Abstract Review Committee

Arezou Khosroshahi, MD
Assistant Professor of Medicine
Division of Rheumatology
Emory University

Kyle T. Bradley, MD
Assistant Professor, Hematopathology
Department of Pathology & Laboratory Medicine
Emory University School of Medicine

Emanuel Della Torre, MD
Università Vita-Salute San Raffaele
San Raffaele Scientific Institute
Unit of Medicine, Allergy and Clinical Immunology

Joanne Eunhee Yi, MD
Professor of Pathology
Department of Laboratory Medicine and Pathology
Mayo Clinic

Field Willingham, MD
Assistant Professor of Medicine
Division of Gasteroenterology
Emory University

George Webster, BSc, MD, FRCP
Consultant Gastroenterologist and Hepatologist
Clinical Lead for HPB Medicine
University College London Hospitals

Hamid Mattoo, PhD
Harvard Medical School
Center for Cancer Research
Massachusetts General Hospital

John H Stone, MD, MPH
Professor of Medicine
Harvard Medical School
Director, Clinical Rheumatology
Massachusetts General Hospital

John K.C. Chan, MD
Consultant Pathologist
Department of Pathology
Queen Elizabeth Hospital
Hong Kong

Lizhi Zhang, MD
Associate Professor of Pathology
Department of Laboratory Medicine and Pathology, MAYO Clinic

Mitsuhiro Kawano, MD, PhD
Assistant Professor
Division of Rheumatology
Department of Internal Medicine
Kanazawa University Hospital

Mollie Carruthers, MD
Division of Rheumatology
Massachusetts General Hospital
Harvard Medical School

Motohisa Yamamoto, MD
Dept. of Gastroenterology, Rheumatology and Clinical Immunology,
Sapporo Medical University School of Medicine

Nicolas Schleinitz
Department of Internal Medicine
Assistance publique Hopitaux de Marseille
Aix-Marseille Université

Seiji Nakamura, DDS, PhD
Professor & Chairman Vice-Director of Kyushu University Hospital
Professor & Chairman Section of Oral and Maxillofacial Oncology
Division of Maxillofacial Diagnostic and Surgical Sciences
Faculty of Dental Science Kyushu University

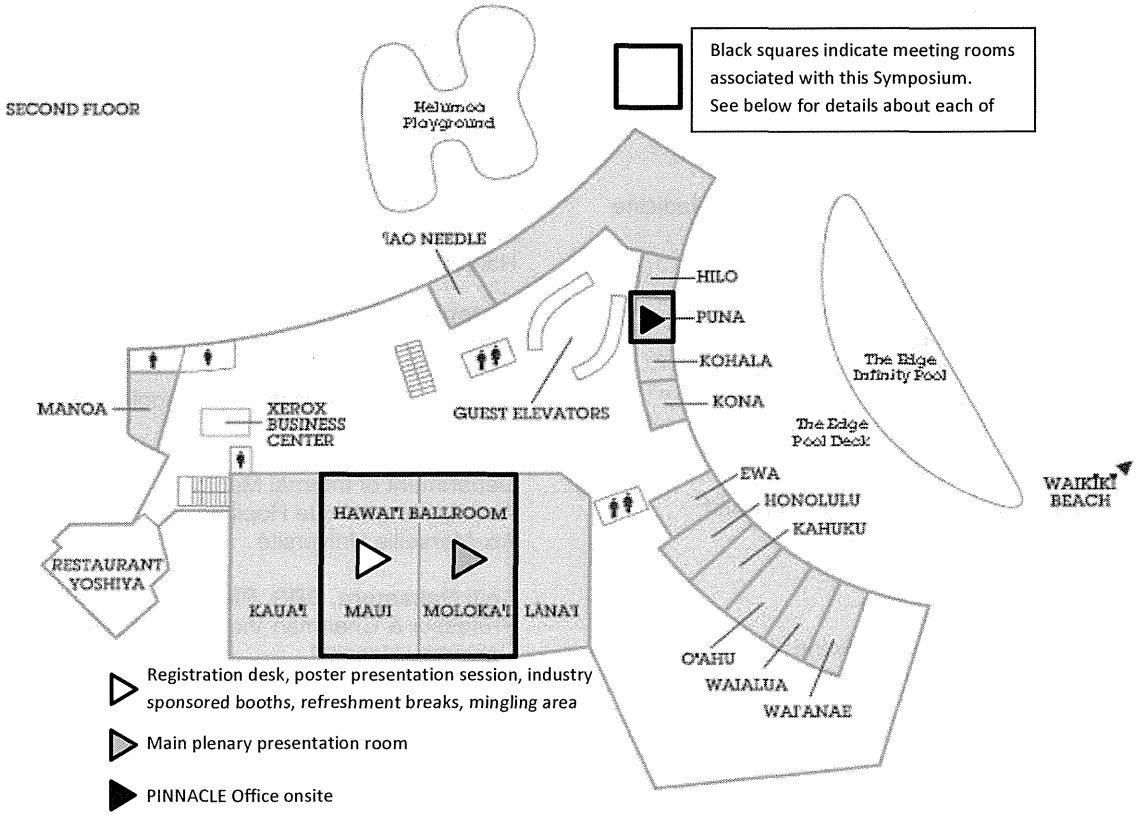
Vinay Mahajan, MD, PhD
Harvard Medical School
Center for Cancer Research
Massachusetts General Hospital

Yasufumi Masaki, MD, PhD
Hematology & Immunology
Kanazawa Medical University

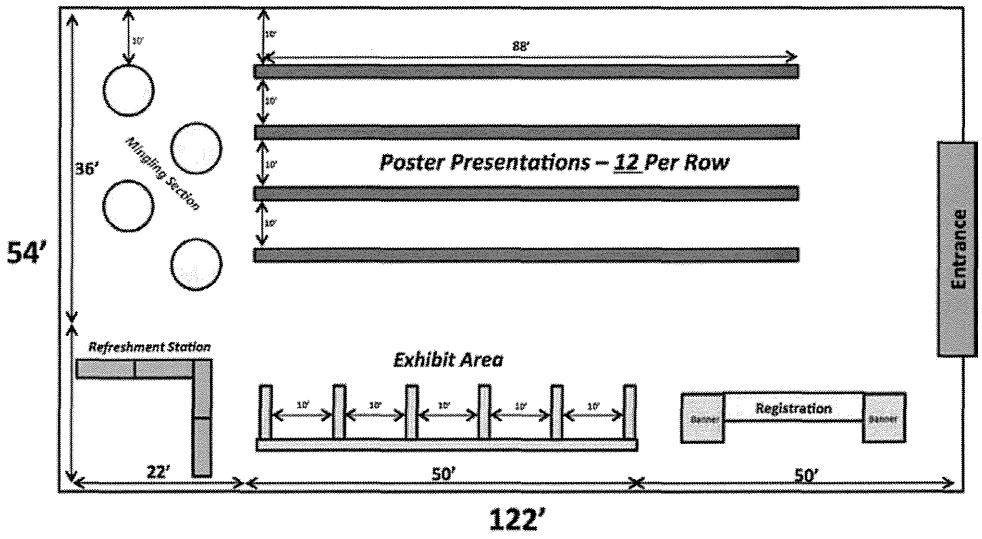
Yasuni Nakanuma, MD
Professor of Pathology
Institute of Medical, Pharmaceutical and Health Sciences
Kanazawa University

Zachary Wallace, MD
Division of Rheumatology
Massachusetts General Hospital
Harvard Medical School

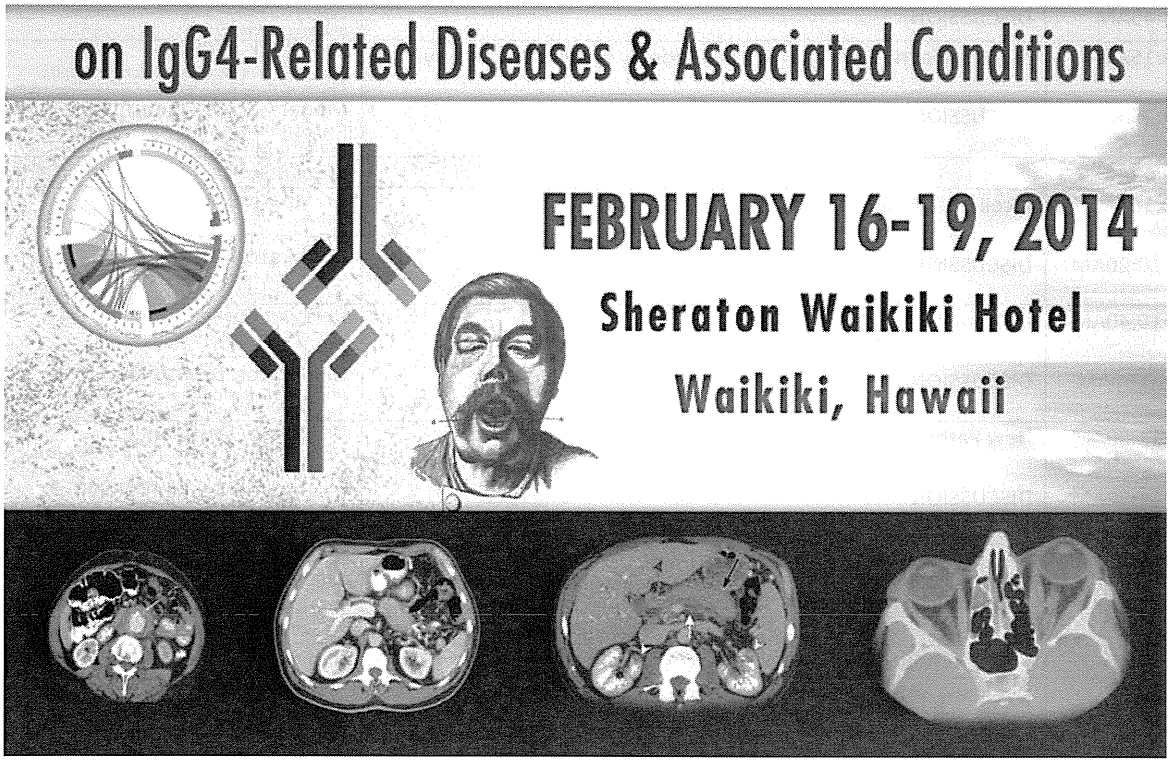
Conference Hotel Map



Maui Ball Room



Plenary Agenda



Scientific program

Sunday, February 16, 2014 — **Maui Room**

1:00 – 5:00	Registration
5:00	Wine & Cheese / Poster Viewing

Moloka'i Room

6:30	Welcome – Dr. John Stone & Dr. Tsutomu Chiba
6:45	The Recognition of IgG4-related Autoimmune Pancreatitis – Dr. Shigeyuki Kawa
7:00	Overview of Pathophysiology – Dr. Shiv Pillai

Monday, February 17, 2014 **Moloka'i Room**

7:30 – 8:00AM	*BREAKFAST*	*(Provided by Conference)*
8:00 – 8:05AM	Welcome	Dr. Arezou Khosroshahi *Division of Rheumatology* *Emory University, Atlanta, GA USA*
	Pathology	
8:05 – 8:35AM	The Pathology of IgG4-RD: What have we learned since 2011?	Dr. Yoh Zen *King's College Hospital, Institute of Liver Studies, London UK*
8:35 – 8:45AM	DISCUSSION	Moderator: Dr.Giuseppe Zamboni *Dept of Pathology, S. Cuore-Don Calabria Hospital, University of Verona, Negrar, Italy*
8:45 – 9:15AM	Can the diagnosis of IgG4-RD be made by lymph node biopsy?	Dr. John K.C. Chan *Dept of Pathology, Queen Elizabeth Hospital* *Kowloon, Hong Kong, China*
9:15 – 9:25AM	DISCUSSION	Moderator: Dr. Tadashi Yoshino *Dept of Pathology, Okayama University Medical School* *Okayama, Japan*
9:25 – 9:40AM	*BREAK*	*Maui Room*
9:40–10:10AM	B cells, plasmablasts, and plasma cells in IgG4-RD	Dr. Ignacio Sanz *Division of Rheumatology* *Emory University, Atlanta, GA USA*
10:10 – 10:20AM	DISCUSSION	Moderator: Dr. Zhan-Guo Li *Dept of Rheumatology and Immunology,* *Beijing University Medical School People's Hospital*
10:20 – 10:40AM	Immune complexes in IgG4-RD	Dr. Lynn Cornell *Dept of Pathology, Mayo Clinic,* *Rochester, MN USA*
10:40 –10:50AM	DISCUSSION	Moderator: Dr. MH Kim *Asan Medical Center/University of Ulsan College of Medicine,* *Asan Medical Center, Seoul, Korea*
10:50 – 11:20AM	New Pathology Techniques	Dr. Vikram Deshpande *Dept of Pathology, Massachusetts General Hospital* *Boston, MA USA*
11:20 – 11:30AM	DISCUSSION	Moderator: Dr. Kenji Notohara *Dept of pathology, Kurashiki Central Hospital, Kurashiki, Japan*
11:30 – Noon	Abstract presentation (#142 and #230) 1-Epstein-Barr virus reactivation in IgG4-RD – *Dr. Takeuchi* 2-Active IgG4-RD Is Characterized By Substantial Elevations In Circulating Plasmablasts – *Dr. Wallace*	Moderator: Dr. Tooru Shimosegawa *Dept of Gastroenterology, Tohoku University, Japan*
Noon – 1:30PM	*LUNCH*	*At Leisure*
	Challenging Individual Organ Manifestations	
1:30 –2:00PM	Overview of New Entities within the IgG4-RD spectrum	Dr. Mitsuhiro Kawano *Dept of Rheumatology & Internal Medicine, Kanazawa University Hospital, Kanazawa, Japan*
2:00 – 2:10PM	DISCUSSION	Moderator: Dr. Nicolas Schleinitz *Dept of Internal Medicine, AP-HM, Aix Marseille Université Marseille, France*
2:10 – 2:30PM	Pulmonary manifestations of IgG4-RD and their management	Dr. Jay H. Ryu *Pulmonary and Critical Care Medicine, Mayo Clinic* *Rochester, MN USA*
2:30- 2:40	Abstract 152 Proposal for diagnostic criteria for IgG4-related lung disease – *Shoko Matsui*	
2:40 – 2:50PM	DISCUSSION	Moderator: Dr. Shoko Matsui *Toyama Medical University, Toyama, Japan*
2:50 – 3:15PM	*BREAK*	*Maui Room*
3:15 – 3:45PM	Cancer & IgG4-RD: Is there a real relationship?	Dr. Tsutomu Chiba *Dept of Gastroenterology and Hepatology* *Graduate School of Medicine, Kyoto University, Kyoto, Japan*
3:45 – 4:00PM	DISCUSSION	Moderator: Dr. John K.C. Chan *Dept of Pathology, Queen Elizabeth Hospital* *Kowloon, Hong Kong, China*
4:00 – 4:30PM	Thoracic and abdominal aortitis	Dr. James Stone *Anatomic Pathology, Massachusetts General Hospital* *Boston, MA USA*
4:30 – 4:40PM	DISCUSSION	Moderator: Dr. Satomi Kasashima *Dept of Pathology and Clinical Laboratory, National Hospital Organization, Kanazawa Medical Center, Kanazawa, Japan*
4:40 – 5:10PM	IgG4 and the Kidney	Dr. David Salant *Dept of Medicine, Division of Nephrology, Boston University, Boston, MA USA*
5:10 – 5:20PM	DISCUSSION	Moderator: Dr. Takako Saeki *Nagaoka Red Cross Hospital, Rheumatology & Internal Medicine & Nephrology, Niigata, Japan*
5:20 – 6:05PM	Abstract presentation (#202, #160, #179) 1- Phenotypic differences between IgG4+ & IgG1+ B cells – *Dr. Rispens* 2- Inhibition of APRIL suppresses disease progression: Analysis from a novel mouse model for IgG4-related disease – *Dr. Yamada* 3-Polarized M2 macrophages promote fibrosis of glandular tissue in IgG4-related dacryoadenitis and sialoadenitis – *Dr. Furukawa*	Moderator: Dr. Hisanori Umehara *Dept of Hematology and Immunology* *Kanazawa Medical University*

Tuesday, February 18 — Moloka'i Room

7:30 – 8:00AM	*BREAKFAST*	*Maui Room*
8:00 – 8:05AM	Welcome	Dr. Kazuichi Okazaki *The Third Dept of Internal Medicine. Division of Gastroenterology and Hepatology, Kansai Medical University, Osaka, Japan*
	Pathophysiology	
8:05 – 8:45AM	What can we learn about IgG4-RD from parasitic diseases?	Dr. Thomas A. Wynn *Immunopathogenesis Section, NIH, Bethesda, MD USA*
8:45 – 9:00AM	DISCUSSION	Moderator: Dr.Tomohiro Watanabe *Dept of Gasteroenterology,Kyoto University, Kyoto, Japan*
9:00 – 9:30AM	The Genetic Determinants of Pulmonary Fibrosis	Dr. David Schwartz *University of Colorado, Denver, Colorado USA*
9:30 – 9:45AM	DISCUSSION	Dr. Vinay Mahajan *MGH Center for Cancer Research, Massachusetts General Hospital, Boston MA USA*
9:45 – 10:00AM	*BREAK*	*Maui Room*
10:00 – 10:30AM	T cells and IgG4-RD	Dr. Hamid Mattoo *MGH Center for Cancer Research, Massachusetts General Hospital, Boston, MA USA*
10:30 – 10:40AM	DISCUSSION	Moderator:Dr. Seiji Nakamura *Kyushu University, oral surgery, Fukuoka, Japan*
10:40 – 11:05AM	B-T cell interaction in IgG4-RD	Dr. Vinay Mahajan *MGH Center for Cancer Research, Massachusetts General Hospital, Boston MA USA*
11:05 – 11:15AM	DISCUSSION	Moderator: Dr. Kenji Notohara *Dept of pathology, Kurashiki Central Hospital, Kurashiki, Japan*
11:15 – 11:45AM	IgE: How does it fit into the IgG4-RD milieu?	Dr. Frances Lee *Division of Pulmonary and critical care,, Emory University, Atlanta, GA USA*
11:45 – Noon	DISCUSSION	Moderator: Dr. Emanuel Della Torre *Massachusetts General Hospital, Boston MA USA*
Noon – 1:30PM	*LUNCH*	*At Leisure*
	Epidemiology & Clinical Assessment	
1:30 – 1:50PM	Genome-wide association studies in IgG4-RD	Dr. Fumihiko Matsuda *Kyoto University Graduate School of Medicine Kyoto, Japan*
1:50 – 2:00PM	DISCUSSION	Moderator: Dr. Shiv Pillai *Massachusetts General Hospital, Boston MA USA*
2:00 – 2:30PM	Imaging in IgG4-RD	Dr. Dai Inoue *Dept of Radiology, Kanazawa University Graduate School of Medical Science, Kanazawa, Ishikawa, Japan*
2:30 – 2:45PM	DISCUSSION	Moderator: Dr. Yoh Zen *King's College Hospital, Institute of Liver Studies, London UK*
2:45 – 3:00PM	*BREAK*	*Maui Room*
3:00 – 3:20PM	Multi-centric Castleman's disease	Dr. Yasuharu Sato *Dept of Pathology, Okayama University Okayama, Japan*
3:20 – 3:40PM	DISCUSSION	Moderator: Dr. Hiroki Takahashi *Dept of Gastroenterology, Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, Sapporo, Japan*
3:40 – 4:00PM	Inflammatory Myofibroblastic Tumors	Dr. Adrian Bateman *University Hospital Southampton NHS Foundation Trust, Dept of Cellular Pathology, Southampton, Hampshire, UK*
4:00 – 4:10PM	DISCUSSION	Moderator: Dr. Vikram Deshpande *Dept of Pathology, Massachusetts General Hospital Boston MA USA*
4:10 – 4:30PM	Monitoring IgG4-RD activity through the blood	Dr. Arezou Khosroshahi *Division of Rheumatology Emory University, Atlanta, GA USA*
4:30 – 4:45PM	DISCUSSION	Moderator: Dr. Kazuichi Okazaki *The Third Dept of Internal Medicine, Division of Gastroenterology and Hepatology, Kansai Medical University, Osaka, Japan*
4:45 – 5:30PM	Abstract presentation (#233 and #167) 1- Aberrant activation of Th2 cells by IL-33 in IgG4-related dacryoadenitis and sialoadenitis – *Dr. Nakamura* 2- Activation of Toll-like receptors and NOD-like receptors in monocytes and basophils is involved in the immuno-pathogenesis of IgG4-related disease – *Dr. Watanabe*	Moderator: Dr. Terumi Kamisawa *Dept of Gastroenterology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan*
7:00PM	Symposium Dinner: Private Patio – Kai Market, Ground Floor	**Ticket Purchase** *Dressy Casual (no jackets please)*

Wednesday, February 19 — Moloka'i Room

7:30 – 8:00AM	*BREAKFAST*	*Maui Room*
8:00 – 8:05AM	Welcome	Dr. John Stone *Division of Rheumatology, Massachusetts General Hospital Harvard Medical School. Boston, MA USA*
	Treatment Session	
8:05 – 8:25AM	Glucocorticoid Treatment in IgG4-RD	Dr. Yasufumi Masaki *Kanazawa Medical University, Hematology and Immunology, Kahoku, Ishikawa, Japan*
8:25 – 8:30AM	DISCUSSION	Moderator: Dr. Suresh Chari *Dept of Gastroenterology, Mayo Clinic, Rochester, MN USA*
8:30 – 8:50AM	Conventional Steroid sparing agents for IgG4-RD	Dr. Mark Topazian *Division of Gastroenterology, Mayo Clinic Rochester, MN, USA*
8:50 – 9:00AM	DISCUSSION	Moderator: Dr. Arezou Khosroshahi *Division of Rheumatology Emory University, Atlanta, GA USA*
9:00 – 9:20AM	B cell depletion strategies	Dr. John Stone *Division of Rheumatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA USA*
9:20 – 9:25AM	DISCUSSION	Moderator: Dr. Hisanori Umehara *Dept of Hematology and Immunology Kanazawa Medical University*
9:25 – 9:45AM	Current & Future Treatment for Pulmonary Fibrosis	Dr. David Schwartz *University of Colorado, Denver, Colorado USA*
9:45 – 9:50AM	DISCUSSION	Moderator: Dr. Hamid Mattoo *Cancer Center, Massachusetts General Hospital, Boston, MA USA*
9:50 – 10:00AM	*BREAK*	*Maui Room*
10:00 – 11:45AM	**Panel Discussion on Treatment** Drs. Chari, Khosroshahi, Kamisawa, Topazian, Hart, Umehara, Kawano, Saeki, Ryu, Yamamoto, Shimosegawa, Masaki, Schwartz, and others	Moderator: Dr. John Stone *Division of Rheumatology, Massachusetts General Hospital Harvard Medical School, Boston, MA USA*
11:45 – Noon	Wrap up for treatment	
Noon – 1:30PM	*LUNCH*	*At Leisure*
1:30 – 5:00PM	***Biliary Session***	Chair: Dr. Suresh Chari *Dept of Gastroenterology, Mayo Clinic, Rochester, MN USA*
1:30 –1:40 PM	Clinical Features: Are there clinical features that distinguish IgG4-SC from other biliary pathologies?	Dr. Roger Chapman *Dept of Gastroenterology, Oxford University, Oxford, UK*
1:40 – 1:45 PM	DISCUSSION	Dr. Atsushi Tanaka *Teikyo University, Japan*
1:45 – 1:50 PM	Consensus summary: Role of clinical features in distinguishing IgG4-SC from other biliary pathologies.	Moderator: Dr. Suresh Chari *Dept of Gastroenterology, Mayo Clinic, Rochester, MN USA*
1:50– 2:20PM	Do imaging findings distinguish IgG4-SC from other biliary pathologies? *CT/MRI, ERCP, EUS*	Dr. Dai Inoue *Dept of Radiology, Kanazawa University Graduate School of Medical Science, Kanazawa, Ishikawa, Japan* Dr. Naoki Takahashi *Dept of Radiology, Mayo Clinic Rochester,MN, USA* Dr. Takahiro Nakazawa *Dept of Gastroenterology, Nagoya City university, Japan* Dr. George Webster *Dept of Gastroenterology and Hepatology University College London Hospitals, London, UK* Dr. Kazuo Inui *Dept of Gastroenterology, Fujita Health University, Second Teaching Hospital, Nagoya, Japan* Dr. Michael Levy *Dept of Gastroenterology, Mayo Clinic Rochester, MN, USA*
2:20– 2:25PM	DISCUSSION	
2:25 – 2:35PM	Consensus summary: Role of imaging in distinguishing IgG4-SC from other biliary pathologies	Moderator: Dr. Suresh Chari *Dept of Gastroenterology, Mayo Clinic, Rochester, MN USA*
2:35 – 2:45PM	Do IgG4 levels distinguish IgG4-SC from PSC?	Dr. Hirotaka Ohara *Dept of Gastroenterology, Nagoya City university, Japan*
2:45 – 2:50PM	DISCUSSION	Dr. Roger Chapman *Dept of Gastroenterology, Oxford University, Oxford, UK*
2:50 – 2:55PM	Consensus summary: What is the role of serum IgG4 levels in distinguishing IgG4-SC from PSC?	Moderator: Dr. Kazuichi Okazaki *The Third Dept of Internal Medicine, Division of Gastroenterology and Hepatology, Kansai Medical University, Osaka, Japan*

2:55 – 3:10PM	*BREAK*	
3:10 – 3:50PM 3:50 – 4:00PM	Does histology distinguish IgG4 SC from PSC? *Resection* *Bile duct Biopsy* *Ampulla Biopsy* *Bile duct brush* *Liver Biopsy* DISCUSSION	Dr. Yasuni Nakanuma *Kanazawa University, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Japan* Dr. Lizhi Zhang *Dept of Pathology, Mayo Clinic, Rochester, MN USA* Dr. Kenji Notohara *Dept of pathology, Kurashiki Central Hospital, Kurashiki, Japan* Dr. Giuseppe Zamboni *Dept of Pathology, S. Cuore-Don Calabria Hospital, University of Verona, Negrar, Italy* Dr. Kensuke Kubota *Yokohama City University, Graduate School of Medicine, Yokohama, Japan* Dr. Thomas Smyrk *Dept of Pathology, Mayo Clinic, Rochester, MN USA* Dr. Vikram Deshpande *Dept of Pathology, Massachusetts General Hospital, Boston MA USA* Dr. Yoh Zen *Dept of Pathology, King's College Hospital, London UK*
4:00 – 4:10PM	Consensus Summary: Role of histopathology in distinguishing IgG4-SC from PSC	Moderator: Dr. Suresh T. Chari *Dept of Gastroenterology, Mayo Clinic, Rochester, MN USA*
4:10 – 4:20PM 4:20 – 4:25PM	Does response to steroids distinguish IgG4-SC from PSC? *IgG4-Sclerosing cholangitis* *Primary sclerosing cholangitis* DISCUSSION	Dr. Myung-Hwan Kim *Asan Medical Center/University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea* Dr. Terumi Kamisawa *Dept of Gastroenterology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan* Dr. Roger Chapman *Dept of Gastroenterology, Oxford University, Oxford, UK* Moderator: Dr. Tooru Shimosegawa *Dept of Gastroenterology, Tohoku University, Japan*
4:25 – 4:30PM	Consensus summary: Role of steroid response in distinguishing igG4-SC from PSC	Moderator: Dr. Tooru Shimosegawa *Dept of Gastroenterology, Tohoku University, Japan*
4:30 –4:35PM 4:35 – 4:45PM	What OOI is seen in IgG4-SC and PSC? DISCUSSION	Dr. Suresh Chari *Professor of Medicine, Mayo Clinic, Rochester, MN USA*
4:45 – 4:50PM	Consensus: Role of OOI in distinguishing IgG4-SC from PSC?	Moderator: Dr. Suresh Chari *Dept of Gastroenterology, Mayo Clinic, Rochester, MN USA*
4:50 – 5:10PM	Wrap up for Diagnostic criteria for IgG4-SC	Moderator: Dr. Suresh Chari *Dept of Gastroenterology, Mayo Clinic, Rochester, MN USA*

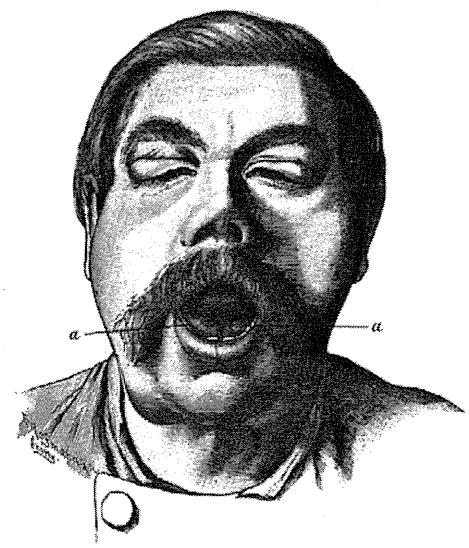
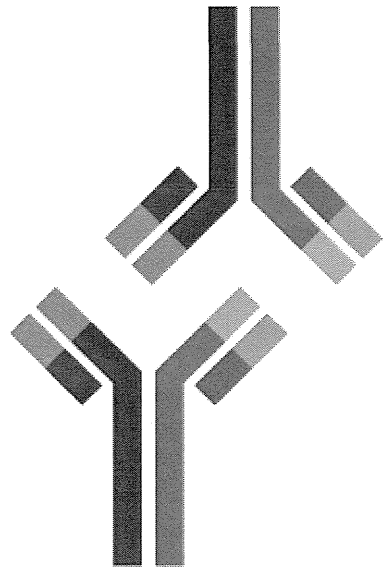


Fig. A.



Abstract Submissions

We received a total of 96 outstanding abstracts from all around the globe for the Second International Symposium on IgG4-RD and Associated Conditions. All the abstracts were evaluated by the Abstract Review Committee and accepted for either oral or poster presentations. This not only speaks to the growing interest in the area of IgG4-RD, but also the quality of data that is being produced.

We would like to thank you all for your interesting and thought-provoking abstracts, and also thank the Abstract Review Committee members for their excellent effort in evaluating the many submitted abstracts.

We are looking forward to both the poster presentations on the opening night of our Symposium, and the oral presentations during the meeting. All attendees will receive a USB flash drive containing the submitted abstracts in PDF format.

Oral Abstract Presentations

Abstracts that were accepted for oral presentation will be presented throughout our meeting agenda. See the meeting agenda to follow for more details. See below for a summary of oral abstract presentations.

Presenter Name	Abstract title	Topic	Category
Sachiko Furukawa	Polarized M2 macrophages promote fibrosis of glandular tissue in IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS).	Pathophysiology	Investigator initiated
Shoko Matsui	Proposal for diagnostic criteria for IgG4-related respiratory disease	Clinical Aspects & Treatment	Investigator initiated
Seiji Nakamura	Aberrant activation of Th2 cells by IL-33 in IgG4-related dacryoadenitis and sialoadenitis	Pathophysiology	Investigator initiated
Theo Rispens	Phenotypic differences between IgG4+ and IgG1+ B cells	Pathophysiology	Investigator initiated
Mai Takeuchi	Epstein-Barr virus reactivation in IgG4-related lymphadenopathy with comparison to extranodal IgG4-related disease	Pathology	Investigator initiated
Zachary Wallace	Active IgG4-Related Disease Is Characterized By Substantial Elevations In Circulating Plasmablasts	Clinical Aspects & Treatment	Investigator initiated
Tomohiro Watanabe	Activation of Toll-like receptors and NOD-like receptors in monocytes and basophils is involved in the immuno-pathogenesis of IgG4-related disease	Pathophysiology	Investigator initiated
Kazunori Yamada	Inhibition of APRIL suppresses disease progression: Analysis from a novel mouse model for IgG4-related disease	Pathophysiology	Investigator initiated

Poster Presentations

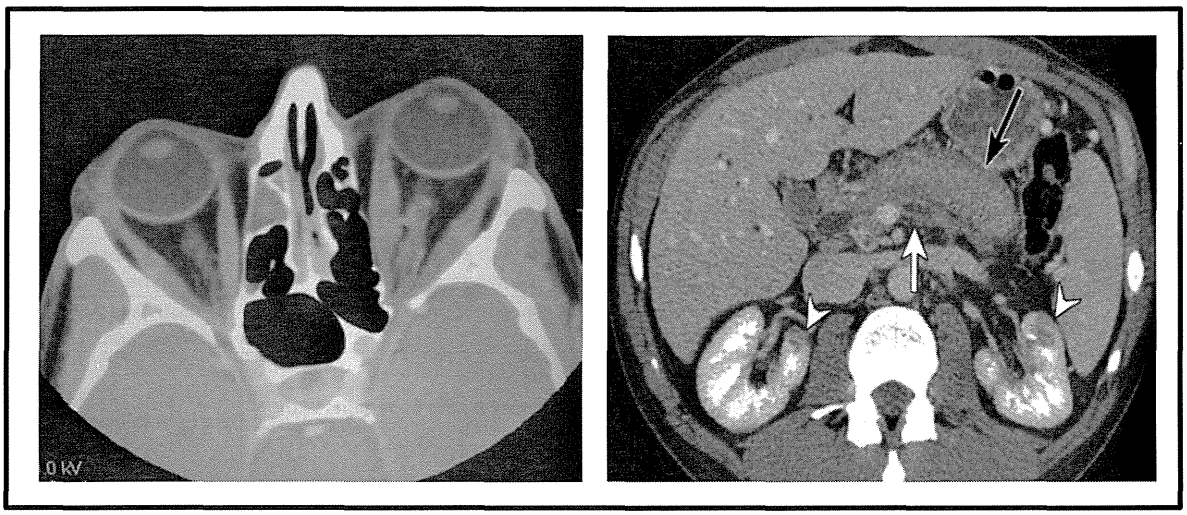
The poster presentation session will be taking place on Sunday February 16th from 5:00pm-6:30pm in the Maui Ballroom. Below you will find a list of all poster numbers, presenters, and topics. If you are presenting a poster, please make sure that the poster has been installed prior to 4:30pm on Sunday February 16th.

Poster #	Presenter Name	Abstract Title	Topic	Category
101	Takashi Akamizu	Clinical characteristics of Graves' patients with elevated serum IgG4 concentrations	Clinical Aspects & Treatment	Investigator initiated
102	Yasuyuki Arai	Plasmacytoid dendritic cells activated by neutrophil extracellulart traps (NETs) contribute to the pathophysiology of IgG4-RD	Pathophysiology	Investigator initiated
103	Luke Chen	Polyclonal hyperviscosity syndrome in IgG4-Related Disease	Clinical Aspects & Treatment	Investigator initiated
104	Emma Culver	Gene expression analysis identifies immune signaling and complement pathways in IgG4-Related Disease	Pathophysiology	Investigator initiated
105	Emma Culver	Elevated serum IgG4 and abundant IgG4-positive plasma cells in the colon of patients with ulcerative colitis in the presence and absence of IgG4-Related Disease	Pathology	Investigator initiated
106	Emma Culver	Elevated serum IgG4 and IgE in IgG4-RD and other disease mimics	Pathophysiology	Investigator initiated
107	Emma Culver	Autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extra-pancreatic organ failure, malignancy and mortality in a prospective UK cohort.	Clinical Aspects & Treatment	Investigator initiated
108	Emanuel Della Torre	Diagnostic value of cerebrospinal fluid IgG4 indices in IgG4-Related hypertrophic pachymeningitis	Clinical Aspects & Treatment	Investigator initiated
109	Emanuel Della Torre	Prevalence of atopy, eosinophilia and IgE elevation in IgG4-Related Disease	Clinical Aspects & Treatment	Investigator initiated
110	Emanuel Della Torre	IgG4-Related Midline Destructive Lesion	Clinical Aspects & Treatment	Investigator initiated
111	Mikael Ebbo	FDG-PET/CT in staging and evaluation of treatment response in IgG4-Related Disease: analysis of 46 FDG-PET/CT examinations	Clinical Aspects & Treatment	Investigator initiated
112	Mikael Ebbo	Serum immunoglobulin free light chain in IgG4-related disease: a potential novel biomarker?	Pathophysiology	Investigator initiated
113	Sachiko Furukawa	Clinical relevance of Küttner tumor and IgG4-Related dacryoadenitis and sialoadenitis	Pathophysiology	Investigator initiated
114	James Garrity	Diagnostic confusion regarding orbital IgG4-RD	Clinical Aspects & Treatment	Investigator initiated
115	Jovan Popovich	IgG4 Related retroperitoneal fibrosis with involvement of the spleen- clinical, radiological and pathologic correlation	Clinical Aspects & Treatment	Investigator initiated
116	Shin Hamada	Comprehensive analysis of serum miRNA in autoimmune pancreatitis	Pathophysiology	Investigator initiated
117	Shoko Hamaoka	Cases of IgG4-related ophthalmic disease without serum IgG4 elevation: the probable cases according to the comprehensive diagnostic criteria	Pathology	Investigator initiated
118	Tomohiro Handa	Evaluation of 18F-fluorodeoxyglucose uptake by positron emission tomography in IgG4 Related Disease	Clinical Aspects & Treatment	Investigator initiated
119	Satoshi Hara	Components and distribution of interstitial fibrosis in IgG4-related kidney disease; an autopsy series of 5 cases	Pathology	Investigator initiated
120	Ikuko Haruta	Analysis of a commensal bacteria triggered autoimmune pancreatitis mouse model	Pathophysiology	Investigator initiated
121	Noriko Hayami	IgG subclass and PLA2R in membranous nephropathy associated with IgG4-Related Disease	Pathology	Investigator initiated
122	Kenji Hirano	Intrapancreatic biliary stricture in autoimmune pancreatitis should not be classified into IgG4 related sclerosing cholangitis	Clinical Aspects & Treatment	Investigator initiated

Poster #	Presenter Name	Abstract Title	Topic	Category
123	Kenji Hirano	Incidence of malignancies in patients with IgG4-Related Disease	Clinical Aspects & Treatment	Investigator initiated
124	Kenji Hirano	Prognosis of patients with AIP in whom steroid was ceased after at least three-year maintenance therapy	Clinical Aspects & Treatment	Investigator initiated
125	Kenji Hirano	Indication for steroid therapy in AIP patients without obstructive jaundice	Clinical Aspects & Treatment	Investigator initiated
126	Shintaro Harata	Characterization of peripheral blood immune cell subsets in patients with IgG4 related disease: A comparative analysis with patients with Sjögren syndrome and healthy donors	Pathophysiology	Investigator initiated
127	Soon Auck Hong	Xanthogranulomatous cholecystitis manifestating IgG4-related cholecystitis	Pathology	Investigator initiated
128	Abbie Husman	Increased IgG4+ plasma cells and IgG4/IgG ratio may be seen in lymph nodes from patients without IgG4-Related Disease	Pathology	Investigator initiated
129	Satoshi Ikeda	Interstitial pneumonia with marked IgG4 positive plasma cells infiltration: are they classified as a spectrum of IgG4-related lung disease?	Clinical Aspects & Treatment	Investigator initiated
130	Joanne E. Yi	Cavitating lung disease: A novel presentation of IgG4 pulmonary involvement	Clinical Aspects & Treatment	Investigator initiated
131	George Webster	Cerebral manifestations of IgG4-Related Disease	Clinical Aspects & Treatment	Investigator initiated
132	Keita Kanai	Two siblings with type 1 autoimmune pancreatitis	Clinical Aspects & Treatment	Investigator initiated
133	Atsushi Kanno	The diagnosis of autoimmune pancreatitis by EUS-FNA based on the International Consensus Diagnostic Criteria (ICDC)	Pathology	Investigator initiated
134	Fuminori Kasashima	IgG4-Related periaortitis associated with rupture during low-dose steroid administration and aortoduodenal fistula following endovascular repair	Clinical Aspects & Treatment	Investigator initiated
135	Yuri Kato	Is corticosteroid administration not always required in patients with type 1 autoimmune pancreatitis?	Clinical Aspects & Treatment	Non-investigator initiated
136	Arezou Khosroshahi	Distinct phases of IgG4-RD, exhibit unique phenotype of B cell activation and clonal expansion	Pathophysiology	Investigator initiated
137	Sigeru Ko	Autoimmune pancreatitis: Reorienting the goals of steroid therapy to repair, regeneration, and functional recovery of pancreatic tissues	Clinical Aspects & Treatment	Investigator initiated
138	Toshinobu Kubota	Monitoring IgG4-RD activity through the blood in Ophthalmology	Pathophysiology	Investigator initiated
139	Katsutoshi Kuriyama	Clinical characteristics of IgG4-RD patients; multicenter retrospective cohort study in Japan	Clinical Aspects & Treatment	Investigator initiated
140	Jong Kyun Lee	Comparison of ERCP with papillary biopsy and EUS-guided pancreatic biopsy in the diagnosis of autoimmune pancreatitis	Clinical Aspects & Treatment	Investigator initiated
141	Wen Zhang	IgG4-RD in China: A prospective cohort study of 118 patients	Clinical Aspects & Treatment	Investigator initiated
142	Wen Zhang	B cell subsets and dysfunction of regulatory B cells in IgG4-related diseases and primary Sjögren's syndrome: the similarities and differences	Pathophysiology	Investigator initiated
143	Takashi Maehara	IL-21 contributes to ectopic germinal center formation and IgG4 production in IgG4-Related dacryoadenitis and sialoadenitis	Pathology	investigator initiated
144	Vinay S Mahajan	Individuals with IgG4-Related Disease do not have an increased frequency of the K409 variant of IgG4 that compromises Fab-arm exchange	Pathophysiology	Investigator initiated
145	Vinay S Mahajan	De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4-Related Disease	Pathophysiology	Investigator initiated
146	Masahiro Maruyama	Long term outcomes of type 1 autoimmune pancreatitis: development to pancreatic stone formation and chronic pancreatitis	Clinical Aspects & Treatment	Investigator initiated
147	Hamid Mattoo	Response to rituximab in IgG4-Related Disease is mediated by depletion of clonally expanded CD4+ effector T cells	Pathophysiology	Non-investigator initiated

Poster #	Presenter Name	Abstract Title	Topic	Category
148	Hamid Mattoo	Circulating Th2 memory cells in IgG4 Related Disease are restricted to a defined subset of subjects with concomitant atopy	Pathophysiology	Investigator initiated
149	Katsuyuki Miyabe	Comparison study of the immunohistochemical stainings for the diagnosis of type 1 autoimmune pancreatitis	Pathology	Investigator initiated
150	Masaki Miyazawa	A clinical study on steroid therapy for AIP	Clinical Aspects & Treatment	Investigator initiated
151	Ichiro Mizushima	Clinical course after corticosteroid therapy	Clinical Aspects & Treatment	Investigator initiated
152	Sung-Hoon Moon	Clinical differences between primary and IgG4-related sclerosing cholangitis	Clinical Aspects & Treatment	Investigator initiated
153	Masafumi Moriyama	The diagnostic usability of labial salivary and submandibular gland biopsy in IgG4-Related dacryoadenitis and sialoadenitis	Clinical Aspects & Treatment	Non-investigator initiated
154	Alfredo Musumeci	Isolated abdominal aortitis in the ER	Clinical Aspects & Treatment	Investigator initiated
155	Yoshimasa Nakazato	Lung cancer complicated with IgG4-Related Disease of the lung; A case report	Clinical Aspects & Treatment	Investigator initiated
156	Takayoshi Nishino	Incidence of cancer and risk factors for complication by cancer in IgG4-Related Diseases	Clinical Aspects & Treatment	Investigator initiated
157	Susumu Nishiyama	Features of quantitative salivary gland scintigraphy in patients with IgG4-Related sialadenitis, so-called Mikulicz disease	Clinical Aspects & Treatment	Investigator initiated
158	Takaya Oguchi	Genome-wide association study for lachrymal/salivary gland lesion susceptibility genes in type I autoimmune pancreatitis	Pathophysiology	Investigator initiated
159	Miho Ohta	A case of malignant lymphoma strongly suspected IgG4-Related dacryoadenitis and sialoadenitis	Clinical Aspects & Treatment	Investigator initiated
160	Masao Ota	Risk HLA allele for predisposition to type I autoimmune pancreatitis	Pathophysiology	Investigator initiated
161	Eva Amin	IgG4 related disease with great vessels and cardiac involvement	Clinical Aspects & Treatment	Investigator initiated
162	Erika Resetkova	IgG4-Related Sclerosing Mastitis (IgG4-RSM)	Pathology	Investigator initiated
163	Jikon Ryu	Clinical and Pathological Differences between Serum IgG4-positive and IgG4-negative type 1 autoimmune pancreatitis	Clinical Aspects & Treatment	Investigator initiated
164	Takako Saeki	Initial corticosteroid therapy in IgG4-Related kidney disease	Clinical Aspects & Treatment	Investigator initiated
165	Aurelie Grados	Increase of T regulatory and T folliculer helper cells in peripheral blood of IgG4 RD patients	Pathophysiology	Investigator initiated
166	Aurelie Grados	Characterization of IgG4 RD patients- subgroups by multiple correspondence and cluster analysis	Clinical Aspects & Treatment	Investigator initiated
167	Yusuke Sekino	Therapeutic strategy for patients with type 1AIP developed with cyst formation	Clinical Aspects & Treatment	Non-investigator initiated
168	Masahiro Shiokawa	Undifferentiated IgG4-positive cholangitis; primary sclerosing cholangitis or IgG4-Related sclerosing cholangitis?	Clinical Aspects & Treatment	Investigator initiated
169	Masahiro Shiokawa	Risk of cancer in patients with autoimmune pancreatitis	Clinical Aspects & Treatment	Investigator initiated
170	Evgeniya Sokol	Unusual site of IgG4-RD manifestation: vertebral lesions	Clinical Aspects & Treatment	Investigator initiated
171	Jin Woo Song	Clinical course and outcome of patients with pulmonary involvement of immunoglobulin G4 related sclerosing disease	Clinical Aspects & Treatment	Investigator initiated
172	John Stone	The Diagnostic utility of serum IgG4 concentrations in IgG4-Related Disease	Clinical Aspects & Treatment	Investigator initiated
173	Kimi Sumimoto	Circulating CD19+CD24hiCD38hi regulatory B Cells in patients with type 1 autoimmune pancreatitis	Pathophysiology	Non-investigator initiated

Poster #	Presenter Name	Abstract Title	Topic	Category
174	Junko Tahara	Assessment of the rate of change in the serum IgG4 level of autoimmune pancreatitis as a predictor of a relapse.	Clinical Aspects & Treatment	Investigator initiated
175	Masayuki Takahira	Outcome of steroid therapy for cases with IgG4-related ophthalmic disease	Clinical Aspects & Treatment	Investigator initiated
176	Kenichi Takano	Evaluation of submandibular versus labial salivary gland fibrosis in IgG4-related disease	Pathology	Investigator initiated
177	Christin Tiegs-Heiden	Imaging of IgG4-Related Disease of the orbit	Clinical Aspects & Treatment	Investigator initiated
178	Kazushige Uchida	Comparison of IgG4-positive plasma cell infiltration between type 1 autoimmune pancreatitis and pancreatic ductal adenocarcinoma based on comprehensive diagnostic criteria for IgG4-Related Disease, 2011	Clinical Aspects & Treatment	Investigator initiated
179	Kaori Uchino	Comparison of macrophage morphology and phenotypes in type 1 autoimmune pancreatitis and other inflammatory diseases of the digestive organs	Pathology	Investigator initiated
180	Vladimir Vasilyev	IgG4-Related Disease: patients group characterization and rituximab therapy	Clinical Aspects & Treatment	Investigator initiated
181	Zachary Wallace	Ophthalmic manifestations of IgG4-Related Disease: single-center experience and literature review	Clinical Aspects & Treatment	Investigator initiated
182	Takayuki Watanabe	Clinical features of a new disease concept, IgG4-Related thyroiditis	Clinical Aspects & Treatment	Investigator initiated
183	Kazunori Yamada	Role of APRIL in IgG4-Related kidney disease	Pathophysiology	Investigator initiated
184	Motohisa Yamamoto	Can only the monitoring serum levels of IgG4 prevent the relapse in IgG4-RD?	Clinical Aspects & Treatment	Investigator initiated
185	Satoshi Yamamoto	Problems related to steroid therapy in patients with autoimmune pancreatitis	Clinical Aspects & Treatment	Non-investigator initiated
186	Hiroaki Yamashita	Evaluation of IgG4/IgG immunostaining and counting method for the supporting diagnosis of type 1 autoimmune pancreatitis: A comparative biopsy study from 8 organs	Clinical Aspects & Treatment	Investigator initiated
187	Hajime Yoshifuji	Subclass-based analysis of anti-nuclear antibody in IgG4-Related Disease and systemic autoimmune diseases	Clinical Aspects & Treatment	Investigator initiated
188	Wajeeha Yousaf	IgG4 Related Disease: A 23-year follow up.	Clinical Aspects & Treatment	Investigator initiated



Ⅷ. 研究成果の刊行物・別刷

Risk of Cancer in Patients With Autoimmune Pancreatitis

Masahiro Shiokawa, MD[1], Yuzo Kodama, MD, PhD[1], Kenichi Yoshimura, MD, PhD[2], Chiharu Kawanami, MD[3], Jun Mimura, MD[4], Yukitaka Yamashita, MD, PhD[5], Masanori Asada, MD, PhD[6], Masataka Kikuyama, MD, PhD[7], Yoshihiro Okabe, MD, PhD[8], Tetsuro Inokuma, MD, PhD[9], Masaya Ohana, MD, PhD[10], Hiroyuki Kokuryu, MD[11], Kazuo Takeda, MD, PhD[12], Yoshihisa Tsuji, MD, PhD[13], Ryuki Minami, MD[1], Yojiro Sakuma, MD[1], Katsutoshi Kuriyama, MD[1], Yuji Ota, MD[1], Wataru Tanabe, MD[1], Takahisa Maruno, MD[1], Akira Kurita, MD[1], Yugo Sawai, MD[1], Norimitsu Uza, MD, PhD[1], Tomohiro Watanabe, MD, PhD[1], Hironori Haga, MD, PhD[14] and Tsutomu Chiba, MD, PhD[1]

OBJECTIVES: **Although simultaneous occurrences of autoimmune pancreatitis (AIP) and cancer are occasionally observed, it remains largely unknown whether cancer and AIP occur independently or these disorders are interrelated. The aim of this study was to examine the relationship between AIP and cancer.**

METHODS: **We conducted a multicenter, retrospective cohort study. One hundred and eight patients who met the Asian diagnostic criteria for AIP were included in the study. We calculated the proportion, standardized incidence ratio (SIR), relative risk, and time course of cancer development in patients with AIP. We also analyzed the clinicopathological characteristics of AIP patients with cancer in comparison with those without cancer.**

RESULTS: **Of the 108 AIP patients, 18 cancers were found in 15 patients (13.9%) during the median follow-up period of 3.3 years. The SIR of cancer was 2.7 (95% confidence interval (CI) 1.4–3.9), which was stratified into the first year (6.1 (95% CI 2.3–9.9)) and subsequent years (1.5 (95% CI 0.3–2.8)) after AIP diagnosis. Relative risk of cancer among AIP patients at the time of AIP diagnosis was 4.9 (95% CI 1.7–14.9). In six of eight patients whose cancer lesions could be assessed before corticosteroid therapy for AIP, abundant IgG4-positive plasma cell infiltration was observed in the cancer stroma. These six patients experienced no AIP relapse after successful cancer treatment.**

CONCLUSIONS: **Patients with AIP are at high risk of having various cancers. The highest risk for cancer in the first year after AIP diagnosis and absence of AIP relapse after successful treatment of the coexisting cancers suggest that AIP may develop as a paraneoplastic syndrome in some patients.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis characterized by immunological abnormalities, including elevated serum immunoglobulin 4 (IgG4) levels and IgG4-positive lymphoplasmacytic infiltration. In addition, AIP is associated with imaging abnormalities such as pancreatic parenchyma enlargement and pancreatic duct narrowing (1,2). Patients with AIP often exhibit IgG4-positive cell infiltration in not only the pancreas but also in various extrapancreatic organs (3), suggesting that AIP is a manifestation of a systemic IgG4-related disease. Despite accumulating evidence of autoimmune features in this disease, however, the pathogenesis of AIP remains unknown.

Recent reports demonstrated that patients with AIP occasionally have various types of cancer, such as pancreatic cancer (4–6), lymphoma (7,8), bile duct cancer (9), gastric cancer (10), colon cancer (11), and thyroid cancer (12). Yamamoto *et al.* (13) reported

[1]Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto, Japan; [2]Translational Research Center, Kyoto University Hospital, Kyoto, Japan; [3]Department of Gastroenterology and Hepatology, Japanese Red Cross Otsu Hospital, Otsu, Japan; [4]Department of Gastroenterology and Hepatology, Nishikobe Medical Center, Kobe, Japan; [5]Department of Gastroenterology and Hepatology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan; [6]Department of Digestive Disease Center, Kitano Hospital, Osaka, Japan; [7]Department of Gastroenterology and Hepatology, Shizuoka General Hospital, Shizuoka, Japan; [8]Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Osaka, Japan; [9]Department of Gastroenterology and Hepatology, Kobe City Medical Center General Hospital, Kobe, Japan; [10]Department of Gastroenterology and Hepatology, Tenri Hospital, Tenri, Japan; [11]Department of Gastroenterology and Hepatology, Kyoto Katsura Hospital, Kyoto, Japan; [12]Kyoto Industrial Health Association, Kyoto, Japan; [13]Division of Radiology/Gastroenterology and Hepatology, Mayo clinic, Rochester, Minnesota, USA; [14]Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto, Japan. **Correspondence:** Yuzo Kodama, MD, PhD, Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, 54 Shogoin-kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: kodamayu@kuhp.kyoto-u.ac.jp

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that patients with IgG4-related disease are at high risk for cancer development based on an analysis of 105 patients, including 10 AIP patients. The precise prevalence of cancers in patients with AIP and the causal relationship between AIP and cancer, however, have not been elucidated.

In general, two mechanisms are proposed regarding co-occurrence of cancer and autoimmunity (14–16). First, sustained inflammation in the presence of autoimmune disease is considered to create the immunological environments for the development of cancer, e.g., lymphomas in Sjögren's syndrome or colitic cancers in inflammatory bowel diseases (17,18). In this case, the risk of cancer increases along with the duration of the underlying disease. Alternatively, cancers may induce autoimmune disease as a paraneoplastic syndrome, as represented by dermatomyositis (DM) and polymyositis (PM) (19–21). An important characteristic of paraneoplastic syndrome is that the risk of cancer is highest within the first year after diagnosis of the disease (14,22), and clinical improvement of the disease is frequently achieved after successful treatment of the accompanying cancer (23). Buchbinder *et al.* (20) reported that standardized incidence ratio (SIR) of cancer in the first year after diagnosis of myositis (DM/PM) was 4.4 (95% confidence interval (CI) 2.7–7.1) in the population-based cohort study.

In the present study, to examine the clinicopathological association between AIP and cancer, we conducted a multicenter, retrospective cohort study. We assessed the proportion of cancer in patients with AIP, the chronological relationship between the time of AIP diagnosis and diagnosis of cancers, IgG4 expression in cancer lesions in patients with AIP, and effects of cancer treatment on AIP.

METHODS

Patients

AIP patients. The study was approved by the institutional review boards of Kyoto University Hospital and affiliated hospitals of Kyoto University. Using K861 internal coding data, which includes AIP and chronic pancreatitis, we retrospectively identified 135 patients diagnosed as AIP between 2001 and 2011 at the Kyoto University Hospital or the affiliated hospitals of Kyoto University.

Patients who did not meet the Asian Criteria for AIP (see **Supplementary Table 1** online) (24) were excluded from the study. All the AIP diagnosis was made at the patients' initial visit or first admission for pancreatic examination. A total of 108 patients were included in this study (**Table 1**). According to the Asian diagnostic criteria, we diagnosed 94 AIP patients with criterion I (imaging) + II (serology), and 10 patients with criterion III (histopathology) alone in the resected pancreas, indicating the diagnosis of type I AIP (25). All of these patients fulfilled HISORt criteria in the United States (26). The remaining four patients were diagnosed with criterion I + optional criterion (response to steroid therapy). These four patients had no serology, no histology, and no extrapancreatic lesion, thus were considered to have type II AIP (25). The duration of the follow-up was defined as the period from the date of the diagnosis of AIP until death, the most recent contact, or the study closure date (31 October 2011), whichever occurred first.

Table 1. **Characteristics of the 108 patients with AIP**

Characteristic	Value
Male patients (%)	89 (82.4)
Age (years at diagnosis of AIP)	
Median	67
Range	21–86
Follow-up (years)	
Median	3.25
Range	0.3–11.7
Serum IgG4 at diagnosis of AIP (mg/dl)	
Median	259
Range	2.8–3640
Increased serum IgG4 (number of patients)	77 (11 NA)
Asian diagnostic criteria for AIP (number of patients)	
Criterion I + criterion II	94
Criterion III in the resected pancreas	10
Criterion I + optional (response to steroid therapy)	4
Number of patients with cancer	15
Number of cancers	18
Stomach	7
Lung	3
Non-Hodgkin lymphoma	2
Prostate	2
Colon	2
Bile duct	1
Thyroid	1

AIP, autoimmune pancreatitis, the normal values for serum IgG4 level; <135 mg/dl. NA, number of patients whose data were not available.

Ninety-one patients (84.2%) received corticosteroid treatment and all these patients showed an initial response. Twelve patients (11.1%) were observed without corticosteroid treatment. Ten of the 12 patients had spontaneous remission, and the remaining 2 patients showed deterioration of AIP and received corticosteroid treatment. The remaining five patients (4.6%) had surgical resection for suspicion of pancreatic cancer, and there was no relapse of AIP in the remaining pancreas after surgical resection of the AIP lesion without corticosteroid treatment. We defined AIP relapse as the recurrence of radiological manifestations of AIP with or without symptoms in the pancreas or extrapancreatic lesions after excluding other diseases (27,28). We expressed relapse rate of AIP by dividing the sum of AIP relapse by the follow-up period (person-years).

Gastric cancer patients without AIP. To compare gastric cancers with AIP and without AIP, we examined serum IgG4 levels in 20 gastric cancer patients without AIP, and IgG4-positive plasma cell infiltration in 40 gastric cancer patients without AIP. We randomly selected the patients, diagnosed between 2001 and 2011 at

Kyoto University Hospital, whose serum and/or tissues specimens were available.

Calculation of proportion of AIP patients with cancer and SIRs of cancer in AIP patients

We analyzed all cancers that were diagnosed concurrently with or after the diagnosis of AIP.

We calculated the proportion of AIP patients with cancer by dividing the number of AIP patients with cancer during the follow-up period by the number of all AIP patients. The result is expressed as a percentage.

We calculated the SIRs of cancer in AIP patients using the national cancer rates in the population of Japan, stratified by age, sex, and calendar period (29). We calculated SIR based on the number of cancers, and each cancer was counted once, so if a patient had two malignancies, they were each counted once. The SIR of cancer compared the incidence of cancer observed in the AIP cohort with that expected if the cohort developed cancer at the same rate as the standard population of Japan. An SIR greater than 1 indicates an elevated incidence of cancer in the AIP patients relative to the general population of Japan.

Calculation of relative risk of cancer in AIP patients and controls

The control population consisted of those who first had a medical checkup with the full examinations including blood examination, urine analysis, fecal occult blood, chest X-ray, abdominal ultrasonography, gastrointestinal endoscopy, and computed tomography (CT) in the lung in Kyoto Industrial Health Association. Control subjects not having AIP were matched to the cases for age (±5 years) and gender with a 2:1 ratio, leading to the inclusion of 216 controls.

For calculation of relative risk of cancer, we analyzed cancers in AIP patients, which were diagnosed between 1 month before and 1 month after the AIP diagnosis. We analyzed cancers in controls that were diagnosed in the medical checkup.

We defined smoking as >10 pack-year and < 10 year since smoking cessation. We defined alcohol intake as >30 g alcohol per day.

Immunohistochemical study

Immunohistochemistry of the cancer lesions was performed on two representative sections from each case, using antibodies against IgG4 (clone HP6025; dilution 1:500; Serotec, Oxford, UK). Immunostaining was performed on an autoimmunostainer (Ventana XT System Benchmark; Ventana Medical Systems, Tucson, AZ). We selected two sections in which IgG4-positive plasma cells infiltration was most abundant, and photographed them with ×20 objective lens using a Nikon DX1200 digital camera (Nikon, Tokyo, Japan). We defined more than 29 cells per high-power field (HPF) as "abundant" infiltration of IgG4-positive plasma cells, between 10 and 29 cells per HPF as "moderate" infiltration, and fewer than 10 cells per HPF as "few" infiltration (30,31).

Statistical analysis

General characteristics are expressed as median and ranges. Differences concerning clinical characteristics were assessed using Student's *t*-test for continuous data, and the χ^2-test, the Fisher's exact test, and multiple logistic regression analysis for categorical data. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 17.0, Chicago, IL). All statistical tests were two-sided. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Proportion and sites of cancers in AIP patients

Table 1 summarizes the characteristics of the AIP patients. Among the 108 patients with AIP, 18 cancers were found in 15 patients either at the same time or after the diagnosis of AIP during the median follow-up period of 3.3 years. Three patients had multiple cancers. One patient had gastric cancer and lymphoma. Another patient had gastric cancer and colon cancer, and the other patient had bile duct cancer and lung cancer. The proportion of AIP patients with cancer was 13.9% (15/108).

The site of cancers in the AIP patients are shown in **Table 1**. Gastric cancer was the most common. Because of the small numbers of individual cancers, we were unable to determine whether the risk for any individual type of cancer was high compared with the general population.

SIRs of cancer in AIP patients

Eighteen cancers were found in the 108 AIP patients during the overall follow-up of 415.7 person-years. The incidence of cancer expected from the rates of Japanese population in this cohort was 6.7. Accordingly, the SIR of cancer in the patients after the diagnosis of AIP was 2.7 (95% CI 1.4–3.9; **Table 2**).

Time period between the diagnosis of cancer and AIP

Figure 1 shows the chronological relationship between the time of diagnosis of AIP and that for cancer. Of 18 cancers, 10 were detected within the first year after the diagnosis of AIP, including 8 cancers that were concurrently diagnosed. All the eight patients had no symptom/signs related to the cancer, and their cancers were incidentally diagnosed during the process of AIP diagnosis. The remaining 8 cancers were found after the first year of AIP diagnosis. The SIRs of cancer in the first year and in subsequent years after AIP diagnosis were 6.1 (CI 2.3–9.9) and 1.5 (CI 0.3–2.8), respectively (**Table 2**), indicating that the occurrence of cancer was significantly higher in the first year. The cancer sites stratified by time period between the diagnosis of AIP and cancer are shown in **Table 2**.

Relative risk of cancer at diagnosis of AIP

AIP patients underwent intensive testing, which may have enhanced the detection of cancer. Thus, it is possible that this intensive examination raised the SIR for cancer in our cohort, especially in the first year. To solve this concern, we calculated the relative risk of cancer at the diagnosis of AIP in our cohort in comparison with age- and sex-matched controls who first had a medical checkup with almost the same examinations as our cohort. The number of concurrent cancers at the diagnosis of AIP

Table 2. SIRs of cancer in patients with AIP

Variable	Follow-up (person-years)	Observed cases of cancer (no.)	Expected cases of cancer (no.)	Standardized incidence ratio (95% CI)	Site of cancers (no.)
Overall	415.7	18	6.7	2.7 (1.4–3.9)	
Time since diagnosis of AIP					
<1 year	103.6	10	1.6	6.1 (2.3–9.9)	Stomach (4)
					Lung (2)
					Prostate (2)
					Bile duct (1)
					Thyroid (1)
≧1 year	312.1	8	5.2	1.5 (0.3–2.8)	Stomach (3)
					Non-Hodgkin lymphoma (2)
					Colon (2)
					Lung (1)

AIP, autoimmune pancreatisis; CI, confidence interval; no., number of patients; SIR, standardized incidence ratio.
The overall SIR of cancer in the patients after the diagnosis of AIP was 2.7 (95% CI 1.4–3.9). The SIR in the first year and the subsequent years after the AIP diagnosis were 6.1 (95% CI 2.3–9.9) and 1.5 (95% CI 0.3–2.8), respectively. The site of cancers in the first year and following years after the AIP diagnosis were also shown.

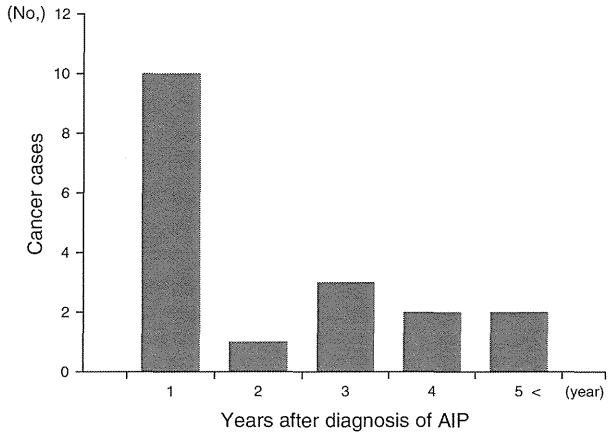

Figure 1. Time of cancer diagnosis in patients with AIP. Blue columns show the number of cancers diagnosed each year after the diagnosis of AIP. Ten cancers were diagnosed at or within 1 year after AIP diagnosis (eight cancers at the time of the diagnosis of AIP). AIP, autoimmune pancreatitis; no., number of cancers.

Table 3. Characteristics of the 108 patients with AIP and the 216 controls

Characteristic	AIP patients	Controls	*P* value
Number	108	216	
Number of cancers	8	3	0.008*
Male patients (%)	89 (82.4)	178 (82.4)	1
Age (years at diagnosis of AIP)			
Median	67	66	0.96
Range	21–86	19–83	
Familial history of cancer[a]	21.8 (30 NA)	32	0.36
Smoking[a]	34.5 (21 NA)	44.3	0.91
Alcohol intake[a]	9.4 (23 NA)	8	0.65

AIP, autoimmune pancreatitis; NA, number of patients whose data were not available.
[a]Data are expressed as percentages.
*Significant difference.

was eight (8/108) and the number of cancers in controls was three (3/216, $P=0.008$; **Table 3**). The incidence of malignancy in the control group (1,388 per 100,000 people) was higher than that in the overall population of Japan (551 per 100,000 people), but comparable to that in age- and sex-matched population according to data from the National Cancer Center in Japan (1,527 per 100,000 people) (29). Relative risk of cancer at AIP diagnosis was 4.9 (95% CI 1.7–14.9). In the eight AIP patients with cancer, no cancer was detected by abdominal CT or Positron Emission Tomography-CT, which were not included in the examinations in the controls. The differences of familial history of cancer, smoking, and alcohol intake between AIP patients and controls were not significant.

Clinicopathological characteristics of AIP patients with cancer

Serum IgG4 levels. Serum IgG4 levels at the diagnosis of AIP were significantly higher in AIP patients with cancers than in those without cancer (738 vs. 389, $P=0.02$).

Extrapancreatic lesions. Extrapancreatic lesions were found in 75 of the 108 (69.4%) patients with AIP. The frequencies of sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis, renal involvement, and lung involvement were 52.8% (57 patients), 9.3% (10 patients), 9.3% (10 patients), 3.7% (4 patients), and 3.7% (4 patients), respectively. In the 15 AIP patients with cancer, extrapancreatic lesions occurred in 11 (73.4%) patients. The frequencies of sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal

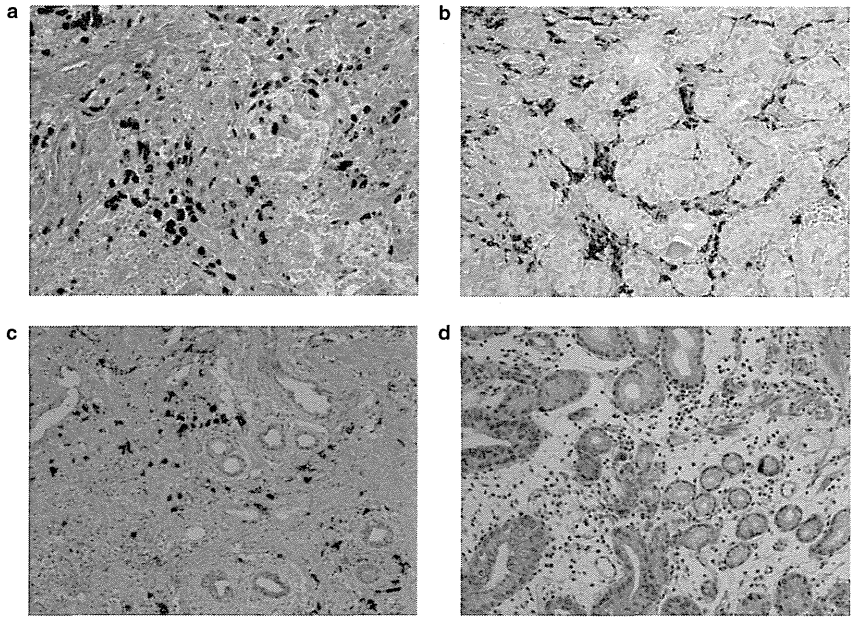

Figure 2. Infiltration of IgG4-positive plasma cells around the cancer before corticosteroid therapy. Representative cases of bile duct cancer (**a**), thyroid cancer (**b**), and prostate cancer (**c**) coexisting with AIP show abundant infiltration of IgG4-positive plasma cells before corticosteroid treatment (159, 214, and 50 cells/HPF, respectively). In contrast, one case of gastric cancer showed few infiltration of IgG4-positive cells before corticosteroid treatment (4 cells/HPF) (**d**). We defined more than 29 IgG4-positive cells/HPF as "abundant", between 10 and 29 cells/HPF as "moderate" infiltration and less than 10 cells/HPF as "few". AIP, autoimmune pancreatitis; HPF, high-power field.

fibrosis, renal involvement and lung involvement were 60% (nine patients), 13.3% (two patients), 20.0% (three patients), 0 and 6.7% (one patient), respectively. In the 93 AIP patients without cancer, extrapancreatic lesions occurred in 64 (68.9%) patients. The frequencies of sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis, renal involvement, and lung involvement were 51.6% (48 patients), 8.6% (8 patients), 7.5% (7 patients), 4.3% (4 patients), and 3.2% (3 patients), respectively. Thus, frequencies of overall extrapancreatic lesions were similar between AIP patients with and without cancer. Moreover, univariate and multivariate analyses revealed no significant difference in the frequency of each extrapancreatic lesion between AIP patients with and without cancer. However, when we compared 8 patients concurrently diagnosed with AIP and cancer and 93 AIP patients without cancer, univariate ($P=0.04$) and multivariate analyses ($P=0.02$) revealed that frequency of retroperitoneal fibrosis was significantly higher in the patients concurrently diagnosed with AIP and cancer than AIP patients without cancer (3/8 vs. 8/93).

IgG4-positive plasma cell infiltration in the cancer lesions and relapse of AIP. Next, we evaluated IgG4-positive plasma cell infiltration in the cancer lesions by immunohistochemistry (**Figure 2**). To exclude the effect of corticosteroid therapy, we selected eight patients concurrently diagnosed with AIP and cancer, whose cancer lesions were assessed before corticosteroid treatment (**Table 4**). Of these eight cancer lesions, six showed abundant IgG4-positive plasma cell infiltration in the tissues surrounding the tumor cells, whereas the other two cancer lesions had few infiltration. All eight patients were successfully treated for cancer (surgery, chemotherapy, or radiotherapy), followed by corticosteroid treatment for AIP. None of the six AIP patients with abundant IgG4-positive plasma cell infiltration around the cancers developed a relapse of AIP during the median follow-up of 4.7 years, whereas one of the two patients with few IgG4 plasma cell infiltration relapsed during the follow-up of 0.5 and 4.4 years and relapse rate was 0.20. Sixteen of 93 AIP patients without cancer had a relapse of AIP during the median follow-up of 3.1 years and relapse rate was 0.046.

As gastric cancer was the primary malignancy in our AIP patients, we examined serum IgG4 levels in 20 gastric cancer patients without AIP, and IgG4-positive plasma cell infiltration in the surrounding tissues in 40 gastric cancer patients without AIP. We found that serum IgG4 levels were above 135 mg/dl in 5 out of 20 gastric cancer patients with a maximum level of 227 mg/dl. On the other hand, moderate IgG4-positive plasma cell infiltration (10 to 29/HPF) were observed in only 2 out of 40 patients, and there were no gastric cancer with abundant IgG4-positive plasma cell infiltration (more than 29/HPF). The frequency of the patients with abundant IgG4-positive plasma cells around gastric cancer was significantly higher in AIP patients than non-AIP patients (2/3 vs. 0/40, $P=0.003$).

DISCUSSION

Although recent studies reported cases of AIP associated with cancers (4–12), no studies have examined the association between AIP and cancers in a large number of patients. In the present study

Table 4. **IgG4-positive plasma cell infiltration in cancer stroma coexisting with AIP**

Patients	Site of cancer	IgG4-positive cells (cells/HPF)	Serum IgG4 level (mg/dl)	AIP relapse	Follow-up period of AIP (years)
1	Stomach	332	360	(−)	5.8
2	Stomach	251	1,040	(−)	0.8
3	Stomach	4	194	(+)	4.4
4	Prostate	56	151	(−)	1.4
5	Prostate	4	1,170	(−)	0.5
6	Bile duct	159	NE	(−)	5.6
7	Thyroid	214	NE	(−)	4.7
8	Lung	55	528	(−)	1.9

AIP, autoimmune pancreatitis; NE, not examined; HPF, high-power field.
Numbers of IgG4-positive plasma cells showing infiltration around the cancer before corticosteroid treatments were counted (cells/HPF). Serum IgG4 levels at the diagnosis of AIP, and relapse of AIP after successful treatments for cancer were evaluated.

we analyzed a relatively large number of patients, and our findings demonstrated that cancer frequently occurs in patients with AIP. In a recent analysis of 105 patients with IgG4-related disease, including 10 AIP cases, Yamamoto *et al.* (13) reported that IgG4-related disease is a high-risk factor for cancer development. In their study, 20% of the patients with AIP had cancers, comparable to our data. Based on the findings of these two studies, patients with AIP are at high risk for cancer.

In previous reports, pancreatic cancer was the most common cancer found in patients with AIP (4–6). In contrast, none of the patients had pancreatic cancer in the present study. The reason for the discrepancy between our data and previous data is unknown. One possibility is that the awareness of differentiating AIP from pancreatic cancer may have enhanced the publication number of pancreatic cancer with AIP in previous studies. Another possibility is that AIP associated with pancreatic cancer might not have been diagnosed as AIP in our cohort, because we usually did not sample serum and tissue IgG4 levels in typical cases with pancreatic cancer. Nevertheless, no incidence of pancreatic cancer in patients with AIP in our cohort may support the notion that the cancer development in patients with AIP does not depend directly upon underlying chronic inflammation. In any event, patients with AIP have various type of cancers. The finding that the serum IgG4 levels were significantly higher in AIP patients with cancers than in those without cancers indicates that high IgG4 might be a useful marker for concurrent cancers.

The reason for the high risk of cancer in patients with AIP is unknown at present. In the present study, cancer tissues in AIP patients that were examined histologically before the administration of corticosteroids were frequently infiltrated with IgG4-positive plasma cells. This finding may suggest that the cancers in patients with AIP arise in the background of IgG4-related inflammation. It is well known that chronic inflammation has an important role in the development of various types of cancer, including *Helicobacter pylori*-induced gastric cancer, hepatitis C virus-related hepatocellular carcinoma, and colitic cancer (17,18,32,33). However, it should be noted in our study that no AIP patient developed cancer in the pancreas, a major site of inflammation. This fact seems to contradict to an idea that chronic inflammation due to AIP is responsible for the development of cancer. In this context, it is worth noting that the risk of cancer development was the highest in the first year of AIP diagnosis in our study. Moreover, seven of eight patients, in whom cancer was histologically diagnosed before corticosteroid administration, did not have a recurrence of AIP after successful cancer treatment. In addition, curative cancer treatment prevented the relapse of AIP in the six patients whose cancer tissue showed abundant IgG4-positive plasma cell infiltration. Taken together, the data may indicate that the existing cancers have some roles in the development of AIP, raising an idea that AIP is a manifestation as a paraneoplastic syndrome in some patients. The fact that the relative risk of cancer at AIP diagnosis was significantly high in comparison with age- and sex-matched control subjects who received similar levels of examinations may further support an idea that certain portion of AIP is categorized as paraneoplastic syndrome.

Another well-known paraneoplastic syndrome that has an autoimmune nature is DM/PM (14–16). In patients with DM and PM, the SIR for cancers ranges from 3.7 to 8.8 and 1.7 to 2.2, respectively (20,21). AIP and PM/DM share several clinical findings as paraneoplastic syndrome. For instance, in our cohort with 108 patients, cancer was diagnosed concomitantly with AIP or within the first year after the AIP diagnosis in eight and two patients, respectively. Thus, similar to the previous reports on PM/DM (14,22), the risk for cancer diagnosis is highest within the first year after diagnosis of AIP, including the time of diagnosis of AIP. Notably, the cancers concurrently diagnosed with AIP were not detected by abdominal CT or Positron Emission Tomography-CT, which were not included in the examinations in the controls, excluding the possibility that the higher level of diagnostic work-up in AIP patients increased the probability of cancer diagnosis in our cohort. In addition, clinical and immunological abnormalities seen in both AIP and DM/PM are improved after successful treatment of the cancers (34). These similarities between DM/PM and AIP with regard to the relationship between

each disease and cancer further support the paraneoplastic nature of AIP, although we did not clarify the distinct immunological characteristics of AIP patients with cancers from those without cancers.

In DM/PM, the common cancers are different in different countries. The most common site of cancer is the stomach in Japan (35), whereas the ovary, lung, or gastrointestinal tracts are major sites of cancers in Western countries, and nasopharynx in Southeast Asia, South China, and North Africa (21). Similar to DM/PM, the most common cancer was gastric cancer in our cohort of Japanese patients with AIP. The high prevalence of gastric cancer in not only DM/PM but also AIP patients may reflect high incidence of gastric cancer in Japanese population (29).

In this study, we observed that the cancer tissues in AIP patients were frequently infiltrated with IgG4-positive plasma cells. The reason for the accumulation of IgG4-positive cells in the tumor tissues and the role of these cells in the pathophysiology of IgG4-related AIP, however, remain unknown. Previously, we reported that abnormal innate immune responses contribute to IgG4 production in B cells in patients with AIP (36). Moreover, tumor cells provoke innate immune responses by various mechanisms, such as release of various proinflammatory cytokines, or ligands for pattern-recognition molecules (37–39). Thus, it is possible that the tumor tissues or tumor cells activate IgG4-related immune responses. However, whether or not such immunological response contributes to the development of IgG4-related disease/AIP remains to be elucidated in future studies.

As for diagnosis of AIP, it has been reported that the specificity of AIP diagnosis was higher in HISORt criteria (97%) than in Japanese criteria (89%) or Asian criteria (89%) (40,41). In Asian criteria, AIP can also be diagnosed by response to steroid therapy (24), which might lead to the increased sensitivity and reduced specificity. Accordingly, we re-evaluated the AIP patients in our cohort by using Japanese or HISORt criteria. As a result, 94 out of the 108 AIP patients in our cohort fulfilled Japanese criteria. In the remaining 14 patients who did not meet Japanese criteria, AIP was diagnosed by Asian criteria with typical histology in resected pancreas in 10 patients or with optional criterion (image + response to steroid therapy) in 4 patients. On the other hand, 104 out of the 108 patients fulfilled HISORt criteria, and the remaining 4 patients were diagnosed by Asian criteria with optional criterion (image + response to steroid therapy). From these results, we believe that the accuracy of the AIP diagnosis was comparable to that made by Japanese or HISORt criteria, and therefore, that our cases of AIP were based on the accepted criteria.

Despite the importance of our findings, the present study has several limitations. Because we used national cancer rates as the control, SIR of cancer in the first year after diagnosis of AIP (6.1 (95% CI 2.3–9.9)) could be overestimated in our cohort who may be more carefully scrutinized than the general population. However, SIR of cancer in the first year after diagnosis of myositis (DM/PM) was reported 4.4 (95% CI 2.7–7.1) by the similar method of the population-based cohort study (20). These comparable values between AIP and myositis might support the high risk for cancer in the first year after AIP diagnosis. Moreover, to solve this concern, we calculated the relative risk of cancer in comparison with age- and sex-matched control people who first had a medical checkup with almost the same examinations as our cohort. In additional limitation, the sample size was relatively small and retrospective studies are more prone to bias than prospective studies, and this may have contributed to the higher SIR and relative risk. A prospective study with a large number of patients should be performed.

In conclusion, patients who fulfilled the accepted criteria for AIP are at high risk for having cancer. The highest risk for cancer is in the first year after AIP diagnosis, including the time at the diagnosis of AIP, and there is a very low relapse rate of AIP after successful treatment of the accompanying cancer. These data might indicate that a certain portion of AIPs can be categorized as a paraneoplastic syndrome. Finally, more studies are needed to determine whether screening for neoplasia should be done in patients with AIP, and also to decide whether high prevalence of cancer in our cohort really reflects its paraneoplastic phenomenon or merely an epiphenomenon.

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CONFLICT OF INTEREST

Guarantor of the article: Yuzo Kodama, MD, PhD.

Specific author contributions: Study concept and design, data acquisition, data analysis and interpretation, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and study supervision: M.S., K.Y., and T.C. Statistical analysis, study supervision, data acquisition, and drafting of the manuscript: H.H. and K.Y. Patient enrollment, data acquisition, and drafting of the manuscript: J.M., C.K., M.K., S.Y., R.M., Y.S., K.K., Y.O., M.O., H.K., T.I., K.T., Y.O., W.T., T.M., S.K., Y.D., N.U., and T.W.

Competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Recent reports indicate that patients with autoimmune pancreatitis (AIP) occasionally have various cancers.
- ✓ It was also reported that patients with IgG4-related disease are at high risk for cancer.

WHAT IS NEW HERE

- ✓ Increased cancer risk was observed in patients with AIP during the first year after AIP diagnosis.
- ✓ Successful treatment for cancers with abundant IgG4-positive plasma cell infiltration may be associated with remission of AIP.
- ✓ These findings suggest that AIP may develop as a paraneoplastic syndrome in some patients.