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Association of IgG4-Related Disease With History of Malignancy

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Abstract

Objective.—IgG4-related disease (IgG4-RD) is a fibroinflammatory disease of unclear etiology. Some studies suggest that IgG4-RD predisposes patients to malignancy or is a forme fruste of cancer, but we have frequently observed IgG4-RD patients who have a history of malignancy preceding the clinical onset of IgG4-RD. This study was undertaken to characterize IgG4-RD in the setting of previous malignancy diagnosis.

Methods.—We identified IgG4-RD patients with a history of invasive malignancy from a well-defined cohort of 125 patients and compared their malignancy history to those of 2 reference groups. First, we calculated a standardized prevalence ratio against general US population estimates from the Surveillance, Epidemiology, and End Results (SEER) database. Second, we identified up to 5 age- and sex-matched controls for each case and calculated the odds of malignancy among those with IgG4-RD compared to controls, using conditional logistic regression.

Results.—The mean ± SD age at IgG4-RD onset was 50.3 ± 14.9 years, and 61% of the patients were male. Twenty (16%) had been diagnosed as having malignancies (total 21 malignancies) before the diagnosis of IgG4-RD. The observed prevalence of malignancy in this cohort was 2.5 times higher (95% confidence interval [95% CI] 1.1–3.6) than expected compared to the SEER database. Compared to matched controls, the frequency of history of malignancy was >3-fold higher in IgG4-RD patients (95% CI 1.6–6.2).

Conclusion.—Our findings suggest that, in a subset of patients with IgG4-RD, malignancy may be associated with subsequent IgG4-RD development. Potential explanations include shared risk factors for both IgG4-RD and cancer, the triggering by cancer of autoantigen expression leading to IgG4-RD, and an increased risk of IgG4-RD resulting from cancer treatment.

IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory condition that often causes tumefactive lesions and can affect nearly any anatomic site (1). Given its tendency to occur

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Stone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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as mass lesions in the pancreas, orbits, retroperitoneum, lung, kidneys, lymph nodes, and other organs, IgG4-RD is often mistaken for malignancy. Indeed, because of the frequent confusion with malignancy, patients with IgG4-RD often experience substantial iatrogenic morbidity before the correct diagnosis is established; organ resections designed to treat cancer are common in this patient population (2,3).

Conversely, there has been considerable speculation that IgG4-RD represents a premalignant state or paraneoplastic condition (4–6). However, no robust study has definitively demonstrated such a relationship, and findings of several investigations have contradicted these hypotheses (4,7). IgG4-RD is thought to be an autoimmune condition (8,9), and a growing body of literature indicates that malignancy has an important role in autoimmunity (10–14), suggesting that in some cases there may be a complex relationship between IgG4-RD and cancer.

Before the performance of the present investigation, our own clinical experience suggested that the evolution of IgG4-RD into a cancer was unusual. More-over, anecdotal observations suggest that many IgG4-RD patients have histories of cancer that precede their IgG4-RD diagnoses. Studies in patients with autoimmune conditions have shown a relationship between malignancy and the subsequent development of dermatomyositis, systemic sclerosis, and other conditions (10,15,16). In one recent study, for example, a specific mutation in some cancers was found to trigger the development of systemic sclerosis (10), leading (along with other observations) to hypotheses of cancer-induced autoimmunity in scleroderma and other rheumatic diseases.

The identification of a relationship between malignancy and the subsequent development of IgG4-RD may advance our understanding of the pathogenesis of IgG4-RD and illuminate the hypothesized connection between malignancy and autoimmune disease in some patients. We therefore investigated this by comparing a well-described IgG4-RD patient cohort to the general US population and to matched controls with non–IgG4-RD diagnoses evaluated in the same clinic.

PATIENTS AND METHODS

Overview of the IgG4-RD cohort.

This study was approved by the Partners Healthcare Institutional Review Board. All patients provided written informed consent. The Massachusetts General Hospital Center for IgG4-Related Disease, part of the Division of Rheumatology, Allergy, and Immunology, maintains a database of all patients with IgG4-RD evaluated in the center. Data pertaining to demographic characteristics, IgG4-RD manifestations, and medical history (including oncologic history) at baseline evaluations were derived from the medical record and interviews with the patients, as necessary. The IgG4-RD patients in this study were seen between January 2, 2010 and September 30, 2014.

Age at IgG4-RD onset refers to the age at which the patient first noticed the symptoms ultimately attributed to IgG4-RD, or to the time point at which the disease was first recognized (whichever was earlier). Serum IgG4 concentrations were measured using

commercial nephelometry with serial dilution to prevent the prozone effect. Some of the clinical and laboratory features of this IgG4-RD cohort have been reported previously (2), but their malignancy histories had not been investigated and the analyses pertaining to cancer reported herein are new.

Control subjects.

Controls were identified using the Research Patient Data Registry (RPDR), a centralized clinical data registry at Partners Healthcare. The RPDR consists of ~ 450 million records on ~ 2 million patients, including data on demographic features, diagnoses, medications and procedures, clinic visits, and hospitalizations. For the purposes of this study, controls were ascertained from the large number of patients evaluated in the Massachusetts General Hospital Division of Rheumatology, Allergy, and Immunology.

Because of the putatively increased risk of malignancy in some rheumatic conditions and the association of certain commonly used treatments with an increased malignancy risk, patients with rheumatoid arthritis, systemic lupus erythematosus, idiopathic inflammatory myositis, Sjögren's syndrome, vasculitis, polymyalgia rheumatica, and scleroderma were excluded. Up to 5 controls with a diagnosis of either osteoarthritis or fibromyalgia were matched to each case by sex and age (same 10-year decade). The age of control patients at their first visit was matched to the age of cases at the onset of IgG4-RD (index date). The RPDR also accounts for "comparative health" when matching cases and controls; this takes into consideration certain common comorbidities (e.g., hypertension) and frequency of visits. Each case had at least 2 controls. For the purposes of control cohort development, medical history was based on International Classification of Diseases, Ninth Revision codes from encounter and billing data from the RPDR.

US cancer statistics.

We used the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (Cite SEER database) (17) to obtain data on cancer prevalence in the general US population. SEER data are available by sex and age group (at prevalence measurement). The SEER program estimated the US cancer prevalence counts in 2011 based on SEER 9 registries and averaged US population estimates from the years 2010 and 2011 from the US Bureau of the Census. The SEER program considers only an individual's first invasive cancer when determining US cancer prevalence counts.

Malignancy ascertainment.

For the purposes of this study, malignancy was defined as any invasive carcinoma, including melanoma. Nonmelanoma skin cancers, carcinoma in situ, and high-grade dysplasia were not analyzed. For cases, the history of malignancy was based on the patient's self-report as well as a review of the available medical record. For controls, the history of malignancy was based on a review of the electronic medical record including clinic visits, pathology records, billing records, and electronic problem lists.

Statistical analysis.

Categorical data are presented as the percentage of subjects, and continuous data as the mean ± SD or the median and interquartile range (IQR). The statistical significance of differences between groups was assessed by Fisher's exact test (for categorical data) or by unpaired *t*-test or Wilcoxon rank sum test (for continuous data). To examine the association between malignancy among patients with IgG4-RD compared to malignancy in the general US population, we computed the standardized prevalence ratio (SPR) for malignancy, using the indirect standardization method and controlling for age and sex. The SPR was computed by comparing the observed number of malignancies to the expected number of malignancies based on prevalence estimates calculated from the SEER database. A Poisson model was used to calculate the 95% confidence interval (95% CI) of the SPR. The prevalence of malignancy in the cases and controls was compared (prior to adjustment) by calculating the odds ratio (OR) and 95% CI; *P* values were determined by Fisher's exact test. Univariate conditional logistic regression was used to compare the odds of malignancy in cases and controls after adjustment for matching (age and sex). For all analyses, *P* values (2-sided) less than 0.05 were considered significant. SAS version 9.2 (SAS Institute) was used for all statistical analyses.

RESULTS

Characteristics of the patients in the IgG4-RD cohort.

Of the 125 patients with IgG4-RD, 76 (61%) were men and 96 (77%) were non-Hispanic white (Table 1). The mean ± SD age at disease onset was 50.3 ± 14.9 years. The mean ± SD number of involved organs was 2.3 ± 1.3. The organs most commonly involved were the submandibular glands (35 cases [28%]), lymph nodes (34 cases [27%]), orbits (28 cases [22%]), pancreas (24 cases [19%]), and retroperitoneum (25 cases [20%]). Duration of disease prior to initial evaluation at our center was 5.2 ± 68.5 years.

IgG4-RD patients with prior malignancy.

Twenty of the 125 patients (16% [95% CI 11.2–28.8]) had been diagnosed as having malignancies (21 malignancies) before the onset of IgG4-RD (Table 1). Those with a history of malignancy were significantly older at onset of IgG4-RD than those without prior malignancy (mean6 age 59.8 ± 14.6 years versus 48.5 ± 14.3 years; $P = 0.002$). There was no significant difference in the sex distribution in the group of IgG4-RD patients with prior malignancy and the group without (75% male and 58% male, respectively; $P = 0.2$). The mean age at malignancy diagnosis was 51.0 ± 18.0 years. Among the 20 patients with a history of malignancy, 18 had active disease and 14 had an elevated serum IgG4 concentration (>135 mg/dl) at the time of initial evaluation. The median IgG4 concentration in these 18 patients with active disease was 407.5 mg/dl (IQR 139–655). This was significantly higher than the serum IgG4 concentration among patients with active disease and no history of malignancy (n = 104) (median 121 mg/dl [IQR 49.8–319]) ($P = 0.03$). However, after adjustment for age at the time of measurement, the difference in serum IgG4 concentrations between the 2 groups did not remain significant.

Malignancy was diagnosed an average of 8.8 years (range 1–39) prior to the diagnosis of IgG4-RD (Table 2). Prostate cancer (n = 7) and lymphoma (n = 4) were the most common malignancies. Among patients with a history of lymphoma, there was 1 case of Burkitt's lymphoma (patient 9), 2 cases of non-Hodgkin's lymphoma (patients 16 and 18), and 1 case of diffuse large B cell lymphoma (patient 17). The other malignancies diagnosed in these patients are summarized in Table 3. At the time of IgG4-RD diagnosis, cancer seemed to be in remission in all patients with a previous diagnosis of malignancy.

Characteristics of the disease controls.

We identified a total of 350 controls, of whom 58% were male (Table 4). The mean ± SD age of the controls was 51.5 ± 14.8 years. The control group did not differ significantly from the cases in the proportion of male subjects, proportion of non-Hispanic white subjects, or average age. Of the 350 controls, 23 (6.6%) had a history of malignancy prior to their first clinic visit. The most common malignancies were prostate cancer in 5 patients and melanoma in 3 patients (Table 3). Only 1 control subject had a history of lymphoma.

Case–control comparison.

Prior to adjustment for matched pairs, patients with IgG4-RD had a 2.7-fold increased odds (95% CI 1.4–5.1) of having a history of malignancy compared to controls ($P = 0.003$) (Table 4). After adjustment for age and sex, a history of malignancy remained significantly more common among those with IgG4-RD (OR 3.1 [95% CI 1.6–6.2], $P = 0.01$) compared to controls. A history of lymphoma was significantly more common among IgG4-RD patients compared to controls (3.2% versus 0.3%; $P = 0.02$).

General US population comparison.

Based on US population estimates, the expected number of malignancies in a cohort of 125 IgG4-RD patients (with adjustment for age group by decade) would be 8.0. We observed 20 first-time malignancies in our cohort of IgG4-RD patients. The SPR for malignancy among IgG4-RD patients compared to the general US population was 2.5 (95% CI 1.1–3.6) (Table 5). Among male patients with IgG4-RD, 5.8 malignancies would be expected but 15 were observed, corresponding to an SPR of 2.6 (95% CI 1.9–3.3). Among female patients, 2.6 malignancies would be expected but 5 were observed (SPR 1.9 [95% CI 1.1–2.7]).

Malignancy diagnoses following IgG4-RD onset.

The 125 IgG4-RD patients have been followed up for a total of 996 patient-years since the onset of IgG4-RD. During this follow-up, a new malignancy has been diagnosed in 6, a median of 6.5 years (range 3–18) after the onset of IgG4-RD. Thus, the incidence of new malignancy after the onset of IgG4-RD in this cohort was 0.6 per 100 patient-years. There were 2 cases of bladder cancer, 2 cases of prostate cancer, 1 case of diffuse large B cell lymphoma, and 1 case of esophageal cancer. In addition to these new diagnoses of malignancies, 1 patient (patient 10), with a history of prostate cancer prior to the onset of IgG4-RD, developed metastatic disease during follow-up. In 2 patients, malignancy was diagnosed at the same time as their diagnosis of IgG4-RD (1 case of bladder cancer and 1 case of appen-diceal cancer); it could not be determined whether 1 preceded the other.

DISCUSSION

Our present findings suggest that a history of malignancy may be associated with the development of IgG4-RD. This observation, based on comparisons of our IgG4-RD cohort to age-and sex-matched controls identified from the same clinic and to population-based data from the SEER program, may have important implications for understanding of the pathogenesis of IgG4-RD. In this study, a history of malignancy was 2.5 times more likely in IgG4-RD patients compared to the general US population. Further, a history of malignancy was 3-fold more common in IgG4-RD patients than in control patients in a case–control analysis.

Prostate cancer was the most common malignancy in both the IgG4-RD patients and the controls, but lymphoma accounted for 19% of the malignancies in the IgG4-RD cohort, compared to only 4% in the control cohort. Patients were treated for malignancy with a variety of approaches including surgery, radiation, and chemotherapy, but no single modality was universal.

There appear to be important differences between IgG4-RD patients with and those without a history of malignancy. IgG4-RD patients with malignancy developed IgG4-RD at a later age and had higher serum IgG4 concentrations compared to the subgroup without malignancy. Due to the limited number of cases, we could not conduct a robust evaluation of the differences in organ involvement between the 2 subgroups. However, a wide variety of manifestations of IgG4-RD were observed in the group with malignancy. It is important to note that no cases of IgG4-RD involved the organ previously affected by cancer.

One previous study has evaluated the prevalence of malignancy at the time of diagnosis of IgG4-related pancreatitis (type 1 autoimmune pancreatitis [AIP]) (4). In that study, which compared the malignancy histories of 116 AIP patients to those of appropriately matched controls (~3 controls per case), 12 AIP patients (10.3%) had a history of malignancy, including 3 cases of lymphoma and 1 of prostate cancer. There was no statistically significant relationship between a diagnosis of AIP and a history of malignancy compared to controls from the same center. One important difference between that study and ours is that we included patients with diverse manifestations of IgG4-RD; in fact, only 19% of the patients in our cohort have had pancreatic involvement, and only 3 of the patients who had a history of malignancy had IgG4-related AIP.

The pathogenesis of IgG4-RD remains poorly understood, but it is generally recognized as an immune-mediated condition (9) which may be mediated by autoimmunity (18,19), Th2-polarized and T regulatory lymphocytes (20), and/or oligoclonally expanded circulating plasmablasts (8,21). Associations between allergic conditions and IgG4-RD may suggest a shared pathogenesis between the 2 conditions (22). Finally, environmental exposures—to tobacco and occupational hazards—have also been invoked as possible contributors to, or triggers of, the development of IgG4-RD (23), but this has not been specifically studied.

Although the precise steps leading to the establishment of IgG4-RD remain unclear, our findings suggest that malignancy may be a predisposing condition in some patients. One possible explanation is that the treatment of malignancy (e.g., radiation, chemotherapy)

fosters immune dysregulation, leading to IgG4-RD in patients with other risk factors for that condition. While no common treatment modality was recognized in our cohort to suggest such a link, we had limited details regarding treatment in both cases and controls to address this possibility. Alternatively, malignancy and IgG4-RD may share common genetic predispositions. The fact that no IgG4-RD manifestation occurred at the site of a prior malignancy suggests that local changes in the immunologic milieu related to malignancy, its treatment, or subsequent damage are not a likely explanation. However, malignancy may generate CD+ cytotoxic T lymphocytes (24), which have recently been implicated in IgG4-RD pathogenesis. The persistence of these cells following the treatment of malignancy may link the 2 disorders (25). A final possibility is that mutations in malignancies expose the immune system to neoantigens that can precipitate a cascade of events culminating in autoimmune disease, as observed in other immune-mediated conditions (10).

Previous studies, in dermatomyositis and systemic sclerosis in particular, have demonstrated a temporal relationship between autoimmune disease and malignancy (10,11); in many cases, the autoimmune condition develops after the malignancy and improves with treatment of the underlying malignancy (11). Further work is needed to determine whether IgG4-RD patients with a history of malignancy have specific autoantibodies that might be pathogenic and may distinguish them from patients without a similar history of malignancy.

This study has a number of strengths. All 125 IgG4-RD patients in our cohort have biopsy-proven disease that is well characterized (2). Further, the association between IgG4-RD and malignancy in this cohort was assessed by comparisons both to the general US population using national cancer data as well as to control patients evaluated at the same center.

The study also has some limitations. The majority of patients in our cohort are non-Hispanic white, which may limit generalizability of the findings. Because of the limited number of cases, we were unable to detect potentially significant differences in IgG4-RD organ involvement, ethnicity, and other factors between those with and those without a history of malignancy. In this retrospective study, it is possible that patients may have been misclassified with regard to previous cancer status. However, there is no reason to suspect differential misclassification between the case group and the control group. Because of incomplete records regarding risk factors (e.g., smoking), we were unable to assess the impact of potential confounders on the relationship between malignancy and IgG4-RD. There is no clear evidence that smoking is related to the development of IgG4-RD, but 1 study identified smoking as a risk factor for idiopathic retroperitoneal fibrosis (23), and some of these cases were likely IgG4-RD. Prospective studies will be needed to rigorously investigate the potential relationship between smoking and IgG4-RD.

In conclusion, a history of invasive malignancy appears to be associated with the subsequent development of IgG4-RD. This finding may support and advance contemporary hypotheses about the relationships between malignancy and the subsequent development of immune-mediated conditions.

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REFERENCES

1. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet 2015;385:1460–71. [PubMed: 25481618]
2. Wallace ZS, Deshpande V, Mattoo H, Mahajan VS, Kulikova M, Pillai S, et al. IgG4-related disease: clinical and laboratory features in one hundred twenty-five patients. Arthritis Rheumatol 2015;67:2466–75. [PubMed: 25988916]
3. Hardacre JM, Iacobuzio-Donahue CA, Sohn TA, Abraham SC, Yeo CJ, Lillemoe KD, et al. Results of pancreaticoduodenectomy for lymphoplasmacytic sclerosing pancreatitis. Ann Surg 2003;237:853–8. [PubMed: 12796582]
4. Hart PA, Law RJ, Dierkhising RA, Smyrk TC, Takahashi N, Chari ST. Risk of cancer in autoimmune pancreatitis: a case-control study and review of the literature. Pancreas 2014;43:417–21. [PubMed: 24622072]
5. Gupta R, Khosroshahi A, Shinagare S, Fernandez C, Ferrone C, Lauwers GY, et al. Does autoimmune pancreatitis increase the risk of pancreatic carcinoma? A retrospective analysis of pancreatic resections. Pancreas 2013;42:506–10. [PubMed: 23271394]
6. Shiokawa M, Kodama Y, Yoshimura K, Kawanami C, Mimura J, Yamashita Y, et al. Risk of cancer in patients with autoimmune pancreatitis. Am J Gastroenterol 2013;108:610–7. [PubMed: 23318486]
7. Hirano K, Tada M, Sasahira N, Isayama H, Mizuno S, Takagi K, et al. Incidence of malignancies in patients with IgG4-related disease. Intern Med 2014;53:171–6. [PubMed: 24492683]
8. Mattoo H, Mahajan VS, Della-Torre E, Sekigami Y, Carruthers M, Wallace ZS, et al. De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG-related disease. J Allergy Clin Immunol 2014;134:679–87. [PubMed: 24815737]
9. Mahajan VS, Mattoo H, Deshpande V, Pillai SS, Stone JH. IgG4-related disease. Annu Rev Pathol 2014;9:315–47. [PubMed: 24111912]
10. Joseph CG, Darrah E, Shah AA, Skora AD, Casciola-Rosen LA, Wigley FM, et al. Association of the autoimmune disease scleroderma with an immunologic response to cancer. Science 2014;343:152–7. [PubMed: 24310608]
11. Shah AA, Casciola-Rosen L, Rosen A. Cancer-induced autoimmunity in the rheumatic diseases [review]. Arthritis Rheumatol 2015;67:317–26. [PubMed: 25371098]
12. Chow WH, Gridley G, Mellemkjaer L, McLaughlin JK, Olsen JH, Fraumeni JF Jr. Cancer risk following polymyositis and dermatomyositis: a nationwide cohort study in Denmark. Cancer Causes Control 1995;6:9–13. [PubMed: 7718740]
13. Sigurgeirsson B, Lindelof B, Edhag O, Allander E. Risk of cancer in patients with dermatomyositis or polymyositis: a population-based study. N Engl J Med 1992;326:363–7. [PubMed: 1729618]
14. Buchbinder R, Forbes A, Hall S, Dennett X, Giles G. Incidence of malignant disease in biopsy-proven inflammatory myopathy: a population-based cohort study. Ann Intern Med 2001;134:1087–95. [PubMed: 11412048]
15. Zantos D, Zhang Y, Felson D. The overall and temporal association of cancer with polymyositis and dermatomyositis. J Rheumatol 1994;21:1855–9. [PubMed: 7837150]
16. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003;349:1543–54. [PubMed: 14561798]
17. Surveillance, Epidemiology, and End Results (SEER) Program. US population data 1969–2014. Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute: National Institutes of Health. 1 2015 URL: www.seer.cancer.gov/popdata.
18. Okazaki K, Uchida K, Ohana M, Nakase H, Uose S, Inai M, et al. Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2-type cellular immune response. Gastroenterology 2000;118:573–81. [PubMed: 10702209]
19. Du H, Shi L, Chen P, Yang W, Xun Y, Yang C, et al. Prohibitin is involved in patients with IgG4 related disease. PLoS One 2015;10:e0125331. [PubMed: 25932630]
20. Tanaka A, Moriyama M, Nakashima H, Miyake K, Hayashida JN, Maehara T, et al. Th2 and regulatory immune reactions contribute to IgG4 production and the initiation of Mikulicz disease. Arthritis Rheum 2012;64:254–63. [PubMed: 21898360]

21. Wallace ZS, Mattoo H, Carruthers M, Mahajan VS, Della Torre E, Lee H, et al. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. Ann Rheum Dis 2015;74:190–5. [PubMed: 24817416]

22. Kamisawa T, Anjiki H, Egawa N, Kubota N. Allergic manifestations in autoimmune pancreatitis. Eur J Gastroenterol Hepatol 2009;21:1136–9. [PubMed: 19757521]

23. Goldoni M, Bonini S, Urban ML, Palmisano A, De Palma G, Galletti E, et al. Asbestos and smoking as risk factors for idiopathic retroperitoneal fibrosis: a case-control study. Ann Intern Med 2014;161:181–8. [PubMed: 25089862]

24. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD41 T cells against NY-ESO-1. N Engl J Med 2008;358:2698–703. [PubMed: 18565862]

25. Mattoo H, Mahajan VS, Maehara T, Deshpande V, Della-Torre E, Wallace ZS, et al. Clonal expansion of CD41 cytotoxic T lymphocytes in patients with IgG4-related disease. J Allergy Clin Immunol 2016 E-pub ahead of print.

Table 1.

Characteristics of the IgG4-RD patients according to history of malignancy*

Variable	All (n = 125)	No history of malignancy (n = 105)	History of malignancy (n = 20)	*P*
Age at IgG4-RD onset, mean ± SD years	50.3 ± 14.9	48.5 ± 14.3	59.8 ± 14.6	0.002
Male sex	76 (60.8)	61 (58.1)	15 (75)	0.2
White race	96 (77)	77 (73)	19 (95)	0.04
Disease duration prior to evaluation, median (IQR) years	2 (1–6)	2.5 (1–6)	1 (0.5–4.5)	0.14
No. of involved organs, mean ± SD	2.3 ± 1.3	2.3 ± 1.4	2.4 ± 1.1	0.7
Serum IgG4, median (IQR) mg/dl†	140 (55.1–408)	121 (49.8–319)	407.5 (139–655)	0.03
Organ involvement				
Submandibular gland	35 (28)	30 (29)	4 (20)	0.6
Lymph nodes	34 (27)	29 (28)	5 (25)	1
Orbit	28 (22)	23 (22)	4 (20)	1
Pancreas	24 (19)	20 (19)	4 (20)	1
Retroperitoneum	25 (20)	21 (20)	4 (20)	1

*Except where indicated otherwise, values are the number (%). IgG4-RD = IgG4-related disease; IQR = interquartile range.

†Among patients with active disease at the initial visit.

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Table 2.

Characteristics of the IgG4-RD patients with malignancies (n = 20)*

Patient	Sex	Age at malignancy diagnosis, years	Age at IgG4-RD onset, years	IgG4-RD organ involvement	Malignancy site	Malignancy treatment
1	M	72	82	RPF	Colon	Surgery, chemotherapy
2	M	63, 30	69	AIP, biliary	Prostate, testicle	Surgery
3	M	66	71	ENT, thyroid, lung, aorta	Prostate	Surgery
4	F	69	71	Orbit, parotid, submandibular, skin	Breast	Surgery, radiation
5	M	76	78	Sclerosing mediastinitis, LAD, thyroid, ENT	Prostate	Radiation
6	M	39	61	ENT	Rectal	Surgery, radiation, chemotherapy
7	F	25	34	LAD, orbit	Cervix	Surgery
8	M	54	57	RPF	Prostate	Surgery
9	M	13	32	Aorta	Lymphoma	Chemotherapy
10	M	51	65	LAD, aorta	Prostate	Surgery
11	M	74	79	Parotid, biliary	Lung	Surgery, radiation
12	M	44	51	Parotid, submandibular, LAD	Leukemia	Surgery, chemotherapy
13	M	67	69	Aorta, RPF	Prostate	Radiation
14	F	47	48	Kidney, biliary, pancreas	Breast	Surgery, chemotherapy
15	M	57	61	RPF	Lung	Surgery, chemotherapy
16	M	46	52	Aorta, kidney, heart	Lymphoma	Chemotherapy
17	F	67	69	Parotid, submandibular, LAD	Lymphoma	Chemotherapy
18	M	34	47	Orbital, parotid, submandibular, pancreas	Lymphoma	Chemotherapy
19	M	57	61	Orbital, aorta, pancreas	Prostate	Surgery
20	M	32	39	ENT	Testicle	Surgery

* IgG4-RD = IgG4-related disease; RPF = retroperitoneal fibrosis; AIP = autoimmune pancreatitis; ENT = ear, nose, throat; LAD = lymphadenopathy.

Table 3.

Distribution of malignancies in cases and controls

Cancer site	IgG4-RD cases	Clinic controls
Prostate	7*	5
Breast	2	2
Melanoma	0	3
Bladder	0	2
Lymphoma	4	1
Kidney	0	1
Lung	2	
Leukemia	1	1
Colorectal	2	1
Endometrial	0	1
Sarcoma	0	1
Testicle	2	1
Throat	0	1
Thyroid	0	1
Cervix	1	0

*In addition to these 7 cases of prostate cancer, 1 of the 2 patients who had testicular cancer prior to the diagnosis of IgG4-related disease (IgG4-RD) had prostate cancer 33 years prior to having testicular cancer.

Table 4.

Demographic characteristics of the IgG4-RD cases and controls and association with history of malignancy

	IgG4-RD cases (n = 125)	Clinic controls (n = 350)
Age, mean ± SD years *	50.3 ± 14.9	51.5 ± 14.8
Male, no. (%)	76 (61)	204 (58)
White, no. (%)	96 (77)	268 (77)
History of malignancy, no. (%) †	20 (16)	23 (6.6)
Unadjusted OR (95% CI)	2.7 (1.4–5.1)	Referent
Adjusted OR (95% CI)	3.1 (1.6–6.2)	Referent

* At the time of first visit (controls), matched to age at IgG4-related disease (IgG4-RD) onset (cases).

† OR = odds ratio; 95% CI = 95% confidence interval.

Table 5.

Standardized prevalence ratios for malignancy in the IgG4-RD cohort compared to the US general population*

Sex, age (years)	No. of IgG4-RD cases	Observed malignancies	Cohort prevalence	US prevalence	Expected malignancies
Men and women combined					
20–29	6	0	0	0.003	0.02
30–39	13	1	0.08	0.008	0.1
40–49	22	2	0.09	0.02	0.4
50–59	32	4	0.13	0.04	1.4
60–69	33	5	0.2	0.09	3.1
70–79	16	6	0.4	0.2	2.5
80–89	3	2	0.7	0.2	0.5
Total		20 (95% CI 11.2–28.8)			8.0 (SPR 2.51 [95% CI 1.14–3.61])
Men					
20–29	2	0	0	0.003	0.006
30–39	7	1	0.1	0.006	0.04
40–49	13	1	0.08	0.01	0.2
50–59	20	3	0.2	0.04	0.7
60–69	21	4	0.2	0.1	2.1
70–79	10	4	0.4	0.2	2.0
80–89	3	2	0.7	0.3	0.8
Total		15 (95% CI 11.1–18.9)			5.8 (SPR 2.60 [95% CI 1.93–3.27])
Women					
20–29	4	0	0	0.003	0.01
30–39	6	0	0	0.01	0.06
40–49	9	1	0.1	0.02	0.2
50–59	12	1	0.08	0.05	0.6
60–69	12	1	0.08	0.09	1.0
70–79	6	2	0.3	0.1	0.7
Total		5 (95% CI 2.8–7.2)			2.6 (SPR 1.89 [95% CI 1.05–2.74])

*IgG4-RD = IgG4-related disease; 95% CI = 95% confidence interval; SPR = standardized prevalence ratio.

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