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Expression of IgG and IgG4 in Lymphoma

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Abstract

Objectives: Although IgG4-related disease has been gradually recognized, its relationship with malignant diseases, especially lymphoma has been an eternal topic. Therefore we set out to explore the expression of IgG4 positive cells in lymphoma.

Methods: Surgical excision specimens with definite diagnosis of lymphoma from January to December, 2013 were collected. Hematoxylin-eosin staining and immunohistochemical staining of IgG and IgG4 were then evaluated on dense lymphoplasmacytic infiltration, storiform fibrosis and obliterative phlebitis. For the quantification of IgG and IgG4 positive cells, the areas with the highest density of positive cells were evaluated. Three high-powered fields (hpf) in each section were analyzed, and the average number of positive cells per hpf was calculated.

Results: 16 patients with lymphoma were included in our study. There were 9 males and 7 females with an average age of 51 years old. 3 cases were diagnosed as Hodgkin lymphoma while 13 were non-Hodgkin lymphoma (diffuse large B cell lymphoma 8 cases, small B cell lymphoma 2 cases, mucosa associated lymphoid tissue marginal zone B cell lymphoma (MALToma) 1 case, follicular lymphoma, peripheral T-cell lymphoma and hepatosplenic T-cell lymphoma 1 case. Dense lymphocytic infiltration accompanied by atypical lymphocytes was observed in all the specimens. Proliferation of fibrous tissue was only seen in one specimen. IgG positive cells were detectable in 14 cases with the highest cell count from 20-350/hpf. 2 Hodgkin lymphoma cases showed of IgG4 positivity with the highest cell counts were 11 and 12/hpf respectively.

Conclusion: IgG4 positive cells, fibrosis and obliterative phlebitis barely appeared in lymphoma. In combination with specific tumor signature molecules, it may not be difficult to distinguish lymphoma from IgG4-related disease.

Keywords: Lymphoma; IgG4-related disease; IgG; IgG4

Introduction

IgG4-related disease (IgG4-RD) is a newly recognized disease spectrum. Several organs or tissues, for instance pituitary gland, lacrimal gland, salivary gland, thyroid, pancreas, bile duct, kidney, lung, and retroperitoneum can be involved. IgG4-RD is a fibro-inflammatory condition characterized by several features: a tendency to form tumefactive lesions at multiple sites; a dense lymphoplasmacytic infiltrate rich in IgG4+ plasma cells; storiform fibrosis; and-often but not always-elevated serum IgG4 concentration [1]. IgG4-RD is entirely different from malignant diseases. However it is always necessary to differentiate it from malignant diseases in patients with single or multiple organ enlargements. It has been reported that the standardized incidence ratio for malignancies in IgG4-RD was higher than that in the general population [2]. Takahashi et al. further reported patients with IgG4-RD may be at an increased risk of developing non-Hodgkin lymphoma [3]. Significant numbers of IgG4+ plasma cells were found within inflammatory pseudotumor-like follicular dendritic cell sarcoma [4]. Recently we also reported a case of IgG4-RD who was diagnosed as small B cell lymphoma, received chemotherapy and autologous stem cell transplantation 10 years ago and eventually developed diffuse large B-cell lymphoma two years after the diagnosis of IgG4-RD (unpublished data). Besides it is well known that neoplastic cells can be IgG+ [5,6], but the positivity of IgG4 remains unknown. Therefor we set out to explore the relationship between lymphoma and IgG4-RD.

Materials and Methods

Case selection

Cases with lymphoma confirmed by experts form the pathology department of Peking University First Hospital between January and December 2013 were included in this study. All of the lymphomatous specimens were obtained by operation.

Histopathological examination

Formalin-fixed and paraffin-embedded sections were prepared and used for the histopathological examination. 4 um-thick histological sections were obtained for hematoxylin-eosin and immunohistochemical staining. The histopathological features including storiform fibrosis, lymphoplasmacytic infiltration and obliterative phlebitis were collected.

Immunohistochemical analysis was performed using antibodies against IgG and IgG4 by the standard streptacidin-biotin-peroxidase

method. Primary antibodies used were rabbit polyclonal antibody against human IgG (Abcam,USA), a mouse monoclonal antibody against human IgG4 (Abcam, USA). Sections were pre-treated with pepsin (for IgG and IgG4). Secondary antibody was anti-mouse/rabbit antibody (GTVision III Detection System/Mo&Rb).

The dense areas with positive IgG4+ cells were selected and the numbers of IgG4+ plasma cells were counted in three different high power fields (hpf, 10Xeyepiece and 40Xlens). The mean values were adopted in the results. Meanwhile the numbers of IgG-positive plasma cells in the hpf of the continuous section was also counted. The ratios of IgG4/IgG were calculated in each specimen. Tonsil tissues were used as positive controls. Negative controls were established by replacing the primary antibody with PBS.

Results

16 patients with lymphoma were included in our study. There were 9 males and 7 females with an average age of 51 years old. 3 cases were pathologically defined as Hodgkin lymphoma and 13 cases were non-Hodgkin lymphoma which contained 7 cases of diffuse large B cell lymphoma, 2 cases of small B cell lymphoma, 1 case of follicular lymphoma, MALToma, peripheral T-cell lymphoma and hepatosplenic T-cell lymphoma respectively (Table 1).

S. No	sex	age	diagnosis	IgG+cells /hpf	IgG4+cells /hpf	fibrosis	Obliterative phlebitis
1	F	60	DLBCL	58	0	N	N
2	F	45	DLBCL	352	0	N	N
3	F	31	DLBCL	110	0	N	N
4	M	71	DLBCL	50	0	N	N
5	M	43	DLBCL	0	0	N	N
6	F	59	DLBCL	130	0	N	P
7	M	49	DLBCL	50	0	N	N
8	F	39	SBCL	80	0	N	N
9	F	57	SBCL	60	0	N	N
10	M	79	MALToma	15	0	N	N
11	M	67	FL	0	0	N	N
12	F	49	PTCL	80	0	N	N
13	M	22	HTCL	20	0	N	N
14	M	30	HL	120	12	N	N
15	M	73	HL	120	11	N	N
16	M	42	HL	70	0	1	N

Table 1: Histopathological features of lymphoma

N: Not present; P: Present; DLBCL: Diffused Large B Cell Lymphoma; SBCL: Small B Cell Lymphoma; MALToma: Mucosa Accociated Lymphoid Tissue Marginal Zone B Cell Lymphoma; FL: Follicular Lymphoma; PTCL: Peripheral T Cell Lymphoma; HTCL: Hepatosplenic T-Cell Lymphoma

Dense lymphocytic infiltration accompanied by atypical lymphocytes was detectable in all 16 specimens. The storiform was only observed in one specimen with proliferation of fibrous. Obliterative phlebitis appeared in only one specimen.

IgG was positive in 14 specimens with the highest IgG+ cells 20~350/hpf. IgG was expressed in cytoplasm. 2 specimens form Hodgkin lymphoma were IgG4 positive with highest cell counts were 11 and 12/hpf respectively (Figure 1).

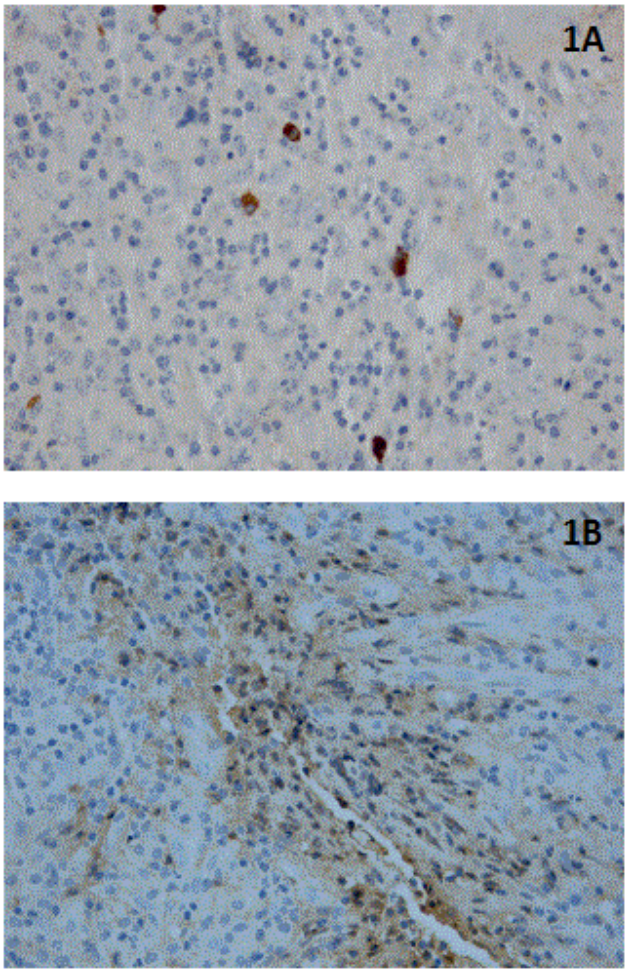

Figure 1: The expression of IgG4 (A) and IgG (B) in lymphoma.

Discussion

IgG4-RD was first proposed in 2003 [7]. Since then it has been gradually recognized. Increased IgG4 positive plasma cells were first found in autoimmune pancreatitis, followed by many swollen or tumid organs, such as parotitis, sialadenitis, orbit pseudotumor, thyroiditis, lymph nodes, pulmonary nodules, aneurysm and so on [8]. The diagnosis of IgG4-RD must be based on the premise that malignancy has been excluded. Patients with IgG4-RD were reported to be at risk of malignant disease [2]. However some researchers found that the incidence of total malignancies in IgG4-RD patients was similar to that in the general population [9]. One thing is sure that IgG4-RD should be differentiated from malignant diseases.

Recently some researches showed that patients with IgG4-RD were at the risk of malignant tumors [10,11] or hematological malignancies such as lymphoma [12,13]. IgG4-RD can happen before or after the diagnosis of lymphoma. Moreover, lymphoma can present simultaneously with IgG4-RD [14]. Additionally ocular adnexal extra nodal marginal zone B cell lymphoma had the manifestation of sclerosing inflammation in the background and numerous IgG4+ monotypic plasma cells [12,15]. IgG4-producing plasma cells can also be neoplastic [16].

In this study, we described 16 cases of lymphoma with various pathological subtypes. The diagnosis was established based on the pathological changes of the surgical excision specimen and the specific tumor markers. The proportion of IgG4+ cells as well as the maximal number of IgG4+ cells/hpf was low in these confirmed lymphomatous tissues. However this did not mean that the two entirely different diseases could not exist in the same patient, or even in the same organ or tissue. Based on currently studies we do not know the exact mechanism of IgG4-RD. But definitely, we believe that malignant diseases should be carefully screened and followed up in patients with IgG4-RD.

Conclusion

IgG positive cells can appear in lymphoma tissues. However IgG4 positive cells, fibrosis and obliterative phlebitis seldom present in lymphoma. With the aid of specific tumor signature molecules, it may not be difficult to distinguish lymphoma from IgG4-RD.

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