells for Diagnosis of Patients with IgG4-Related Disease. Int J Rheumatol. 2012; 2012: 580814.
20. Khosroshahi A, Stone JH. A clinical overview of IgG4-related systemic disease. Curr Opin Rheumatol 2011; 23: 57–66.
21. Takeshima K, Inaba H, Furukawa Y et al. Elevated serum immunoglobulin G4 levels in patients with Graves' disease and their clinical implications. Thyroid 2014; 24: 736–743.
22. Bozkirli E, Bakiner OS, Ersozlu Bozkirli ED et al. Serum Immunoglobulin G4 levels are elevated in patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf) 2014. doi: 10.1111/cen.12671.
23. Hennessey JV. Clinical review: Riedel's thyroiditis: a clinical review. J Clin Endocrinol Metab 2011; 96: 3031–3041.
24. Takeshima K, Inaba H, Ariyasu H et al. Clinicopathological features of Riedel's thyroiditis associated with IgG4-related disease in Japan. Endocr J 2015; 62: 725–731.
25. Takeshima K, Ariyasu H, Inaba H et al. Distribution of serum immunoglobulin G4 levels in Hashimoto's thyroiditis and clinical features of Hashimoto's thyroiditis with elevated serum immunoglobulin G4 levels. Endocrine Journal 2015; 62: 711–717.
26. Li Y, Nishihara E, Hirokawa M et al. Distinct clinical, serological, and sonographic characteristics of hashimoto's thyroiditis based with and without IgG4-positive plasma cells. J Clin Endocrinol Metab 2010; 95: 1309–1317.
27. Deshpande V, Chicano S, Chiocca S et al. Autoimmune pancreatitis: a systemic immune complex mediated disease. Am J Surg Pathol 2006; 30: 1537–1545.
28. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4--related sclerosing disease. J Gastroenterol 2006; 41: 613–625.
29. Zhang J, Zhao L, Gao Y et al. A classification of Hashimoto's thyroiditis based on immunohistochemistry for IgG4 and IgG. Thyroid 2014; 24: 364–370.
30. Iseda I, Hida K, Tone A et al. Prednisolone markedly reduced serum IgG4 levels along with the improvement of pituitary mass and anterior pituitary function in a patient with IgG4-related infundibulo-hypophysitis. Endocr J 2014; 61: 195–203.
31. Blizzard RM, Hung M, Chandler RW et al. Hashimoto's thyroiditis. Clinical and laboratory response to prolonged cortisone therapy. N Engl J Med 1962; 267: 1015–1020.
32. Ito S, Tamura T, Nishikawa M. Effects of desiccated thyroid, prednisolone and chloroquine on goiter and antibody titer in chronic thyroiditis. Metabolism 1968; 17: 317–325.