

# Hemochromatosis and Hepatocellular Carcinoma Secondary to Immunoglobulin G4-Related Disease with Hepatopathy: A Case Report

Shintaro Kanaka<sup>1</sup>, Youichi Kawano<sup>2</sup>, Shigeki Yokomuro<sup>2</sup>, Fumihiko Ando<sup>2</sup>,  
Norio Itokawa<sup>3</sup>, Tsutomu Hatori<sup>4</sup>, Koshi Matsumoto<sup>5</sup>, Yoh Zen<sup>6</sup>,  
Masao Miyashita<sup>2</sup> and Hiroshi Yoshida<sup>1</sup>

<sup>1</sup>Department of Surgery, Nippon Medical School, Tokyo, Japan

<sup>2</sup>Department of Surgery, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan

<sup>3</sup>Division of Gastroenterology, Department of Internal Medicine, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan

<sup>4</sup>Department of Clinical Pathology, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan

<sup>5</sup>Department of Pathology, Ebina General Hospital, Kanagawa, Japan

<sup>6</sup>Department of Diagnostic Pathology, Kobe University Graduate School of Medicine, Hyogo, Japan

Immunoglobulin G4-related disease (IgG4-RD) is a recently characterized illness in which lymphocytes and plasma cells infiltrate various anatomical sites. IgG4-hepatopathy, a manifestation of IgG4-RD, is a broader term covering various patterns of liver injury. The clinical course, including the malignant potential of IgG4-RD, remains unclear. Here we report the first case of secondary hemochromatosis and hepatocellular carcinoma (HCC) developing from IgG4-hepatopathy. A 67-year-old man was admitted to our hospital for treatment of deteriorating glucose tolerance. Blood test results showed hypergammaglobulinemia, especially IgG4. He was readmitted 2 months later with dyspnea due to lung disease and pleural effusion, and elevated transaminase levels. He underwent liver and lung biopsies. IgG4-RD was diagnosed and he was treated with steroid therapy, which improved serum IgG4 levels and imaging abnormalities. A follow-up computed tomography (CT) scan conducted 38 months later revealed a tumor (diameter, 50 mm) in liver segments 7 and 8. The resected specimen revealed HCC and abundant siderosis in the background liver, indicating a diagnosis of hemochromatosis. IgG4-positive cells were scarce, probably because of corticosteroid therapy. In the present case, IgG4-RD was well controlled with prednisolone (PSL) and an immunosuppressive agent, and chronic hepatitis was not severe, even though the patient subsequently developed HCC. However, extensive siderosis consistent with hemochromatosis was unexpectedly noted. These findings suggest that secondary hemochromatosis and HCC developed during IgG4-RD with hepatopathy. We believe this case sheds light on IgG4-RD.

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**Key words:** IgG4-related disease, IgG4-hepatopathy, secondary hemochromatosis, hepatocellular carcinoma

## Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently characterized illness in which a massive inflammatory infiltrate rich in IgG4-positive plasma cells and fibrosis affects various organs<sup>1,2</sup>. Its pathophysiology and natural clinical course, including the relationship with

carcinogenesis, are unclear. Herein, we report a case of hemochromatosis and hepatocellular carcinoma (HCC) secondary to IgG4-RD with hepatopathy.

## Case Report

A 67-year-old man was referred to our hospital because

Correspondence to Shintaro Kanaka, Department of Surgery, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan

E-mail: ks32814@nms.ac.jp

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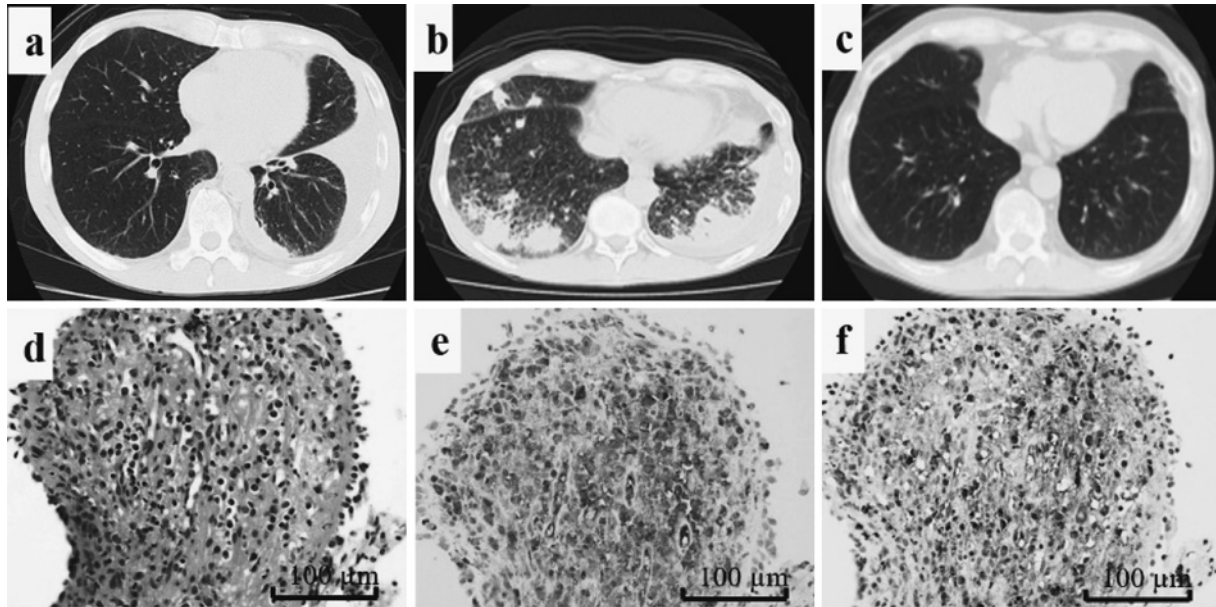


Fig. 1 (a) Thoracic CT at first admission showed left-sided pleural effusion with pleural thickening and atelectasis of the inferior lobe. (b) Thoracic CT at second admission showed bilateral pneumonia and ground-glass opacity and worsening left-sided atelectasis. (c) Pleural CT improved rapidly after mPSL therapy. (d, e, f) Lung biopsy findings. (d) Plasma cells and lymphocyte infiltration in the bronchial wall and alveoli (hematoxylin and eosin (H&E) staining,  $\times 100$ ). (e, f) Immunostaining showed  $>10$  IgG4-positive plasma cells per HPF. The IgG4/IgG ratio was approximately 40%. (e) IgG stain ( $\times 100$ ). (f) IgG4 stain ( $\times 100$ ).

of deteriorating glucose tolerance. He had diabetes that had been treated with the oral antidiabetic agents repaglinide, alogliptin, and pioglitazone for 3 years. Although his serum hemoglobin A1c level had stabilized at around 7.0% during that period, it had increased to 14.1%, in line with a blood glucose level of 486 mg/dL. Diabetic ketoacidosis was diagnosed and he was admitted to our hospital. Blood tests revealed high levels of liver enzymes and globulins, particularly IgG. Chest radiography showed blunting of the left costophrenic sulcus, and CT showed left-sided pleural effusion with pleural thickening and atelectasis of the inferior lobe; however, a concurrent abdominal CT scan showed no abnormalities (Fig. 1a). For diagnostic purposes, we aspirated pleural effusion, which was negative for malignancy but contained many plasma cells. This plasma cell-rich inflammation raised the possibility of IgG4-related pulmonary disease. Additional serological tests confirmed elevated serum IgG4. Immunostaining of a cell block prepared from the pleural effusion also showed many IgG4-positive plasma cells. A diagnosis of lung disease was not established because of the lack of a biopsy, and he was discharged when his blood glucose concentration improved after insulin therapy.

The patient was readmitted to our hospital 2 months later with respiratory distress and fatigue. Results of arte-

rial blood testing are shown in Table 1. Chest CT revealed deterioration of pulmonary abnormalities, with bilateral consolidation and ground-glass opacity, left-sided atelectasis, and enlarged mediastinal lymph nodes (Fig. 1 b). Transbronchial lung biopsy demonstrated infiltration of plasma cells and lymphocytes in the bronchial wall and alveolar septa. Immunostaining revealed  $>10$  IgG4-positive plasma cells per high-power field (HPF) (Fig. 1d, e, f). He also underwent a liver biopsy because of liver dysfunction. Microscopically, the liver was moderately fibrotic, and periportal and bridging fibrosis was observed. Portal tracts were densely infiltrated by lymphocytes and plasma cells with mild interface hepatitis (Fig. 2a, b). Immunostaining showed many IgG4-positive plasma cells ( $>10$  IgG4-positive cells per HPF) and an IgG4/IgG-positive cell ratio of 50% to 60% (Fig. 2c, d). No iron deposition was present in liver specimens. Additionally, dysarthria and left-sided hemiplegia occurred during hospitalization. CT revealed no obvious abnormalities, but magnetic resonance imaging (MRI) showed thickening of the meninges, which is consistent with hypertrophic pachymeningitis and a characteristic of IgG4-RD in the central nervous system (CNS). A retrospective comparison of CT images before and after steroid therapy showed a decrease in pancreatic tail thickness, suggesting that the deterioration in glucose tolerance might

Table 1 Arterial blood test on second visit

Blood gas		Biochemistry	
pH	7.494	CRP	4.8 mg/dL
pO <sub>2</sub>	61.5 mmHg	IgG	7,329 mg/dL
pCO <sub>2</sub>	31.3 mmHg	IgG4	3,510 mg/dL
HCO <sub>3</sub>	25.2 mmol/L	AST	105 U/L
BE	2.8 mmol/L	ALT	106 U/L
		γGT	322 U/L
Hematology		ALP	790 IU/L
WBC	13,000 /μL	AMY	27 IU/L
RBC	448×10 <sup>4</sup> /μL	ANA	1:80
Hb	11.9 g/μL	AMA	1:20
Plt	20.9×10 <sup>4</sup> /μL	Virus marker	(-)

pH: potential of hydrogen  
pO<sub>2</sub>: partial pressure of oxygen  
pCO<sub>2</sub>: partial pressure of carbon dioxide  
BE: base excess  
WBC: white blood cell  
RBC: red blood cell  
Hb: hemoglobin  
Plt: platelet  
CRP: C-reactive protein  
AST: aspartate aminotransferase  
ALT: alanine aminotransferase  
γGT: gamma-glutamyl transpeptidase  
ALP: alkaline phosphatase  
AMY: amylase  
ANA: antinuclear antibody  
AMA: antimitochondrial antibodies

have been partly due to autoimmune pancreatitis (AIP). On the basis of these findings, we diagnosed IgG4-RD with manifestations in the lungs, pleura, liver, CNS, and pancreas. He was treated with steroid pulse therapy (500 mg methylprednisolone [mPSL] daily by intravenous drip for 3 days), to address respiratory failure, followed by 20 mg/day of prednisolone (PSL), which improved his symptoms and imaging and laboratory results (Fig. 1 c, 3).

PSL was slowly tapered to 10 mg/day, with no relapse over the next 2 years; however, he then returned to hospital with fatigue and nausea. Blood test results were WBC, 14,660/μL; Hb, 14.7 g/dL; PLT, 11.3 × 10<sup>4</sup>/μL; IgG, 1,388 mg/dL; IgG4, 739 mg/dL; AST, 42 IU/L; and ALT, 50 IU/L. CT and endoscopy showed no abnormalities. We suspected that his symptoms might be due to worsening IgG4-RD and added an immunosuppressive agent to PSL as diagnostic therapy. After that, serum IgG and IgG4 levels remained around 100 to 200 mg/dL after discharge (Fig. 3). A follow-up CT, 14 months later, showed a 50-mm tumor in liver segments 7 and 8 (S7/8). The tumor was nonuniformly hyperattenuated in the early

phase, washed-out immediately, and showed faint enhancement in the late phase (Fig. 4a, b). MRI using gadolinium ethoxybenzyl-diethylenetriamine pentaacetic acid showed a well-defined solitary tumor that was enhanced in the early phase and washed-out in the late phase (Fig. 4c). Protein induced by vitamin K absence or antagonist-II (PIVKA II) was elevated (1,255 mAU/mL; normal range, 4-108 mg/dL), but all other tumor markers, including alpha-fetoprotein, were within normal limits. These findings suggested HCC, but a benign IgG4-related lymphoplasmacytic inflammatory pseudotumor was also a possibility. We performed a liver biopsy, which confirmed the diagnosis of HCC.

The patient underwent liver resection of the right paramedian sector 1 month later. Pathologically, the tumor consisted of atypical hepatocytes arranged in a thin trabecular pattern, consistent with moderately differentiated HCC (Fig. 4d). The background liver showed multiple bridging fibrosis and mild, focal portal inflammation. At the first liver biopsy, the liver was moderately fibrotic, and periportal and bridging fibrosis was graded as F1 on the New Inuyama classification. However, at the time of

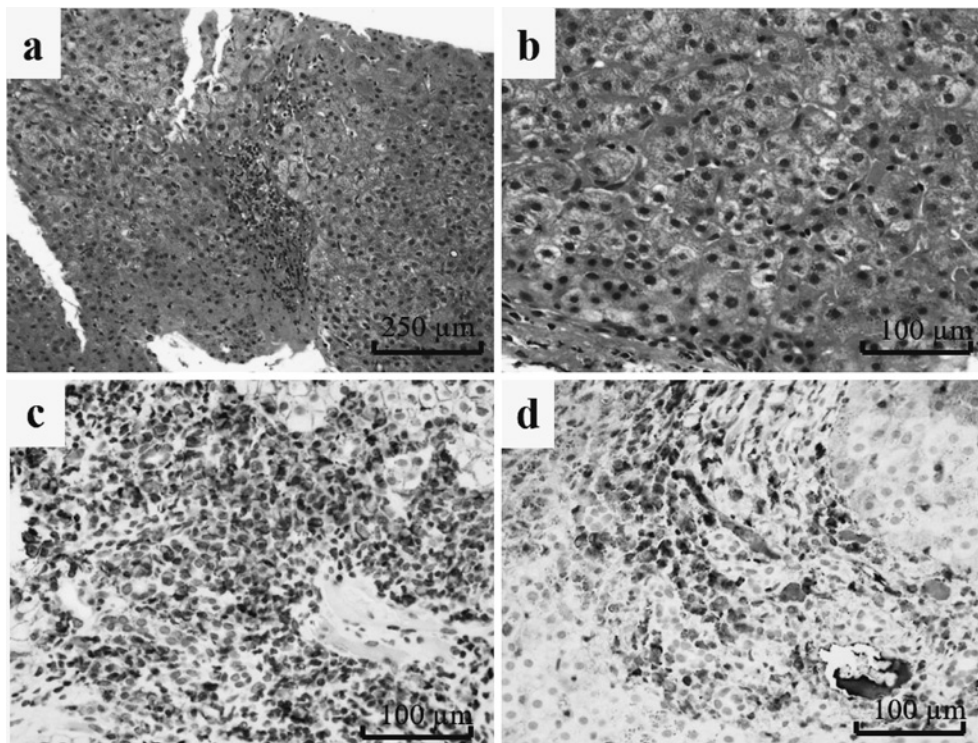


Fig. 2 Liver biopsy findings. (a) Bridging fibrosis and interface hepatitis (H&E stain,  $\times 40$ ). (b) Incomplete hepatocyte rosette formation (H&E stain,  $\times 100$ ). (c, d) More than 10 IgG4-positive cells were observed per high power field and almost 50% to 60% of IgG-positive cells were IgG4-positive plasma cells. (c) IgG stain ( $\times 100$ ). (d) IgG4 stain ( $\times 100$ ).

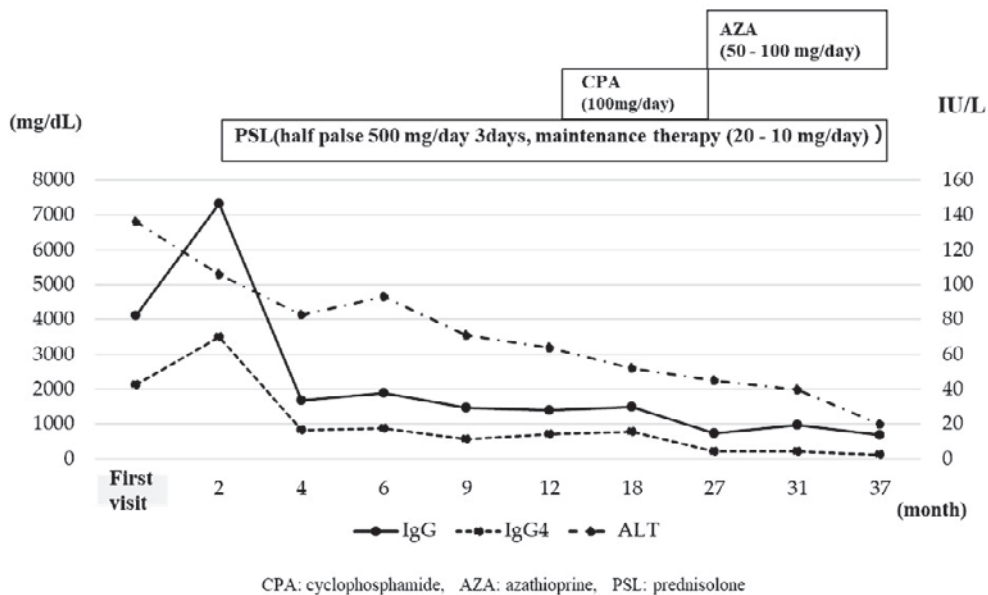


Fig. 3 Serum IgG, IgG4, and ALT levels during the patient's clinical course.

surgery, the background liver showed multiple sites of bridging fibrosis, which was graded as F2. Immunostaining showed a small number of IgG4-positive cells, and hepatocytes contained brown granules suggesting underlying hemochromatosis (Fig. 4e, f). After surgery, blood

tests revealed a ferritin level of 3,388.7 ng/mL (normal range, 21.0-282.0 ng/mL). The patient had no family history of hemochromatosis, and the first liver biopsy had not revealed iron deposition. We ultimately concluded that hemochromatosis and HCC were secondary to IgG4-

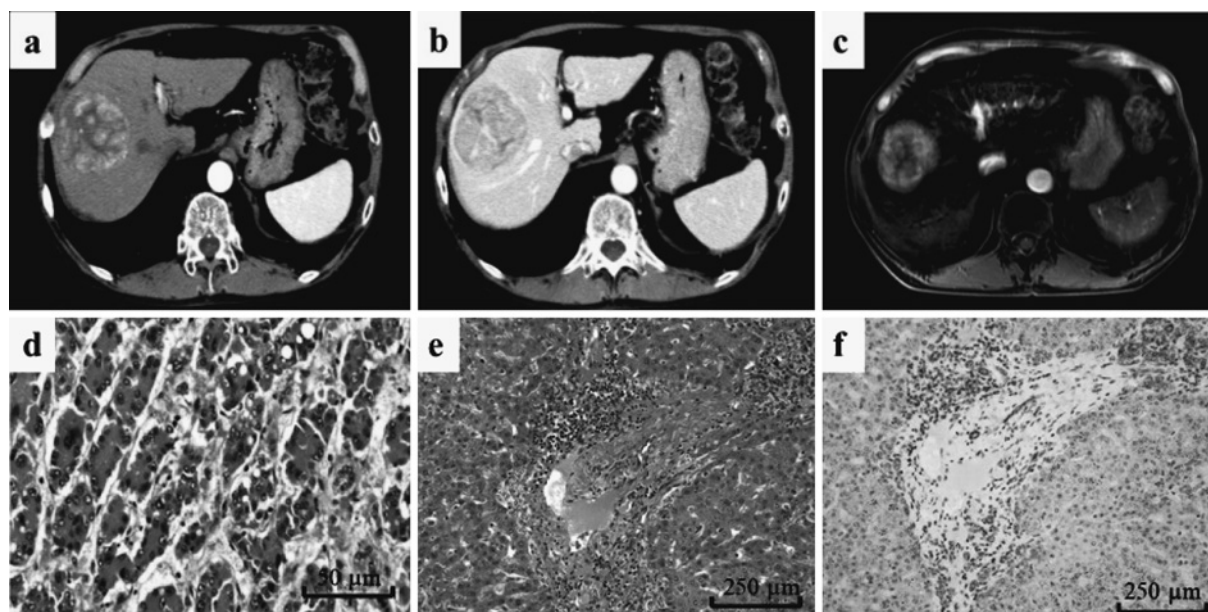


Fig. 4 (a, b) CT showing a 50-mm tumor in S7/8. The tumor was nonuniformly hyperattenuated in the early phase, washed-out immediately, and showed faint enhancement in the late phase. (c) MRI showed a well-defined tumor that was enhanced in the early phase. (d, e, f) Pathological findings. (d) Pathologically, the patient was diagnosed with well- and/or moderately differentiated HCC. Multinuclear atypical epithelial cells with abundant eosinophilic cytoplasm were arranged in a cord-like pattern with partial necrosis (H&E stain,  $\times 200$ ). (e) The remaining hepatic tissue showed multiple site of bridging fibrosis and mild, focal portal inflammation (H&E stain,  $\times 40$ ). (f) Immunostaining showed a small number of IgG4-positive cells. Hepatocytes also contained brown granules. IgG4 stain ( $\times 40$ ).

hepatopathy. The patient died of multiple recurrences of HCC, 1 year later.

### Discussion

This case indicates that hemochromatosis and HCC can develop during IgG4-RD with hepatopathy. IgG4-RD is newly characterized illness in which a massive inflammatory infiltrate rich in IgG4-positive plasma cells and fibrosis affects various organs. However, its pathophysiology is unclear. The most common site of IgG4-RD is the pancreas, followed by the salivary glands, kidneys, lacrimal glands, and aorta<sup>3</sup>. Sclerosing cholangitis, cholecystitis, lymphoplasmacytic inflammatory pseudotumor, and microscopic liver injury are part of the IgG4-RD spectrum of hepatobiliary tract disorders<sup>4,5</sup>. IgG4-related liver injury has been described as IgG4-auto immune hepatitis (IgG4-AIH), which resembles classic AIH, except for elevation in serum and tissue IgG4 levels, or as IgG4-hepatopathy, which is a broader entity that encompasses various microscopic changes (e.g., portal inflammation, lobular injury, cholestasis) and is related to systemic IgG4-RD<sup>6</sup>.

In 2016, Nakanuma et al.<sup>5</sup> proposed new diagnostic criteria for IgG4-related AIH. They suggested that, by using

the IAIHG scoring system, AIH could be classified as definite or probable<sup>7</sup>. IgG4-related AIH could be definitively diagnosed if patients met four conditions: (1) serum IgG4 concentration  $\geq 135$  mg/dL; (2)  $\geq 10$  IgG4-positive cells per HPF in liver tissue; (3) chronic hepatitis with zonal and bridging necrosis or broad collapse; and (4) metachronous or synchronous association with other organ manifestations of IgG4-RD. Our patient had an IAIHG score of 17, indicating definite AIH. However, his specimen revealed no zonal necrosis and no interface hepatitis, and lobular injury was less conspicuous than in typical AIH, although he met three of the four criteria. Furthermore, a recent clinicopathological analysis identified IgG4-AIH as a subtype of AIH rather than as a hepatic manifestation of systemic IgG4-RD<sup>8</sup>. We therefore feel that the diagnostic term IgG4 hepatopathy is more appropriate for the present case.

Steroids are an effective treatment for IgG4-RD symptoms. The present patient's symptoms deteriorated when mPSL was slowly tapered to 10 mg daily. There are no guidelines for treating PSL-resistant IgG4-RD<sup>9</sup>, and the combination of steroids and immunosuppressive agents for PSL-resistant IgG4 is controversial<sup>10</sup>. The efficacy of rituximab as a chimeric IgG1 monoclonal antibody against

CD20 has been studied<sup>11</sup>. Although rituximab is not currently approved for IgG4-RD in Japan, it might be useful in patients whose symptoms are difficult to control with corticosteroids or who have a long history of diabetes. In the present case, IgG4-RD was well controlled after addition of the immunosuppressive agent—even though he later developed HCC—as indicated by the lack of dense inflammatory infiltrate in the resected liver tissue. However, extensive siderosis consistent with hemochromatosis was unexpectedly noted.

Hemochromatosis is classified by cause as hereditary (HH) and secondary. Secondary hemochromatosis can occur after ineffective erythropoiesis, such as in myelodysplastic syndrome (MDS) or aplastic anemia, in patients who have received a large number of erythrocyte transfusions, in chronic hepatitis from nonalcoholic steatohepatitis (NASH), or in hepatitis C and cirrhosis<sup>12</sup>. HCC develops in approximately 30% of HH cases<sup>13</sup>. However, there have been only five reported cases of HCC developing in patients with secondary hemochromatosis<sup>14,15</sup>. Recent case studies of hepatitis C and NASH reported that even when liver damage was mild, iron absorption and iron deposition on hepatocytes was excessive, resembling that of secondary hemochromatosis<sup>16-18</sup>. Furthermore, some reports indicate that such hepatic iron overload might induce HCC<sup>19</sup>. If there is a relationship between IgG4-hepatopathy and iron overload, such as in hepatitis C or NASH, HCC might have developed from IgG4-hepatopathy.

The relationship between IgG4-RD and carcinogenesis is unclear. Some reports have suggested that pancreatic carcinoma could develop from AIP, and various carcinomas developed in IgG4-RD patients during long-term follow-up<sup>20</sup>. IgG4 has a role in cancer inflammation<sup>21</sup>. One hypothesis holds that cancer could become a trigger for IgG4-RD, as in paraneoplastic syndrome<sup>22,23</sup>. Although evidence is limited, IgG4-hepatopathy might be related to HCC.

### Conclusion

We presented a rare case of hemochromatosis and HCC that developed during the clinical course of IgG4-related disease. Further studies are needed in order to clarify the clinical course of IgG4-related disease.

**Conflict of Interest:** The authors have no financial or institutional interest to declare in relation to the content of this article.

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