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解剖病理科
蕭正祥主任

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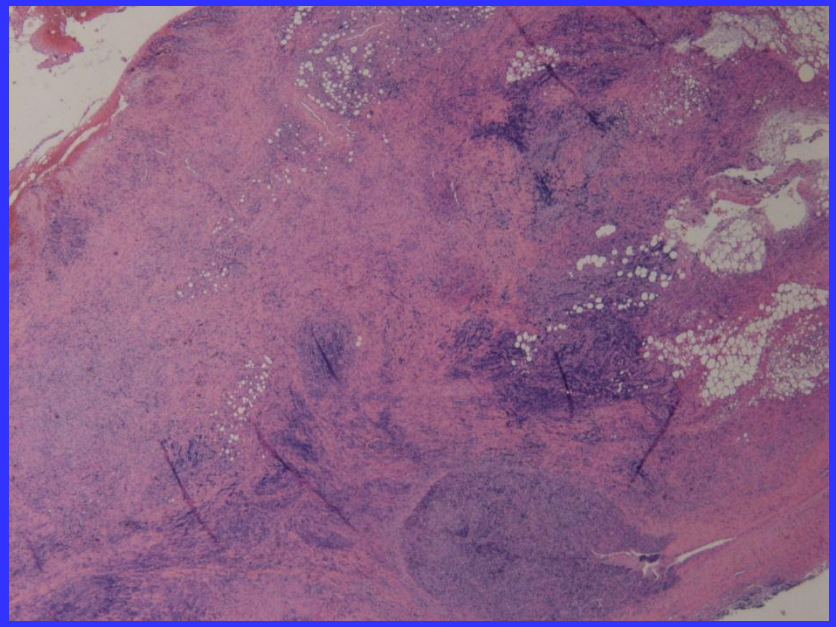
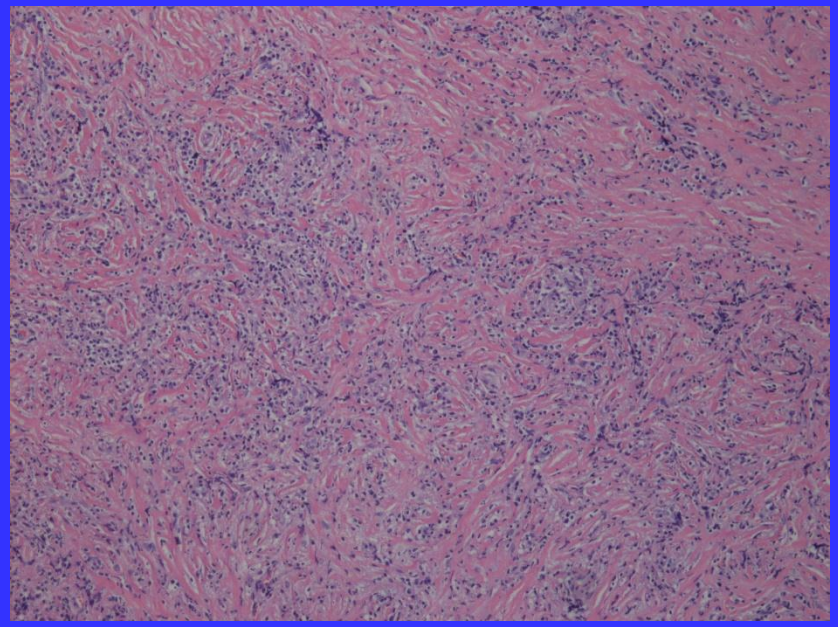
72/M

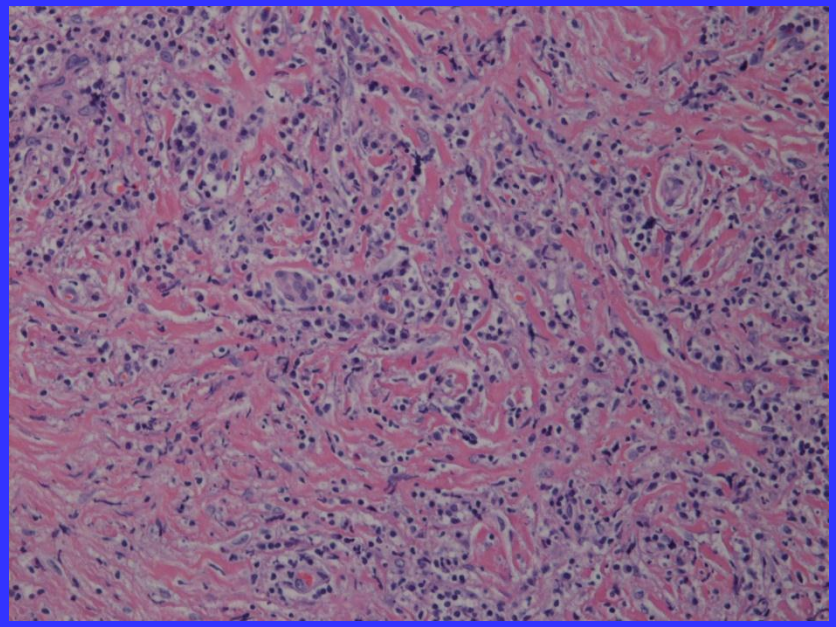
104-13249
Posterior mediastinal soft tissue

Inflammatroy infiltrate and fibrosis

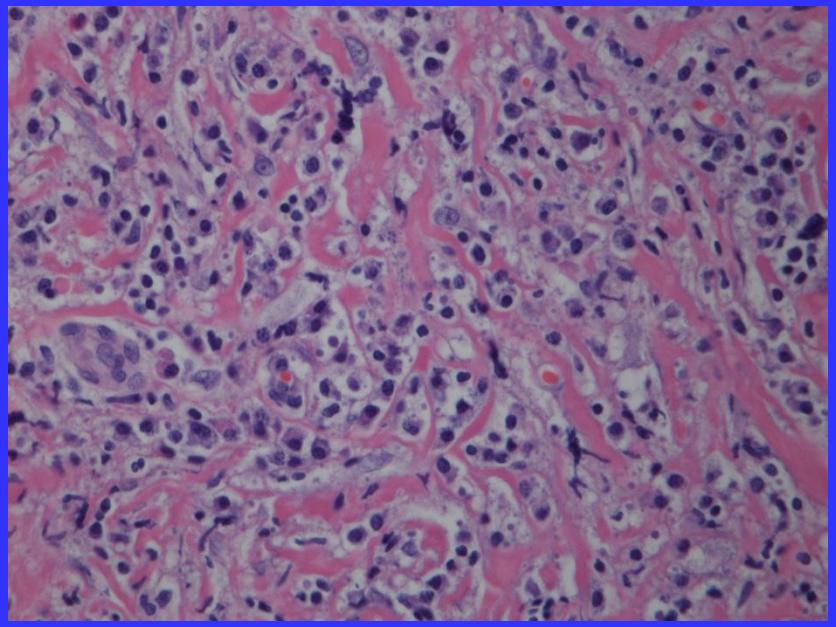


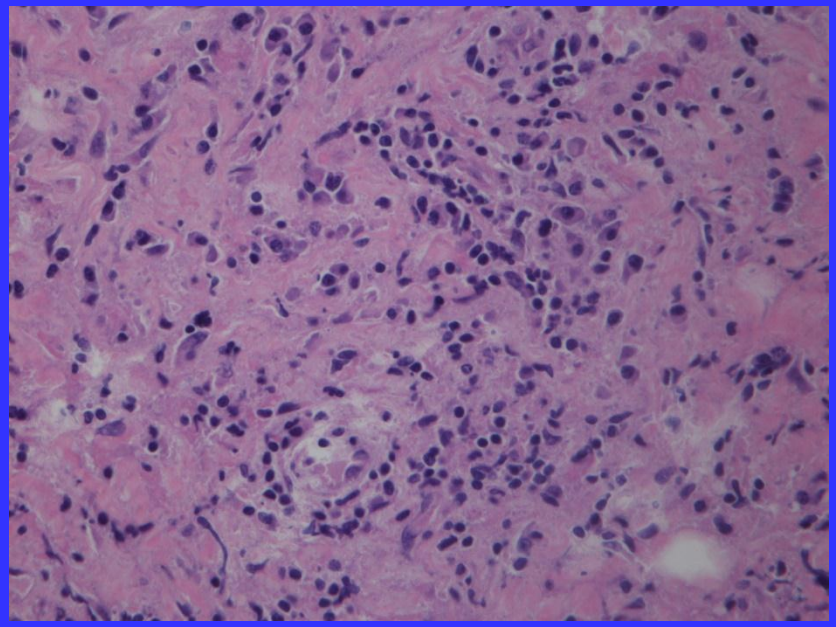


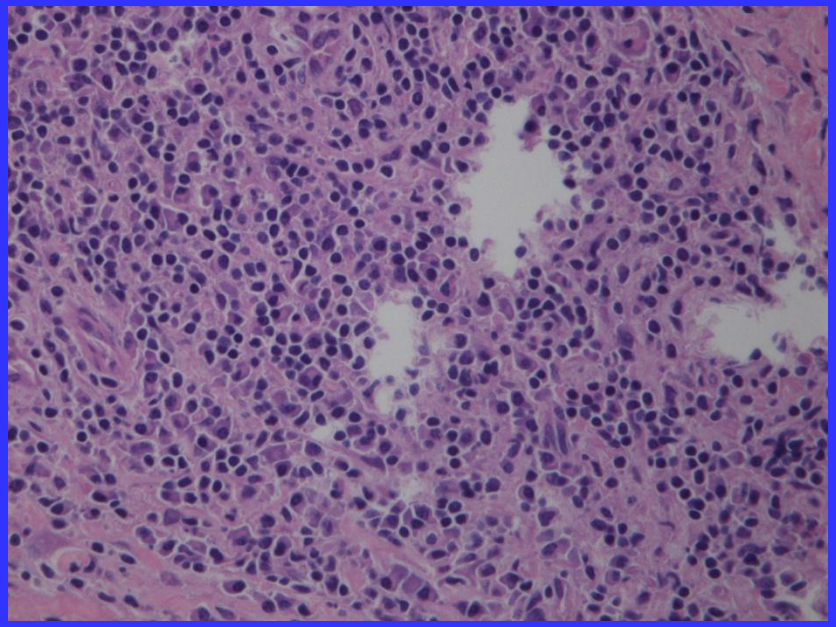
Storiform fibrosis and inflammation



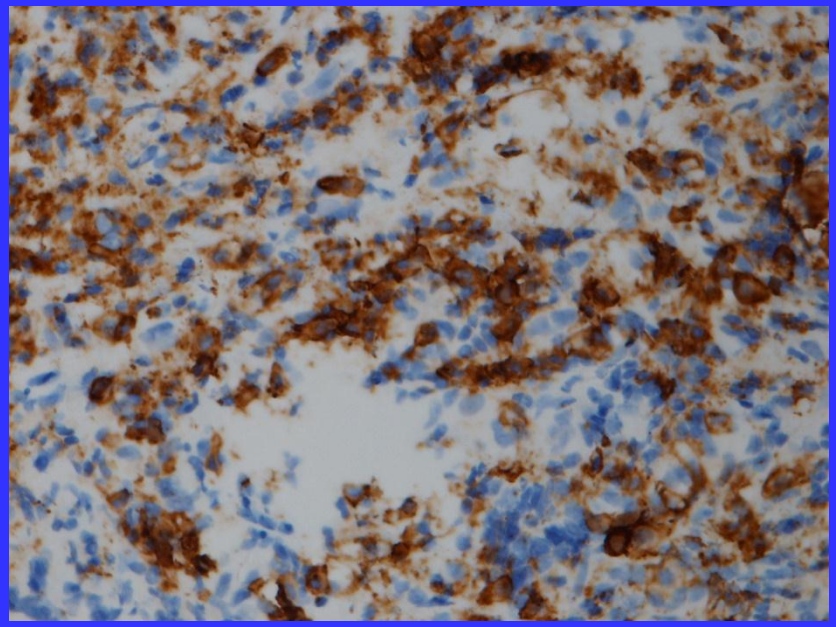
Profuse plasma cell infiltration







CD 138



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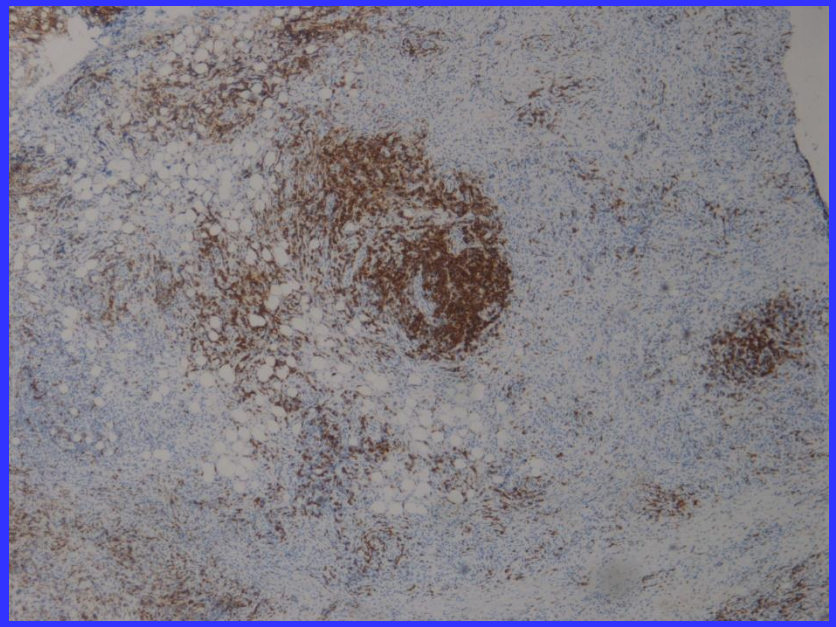
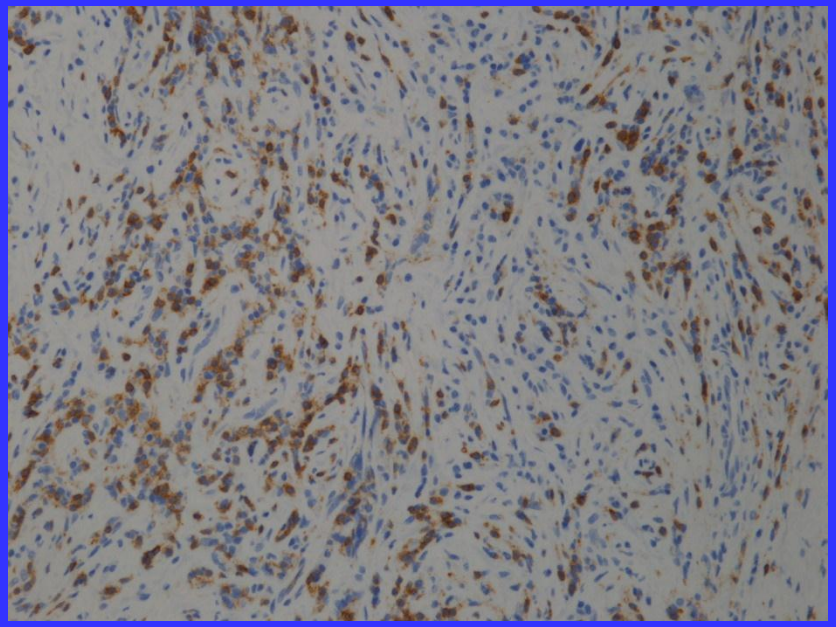
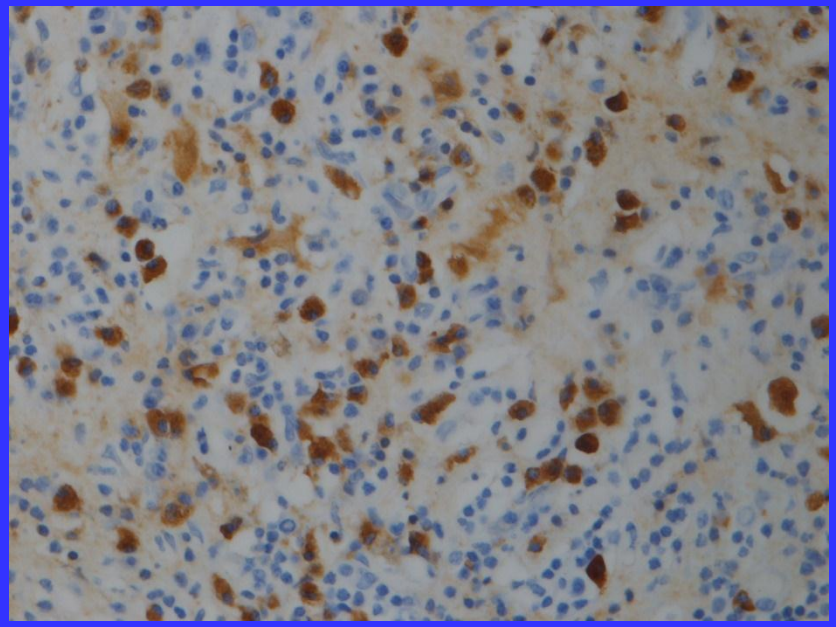


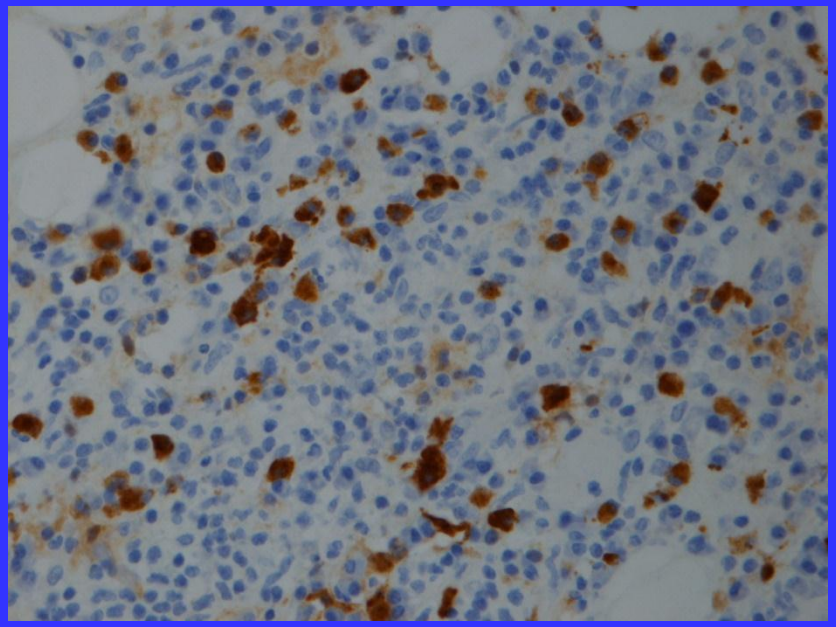
CD3



Ig G



Ig G4



IgG4-Related Disease

- A newly recognized fibro-inflammatory disease characterized by tumefactive lesions, dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and, often but not always elevated serum IgG4 concentration.

Autoimmune pancreatitis (Prototype of IgG4-related sclerosing disease)

- Proposed by Yoshida in 1995
- A mass lesion in the pancreas with obstructive jaundice, pancreatic duct narrowing and DM; usually response to steroid therapy.
- May associated with other immune-mediated disease, such as scleroisng cholangitit, PBC, Sjogren syndrome and IBD.
- Two types:
  - Lymphoplasmacytic sclerosing pancreatitis (LPSP)
  - Idiopathic duct-centric chronic pancreatitis (IDCP)
- Pathology: lymphoplasmacytic infiltrate, sclerosis, obliterative phlebitis
- In 2001, Hamano reported elevated serum IgG4 level in patients with AIP

Table 1. Asian Diagnostic Criteria (Japan-Korea Consensus) for Autoimmune Pancreatitis (IgG4-related Sclerosing Pancreatitis)

Criterion I-Imaging (both required)	1. Pancreatic parenchyma-diffuse/segmental/focal enlargement of the gland, occasionally with a mass and/or hypoattenuation rim 2. Pancreaticobiliary ducts-diffuse/segmental/focal pancreatic duct narrowing, often with stenosis of bile duct
Criterion II-Serology (1 required)	1. High levels of serum IgG or IgG4 2. Detection of autoantibodies
Criterion III-Histopathology of pancreatic biopsy	Lymphoplasmacytic infiltration with fibrosis and abundant IgG4+ cells
Criterion IV-Histopathology of resected pancreas	Lymphoplasmacytic sclerosing pancreatitis (storiform fibrosis, lymphoplasmacytic infiltration, periductal inflammation, obliterative phlebitis, numerous IgG4+ cells)
Optional criterion-Response to steroid therapy	Diagnostic trial of steroid therapy should be conducted only in patients fulfilling criterion I alone with negative work-up results for pancreatobiliary cancer
Diagnostic of autoimmune pancreatitis when any of the following is fulfilled:	1. Criterion I+II 2. Criterion I+III 3. Criterion I+II+III 4. Criterion IV

IgG4, immunoglobulin G4.

Ig G4 related sclerosing disease

- absolute number of IgG4+ cells >50/high-power fields (HPF)
- ratio of IgG4+/IgG+ cells > 40%.

- A raised serum IgG4 level is not mandatory for the diagnosis but may be of valuable assistance.

Table 3. Body Sites Affected by IgG4-Related Sclerosing Disease

Body site	Clinicopathologic features
Pancreas	Lymphoplasmacytic sclerosing pancreatitis (type 1 AIP) and idiopathic duct centric chronic pancreatitis (type 2 AIP)
Bile duct	Sclerosing cholangitis
Gall bladder	Acalculous sclerosing cholecystitis
Liver	Sclerosing cholangitis involving intrahepatic ducts, inflammatory pseudotumor, portal inflammation with or without interface hepatitis, portal sclerosis, large bile duct obstruction, lobular hepatitis, canalicular cholestasis
Salivary glands	Chronic sclerosing sialadenitis (Kuttner tumor), Mikulicz disease
Lacrimal glands and orbit	Chronic sclerosing dacryoadenitis, inflammatory pseudotumor
Retroperitoneum and mesentery	Retroperitoneal fibrosis, sclerosing mesenteritis
Cardiovascular/Aorta	Inflammatory abdominal aortic aneurysm
Mediastinum	Sclerosing mediastinitis
Kidney and ureter	Tubulointerstitial nephritis, membranous glomerulopathy, inflammatory pseudotumor
Thyroid	Hypothyroidism, Riedel's thyroiditis
Breast	Sclerosing mastitis
Lung	Inflammatory pseudotumor, interstitial pneumonia
Central nervous system	Hypophysitis, sclerosing pachymeningitis
Prostate	Prostatitis
Lymph node	Lymphadenopathy with Castleman disease like features, follicular hyperplasia, interfollicular expansion by plasma cells and immunoblasts

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A case of retroperitoneal and mediastinal fibrosis exhibiting elevated levels of IgG4 in the absence of sclerosing pancreatitis (autoimmune pancreatitis)

Yoh Zen MD[a,b,*], Aiko Sawazaki MD[c], Shiro Miyayama MD[d], Kazuo Notsumata MD[c], Nobuyoshi Tanaka MD[c], Yasuni Nakanuma MD[e]

[a]*Division of Pathology, Kanazawa University Hospital, Kanazawa 920-8641, Japan*
[b]*Department of Pathology, Fukui Saiseikai Hospital, Fukui 918-8503, Japan*
[c]*Department of Internal Medicine, Fukui Saiseikai Hospital, Fukui 918-8503, Japan*
[d]*Department of Radiology, Fukui Saiseikai Hospital, Fukui 918-8503, Japan*
[e]*Department of Human Pathology, Kanazawa University Graduate School of Medicine, Kanazawa 920-8640, Japan*

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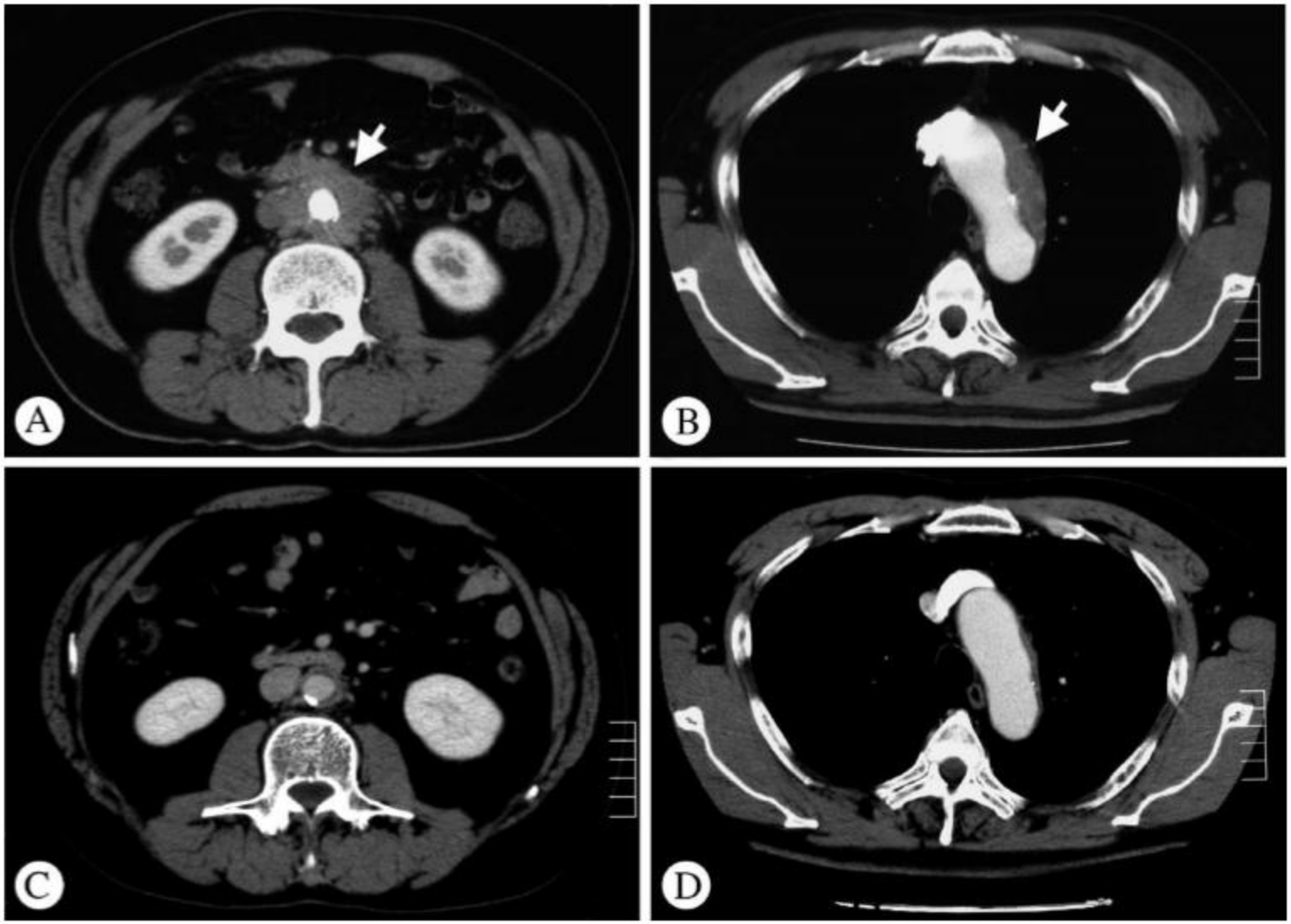

Fig. 1 A and B, Contrast material–enhanced computed tomography of the abdomen and chest showing paraaortic masses in the retroperitoneum and mediastinum before corticosteroid therapy (arrows). C and D, The paraaortic mass was markedly reduced in size after corticosteroid therapy for 8 weeks.

CASE REPORT

IgG4-related Sclerosing Pachymeningitis

A Previously Unrecognized Form of Central Nervous System Involvement in IgG4-related Sclerosing Disease

Siu-Ki Chan, MBChB, Wah Cheuk, MBBS,† Kwan-Tsz Chan, MBChB,‡ and John K. C. Chan, MBBS†*

AJSP 2009

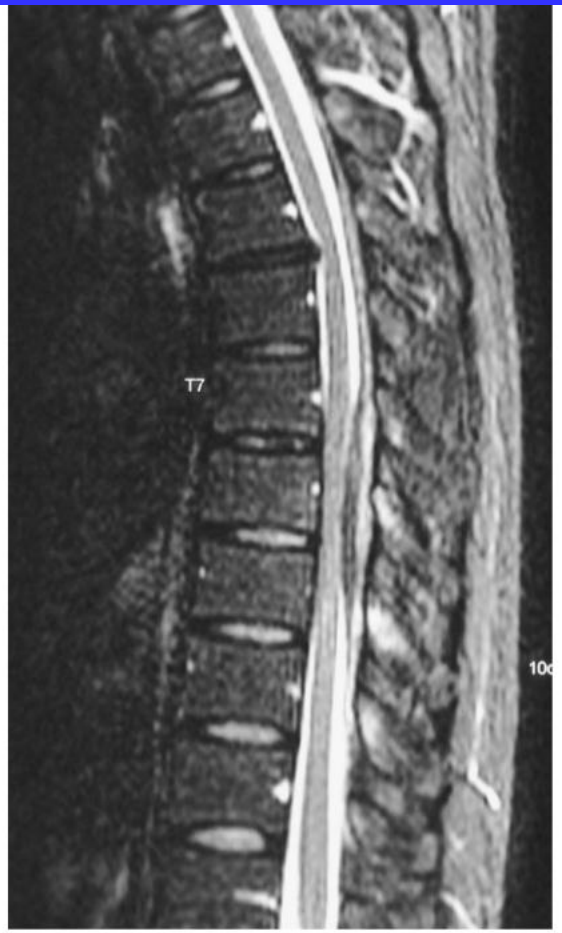

FIGURE 1. The sagittal T2-weighted magnetic resonance image showed a hyperintense extradural spindle-shaped lesion over the dorsal aspect of the spinal canal extending from the fifth to tenth thoracic vertebra. The lesion showed homogeneous gadolinium enhancement.

Abstract: IgG4-related sclerosing disease is a distinctive mass-forming lesion with frequent systemic involvement, most frequently the pancreas, salivary glands, and lacrimal glands. This report describes a case manifesting with a previously unrecognized form of central nervous system involvement. The 37-year-old man presented with signs and symptoms of spinal cord compression at the thoracic level 9. Magnetic resonance imaging revealed an elongated dural mass extending from the fifth to tenth thoracic vertebra. Laminectomy and excision of the mass revealed dura expanded by a dense lymphoplasmacytic infiltrate accompanied by stromal fibrosis and phlebitis. IgG4+ plasma cells were increased and the proportion of IgG4+/IgG+ plasma cells was 85%. The patient also had a 1-year history of bilateral submandibular swelling due to chronic sialadenitis. Thus, IgG4-related sclerosing pachymeningitis represents a new member of the IgG4-related sclerosing disease family affecting the central nervous system. It seems that at least a proportion of cases described in the literature as idiopathic hypertrophic pachymeningitis belong to this disease, especially as some patients have other clinical manifestations compatible with IgG4-related sclerosing disease, such as cholangitis and orbital pseudotumor.

Key Words: IgG4-related sclerosing disease, IgG4-related pachymeningitis, spinal cord compression, central nervous system, idiopathic hypertrophic pachymeningitis

(*Am J Surg Pathol* 2009;33:1249–1252)

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

IgG4-Related Disease

John H. Stone, M.D., M.P.H., Yoh Zen, M.D., Ph.D., and Vikram Deshpande, M.D.

IgG4-RELATED DISEASE IS A NEWLY RECOGNIZED FIBROINFLAMMATORY CONdition characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and, often but not always, elevated serum IgG4 concentrations. The disease was not recognized as a systemic condition until 2003, when extrapancreatic manifestations were identified in patients with autoimmune pancreatitis.[1] Autoimmune pancreatitis had been linked to elevated serum IgG4 concentrations as early as 2001,[2] and pancreatic specimens from patients with this condition were found to contain large numbers of IgG4-positive plasma cells. This disease is now considered to encompass two separate disorders: type 1, which is associated with IgG4-related disease; and type 2, which has substantial clinical overlap with type 1 but distinctive pathological features.[3]

IgG4-related disease has been described in virtually every organ system: the biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, and skin.[1,4-7] The histopathological features bear striking similarities across organs, regardless of the site of disease. IgG4-related disease is therefore analogous to sarcoidosis, another systemic disease in which diverse organ manifestations are linked by the same histopathological characteristics.

The nomenclature for IgG4-related disease continues to evolve. In a consensus meeting, Japanese investigators[8] recommended the adoption of "IgG4-related disease" among many suggested names.[9] IgG4-related disease is the name we have chosen to use.

Many medical conditions that have long been viewed as conditions confined to single organs are part of the spectrum of IgG4-related disease (Table 1). Mikulicz's syndrome, Küttner's tumor, and Riedel's thyroiditis — names embedded in the medical literature for more than a century in some cases — may now be replaced by designations that describe a key pathological feature and perhaps provide more insight into the pathophysiology. However, much remains unknown about the behavior of IgG4 in vivo, the participation of this molecule in disease, and whether its role in IgG4-related disease is primary or secondary. We describe the clinical, pathological, and radiologic features of IgG4-related disease; review potential disease mechanisms; and discuss early observations related to treatment.

From Harvard Medical School (J.H.S., V.D.) and the Departments of Medicine (Division of Rheumatology, Allergy, and Immunology) (J.H.S.) and Pathology (V.D.), Massachusetts General Hospital — both in Boston; and the Institute of Liver Studies, King's College Hospital, London (Y.Z.). Address reprint requests to Dr. Stone at the Rheumatology Unit, Massachusetts General Hospital, 55 Fruit St., Yawkey 2C, Boston, MA 02114, or at jhstone@partners.org.

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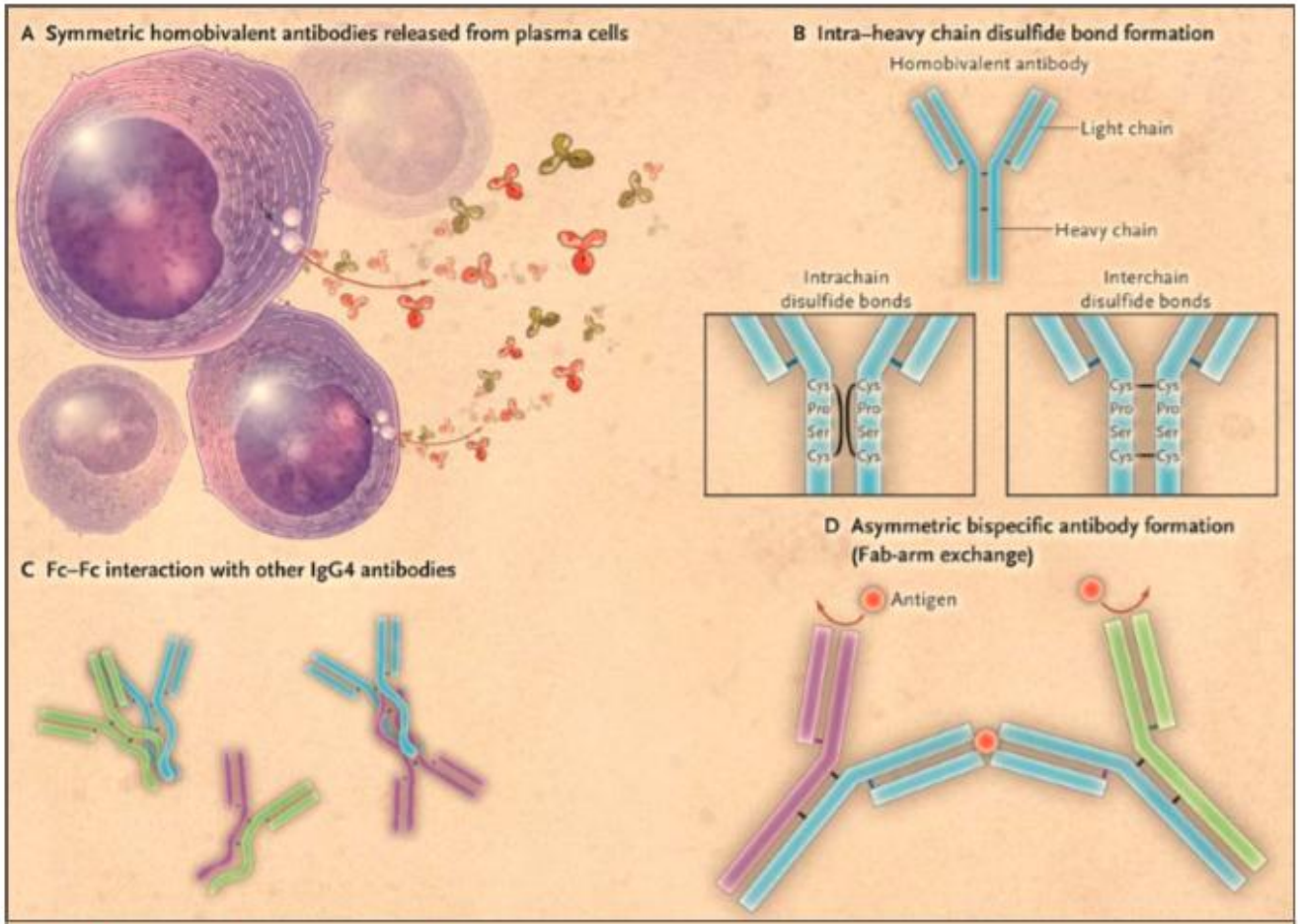

Figure 1. Biologic Characteristics of IgG4.

IgG4 molecules are released from plasma cells as symmetric homobivalent antibodies (Panel A). Because of the instability of the disulfide bonds between heavy chains of IgG4, some IgG4 antibodies form intrachain disulfide bonds in the hinge region and consist of heavy chains linked by noncovalent interaction (Panel B). In vitro analyses suggest that Fc interactions between IgG4 molecules are an intermediate stage preceding Fab-arm exchange (Panel C). These interactions may prevent inflammatory responses by shielding Fc portions from other immune-related molecules. IgG4 is transformed to an asymmetric, bispecific antibody by exchanging half-molecules with other IgG4 molecules (Panel D). IgG4 with two different antigen-combining sites behaves as a monovalent antibody. Fab-arm exchange results in the loss of the antibody's ability to cross-link antigens and to form immune complexes, leading to ineffective immune-complex formation with other IgG4 antibodies and other antibody isotypes.

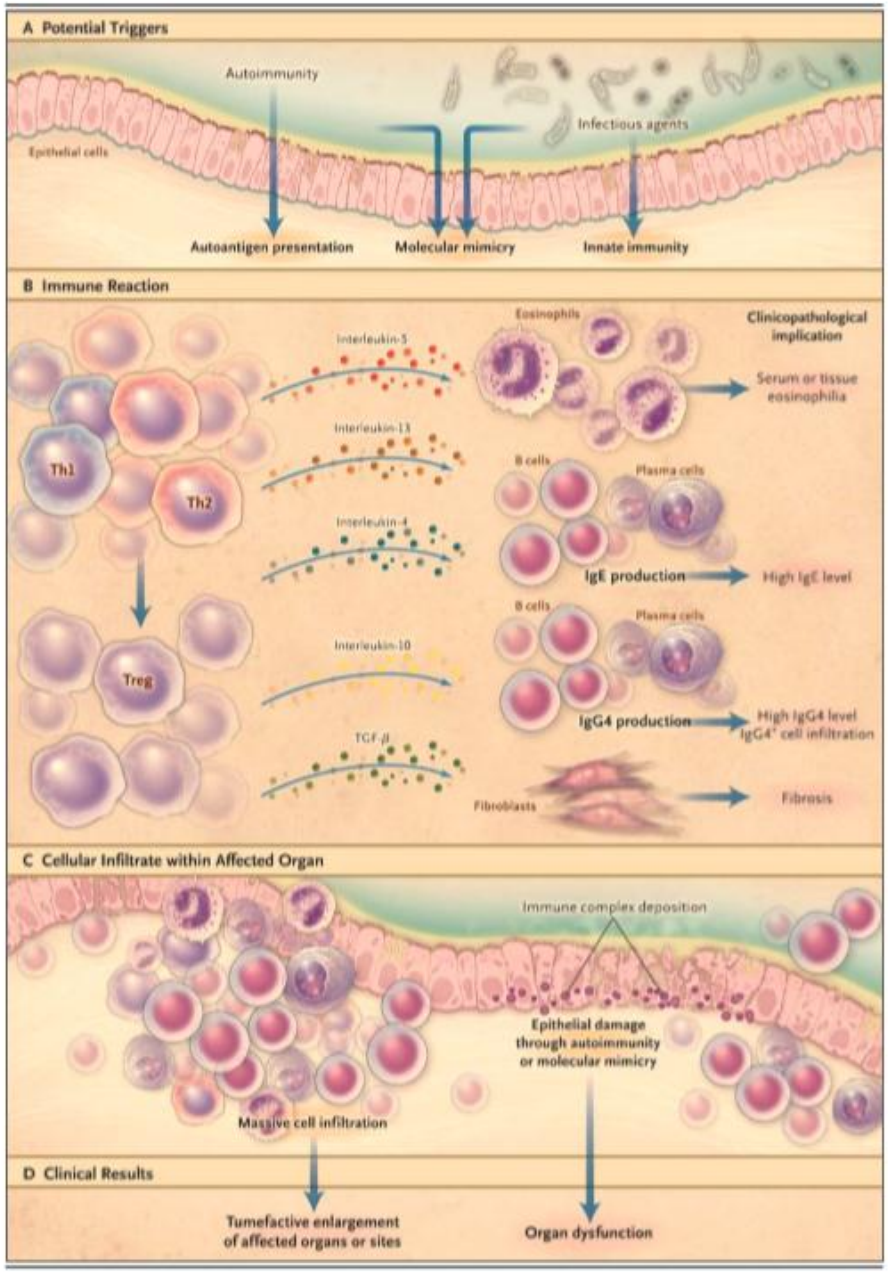

Figure 3 (facing page). Pathogenetic Mechanisms in IgG4-Related Disease and Clinical Implications.

Autoimmunity and infectious agents are potential immunologic triggers in IgG4-related disease (Panel A). Interleukins 4, 5, 10, and 13 and transforming growth factor β (TGF-β) are overexpressed through an immune reaction in which type 2 helper T (Th2) cells predominate, followed by activation of regulatory T (Treg) cells (Panel B). These cytokines contribute to the eosinophilia, elevated serum IgG4 and IgE concentrations, and progression of fibrosis that are characteristic of IgG4-related disease. Massive infiltration by inflammatory cells results in organ damage (Panel C). The inflammatory-cell infiltrate leads to tumefactive enlargement of the affected sites and organ dysfunction (Panel D). Epithelial damage may result from tissue inflammation and immune-complex deposition.

Steroid is the first line Tx

- prednisolone at a dose of 0.6 mg per kilogram of body weight per day for 2 to 4 weeks.87 The authors suggested further that the prednisolone be tapered over a period of 3 to 6 months to 5.0 mg per day, and then continued at a dose between 2.5 and 5.0 mg per day for up to 3 years.
- Another approach has been to discontinue glucocorticoids entirely within 3 months.

- A multicenter study from Japan showed that IgG4 levels failed to normalize in 115 of 182 patients (63%) treated with glucocorticoids.
- For patients with recurrent or refractory disease, B-cell depletion with rituximab appears to be a useful approach.
- Patients in whom fibrosis has become well established are less likely to have a response to glucocorticoids and rituximab.

Table 2. Mayo Clinic Diagnostic Criteria for Autoimmune Pancreatitis (IgG4-related Sclerosing Pancreatitis): The HISORt Criteria

Criterion H-Histology (at least one of the following)	1. Periductal lymphoplasmacytic infiltrate, obliterative phlebitis, storiform fibrosis 2. Lymphoplasmacytic infiltrate, storiform fibrosis, abundant IgG4+ cells (≥10 HPF)
Criterion I-Imaging of pancreas	1. Typical-diffusely enlarged gland with delayed (rim) enhancement; diffusely irregular, attenuated main pancreatic duct 2. Others-Focal pancreatic mass/enlargement; focal pancreatic duct stricture; pancreatic atrophy; pancreatic calcification; pancreatitis
Criterion S-Serology	Elevated serum IgG4 (normal: 8-140 mg/dL)
Criterion O-Other organ involvement (can be confirmed by biopsy or resolution/ improvement with steroid therapy)	Hilar/intrahepatic biliary strictures; persistent distal biliary stricture; parotid/lacrimal gland involvement; mediastinal lymphadenopathy; retroperitoneal fibrosis
Criterion R-Response to steroid therapy	Resolution or marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy
Diagnostic of autoimmune pancreatitis when any of the following is fulfilled	1. Criterion H 2. Criterion I+S 3. Strong clinical suspicion of autoimmune pancreatitis (idiopathic pancreatic disease+Criterion S and/or O)+Criterion R

IgG4, immunoglobulin G4; HPF, high-power fields.