

## Development of IgG4-related disease 10 years after chemotherapy for diffuse large B cell lymphoma and longstanding bronchial asthma

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**Abstract** Reported is a rare case IgG4-related disease that developed 10 years after combination chemotherapy for non-Hodgkin lymphoma. A 59-year-old Japanese man with longstanding bronchial asthma was referred to our hospital for bilateral hilar lymph node enlargement. The initial diagnosis was diffuse large B cell lymphoma (DLBCL) by supraclavicular lymph node biopsy. Serum IgG was high (4550 mg/dL) at diagnosis. The patient achieved complete response following six cycles of combination chemotherapy. Ten years later, bilateral submaxillary gland swelling was observed. Serum IgG and IgG4

were 2909 and 1470 mg/dL, respectively. The patient was diagnosed with IgG4-related disease by submandibular lymph node biopsy. Due to the difficulty in distinguishing IgG4-related disease from DLBCL through imaging findings alone, pathological confirmation of such lesions by biopsy is mandatory before proceeding to treatment.

**Keywords** Non-Hodgkin lymphoma · IgG4-related disease · Bronchial asthma · DLBCL

### Introduction

IgG4-related disease is a recently proposed clinical entity with characteristic clinicopathological features [1, 2]. It is a systemic fibroinflammatory disease characterized by elevated serum IgG4, increased IgG4-positive plasma cells and lymphocytes, and tumor-like involvement of either one or more exocrine glands or other extranodal sites with lymphoplasmacytic infiltrates and sclerosis. Another feature of IgG4-related disease is glucocorticoid responsiveness [3]. The most common components of this disease are autoimmune pancreatitis, chronic sclerosing sialadenitis of the submandibular gland (Küttner tumor), and chronic sclerosing dacryoadenitis [1, 4–6]. The many synonyms for IgG4-related disease include IgG4-multiorgan lymphoproliferative syndrome (IgG4 + MOLPS) [7], IgG4-related sclerosing disease [8], and systemic IgG4-related plasmacytic syndrome (SIPS) [9].

A relationship between several autoimmune and inflammatory disorders and the risk of non-Hodgkin lymphoma (NHL) has been suggested [10, 11]. As for IgG4-related disease, there have been several reports on the development of NHL superimposed on IgG4-related disease, in which mucosa associated lymphoid tissue (MALT)

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lymphoma is the most frequent [12–14]. In the present report, a patient who was diagnosed with IgG4-related disease 10 years after the initial development of diffuse large B cell lymphoma (DLBCL) is described.

### Case report

A 59-year-old Japanese man was referred to our hospital because of bilateral hilar lymph node enlargement in August 1999. He had been treated for bronchial asthma for 24 years in another hospital. Physical examination revealed no remarkable findings except for left supraclavicular lymph node swelling. Blood cell counts were normal. Serum lactate dehydrogenase (LDH) was not elevated. Serum IgG was 4550 mg/dL (normal range 770–1700), but other immunoglobulin levels were in the normal range. Soluble interleukin-2 receptor (sIL-2R) was 2920 U/mL (normal range 246–742). The patient underwent supraclavicular lymph node biopsy and was diagnosed with DLBCL. Computed tomography (CT) revealed bilateral mediastinal lymph node swelling and swelling of a supraclavicular lymph node (Fig. 1a). Gallium-67 ( $^{67}\text{Ga}$ ) scintigraphy showed accumulation of  $^{67}\text{Ga}$  in the bilateral mediastinal lymph nodes and a supraclavicular lymph node (Fig. 1b). With six cycles of combination chemotherapy containing cyclophosphamide, doxorubicine, vincristine, and prednisolone (CHOP), complete response (CR) was obtained. In 2001, CT revealed bilateral mediastinal lymph node swelling. Although lymph node biopsy was not performed, we considered relapse of DLBCL from these clinical findings. Three cycles of CHOP chemotherapy followed by radiotherapy of the bilateral mediastinal lymph nodes at a dose of 40 Gy was performed and CR was obtained. However, in September 2008,  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography ( $^{18}\text{F}$ -FDG-PET) showed accumulation of  $^{18}\text{F}$ -FDG in the bilateral hilar lymph nodes, mediastinal lymph nodes, and para-aorta lymph nodes (Fig. 1c). Because the patient exhibited no symptoms, watchful waiting was pursued. For 9 months, the patient had no symptoms and no enlargement of the superficial lymph nodes. In June 2009, bilateral submaxillary gland swelling was observed.  $^{18}\text{F}$ -FDG-PET showed accumulation of  $^{18}\text{F}$ -FDG in the nasal sinuses, bilateral submaxillary glands, right submandibular lymph node, and bilateral mediastinal lymph nodes (Fig. 1d). Laboratory data showed that the blood cell counts, liver function, and renal function were normal. Serum LDH was 164 IU/L (normal range 119–229). Serum IgG and IgG4 were 2909 mg/dL and 1470 mg/dL (normal range 4.8–105), respectively. The sIL-2R level was 604 U/mL. Biopsy of the submandibular lymph node was performed and IgG4-related disease was diagnosed. With daily administration of 10 mg prednisolone, the superficial lymph node and bilateral

submaxillary glands shrunk, and serum IgG and IgG4 levels decreased. Clinical course is shown in Fig. 1e.

### Initial biopsy specimen findings

The initial biopsy specimen was obtained from a supraclavicular lymph node in 1999. Pathological findings showed that the lesion was characterized by diffuse proliferation of large atypical lymphoid cells and effacement of normal lymph node architecture on low-power examination (Fig. 2a). On high-power examination, large atypical lymphoid cells were found to have oval to round, vesicular nuclei with one to four nucleoli. Many mitotic cells were observed (Fig. 2b). Immunostaining demonstrated that large atypical lymphoid cells expressed CD20 antigen but were CD3 negative (Fig. 2c, d), consistent with the diagnosis of DLBCL.

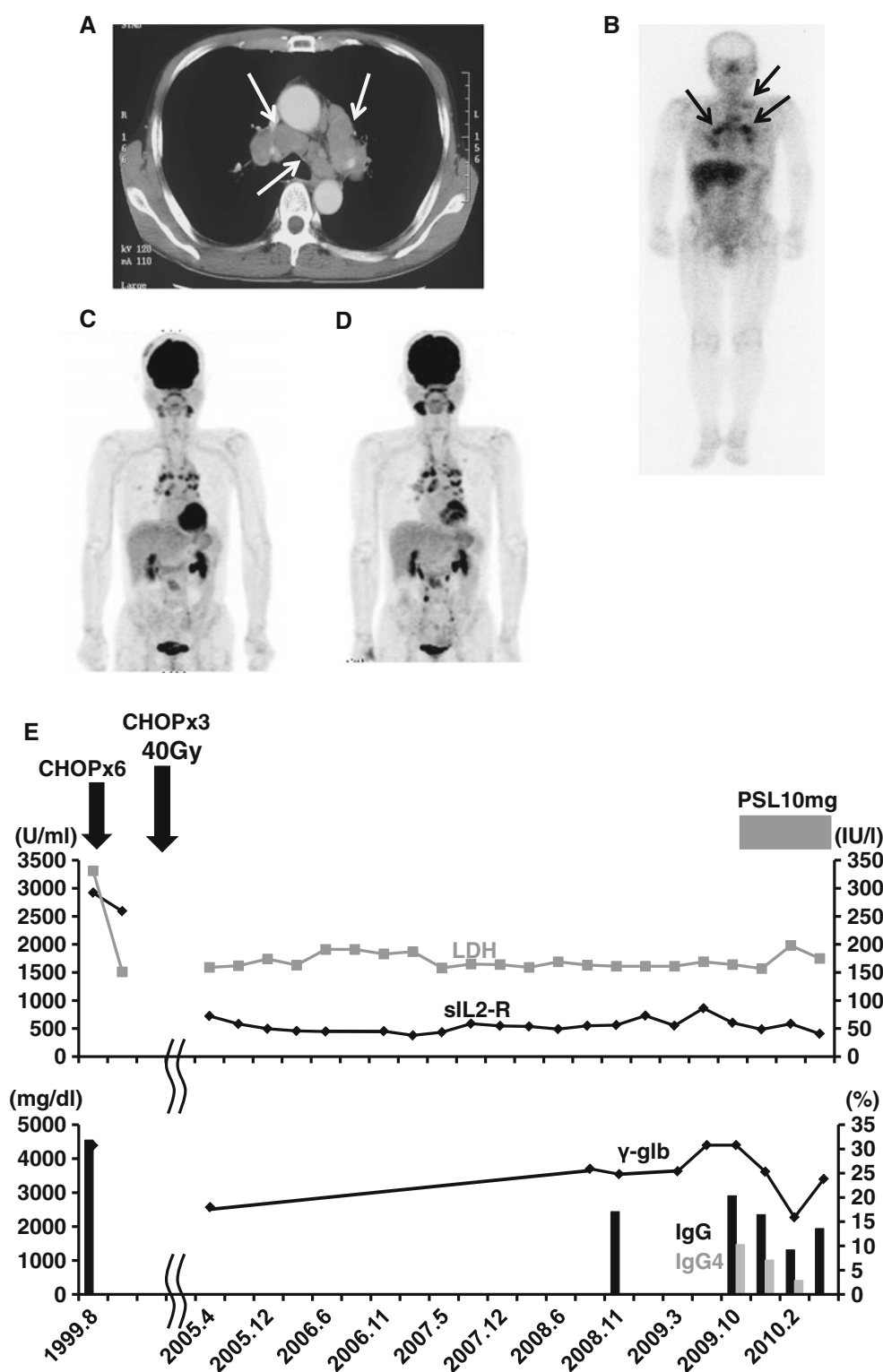
### Second lymph node biopsy specimen findings

The second biopsy specimen was obtained from a submandibular lymph node in 2009. Flowcytometric analysis showed that a normal kappa/lambda ratio was observed in the lymphocyte population (Fig. 3a). On low-power examination, pathological findings showed that various sizes of follicles were distributed irregularly in the lymph node (Fig. 3b). Slightly atrophic germinal centers containing fibrosis and infiltrating small vessels was observed (Fig. 3c). On examination at high-power, the paracortical area was diffusely infiltrated by a polymorphous population consisting of numerous mature plasma cells, plasmacytoid cells, large basophilic transformed lymphocytes (immunoblasts), and small- to medium-sized lymphocytes (Fig. 3d). The capsule also showed fibrosis and infiltration of mature plasma cells and small lymphocytes. Staining with CD3 and CD20 showed a mixture of small and medium lymphocytes and immunoblasts. Immunohistochemical studies of light chain determinants for interfollicular plasma cells, plasmacytoid cells, and B-immunoblasts demonstrated a polyclonal pattern. There were numerous IgG-positive plasma cells in the lesion (Fig. 3e). IgG4-positive cells comprised 90 % of the IgG-positive plasma cells (Fig. 3f). Based on these histomorphological and immunohistochemical findings of the second lymph node specimen, IgG4-related disease was diagnosed.

### Review of initial biopsy specimen findings

After IgG4-related disease was diagnosed from the second lymph node specimen, the initial biopsy specimen was

**Fig. 1** **a** CT showing bilateral mediastinal lymph node swelling at diagnosis in 1999. **b**  $^{67}\text{Ga}$  scintigraphy showing accumulation of  $^{67}\text{Ga}$  in the bilateral mediastinal lymph nodes and a left supraclavicular lymph node at initial diagnosis. **c**  $^{18}\text{F}$ -FDG-PET showing accumulation of  $^{18}\text{F}$ -FDG in the bilateral hilar lymph nodes, mediastinal lymph nodes, and para-aorta lymph nodes in 2008. **d**  $^{18}\text{F}$ -FDG-PET showing accumulation of  $^{18}\text{F}$ -FDG in the nasal sinuses, bilateral submaxillary glands, right submandibular lymph node, and bilateral mediastinal lymph nodes in 2009. **e** Clinical course of this patient

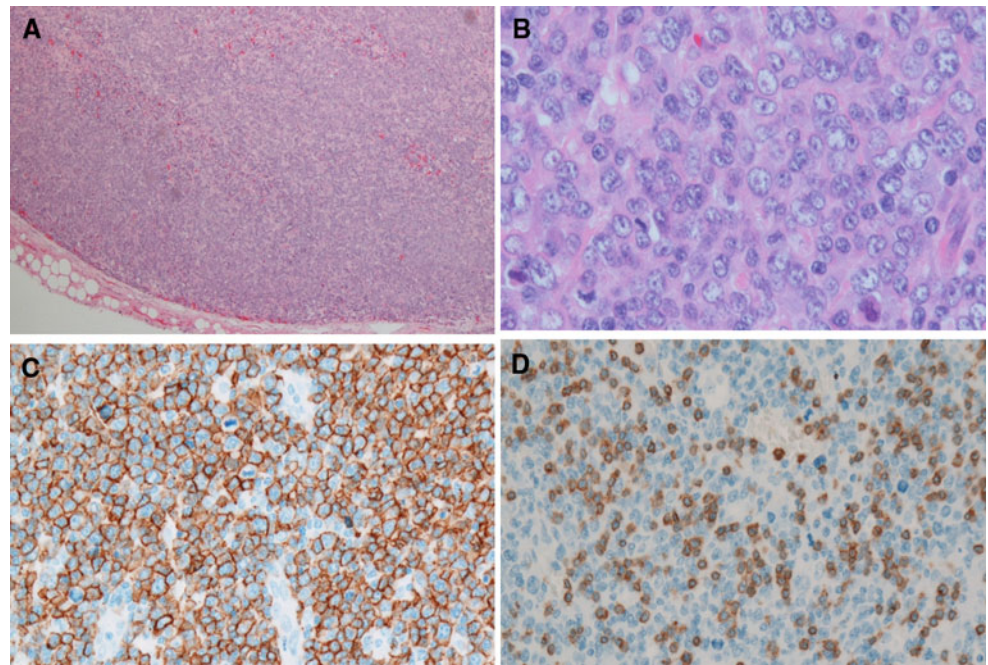


evaluated for IgG4-related disease lesions. Immunohistochemistry showed that many IgG- and IgG4-positive cells infiltrated the outside of the DLBCL lesion. The IgG4/IgG ratio was over 90 % (Fig. 4a, b). To examine the clonality

of initial and second biopsy specimens, PCR of the immunoglobulin heavy chain gene was performed using DNAs extracted from paraffin-embedded sections as templates [15]. Total of 100 ng DNA was amplified by PCR. PCR

**Fig. 2** Histological findings from the initial biopsy of the left supraclavicular lymph node at initial diagnosis in 1999.

**a** Hematoxylin-eosin staining ( $\times 40$ ). Diffuse proliferation of large atypical lymphoid cells and effacement of normal lymph node architecture are observed. **b** Hematoxylin-eosin staining ( $\times 400$ ). Large atypical lymphoid cells have *oval to round* vesicular nuclei with one to four nucleoli. Many mitotic cells are observed. **c** Large atypical lymphoid cells express CD20 antigen ( $\times 200$ ). **d** CD3 is negative in the large atypical lymphoid cells ( $\times 200$ )



consisted of an initial denaturation step of 10 min at 95 °C, followed by 45 cycles of 95 °C for 30 s, 55 °C for 30 s, and 72 °C for 30 s with a final extension step of 10 min at 72 °C. When PCR products were electrophoresed on a 3 % agarose gel, a single band representing rearrangement was detected in the initial lymph node specimen. On the contrary, smear representing polyclonal pattern was observed in the second biopsy specimen (Fig. 4c). Therefore, it was concluded that the IgG4-related disease existed over a background of DLBCL in the initial lymph node specimen.

## Discussion

IgG4-related disease frequently involves the pancreas [1], submandibular gland [16], lacrimal gland [12], and lymph nodes [17]. It is characterized by mass-forming lesions infiltrating IgG4-positive plasma cells and lymphoplasmacytic cells and shows sclerosis. Among the cases of IgG4-related disease occurring with malignant lymphoma, especially on ocular adnexa and salivary gland, most cases show MALT lymphoma [12, 18], and some IgG4-producing cells have been identified as neoplastic [13]. To our knowledge, only four cases are reported about IgG4-related disease following DLBCL [19, 20].

In this patient, IgG-4 related disease developed 10 years after the initial development of DLBCL and treatment with combination chemotherapy. One other case has been reported that has shown local recurrence of IgG4-related

disease 10 years after radiotherapy for ocular adnexa MALT lymphoma [21]. On the initial biopsy specimen in the present case, the lesion was characterized by diffuse proliferation of large atypical lymphoid cells and effacement of normal architecture consistent with DLBCL. Indeed, the serum IgG level at diagnosis was high (4550 mg/dL), but IgG4 was not measured because no IgG4-related disease categories had been described in 1999. As there were many infiltrating IgG- and IgG4-positive cells outside the DLBCL lesion seen by immunohistochemical studies, the patient was determined to have had subclinical IgG4-related disease before he developed DLBCL. So, it was speculated that IgG4-producing plasma cells served as a background for DLBCL, non-neoplastic IgG4 producing plasma cells survived after chemotherapy, and then IgG4-related disease subsequently developed.

Another outstanding feature in this patient is the coexistence of the allergic disorder of bronchial asthma and IgG4-related disease. There have been some reports regarding allergic manifestations in patients with IgG4-related disease. Allergic diseases were found to coexist in 20 of 45 patients with autoimmune pancreatitis: three of those 20 had bronchial asthma [22]. Likewise, seven of 25 patients with Mikulicz's disease were found to have bronchial asthma [23]. Further, one patient with IgG4-related kidney disease complicated by Churg-Strauss Syndrome has been reported [24]. Thus, bronchial asthma is suggested to be one complication of IgG4-related disease [22, 25].

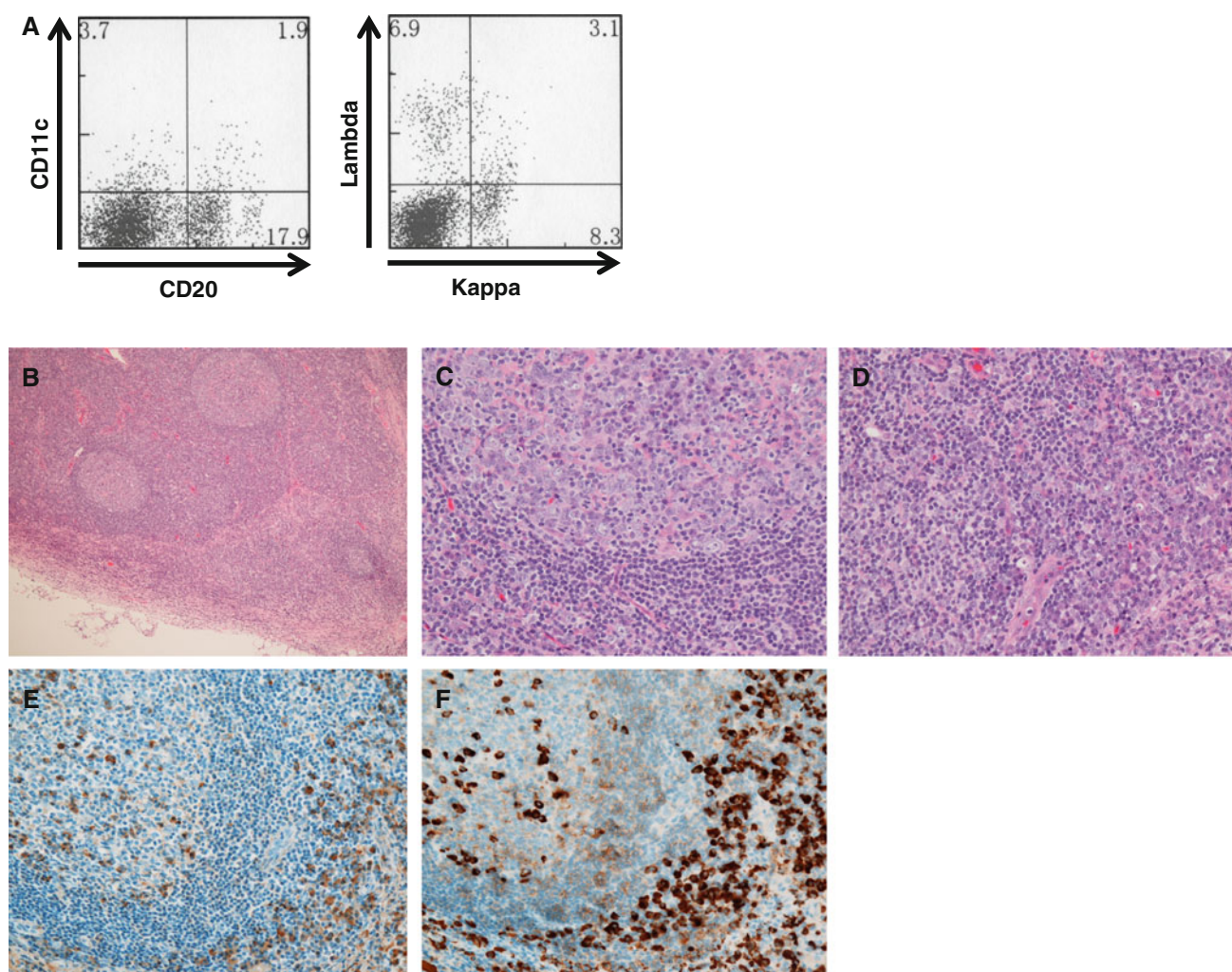


**Fig. 3** Histological findings from the second biopsy specimens of the submandibular lymph node in 2009. **a** Flowcytometric analysis reveals a normal range of the kappa/lambda ratio. **b** Hematoxylin-eosin staining ( $\times 40$ ). Various sizes of follicles are distributed irregularly in the lymph node. **c** Hematoxylin-eosin staining ( $\times 200$ ). Slightly atrophic germinal centers containing fibrosis and

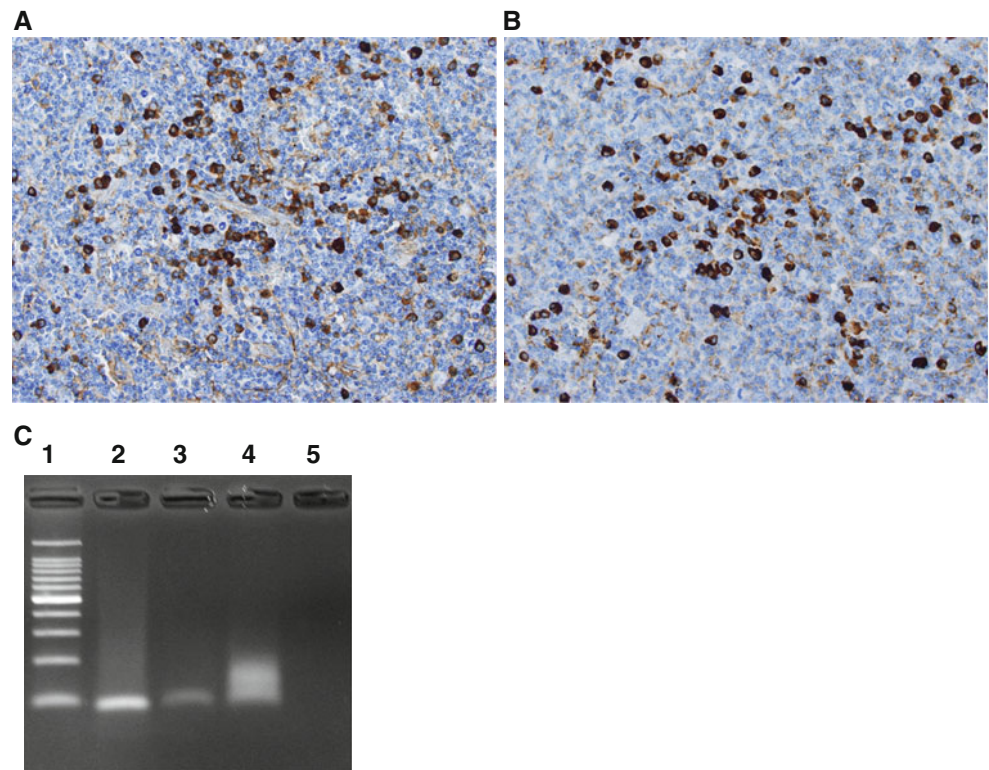
infiltration of small vessels are observed. **d** Hematoxylin-eosin staining ( $\times 200$ ). Proliferation of immunoblast-like cells and heavy infiltration of mature plasma cells and small lymphocytes are observed in the interfollicular area. **e** There are numerous IgG-positive cells in the paracortical area. ( $\times 200$ ). **f** Ninety percent of the IgG-positive plasma cells are IgG4-positive. ( $\times 200$ )

The relationship between allergic disorders and IgG4-related disease remains unclear. However, deviation of the Th1/Th2 balance toward a predominance of Th2 in the peripheral blood and elevated expression of Th2-type cytokines have been observed in patients with autoimmune pancreatitis and Mikulicz's disease [26]. In addition, IL-4 induces naïve human B cells to produce IgG4 [27]. These reports indicate that IgG4-related disease pushes the Th1/Th2 balance toward Th2. On the other hand, many allergic diseases are known to be caused by a shift of the Th1/Th2 balance toward Th2 [28]. So, IgG4-related disease and allergic disorders have Th2 predominance in common

[29]. In this respect, the present patient had bronchial asthma at the onset of DLBCL, and the bronchial asthma might have contributed to the pathogenesis of the IgG4-related disease.

$^{18}\text{F}$ -FDG-PET/CT has become an important tool in management of malignant lymphoma [30]. However, as FDG accumulates in IgG4-related disease lesions [31, 32], it is difficult to distinguish IgG4-related disease lesions from lymphoma lesions. As shown in the present patient, clinical signs and imaging findings suggested recurrence of NHL, but the second biopsy specimens showed manifestation of IgG4-related disease. In order to avoid

**Fig. 4** Immunohistological findings from the initial biopsy specimen of the left supraclavicular lymph node at initial diagnosis in 1999. **a** IgG-positive cells infiltrate outside of the DLBCL lesion ( $\times 200$ ). **b** The majority of IgG-positive cells are positive for IgG4 ( $\times 200$ ). **c** PCR analysis for clonal IgH rearrangement in the initial biopsy specimen and the second biopsy specimen. The lanes 1 marker, 2 positive control, 3 initial biopsy, 4 second biopsy, and 5 negative control



inappropriate treatment in patients with suspected malignant lymphoma, pathological confirmation of lesions by biopsy is mandatory.

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**Conflict of interest** The authors declare that they have no conflict of interest.

## References

- Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med*. 2001;344:732–8.
- Sato Y, Notohara K, Kojima M, Takata K, Masaki Y, Yoshino T. IgG4-related disease: historical overview and pathology of hematological disorders. *Pathol Int*. 2010;60:247–58.
- Masaki Y, Kurose N, Umehara H. IgG4-related disease: a novel lymphoproliferative disorder discovered and established in Japan in the 21st century. *J Clin Exp Hematop*. 2011;51:13–20.
- Hamano H, Arakura N, Muraki T, Ozaki Y, Kiyosawa K, Kawa S. Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. *J Gastroenterol*. 2006;41:1197–205.
- Cheuk W, Yuen HK, Chan JK. Chronic sclerosing dacryoadenitis: part of the spectrum of IgG4-related sclerosing disease? *Am J Surg Pathol*. 2007;31:643–5.
- Kitagawa S, Zen Y, Harada K, Sasaki M, Sato Y, Minato H, et al. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Küttner's tumor). *Am J Surg Pathol*. 2005;29:783–91.
- Masaki Y, Dong L, Kurose N, Kitagawa K, Morikawa Y, Yamamoto M, et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis*. 2009;68:1310–5.
- Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol*. 2006;41:613–25.
- Yamamoto M, Takahashi H, Hasebe K, Suzuki C, Naishiro Y, Hayashi T, et al. The analysis of interleukin-6 in patients with systemic IgG4-related plasmacytic syndrome—expansion of SIPS to the territory of Castleman's disease. *Rheumatology (Oxford)*. 2009;48:860–2.
- Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med*. 2005;165:2337–44.
- Smedby KE, Baecklund E, Askling J. Malignant lymphomas in autoimmunity and inflammation: a review of risks, risk factors, and lymphoma characteristics. *Cancer Epidemiol Biomarkers Prev*. 2006;15:2069–77.
- Cheuk W, Yuen HK, Chan AC, Shih LY, Kuo TT, Ma MW, et al. Ocular adnexal lymphoma associated with IgG4 + chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4-related sclerosing disease. *Am J Surg Pathol*. 2008;32:1159–67.
- Sato Y, Takata K, Ichimura K, Tanaka T, Morito T, Tamura M, et al. IgG4-producing marginal zone B-cell lymphoma. *Int J Hematol*. 2008;88:428–33.
- Kubota T, Moritani S, Yoshino T, Nagai H, Terasaki H. Ocular adnexal marginal zone B cell lymphoma infiltrated by IgG4-positive plasma cells. *J Clin Pathol*. 2010;63:1059–65.
- Yokohama A, Karasawa M, Sakai H, Okamoto K, Maehara T, Tsukamoto N, et al. Molecular detection of tumor cells at

- diagnosis invading the bone marrow and peripheral blood of patients with aggressive or indolent lymphomas. *Leuk Res.* 2001;25:749–55.
16. Kamisawa T, Egawa N, Inokuma S, Tsuruta K, Okamoto A, Kamata N, et al. Pancreatic endocrine and exocrine function and salivary gland function in autoimmune pancreatitis before and after steroid therapy. *Pancreas.* 2003;27:235–8.
  17. Cheuk W, Yuen HK, Chu SY, Chiu EK, Lam LK, Chan JK. Lymphadenopathy of IgG4-related sclerosing disease. *Am J Surg Pathol.* 2008;32:671–81.
  18. Oyama T, Takizawa J, Nakamura N, Aoki S, Aizawa Y, Abe H. Multifocal mucosa-associated lymphoid tissue lymphoma associated with IgG4-related disease: a case report. *Jpn J Ophthalmol.* 2011;55:304–6.
  19. Takahashi N, Ghazale AH, Smyrk TC, Mandrekar JN, Chari ST. Possible association between IgG4-associated systemic disease with or without autoimmune pancreatitis and non-hodgkin lymphoma. *Pancreas.* 2009;38:523–6.
  20. Uehara T, Ikeda S, Hamano H, Kawa S, Moteki H, Matsuda K, et al. A case of Mikulicz's disease complicated by malignant lymphoma: a postmortem histopathological finding. *Intern Med.* 2012;51:419–23.
  21. Matsuo T, Ichimura K, Yoshino T. Local recurrence as immunoglobulin G4 (IgG4)-related disease 10 years after radiotherapy to ocular adnexal extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *J Clin Exp Hematop.* 2011; 51:125–33.
  22. Kamisawa T, Anjiki H, Egawa N, Kubota N. Allergic manifestations in autoimmune pancreatitis. *Eur J Gastroenterol Hepatol.* 2009;21:1136–9.
  23. Matsui S, Taki H, Shinoda K, Suzuki K, Hayashi R, Tobe K, et al. Respiratory involvement in IgG4-related Mikulicz's disease. *Mod Rheumatol.* 2012;22:31–9.
  24. Ayuzawa N, Ubara Y, Keiichi S, Masayuki Y, Hasegawa E, Hiramatsu E, et al. Churg-Strauss syndrome with a clinical condition similar to IgG4-related kidney disease: a case report. *Intern Med.* 2012;51:1233–8.
  25. Ito S, Ko SB, Morioka M, Imaizumi K, Kondo M, Mizuno N, et al. Three cases of bronchial asthma preceding IgG4-related autoimmune pancreatitis. *Allergol Int.* 2012;61:171–4.
  26. 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.
  27. Punnonen J, Aversa G, Cocks BG, McKenzie AN, Menon S, Zurawski G, et al. Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human b cells. *Proc Natl Acad Sci USA.* 1993;90:3730–4.
  28. Romagnani S. Immunologic influences on allergy and the Th1/Th2 balance. *J Allergy Clin Immunol.* 2004;113:395–400.
  29. Zen Y, Nakanuma Y. Pathogenesis of IgG4-related disease. *Curr Opin Rheumatol.* 2011;23:114–8.
  30. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25:579–86.
  31. Nakatani K, Nakamoto Y, Togashi K. Utility of FDG PET/CT in IgG4-related systemic disease. *Clin Radiol.* 2012;67:297–305.
  32. Matsubayashi H, Furukawa H, Maeda A, Matsunaga K, Kanemoto H, Uesaka K, et al. Usefulness of positron emission tomography in the evaluation of distribution and activity of systemic lesions associated with autoimmune pancreatitis. *Pancreatol.* 2009;9:694–9.