Case Report

DOI: 10.6966/EDMJ.202306_10(2).0005

IgG4-Related Disease Mimicking Lymphoma: A Case Report

I-Ting Hu[1], Chi-Wei Lin[1,6], Jiun-Nong Lin[2,3], Yu-Chieh Su[4,6,], Chung-I Huang[5,*]*

Immunoglobulin G4-related disease (IgG4-RD) is a systemic inflammatory condition with tissue infiltration of IgG4-rich plasma cells. It can present as tumefactive lesions in nearly any organ, sometimes mimicking malignancy. Lymphadenopathy is observed in some patients with IgG4-RD, and is often asymptomatic and slowly-growing. Diagnosis of IgG4-RD requires histologic confirmation, along with serologic and radiographic findings. Herein, we present a 38-year-old man who developed painless neck lymphadenopathy within weeks prior to visiting our outpatient clinic. The lymphadenopathy in our patient was first identified as lymphoma. However, the diagnosis of IgG4-RD was confirmed after repeating a lymph node biopsy.

Key words: IgG4-related disease, lymphoma, lymphadenopathy

Introduction

Lymphadenopathy is commonly observed in primary care settings. A wide range of etiologies may contribute to lymphadenopathy, such as infectious diseases, metastatic cancer, lymphoma, lymphoproliferative diseases, drug reaction, sarcoidosis, and immunoglobulin G4-related disease (IgG4-RD). In some cases, the cause of lymphadenopathy, such as upper respiratory tract infection or periodontitis, can be identified through careful history taking and physical examination. In other cases, it is necessary to distinguish whether the lymphadenopathy is generalized or localized. Sometimes, it is essential to identify the location of the enlarged lymph nodes. Generalized lymphadenopathy may arise from systemic conditions such as human immunodeficiency virus (HIV) infection and systemic lupus erythematosus, or it may be a result of medication-related conditions. In localized lymphadenopathy, different locations of enlarged lymph nodes indicate different etiologies. For instance, submental lymph node enlargement is typically linked with mononucleosis syndrome, Epstein-Barr virus (EBV) infection and toxo-

From the [1]Department of Family Medicine and Community Medicine, [2]Department of Critical Care Medicine, [3]Division of Infectious Diseases, Department of Internal Medicine and [4]Division of Hematology-Oncology, Department of Internal Medicine, E-Da Hospital, I-Shou University; [5]Department of Radiation Oncology, E-Da Cancer Hospital, I-Shou University; [6]College of Medicine, I-Shou University, Kaohsiung, Taiwan.
(* Signifies equal contributions as corresponding authors)
Received: June 16, 2021 Accepted: September 15, 2021
* Address reprint request and correspondence to: Yu-Chieh Su and Chung-I Huang
Division of Hematology-Oncology, Department of Internal Medicine, E-Da Hospital, No. 1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 824005, Taiwan, Tel: +886-7-615-0011 ext. 252766, E-mail: hepatoma@gmail.com (YCS)
Department of Radiation Oncology, E-Da Cancer Hospital, No. 21, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 824005, Taiwan, Tel: +886-7-615-0011 ext. 252753, E-mail: ed108856@edah.org.tw (CIH)

plasmosis.[1] IgG4-RD is one of the various conditions that may lead to lymphadenopathy. And it can present with either generalized or localized lymphadenopathy.

IgG4-RD is an immune-mediated disorder characterized by fibroinflammatory infiltration of various organs. Because it can affect almost any organ, different manifestations of IgG4-RD had been previously linked with a series of different diseases. IgG4-RD was not identified as a distinct diagnostic entity until recent years, making it a relatively new term. Clinical presentation of IgG4-RD may vary depending on the organs involved. Generally, a mass will develop sub-acutely at the affected site. Weight loss and fatigue might be seen in patients with IgG4-RD. However, a lack of symptoms is often reported, and the disease could be recognized incidentally upon imaging. Patients with IgG4-RD rarely present with fever.[2,3] The hallmark pathological presentation of IgG4-RD include lymphoplasmacytic tissue infiltration of IgG4-positive plasma cells, "storiform" fibrosis, and some degree of tissue eosinophilia.[4] IgG4-RD is often mistaken clinically as other malignant diseases because of the possibility of multiple organs and sites being affected.

In this paper, we describe a 38-year-old man with IgG4-RD presenting as neck lymphadenopathy, who was initially diagnosed with lymphoma.

Case Report

A 38-year-old man with a medical history of type II diabetes mellitus presented to our outpatient clinic for the evaluation of neck masses. He noticed some prominent swollen lumps around his neck in the past few weeks. However, he did not experience any pain in his neck, nor did he have fever or weight loss recently. The swollen neck masses did not present any difficulty in swallowing or breathing either. Upon physical examination, multiple enlarged lymph nodes scattered around both sides of his neck, most prominently localized at level II, were observed. The cervical lymphadenopathy was non-tender on palpation. No lymphadenopathy was detected at the axilla or inguinal area. An endoscopic procedure revealed no gross tumor in nasopharynx, base of tongue or hypopharynx. Computed tomography of the head and neck showed multiple lymph nodes over bilateral facial, neck, and supraclavicular regions. The possible diagnosis includes lymphoma, inflammation, or metastatic lymph nodes (Fig.1). A biopsy of the lymph node at the right side of the neck was hence performed; the histopathological analysis showed polymorphic B-cell lymphoproliferative disorder, in which the polymorphic infiltrates resemble polymorphic post-transplant lymphoproliferative disorder (PTLD). The lymph node was negative for both EBV-encoded mRNA (EBER) and HIV antibodies. Immunohistochemistry (IHC) yielded CD20+, CD3+, BCL-2+, CD15-, CD19+, CD30+, CD138+, CD163+, kappa+, and lambda+ without any definite evidence of light chain restriction. Diffuse large B-cell lymphoma was the probable diagnosis in the pathology report.

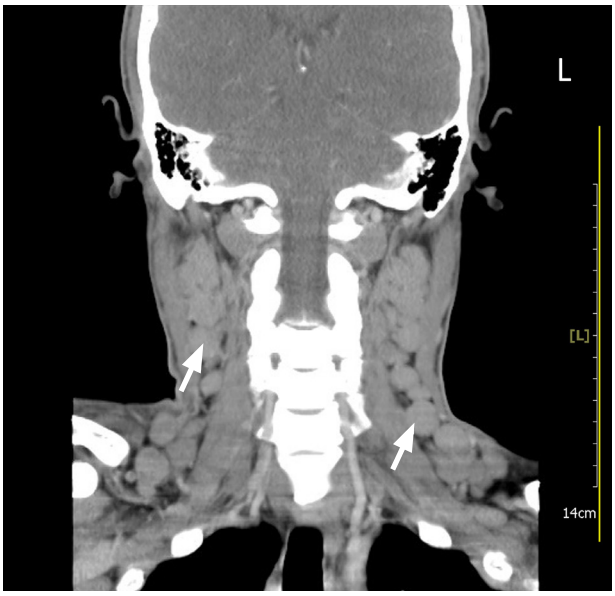

Fig. 1 Computed tomography showing multiple lymph nodes at the neck (white arrow).

The patient started to have blurred vision in the left eye and dropping of the left eyelid around the same period, and he sought help at the neurology clinic where brain magnetic resonance imaging (MRI) was performed (Fig. 2). The MRI results demonstrated an enlargement of the bilateral lacrimal glands and extraocular soft tissue at the bilateral orbital roof, premaxillary regions and bilateral pterygopalatine fossa, suggestive of lymphoproliferative disease.

From the results of radiographic examinations and lymph node biopsy, a diagnosis of lymphoma was suggested for this patient. And it was also suggested that he should be started on chemotherapy. However, because the histopathology report was somewhat indefinite and insufficient to determine the precise chemotherapy regimen, the patient underwent another lymph node biopsy at the left side of the neck. A more detailed pathology report this time showed effacement of the normal lymph node architecture by a polymorphous population consisting of numerous mature plasma cells, plasmacytoid cells, large basophilic transformed lymphocytes (immunoblasts), small to medium-sized lymphocytes and histiocytes.

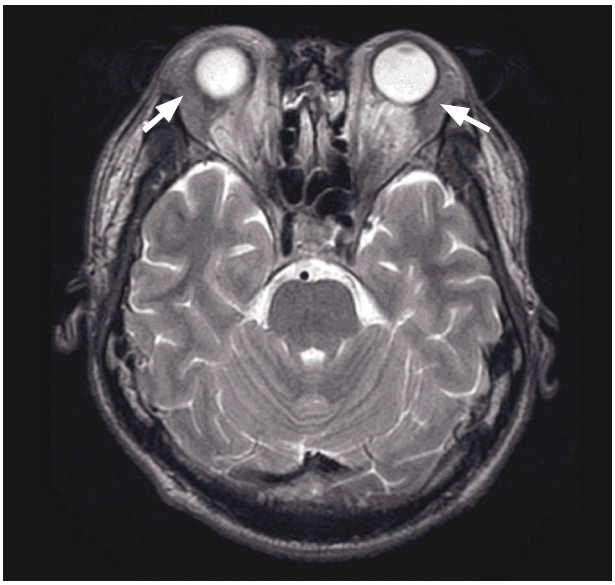

Fig. 2 Magnetic resonance imaging showing enlargement of bilateral lacrimal glands (white arrow).

Perivascular fibrosis was present, and IHC staining revealed dense IgG4-positive cells [> 100 cells/high-power field (HPF)]. PCR-based clonality analysis of B-cell lymphomas showed a polyclonal pattern. These features indicate that our patient had IgG4-related lymphadenopathy presenting with plasmacytosis and immunoblastosis (Fig. 3). The diagnosis of IgG4-RD was finally confirmed in this patient. Hence, he was started on low-dose glucocorticoid treatment, which shrank the enlarged lymph nodes. The patient continued to visit the outpatient department of our hospital; no more enlarged lymph nodes were noted during the follow-up period of 4 years.

Discussion

As IgG4-RD is a relatively novel clinical entity, its diagnosis can be easily overlooked. Because of the heterogenous presentation of IgG4-RD and the fact that no specific ICD-10 code for IgG4-RD has yet been developed, patients with IgG4-RD are often diagnosed as a wide range of diverse diseases. These include Mikulicz syndrome, type I autoimmune pancreatitis, retroperitoneal fibrosis, sclerosing sialadenitis, Reidel's thyroiditis and IgG4-related sclerosing cholangitis, inflammatory orbital pseudotumor, etc. IgG4-RD was first described in 2003,[5] and its prevalence is largely determined on estimation. The estimated prevalence of the disease ranges from 0.28 to 1.08 per 100,000 of population.[4] IgG4-RD is reported to have a male predominance, especially in the middle-aged and older population.

The diagnosis of IgG4-RD can be made through a combination of tissue biopsy, clinical presentation, and serologic and radiographic findings. An elevation of serum IgG4 level is indicative, but not specific for the diagnosis. Histopathologic appearance of IgG4-RD includes a dense lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis and sometimes mild tissue eosinophilia. The

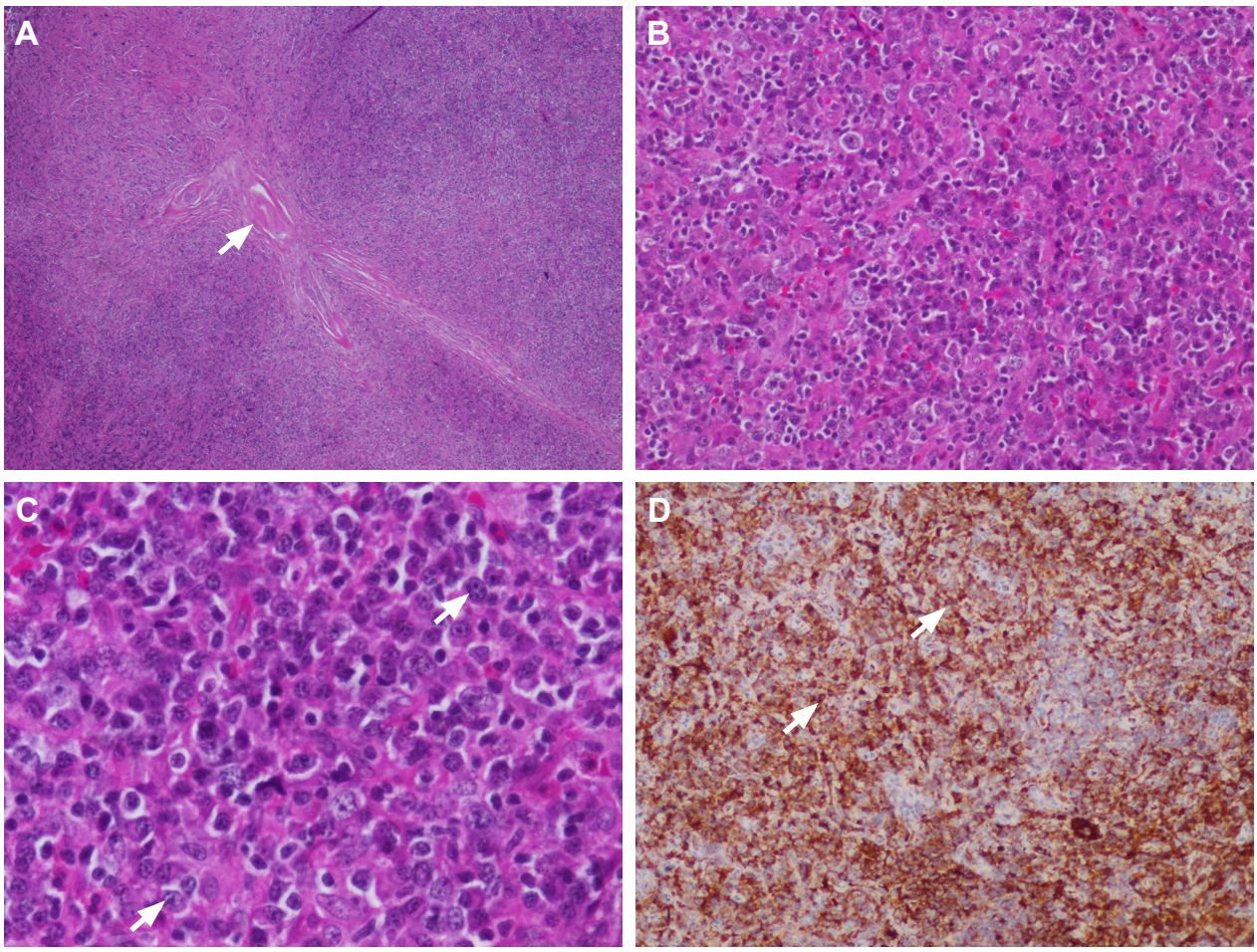

Fig. 3 (A) Lymph node biopsy showing perivascular fibrosis (arrow) (40X). (B) Polymorphous infiltration of numerous mature plasma cells, plasmacytoid cells, large basophilic transformed lymphocytes, small to medium-sized lymphocytes, and histiocytes (200X). (C) Polymorphous infiltrate rich in plasma cells (arrow) (400X). (D) Dense IgG4-positive cells (arrow) in immunohistochemical staining (200X).

presence of IgG4-positive plasma cells upon immunostaining is crucial for the diagnosis to be made. However, various studies have proposed that the threshold of IgG4+ cells ranges from > 10 to > 100 per HPF according to the affected sites. An IgG4/IgG ratio of ≥ 40% is more indicative of IgG4-RD regardless of the sites affected.[6]

Characteristic histopathologic presentation of IgG4-RD might not apply to IgG4-related lymphadenopathy, given that storiform fibrosis and obliterative phlebitis are rarely found in lymph node biopsy. According to literature,[5] types of morphology can be seen in IgG4-related lymphadenopathy: multicentric Castleman disease-like changes, follicular hyperplasia, interfollicular expansion, progressive transformation of germinal centers, and inflammatory pseudotumor-like lesions.[6,7]

IgG4-related lymphadenopathy is frequently mistaken as lymphoma owing to its relatively nonspecific histopathologic appearance. The key to differentiating the two diseases lies in the response to steroid treatment. IgG4-RD usually responds well to steroid therapy, with the recommended initial daily dose of prednisolone being 0.6 – 1 mg/kg.[3] Rituximab is another drug of choice for treating IgG4-RD if treatment with glucocorticoid is ineffective or not feasible for patients.

While there are case reports suggesting the co-existence of IgG4-RD and lymphoma, the causality and mechanism of the two remain unclear. The treatment decision of which disease to be targeted should be based on the individual condition.[8]

Some case reports also described patients with IgG4-RD who developed lymphoma months or years later.[9,10] Hence, further studies are necessary to define the relationship between IgG4-RD and lymphoma.

In our case report, the patient exhibited swelling of the lymph nodes of the neck, lacrimal glands enlargement, and swelling of the soft tissue around the orbital region. The patient was initially suspected to have diffuse large B-cell lymphoma, and he was very close to starting chemotherapy. The diagnostic process in our patient could have been improved through a blood test of serum IgG4, immunohistochemical staining of IgG4, and the determination of an IgG4/IgG ratio upon the first pathological examination. A crucial element to optimize our practice is to keep the diagnosis of IgG4-RD in mind while approaching a patient with asymptomatic lymphadenopathy.

Conclusion

Neck mass or swelling of the neck is a common complaint in the setting of outpatient clinics, and lymphadenopathy accounts for a large proportion of these complaints. When approaching patients with enlarged neck lymph nodes, it is essential to keep in mind the possibility of IgG4-RD, especially in middle-aged and old-aged men. IgG4-RD is a relatively new clinical entity and a mimicker of malignancy, and patients are vulnerable to over-treatment with chemotherapy or unnecessary surgical procedures if not diagnosed correctly. It is also important to note that repeating lymph node biopsy is sometimes necessary in patients whose diagnosis is inconclusive, in order to determine the best treatment plan for such patients.

Author Contributions

Conception and design of the study: Hu IT, Su YC, and Huang CI; Interpretation of the data: Hu IT, Lin CW, Lin JN, and Su YC; Drafting and editing of the article: Hu IT, Su YC, and Huang CI. All authors have read and agreed to the published version of the manuscript.

Funding

The study was supported by the funding from E-Da Cancer Hospital (Grant number: EDCHP110003).

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Ferrer R: Lymphadenopathy: differential diagnosis and evaluation. Am Fam Physician 1998;58:1313-20.
2. Khosroshahi A, Stone JH: A clinical overview of IgG4-related systemic disease. Curr Opin Rheumatol 2011;23:57-66. doi: 10.1097/BOR.0b013e3283418057.
3. Legatowicz-Koprowska M: IgG4-related disease: why is it so important? Cent Eur J Immunol 2018;43:204-8. doi: 10.5114/ceji.2018.77391.
4. Umehara H, Okazaki K, Masaki Y, et al: A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol 2012;22:1-14. doi: 10.1007/s10165-011-0508-6.
5. Kamisawa T, Egawa N, Nakajima H: Autoimmune pancreatitis is a systemic autoimmune disease. Am J Gastroenterol 2003;98:2811-2. doi: 10.1111/j.1572-0241.2003.08758.x.

6. Cheuk W, Chan JK: Lymphadenopathy of IgG4-related disease: an underdiagnosed and overdiagnosed entity. Semin Diagn Pathol 2012;29:226-34. doi: 10.1053/j.semdp.2012.07.001.
7. Zhou W, Murray T, Cartagena L, et al: IgG4-related disease as mimicker of malignancy. SN Compr Clin Med 2021;3:1904-13. doi: 10.1007/s42399-021-00957-6.
8. Hornstein N, Razmjou A, Weinreb A, et al: Mimic of malignancy: delineating IgG4-related disease and lymphoma. BMJ Case Rep 2021;14:e237466. doi: 10.1136/bcr-2020-237466.
9. Igawa T, Hayashi T, Ishiguro K, et al: IgG4-producing lymphoma arising in a patient with IgG4-related disease. Med Mol Morphol 2016;49:243-9. doi: 10.1007/s00795-016-0139-2.
10. Wang H, Su T, Kang L, et al: Diffuse large B cell lymphoma in a preceding IgG4-related disease with kidney restricted lambda light chain expression: case report and literature review. BMC Nephrol 2020;21:315. doi: 10.1186/s12882-020-01975-7.