Perifollicular granulomas with IgG4 plasmacytosis: A case report and review of literature

Li Liang, Jain Zhou, Lei Chen

Li Liang, Jain Zhou, Lei Chen, Department of Pathology, the University of Texas Medical School at Houston, Houston, TX 77030, United States

Li Liang, Department of Pathology, the University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States

Author contributions: Liang L and Chen L designed the report, collected the patient’s clinical data and wrote the paper; Zhou J collected the patient’s clinical data and revised the manuscript.

Supported by Department of Pathology, the University of Texas Health Science Center at Houston, United States.

Institutional review board statement: This study was conducted with an approved IRB protocol from the University of Texas Medical School in Houston.

Informed consent statement: This study was exempted by the Committee for Protection of Human Subjects.

Conflict-of-interest statement: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Lei Chen, MD, Department of Pathology, the University of Texas Medical School at Houston, 6431 Fannin, MSB 2.136, Houston, TX 77030.

Telephone: +1-713-5664690

Received: January 26, 2015
Peer-review started: January 28, 2015
First decision: March 20, 2015
Revised: April 13, 2015
Accepted: May 16, 2015
Article in press: May 18, 2015

Published online: July 16, 2015

Abstract

Perifollicular granuloma is a unique histologic feature and whether it is associated with immunoglobulin G4 (IgG4)-related disease is controversial. We report a case of a 38-year-old man who presented with worsening left eye pain, proptosis, tearing, gritty sensation, blurred vision and multiple lymphadenopathy. An axillary lymph node resection showed reactive follicular and interfollicular lymph node hyperplasia, and increased eosinophils and plasma cells (at least 80% of IgG+ plasma cells were positive for IgG4). A distinct feature was the presence of multifocal, perifollicular histiocytic granulomas, which formed a wreath around the entire follicles. The human herpes virus 8 was not detected by immunohistochemistry. In addition, an extensive panel of special stains, immunohistochemistry, and flow cytometry was negative for lymphoma, fungal, or mycobacterial infection. The findings were suggestive of IgG4-related sclerosing disease-associated lymphadenopathy. Further laboratory testing showed a significant increase of serum immunoglobulin E (> 23000 IU/mL) and slight increase of total IgG, but normal serum IgG4. Even though perifollicular granuloma is a nonspecific histopathologic feature and can be seen in other diseases, such as nodular lymphocyte predominant Hodgkin lymphoma, IgG4-related lymphadenopathy should be listed in the differential diagnoses of benign reactive lymph nodes, especially when perifollicular granuloma and plasmacytosis coexist.

Key words: Immunoglobulin G4-related disease; Lymphadenopathy; Plasma cells; Granuloma

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We report a case of a 38-year-old man who...
It is characterized by a lymphoplasmacytic infiltrate positive for IgG4 and the presence of multifocal, perifollicular histiocytic granulomas, which formed a wreath around the entire follicles. An extensive workup was negative for lymphoma, fungal, or mycobacterial infection. The findings were suggestive of IgG4-related sclerosing disease-associated lymphadenopathy. Thus, IgG4-related lymphadenopathy should be listed in the differential diagnoses of benign reactive lymph nodes, especially when perifollicular granuloma and plasmacytosis coexist.

INTRODUCTION

Immunoglobulin G4 (IgG4)-related disease is a recently recognized fibro-inflammatory condition that can involve multiple organs and cause tumor-like enlargement[1-2]. It is characterized by a lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells, while elevated serum concentrations of IgG4 are found in 60% to 70% of patients[3]. IgG4-related disease has a male predilection (male to female ratio 8:1)[4].

According to the consensus statement from a multinational, multidisciplinary group of experts, the major histopathological features to make the diagnosis of IgG4-related disease include a dense lymphoplasmacytic infiltrate, plasma cells, storiform fibrosis, and obliterative phlebitis[5]. However, these features are usually uncommonly seen in certain organs, such as lymph nodes.

We describe a case of a 38-year-old man with swelling of soft tissue surround the eye and multiple lymphadenopathy and an axillary lymph node resection showed reactive follicular and interfollicular lymph node hyperplasia, increased eosinophils and plasma cells (at least 80% of immunoglobulin IgG plasma cells were positive for IgG4) and multifocal, perifollicular histiocytic granulomas, which formed a wreath around the entire follicles. Review of literature also found our findings may add to the knowledge of IgG4-related disease.

CASE REPORT

Clinical history

We report a case of a 38-year-old man who presented with worsening left eye pain and multiple lymphadenopathy. An axillary lymph node resection showed increased eosinophils and plasma cells (at least 80% of immunoglobulin IgG plasma cells were positive for IgG4 and the presence of multifocal, perifollicular histiocytic granulomas, which formed a wreath around the entire follicles. An extensive workup was negative for lymphoma, fungal, or mycobacterial infection. The findings were suggestive of IgG4-related sclerosing disease-associated lymphadenopathy. Thus, IgG4-related lymphadenopathy should be listed in the differential diagnoses of benign reactive lymph nodes, especially when perifollicular granuloma and plasmacytosis coexist.

Microscopic and immunohistochemical features

An axillary lymph node resection showed reactive follicular and interfollicular lymph node hyperplasia, and increased eosinophils and plasma cells (at least 80% of IgG plasma cells were positive for IgG4). A distinct feature was the presence of multifocal, perifollicular histiocytic granulomas, which formed a wreath around the entire follicles (Figure 1A). Increased plasma cells were marked by CD138 immunohistochemical stain (Figure 1B). IgG4 plasma cells are markedly increased (Figure 1D), compared with total IgG stain (Figure 1C). EBER (EBV encoded small RNA by in situ hybridization) was negative. The human herpes virus 8 was not detected by immunohistochemistry. In addition, an extensive panel of special stains, immunohistochemistry, and flow cytometry was negative for lymphoma, fungal, or mycobacterial infection. The findings were suggestive of IgG4-related sclerosing disease-associated lymphadenopathy.

Follow-up

Further laboratory testing showed a significant increase of serum IgE (> 23000 IU/mL) and slight increase of total IgG (1802 mg/dL), but normal serum IgG4 (27 mg/dL). The patient was started on prednisone and methotrexate with reduction in proptosis and in the size of orbital mass by computerized tomography (CT) scan. While patient was maintained with methotrexate and tapering on steroid, he was noted to have left eye redness and itching. Rituximab was added and methotrexate was discontinued. The patient’s symptom subsided.

DISCUSSION

According to the consensus statement from a multinational, multidisciplinary group of experts, the major histopathological features to make the diagnosis of IgG4-related disease include a dense lymphoplasmacytic infiltrate, plasma cells, storiform fibrosis, and obliterative phlebitis[5]. However, these features are usually not seen in certain organs, such as lymph nodes. Fibrosis and obliterative phlebitis are usually not present in lymph nodes.

Lymph nodes in IgG4-related disease may show variable histopathologic features. Cheuk et al[6] divided it into five different categories, including multicentric
Castleman disease-like (type 1), follicular hyperplasia (type II), interfollicular expansion (type III), progressive transformation of germinal centers (type IV), and inflammatory pseudotumor-like (type V). Nevertheless, an increase in IgG4+ plasma cells with an IgG4/IgG plasma cell ratio exceeding 0.4, and/or an absolute number of IgG4+ plasma cells of more than 50/high-power field (hpf) are the currently accepted cutoff for IgG4-related disease. However, presence of IgG4+ plasma cells in isolated reactive lymphadenopathy is not exclusively specific for IgG4-related disease [6]. Martinez et al. [6] reported seven of the 55 solitary reactive lymph nodes with increased IgG4/IgG plasma cell ratio of more than 0.4, and six of them showed more than 50 IgG4+ plasma cells per high power field, but none of these patients had history of IgG4-related disease. However, presence of IgG4+ plasma cells in isolated reactive lymphadenopathy is not exclusively specific for IgG4-related disease [6].

Martinez et al. [6] reported seven of the 55 solitary reactive lymph nodes with increased IgG4/IgG plasma cell ratio of more than 0.4, and six of them showed more than 50 IgG4+ plasma cells per high power field, but none of these patients had history of IgG4-related disease. On the other hand, Uehara et al. [7] reported that presence of fibrosis in lymph nodes, together with increased IgG4 ratio and other features of IgG4-related disease, may suggest the diagnosis of IgG4-related lymphadenopathy.

Even though epithelioid cell granulomas is usually not considered a feature of IgG4-related disease at extranodal sites, it has been described in lymph nodes. Siddiqi et al. [8] described seven cases with perifollicular granuloma in a concentric or crescent-like arrangement encircling lymphoid follicles and associated with a marked elevation of intra-germinal center IgG4+ plasma cells. However, the specificity of these findings were debated by Cheuk et al. [9]. Grimm et al. [9] reported histiocytic proliferation in 11 of 29 cases of lymphadenopathy with increased IgG4 plasma cells, and a prominent ringing of follicles by epithelioid histiocytes in 3 patients (Table 1). In addition, Takahashi et al. [10] reported a case of IgG4-related lymphadenopathy with prominent granulomatous inflammation, most likely due to reactivation of Epstein-Barr virus. Takeuchi et al. [11] performed Epstein-Barr virus (EBV)-encoded RNA (EBER) in situ hybridization and identified EBER-positive cells in 18 of 31 cases (58%) of IgG4-related lymphadenopathy, significantly higher rate than non-IgG4-related reactive lymphoid hyperplasia. However, EBER was negative in our case, and either negative or rarely positive in the two cases with EBER performed in Grimm group’s study (Table 1). Further study is needed to determine whether there is a causal relationship.

IgG4-related disease is a great mimicker. One of the differential diagnoses is multicentric Castleman’s disease. However, IgG4+/IgG+ plasma cell ratio is usually less than 0.4 in multicentric Castleman disease. Furthermore, elevated serum levels of interleukin-6 and vascular endothelial growth factor favor the diagnosis of multicentric Castleman’s disease [12]. Rosai-Dorfman disease can also show increased IgG4-positive plasma cells, as well as other autoimmune diseases including rheumatoid lymphadenopathy, are also in the differential diagnosis [13,14]. Moreover, bacterial, viral, fungal and parasitic infections have to be carefully ruled out. In our case, special stains and cultures were performed and the results were negative. The patient

![Figure 1: Perifollicular histiocytic granulomas that formed a wreath around the entire follicle. A: Hematoxylin and eosin stain; B: CD138 immunohistochemical stain highlights the plasma cells; C: Immunoglobulin G (IgG) immunohistochemical stain; D: IgG4 immunohistochemical stain demonstrated that more than 80% of IgG+ cells were positive for IgG4.](image-url)
IgG4-related disease is a recently recognized fibro-inflammatory condition that can present with multiorgan involvement and lymphadenopathy. The pathologic hallmark of IgG4-related disease is the presence of perifollicular granulomas with IgG4 plasmacytosis. The diagnosis of IgG4-related disease is based on clinical presentation, laboratory findings, and histopathologic features.

**Case characteristics**
A 38-year-old man who presented with worsening left eye pain, proptosis, tearing, gritty sensation and blurred vision. Multiple lymphadenopathy was identified.

**Clinical diagnosis**
Lymphoma, Castleman’s disease, fungal or mycobacterial infection, autoimmune disorders, etc.

**Differential diagnosis**
Lymphoma, Castleman’s disease, fungal or mycobacterial infection, autoimmune disorders, etc.

**Laboratory diagnosis**
Serum immunoglobulin E (> 23000 IU/mL) and slight increase of total immunoglobulin G (IgG), but normal serum IgG4. An extensive panel of special stains, immunohistochemistry, and flow cytometry was negative for lymphoma, fungal, or mycobacterial infection.

**Imaging diagnosis**
Magnetic resonance imaging of orbits showed enlargement of the left medial rectus, superior oblique and inferior rectus muscle, and enhancing soft tissue signal encasing the left optic nerve sheath. Computed tomography scan of chest and abdomen showed multiple lymphadenopathy.

**Pathological diagnosis**
An axillary lymph node resection showed reactive follicular and interfollicular lymph node hyperplasia, and increased eosinophils and plasma cells (at least 80% of IgG plasma cells were positive for IgG4). A distinct feature was the presence of multifocal, perifollicular histiocytic granulomas, which formed a wreath around the entire follicles.

**Treatment**
The patient was started on prednisone and methotrexate with reduction in proptosis and in the size of orbital mass by computed tomography scan. While patient was maintained with methotrexate and tapering on steroid, he was noted to have left eye redness and itching. Rituximab was added and methotrexate was discontinued. The patient’s symptom subsided.

**Related reports**
Perifollicular granuloma is a unique histologic feature and whether it is associated with IgG4-related disease is controversial. Very few cases have been reported in the English literature.

**Term explanation**
IgG4-related disease is a recently recognized fibro-inflammatory condition that can involve multiple organs and cause tumor-like enlargement, which is characterized by the presence of perifollicular granulomas with IgG4 plasmacytosis.

---

**Table 1 Perifollicular granulomatous inflammation and immunoglobulin G4-related disease**

| Case | Ref. | Age (yr) | Gender | Location | IgG4/IgG ratio | Eosinophils | Fibrosis | EBER |
|------|------|----------|--------|----------|----------------|-------------|----------|------|
| 1    | Siddiqi et al[8] | 47 | M | Cervical | 0.7 | Mild | Marked | NA |
| 2    | Siddiqi et al[8] | 63 | M | Axillary | 0.7 | None | None | NA |
| 3    | Siddiqi et al[8] | 50 | F | Cervical | 0.5 | Minimal | Mild | NA |
| 4    | Siddiqi et al[8] | 34 | M | Cervical | 0.6 | None | None | NA |
| 5    | Siddiqi et al[8] | 12 | M | Cervical | 0.7 | Mild | None | NA |
| 6    | Siddiqi et al[8] | 58 | M | Unknown | 0.7 | None | None | NA |
| 7    | Siddiqi et al[8] | 38 | M | Axillary | 0.7 | Mild | Mild | NA |
| 8    | Grimm et al[9] | 47 | M | Cervical | > 0.4 | NA | NA | NA |
| 9    | Grimm et al[9] | 58 | F | NA | > 0.4 | NA | NA | Negative |
| 10   | Grimm et al[9] | 83 | M | Axillary | > 0.4 | NA | Present | Rarely positive |
| 11   | Current case | 38 | M | Axillary | > 0.8 | Increased | None | NA |

NA: Not available; EBER: EBV encoded small RNA by in situ hybridization; M: Male; F: Female.
by a lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells.

**Experiences and lessons**

IgG4-related lymphadenopathy should be listed in the differential diagnoses of benign reactive lymph nodes, especially when perifollicular granuloma and plasmacytosis coexist.

**Peer-review**

The authors have performed a good study, the manuscript is interesting.

**REFERENCES**

1. Zen Y, Nakamura Y. IgG4-related disease: a cross-sectional study of 114 cases. *Am J Surg Pathol* 2010; 34: 1812-1819 [PMID: 21107087 DOI: 10.1097/PAS.0b013e3181f7266b]
2. Palazzo E, Palazzo C, Palazzo M. IgG4-related disease. *Joint Bone Spine* 2014; 81: 27-31 [PMID: 23849464 DOI: 10.1016/j.jbspin.2013.06.001]
3. Sah RP, Chari ST. Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. *Curry Opin Rheumatol* 2011; 23: 108-113 [PMID: 21124093 DOI: 10.1097/BOR.0b013e3283413469]
4. Cheuk W, Chan JK. Lymphadenopathy of IgG4-related disease: an underdiagnosed and undiagnosed entity. *Semin Diagn Pathol* 2012; 29: 226-234 [PMID: 23068302 DOI: 10.1053/j.semdp.2012.07.001]
5. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshiino T, Klockee G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del Castillo C, Forcione DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakamura Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H, Stone JH. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012; 25: 1181-1192 [PMID: 22596100 DOI: 10.1038/modpathol.2012.72]
6. Martinez LL, Friedländer E, van der Laak JA, Hebeda KM. Abundance of IgG4+ plasma cells in isolated reactive lymphadenopathy is no indication of IgG4-related disease. *Am J Clin Pathol* 2014; 142: 459-466 [PMID: 25239412 DOI: 10.1309/AJCPX6V67B3V3JE]
7. Uehara T, Masumoto J, Yoshizawa A, Kobayashi Y, Hamano H, Kawa S, Oki K, Okawa N, Honda T, On H. IgG4-related disease-like fibrosis as an indicator of IgG4-related lymphadenopathy. *Ann Diagn Pathol* 2013; 17: 416-420 [PMID: 23702322 DOI: 10.1016/j.amdiap ath.2013.04.010]
8. Siddiqi IN, Brynes RK, Grimm K, O’Malley DP, Wang E. Perifollicular granulomatous inflammation in reactive lymph nodes: a possible morphologic marker for IgG4 plasmacytosis. *J Hematopathol* 2011; 4: 207–214 [DOI: 10.1016/s12308-011-0117-5]
9. Grimm KE, Barry TS, Chauhevsky V, Hii A, Weiss LM, Siddiqi IN, Brynes RK, O’Malley DP. Histopathological findings in 29 lymph node biopsies with increased IgG4 plasma cells. *Mod Pathol* 2012; 25: 480-491 [PMID: 22808064 DOI: 10.1038/modpathol.2011.177]
10. Takahashi E, Kojima M, Kobayashi M, Kitamura A, Yokoi T, Hara K, Nakamura S. Primary IgG4-related lymphadenopathy with prominent granulomatous inflammation and reactivation of Epstein-Barr virus. *Virchows Arch* 2012; 460: 225-229 [PMID: 22249559 DOI: 10.1007/s00428-011-1186-7]
11. Takeuchi M, Sato Y, Yasui H, Otsawa H, Ohno K, Takata K, Gion Y, Orita Y, Tachibana T, Itoh T, Asano N, Nakamura S, Swerdlow SH, Yoshino T. Epstein-Barr virus-infected cells in IgG4-related lymphadenopathy with comparison with extranodal IgG4-related disease. *Am J Surg Pathol* 2014; 38: 946-955 [PMID: 24705309 DOI: 10.1097/PAS.0000000000000206]
12. Izumi Y, Takeshita H, Moriwaki Y, Hisatomi K, Matsuura M, Yamashita N, Kawahara C, Shigemitsu I, Iwanaga N, Kawakami A, Kurohama H, Niino D, Ito M, Migita K. Multicentric Castleman disease mimicking IgG4-related disease: A case report. *Mod Rheumatol* 2014; (22): 1-4 [PMID: 25528859 DOI: 10.3109/14397595.2014.985356]
13. Zhang X, Hyjek E, Vardiman J. A subset of Rosai-Dorfman disease exhibits features of IgG4-related disease. *Am J Clin Pathol* 2013; 139: 622-632 [PMID: 23596114 DOI: 10.1309/AJCPAR3YQ0KLIOA]
14. Asano N, Sato Y. Rheumatoid lymphadenopathy with abundant IgG4(+) plasma cells: a case mimicking IgG4-related disease. *J Clin Exp Hematol* 2012; 57: 56-71 [PMID: 22706532 DOI: 10.3960/jclinexp.08.52.57]
15. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azami A, Carruthers MN, Chari ST, Della-Torre E, Frulloni L, Hart PA, Kamisawa T, Kawa S, Kawano M, Kim MH, Kodama Y, Kubota K, Lerce MM, Lühr M, Masaki Y, Matsui S, Mimori T, Nakamura S, Nakazawa T, Ohara H, Okazaki K, Ryu JH, Saeki T, Schleinitz N, Shimatsu A, Shimoejima T, Takahashi H, Takahira M, Tanaka A, Topazian M, Umehara H, Webster GJ, Witzig TE, Yamamoto M, Zhang W, Chiba T, Stone JH. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. *Arthritis Rheumatol* 2015; 67: 1688-1699 [PMID: 25809420 DOI: 10.1002/art.39132]
16. Wallace ZS, Deshpande V, Stone JH. Ophthalmic manifestations of IgG4-related disease: single-center experience and literature review. *Semin Arthritis Rheum* 2014; 43: 806-817 [PMID: 24513111 DOI: 10.1016/j.semarthrit.2013.11.008]

P-Reviewer: Gonzalez-Granado LI, Sugimura H S-Editor: Tian YL L-Editor: A E-Editor: Wu HL
