CASE REPORT

Unrecognised IgG4 association in progressively transformed germinal centers of lymph nodes with subsequent full-blown IgG4-related chronic fibrosing pancreatitis: A case report

Hyun-Jin SON* MD, PhD, Hyekyung LEE* MD, PhD, Ji Hoon KIM** MD, In Kyu YU*** MD, PhD and Hyun-Young HAN*** MD, PhD

*Department of Pathology, **Surgery, and ***Radiology, Eulji University School of Medicine, Daejeon, Republic of Korea

Abstract

Progressively transformed germinal centers (PTGC) is a benign process characterised by a morphological variant of reactive follicular hyperplasia in lymph nodes. It was recently shown that some cases of PTGC are associated with IgG4-related disease (IgG4-RD) or increased IgG4 plasma cells. Five years ago, a 57-year-old woman presented with enlargement of multiple lymph nodes in the left parotid, submandibular, and neck areas, pathologically diagnosed as PTGC after excisional biopsy. Since then, she has experienced numbness in her extremities, especially the left shoulder and arm, pruritus on the left side of the face and intermittent facial palsy, for which she has been receiving regular symptomatic treatment. Recently the patient developed diabetes mellitus (approximately seven months ago). In routine follow-up scans, a mass was detected in left kidney and magnetic resonance imaging of the abdomen prior to surgery revealed a slightly enhanced bulky mass replacing the pancreatic tail and uncinate process. The mass in left kidney was diagnosed as clear cell renal cell carcinoma, and the pathological features of the pancreatic lesion were those of IgG4-related chronic fibrosing pancreatitis. Retrograde examination of the neck lymph node diagnosed as PTGC showed increased deposition of IgG4-positive plasma cells.

Keywords: Progressively transformed germinal centers, lymph node, IgG4, renal cell carcinoma, IgG4-related pancreatitis

INTRODUCTION

Progressively transformed germinal centers (PTGC), first described by Lennert and Müller-Hermelink in 1975, is a benign process of unknown pathogenesis leading to reactive follicular hyperplasia characterised by enlarged germinal centers that are mainly composed of mantle zone lymphocytes and remnants of germinal center cells. IgG4-related disease (IgG4-RD) is a recently defined chronic disease and its diagnosis is based on a combination of clinical, serological, histological, and immunohistochemical features. Sato et al. reported of an association between IgG4-RD and PTGC of lymph nodes, with two-thirds of the PTGC demonstrating increased deposition of IgG4 plasma cells; thereby, pathogenetically indicating IgG4-related lymphadenopathy. Studies have shown that IgG4 positive PTGC is more prevalent in the older age group with a higher incidence of submandibular lymph node involvement compared to those with IgG4 negative PTGC. IgG4-RD is a systemic and progressive condition and responds well to steroids and rituximab, hence timely diagnosis is critical. Considering that histopathological differences between IgG4 positive and IgG4 negative PTGC were not evident apart from an increased deposition of IgG4 plasma cells, it is crucial to determine which patients benefit from IgG/IgG4 immunostaining. Herein, we report a case where IgG4 association in PTGC-type lymphadenopathy went unrecognised and progressed to a full-blown mass-forming IgG4-related chronic fibrosing pancreatitis, resulting in total pancreatectomy that could have been prevented with timely diagnosis.

Address for correspondence: Hyun-Jin Son, Department of Pathology, Eulji University Hospital, 95, Dunsanseo-ro, Seogu, Daejeon 35233, Korea. Tel: +82-42-611-3451. Fax: +82-42-611-3459. Email: shjpathol@eulji.ac.kr
CASE REPORT

Five years ago, a 57-year-old woman presented with a palpable mass on the left side of her neck. Neck ultrasonography (US) and computed tomography (CT) revealed multiple enlarged oval or round shaped hypoechoic lymph nodes in left parotid, submandibular, and internal jugular chain area measuring up to 2.5 cm in diameter, with increased echogenicity and oedema in the surrounding soft tissue (Fig. 1A). Lymphoproliferative diseases such as malignant lymphoma were suspected and excisional biopsy was performed. Histopathologic and immunohistochemical findings were compatible with those of progressively transformed germinal center (PTGC) and since then, the patient has been undergoing regular follow-up examinations. She had experienced numbness and unexplained pain in her extremities, intermittent facial palsy, and pruritus on the left side of her face, approximately thirty years prior, and had received symptomatic medical treatment. Electroneurographic and evoked potential tests showed electrophysiological abnormalities, suggesting lesions in both the superficial peroneal nerve and the nerves between the popliteal fossa and cauda equina or the somatosensory cortex. She had smoked about a pack of cigarettes a day for 10 years, consumed alcohol, and taken medications for hypertension. The patient also had a family history (her father and sister) of surgical intervention for gastric cancer.

A year ago, she presented to the department of neurology and otorhinolaryngology complaining of a tingling sensation and swelling in her left cheek. US examination revealed sialadenitis and lymphadenopathy (LAP) in the left parotid gland. She developed diabetes mellitus seven months ago. At the same time, routine follow-up scans revealed a 4.0 cm bulging mass with heterogeneous enhancement and delayed phase washout in the left kidney (Fig. 1B). Magnetic resonance imaging (MRI) taken preoperatively showed not only the renal mass, but also a slightly delayed enhancing bulky mass replacing the pancreatic tail, measuring about 9.0 x 2.5 cm and another in the uncinate process, measuring about 2.0 x 1.5 cm. The pancreatic lesions showed low signal intensity (SI) on T1-weighted, high SI on T2-weighted images, and diffuse restriction, highly suggestive of multifocal pancreatic cancer (Fig. 1C). Positron emission tomography-computed tomography (PET-CT) disclosed hypermetabolic lesions in the pancreatic tail, uncinate process, left renal cortex and left parapharyngeal space, alongside multiple LAP in the left parotid, cervical, and supraclavicular areas (Fig. 1D, E, F). Total pancreatectomy and splenectomy, left radical nephrectomy, left adrenalectomy, and cholecystectomy were performed. Since the operation, she has been receiving insulin therapy and was admitted twice owing to epigastric and periumbilical pain and symptoms of acute enterocolitis. She has also been hospitalised several times for uncontrolled hyperglycemia and drug-induced hypoglycemia. Currently, the patient’s condition is relatively stable, and she has been undergoing regular follow ups and treatments.

Excisional biopsy of the enlarged neck lymph nodes, measuring up to 2.2 cm in diameter, was performed. Large follicles with germinal centers, showing indistinct borders and irregular shapes, were seen in conjunction with more typical reactive germinal centers (Fig. 2A). Residual “starry sky” macrophages were present in these dysmorphic germinal centers. In high-power view, the cytologic composition was not too dissimilar from that of ordinary hyperplastic follicles (Fig. 2B). Expansion of the interfollicular zone was not identified and the transition zone was indistinct (Fig. 2C).

Immunostaining were performed to exclude the possibility of neoplastic entities. The heterogeneous cell population and distribution of CD3 (1:100, Novocastra, Newcastle, UK), CD5 (1:40, Novocastra), and CD20 (1:20, Dako, CA, USA) positive lymphoid cells was compatible with that of reactive follicular hyperplasia. Bcl-2 (1:25, Dako) and cyclin D1 (1:20, Dako) were negative in these germinal centers and Bcl-6 (pre-dilution, Dako) and CD10 (1:50, Novocastra) were only weakly positive in germinal centers (Fig. 2D, E). Infiltration of plasma cells and plasmacytoid cells in the germinal center and interfollicular zone was not conspicuously detected on haematoxylin-eosin (HE) stained sections. Immunostaining for IgG (1:500, Leica, UK) and IgG4 (1:250, Invitrogen, IL, USA) were performed retrospectively and IgG4-positive plasma cells were detected in both the germinal centers and interfollicular zone. The IgG4-positive plasma cells were approximately 60/high-power field (HPF) with an IgG4/IgG ratio of 80% (Fig. 2F, G). Immunoglobulin light-chain restriction was not detected.

The excised pancreas was divided into two parts (head, 5.5 x 4.0 x 3.0 cm; body and tail, 12.0 x 5.0 x 4.0 cm). The cut surface showed diffuse...
FIG. 1: (A) Axial computed tomography (CT) of head and neck revealing multiple enlarged oval or round shaped hypoechogenic lymph nodes in left parotid and submandibular area measuring up to 2.5 cm in diameter. (B) In abdominal CT, a 4.0 cm bulging mass with heterogeneous enhancement and delayed phase washout in the left kidney. (C) Bulky mass replacing pancreas on MRI. The mass shows low signal intensity (SI)-on T1-weighted, high SI on T2-weighted images, and diffuse restriction in addition to left renal mass. Positron emission tomography-computed tomography revealing hypermetabolic lesions in the pancreatic tail (D), left renal cortex (E), and multiple lymphadenopathies in the left cervical area (F).

FIG. 2: (A) Large follicles with germinal centers showing indistinct borders and irregular shapes alongside more typical reactive germinal centers. (B) Residual “starry sky” macrophages in these dysmorphic germinal centers. The cytologic composition in high-power view was not too dissimilar from that of ordinary hyperplastic follicles. (C) No expansion of the interfollicular zone along with an indistinct transition zone. (D) Immunostaining for Bcl-2 was negative in these germinal centers. (E) High magnification of Bcl-2 immunostaining. Immunostaining for IgG (F) and IgG4 (G); IgG4-positive plasma cells were detected in the germinal centers and IgG4-positive plasma cells were approximately 60/HPF.
fibrosis with vague nodularity, but no distinct mass lesion was observed (Fig. 3A). Microscopic examination showed a dense lymphoplasmacytic infiltrate, storiform fibrosis, and marked atrophy of the acinar component (Fig. 3B, C). A few foci of obliterative phlebitis was detected (Fig. 3D). Perineural infiltration of plasma cells in the nerve bundles of peri-pancreatic soft tissue was significant (Fig. 3E). The IgG4-positive plasma cells were approximately 50/HPF with an IgG4/IgG ratio of 70% (Fig. 3F, G). The nephrectomy sample revealed a relatively well-demarcated mass measuring 4.5 x 3.5 cm on the upper pole of the left kidney, limited to renal parenchyma (pT1b) (Fig. 3H). Histologic sample of the specimen revealed a Fuhrman nuclear grade 2 clear cell renal cell carcinoma (Fig. 3I). Gross and microscopic examination of the spleen, left adrenal gland, and gallbladder were all unremarkable.

**DISCUSSION**

PTGC is characterised by the presence of follicles that are several times larger than those of the surrounding reactive follicles. They comprise a higher number of small mantle zone lymphocytes, a relatively large number of T lymphocytes, an increased network of follicular dendritic cells, residual “starry sky” macrophages and scattered large lymphoid cells. The existence of small mantle zone lymphocytes in PTGC results in the poor demarcation of the germinal center-mantle zone junction. These findings facilitate the differential diagnosis between PTGC and follicular lymphoma in most cases. PTGC generally presents as asymptomatic cervical lymphadenopathy and is a self-limited reactive process in young men. However, in some cases it is very difficult to differentiate PTGC in routinely stained sections and the

---

**FIG. 3:** (A) Cut surface of pancreas. There is diffuse fibrosis with vague nodularity but no distinct mass lesion. (B,C) Dense lymphoplasmacytic infiltrate, storiform fibrosis, and marked atrophy of the acinar component can be seen on microscopic examination. (D) Foci of obliterative phlebitis and (E) perineuritis by plasma cell infiltrates in peri-pancreatic soft tissue. Immunostaining for IgG (F) and IgG4 (G); IgG4-positive plasma cells approximately 50/HPF. (H) Relatively well-demarcated mass measuring 4.5 x 3.5 cm in the upper pole of left kidney, which was diagnosed as (I) nuclear grade 2 clear cell renal cell carcinoma histologically.
controversial cases illustrating PTGC are either considered as precursors to nodular lymphocyte predominant Hodgkin’s lymphoma (NLPHL) or are associated with in situ follicular neoplasia.\textsuperscript{7,8} The early phase of angioimmunoblastic T cell lymphoma is difficult to distinguish from reactive follicular hyperplasia and PTGC, and immunohistochemical stains are necessary to highlight the neoplastic T cells with their characteristic T follicular helper (TFH)-cell phenotype. The neoplastic TFH cells are positive for CD4, CD10, Bcl-6, and programmed death-1 (PD-1), but in our patient, CD4 was negative, CD10 and Bcl-6 were only weakly positive in germinal centers, and a small number of cells positive to PD-1 were scattered only in the germinal centers.\textsuperscript{9}

Normally, IgG4 plasma cells represent 3-6\% of total IgG plasma cells in tissues and an increased number of IgG4 cells in lymph nodes or IgG4-related lymphadenopathy may precede, coexist with, or follow extranodal manifestations of IgG4-RD. Although the pathogenesis driving IgG4-RD remains unclear, some activated or innate immune cells including T-helper cell 2, regulatory T cells, CD4\textsuperscript{+} cytotoxic T lymphocytes, dysregulated follicular T helper cells, and activated macrophages are thought to be involved in the pathogenesis of this disease. Interleukin (IL)-4, IL-10, and IL-21 are considered major inducers of IgG4 class switching in naive B lymphocytes.\textsuperscript{10-12} Increased numbers of IgG4 plasma cells are seen in other diseases of lymph nodes. Hence, interpreting laboratory findings in the setting of clinical findings is essential to exclude specific entities such as multicentric Castleman disease, Rosai-Dorfman disease, and lymphoma.\textsuperscript{13} Besides, the exact enumeration and threshold of IgG4 and IgG positive plasma cells is very important to diagnose IgG4-related lymphadenopathy. The proposed threshold for IgG4/IgG ratio is >40\% and for IgG4 positive plasma cells >50 or >100 per HPF.\textsuperscript{14}

Five histologic patterns have been reported in the literature to be associated with IgG4-related lymphadenopathy: multicentric Castleman disease-like, follicular hyperplasia, interfollicular expansion, PTGC, and nodal inflammatory pseudotumour-like.\textsuperscript{14,15} Unlike IgG4-RD in other tissues, the above mentioned histologic patterns in lymph nodes do not show the morphological hints of IgG4 association such as storiform fibrosis except for nodal inflammatory pseudotumour-like. No significant morphological differences were found between IgG4-related lymphadenopathy and nonspecific reactive lymph nodes. Sato \textit{et al.} reported that patients with IgG4 positive PTGC showed no expansion of the interfollicular zone, and a significant increase in the number of eosinophils and indistinct T-zones, in contrast to those with IgG4 negative PTGC.\textsuperscript{3} Grimm \textit{et al.} suggested that a number of lymph nodes with a broad range of reactive features may be part of the spectrum of IgG4-RD and although the findings in each of these differential diagnoses had some distinctive features, they were not sufficiently distinctive to exclude a diagnosis of IgG4-related lymphadenopathy.\textsuperscript{16} They also proposed that IgG4 testing in the lymph nodes with a broad range of histological features may be warranted, especially in older patients. Sato \textit{et al.} also described an older age distribution for IgG4 positive PTGC along with significantly higher incidence of submandibular lymph node involvement than those with IgG4 negative PTGC.\textsuperscript{3} Previous studies have shown that PTGC is a rare finding in older age, with the mean age of diagnosis in adults being 28 years.\textsuperscript{2} Our patient was a 57-year-old woman who presented with multiple enlarged lymph nodes in left parotid, submandibular, and internal jugular chain area and we think it would be better if we try to perform IgG/IgG4 immunostaining when she had been diagnosed as PTGC. Histologically, we did neither observed any expansion of the interfollicular zones, nor a significant increase in the number of eosinophils in the interfollicular zone.

IgG4-RD is an emerging systemic condition, in which the involvement of various organs are linked to a similar pathology. According to a recent study, the most common manifestations are pancreatitis, followed by sialadenitis, tubulointerstitial nephritis, dacryoadenitis, and periaortitis.\textsuperscript{17} More than 10\% of patients present with lymph node enlargement at various sites as a first manifestation of IgG4-RD\textsuperscript{7}, many of whom progress to extranodal lesions and systemic disease in the follow-up period.\textsuperscript{7} What should we do when encounter reactive lymph nodes found to have increased IgG4 positive cells without documented extranodal IgG4-RD? The recommended work-up for IgG4-related lymphadenopathy is still evolving,\textsuperscript{14} but we suggest that considering the systemic nature of the disease and its responsiveness to steroids and rituximab, a more active intervention should be sought. Fujii \textit{et al.} described a case that progressed from PTGC-type IgG4-related
lymphadenopathy to systemic IgG4-RD, where the patient showed the infiltration of plasma cells through the epineurium of the nerve fascicles in several organs suggesting that IgG4-RD may affect many organs through peripheral nerve involvement. In our patient, PTGC-type lymphadenopathy and sialadenitis were the initial presentations, followed by mass-forming chronic fibrosing pancreatitis, which replaced the entire pancreas 5 years later, all of which were consistent with IgG4-RD. We also detected perineuritis due to infiltration of IgG4 positive plasma cells around the nerve bundles of peripancreatic soft tissue. We believe that there might be some association between this feature and the neural symptoms of the patient such as numbness and facial palsy. Whether IgG4-RD can increase the risk of malignancy remains controversial with only a marginal increase described in a previous study. Our patient revealed conventional clear cell renal cell carcinoma around the time of total pancreatectomy but the infiltration of plasma cells was not detected in the left kidney.

In summary, we present a case where association of IgG4 in PTGC-type lymphadenopathy had been undiagnosed, consequently allowing for its progression to a full-blown mass-forming IgG4-related chronic fibrosing pancreatitis, providing further proof that PTGC is occasionally associated with IgG4-RD and may be an initial presentation of this disease. We also suggest that the diagnostic approach in PTGC and treatment toward IgG4-related lymphadenopathy be modified into a more active intervention to ensure timely treatment to reduce the chance of systemic progression.

REFERENCES