

Original Article

Clinical significance and diagnostic value of IgG4 in patients with sicca syndrome

Quanhong Qin^{1*}, Yan Li^{1*}, Zhiqi Yin¹, Huiping Xu², Zhandong Hu¹, Lili Zhai¹, Mingfang Zhang¹

Departments of ¹Pathology, ²Immunology, Tianjin First Center Hospital, Tianjin 300192, China. *Equal contributors and co-first authors.

Received April 26, 2017; Accepted July 25, 2018; Epub August 15, 2018; Published August 30, 2018

Abstract: Objective: To study the sensitivity and specificity of IgG4 in the diagnosis of Sicca syndrome (SS) and to explore its clinical application value in the diagnosis of SS. Methods: The medical records of 215 patients with Sicca syndrome (SS group), 304 cases with simple connective tissue disease (CTD group) and 100 healthy volunteers (control group) were analyzed retrospectively. Results: A difference in course of disease was found between the SS and CTD groups ($P < 0.05$). The course of disease in patients with sSS was longer than that in patients with pSS ($P < 0.05$). The serum IgG4 levels in the SS and CTD groups were higher than that in the control group and the serum IgG4 levels were higher in the SS group than that in CTD group ($P < 0.05$). Moreover, the AUC of IgG4 in diagnosing SS from healthy people was 0.868, the diagnostic level of IgG4 was 0.485 g/L. AUC of IgG4 in diagnosing SS from CTD was 0.675, the IgG4 diagnostic level was 0.541 g/L, the sensitivity was 71.7% and the specificity was 59.1%. Conclusion: IgG4 has good application value in SS diagnosis and IgG4 is applicable as a supplement to routine diagnosis of SS patients so as to increase sensitivity.

Keywords: IgG4, sicca syndrome, clinical significance, diagnostic value

Introduction

Sicca syndrome (SS) is a diffuse connective tissue disease (CTD) with the clinical feature of frequently observed high lymphocytic infiltration. The incidence of SS in females is higher than that in males and mechanisms of occurrence have not been clearly studied [1, 2]. Patients with SS often suffer from joint pain, arthritis and systemic injury of exocrine glands and various autoimmune antibodies appear in serum [3]. These clinical features and serum antibodies are the main basis for the diagnosis of SS. However, patients with primary sicca syndrome (pSS) and patients with SS combined with early rheumatoid arthritis may present clinical symptoms such as polyarthritis and dryness without bone destruction accompanied by positive rheumatoid factor [4]. Therefore, the sensitivity and specificity of SS diagnosis remain to be improved.

Immunoglobulin G (IgG) is the main component of immunoglobulin produced by plasma cells, which accounts for approximately 75% of

all immunoglobulin and is an important functional molecule in the immune system. IgG is composed of four subtypes, including IgG1, IgG2, IgG3, and IgG4, of which IgG4 is the least abundant, accounting for about 4% of all IgG. Its content in normal adult serum is 0.08-1.40 g/L, and there are significant differences in structure compared to other IgG subtypes [5, 6], so better sensitivity and specificity will be achieved when it is applied for diagnosis. Autoimmune diseases often present abnormal changes in expression levels of IgG4, such as the elevated level of IgG4 in patients with systemic lupus erythematosus (SLE) [7]. Reports on application of IgG4 in diagnosis of IgG-related diseases have increased [8, 9], but reports of IgG4 in SS are rare.

Therefore, this study was expected to explore the diagnostic value of IgG4 in SS by detecting the level of expression of IgG 4 in serum of patients with SS, CTD and in healthy individuals, and provide a supplementary basis for the clinical diagnosis of SS.

To study the sensitivity and specificity of IgG4 in the diagnosis of sicca syndrome

Table 1. General information for three groups of subjects

	SS group	CTD group	Control group	Statistic	P-value
Group number	215	304	100		
Sex [n (%)]				30.062	< 0.001
Male	29 (13.5)	41 (13.5)	45 (45.0)		
Female	186 (86.5)	263 (86.5)	55 (55.0)		
Age (year)	46.2±10.7 ^a	38.6±15.7 ^{a,b}	35.7±10.2	29.091	< 0.001
pSS	139 (64.7)				
sSS	76 (35.3)				
RA		167 (54.9)			
SLE		137 (45.1)			
Course of disease (year)	3.2±1.2	2.7±1.2		4.676	< 0.001

Note: a: compared with control group, P < 0.05; b: compared with SS group, P < 0.05.

Table 2. Comparison of General Information between SS Group and CTD Group

	Group number	Men	Female	Age (year)	Course of disease (year)
SS group	pSS 139	17 (12.2)	122 (87.8)	46.1±11.7	2.8±1.6
	sSS 76	12 (15.8)	64 (84.2)	46.3±9.6	3.6±1.2
Statistic		0.272		0.127	3.811
P-value		0.532		0.899	< 0.001
CTD group	RA 167	29 (17.4)	138 (82.6)	38.4±11.3	2.5±0.9
	SLE 137	15 (10.9)	122 (89.1)	38.8±16.5	2.9±1.5
Statistic		2.012		0.250	2.873
P-value		0.140		0.803	0.004

Table 3. Expression Level Analysis Result of IgG4 in Each Group of Patients

		IgG4 (g/L)	Statistic	P-value
SS group	pSS	0.515±0.101	67.76	< 0.001
	sSS	0.629±0.133		
Statistic		2.598		
P-value		0.010		
CTD group	RA	0.462±0.128	0.483±0.125 ^a	
	SLE	0.504±0.117		
Statistic		2.985		
P-value		0.003		
Control group		0.411±0.069 ^{a,b}		

Note: a: compared with SS group, P < 0.05; b: compared with CTD group, P < 0.05.

Materials and methods

Research subjects

A retrospective analysis was conducted involving 215 cases with SS (SS group) enrolled in Tianjin First Center Hospital. Among them 139 were suffering pSS and a further 76 cases were

diagnosed with secondary SS (sSS). All patients were in compliance with the SS international diagnosis standard (2011) [10] and none of the patients were given hormones or immunotherapy. Sicca syndrome classification criteria are as follows: A, Oral symptoms (one or more of the three items): 1. Daily sense of dry mouth lasts more than 3 months; 2. Repeated or continuous swelling of the parotid glands in adulthood; 3. Use water to help dry food. B, Ocular symptoms (one or more of the three items): 1. The dry eye that cannot be tolerated for more than 3 months; 2. There are repeated sand into the eyes or sanding feeling; 3. Daily use of artificial tears 3 or more times. C, Eye signs (one or more of the following tests are positive): 1. Schirmer I test (+); 2. Corneal staining (+). D, Histological examination of the lower lip gland pathology showed that the lymphocyte stove. E, Autoantibodies: Anti-SSA or Anti-SSB (+) (Double Diffusion). 304 cases of simple CTD (CTD

group) were selected during the same period including 167 cases with rheumatoid arthritis (RA) and 137 cases with systemic lupus erythematosus (SLE), excluding patients diagnosed with other CTDs, such as systemic sclerosis and polymyositis. All of the 519 patients were primarily diagnosed in our hospital and 100 healthy volunteers over the same period (con-

To study the sensitivity and specificity of IgG4 in the diagnosis of sicca syndrome

trol group) were selected. This study was approved by the medical ethics committee of our hospital and 619 subjects or their family members gave informed consent.

Methods

Fasting peripheral venous blood was collected in the early morning before treatment. IgG4 was detected by scatter turbidimetry, and anti-nuclear antibody (ANA) was detected by an indirect immunofluorescence technique. The IgG4 kit was purchased from Siemens Shanghai Medical Equipment Ltd., and the ANA kit was purchased from Oumeng Medical Laboratory Diagnosis Co., Ltd. The experimental operation of IgG4 was strictly implemented in compliance with the standard operating procedure from Beckman Coulter, Inc.

Statistical analysis

SPSS 19.0 (Asia Analytics, formerly SPSS China) was employed for statistical analysis. The count data were expressed as rate, and Chi-squared (χ^2) tests were used for comparison of the rates. The measurement data were expressed as $\bar{x} \pm \text{sd}$, and analyzed by application of t tests. Multiple groups were analyzed by application of ANOVA. The receiver operating characteristic curve (ROC) was used to analyze the diagnostic value of IgG4 in SS. $P < 0.05$ indicates statistical significance.

Results

General information

There were 215 patients diagnosed with SS enrolled, including 29 males and 186 females, with the male/female ratio of 1: 6.41 and an average age of 46.2 ± 10.7 years. Among all the patients with SS, 139 suffered pSS and 76 patients had sSS with an average course of illness of 3.2 ± 1.2 years. There were 304 patients with CTD, including 44 males and 260 females, with a male/female ratio of approximately 1:6.41 and an average age of about 38.6 ± 15.7 years old, of which 167 patients suffered RA and 137 patients had SLE, with an average course of disease of 2.7 ± 1.2 years. There were 100 healthy volunteers enrolled, including 45 males and 55 females with an average age of 35.7 ± 10.2 years old. Gender and age varied across the three groups ($P <$

0.05). The proportion of female patients in the SS and CTD groups was significantly higher than that of male patients ($P < 0.05$). The course of disease in the SS group was significantly longer than that of the CTD group (**Table 1**).

General data comparison between the sub-groups of SS group and the CTD group demonstrated that the male/female ratio and patient age were not statistically different between the SS and the CTD groups ($P > 0.05$), but the course of disease in patients with sSS and SLE was longer than that in patients with pSS and RA, respectively ($P < 0.05$) (**Table 2**).

Analysis results of the expression level of IgG4 in each group of subjects

The mean serum IgG4 levels in patients of the SS group was 0.572 ± 0.069 g/L, that in CTD patients was 0.483 ± 0.125 g/L, and the serum IgG4 level in the subjects of the control group was 0.411 ± 0.123 g/L. The serum levels of the three groups of patients were statistically different ($P < 0.05$); the levels of serum IgG4 in patients of the SS and CTD groups were higher than that in the control group ($P < 0.05$) and the serum IgG4 level in the SS group was higher than that in the CTD group ($P < 0.05$). Intragroup analysis results illustrated that the serum IgG4 levels in patients with pSS and RA was lower than those with sSS and SLE, respectively ($P < 0.05$) (**Table 3**).

Diagnostic value analysis of IgG4 in patients with SS and healthy volunteers

The ROC curve analysis displayed that the AUC for SS diagnosis with IgG4 was 0.868 and the 95% confidence interval was 82.9%-90.8%, the cut-off value of the IgG4 level was 0.485 g/L with the 84.8% sensitivity and the 74.4% specificity (**Figure 1**).

Differential diagnosis value of IgG4 in patients with SS and CTDs

The results of ROC curve analysis displayed that the AUC of the differential diagnosis of SS and CTD with IgG was 0.675, the 95% confidence interval was 62.8%-72.1%, the cut-off value of the IgG4 level was 0.541 g/L with sensitivity 71.7% and specificity 59.1% (**Figure 2**).

To study the sensitivity and specificity of IgG4 in the diagnosis of sicca syndrome

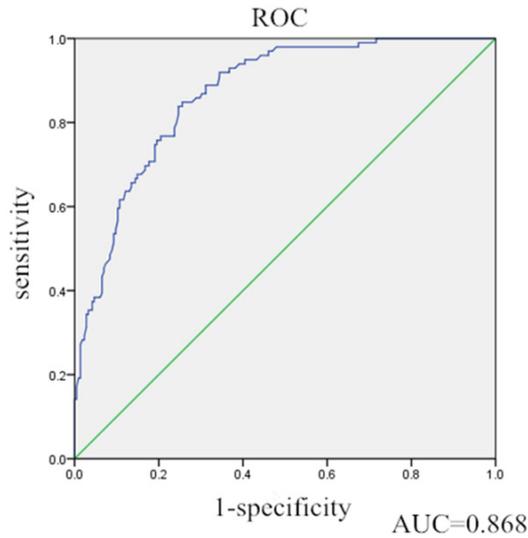


Figure 1. IgG4 differential diagnosis of SS patients and normal ROC curves. AUC = 0.868.

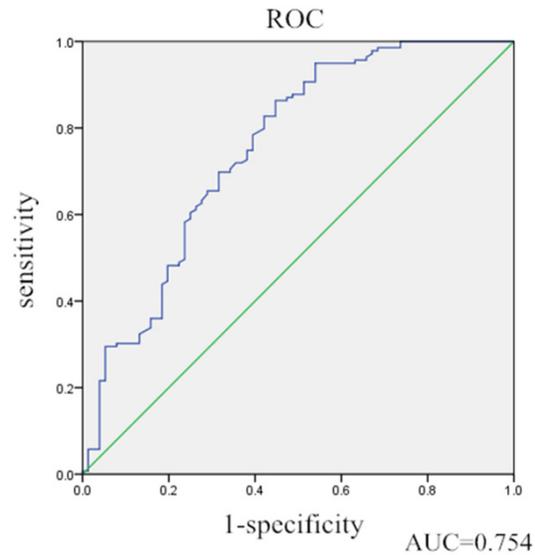


Figure 3. IgG4 differential diagnosis of the ROC curve of pSS and sSS patients. AUC = 0.754.

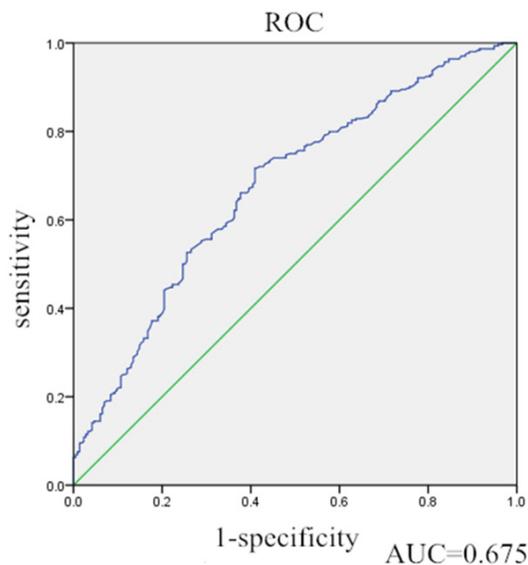


Figure 2. IgG4 differential diagnosis of SS patients with CTD ROC curve. AUC = 0.675.

The differential diagnosis value of IgG4 in patients with pSS and sSS via IgG4

The ROC curve analysis displayed that the AUC of pSS and sSS in the differential diagnosis of IgG4 was 0.754, the 95% confidence interval was 68.3%-82.6%, the cut-off value of the IgG4 level was 0.629 g/L with 86.3% sensitivity and 55.3% specificity (**Figure 3**).

Discussion

The pathogenesis of SS has not been studied clearly so far, but it is reported that damage to

normal immune tolerance mechanisms may be one of the important reasons. The level of autoimmune antibodies in peripheral blood of SS patients is often increased and IgG is a very important component [11, 12]. IgG has high specificity and affinity and is often expressed abnormally in some autoimmune diseases, so it has significant diagnostic value for autoimmune diseases [8, 13, 14]. IgG4 is present at extremely low levels in the healthy human body and is also the least abundant of all IgG antibodies [15]. Therefore, this study hopes to explore the diagnostic value of IgG4 in SS, and provide reference levels for the clinical diagnosis of SS.

This study used scattering turbidimetry to detect the expression level of IgG4 in serum of all subjects and the analysis showed that the abnormal expression of IgG4 increased in both SS and CTD, and the expression level of IgG4 in sSS patients was significantly higher than that of pSS patients. Also, the expression level of IgG4 in SLE patients was significantly higher than in RA patients. The pathogenesis of SS has not yet been studied clearly; therefore, the abnormal increase of IgG4 expression may be related to an imbalance of immune function. However, many scholars have found during the study of IgG4-related diseases that the immune activity of Th2 cells and Treg cells is enhanced with higher levels of IL-4 expressed by Th2 and more IgG4 secreted by B-lymphocytes under the induction of IL-13. The IL-10 expressed by

To study the sensitivity and specificity of IgG4 in the diagnosis of sicca syndrome

Th2 cells and Treg cells also tends to be converted to IgG4 [16-18].

Further study is necessary for the exploration of the reason for the abnormal increase in IgG4 levels in SS patients. Studies [19-21] have found that IgG4 expression is positive or elevated in SS patients, which is similar to our results. The IgG4 in normal conditions is at the lowest serum level among all the IgG subtypes [22], thus, it may be the most sensitive to the occurrence and development of disease. We analyzed the value of application of IgG4 in the diagnosis of SS, and the results comparing the diagnostic value of IgG4 between the SS group and the healthy volunteer group identified that when the IgG4 was 0.485 g/L, the sensitivity of SS diagnosis may reach 84.8%, which is significantly improved compared with that for ANA (68.8%), Anti-SSA (63.7%), and Anti-SSB (37.7%), and the area under the curve for ROC could reach 0.868. However, the IgG4 specificity in SS diagnosis is only 74.4%.

Therefore, we can expect IgG4 as a supplement to the routine diagnosis of SS to effectively improve the sensitivity, whereas how to improve the specificity of SS diagnosis remains to be explored further. Few reports have been emerged regarding the diagnosis of SS by IgG4 in recent years. However, it was reported [23] that the sensitivity and specificity of IgG4 in the diagnosis of IgG4-related diseases could reach 95.10% and 90.76%, respectively. There is also a study [24] reporting that IgG4, when used in the diagnosis of IgG4-related diseases and combined with IgG4/IgG, would effectively improve the specificity and improve the relatively low specificity in diagnosis compared with using the single IgG4 level. Due to defects of experimental design, we did not analyze IgG4/IgG and will make corrections in future research. We further analyzed the application value of IgG4 in the diagnosis of pSS and sSS and the results demonstrated that the optimal diagnostic level of IgG4 was 0.629 g/L and, at this time, the sensitivity was 71.7%, the specificity was only 59.1%. Therefore, the value of the differential diagnosis of pSS and sSS still needs to be further explored despite its area under curve of ROC was greater than 0.7.

We also analyzed the value of IgG4 in the differential diagnosis of SS and CTD, but the results were still not satisfactory and the area under curve of the ROC was only 0.675.

Therefore, the diagnosis of SS by application of IgG4 still needs more diagnostic indices included for combination diagnosis. The results of the basic data analysis found that there was a difference in age among the three groups and we speculated that with increasing age, the immune function gradually declines and the degree of imbalance also increases, which causes the exposure of related epitopes and leads to autoimmune diseases. This study only included two kinds of CTDs, including SLE and RA as well as pSS; other CTDs and pSS cases were excluded due to too few patients. Therefore, the results of this study were also satisfactory and we hope to enlarge the number of cases in future studies as a supplement to the study results.

To sum up, IgG4 has a significant application value in SS diagnosis and is applicable as a supplement to routine diagnosis of SS patients with increased sensitivity.

Acknowledgements

This work was supported by Science & Technology Foundation of Tianjin Health Bureau (2013KZ027).

Disclosure of conflict of interest

None.

Address correspondence to: Mingfang Zhang, Department of Pathology, Tianjin First Center Hospital, 24 Fukang Road, Nankai District, Tianjin 300192, China. Tel: +86-022-23626345; Fax: +86-022-23626199; E-mail: Zhangmingfang09@163.com

References

- [1] Atzeni F, Galaverna S, Colombo D, Gianturco L, Boccassini L, Sarzi-Puttini P and Turiel M. AB0568 can speckle tracking echocardiography detect left subclinal ventricular dysfunction in patients with primary sicca syndrome? *Ann Rheum Dis* 2015; 74: 1090.
- [2] Nocturne G and Mariette X. Sjögren syndrome-associated lymphomas: an update on pathogenesis and management. *Br J Haematol* 2015; 168: 317-327.
- [3] Fragkioudaki S, Mavragani CP and Moutsopoulos HM. Predicting the risk for lymphoma development in Sicca syndrome: an easy tool for clinical use. *Medicine* 2016; 95: e3766.
- [4] Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F and Zhong R. Epidemiology of primary Sjögren's syndrome: a systematic review and me-

To study the sensitivity and specificity of IgG4 in the diagnosis of sicca syndrome

- ta-analysis. *Ann Rheum Dis* 2015; 74: 1983-1989.
- [5] Besser TE, McGuire T, Gay C and Pritchett L. Transfer of functional immunoglobulin G (IgG) antibody into the gastrointestinal tract accounts for IgG clearance in calves. *J Virol* 1988; 62: 2234-2237.
- [6] Zeng MY, Cisalpino D, Varadarajan S, Hellman J, Warren HS, Cascalho M, Inohara N and Núñez G. Gut microbiota-induced immunoglobulin G controls systemic infection by symbiotic bacteria and pathogens. *Immunity* 2016; 44: 647-658.
- [7] Boonstra K, Culver EL, de Buy Wenniger LM, Heerde MJ, Erpecum KJ, Poen AC, Nieuwkerk KM, Spanier B, Witteman BJ and Tuynman HA. Serum immunoglobulin G4 and immunoglobulin G1 for distinguishing immunoglobulin G4-associated cholangitis from primary sclerosing cholangitis. *Hepatology* 2014; 59: 1954-1963.
- [8] Nakanuma Y, Ishizu Y, Zen Y, Harada K and Umemura T. Histopathology of IgG4-related autoimmune hepatitis and IgG4-related hepatopathy in IgG4-related disease. *Semin Liver Dis* 2016; 36: 229-241.
- [9] Carruthers MN, Topazian MD, Khosroshahi A, Witzig TE, Wallace ZS, Hart PA, Deshpande V, Smyrk TC, Chari S and Stone JH. Rituximab for IgG4-related disease: a prospective, open-label trial. *Ann Rheum Dis* 2015; 74: 1171-1177.
- [10] Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK and Piano S. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol* 2015; 62: 968-974.
- [11] Seror R, Theander E, Brun JG, Ramos-Casals M, Valim V, Dörner T, Bootsma H, Tzioufas A, Solans-Laqué R, Mandl T, Gottenberg JE, Hachulla E, Sivils KL, Ng WF, Fauchais AL, Bombardieri S, Valesini G, Bartoloni E, Saraux A, Tomsic M, Sumida T, Nishiyama S, Caporali R, Kruize AA, Vollenweider C, Ravaud P, Vitali C, Mariette X, Bowman SJ; EULAR Sjögren's Task Force. Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). *Ann Rheum Dis* 2015; 74: 859-866.
- [12] Brito-Zerón P, Acar-Denizli N, Zeher M, Rasmussen A, Seror R, Theander E, Li X, Baldini C, Gottenberg JE, Danda D, Quartuccio L, Priori R, Hernandez-Molina G, Kruize AA, Valim V, Kvarnstrom M, Sene D, Gerli R, Praprotnik S, Isenberg D, Solans R, Rischmueller M, Kwok SK, Nordmark G, Suzuki Y, Giacomelli R, Devauchelle-Pensec V, Bombardieri M, Hofauer B, Bootsma H, Brun JG, Fraile G, Carsons SE, Gheita TA, Morel J, Vollenweider C, Atzeni F, Retamozo S, Horvath IF, Sivils K, Mandl T, Sandhya P, De Vita S, Sanchez-Guerrero J, van der Heijden E, Trevisani VFM, Wahren-Herlenius M, Mariette X, Ramos-Casals M; EULAR-SS Task Force Big Data Consortium. Influence of geolocation and ethnicity on the phenotypic expression of primary Sjögren's syndrome at diagnosis in 8310 patients: a cross-sectional study from the big data Sjögren project consortium. *Ann Rheum Dis* 2017; 76: 1042-1050.
- [13] Zuo Y, Evangelista F, Culton D, Guilabert A, Lin L, Li N, Diaz L and Liu Z. IgG4 autoantibodies are inhibitory in the autoimmune disease bullous pemphigoid. *J Autoimmun* 2016; 73: 111-119.
- [14] Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, Chari ST, Della-Torre E, Frulloni L, Goto H, Hart PA, Kamisawa T, Kawa S, Kawano M, Kim MH, Kodama Y, Kubota K, Lerch MM, Lohr M, Masaki Y, Matsui S, Mimori T, Nakamura S, Nakazawa T, Ohara H, Okazaki K, Ryu JH, Saeki T, Schleinitz N, Shimatsu A, Shimosegawa T, Takahashi H, Takahira M, Tanaka A, Topazian M, Umehara H, Webster GJ, Witzig TE, Yamamoto M, Zhang W, Chiba T, Stone JH; Second International Symposium on IgG4-Related Disease. International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheumatol* 2015; 67: 1688-1699.
- [15] Wallace ZS, Deshpande V, Mattoo H, Mahajan VS, Kulikova M, Pillai S and Stone JH. IgG4-related disease: clinical and laboratory features in one hundred twenty-five patients. *Arthritis Rheumatol* 2015; 67: 2466-2475.
- [16] Wallace ZS, Mattoo H, Carruthers M, Mahajan VS, Della Torre E, Lee H, Kulikova M, Deshpande V, Pillai S and Stone JH. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. *Ann Rheum Dis* 2015; 74: 190-5.
- [17] Krishna R, Civan J, Sass D, Farber J and Hehn BT. IgG4 related disease in the pleura manifested as weight loss in an immunocompromised patient. In: editors. A35. Case reports in autoimmune lung disease. *American Thoracic Society* 2016; p. A1374-A1374.
- [18] Charrow A, Imadojemu S, Stephen S, Ogunleye T, Takeshita J and Lipoff JB. Cutaneous manifestations of IgG4-related disease (RD): a systematic review. *J Am Acad Dermatol* 2016; 75: 197-202.
- [19] Furukawa S, Moriyama M, Tanaka A, Maehara T, Tsuboi H, Iizuka M, Hayashida JN, Ohta M, Saeki T and Notohara K. Preferential M2 macrophages contribute to fibrosis in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease. *Clin Immunol* 2015; 156: 9-18.

To study the sensitivity and specificity of IgG4 in the diagnosis of sicca syndrome

- [20] Zeron PB, Retamozo S, Gheitasi H, Bové A, Kostov B, Sisó-Almirall A, Ramos-Casals M and Stone J. THU0396 Igg4-related disease or primary sicca syndrome? Organ-specific involvement and immunological profile are clues in differentiating two diseases with a common clinical presentation. *Ann Rheum Dis* 2014; 73: 318-319.
- [21] Moriyama M, Tanaka A, Maehara T, Furukawa S, Nakashima H and Nakamura S. T helper subsets in Sjögren's syndrome and IgG4-related dacryoadenitis and sialoadenitis: a critical review. *J Autoimmun* 2014; 51: 81-88.
- [22] Asano J, Watanabe T, Oguchi T, Kanai K, Maruyama M, Ito T, Muraki T, Hamano H, Arakura N and Matsumoto A. Association between immunoglobulin G4-related disease and malignancy within 12 years after diagnosis: an analysis after longterm followup. *J Rheumatol* 2015; 42: 2135-2142.
- [23] Yamamoto M, Tabeya T, Naishiro Y, Yajima H, Ishigami K, Shimizu Y, Obara M, Suzuki C, Yamashita K and Yamamoto H. Value of serum IgG4 in the diagnosis of IgG4-related disease and in differentiation from rheumatic diseases and other diseases. *Mod Rheumatol* 2012; 22: 419-425.
- [24] Astorri E, Croia C, Picarelli G, Sutcliffe N, Tappuni A, Bombardieri M and Priori R. AB0565 routine investigations for circulating Igg4 and/or Igg4+ salivary gland histopathology fail to reveal undiagnosed cases of Igg4 related disease in sicca patients not fulfilling the diagnosis of sjogren's syndrome. *Ann Rheum Dis* 2015; 74: 1089.