A Retrospective Study of 92 Patients with IgG4 Related Diseases

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ABSTRACT

Background: To analyze the clinical characteristics of IgG4 related diseases (IgG4-RD), identify the most commonly used therapeutic drugs, and explore the potential tumor markers of IgG4-RD.

Methods: 92 patients with IgG4 related diseases hospitalized in the Affiliated Hospital of Qingdao University from January 1, 2017 to December 31, 2021 were selected as the research object through the Yidu cloud system. Their clinical data were summarized and analyzed to summarize the clinical characteristics of IgG4-RD.

Results: The age of diagnosis of IgG4 related diseases in this group was 31-84 years old, and the average age of diagnosis was (58.098 ± 11.344) years old, including 65 males (70.65%) and 27 females (29.35%). The most frequently involved organs and tissues were lymph nodes (37 cases, accounting for 40.2%), pancreas (33 cases, accounting for 35.9%), and salivary glands (31 cases, accounting for 33.7%). In this group, 28 cases (30.4%) were involved in single organ tissue, 32 cases (34.8%) were involved in double organ and multiple organs, respectively. 91 patients were treated with hormone for IgG4 related diseases, and 71 patients were treated with immunosuppressive agents, of which 45 cases were treated with cyclophosphamide (63.38%). In this group, the proportion of IgG4 level greater than 40 g /L in tumor patients (18.18%) was significantly higher than that in non-tumor patients (1.23%) ($P<0.05$).

Conclusion: The incidence of IgG4 related diseases is more common in middle-aged and elderly men, and the patients with lymph node, salivary gland and pancreas are more common. About 2/3 of the patients are double organ and multi organ patients. The most common rheumatic complications in patients with IgG4-RD are primary biliary cirrhosis, rheumatoid arthritis and Sjogren's syndrome. The most common tumor in patients with IgG4-RD is malignant tumor of digestive system. IgG4 levels greater than 40 g/l in patients with IgG4 related diseases may be a potential indicator for predicting IgG4-RD associated tumors.

Keywords: IgG4 related disease; Involved organs; Rheumatic complications; Malignant tumor; IgG4 levels

INTRODUCTION

IgG4 associated disease (IgG4 RD) is a newly recognized rare chronic, progressive inflammatory disease with fibrosis. Kamisawa et al. [1] First introduced the concept of "IgG4 related diseases", also known as "IgG4 positive multiple organ lymphoproliferative syndrome". The Journal of autoimmunity officially announced the birth of IgG4 related diseases [2]. The main pathological feature of the disease is a large number of lymphocytes and IgG4 positive plasma cells in the lesion. IgG4 related diseases can involve multiple organs and tissues, such as lymph nodes, salivary glands, pancreas, bile ducts, etc. [3-7]. Due to the different affected organs and great differences in clinical manifestations, there were many former names of the disease in the past, such as mikulic disease, autoimmune pancreatitis and so on. Because the disease is often manifested as space occupying lesions and lack of doctors' cognition, doctors often misdiagnose it as a tumor and perform unnecessary surgical treatment, which

brings huge trauma and economic losses to patients and families. In recent years, the relationship between IgG4 related diseases and malignant tumors have attracted more and more attention. There are significant differences in the risk of tumor occurrence Standardized Incidence Ratio (SIR) in patients with IgG4-RD reported by various countries (1.04-23.08) [8-16].

The purpose of this study is to deepen the understanding of IgG4 related diseases and explore potential tumor markers of IgG4 related diseases.

METHODOLOGY

Study design and general information

The medical cloud system of the Affiliated Hospital of Qingdao University was used to search and collect the patients with IgG4 related diseases hospitalized and treated in the Affiliated Hospital of Qingdao University in the past five years from January 1, 2017 to December 31, 2021. A total of 110 patients were retrieved, of which 18 patients were excluded due to incomplete information, and the remaining 92 patients met the international classification diagnostic criteria for IgG4 related diseases [17]. This study was approved by the medical ethics committee of the Affiliated Hospital of Qingdao University.

Research methods

The clinical diagnosis and treatment data of 92 patients with IgG4 related diseases were retrieved through his system. The clinical manifestations, affected organs, laboratory tests and treatment were retrospectively analyzed, and the clinical characteristics of IgG4 related diseases were summarized. We confirm that all methods were performed in accordance with the relevant guidelines and regulations.

Statistical methods

All the data in this study were analyzed by SPSS 22.0. The counting data were expressed by (x ± s). T test was used for conforming to the normal distribution, and two independent sample rank sum test was used for non-conforming to the normal distribution. Count data are expressed in (%) and test is used. When n<40 or theoretical number [T]<1, rank sum test is used. The difference between groups was statistically significant (P<0.05).

The medical ethics committee

The medical ethics committee of the Affiliated Hospital of Qingdao University approved the study with a waiver of informed consent because all laboratory tests had received the informed consent of all subjects and/or their legal guardians and all clinical data were anonym zed before the study.

RESULTS

Analysis of basic data of this group of patients

The average age of diagnosis of 92 patients with IgG4 related diseases was 58.098 ± 11.344 years old (31-84 years old). The patients included 65 males (70.65%) and 27 females (29.35%);

38 smokers (41.3%) and 54 nonsmokers (58.7%); 25 drinkers (27.2%) and 67 nondrinkers (72.8%). The most common first visit departments of the above patients were digestive department (17 cases), maxillofacial surgery (14 cases), nephrology department (11 cases), rheumatology department (9 cases), hepatobiliary surgery and ophthalmology department (8 cases each), hematology department (4 cases), respiratory department, urology department, emergency department and otorhinolaryngology Department (3 cases each), gastrointestinal surgery and neurosurgery department (2 cases each), vascular surgery, cardiology department, lymphoma department and spine surgery department (1 case).

Analysis of affected organs and tissues of patients in this group

In this group, 33 cases (35.9%) had pancreatic involvement; 21 cases (22.8%) had bile duct involvement; 31 cases (33.7%) had salivary glands involvement; 16 cases (17.4%) had lacrimal gland involvement; 37 cases (40.2%) had lymph nodes involvement; There were 14 cases of retroperitoneal fibrosis, accounting for 15.2%; 13 cases (14.1%) had renal involvement; 7 cases (7.6%) had lung involvement; 6 cases (6.5%) had orbital mass; 3 cases (3.3%) had abdominal aorta involvement; 2 cases (2.2%) had brain involvement; 1 case (1.1%) had liver involvement; 1 case (1.1%) had oral mucosa involvement; 1 case (1.1%) had skin involvement. The three most frequently affected sites in this group were lymph nodes, pancreas and salivary glands. In this group, 28 cases (30.4%) were involved in single organ tissue; there were 32 cases of double organ involvement and multiple organ involvement, accounting for 34.8% respectively.

Analysis of rheumatic complications in this group

There were 3 patients with primary biliary cirrhosis; 3 cases with rheumatoid arthritis complicated; 3 cases with Sjogren's syndrome complicated; 1 cases with connective tissue disease; 1 cases with ankylosing spondylitis; 1 cases with antiphospholipid antibody syndrome; 1 cases with systemic lupus erythematosus. The most common rheumatic complications were primary biliary cirrhosis, rheumatoid arthritis and Sjogren's syndrome.

Analysis of patients with tumor in this group

There were 11 patients with tumor in this group, and the incidence of tumor was 11.96%. There were 8 males and 3 females; the age of diagnosis ranged from 55 to 74 years, with an average age of 63.6 ± 7.2 years; there were 3 smokers and 8 non-smokers; there were 3 drinkers and 8 nondrinkers. In this group, there were 6 cases of digestive system malignant tumors, accounting for 54.5% (2 cases of cholangiocarcinoma, 2 cases of pancreatic cancer (1 case of liver metastasis), 1 case of pancreatic cancer with cholangiocarcinoma, and 1 case of high-grade intraepithelial neoplasia of sigmoid colon); There were 2 cases of malignant tumors of reproductive system, accounting for 18.2% (1 case of breast cancer and 1 case of endometrial cancer); There were 2 cases of hematological malignancies, accounting for 18.2% (1 case of lymphoma and 1 case of chronic leukemia); Thyroid carcinoma was complicated in 1 case (9.1%). Six patients

with tumor and IgG4 related diseases were diagnosed at the same time (within half a year before and after the diagnosis), three patients with IgG4 related diseases were diagnosed later than the tumor (1 case was 1 year after cancer, 2 cases were 8 years after cancer), and two patients with IgG4 related diseases were diagnosed earlier than the tumor (1 case was 1 year before cancer, 1 case was 5 years before cancer).

Analysis on the use of hormones and immune suppressants in this group of patients

A total of 89 patients in this group were treated with hormone during treatment, and 71 patients were treated with immunosuppressant during treatment, of which cyclophosphamide was the most commonly used immunosuppressant. Among the patients in this group, 45 cases (63.38%) were treated with cyclophosphamide, 18 cases (25.35%) with leflunomide, 14 cases (19.72%) with matemicophenol ester, 7 cases (9.86%) with Tripterygium wilfordii, 3 cases (4.23%) with methotrexate, 2 cases (2.82%) with thiazolidine, and 1 case (1.41%) with cyclosporine, tacrolimus and thalidomide. Methotrexate users often have joint manifestations.

Analysis of IgG4 level in this group of patients

In this group, 41 patients (44.57%) had IgG4 levels between 0-10 g/l, and the median was 4.67 g/l. There were 3 cases (3.26%) with more than 40 g/l, and the median was 49.9 g/l. There were 3 cases (27.27%) with IgG4 level between 0-10 g/l in patients with tumor, and the median was 4.67 g/l. There were 2 cases (18.18%) with more than 40 g/l, and the median was 47.65 /l. 38 cases (46.91%) had IgG4 levels between 0-10 g/l in non-tumor patients, with a median of 4.765 g/l There was one case (1.23%) with more than 40 g/l, and the median was 78.3 g/l. The proportion of IgG4 level greater than 40 g/l in patients with tumor was higher than that in patients without tumor (P<0.05) (Table 1).

DISCUSSION

IgG4 related diseases are a group of relatively rare chronic autoimmune diseases in clinic, lacking specific clinical features. At present, the main means of diagnosis is histopathological biopsy. The disease can involve multiple organs and tissues. The predilection age of IgG4 related diseases is 50-70 years old, the average age of onset is 54.6 ± 13.1 years old, and the male to female ratio is (1.6-4): 1[18]. The age of diagnosis of IgG4 related diseases in this study was 31-84 years old, and the average age of diagnosis was (58.098 ± 11.344) years old, which was greater than the age at which IgG4 occurred. In this group, there were 65 male patients (70.65%) and 27 female patients (29.35%), with a male to female ratio of 2.62:1.

In this study, the most frequently involved organs and tissues in patients with IgG4 RD were lymph nodes (37 cases, 40.2%), pancreas (33 cases, 35.9%), and salivary glands (31 cases, 33.7%). A Chinese study involving 106 patients with IgG4-RD showed that the top three organs most frequently affected by IgG4 related diseases were lymph nodes in 71 cases (67%), salivary glands in 40 cases (37.7%), and pancreas in 38 cases (35.8%).

In this group, 28 cases (30.4%) were single organ tissue involvement, and 64 cases (69.6%) were double organ and multiple organ involvement. At present, there are great differences in reports on the number of organ involvement in patients with IgG4-RD at home and abroad. Inoue et al. reported that 42% of IgG4-RD patients had single organ involvement; Yamada et al. found that the number of single organ involvement in patients with IgG4-RD was 11.4% [19], and Zhang et al. reported that the number of single organ involvement in patients with IgG4-RD was only 7.5% [20]. There were 11 patients with tumor in this group, and the incidence was 11.96%. Two patients (18.18%) were hematological tumors, and nine patients (81.82%) with IgG4-RD were diagnosed as solid tumors, of which the most common tumor was malignant tumors of the digestive system (6 cases, 54.5%). Three patients

IgG4 levels	All patients			Patients with tumor			Patients without tumor			Comparison of patients with and without tumor	
IgG4 (g/L)	n	Proportion (%)	median	n	Proportion (%)	median	n	Proportion (%)	median	c2/Z	p-value
0-10	41	44.57	4.67	3	27.27	4.67	38	46.91	4.765	c2=0.8217	P>0.05
Oct-20	17	18.48	13.8	4	36.36	15.6	13	16.05	13.2	c2=1.4759	P>0.05
20-30	6	6.52	22.55	0	-	-	6	7.41	22.55	-	-
30-40	2	2.17	36.1	0	-	-	2	2.47	36.1	-	-
>40	3	3.26	49.9	2	18.18	47.65	1	1.23	78.3	Z=2.9533	P<0.01
>3.56 (details unknown)	21	22.8	-	2	18.18	-	19	2.36	-	c2=0.0001	P>0.05

Note: The IgG4 count data of patients in this group are expressed in (%). The test is used to compare the IgG4 count data between the patients with tumor (c) and those without tumor (Z). When n<40 or the theoretical number (T) <1, the rank sum test is used.

Table 1: Analysis of IgG4 level in this group of patients.

(27.27%) with IgG4-RD had a history of malignant tumors, and the other eight patients (72.72%) developed malignant tumors at or after the diagnosis of IgG4-RD. Hanqi Tang et al reported that among patients with IgG4-RD combined with tumors, 5.9% patients were lymphoma, and 16 patients (94.1%) had solid tumors, of which gastrointestinal tumors were the most common (4 cases, 23.5%), followed by thyroid tumors (3, 17.6%), and 23.5% of patients with tumors reported a history of malignancy, and 76.5% of patients with tumors had no history of malignancy. The proportion of IgG4 level greater than 40 g/l in patients with tumor was significantly higher than that in patients without tumor (P<0.05).

In terms of treatment, hormone is still the cornerstone for the treatment of IgG4 related diseases, and it is also a first-line therapeutic drug, which can be used in the induction treatment and maintenance stage of diseases. If the hormone control is poor or the hormone must be used in large doses for a long time, immunosuppressant treatment can be added, such as cyclophosphamide, leflunomide, matimecol ester, etc. Combined use of immune suppressants and glucocorticoids can reduce the cumulative dose of hormones, improve the therapeutic efficacy, and reduce disease recurrence [21,22]. The limitation of this article is that the number of patient medical records is small, all patients are Asian population, and lack of universality.

CONCLUSION

In conclusion, the onset of IgG4 related diseases are more common in middle-aged and elderly men, often involving lymph nodes, salivary glands and pancreas. About 2/3 of patients are double organ and multiple organ affected. The most common rheumatic complications in patients with IgG4-RD are primary biliary cirrhosis, rheumatoid arthritis and Sjogren's syndrome. The most common tumor in patients with IgG4-RD is malignant tumor of digestive system. IgG4 levels greater than 40 g/l in patients with IgG4-RD may be a potential indicator for predicting IgG4-RD associated with tumors.

DATA AVAILABILITY

The datasets generated during and analyzed during the current study are not publicly available due to the requirement of the Department of scientific research and foreign affairs of the Affiliated Hospital of Qingdao University but are available from the corresponding author on reasonable request.

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