Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9818-17
Intern Med 57: 1725-1732, 2018
http://internmed.jp

【 CASE REPORT 】

Autoimmune Hemolytic Anemia Obscured by the Obstructive Jaundice Associated with IgG4-related Sclerosing Cholangitis in a Patient with Type 1 Autoimmune Pancreatitis: A Case Report and Review of the Literature

Michihiro Yoshida[1], Yoshiaki Marumo[2], Itaru Naitoh[1], Kazuki Hayashi[1], Katsuyuki Miyabe[1], Yuji Nishi[1], Yasuaki Fujita[1], Naruomi Jinno[1], Yasuki Hori[1], Makoto Natsume[1], Akihisa Kato[1], Shinsuke Iida[2] and Takashi Joh[1]

Abstract:
Type 1 autoimmune pancreatitis (AIP) is a pancreatic manifestation of IgG4-retated disease that is often associated with IgG4-related sclerosing cholangitis (IgG4-SC). Autoimmune hemolytic anemia (AIHA) is an immune-related disease that causes hemolytic anemia. Although type 1 AIP/IgG4-SC and AIHA have a shared etiology as a presumed autoimmune disease, they rarely overlap, and their association has not been clarified. Secondary AIHA might not be diagnosed appropriately because the obstructive jaundice observed in type 1 AIP/IgG4-SC can obscure the presence of hemolytic jaundice. We herein report a case of type 1 AIP/IgG4-SC overlapping with secondary AIHA along with a review of the literature.

Key words: autoimmune pancreatitis (AIP), autoimmune hemolytic anemia (AIHA), IgG4-related disease (IgG4-RD), IgG4-related sclerosing cholangitis (IgG4-SC)

(Intern Med 57: 1725-1732, 2018)
(DOI: 10.2169/internalmedicine.9818-17)

Introduction

Type 1 autoimmune pancreatitis (AIP) is recognized as an inflammatory disease. The characteristic clinical features of type 1 AIP include an increased serum IgG4 level and the frequent presence of obstructive jaundice with pancreatic swelling and ductal stricture, which is supported by histological evidence of a lymphoplasmacytic infiltration and fibrosis, with a dramatic response to steroid therapy (1-3). Type 1 AIP is the pancreatic manifestation of IgG4-related disease (IgG4-RD), and type 1 AIP is often associated with IgG4-related sclerosing cholangitis (IgG4-SC). In patients with type 1 AIP, various diseases have been reported as other organ involvement of IgG4-RD (4, 5).

Autoimmune hemolytic anemia (AIHA) is a group of disorders caused by a malfunction of the immune system, which leads to the production of autoantibodies that harm red blood cells (6, 7). Patients with hemolytic anemia often present with jaundice in addition to anemia. The direct Coombs test establishes the diagnosis and may suggest the cause. However, while AIHA and type 1 AIP have a shared etiology as a presumed autoimmune disease, they rarely overlap clinically, and the association between AIHA and IgG4-RD has not been clarified. To the best of our knowledge, there are only three case reports indicating an association between AIHA and type 1 AIP/IgG4-SC. Jaundice is observed both in patients with obstructive jaundice caused by type 1 AIP/IgG4-SC and in patients with hemolytic jaundice caused by AIHA. Secondary AIHA might not be appro-

[1]Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Japan and [2]Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, Japan
Received: July 13, 2017; Accepted: August 17, 2017; Advance Publication by J-STAGE: December 21, 2017
Correspondence to Dr. Itaru Naitoh, inaito@med.nagoya-cu.ac.jp

Table 1. Laboratory Findings.

		Initial presentaion	8 months after tapering PSL	2 months after re-escalation of PSL
WBC	(/μL)	9,300	12,400	10,100
RBC	($\times10^4$/μL)	346	200	449
Hb	(g/dL)	10.5	7.0	14.4
MCV	(fL)	89.3	104.5	95.5
Reticulocytes	(‰)	n.d.	104	15
Haptoglobin	(mg/dL)	n.d.	<3	220
Platelets	($\times10^4$/μL)	50.9	62.3	33.4
AST	(U/L)	90	63	24
ALT	(U/L)	70	58	34
LDH	(U/L)	180	316	182
ALP	(U/L)	806	936	431
γGTP	(U/L)	48	176	69
T-bil	(mg/dL)	14.6	3.3	0.7
D-bil	(mg/dL)	9.9	2.1	0.2
AMY	(U/L)	59	55	70
Lipase	(U/L)	59	23	16
CRP	(mg/dL)	0.81	3.68	0.24
IgG	(mg/dL)	3,247	4,023	1,627
IgG4	(mg/dL)	1,230	1,790	473

Direct Coombs test	(+)
Specificity	C3d, IgG
Indirect Coombs test	(+)
Cold agglutinin	1:32
ANA	(-)
Cryoglobulin	(-)

Alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AMY: amylase, ANA: antinuclear antibody, AST: aspartate aminotransferase, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, CRP: C-reactive protein, D-bil: direct bilirubin, GLU: glucose, γGTP: γ-glutamyltransferase, LDH: lactate dehydrogenase, MCV: mean corpuscular volume, n.d.: no data, PSL: prednisolone, RBC: red blood cells, T-bil: total bilirubin

priately diagnosed because obstructive jaundice can obscure the presence of hemolytic jaundice. We herein report a case of type 1 AIP overlapping with secondary AIHA along with a review of the literature.

Case Report

A 72-year-old man with fatigue was found to have diffuse enlargement of the pancreas with obstructive jaundice [total bilirubin (T-bil), 14.6 mg/dL; direct bilirubin (D-bil), 9.9 mg/dL] in an affiliated hospital. He was referred to our university hospital for further examination and treatment. The patient's blood test results are shown in Table 1. The serum IgG4 level was elevated (1,230 mg/dL), and computed tomography (CT) showed diffuse enlargement of the pancreas with a capsule-like rim without dilation of the pancreatic duct (Fig. 1a). Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) showed a stricture of the distal common bile duct with dilation of the upstream bile duct and segmental narrowing of the main pancreatic duct (MPD) in the head of the pancreas (Fig. 1b-d). Endoscopic retrograde biliary drainage (ERBD) was then performed with a plastic stent. Endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) was performed to obtain pancreatic tissue, the pathological examination of which showed the presence of lymphoplasmacytic infiltration with fibrosis (Fig. 2a). Immunohistochemical staining showed abundant IgG4-positive plasma cells (≥20 positive cells/HPF) (Fig. 2b). These findings resulted in the diagnosis of type 1 AIP with IgG4-SC (type 1), according to the International Consensus Diagnostic Criteria (ICDC) (3). The administration of prednisolone (PSL) (30 mg/day) improved the pancreatic swelling, segmental narrowing of the MPD, and the distal biliary stricture on CT and ERCP, and the serum IgG4 level decreased significantly to 467 mg/dL. The ERBD stent was removed, and the PSL dose was then gradually tapered.

Although constant follow-up observation confirmed a good clinical course with the dose of PSL reduced to 5 mg/day, the patient's bilirubin level became elevated (T-bil, 4.1

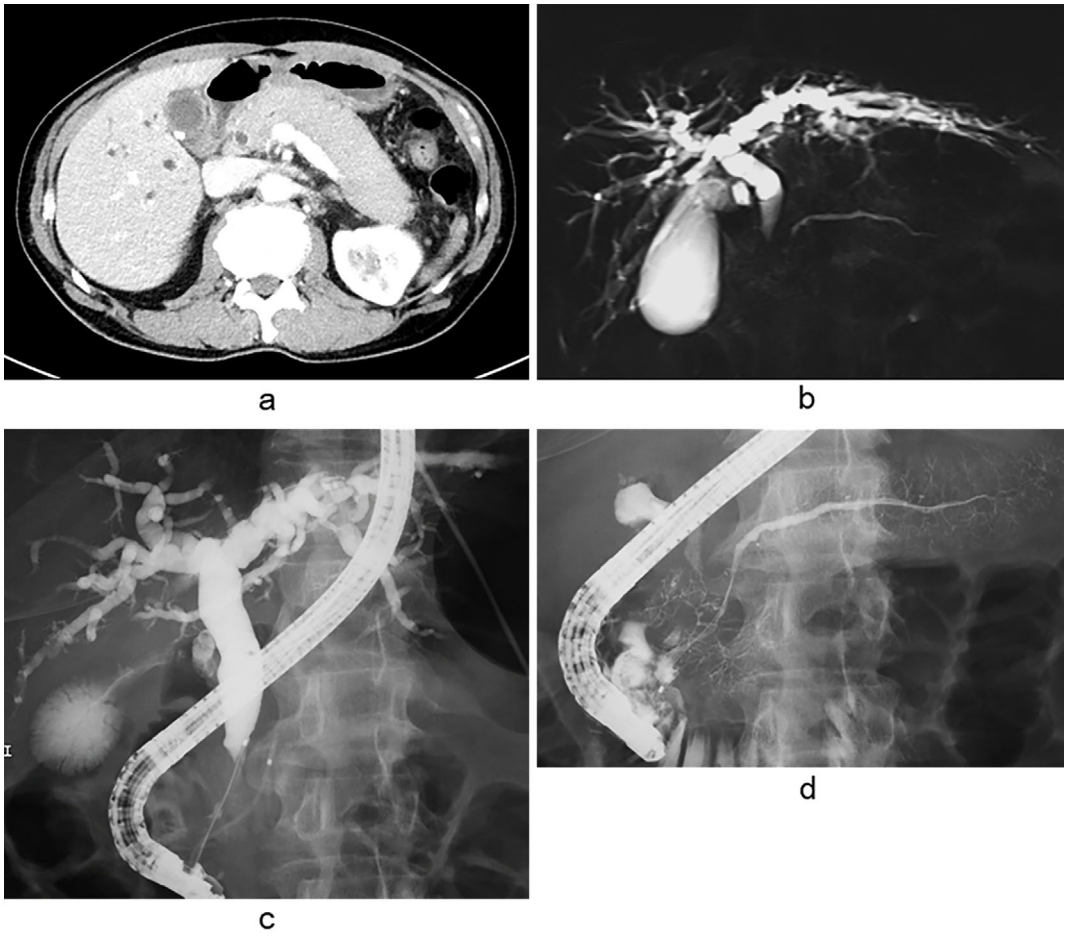

Figure 1. **Images obtained before treatment. (a) Computed tomography (CT) shows a bulky pancreas with a capsule-like rim without dilation of the pancreatic duct. (b) Magnetic resonance cholangiopancreatography (MRCP) shows a distal stricture of the common bile duct with dilation of the upstream bile duct. The main pancreatic duct of the pancreatic head is not detected. (c, d) Endoscopic retrograde cholangiopancreatography (ERCP) shows a distal stricture of the common bile duct with dilation of the upstream bile duct and segmental constriction of the main pancreatic duct at the head of the pancreas. The pancreatic duct at the tail side is not dilated.**

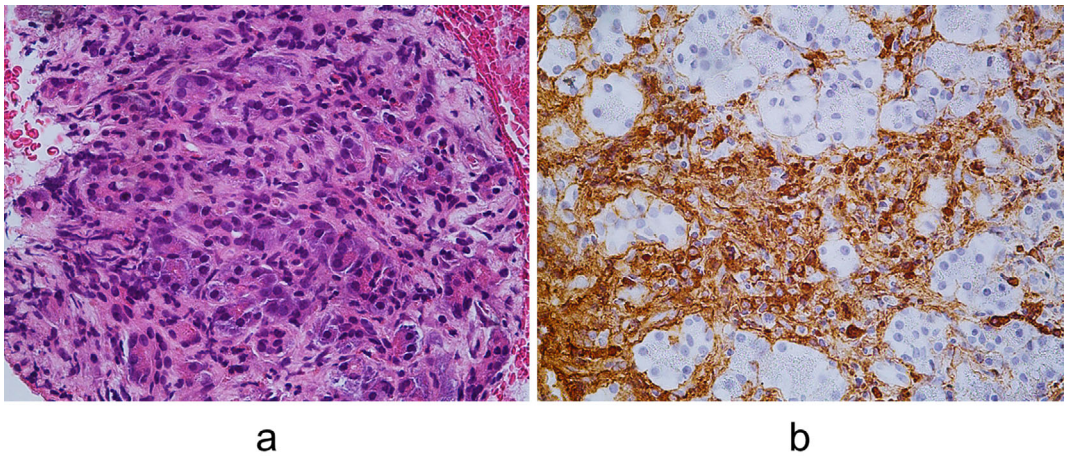

Figure 2. **Pathological images of pancreatic tissue specimens obtained by EUS-FNA. (a) Hematoxylin and Eosin staining shows the presence of lymphoplasmacytic infiltration (Original magnification, ×400). (b) IgG4-immunohistochemical staining shows abundant IgG4-positive plasma cells (≥20 positive cells/HPF) (Original magnification, ×400).**

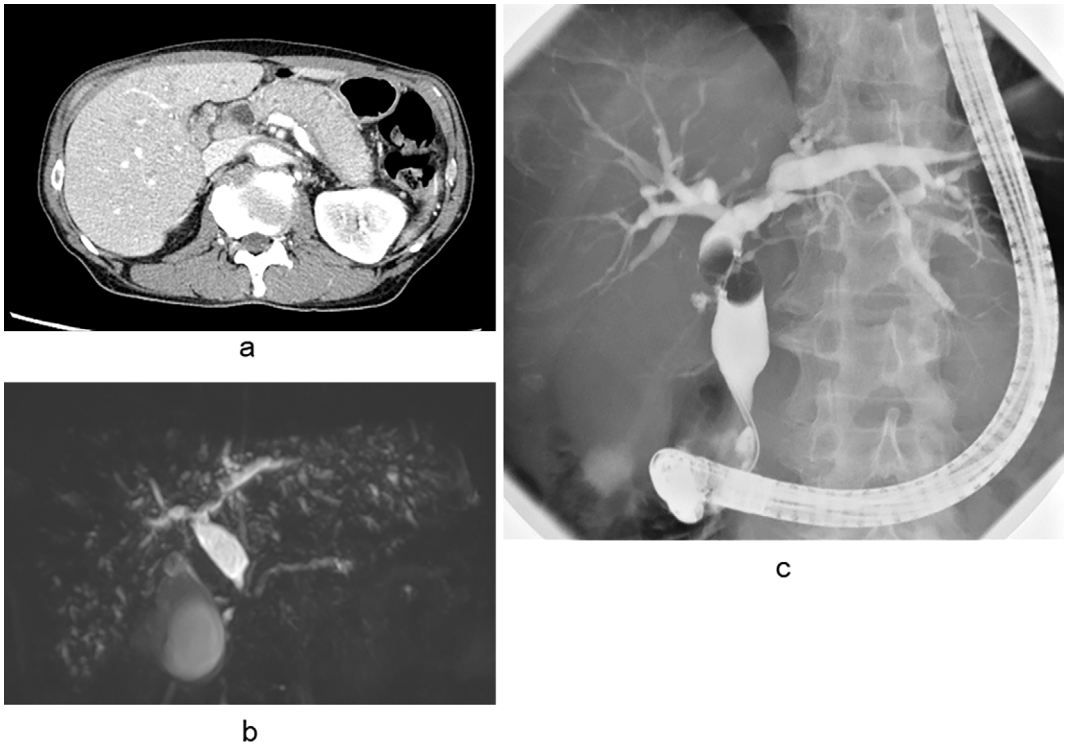

Figure 3. Images obtained at 8 months after tapering prednisolone treatment. (a) CT shows a bulky pancreas with a capsule-like rim without dilation of the pancreatic duct, as seen previously. (b) MRCP shows a distal stricture of the common bile duct with dilation of the hilar bile duct. In addition, the intrahepatic bile duct shows multiple strictures. (c) ERCP shows a distal stricture of the common bile duct with dilation of the hilar bile duct. Moreover, the intrahepatic bile duct shows multiple sclerotic changes with mild strictures.

mg/dL; D-bil, 2.6 mg/dL) and the patient reported general fatigue at eight months after the initial diagnosis of type 1 AIP. The patient's serum IgG4 level had again increased (1,790 mg/dL), and multiple images showed a relapse of the diffuse pancreatic enlargement and lower biliary stricture (Fig. 3a and b). In addition, multiple strictures of the intrahepatic bile duct without prestenotic dilation were observed on ERCP, and the cholangiogram was classified as type 2b IgG4-SC according to the cholangiographic classification proposed by Nakazawa et al. (8), which was not observed at the initial diagnosis (Fig. 3c). Although ERBD with a biliary plastic stent was performed again, the bilirubin level remained high (T-bil, 3.3 mg/dL; D-bil, 2.1 mg/dL) and the anemia progressed. His complete blood counts showed a macrocytic anemia [Hb, 7.0 g/dL; mean corpuscular volume (MCV), 104.5 fL] with a marked increase in reticulocytes (104 ‰). The laboratory data revealed an elevated lactate dehydrogenase level (316 U/L) and a low haptoglobin level (<3 mg/dL), which indicated hemolysis (Table 1). On subsequent examinations a direct Coombs test was positive with C3d and IgG specificity and the cold agglutinin titer was negative (1:32), resulting in a diagnosis of warm AIHA. Bone marrow aspiration was performed to exclude myeloproliferative disorders, and showed erythroid hyperplasia (M/E ratio, 1.0) with no blast or plasma cell proliferation (Fig. 4a and b).

The administration of PSL (20 mg) gradually improved not only the pancreatic swelling and biliary strictures (Fig. 5), but also the anemia, without blood transfusion. The ERBD stent was removed after the improvement of the biliary strictures. The slower tapering of PSL was continued, with the bilirubin (T-bil, 0.7 mg/dL; D-bil, 0.2 mg/dL) and Hb (14.4 g/dL) levels remaining within the normal ranges (Table 1).

Discussion

AIP is currently classified into two distinct clinical profiles by the ICDC: type 1 and type 2 (3). Type 1 AIP is considered to be a pancreatic manifestation of a novel clinical and pathophysiological entity called 'IgG4-RD'. Type 1 AIP cases usually show a favorable response to steroid therapy. Type 1 AIP is recognized as an autoimmune disease and is often associated with systemic disorders. Other organ involvement is also observed in patients with type 1 AIP and is sometimes a clue to the diagnosis of type 1 AIP (4). Most cases are clinically detected based on a physical examination or CT/MRI imaging. In the current case, the patient-who fulfilled the ICDC criteria-was first diagnosed with type 1 AIP. Eight months after the initial diagnosis followed by the tapering of PSL, type 1 AIP relapsed with the new entity of IgG4-SC, which is one of the IgG4-RDs. Al-

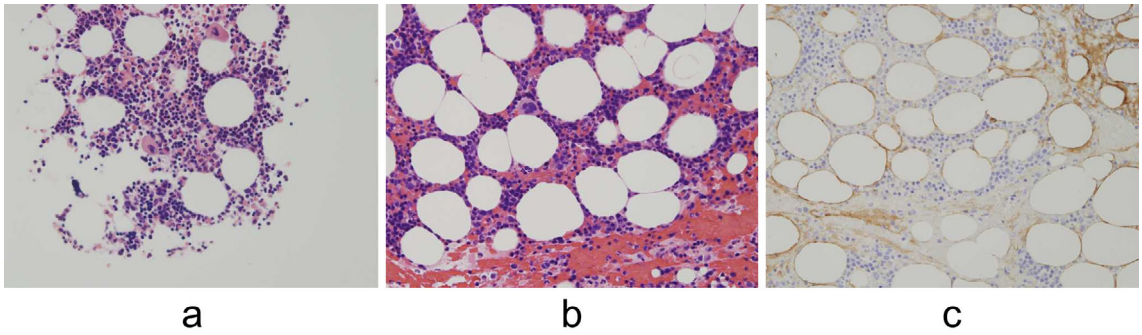

Figure 4. **Pathological images of a bone marrow specimen obtained by bone marrow aspiration. (a, b) Hematoxylin and Eosin staining shows erythroid hyperplasia (M/E ratio, 1.0) with no blast or plasma cell proliferation (Original magnification; a ×100, b ×400). (c) IgG4- Immunohistochemical staining shows no IgG4-positive plasma cells (Original magnification, ×400).**

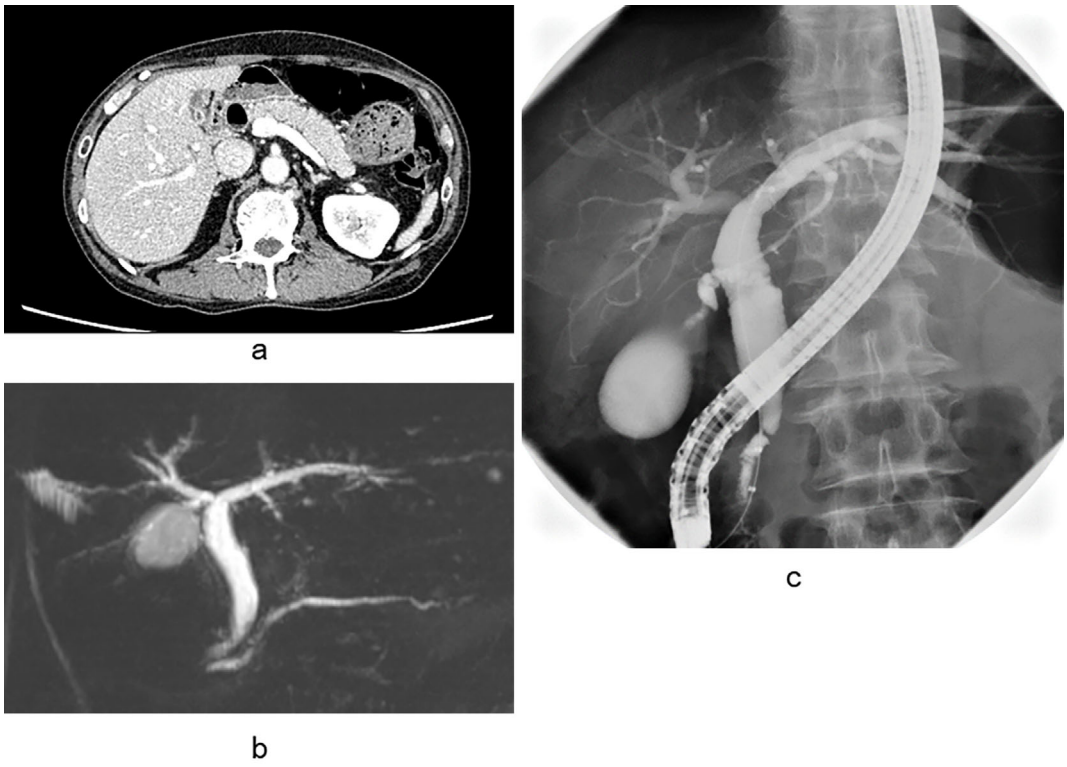

Figure 5. **Images obtained with the re-escalation of the prednisolone dose. (a) CT shows a shrinking pancreas without dilation of the pancreatic duct. (b) MRCP and (c) ERCP show the marked improvement of distal stricture of the common bile duct and multiple sclerotic changes of the intrahepatic bile.**

though positron emission tomography-CT (PET-CT) scanning was not performed, no other organ involvement (*e.g.*, salivary gland disease, orbital disease, or retroperitoneal fibrosis) was observed on CT/MRI or a physical examination. On the other hand, progressive anemia was newly detected, which was diagnosed as secondary AIHA.

AIHA can be associated with not only immune-related diseases (*i.e.,* systemic lupus erythematosus, autoimmune lymphoproliferative syndrome, and common variable immune deficiency) but also hematologic diseases [*i.e.,* chronic lymphocytic leukemia (9)]. In the current case, bone marrow aspiration was performed, which denied a diagnosis of leukemia.

We needed to clarify the possibility of drug-induced immune hemolytic anemia (DIIHA). Cefotetan, ceftriaxione, and pileracillin are most frequently associated with DIIHA; however, many drugs are also listed as causative agents of DIIHA (10, 11). We could exclude DIIHA based on the clinical course, and because the patient did not take any drugs that are suspected to be associated with DIIHA.

Clinical observation revealed that our patient's hemolysis was not precipitated by exposure to cold. Moreover, the Coombs test was performed at 37°C. We confirmed that a direct Coombs test was positive with C3d and IgG specific-

Table 2. Reported Cases of AIHA with Type 1 AIP/IgG4-SC.

Reference	SEX	Age (y)	AIP	IgG4-SC	IgG (mg/dL)	IgG4 (mg/dL)	T-bil (mg/dL)	D-bil (mg/dL)	Hb (g/dL)	Clinical course to diagnosis	Time after AIP/IgG4-SC diagnosis (months)	Treatment	Response to treatment
					At time AIP/IgG4-SC diagnosed								
					At time AIHA diagnosed								
(12)	M	52	○	none	1,920	n.d	13.5	n.d	6.4	Coincident	0	PSL (100 mg) Cyclophosphamide (100 mg)	good
					-	-	-	-	-				
(13)	M	70	○	type 1	3,256	175	6.5	5.1	16.0	Type 1 AIP + type 1 IgG4SC → AIHA	40	PSL (30 mg)	good
					2,965	341	1.9	0.3	9.3				
(14)	M	73	-	type 4	1,800	230	0.4	0.2	12.9	type 4 IgG4-SC → AIHA	3	PSL (60 mg)	good
					1,660	n.d	4.2	3.6	4.1				
Present case	M	72	○	type 2b	3,247	1,230	14.6	9.9	10.5	Type 1 AIP + type 1 IgG4-SC → AIHA + type 2b IgG4-SC	8	PSL (20 mg)	good
					4,023	1,790	4.1	2.6	7				

AIHA: autoimmune hemolytic anemia, AIP: autoimmune pancreatitis, D-bil: direct bilirubin, IgG4-SC: IgG4-related sclerosing cholangitis, n.d: no data, PSL: prednisolone, T-bil: total bilirubin

ity. We also confirmed that the cold agglutinin titer was negative. These results led to the diagnosis of warm AIHA, rather than cold agglutinin disease (CAD). Splenomegaly and thrombopenia were not observed; thus, we could exclude idiopathic thrombocytopenic purpura (ITP). Evans' syndrome, which is a combination of AIHA and ITP, was thus excluded. The current case showed a good response to steroid therapy, which resulted in a recovery from anemia. However, we confirmed that the direct Coombs test remained positive at 13 months after the diagnosis of secondary AIHA and the subsequent treatment, which indicated that this case could be classified as chronic AIHA.

Although both type 1 AIP/IgG4-SC and AIHA have a shared etiology as presumed autoimmune diseases, to the best of our knowledge, there are only three case reports indicating an association between type 1 AIP/IgG4-SC and secondary AIHA (12-14). The previous reports describing patients with type 1 AIP/IgG4-SC and secondary AIHA are summarized in Table 2. This review, which consisted of four cases (including the current case) showed the following. All of the patients were male; the mean age was 67 years. Among the four AIHA patients, three had comorbid type 1 AIP, and three had IgG4-SC. One was diagnosed as coincidentally having both type 1 AIP and AIHA. Three were initially diagnosed as having type 1 AIP/IgG4-SC. Secondary AIHA was newly diagnosed with clinical symptoms, which included severe anemia at 3-40 months after the diagnosis of type 1 AIP. In addition, two cases of type 1 AIP/IgG4-SC were followed over time without steroid maintenance therapy when secondary AIHA was diagnosed. Steroid therapy was administered for the treatment of secondary AIHA in all 4 patients, which resulted in good responses, with the recovery of anemia. These findings indicate that we need to be aware of the possible association of type 1 AIP/IgG4-SC and secondary AIHA, not only at the time of the initial diagnosis of type 1 AIP/IgG4-SC, but also during follow-up.

The retrospective review of the clinical course of the current case revealed data that were overlooked at the initial diagnosis of type 1 AIP (Fig. 6). At the time when this patient suffered from obstructive jaundice due to type 1 AIP, the anemia itself had already slightly progressed before the administration of PSL. We suspect that AIHA might have already developed at the time of the initial diagnosis of type 1 AIP. On reflection, we identified two reasons for the delayed diagnosis. One was obstructive jaundice. Hemolytic anemia is often found with jaundice as well as anemia; however, the underlying diseases that cause jaundice followed by nonspecific clinical symptoms like 'general fatigue' might obscure the presence of hemolytic jaundice. Theoretically, hemolytic jaundice can be distinguished from obstructive jaundice based on the proportion of bilirubin. However, the ratio of D-bil in T-bil is influenced by both hemolytic and obstructive jaundice. Thus, the proportion is not helpful for diagnosing hemolytic jaundice in patients with obstructive jaundice. In this case, the retrospective analysis showed that the Hb level had already dropped to 8.9 g/dL with a high bilirubin level (T-bil, 10.3 mg/dL; D-bil, 7.1 mg/dL) at the time of the initial diagnosis of type 1 AIP. Another reason is steroid therapy. Steroid therapy was administered immediately after the diagnosis of type 1 AIP. Because the steroid therapy was also effective for secondary AIHA, the anemia was overlooked. Actually, when type 1 AIP was first diagnosed,

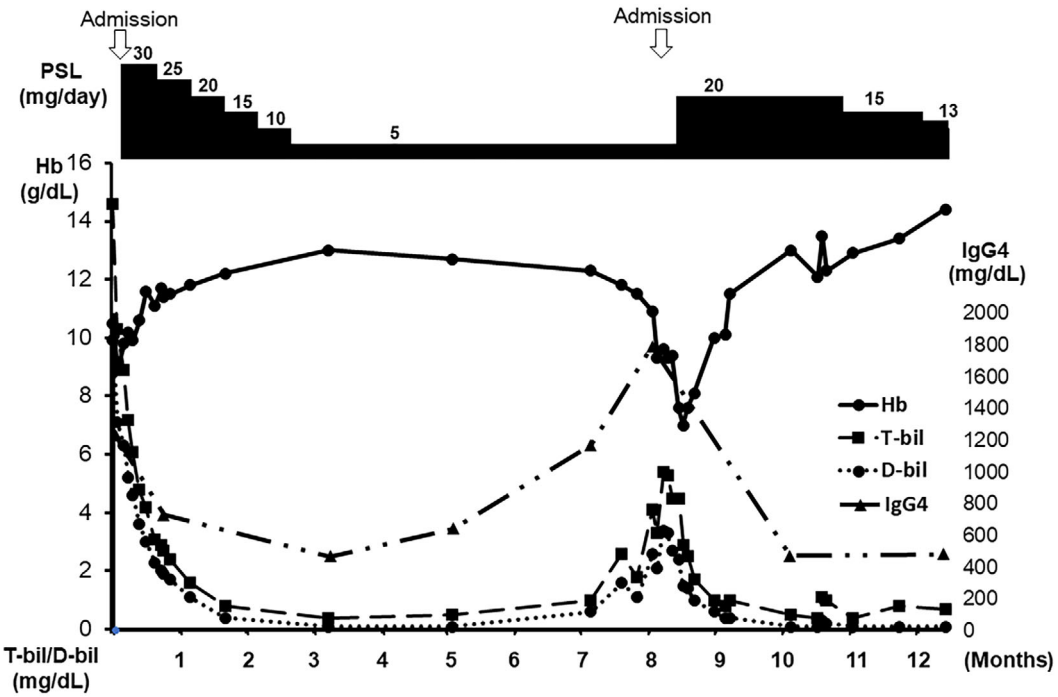

Figure 6. **The clinical course of the present case. D-bil: direct bilirubin, PSL: prednisolone, T-bil: total bilirubin**

the anemia was relatively mild. It became severe when secondary AIHA was diagnosed. After the first diagnosis of type 1 AIP, chronic autoimmune damage, which might have occurred with the tapering of the PSL dose, might have cause more severe hemolysis. In addition, the first diagnosis of type 1 AIP resulted in the immediate administration of PSL before the patient's anemia became serious. However, maintenance treatment with low-dose PSL (5 mg) was continued until anemia became apparent and secondary AIHA was then diagnosed. The re-escalation of the PSL dose was thus delayed, which might have been a reason for increase in the severity of the patient's hemolysis.

In AIHA, the endogenous phagocytes can identify Fc receptors of IgG antibodies bound to erythrocyte membranes and phagocytize them. The phagocytized IgG Fc receptors are specific for IgG1 and IgG3 and show no activity for IgG4. Moreover, phagocytes have receptors for complement C3b to initiate the immune response pathway, whereas IgG4 has no activity in complement activation (15, 16). IgG4-staining of tissue specimens obtained by bone marrow aspiration showed no evidence of IgG4-positive plasma cell agglutination (Fig. 4c). These findings might suggest that IgG4 does not contribute to the development of secondary AIHA. However, whether IgG4 itself induces the inflammation of the tissue in IgG4-RDs remains controversial. Moreover, the lack of IgG4-positive plasma cell agglutination in the bone marrow might not provide a plausible explanation to exclude the diagnosis of 'IgG4-related' AIHA, because AIHA is a disease in which hemolysis occurs in the spleen or peripheral blood, not the bone marrow. The specific criteria for the diagnosis of secondary AIHA still need to be clarified to determine whether secondary AIHA in patients with type 1 AIP should be included as one of the IgG4-RDs. Further studies should be performed to obtain clinical evidence to explain the relationship between secondary AIHA and IgG4-RD.

In conclusion, we described a case of type 1 AIP with IgG4-SC associated with secondary AIHA. Our experience strongly suggests that in patients with type 1 AIP/IgG4-SC, the possibility of secondary AIHA should be considered not only at the initial diagnosis, but also during follow-up with steroid therapy. We need to be aware that jaundice can be caused not only obstructive jaundice, but also by hemolytic jaundice in patients with type 1 AIP/IgG4-SC, because obstructive jaundice can obscure the presence of hemolytic jaundice.

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

References

1. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med **344**: 732-738, 2001.
2. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. N Engl J Med **355**: 2670-2676, 2006.
3. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas **40**: 352-358, 2011.
4. Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol **22**: 1-14, 2012.

5. Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol **22**: 21-30, 2012.
6. Sawitsky A, Ozaeta PB Jr. Disease-associated autoimmune hemolytic anemia. Bull N Y Acad Med **46**: 411-426, 1970.
7. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol **69**: 258-271, 2002.
8. Nakazawa T, Ohara H, Sano H, Ando T, Joh T. Schematic classification of sclerosing cholangitis with autoimmune pancreatitis by cholangiography. Pancreas **32**: 229, 2006.
9. Lechner K, Jager U. How I treat autoimmune hemolytic anemias in adults. Blood **116**: 1831-1838, 2010.
10. Garratty G. Drug-induced immune hemolytic anemia. Hematology Am Soc Hematol Educ Program: 73-79, 2009.
11. Garratty G. Immune hemolytic anemia caused by drugs. Expert Opin Drug Saf **11**: 635-642, 2012.
12. Al-Saif F, Al-Masloom A, Johnson MA, et al. Autoimmune pancreatitis with autoimmune hemolytic anemia. Pancreas **33**: 316-317, 2006.
13. Yokomichi H, Nakahara T, Asamoto Y, Komatsu H, Tokumo H, Ishida K. [Case of autoimmune pancreatitis accompanied by autoimmune hemolytic anemia]. Nihon Shokakibyo Gakkai Zasshi **106**: 698-705, 2009 (in Japanese, Abstract in English).
14. Masutani H, Okuwaki K, Kida M, et al. First case of IgG4-related sclerosing cholangitis associated with autoimmune hemolytic anemia. World J Gastroenterol **20**: 8740-8744, 2014.
15. von dem Borne AE, Beckers D, van der Meulen FW, Engelfriet CP. IgG4 autoantibodies against erythrocytes, without increased haemolysis: a case report. Br J Haematol **37**: 137-144, 1977.
16. Engelfriet CP, Borne AE, Beckers D, Van Loghem JJ. Autoimmune haemolytic anaemia: serological and immunochemical characteristics of the autoantibodies; mechanisms of cell destruction. Ser Haematol **7**: 328-347, 1974.