

# **IgG4-related Tubulointerstitial Nephritis and Hepatic Inflammatory Pseudotumor without Hypocomplementemia**

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## **Abstract**

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Immunoglobulin G4 (IgG4)-related tubulointerstitial nephritis (TIN) is often accompanied by autoimmune pancreatitis (AIP) or chronic sclerosing dacryoadenitis and sialoadenitis. However, IgG4-related TIN without AIP or lacrimal and/or salivary gland lesions has not been well recognized. Here, we report a case of IgG4-related TIN associated with hepatic inflammatory pseudotumor without AIP or lacrimal and/or salivary gland lesions. A 58-year-old Japanese man with epigastralgia underwent contrast-enhanced computed tomography (CT), which revealed multiple low-density lesions in both kidneys and a low density hepatic mass. Laboratory tests showed an extremely high level of serum IgG4. Percutaneous renal and hepatic biopsies showed diffuse infiltration of lymphocytes and IgG4-positive plasma cells with fibrosis in both tissues. Two months after administration of oral prednisolone, both lesions decreased in size on follow-up CT, and the serum creatinine level also improved. No recurrence has been detected for two years with a maintenance dose of prednisolone.

**Key words:** IgG4-related tubulointerstitial nephritis, hepatic inflammatory pseudotumor

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## **Introduction**

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Immunoglobulin G4 (IgG4)-related disease is a recently proposed clinical entity characterized by marked infiltration of lymphocytes and IgG4-positive plasma cells with fibrosis in affected organs and increased serum levels of IgG4 (1). Although autoimmune pancreatitis (AIP) is a well-recognized IgG4-related disease, detailed analysis of patients with AIP has revealed that marked IgG4 positive plasma cell infiltration is not restricted to the pancreas but is also often

found in other organs such as salivary glands, lacrimal glands, lungs, liver, kidneys, and prostate (1-4).

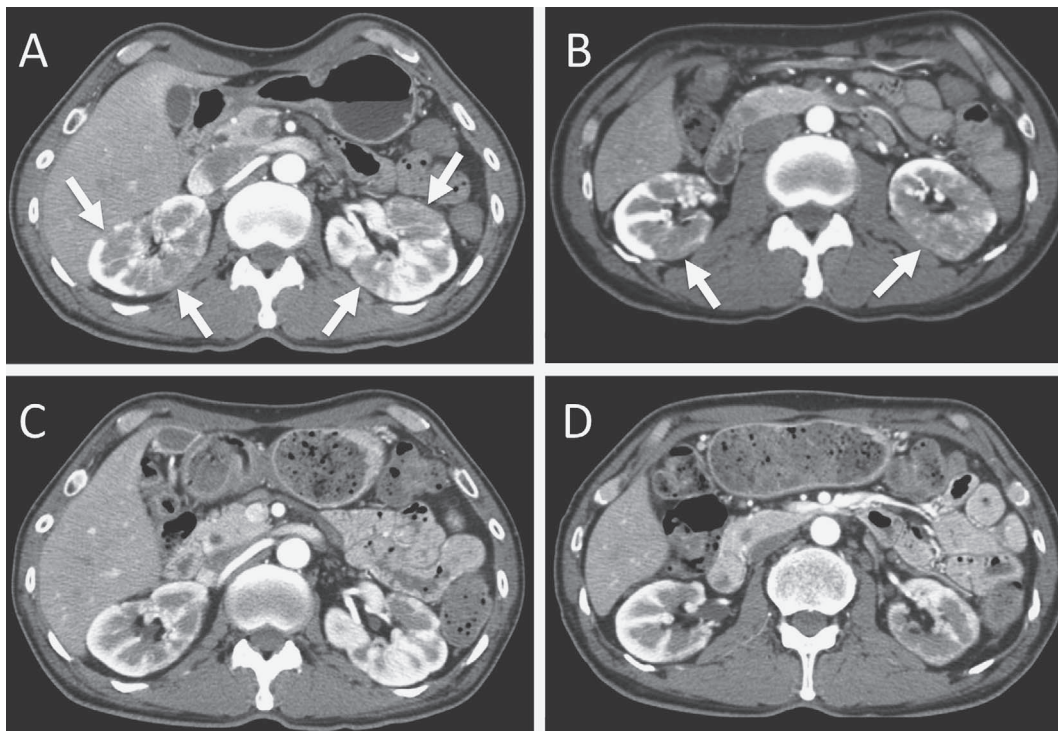
While reports of IgG4-related tubulointerstitial nephritis (TIN) with AIP or chronic sclerosing dacryoadenitis and sialoadenitis have been accumulated recently, IgG4-related TIN without AIP or chronic sclerosing dacryoadenitis and sialoadenitis has not been well recognized, and only a few reports are available in the English language literature (5-9). Here, we describe a case of IgG4-related TIN associated with hepatic inflammatory pseudotumor without AIP or chronic sclerosing dacryoadenitis and sialoadenitis.

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**Figure 1.** Contrast-enhanced computed tomography of the abdomen before (A, B) and after (C, D) treatment. Multiple low-density lesions in both kidneys were observed (A, B), which were ameliorated after steroid administration (C, D). Arrows indicate the abnormal regions in the kidneys.

## Case Report

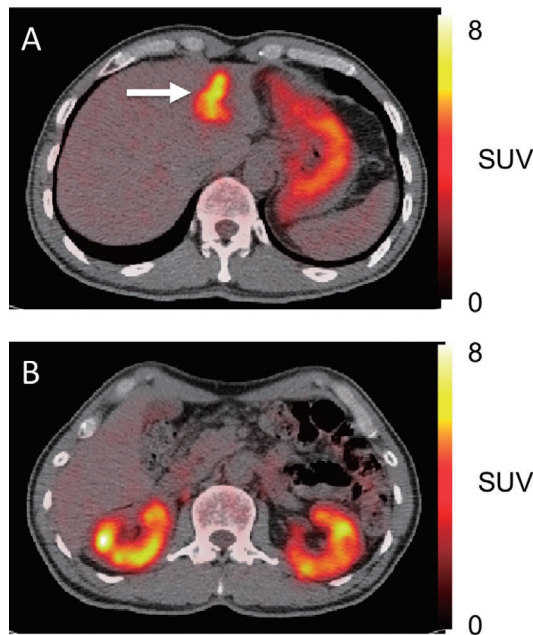
A 58-year-old Japanese man was admitted to our hospital for investigation of a solitary hepatic mass and multiple low-density lesions in the bilateral kidneys on enhanced computed tomography (CT). Two weeks before entry, he had undergone gastroscopy because of a 4-month history of epigastralgia, and a diagnosis of gastric ulcer with *Helicobacter pylori* infection was made. Abdominal ultrasonography showed a heterogeneous mass in the umbilical part of the liver. A contrast-enhanced CT scan of the abdomen revealed multiple low-density lesions in both kidneys (Fig. 1A, B). All lesions were well circumscribed and variously shaped. The hepatic lesion was also detected as a mass of decreased enhancement along with the left portal vein. Based on these CT findings, IgG4-related disease was suspected, and malignant lymphoma was also considered.

Physical findings were normal. He had neither parotid gland nor submandibular gland swelling. Urinalysis revealed no hematuria or proteinuria. The level of urinary N-acetyl- $\beta$ -D-glucosaminidase (NAG) was 1.6 IU/L (normal, 1.0 to 4.2  $\mu$ g/L) and that of urinary  $\beta$ 2-microglobulin was 335  $\mu$ g/L (normal, 16 to 518  $\mu$ g/L). Other laboratory findings were as follows: leukocyte count 7,389/ $\mu$ L, eosinophil count 487/ $\mu$ L, hemoglobin 13.8 g/dL, CRP 0.1 mg/dL, IgG 2,850 mg/dL (normal, 739 to 1,649 mg/dL), IgG4 1,470 mg/dL (normal, 30 to 135 mg/dL), IgE 456 U/mL (normal, less than 250 U/mL), C3 81 mg/dL (normal, 44 to 102 mg/dL), C4 16 mg/dL (normal, 14 to 49 mg/dL), total hemolytic complement

(CH50) 34 U/mL (normal, 31 to 49 U/mL), soluble interleukin-2 receptor (sIL-2R) 1,300 U/mL (normal, 220 to 530 U/mL). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum electrolytes were normal. Serum creatinine (Cr) level was 1.15 mg/dL. Positron emission tomography (PET) showed accumulation of fluorodeoxyglucose (FDG) in liver and kidney lesions suggestive of metastatic tumors (Fig. 2A, B). In addition, accumulation of FDG was detected along the left C6 nerve (Fig. 3).

The renal and hepatic lesions were subjected to percutaneous biopsy, with two samples secured from a renal lesion. Light microscopic examination of the renal lesion showed severe renal interstitial infiltration of lymphocytes and plasma cells with fibrosis and tubular atrophy in one sample (Fig. 4A-C). A lymphatic follicle was also observed (data not shown). However, the other sample showed normal glomeruli with little interstitial fibrosis. In all sections, the glomeruli and blood vessels showed only minor abnormalities. On immunostaining of specimens, more than half of the plasma cells infiltrating the interstitium were IgG4-positive (Fig. 4D). On the biopsied specimens of the hepatic lesion, light microscopic examination showed diffuse infiltration of lymphocytes and plasma cells in fibrous connective tissue without a normal liver architecture, and many plasma cells were IgG4-positive by immunostaining (Fig. 4E, F).

A diagnosis of IgG4-related TIN and IgG4-related hepatic pseudotumor was made based on the imaging studies, pathological findings of kidney and liver, and serum elevated IgG4 levels. His serum Cr level gradually increased to 1.30 mg/dL (eGFR 45.4 mL/min/1.73 m<sup>2</sup>), and 30 mg per day of



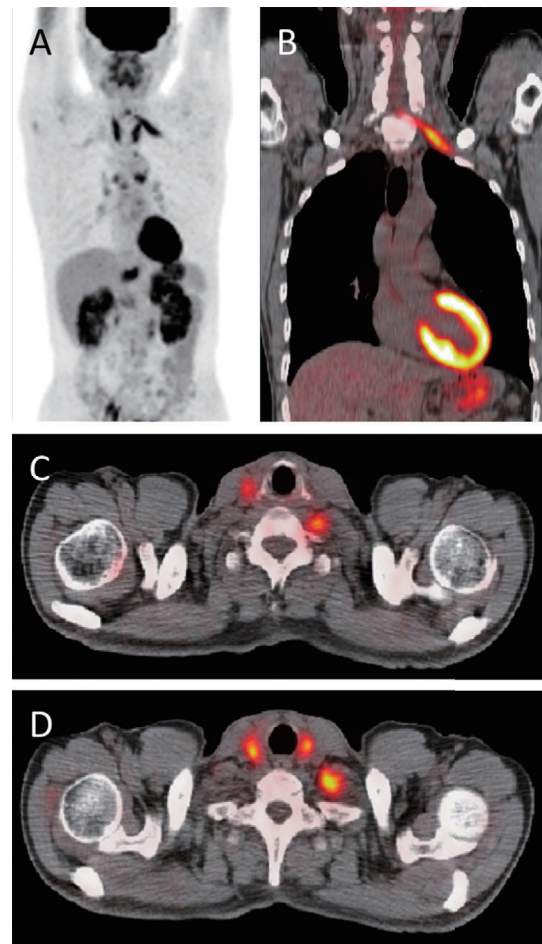
**Figure 2.** Combined positron emission tomography (PET)/computed tomography (CT) scans showed accumulation of  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) in a liver lesion (A) and the kidney lesions (B). More marked FDG uptake was shown in the affected areas of the kidney lesions consistent with the multiple low-density lesions detected by CT. An arrow indicates the abnormal region in the liver.

oral prednisolone was started.

Two months later, his serum IgG4 level was decreased to 470 mg/dL, and Cr level recovered to 1.02 mg/dL (eGFR 58.6 mL/min/1.73 m<sup>2</sup>). Enhanced computed tomography showed that the hepatic pseudotumor and renal low-density lesions had become smaller (Fig. 1C, D). Prednisolone was tapered one month after the start of administration. Two years later, he showed no recurrence with improved renal function (Cr 0.89 mg/dL, eGFR 68.0 mL/min/1.73 m<sup>2</sup>), with a maintenance dose of 7 mg per day of prednisolone (Fig. 5). During the clinical course, serum C3 levels and serum C4 levels fluctuated between 78 mg/dL and 103 mg/dL, and 15 mg/dL and 28 mg/dL, respectively without influence of steroid therapy.

## Discussion

IgG4-related systemic disease sometimes affects the kidneys (4). In early reports, most reported cases of IgG4-related TIN were associated with AIP or Mikulicz's disease (10-12). However, reports of IgG4-related TIN without AIP or chronic sclerosing dacryoadenitis and sialoadenitis have also accumulated recently, because the common clinical features of IgG4-related disease have become more widely recognized (5-9). These include elderly onset, male predominance, positive history of allergies, and hypergammaglobulinemia (4). Therefore, in patients with TIN who have these clinical features, IgG4-related disease should be



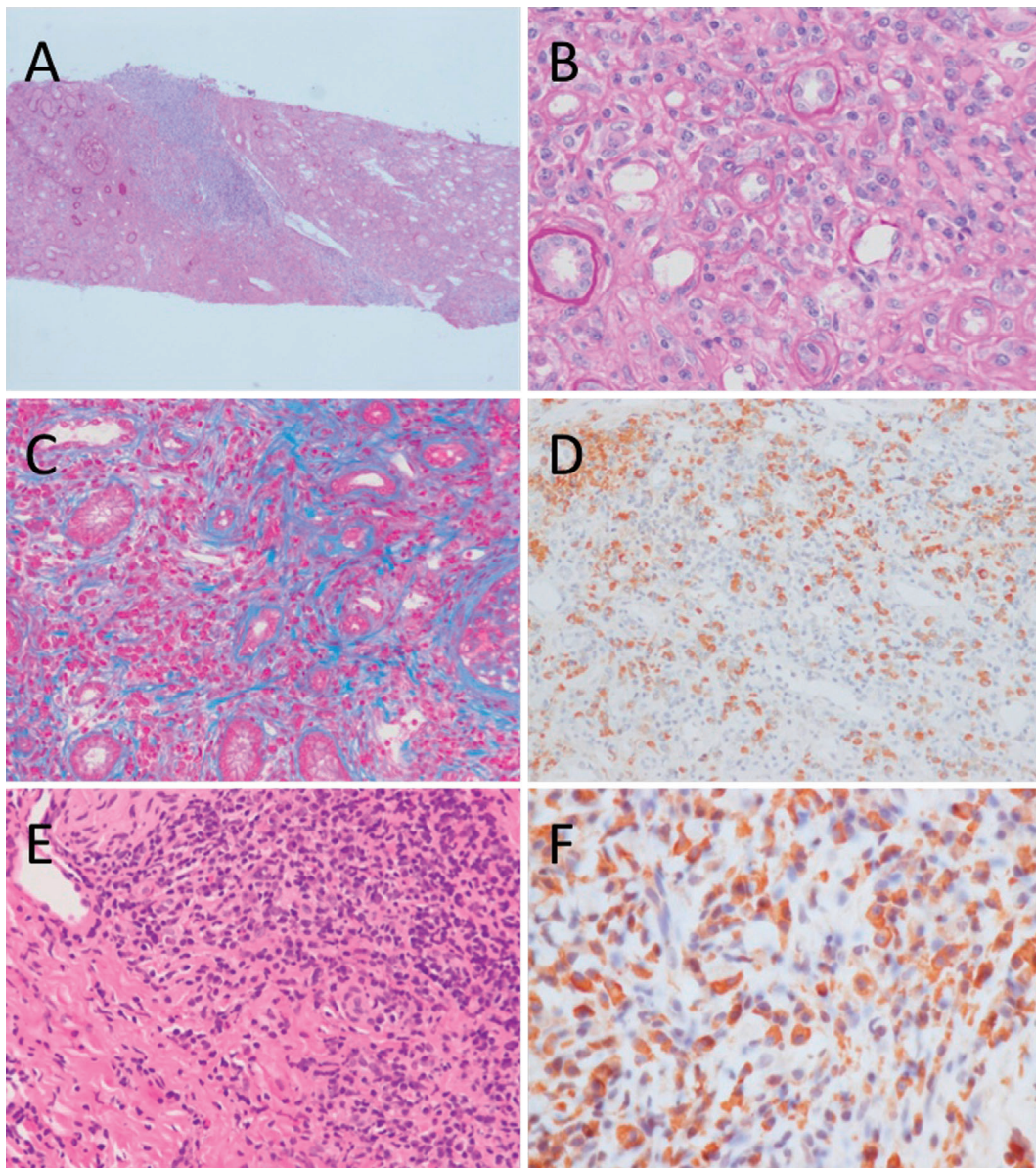
**Figure 3.** FDG-PET coronal maximum intensity projection image showed left C6 nerve involvement in addition to hepatic and renal accumulation (A). This nerve lesion was confirmed anatomically using PET/CT scans (B-D).

considered in the differential diagnosis.

IgG4-related disease is a systemic disease characterized by multi-organ involvement of IgG4 positive plasma cell infiltration and fibrosis. Although the mechanism by which the disease affects multiple organs has not been clarified, the histopathological findings of affected organs are very similar. In this regard, we previously showed the presence of two pairs of genetically related cells between lacrimal glands and circulating peripheral blood in a patient with Mikulicz's disease (13). This finding may support the hypothesis that memory B cells or long-lived plasma cells migrate from lacrimal or salivary glands to bone marrow or directly to other target organs.

To detect extra-pancreatic lesions of this disease, several radiologic approaches are recommended. These include gallium-67 (Ga-67) scintigraphy (14), contrast-enhanced computed tomographic (CT) imaging (15), and FDG-PET/CT imaging (16, 17). In the present case, contrast-enhanced CT and FDG-PET/CT were very useful in detecting the renal lesions. However, interstitial nephritis associated with IgG4-related disease is sometimes suspected in patients with AIP with deteriorated renal function without urinary abnor-



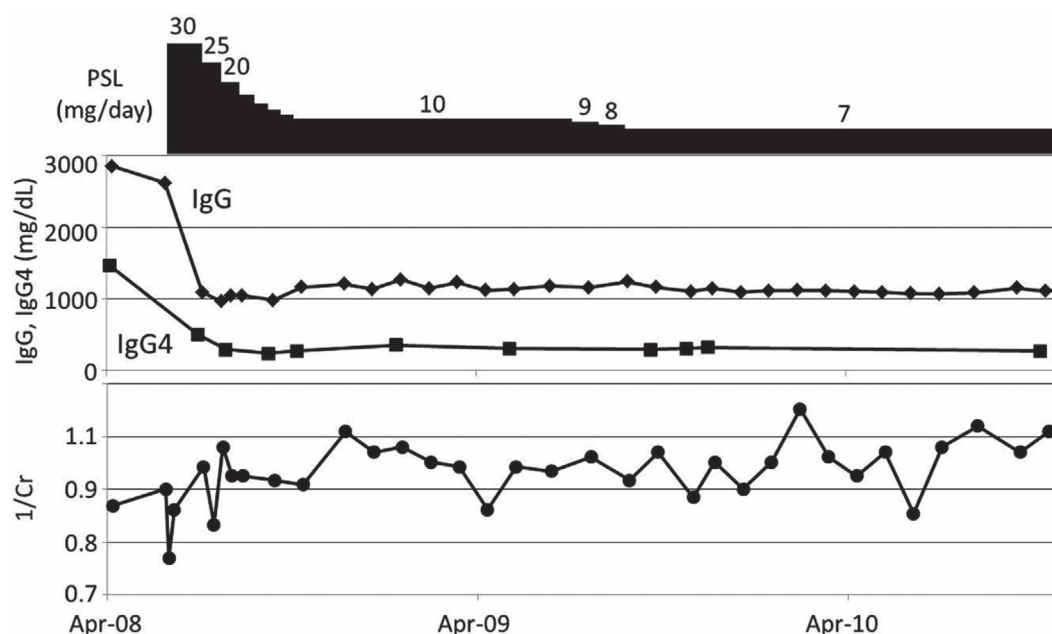


**Figure 4.** Light microscopy findings of the kidney (A-C), immunostaining of IgG4 in renal interstitium (D), light microscopy findings of the liver biopsy specimens (E), and immunostaining of IgG4 in liver parenchyma (F). Severe renal interstitial infiltration of lymphocytes and plasma cells with fibrosis and tubular atrophy were observed (A-C). More than half of the plasma cells infiltrating the interstitium were IgG4-positive (D). Liver biopsy showed diffuse infiltration of lymphocytes and plasma cells in fibrous connective tissue without normal liver architecture (E), and many plasma cells were IgG4-positive by immunostaining (F). [(A) kidney, Periodic acid-Schiff stain, ×40, (B) kidney, Periodic acid-Schiff stain, ×400, (C) kidney, Azan, ×200, (D) kidney, IgG4, ×200, (E) liver, Hematoxylin and Eosin staining, ×200, (F) liver, IgG4, ×400]

malities, and the use of contrast medium in CT should be avoided in such cases. Therefore FDG-PET/CT imaging is a promising tool to detect renal lesions in IgG4-related disease with renal dysfunction.

Hypocomplementemia is a frequently observed characteristic finding in IgG4 related renal disease (4). About 80% of previously reported TIN cases associated with IgG4 related disease had hypocomplementemia. In contrast, Muraki et al reported that 36% of AIP cases have hypocomplementemia (18). This suggests that hypocomplementemia is

closely associated with IgG4-related TIN. In IgG4-related disease, the kidney is the most frequently reported organ in which electron-dense deposits are detected. Cornell et al found electron-dense deposits in the tubular basement membrane (TBM) in four of five IgG4-related TIN cases (19). Only one patient without TBM deposits did not have chronic interstitial fibrotic change. They speculated that immune deposits, which occur after tubular atrophy and interstitial fibrosis, are a late phenomenon of this disease. However, as the relationship between TBM immune deposits and



**Figure 5.** Clinical course of the patient. After steroid administration, serum IgG and IgG4 concentrations decreased, and normal renal function was maintained without recurrence. *Diamonds*, serum IgG (mg/dL); *squares*, serum IgG4 (mg/dL); *circles*, serum creatinine 1/Cr (dL/mg).

hypocomplementemia was not mentioned in their report, whether normal complement levels were limited to the early stage of this disease or not is unclear. The present case had normal complement levels without TBM immune deposits by electron microscopy (EM) and by immunofluorescence (IF), but the light microscopic finding of moderate fibrosis suggested a relatively advanced stage rather than an early stage. Interestingly, two reported cases with normal complement levels also had fibrosis suggestive of chronic change. These findings suggest that marked infiltration of IgG4 positive plasma cells in the interstitium and TBM immune deposits are independent phenomena in the pathogenesis of IgG4-related TIN.

Recently, IgG4-related inflammatory pseudotumor involving a unilateral trigeminal nerve was reported (20). The presenting symptom in this case was left-sided facial numbness. In the present case, although the patient did not have neurological symptoms, and this lesion was not biopsied, the FDG-PET/CT finding suggested that he also had a perineural lesion of IgG4-related disease along the left C6 nerve.

In conclusion, we describe a case of IgG4-related TIN associated with hepatic inflammatory pseudotumor without AIP. The present case suggests that severe TIN can occur without hypocomplementemia, and immune complexes are not always necessary for the pathogenesis of IgG4-related TIN. Further investigations are needed to clarify the etiopathological significance of hypocomplementemia in IgG4-related disease.

**The authors state that they have no Conflict of Interest (COI).**

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