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Case report

Follicular lymphoma with hepatic accumulation on FDG-PET/CT masquerading IgG4-related disease

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ABSTRACT

Follicular lymphoma is clinically classified as a common type of indolent non-Hodgkin's lymphoma, and its clinical diagnosis is difficult because B symptoms and elevated soluble interleukin-2 receptor (sIL-2R) levels are less frequent in follicular lymphoma than in other lymphomas. We report a case of follicular lymphoma masquerading immunoglobulin G4-related disease (IgG4-RD) with elevated IgG4 levels. A 67-year-old man presented to our hospital with a 1-year history of deep right supraclavicular and para-aortic lymph node lymphadenopathy on plain computed tomography (CT) findings along with elevated IgG4 levels, and the ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan showed heterogeneous diffuse FDG uptake in the liver, and FDG uptake was noted at multiple sites in the enlarged right supraclavicular and para-aortic lymph nodes. Excisional biopsy of the right supraclavicular lymph node, performed under general anesthesia, showed a tumor-like structure mimicking a normal germinal center in the lymphoid follicle; immunostaining was positive for B-cell lymphoma 2 and CD10 proteins with some plasma cells stained with IgG, only 30% of them were positive for IgG4, and no marked fibrosis characteristic of IgG4-RD was observed; therefore, follicular lymphoma was diagnosed, and all symptoms, including FDG uptake, improved with rituximab monotherapy. Differential diagnoses of slowly progressive generalized lymphadenopathy over the years with elevated serum IgG4 levels include IgG4-RD, Castleman's disease, and indolent lymphoma. Multiple accumulation in the liver on FDG-PET/CT, if found, may suggest indolent lymphoma among them.

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Introduction

Follicular lymphoma is the second most common type of non-Hodgkin's lymphoma and is classified as indolent lymphoma

[1]. The occurrence of B symptoms and elevated soluble interleukin-2 receptor (sIL-2R) levels is less frequent in follicular lymphoma than in other lymphomas, which makes the clinical diagnosis of follicular lymphoma challenging [2]. We herein report a case of follicular lymphoma masquerad-

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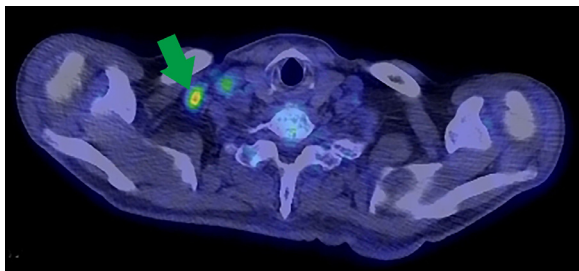


Fig. 1 – FDG-PET/CT scan showed FDG uptake in the enlarged right supraclavicular lymph node (SUVmax, 3.5) (arrow).

ing as immunoglobulin G4-related disease (IgG4-RD) with elevated IgG4 levels.

Case report

A 67-year-old man presented to our hospital with a 1-year history of deep right supraclavicular and para-aortic lymph node lymphadenopathy on plain computed tomography (CT) findings. The patient denied the presence of any B symptoms, such as fever, weight loss, or night sweats. His past medical history included hypertension, diabetes mellitus, and hyperuricaemia. Medications included amlodipine, linagliptin, empagliflozin and febusostat. Physical examination revealed a body temperature of 36.2°C, blood pressure of 138/82 mmHg, and pulse rate of 84 beats/min. He had no superficial lymphadenopathy and hepatomegaly. Laboratory tests showed elevated levels of C-reactive protein (CRP) (11.33 mg/dL, reference range: 0.00 – 0.14 mg/dL), IgG (2456 mg/dL, reference range: 861 – 1747 mg/dL), IgG4 (298 mg/dL, reference range: 4.5 – 117.0 mg/dL), and sIL-2R (1010 U/mL, reference range: 121 – 613 U/mL) but no other abnormal findings including those of hepatobiliary enzymes. Abdominal ultrasonography and liver magnetic resonance imaging did not show any abnormalities. The ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan showed FDG uptake at multiple sites in the enlarged right supraclavicular (SUVmax, 3.5) and para-aortic lymph nodes (SUVmax, 4.9) (Fig. 1). Additionally, heterogeneous diffuse FDG uptake was observed in the liver (SUVmax, 5.7) (Fig. 2). Excisional biopsy of the right supraclavicular lymph node, performed under general anesthesia, showed a tumor-like structure mimicking the normal germinal center of a lymphoid follicle. Immunostaining was positive for B-cell lymphoma 2 (Bcl-2) and CD10 proteins (Fig. 3), consistent with follicular lymphoma. Some plasma cells stained positively with the IgG immunostain, of which only 30% were in the IgG4 subclass. No marked fibrosis, characteristic of IgG4-RD, was noted. Bone marrow examination did not show any abnormalities. A diagnosis of secondary hepatic follicular lymphoma was made, and it was classified as Lugano system stage IV. Rituximab monotherapy was therefore started. Six months after the initiation of rituximab monotherapy, his CRP, IgG, IgG4, and sIL-2R levels improved. FDG uptake in the enlarged lymph nodes also disappeared

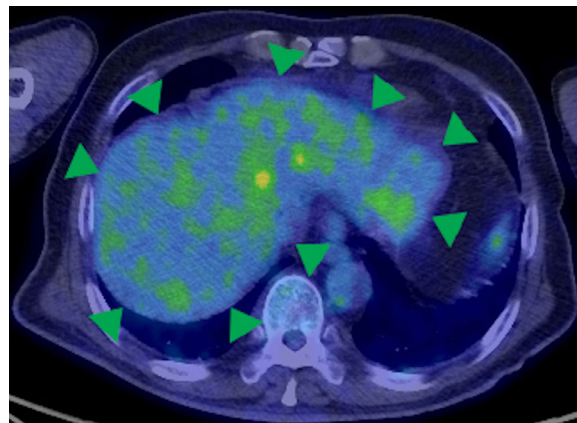


Fig. 2 – FDG-PET/CT scan showed heterogeneous diffuse FDG uptake in the liver (SUVmax, 5.7) (arrow heads).

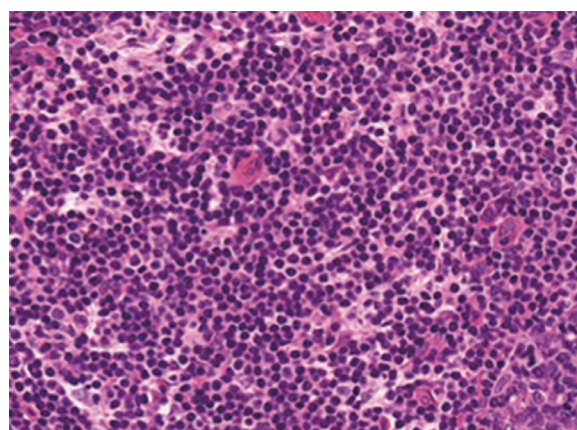


Fig. 3 – Excisional biopsy of the right supraclavicular lymph node, performed under general anesthesia, showed a tumor-like structure mimicking the normal germinal center of a lymphoid follicle. Immunostaining was positive for B-cell lymphoma 2 (Bcl-2) and CD10 proteins.

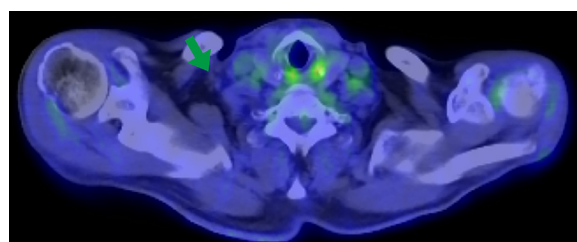


Fig. 4 – FDG uptake in the enlarged right supraclavicular lymph node disappeared (arrow).

(Fig. 4). Additionally, the heterogeneous diffuse FDG uptake in the liver disappeared and normal homogeneous FDG uptake was observed (Fig. 5).

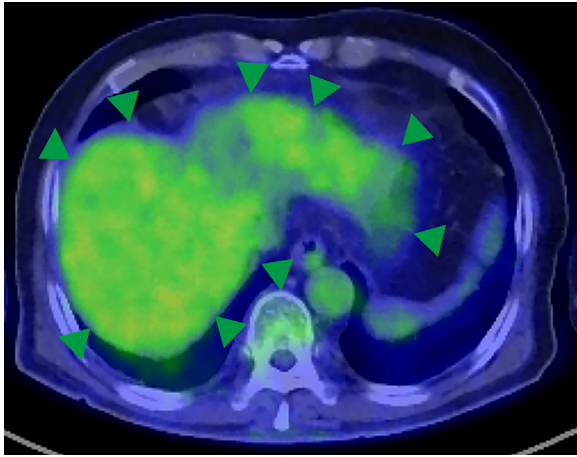


Fig. 5 – Heterogeneous diffuse FDG uptake in the liver disappeared and normal homogeneous FDG uptake was observed (arrow heads).

Discussion

Follicular lymphoma is the second most common type of non-Hodgkin's lymphoma and classified as indolent lymphoma [1]. Clinical diagnosis is difficult because B symptoms and elevated sIL-2R levels are less frequent [2]. Differential diagnoses of slowly progressive generalized lymphadenopathy over years include IgG4-RD, Castleman's disease, and indolent lymphoma. In cases involving indolent lymphoma and Castleman's disease, elevated serum IgG4 levels and numbers of IgG4+ plasma cells in tissues may be seen [3]. The 2011 comprehensive diagnostic criteria for IgG4-RD can be divided into clinical, hematological, and histopathological aspects. In terms of clinical examination, the criteria include diffuse/localized swelling or masses in single or multiple organs, and hematological examination comprises elevated serum IgG4 concentrations (≥ 135 mg/dL). Regarding the histopathological aspect, marked lymphocyte and plasmacyte infiltration and fibrosis are included, in addition to the infiltration of IgG4-positive plasma cells with an IgG4/IgG-positive cell ratio of $> 40\%$ and > 10 IgG4-positive plasma cells per high-power field [4]. In this case report, although some plasma cells were IgG-positive, only 30% of them were in the IgG4 subclass. Studies have measured the IgG4/total IgG ratio and found that it is usually $< 5\%$, and in IgG4-RD, the mean reported ratio was 40%, ranging from 25% to 86% [3]. Okazaki *et al.* focused on the importance of differentiating IgG4-RD from malignant tumors of each organ and other similar diseases such as Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, and Churg-Strauss syndrome, through additional histopathological examination [5]. Elevated IgG4 levels may also be observed in other diseases such as atopic dermatitis, pemphigus, asthma, and Castleman's disease, as well as in about 10% of malignancies [5]. This suggests that a high level of serum IgG4 is not neces-

sarily a specific marker of IgG4-RD [5]. Moreover, with IgG4-positive plasma cell infiltration, reactive fibrosis may be observed in various diseases and clinical conditions, including rheumatoid synovitis, around inflammatory oral, skin, and malignant lesions [5]. Additionally, some immune-mediated conditions with increased serum interleukin-6 (IL-6) levels such as Castleman's disease may exhibit increased serum IgG4 levels and/or increased IgG4/IgG-positive plasma cell ratios [5]. In this case, the medical history, physical examination, laboratory, imaging, and histological tests did not show any findings suggestive of these differential diagnoses other than follicular lymphoma. Regarding IgG4-RD, liver involvement is rare, compared to bile duct or pancreas involvement; the typical manifestations are localized inflammatory pseudotumors and autoimmune hepatitis [6]. In Castleman's disease, lymphadenopathy can occur near the hepatic portal region typically, but hepatic parenchymal lesions are rare [7]. In non-Hodgkin's lymphoma, 57% cases show hepatic infiltration on autopsy and hepatic accumulation is observed in 15% cases on FDG-PET/CT, which is the most useful imaging technique [8,9]. Secondary hepatic lymphoma is defined based on distant involvement, and it typically presents as diffuse infiltration [10]. Rituximab alone has been used as a first-line therapy for the treatment of patients with follicular lymphoma, with overall and complete response rates of around 70% and 30%, respectively [1]. The overall survival (OS) of patients has significantly improved since the introduction of rituximab [1], and a recent analysis of US and French cohorts reported an improved 10-year OS of approximately 80% [1,11]. The Follicular Lymphoma International Prognostic Index is the outcome measure used for these patients and includes five prognostic factors, i.e. age, stage, number of involved nodal areas, serum lactate dehydrogenase, and hemoglobin [12]. The patient in our case report was classified as intermediate risk, and the 2-year OS in these patients is 94%, with a 2-year progression-free survival (PFS) rate of 70% [12]. By contrast, systemic glucocorticoids are the first-line approach currently used in the treatment of IgG4-RD [13]. The short-term clinical, morphological, and functional outcomes of most of these patients treated with steroids are favorable; however, several unknown factors such as relapse, fibrosis, and associated malignancies influence long-term outcomes [13]. Since IgG4-RD is predominantly diagnosed in elderly males and steroid therapy is immunosuppressive, imaging and serum tumor markers should be periodically checked during follow-up [13].

This case report has several limitations. First, although tissue diagnosis by liver biopsy is important for assessing hepatic involvement in follicular lymphoma, it was not performed due to its invasiveness. Six months after the initiation of rituximab monotherapy, the patient's CRP, IgG, IgG4, and sIL-2R levels improved. Additionally, FDG uptake in the enlarged lymph nodes and the liver had disappeared. Therefore, we diagnosed hepatic involvement clinically. Second, it is reported that in patients with indolent lymphoma, the SUV on FDG-PET/CT has a mean of 6.7, ranging from 2.3 to 13.0 [14], which is in line with the findings of this case report. However, the possibility of physiologic hepatic activity cannot be ruled out since a liver biopsy was not performed.

In conclusion, indolent lymphoma should be considered in patients presenting with generalized lymphadenopathy

over the years with elevated IgG4 levels, and multiple accumulation in the liver on FDG-PET/CT may be a key feature that distinguishes it from Castleman disease and other IgG4-RD.

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Authorship

All authors had access to the data and a role in writing the manuscript.

Declaration of Interest

None

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