J Clin Exp Hematopathol
Vol. 52, No. 1, May 2012

Case Study

Rheumatoid Lymphadenopathy with Abundant IgG4$^+$ Plasma Cells : A Case Mimicking IgG4-Related Disease

Naoko Asano[1)] and Yasuharu Sato[2)]

Immunoglobulin (Ig) G4-related disease is a recently confirmed clinical entity with several unique clinicopathological features. Here we report a case of rheumatoid lymphadenopathy mimicking IgG4-related disease. The patient was a 63-year-old woman who had been treated for rheumatoid arthritis (RA) for six years. The patient noted cervical lymphadenopathy. Upon radiological examination, systemic lymphadenopathy was detected, and enlarged right brachial lymph node biopsy was performed. Histologically, the lymph node showed marked follicular hyperplasia and interfollicular plasmacytosis without eosinophil infiltration. Although the histological findings were compatible with rheumatoid lymphadenopathy, numerous plasma cells were IgG4$^+$ (IgG4$^+$/IgG$^+$ plasma cell ratio > 50%). However, laboratory findings revealed elevation of C-reactive protein level, polyclonal hyper-γ-globulinemia, anemia, and hypoalbuminemia. These findings were compatible with hyper-interleukin (IL)-6 syndrome, namely, RA. It is known that hyper-IL-6 syndromes, such as multicentric Castleman's disease, RA, and other autoimmune diseases, fulfill the histological diagnostic criteria for IgG4-related disease. Therefore, hyper-IL-6 syndromes and IgG4-related disease cannot be differentially diagnosed by immunohistochemical staining alone. In conclusion, rheumatoid lymphadenopathy sometimes occurs with abundant IgG4$^+$ plasma cells, which is required for the differential diagnosis of IgG4-related disease. 〔*J Clin Exp Hematopathol 52(1) : 57-61, 2012*〕

Keywords: rheumatoid lymphadenopathy, IgG4-related disease, differential diagnosis

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic disease characterized by polyarthritis, serum antibodies to rheumatoid factor, and extra-articular manifestations including localized or systemic lymphadenopathy.[1-3] Immunoglobulin (Ig)G4-related disease is a recently recognized syndrome characterized by autoimmune pancreatitis and related disorders, such as sclerosing cholangitis, sialoadenitis, retroperitoneal fibrosis, and Mikulicz's disease. Histological findings are uniform : marked lymphoplasmacytic infiltration and lymphoid follicles, admixed with dense fibrosis, and infiltration of abundant IgG4$^+$ plasma cells (IgG4$^+$/IgG$^+$ plasma cell ratio > 40%) as well as scattered eosinophil infiltration.[4-9] Moreover, IgG4-related disease usually shows a good response to steroid therapy;[4-6] therefore, differential diagnosis must be made from RA and other autoimmune diseases.

Here, we report a case of rheumatoid lymphadenopathy that fulfilled the histological diagnostic criteria for IgG4-related disease.

CASE REPORT

The patient was a 63-year-old woman who was admitted to hospital complaining of cervical lymphadenopathy. The patient was diagnosed with RA six years ago, and has been treated with methotrexate (MTX). Upon radiological examination, systemic lymphadenopathy was suspected (Fig. 1). Laboratory findings on admission revealed that serum rheumatoid factor was significantly elevated, with anemia, hypoalbuminemia, elevation of C-reactive protein (CRP), and polyclonal hyper-γ-globulinemia (Table 1). The clinician suspected malignant lymphoma or MTX-related lymphoproliferative disorders. Enlarged right brachial lymph node biopsy was performed.

Histopathological examination of the lymph node revealed marked follicular hyperplasia and marked interfollicular plasmacytosis, but there was no eosinophil infiltration (Fig. 2).

Received : September 12, 2011
Revised : September 15, 2011
Accepted : September 28, 2011

[1)]Department of Clinical Laboratory, Nagoya University Hospital, Nagoya, Japan
[2)]Department of Pathology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan
Address correspondence and reprint requests to : Dr. Yasuharu Sato, Department of Pathology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
E-mail : satou-y@cc.okayama-u.ac.jp
*The authors contributed equally to this work.

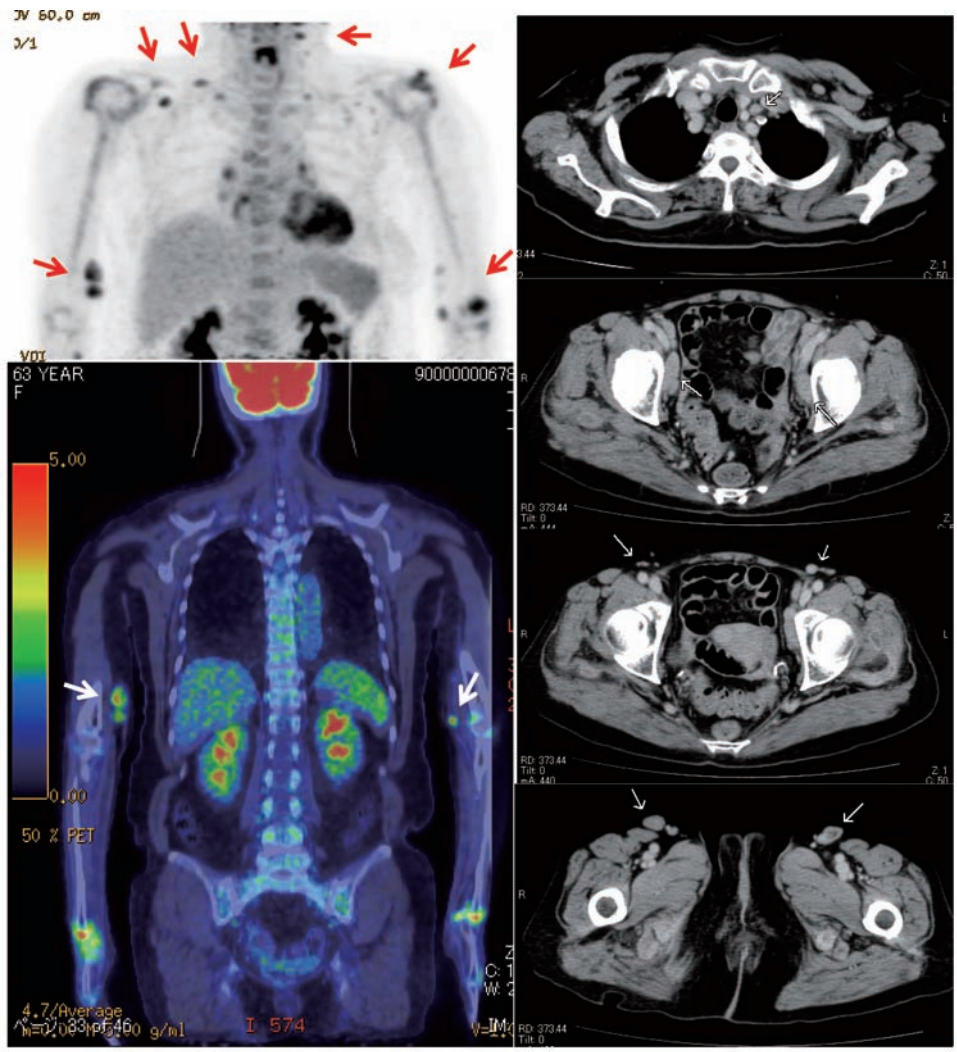

Fig. 1. Radiological images. ^{18}F-fluorodeoxy glucose positron emission tomography and computed tomography revealed systemic lymphadenopathy ; right brachial lymph node was biopsied.

The follicles were increased in number and size with hyperplastic germinal centers, attenuated mantle zones, and compressed paracortex, containing numerous mature plasma cells without atypia. Immunohistochemically, the lymphoid follicles were $CD10^+$ and $Bcl\text{-}2^-$, and infiltrated mature plasma cells showed no immunoglobulin light-chain restriction. *In situ* hybridization with Epstein-Barr virus-encoded small RNA oligonucleotides was not detected in the affected lymph node. These histological findings were compatible with rheumatoid lymphadenopathy.[1-3] However, the numerous plasma cells were $IgG4^+$; moreover, $IgG4^+/IgG^+$ plasma cell ratio was > 50% (Fig. 1). These immunohistochemical findings fulfilled the histological diagnostic criteria for IgG4-related disease.[6,8,9] According to previous reports, some cases of hyper-interleukin (IL)-6 syndromes,[10] such as multicentric Castleman's disease, RA, and other autoimmune diseases, sometimes fulfilled the histologic diagnostic criteria of IgG4-related disease.[9,11,12] Therefore, hyper-IL-6 syndromes and IgG4-related disease cannot be differentially diagnosed by immunohistochemical staining alone. Laboratory findings are important for the differential diagnosis of the two diseases.[8,9] Our case showed anemia, hypoalbuminemia, elevation of CRP level, and polyclonal γ-globulinemia (elevation of IgG, IgA, and IgM). These findings were quite different from IgG4-related disease.[8,9] Therefore, we diagnosed this case as rheumatoid lymphadenopathy.

DISCUSSION

RA is a systemic, autoimmune disease that can affect many organ systems, but it is best known for joint disease, and lymphadenopathy can occur in 50% to 75% of RA

Table 1. Laboratory data

		(normal range)
WBC	5,100/μL	(4,000-8,000)
RBC	361 × 10^3/μL	(110-410)
Hb	9.7 g/dL	(12.0-16.0)
Hct	31.3%	(35.0-48.0)
Plt	24.5 × 10^3/μL	(31.0-36.0)
AST	22 IU/L	(13-34)
ALT	11 IU/L	(7-37)
LDH	221 IU/L	(119-229)
T-bil	0.4 mg/ dL	(0.3-1.2)
D-bil	0.1 mg/ dL	(0.0-0.6)
ALP	264 IU/L	(115-359)
γ-GTP	27 IU/L	(10-47)
TP	8.6 g/dL	(6.7-8.3)
Alb	3.4 g/dL	(4.0-5.0)
A/G ratio	0.65	(1.20-2.00)
BUN	17.8 mg/dL	(8.0-22.0)
Cr	0.56 mg/dL	(0.40-0.70)
Na	138 mEq/L	(138-146)
K	3.9 mEq/L	(3.6-4.9)
Cl	102 mEq/L	(99-109)
CRP	4.0 mg/dL	(0.00-0.30)
IgG	2,782 mg/dL	(870-1700)
IgA	603 mg/dL	(110-410)
IgM	278 mg/dL	(46-260)
RF	713 U/mL	(0-10)
ANA	40-fold	(0-39.9)
sIL2R	1,140 U/mL	(145-519)

Abbreviation : WBC, white blood cell ; RBC, red blood cell ; Hb, hemoglobin ; Hct, hematocrit ; Plt, platelet ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase ; LDH, lactate dehydrogenase ; T-bil, total bilirubin ; D-bil, direct bilirubin ; ALP, alkaline phosphatase ; γGTP, γ-glutamyl transpeptidase TP, total protein ; Alb, albumin ; BUN, blood urea nitrogen ; Cr, creatinine ; Na, natrium ; K, kalium ; Cl, chlorine ; CRP, C-reactive protein ; RF, rheumatoid factor ; ANA, antinuclear antibody ; sIL2R, soluble IL-2 receptor.

patients.[1-3] The histopathological features of rheumatoid lymphadenopathy are characterized by follicular hyperplasia and interfollicular plasmacytosis without atypia.[1,3] In contrast, IgG4-related disease is a recently recognized syndrome characterized by lymphoplasmacytic infiltrates and sclerosis, elevation of serum IgG4 level, and abundant $IgG4^+$ plasma cell infiltration ($IgG4^+/IgG^+$ plasma cell ratio > 40%) in affected tissues.[4-9] IgG4-related disease sometimes involves regional and/or systemic lymph nodes, and there is a variety of five different histological subtypes.[5,8,13]

RA is characterized by high serum IL-6 level,[8,10,14,15] and showed elevation of CRP level, polyclonal hyper-γ-globulinemia, anemia, hypoalbuminemia, and hypocholesterolemia. These symptoms are closely related to high IL-6 levels ; therefore, RA is considered as a hyper-IL-6 syndrome,[8,9,14] and IL-6 acts to elevate the serum levels of IgG4 and other IgG subclasses.[9] In fact, multicentric Castleman's disease sometimes occurs with abundant $IgG4^+$ plasma cells ($IgG4^+/IgG^+$ plasma cell ratio > 40%) and elevated serum IgG4 levels.[9] Moreover, RA also occurs with abundant $IgG4^+$ plasma cells and elevated serum IgG4 levels.[11,16] Therefore, hyper-IL-6 syndromes and IgG4-related disease cannot be differentially diagnosed by immunohistochemical staining alone.

Histologically, although our case is compatible with rheumatoid lymphadenopathy, the lymph node showed abundant $IgG4^+$ plasma cell infiltration and $IgG4^+/IgG^+$ plasma cell ratio > 50%. However, upon laboratory examination, our case showed elevation of CRP level, polyclonal hyper-γ-globulinemia, anemia, and hypoalbuminemia. These findings were consistent with those of hyper-IL-6 syndromes, and quite different from IgG4-related disease.[5,8,9] IgG4-related disease is not characterized by elevated serum IgA, IgM, and CRP levels.[8,9] In addition, histologically, our case did not show eosinophil infiltration.[5,8,9]

Unfortunately, this patient was not examined for serum

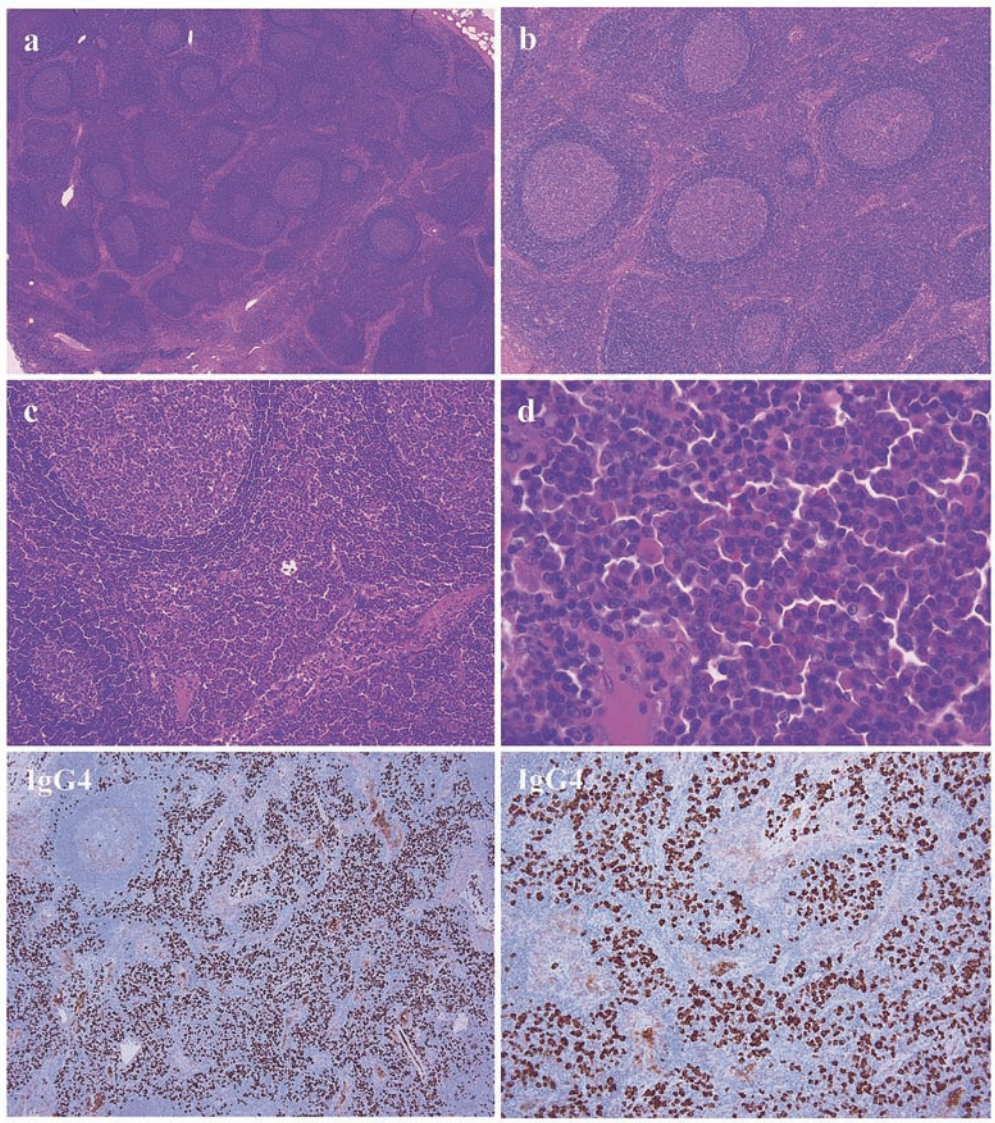

Fig. 2. Histological and immunohistochemical features. The lymph node showed marked follicular hyperplasia and marked interfollicular plasmacytosis, but there was no eosinophil infiltration (*2a-2d*, H&E stain ; *2a*, ×20 ; *2b*, ×40 ; *2c*, x100 ; *2d*, ×400). Numerous plasma cells showed $IgG4^+$. $IgG4^+/IgG^+$ plasma cell ratio was > 50% (*bottom*, IgG4-immunostain ; *left*, ×40 ; *right*, ×100).

IgG4 level. However, Yamamoto *et al*.[16] reported that serum IgG4 level was elevated in patients with RA. Therefore, our case might have shown elevation of serum IgG4 level.

In conclusion, we have reported a case of rheumatoid lymphadenopathy with abundant $IgG4^+$ plasma cells. RA sometimes occurs with abundant $IgG4^+$ plasma cells and fulfilled the histological diagnostic criteria for IgG4-related disease. Therefore, the two diseases cannot be differentially diagnosed by immunohistochemical staining alone. Laboratory findings are crucial for the differential diagnosis of the two diseases.

REFERENCES

1 Ioachim HL, Medeiros LJ: Lymph Node Pathology. 4th ed, Lippincott Williams & Wilkins, Philadelphia, pp.218-222, 2008
2 Robertson MD, Hart FD, White WF, Nuki G, Boardman PL: Rheumatoid lymphadenopathy. Ann Rheum Dis 27:253-260, 1968
3 Kojima M, Motoori T, Nakamura S: Benign, atypical and malignant lymphoproliferative disorders in rheumatoid arthritis patients. Biomed Pharmacother 60:663-672, 2006
4 Sato Y, Ohshima K, Ichimura K, Sato M, Yamadori I, *et al*.: Ocular adnexal IgG4-related disease has uniform clinicopathol-

ogy. Pathol Int 58:465-470, 2008
5 Sato Y, Notohara K, Kojima M, Takata K, Masaki Y, *et al*.: IgG4-related diseases : Historical overview and pathology of hematological disorders. Pathol Int 60:247-258, 2010
6 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 51:13-20, 2011
7 Sato Y, Takata K, Ichimura K, Tanaka T, Morito T, *et al*.: IgG4-producing marginal zone B-cell lymphoma. Int J Hematol 88:428-433, 2008
8 Sato Y, Kojima M, Takata K, Morito T, Asaoku H, *et al*.: Systemic IgG4-related lymphadenopathy : a clinical and pathologic comparison to multicentric Castleman's disease. Mod Pathol 22:589-599, 2009
9 Sato Y, Kojima M, Takata K, Morito T, Mizobuchi K, *et al*.: Multicentric Castleman's disease with abundant IgG4-positive cells : a clinical and pathological analysis of six cases. J Clin Pathol 63:1084-1089, 2010
10 Frizzera G: Atypical lymphoproliferative disorders. In : Knowles DM (ed) : Neoplastic Hematopathology. 2nd ed, Lippincott Williams & Wilkins, Baltimore, pp.569-622, 2000
11 Strehl JD, Hartmann A, Agaimy A: Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. J Clin Pathol 64:237-243, 2011
12 Kojima M, Nakamura N, Tsukamoto N, Itoh H, Matsuda H, *et al*.: Atypical lymphoplasmacytic and immunoblastic proliferation of autoimmune disease : Clinicopathologic and immunohistochemical study of 9 cases. J Clin Exp Hematop 50:113-119, 2010
13 Sato Y, Kojima M, Takata K, Huang H, Hayashi E, *et al*.: Immunoglobulin G4-related lymphadenopathy with inflammatory pseudotumor-like features. Med Mol Morphol 44:179-182, 2011
14 Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, *et al*.: Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood 112:3959-3964, 2008
15 Numata Y, Matsuura Y, Onishi S, Yamamoto Y, Ohno F, *et al*.: Interleukin-6 positive follicular hyperplasia in the lymph node of a patient with rheumatoid arthritis. Am J Hematol 36:282-284, 1991
16 Yamamoto M, Tabeya T, Naishiro Y, Yajima H, Ishigami K, *et al*.: Value of serum IgG4 in the diagnosis of IgG4-related disease and in differentiation from rheumatic diseases and other diseases. Mod Rheumatol. 2011 Sep 28. [Epub ahead of print].[DOI 10.1007/s10165-011-0532-6]