Department of Hematology, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University, Nanjing, People's Republic of China

# Acute lymphoblastic leukemia in a patient with IgG4-related disease

Dan Guo, Dangui Chen, Bing Chen*

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**Corresponding author: Bing Chen, Ph.D., Department of Hematology, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University, Nanjing 210036, People's Republic of China*
*chenbing2004@126.com*

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IgG4-related disease (IgG4-RD) is a multi-organ immune-mediated condition characterized by tumor-like lesions, fibrosis, and lymphoplasmacytic infiltration to every organ. Recently, an association between IgG4-RD and malignant tumors has been suggested and IgG4-RD is closely related to the occurrence of malignant hematologic diseases. In this report, we describe a rare complication of acute lymphoblastic leukemia in a patient with IgG4-RD. An 81-year-old Chinese man was diagnosed with the lymphadenopathy associated with IgG4-related disease. The histopathological study revealed multiple plasma cells infiltration and immunostaining for IgG and IgG4 was performed on plasma cells and the IgG/IgG4 ratio was more than 40%. Eight months later, he developed acute lymphoblastic leukemia. It has been suggested that the incidence of malignant hematologic diseases may be high in patients with IgG4-RD and increased Th2 cells and Treg cells cytokines may result in the occurrence of hematologic malignancies. Therefore, the importance of accurate diagnosis and intense medical follow-up should be emphasized. Once the patients develop hematologic malignancies, they need to receive treatment timely.

## 1. Introduction

IgG4-related disease(IgG4-RD) firstly established in autoimmune pancreatitis in 2001 is a multi-organ immune-mediated condition characterized by tumor-like lesions, fibrosis, and lymphoplasmacytic infiltration to every organ, including the pancreas, salivary glands, kidney, breasts, and lymphnodes (Hamano et al. 2001; Mahajan et al. 2014). Elevated serum IgG4 concentration and high IgG4/IgG-positive plasma cell ratio accompanied by eosinophilic infiltration have been considered important for proper diagnosis (Sato et al. 2010). An association between IgG4-RD and malignant tumors has been suggested because of autoimmune dysfunction (Yamamoto et al. 2012a). For example, the malignancy in many patients with IgG4-RD have occurred including lung cancer, gastrointestinal malignancy, lymphoma and acute myeloid leukemia (Hirano et al. 2014; Takahashi et al. 2009). Herein, we describe a rare complication of acute lymphoblastic leukemia (ALL) in a patient with IgG4-RD.

## 2. Case report

A 81-year-old Chinese man with a history of chronic bronchitis for 4 years was referred to our hospital because of cough and breathing difficulties. The symptoms were relieved obviously by anti-infective treatment, relieving cough and asthma. However, we found that his cervical, submandibular, axillary and inguinal nodes were swollen, the maximal lymph node was generally 3 cm in diameter. At the same time, chest CT demonstrated multiple lymph nodes swelling in his mediastinum, axilla, pulmonary hilum, cardiac diaphragm angle, retroperitoneum and abdominal cavity (Fig. 1A-C). A biopsy from the right inguinal lymph node revealed multiple plasma cell infiltration and short spindle cell proliferation. Plasma cells expressed IgG4 and IgG, and the IgG/IgG4 ratio was more than 40% (Fig. 2A-C). His serum IgG was 56.2 g/L and serum IgG4 was 412.5g/L. These findings led to a possible diagnosis of the lymphadenopathy associated with IgG4-RD. Meanwhile, his platelet count was only $20\times10^9$/L and bone

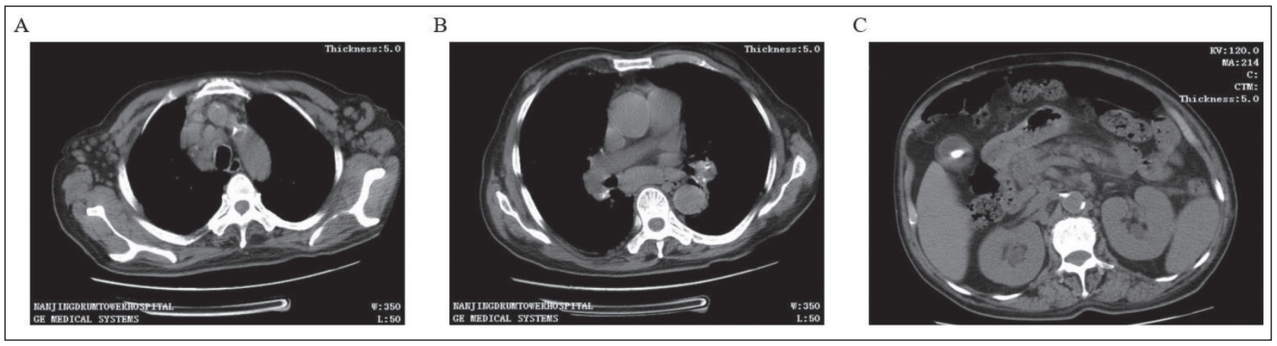


Fig. 1: Radiological findings of the lymphadenopathy associated with IgG4-related disease. A: Chest CT revealed lymph nodes swelling in axilla. B: There were swollen lymph nodes in mediastinum, pulmonary hilum and cardiac diaphragm angle. C: The lymph nodes of retroperitoneum and abdominal cavity were also swollen.

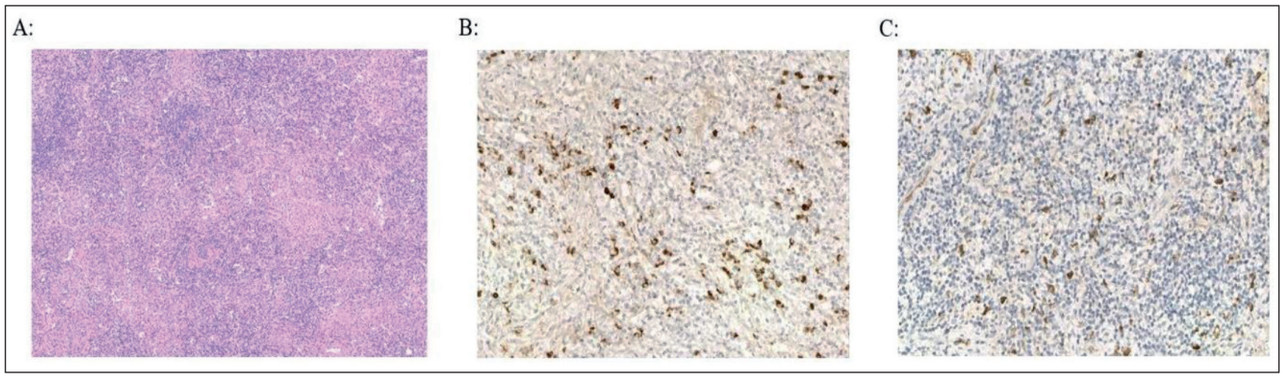


Fig. 2: Histopathological and immunohistochemical features of the inguinal lymph node. A: The plasma cells and spindle cells were observed in the inguinal lymph node, HE, × 40. B: Immunostaining showed that IgG+ plasma cells were found in the inguinal lymph node tissues, × 200. C: Immunostaining for IgG and IgG4 was performed on plasma cells and the IgG4/IgG ratio was more than 40%, × 200.

marrow aspiration showed low bone marrow hyperplasia. After the initiation of steroid therapy, the patient was discharged with a better health condition. Since then, he was often hospitalized due to acute exacerbation of chronic bronchitis and blood tests, lymphocyte subsets and chest CT were monitored regularly. White blood cell count was 5-11.1 $\times 10^9$/L, hemoglobin was 83-101 g/L and platelet was 20-59 $\times 10^9$/L. The ratio of CD4 + T cell was 20.8-41.9 % and the ratio of CD8 + T cell was 45.4-56.2 % (Table 1). However, the proportion of lymphocytes increased significantly and peripheral blood smear indicated that the blast cells accounted for 81% at his fourth visit to hospital. Bone marrow aspiration and flow cytometry revealed the patient developed ALL. Karyotype analysis showed he had complex karyotypes. It was not advisable for him to select chemotherapy due to advanced age and pulmonary infection. So symptomatic treatment was supported by component transfusion. Finally, he succumbed to respiratory failure 12 months after the diagnosis of ALL.

**Table 1: Laboratory data of the patient with IgG4-related disease**

| Laboratory data | Initial diagnosis | After 4 months | After 8 months |
|---|---|---|---|
| WBC×$10^9$/L | 5 | 3.6 | 11.1 |
| NE (%) | 82.5 | 57.9 | 18.4 |
| LY (%) | 13.4 | 16.6 | 51.9 |
| Hb (g/L) | 101 | 121 | 83 |
| PLT×$10^9$/L | 20 | 59 | 36 |
| CD4+T cell (%) | 20.8 | 41.9 | 23.9 |
| CD8+T cell (%) | 50.4 | 45.4 | 56.2 |
| CD4/CD8 | 0.41 | 0.92 | 0.43 |
| lgG (g/L) | 56.2 | 15.9 | 28.4 |

WBC: white blood cell; NE: eosinophils; LY: lymphocyte; Hb: hemoglobin; PLT: Platelets.

## 3. Discussion

IgG4-related disease is a new disease concept which is a multi-organ immune-mediated condition that mimics many malignant, infectious, and inflammatory disorders (Mahajan et al. 2014; Stone et al. 2012a). It is characterized by elevated serum levels of IgG4 and inflammation of various organs, with abundant infiltration of IgG4-bearing plasma cells, storiform fibrosis (Stone et al. 2012b). In contrast to other IgG subclasses, heavy chains in each IgG4 molecule have non-covalent associations and inefficient disulphide bridges because of a single amino acid difference in the hinge region (a serine in lieu of a proline) (Aalberse et al. 2009; Rispens et al. 2011). Most secreted IgG4 is functionally monovalent and IgG4 antibodies do not directly fix complement, they bind poorly to activating Fc receptors. So IgG4 has been viewed as a 'non-inflammatory' molecule, the primary function of which is to dampen rather than to accelerate chronic immune activation (Kamisawa et al. 2014). The pathogenesis of this disorder remains unclear, but inflammation and subsequent fibrosis occur due to excess production of type 2 T-helper-cell (Th2 cell) and regulatory T-cell (Treg cell) cytokines (Yamamoto et al. 2014).

Yamamoto et al. (2012b) reported that the standardized incidence ratio (SIR) for these malignancies in IgG4-RD was 383.0, which was higher than that for the general population. Takahashi et al. (2009) showed in IgG4-RD the SIR for malignant lymphoma is 16.0-fold higher than in the general population and three cases developed non-Hodgkin lymphoma during the follow-up of IgG4-associated systemic disease. These researches revealed that the risk of development of malignant tumors in patients with IgG4-RD has been obviously increased. In this report, we described the first documented case of ALL following IgG4-related disease, which is a rare complication. The case is an 81-years old man who developed ALL after a diagnosis of the lymphadenopathy associated with IgG4-RD. To date, other reports suggest that IgG4-RD can combine with other malignant hematologic diseases including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma and leukemia. Clinicopathological features of previous cases as well as the present one summarized in Table 2. Among 16 patients with IgG4-RD, the median age was 65 years (32–81 years) and most of the patients were male. The subtypes of malignant hematologic diseases were DLBCL (6 cases including the present case) (Takahashi et al. 2009; Mitsui et al. 2013; Uehara et al. 2012; Ishida et al. 2013; Nishimura et al. 2016), follicular lymphoma (1 case) (Oshima et al. 2012), small lymphocytic lymphoma (1 case) (Kim et al. 2008), extranodal marginal zone B-cell lymphoma (1 case) (Mulay and Aggarwal 2014), lymphoma (subtype was not available in 5 case) (Takahashi et al. 2009; Wallace et al. 2016), AML (1 case) (Hirano et al. 2014) and ALL (1 case). Therefore, IgG4-RD is closely related to the occurrence of malignant hematologic diseases.

Although the mechanism of development of malignant hematologic diseases with IgG4-RD remains unresolved, some progress has been made in this field. Voulgarelis and Skopouli (2007) showed that among autoimmune diseases, molecular oncogenic events such as microsatellite instability, loss of the B cell cycle control, and the forced overproduction of specific B cell biologic stimulators seemed to contribute to the emergence and progression of the abnormal lymphocytes, resulting in the occurrence of lymphoma. IgG4-RD, an autoimmune disease, is potentially driven by enhanced Th2 cells and Treg cells responses. Activated Th2 cells and Treg cells may produce an inflammatory cytokine milieu that includes IFN-γ, IL-4, IL-5, IL-10 and IL-13, thereby promoting class-switching to IgG4 and differentiation of B cells into IgG4 plasma cells (Mahajan et al. 2014). In the advanced stages, IgG4-RD is characterized by severe fibrosis caused by the prolonged induction of IL-13, which is a strong inducer of fibrosis and a central cytokine in the Th2 differentiation pathway (Kamisawa et al. 2006). However, increased secretion of Th2 cells and

**Table 2: Characteristics of hematologic malignancy in patients with IgG4-related disease**

| Case | Reference | Age | Sex (M/F) | Type of IgG4-RD or IgG4-RD organ involvement | Type of hematological malignancy |
|---|---|---|---|---|---|
| Case 1 | [14] | 59 | Male | IgG4 related sclerosing cholangitis | Diffuse large B-cell lymphoma |
| Case 2 | [15] | 66 | Male | Mikulicz's disease | Diffuse large B-cell lymphoma |
| Case 3 | [6] | 72 | Male | Autoimmune pancreatitis | Diffuse large B-cell lymphoma |
| Case 4 | [6] | 69 | Male | Chronic parotitis | Diffuse large B-cell lymphoma |
| Case 5 | [16] | 61 | Male | Autoimmune pancreatitis, IgG4-related cholecystitis and rhinitis | Diffuse large B-cell lymphoma |
| Case 6 | [17] | 61 | Male | Autoimmune pancreatitis | Diffuse large B-cell lymphoma |
| Case 7 | [18] | 41 | Male | IgG4-related tubulointerstitial nephritis | Follicular lymphoma |
| Case 8 | [19] | 76 | Male | Autoimmune pancreatitis | Small lymphocytic lymphoma |
| Case 9 | [20] | 65 | Female | IgG4-related dacryoadenitis | Extranodal marginal zone B-cell lymphoma |
| Case 10 | [6] | 65 | Female | Autoimmune pancreatitis | B-cell lymphoma |
| Case 11 | [21] | 52 | Male | Aorta, kidney, heart | Lymphoma |
| Case 12 | [21] | 69 | Female | Parotid, submandibular, lymphadenopathy | Lymphoma |
| Case 13 | [21] | 47 | Male | Orbital, parotid, submandibular, pancreas | Lymphoma |
| Case 14 | [21] | 32 | Male | Aorta | Lymphoma |
| Case 15 | [5] | 70 | Female | Autoimmune pancreatitis | Acute myeloid leukemia |
| Case 16 | This case | 81 | Male | lymphadenopathy | Acute lymphoblastic leukemia |

M: male; F: female; IgG4-RD: IgG4-related disease.

Treg cells cytokines can activate B-cells and the predominance of B-cell lymphoma as a secondary development to IgG4-RD is plausible.

Th1 and Th2 cells regulate and inhibit each other to maintain the body's immune balance. Once this balance is disrupted, it will lead to disease. The results suggested that the migration of Th1 cytokines into Th2 cytokines can affect the cellular immune status *in vivo* which was beneficial for immune evasion of tumor cells (Kusada et al. 2005). In ALL patients, there is a dysregulation in the functionality of Th1 and Th2 cells with a gross reduction of Th1 cell populations and an expansion in Th2 cells (Zhang et al. 2000). So when patients occur lgG4-RD in which Th2 cytokines account for the majority, they are more likely to develop acute lymphoblastic leukemia. In this case, CD8 + T cells of patients were significantly increased, indicating immunosuppressive effect was dominant, so that the capacity of immune clearance and immune surveillance decreased, eventually leading to the occurrence of tumor.

In conclusion, we report a case of ALL following the lymphadenopathy associated with IgG4-RD and summary the characteristics of 17 patients with IgG4-RD. It has been suggested that the incidence of malignant hematologic diseases may be high in patients with IgG4-RD and increased Th2 cells and Treg cells cytokines may result in the occurrence of hematologic malignancies. Therefore, it is necessary for patients with IgG4-RD to detect immune function and undergo medical follow-up. Once patients develop hematologic malignancies, they need to receive treatment timely.

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## References

Aalberse RC, Stapel SO, Schuurman J, Rispens T (2009) Immunoglobulin G4: an odd antibody. Clin Exp Allergy 39: 469-477.

Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K (2001) High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 344: 732-738.

Hirano K, Tada M, Sasahira N, Isayama H, Mizuno S, Takagi K, Watanabe T, Saito T, Kawahata S, Uchino R, Hamada T, Miyabayashi K, Mohri D, Sasaki T, Kogure H, Yamamoto N, Nakai Y, Yoshida H, Ito Y, Akiyama D, Toda N, Arizumi T, Yagioka H, Takahara N, Matsubara S, Yashima Y, Koike K (2014) Incidence of malignancies in patients with IgG4-related disease. Intern Med 53: 171-176.

Ishida M, Hodohara K, Yoshida K, Kagotani A, Iwai M, Yoshii M, Okuno H, Horinouchi A, Nakanishi R, Harada A, Yoshida T, Okabe H (2013) Occurrence of anaplastic large cell lymphoma following IgG4-related autoimmune pancreatitis and cholecystitis and diffuse large B-cell lymphoma. Int J Clin Exp Pathol 6: 2560-2568.

Kamisawa T, Nakajima H, Egawa N, Funata N, Tsuruta K, Okamoto A. (2006) IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. Pancreatology 6: 132-137.

Kamisawa T, Zen Y, Pillai S, Stone JH. (2015) IgG4-related disease. Lancet 385: 1460-1471.

Kim T, Grobmyer SR, Dixon LR, Allan RW, Hochwald SN (2008) Autoimmune pancreatitis and concurrent small lymphocytic lymphoma: not just a coincidence. J Gastrointest Surg 12: 1566-1570.

Kusuda T, Shigemasa K, Arihiro K, Fujii T, Nagai N, Ohama K (2005) Relative expression levels of Th1 and Th2 cytokine mRNA are independent prognostic factors in patients with ovarian cancer. Oncol Rep 13: 1153-1158.

Mahajan VS, Mattoo H, Deshpande V, Pillai SS, Stone JH (2104) IgG4-related disease. Annu Rev Pathol 9: 315-347.

Mitsui T, Yokohama A, Koiso H, Ishizaki T, Uchiumi H, Saitoh T, Handa H, Hirato J, Karasawa M, Murakami H, Kojima M, Nojima Y, Tsukamoto N (2013) Development of IgG4-related disease 10 years after chemotherapy for diffuse large B cell lymphoma and longstanding bronchial asthma. Int J Hematol 98: 122-128.

Mulay K, Aggarwal E (2014) IgG4-related dacryoadenitis evolving into an extranodal, marginal zone B-cell lymphoma (EMZL): a tale of two lacrimal glands. Pathology 46: 464-466.

Nishimura Y, Iwamuro M, Ocho K, Hasegawa K, Kimura K, Hanayama Y, Kondo E, Tanaka T, Otsuka F (2016) A rare case of diffuse large B-cell lymphoma in a patient with IgG4-related autoimmune pancreatitis. Acta Med Okayama 70: 279-283.

Oshima Y, Usui R, Manabe S, Hasegawa N, Kakuta Y, Nitta K, Hatano M (2012) IgG4-related tubulointerstitial nephritis and lymphadenopathy after therapy for malignant lymphoma. Intern Med 51: 1221-1226.

Rispens T, Ooijevaar-de HP, Bende O, Aalberse RC (2011) Mechanism of immunoglobulin G4 Fab-arm exchange. J Am Chem Soc 133: 10302-10311.

Sato Y, Notohara K, Kojima M, Takata K, Masaki Y, Yoshino T (2010) IgG4-related disease: historical overview and pathology of hematological disorders. Pathol Int 60: 247-258.

Stone JH, Khosroshahi A, Deshpande V, Chan JK, Heathcote JG, Aalberse R, Azumi A, Bloch DB, Brugge WR, Carruthers MN, Cheuk W, Cornell L, Castillo CF, Ferry JA, Forcione D, Klöppel G, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Masaki Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani D, Sato Y, Smyrk T, Stone JR, Takahira M, Umehara H, Webster G, Yamamoto M, Yi E, Yoshino T, Zamboni G, Zen Y, Chari S (2012a) Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis Rheum 64: 3061-3067.

Stone JH, Zen Y, Deshpande V (2012b). IgG4-related disease. N Engl J Med 366: 539-551.

Takahashi N, Ghazale AH, Smyrk TC, Mandrekar JN, Chari ST (2009) Possible association between IgG4-associated systemic disease with or without autoimmune pancreatitis and non-Hodgkin lymphoma. Pancreas 38: 523-526.

Uehara T, Ikeda S, Hamano H, Kawa S, Moteki H, Matsuda K, Kaneko Y, Hara E (2012) A case of Mikulicz's disease complicated by malignant lymphoma: a postmortem histopathological finding. Intern Med 51: 419-423.

Voulgarelis M, Skopouli FN (2007) Clinical, immunologic, and molecular factors predicting lymphoma development in Sjogren's syndrome patients. Clin Rev Allergy Immunol 32: 265-274.

Wallace ZS, Wallace CJ, Lu N, Choi HK, Stone JH (2016) Association of IgG4-Related Disease With History of Malignancy. Arthritis Rheumatol 68: 2283-2289.

Yamamoto M, Takahashi H, Shinomura Y (2012a) IgG4-related disease and malignancy. Intern Med 51: 349-350.

Yamamoto M, Takahashi H, Tabeya T, Suzuki C, Naishiro Y, Ishigami K, Yajima H, Shimizu Y, Obara M, Yamamoto H, Himi T, Imai K, Shinomura Y (2012b) Risk of malignancies in IgG4-related disease. Mod Rheumatol 22: 414-418.

Yamamoto M, Takahashi H, Shinomura Y (2014) Mechanisms and assessment of IgG4-related disease: lessons for the rheumatologist. Nat Rev Rheumatol 10: 148-159.

Zhang XL, Komada Y, Chipeta J, Li QS, Inaba H, Azuma E, Yamamoto H, Sakurai M (2000) Intracellular cytokine profile of T cells from children with acute lymphoblastic leukemia. Cancer Immunol Immunother 49: 165-172.