CQ-III-5. Is maintenance steroid therapy necessary?

- To prevent relapse, maintenance therapy (2.5–5 mg/day) is recommended. (Level of recommendation: B)

Description Although there is no clear high-level evidence and consensus regarding maintenance steroid therapy, steroid treatment in Japan and South Korea is often discontinued after a certain period of maintenance therapy. A multicenter study in Japan [10] reported that 377 (82 %) of 459 steroid-treated AIP patients received maintenance therapy with steroids. A maintenance dose of 5 mg/day of oral prednisolone was most common (63 %), followed by 2.5 mg/day (21 %), 10 mg/day (7 %), and 7.5 mg/day (3 %). Relapse occurred significantly less often during maintenance steroid therapy (23 %, 63/273) than after therapy was discontinued (34 %, 35/104; $p < 0.05$). A report from South Korea [17] showed that 13 (33 %) of 40 AIP patients relapsed when steroid therapy was discontinued after a mean of 6 months of oral prednisolone administration (maintenance dose 2.5–7.5 mg/day). Of the 13 patients who relapsed, 7 had been undergoing maintenance therapy at the time and 6 had already discontinued steroid therapy. In the international study [7], the majority of relapse episodes occurred in steroid-treated AIP patients following steroid discontinuation (67 %), as compared to during steroid taper (15 %) or while on maintenance steroid therapy (18 %).

In contrast, steroid therapy protocol without maintenance therapy is common in American and European countries [7, 21, 22]. At the Mayo Clinic, initial therapy with oral prednisolone of 40 mg/day for 4 weeks is tapered by 5 mg/week and discontinued after 11 weeks [21]. Under this regimen, 16 (53 %) of 30 AIP patients associated with sclerosing cholangitis relapsed during median follow-up of 29.5 months. A group from Pittsburgh [22] also conducted short-term (12-week) steroid treatment without maintenance therapy, and reported that of the 15 patients who displayed complete remission, 9 (60 %) relapsed 8–12 weeks after therapy was discontinued.

The survey by the Research Committee for Intractable Pancreatic Disease [23] reported relapse in 38 (40 %) of 96 AIP patients who underwent maintenance therapy. Of these 38 patients, relapse occurred only in the pancreas in 19 (50 %), only in extrapancreatic lesions in 11 (29 %), and in both lesions in 8 (21 %). The relapse rate for patients during maintenance therapy with prednisolone >5 mg/day was 26 % (10/38), which was significantly lower than the rate (54 %, 14/26) in patients who discontinued maintenance therapy ($p < 0.05$) (Fig. 2, [20]).

These findings suggest that maintenance steroid therapy is effective in preventing AIP relapse. As the anti-
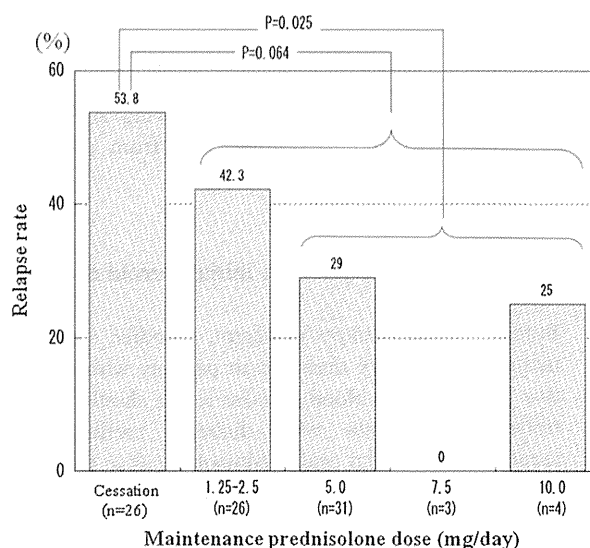

Fig. 2 Relationship between relapse rate of AIP and prednisolone dose during maintenance steroid therapy

inflammatory and immunosuppressive effects of steroids appear to suppress the activity of AIP, maintenance therapy with prednisolone at a minimum of 5 mg/day is recommended. However, as some patients who are not on maintenance therapy do not relapse, and some patients relapse during steroid tapering [21, 24] or during maintenance therapy with relatively high doses of prednisolone, it is important to evaluate disease activity in the patient in order to determine the indications for maintenance therapy. The Research Committee of Intractable Pancreatic Disease compared the clinical features of patients with and without relapse, and reported that the clinical features of patients who tended to relapse included pancreatic enlargement of more than one-third of the entire pancreas, association with extrapancreatic lesions diagnosed by Gallium scintigraphy, and association with extrapancreatic sclerosing cholangitis [23]. The presence of diffuse enlargement of the pancreas [3, 25], elevation of serum IgG4 levels [19], and proximal extrahepatic/intrahepatic strictures [7, 21, 26] have been reported to be predictive of relapse in AIP patients, and maintenance therapy is indicated for these patients.

CQ-III-6. When should steroid therapy be discontinued?

- Steroid therapy should be discontinued based on the disease activity in each case. (Level recommendation: B)
- Cessation of maintenance therapy should be planned within 3 years in cases with radiological and serological improvement. (Level of recommendation: B)

Description There is no consensus regarding duration of steroid therapy in AIP patients. As described in the previous section, maintenance therapy is frequently continued for the relative long-term in Japan. In a Japanese multicenter study [10], the cumulative rate of relapse ($n = 99$) after initiating steroid therapy was 56 % at 1 year, 76 % at 2 years, and 92 % after 3 years.

According to the survey by the Research Committee of Intractable Pancreatic Diseases [23], most patients relapsed within 3 years of the initiation of steroid therapy (Fig. 3, [20]). The incidence of relapse was higher in cases where therapy was discontinued after 3 years than during maintenance therapy. There were no differences in the period of steroid therapy between relapsed cases (12.8 ± 8.9 months, 1–30 months, $n = 14$) and non-relapsed cases (13.5 ± 10.5 months, 1–31 months, $n = 11$) after discontinuation of steroid therapy.

The efficacy of a certain duration of maintenance steroid therapy has been demonstrated from the perspective of improvements in pancreatic exocrine function: when oral prednisolone was administered for 1 year at 5 mg/day, although no changes were observed in the amount of pancreatic juice with secretin test, mean bicarbonate concentration improved within 3 months and the amount of pancreatic enzyme secretion improved within a year [27]. However, as AIP patients are typically elderly and are at high risk of developing steroid-related complications such as osteoporosis and diabetes mellitus, discontinuation of steroid treatment should be attempted. Cessation of maintenance therapy should be planned within 3 years in cases with radiological and serological improvement. When treatment is discontinued, it is necessary to evaluate

disease activity, and patients should be followed up for relapse of AIP [10, 23].

CQ-III-7. Is early prediction of AIP relapse possible?

- Elevated serum IgG4 levels or elevated immune complexes are useful early predictors of AIP relapse. (Level of recommendation: B)

Description In a Japanese multicenter study [10], patients for whom serum IgG4 levels did not normalize after initiation of steroid therapy showed a significantly greater rate of AIP relapse (30 %, 34/115) than those in whom serum IgG4 levels had normalized (10 %, 7/69). Moreover, 37 (69 %) of 54 relapsed patients showed that serum IgG4 levels elevated again prior to relapse. In addition to serum IgG4 levels, circulating immune complexes (monoclonal rheumatoid factor method) have been reported as useful early predictors of relapse [28].

CQ-III-8. How are AIP relapses treated?

- Re-administration or dose-up of steroid is effective for treating AIP relapses. (Level of recommendation: A)
- In most relapsed AIP cases, remission can be achieved with the same prednisolone dose as the initial dose, although it may be necessary to taper more gradually. (Level of recommendation: B)
- Application of immunomodulatory drugs is considered for AIP patients who prove resistant to steroid therapy. (Level of recommendation: B)

Description In most relapsed AIP cases, remission can be achieved with re-administration or dose-up of steroid. In a Japanese multicenter study [10], most patients who relapsed were able to achieve remission again (97 %, 91/94) by increasing prednisolone doses (60 mg/day in 5 % of patients, 40 mg/day in 23 %, 30 mg/day in 47 %, and 20 mg/day in 11 %). In addition, in all 32 patients who were in remission without the use of steroids for initial therapy but subsequently relapsed, remission was achieved with steroid therapy. In the international study [7], remission was successfully induced using steroids in 201 (95 %) of 210 relapsed type 1 AIP patients.

One studied approach to the administration of steroid therapy after relapse was to gradually decrease the dose at a slower rate compared to initial therapy [19, 24]. However, in 11 relapsed patients in whom prednisolone dosage was gradually reduced, 4 of the patients reportedly relapsed again ([21]. Pulse steroid therapy is
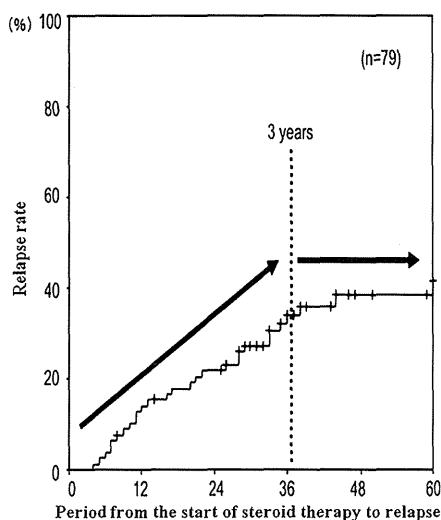

Fig. 3 Relapse rate of AIP and period from the start of steroid therapy to relapse

another method that has been studied in patients who relapsed. Matsushita et al. [18] conducted studies of mini-pulse therapy with methylprednisolone (500 mg/day, 3 days/week, 2 cycles) in patients who experienced recurrence with obstructive jaundice due to sclerosis of the bile duct, demonstrating marked improvements in biliary stricture and subsequent lowering of steroid maintenance doses.

In Western countries, immunomodulatory drugs have recently been introduced in AIP patients who had relapsed or who were resistant to steroid therapy [7, 21, 29]. A study from the Mayo Clinic [21 on the administration of 2–2.5 mg/kg/day of azathioprine (Imuran®, Azanin®) or 1,500 mg/day of mycophenolate mofetil (CellCept®) in 7 patients with AIP and sclerosing cholangitis who had relapsed once or twice, or with IgG4-related sclerosing cholangitis without AIP, reported that no relapse was observed (median observation period 6 months; range 2–19 months). In 2 of the 7 patients, low doses of azathioprine (50 mg/day) and mycophenolate mofetil (1,000 mg/day) were administered initially, but both patients relapsed.

A report from the United Kingdom [29] described the use of steroid therapy in 28 AIP patients and found that 13 patients with sclerosing cholangitis relapsed (5 patients relapsed during maintenance steroid therapy and 8 patients relapsed after steroid discontinuation). Prednisolone dose was increased (20–30 mg/day) in all 13 of the patients who relapsed, and 10 patients also received azathioprine (1–2 mg/kg/day). Remission was subsequently achieved in 12 patients. However, after second remission, 1 of 7 patients who underwent azathioprine monotherapy and 2 of 3 patients who underwent maintenance therapy with concomitant azathioprine and steroid relapsed again.

Rituximab (anti-CD20 antibody) has also been successfully used to treat AIP patients with sclerosing cholangitis who showed resistance to or side effects from treatments including steroid, azathioprine, mycophenolate mofetil, 6-mercaptopurine, and methotrexate [30, 31]. Inhibition of AIP relapse in these cases indicates results that were anticipated from the pathophysiological condition of AIP and the mechanism of action of the drugs. Reports from Japan have also described the use of immunomodulatory drugs to treat AIP complications [32]. While the use of immunomodulatory drugs as second-line therapy for AIP patients who repeatedly relapse or who are resistant to steroid therapy is expected to become increasing significant, these drugs are associated with serious side effects and should be considered with caution. Randomized controlled studies are needed to investigate the use of immunomodulatory drugs in the treatment of patients who relapse.

CQ-III-9. Do pancreatic exocrine and endocrine functions improve after steroid therapy in AIP patients?

- Pancreatic exocrine and endocrine functions improve after steroid therapy in some AIP patients. Many AIP patients with type 2 diabetes mellitus before AIP onset showed worsening of diabetes mellitus control after steroid therapy. (Level of recommendation: C)

Description Many AIP patients have associated pancreatic exocrine and endocrine dysfunction [2, 12, 24, 33–35]. Steroid therapy has been reported to improve pancreatic exocrine and endocrine function in 38 % [24] to 50 % [34] and 25 % [24] to 45 % [34] of AIP patients, respectively. One suggested mechanism posits that steroid suppresses lymphoplasmacytic cell infiltration and fibrosis, permitting the attenuation of blood flow [35] and further regenerating islet cells by suppression of cytokine production [36]. A recent study of activity in pancreatic tissue before and after steroid therapy in AIP patients revealed regeneration of acinar cells during steroid treatment, suggesting that acinar cell regeneration may be associated with CD133-positive pancreatic progenitor cells [27].

Diabetes mellitus (DM) control was shown to worsen in 75 % of AIP patients with type 2 diabetes mellitus before AIP onset after steroid therapy [34]. As DM has been reported to develop in some AIP patients after steroid therapy [33, 34], the occurrence of DM should be taken into consideration in patients who continuously undergo steroid therapy.

CQ-III-10. Is the prognosis of AIP good with steroid therapy?

- The prognosis of AIP appears to be good over the short-term with steroid therapy. (Level of recommendation: B)
- The long-term outcome is less clear, as there are many unknown factors, such as relapse, pancreatic exocrine or endocrine dysfunction, and associated malignancy. (Level of recommendation: I)

Description Several Japanese studies have been conducted to determine the rate of relapse in patients who received steroid therapy, with mean observation periods ≥40 months [24, 26, 37]. Kamisawa and Okamoto [37] reported a 5.6 % rate of relapse, while Nishino et al. [24] reported a rate of 33.3 %. In addition, Hirano et al. [26] investigated the occurrence of adverse events with and without steroid therapy, and demonstrated that adverse events, including relapse, occurred in 31.6 % of patients who received steroid therapy (mean observation period

41 months) and 69.6 % in those who did not (mean observation period, 61 months). Further, various Japanese reports since 2009 have described the long-term clinical course [10, 28, 38]. In one study, Uchida et al. [38] showed relapse in 2 patients (16.7 %) during maintenance steroid therapy, with a mean observation period of 40.8 months. They also reported on the outcome of all 21 patients, indicating that pancreatic cancer and pancreatic cyst developed after 4 years and 2 months and after 2 years, respectively, each in 1 patient. Progression to chronic pancreatitis was reported in 3 patients.

Kamisawa et al. [10] analyzed 563 AIP patients at 17 Japanese institutions, showing relapse in 110 (24.4 %) of 451 patients who underwent steroid therapy and in 32 (41.6 %) of 77 patients who did not undergo therapy. With regard to relapse during maintenance therapy, the rate of relapse in patients who discontinued maintenance therapy was 33.7 % (35/104 patients). In contrast, patients who continued maintenance therapy exhibited a significantly lower rate of relapse, at 23.1 % (63/273). Kawa et al. [28] found that 17 (40.5 %) of 42 patients who received steroid therapy relapsed during a mean observation period of 72 months. Furthermore, pancreatic calcification appeared to be present in 17.6 % (9/51), suggesting that this calcification is common in patients who relapse (7/21 patients, 33.3 %; patients who did not relapse, 6.7 %). They also reported that pancreatic calcification was associated with AIP relapse, with some AIP patients relapsing several times and transitioning to a normal type of chronic pancreatitis. In an analysis of a nationwide Japanese survey, Nishimori et al. [9] found that the rate of relapse was significantly higher among patients exhibiting biliary stricture. This finding was recently corroborated by domestic and international studies after it was reported that biliary stricture may be clinically predictive of relapse [7, 21, 22, 26].

In reports from overseas, Ryu et al. [39] summarized AIP cases from 16 South Korean institutions and demonstrated that 10 (14.9 %) of 67 patients relapsed during a mean observation period of 20 months. Ghazale et al. [21] showed relapse in 16 (53.3 %) of 30 patients who received steroid therapy during a median observation period of 29.5 months. Sahani et al. [40] found pancreatic atrophy in 5 (38.5 %) of 13 patients. Sandanayake et al. [29] showed relapse in 8 (34.8 %) of 23 patients who received steroid therapy during a mean observation period of 27.3 months, and all 8 of these patients displayed extrapancreatic lesions or bile duct lesions at the time of diagnosis. Raina et al. [22] found that 9 (60.0 %) of 15 patients who received steroid therapy relapsed during a mean observation period of 12.8 months, and that the relapse occurred in 8–12 weeks. Frulloni et al. [41] found that 25.3 % (22/87)

of patients relapsed during a mean observation period of 7.4 ± 5.5 years, and that focal AIP was more likely to relapse than diffuse AIP. They also found pancreatic calcification in 11.5 % (10/87) of patients, and reported 3 deaths during the course (due to pancreatic cancer, systemic metastasis of adenocarcinoma of unknown origin, and traffic accident). In addition, a report from India showed that relapse was not detected during an observation period of 6–8 months [42]. In the international study [7], 245 (36 %) of 684 steroid-treated type 1 AIP patients experienced at least one disease relapse, compared with 8 (15 %) of 52 type 2 AIP patients ($p < 0.001$). Most relapses occurred in the biliary system (51 %) or pancreas (43 %) for type 1 AIP, while relapses in type 2 AIP were limited to the pancreas. Pancreatic calcification was more likely to occur in type 1 AIP patients with at least one relapse (14 %) compared with those who had never experienced relapse (4 %, $p < 0.001$).

As described above, AIP responds well to steroids on a short-term basis, with the potential for high rates of remission [23]. From the perspective of AIP prognosis, the rate of relapse was high in patients who did not receive steroid therapy, although relapse was observed in 20–40 % of those undergoing steroid therapy and 20–30 % of those undergoing maintenance therapy. In addition, an increasing number of reports describe pancreatic atrophy and pancreatic stones as long-term complications, so the prognosis is not necessarily satisfactory. Ko et al. [27] recently reported improvements in pancreatic function and histology after steroid therapy, but further investigation is necessary with regard to long-term pancreatic function.

CQ-III-11. Is there any relationship between AIP and pancreatic cancer?

- There are a few papers reporting an AIP case developing pancreatic cancer, but it is unclear whether there is a relationship between AIP and pancreatic cancer. (Level of recommendation: I)

Description   Chronic pancreatitis has been reported as one of the risk factors for pancreatic cancer [43]. Reports also indicate that some AIP patients developed pancreatic atrophy or pancreatic stones [7, 28, 37, 44]. AIP occurred predominantly in elderly males. As steroid therapy is immunosuppressive, it is necessary to investigate whether there is an association with pancreatic cancer and other malignancies in AIP patients on long-term steroid treatment. Periodic checks of serum tumor markers should be performed during follow-up.

There have been 9 recent papers reporting AIP cases developing pancreatic cancer [45–53]. The locations of these cancers were head ($n = 2$), body ($n = 4$), tail ($n = 2$), and whole ($n = 1$) of the pancreas. The male-to-female ratio was 8:1, and average age was 69.3 (59–80) years. Five pancreatic cancers were diagnosed simultaneously with AIP, and the other 4 cancers were diagnosed from 3 to 13 years after the onset of AIP. Elevation of serum tumor markers triggered diagnosis of pancreatic cancer in some cases [50, 54]. Reported rates of associated pancreatic cancer with AIP were 2.4 % [26], 5.6 % [54], 10 % [3], and 3.3 % [21]. A report from China [55] described no progression of pancreatic cancer in AIP patients during a mean observation period of 46 months.

Interestingly, in an investigation of K-ras mutations in gallbladder and pancreas tissues obtained from AIP patients, Kamisawa et al. [56] demonstrated significant K-ras mutation in the pancreatic and biliary regions. While these results suggest that AIP may be a risk factor for pancreatic and bile duct cancer, patients with pancreatic cancer have also been reported as displaying histological similarities to those with lymphoplasmacytic sclerosing pancreatitis (LPSP) around the pancreatic cancer [57]. Therefore, a thorough histopathological investigation is necessary to ensure accurate diagnosis of pancreatic cancer.

Appendix

The Working Committee of the Japan Pancreas Society (JPS) and the Research Committee for Intractable Pancreatic Disease supported by the Ministry of Health, Labour and Welfare of Japan (RCIPD-MHLWJ):

I.   The professional committee for making clinical questions and statements

Chairperson: Kazuichi Okazaki (Department of Gastroenterology and Hepatology, Kansai Medical University)
Co-Chairpersons: Shigeyuki Kawa (Center for Health, Safety and Environmental Management, Shinshu University), Terumi Kamisawa (Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital)
Committee members:
Tetsuhide Ito (Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University), Kazuo Inui (Department of

Gastroenterology, Second Teaching Hospital, Fujita Health University), Hiroyuki Irie (Department of Radiology, Faculty of Medicine, Saga University), Takayoshi Nishino (Department of Gastroenterology, Yachiyo Medical Center, Tokyo Women's Medical University), Kenji Notohara (Department of Anatomic Pathology, Kurashiki Central Hospital), Keishi Kubo (Department of Internal Medicine, Shinshu University School of Medicine), Hirotaka Ohara (Department of Community-Based Medical Education, Nagoya City University Graduate School of Medical Sciences), Atsushi Irisawa (Department of Gastroenterology, Fukushima Medical University Aizu Medical Center), Yasunari Fujinaga (Department of Radiology, Shinshu University School of Medicine), Osamu Hasebe (Department of Gastroenterology, Nagano Municipal Hospital), Isao Nishimori (Nishimori Clinic), Shigeki Tanaka (Department of Acupuncture and Moxibusion, Tokyo Ariake University of Medical and Health Sciences)

II. The expert panelist committee for rating statements by the modified Delphi method

Chairperson: Tooru Shimosegawa
Committee members: Kazuichi Okazaki, Shigeyuki Kawa, Terumi Kamisawa, Tetsuhide Ito, Kazuo Inui, Takayoshi Nishino, Hirotaka Ohara, Isao Nishimori, Shigeki Tanaka

III. The Evaluating Committee

Chairperson: Masao Tanaka (Department of Surgery and Oncology, Kyushu University)

1.   Committee Members:

Toshimasa Nishiyama (Department of Public Health and Hygiene, Kansai Medical University), Koichi Suda (Department of Pathology, Tokyo-West Tokushukai Hospital), Keiko Shiratori (Department of Gastroenterology, Tokyo Women's Medical University), Kenji Notohara, Keishi Kubo, Hiroshi Yamamoto, Hirotaka Ohara, Atsushi Irisawa, Yasunari Fujinaga, Osamu Hasebe, Shigeki Tanaka

2.   Committee Members of the JPS for Autoimmune Pancreatitis:

Kazushige Uchida (Department of Gastroenterology and Hepatology, Kansai Medical University), Atsushi Kanno (Division of Gastroenterology, Tohoku University Graduate School of Medicine), Kensuke Kubota (Department of Gastroenterology, Yokohama City Unicersity), Shigeru Ko (Department of Systems Medicine, Keio University), Junichi Sakagami (Department of Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine), Kyoko Shimizu (Department of Gastroenterology, Tokyo Women's Medical University), Masanori Sugiyama

(Department of Surgery, Kyorin University), Minoru Tada (Department of Gastroenterology, University of Tokyo), Takahiro Nakazawa (Department of Gastroenterology and Metabolism, Nagoya City University), Hirokazu Nishino (Department of Gastroenterology and Hepatology, Jikei University School of Medicine), Hideaki Hamano (Medical Informatics Division and Department of Internal Medicine, Gastroenterology, Shinshu University Hospital), Yoshiki Hirooka (Department of Endoscopy, Nagoya University Hospital), Kenji Hirano (Department of Gastroenterology, University of Tokyo), Atsushi Masamune (Division of Gastroenterology, Tohoku University Graduate School of Medicine), Atsuhiro Masuda (Divison of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine), Nobumasa Mizuno (Department of Gastroenterology, Aichi Cancer Center Hospital), Koji Yamaguchi (Department of Surgery 1, University of Occupational and Environmental Health), Hitoshi Yoshida (Division of Gastroenterology, Department of Medicine, Showa University School of Medicine)

References

1. Wakabayashi T, Kawaura Y, Satomura Y, et al. Long-term prognosis of duct-narrowing chronic pancreatitis. Strategy for steroid treatment. Strategy for steroid treatment. Pancreas. 2005;30:31–9.
2. Kamisawa T, Yoshiike M, Egawa N, et al. Treating patients with autoimmune pancreatitis: results from a long-term follow-up study. Pancreatology. 2005;5:234–40.
3. Kubota K, Iida H, Fujisawa T, et al. Clinical factors predictive of spontaneous remission or relapse in cases of autoimmune pancreatitis. Gastrointest Endosc. 2007;66:1142–51.
4. Ozden I, Dizdaroglu F, Poyanli A, et al. Spontaneous regression of a pancreatic head mass and biliary obstruction due to autoimmune pancreatitis. Pancreatology. 2005;5:300–3.
5. Araki J, Tsujimoto F, Ohta T, et al. Natural course of autoimmune pancreatitis without steroid therapy showing hypoechoic masses in the uncinate process and tail of the pancreas on ultrasonography. J Ultrasound Med. 2006;25:1063–7.
6. Nishimori I, Okazaki K, Kawa S, et al. Treatment for autoimmune pancreatitis. J Biliary Tract Pancreas (in Japanese). 2007;28:961–6.
7. Hart PA, Kamisawa T, Brugge WR, et al. Long-term outcomes of autoimmune pancreatitis: a multicenter, international analysis. Gut. 2013;62:1771–6.
8. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. J Gastroenterol. 2006;41:613–25.
9. Nishimori I, Okazaki K, Suda K, et al. Treatment for autoimmune pancreatitis. Consensus of treatment for autoimmune pancreatitis by research committee of intractable pancreatic diseases supported by Ministry of Health, Labour and Welfare of Japan— Suizou. 2005;20:343–8 (in Japanese).
10. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. Gut. 2009;58:1504–7.
11. Kamisawa T, Okamoto A, Wakabayashi T, et al. Appropriate steroid therapy for autoimmune pancreatitis based on long-term outcome. Scand J Gastroenterl. 2008;43:609–13.
12. Kamisawa T, Egawa N, Inokuma S, et al. Pancreatic endocrine and exocrine function and salivary gland function in autoimmune pancreatitis before and after steroid therapy. Pancreas. 2003;27:235–8.
13. Okazaki K, Kawa S, Kamisawa T, et al. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. J Gastroenterol. 2006;41:626–31.
14. Pearson RK, Longnecker DS, Chari ST, et al. Controversies in clinical pancreatology. Autoimmune pancreatitis: does it exist? Pancreas. 2003;27:1–13.
15. Ghazale A, Chari ST. Optimising corticosteroid treatment for autoimmune pancreatitis. Gut. 2007;56:1650–2.
16. Finkelberg DL, Sahani D, Deshpande V, et al. Autoimmune pancreatitis. N Engl J Med. 2006;355:2670–6.
17. Park DH, Kim MH, Oh HB, et al. Substitution of aspartic acid at position 57 of the DQβ1 affects relapse of autoimmune pancreatitis. Gastroenterology. 2008;134:440–6.
18. Matsushita M, Yamashina M, Ikeura T, et al. Effective steroid pulse therapy for the biliary stenosis caused by autoimmune pancreatitis. Am J Gastroenterol. 2007;102:220–1.
19. Kamisawa T, Egawa N, Nakajima H, et al. Morphological changes after steroid therapy in autoimmune pancreatitis. Scand J Gastroenterol. 2004;11:1154–8.
20. Kamisawa T, Okazaki K, Kawa S, et al. Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP. J Gastroenterol. 2010;45:471–7.
21. Ghazale A, Chari ST, Zhang L, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology. 2008;134:706–15.
22. Raina A, Yadav D, Krasinskas AM, et al. Evaluation and management of autoimmune pancreatitis: experience at a large US center. Am J Gastroenterol. 2009;104:2295–306.
23. Nishimori I, Otsuki M. Study on steroid therapy for autoimmune pancreatitis. Annual reports of research committee of intractable pancreatic diseases supported by Ministry of Health, Labour and Welfare of Japan. 2008;137–44 (in Japanese).
24. Nishino T, Toki F, Oyama H, et al. Long-term outcome of autoimmune pancreatitis after oral prednisolone therapy. Intern Med. 2006;45:497–501.
25. Naitoh I, Nakazawa T, Ohara H, et al. Clinical significance of extrapancreatic lesions in autoimmune pancreatitis. Pancreas. 2010;39:e1–5.
26. Hirano K, Tada M, Isayama H, et al. Long-term prognosis of autoimmune pancreatitis with and without corticosteroid treatment. Gut. 2007;56:1719–24.
27. Ko SB, Mizuno N, Yatabe Y, et al. Corticosteroids correct aberrant CFTR localization in the duct and regenerate acinar cells in autoimmune pancreatitis. Gastroenterology. 2010;138: 1988–96.
28. Kawa S, Hamano H, Ozaki Y, et al. Long-term follow-up of autoimmune pancreatitis: characteristics of chronic disease and recurrence. Clin Gastroenterol Hepatol. 2009;7(11 Suppl): S18–22.
29. Sandanayake NS, Church NI, Chapman MH, et al. Presentation and management of post-treatment relapse in autoimmune pancreatitis/immunoglobulin G4-associated cholangitis. Clin Gastroenterol Hepatol. 2009;7:1089–96.
30. Topazian M, Witzig TE, Smyrk TC, et al. Rituximab therapy for refractory biliary strictures in immunoglobulin G4-associated cholangitis. Clin Gastroenterol Hepatol. 2008;6:364–6.
31. Khosroshahi A, Bloch DB, Deshpande V, et al. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. Arthritis Rheum. 2010;62:1755–62.
32. Naitoh I, Nakazawa T, Ohara H, et al. Autoimmune pancreatitis associated with various extrapancreatic lesions during a long-

term clinical course successfully treated with azathioprine and corticosteroid maintenance therapy. Intern Med. 2009;48:2003–7.

33. Nishimori I, Tamakoshi A, Kawa S, et al. Influence of steroid therapy on the course of diabetes mellitus in patients with autoimmune pancreatitis: findings from a nationwide survey in Japan. Pancreas. 2006;32:244–8.

34. Ito T, Nishimori I, Inoue N, et al. Treatment for autoimmune pancreatitis: consensus on the treatment for patients with autoimmune pancreatitis in Japan. J Gastroenterol. 2007;42(Suppl 18):50–8.

35. Ito T, Kawabe K, Arita Y, et al. Evaluation of pancreatic endocrine and exocrine function in patients with autoimmune pancreatitis. Pancreas. 2007;34:254–9.

36. Tanaka S, Kobayashi T, Nakanishi K, et al. Corticosteroid-responsive diabetes mellitus associated with autoimmune pancreatitis. Lancet. 2000;356:910–1.

37. Kamisawa T, Okamoto A. Prognosis of autoimmune pancreatitis. J Gastroenterol. 2007;42(supplement 18):59–62.

38. Uchida K, Yazumi S, Nishio A, et al. Long-term outcome of autoimmune pancreatitis. J Gastroenterol. 2009;44:726–32.

39. Ryu JK, Chung JB, Park SW, et al. Review of 67 patients with autoimmune pancreatitis in Korea. A multicenter nationwide study. Pancreas. 2008;37:377–85.

40. Sahani D, Sainani N, Deshpande V, et al. Autoimmune pancreatitis: disease evolution, staging, response assessment, and CT features that predict response to corticosteroid therapy. Radiology. 2009;250:118–29.

41. Frulloni L, Scattolini C, Falconi M, et al. Autoimmune pancreatitis: differences between the focal and diffuse forms in 87 patients. Am J Gastroenterol. 2009;104:2288–94.

42. Noor MT, Lal A, Kochhar R, et al. Autoimmune pancreatitis: a report from India. JOP J Pancreas. 2010;11:213–9.

43. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. N Engl J Med. 1993;328: 1422–7.

44. Takayama M, Hamano H, Ochi Y, et al. Recurrent attacks of autoimmune pancreatitis result in pancreatic stone formation. Am J Gastroenterol. 2004;99:932–7.

45. Sakashita F, Tanahashi T, Yamaguchi K, et al. Case of pancreatic tail cancer associated with autoimmune pancreatitis. Jpn J Gastroenterol Surg. 2006;39:78–83.

46. Inoue H, Miyatani H, Sawada Y, et al. A case of pancreatic cancer with autoimmune pancreatitis. Pancreas. 2006;33:208–9.

47. Wayne M, Cooperman A, Kasmin F, et al. Chronic pancreatitis with synchronous and metachronous malignancy: three unusual cases and a literature review. J Surg Educ. 2007;64:158–61.

48. Fukui T, Mitsuya T, Takaoka M, et al. Pancreatic cancer associated with autoimmune pancreatitis in remission. Inter Med. 2008;47:151–5.

49. Ghazale A, Chari S. Is autoimmune pancreatitis a risk factor for pancreatic cancer? Pancreas. 2007;35:376.

50. Witkiewicz AK, Kennedy EP, Kennyon L, et al. Synchronous autoimmune pancreatitis and infiltrating pancreatic ductal adenocarcinoma: case report and review of the literature. Hum Pathol. 2008;39:1548–51.

51. Iida H, Kubota K, Mawatari H, et al. A case of autoimmune pancreatitis developed pancreatic tail cancer. Suizou. 2008;23: 608–14.

52. Matsubayashi H, Matsunaga K, Uesaka K, et al. A case of pancreatic carcinoma with suspected autoimmune pancreatitis. Clin J Gastroenterol. 2009;2:59–63.

53. Motosugi U, Ichikawa T, Yamaguchi H, et al. Small invasive ductal adenocarcinoma of the pancreas associated with lymphoplasmacytic sclerosing pancreatitis. Pathol Int. 2009;59:744–7.

54. Tanaka S, Yoshida H, Ikegami K, et al. Treatment and prognosis of autoimmune pancreatitis. Suizo (in Japanese). 2007;22: 663–71.

55. Song Y, Lui QD, Zhou NX, et al. Diagnosis and management of autoimmune pancreatitis: experience from China. World J Gastroenterol. 2008;14:601–6.

56. Kamisawa T, Tsuruta K, Okamoto A, et al. Frequent and significant K-ras mutation in the pancreas, the bile duct, and the gallbladder in autoimmune pancreatitis. Pancreas. 2009;38: 890–5.

57. Notohara K, Wani Y, Tsukayama C, et al. Comparative study between pancreatic ductal carcinoma-associated histological changes and autoimmune pancreatitis. Annual reports of research committee of intractable pancreatic diseases supported by Ministry of Health, Labour and Welfare of Japan. 2008;246–50 (in Japanese).

IgG4-related disease

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IgG4-related disease is a protean condition that mimics many malignant, infectious, and inflammatory disorders. This multi-organ immune-mediated condition links many disorders previously regarded as isolated, single-organ diseases without any known underlying systemic condition. It was recognised as a unified entity only 10 years ago. Histopathology is the key to diagnosis. The three central pathology features of IgG4-related disease are lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis. The extent of fibrosis is an important determinant of responsiveness to immunosuppressive therapies. IgG4-related disease generally responds to glucocorticoids in its inflammatory stage, but recurrent or refractory cases are common. Important mechanistic insights have been derived from studies of patients treated by B-cell depletion. Greater awareness of this disease is needed to ensure earlier diagnoses, which can prevent severe organ damage, disabling tissue fibrosis, and even death. Identification of specific antigens and T-cell clones that drive the disease will be the first steps to elucidate the pathogenesis of IgG4-related disease.

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Introduction

IgG4-related disease is a multi-organ immune-mediated condition that mimics many malignant, infectious, and inflammatory disorders.[1-3] The diagnosis links many conditions once regarded as isolated, single-organ diseases without any known underlying systemic condition (panel 1). IgG4-related disease, unrecognised as a unified disease for well over a century, has been likened to a "black crow flying through the dark night".[4] The disease has many similarities to sarcoidosis and some forms of systemic vasculitis, other protean diseases in which the histopathological findings are consistent across a wide range of organ systems.

Two introductory points deserve emphasis. First, awareness of IgG4-related disease is essential because the disorder is treatable. The therapeutic approaches contrast starkly with those of some of the disorders in the differential diagnosis (panel 2), especially malignant disorders but also autoimmune diseases, such as Sjögren's syndrome, granulomatosis with polyangiitis, and membranous nephropathy. Second, knowledge of the immune dysregulation associated with IgG4-related disease explains much about the human immune system. Progress in elucidation of the basis of IgG4-related disease has been swift.

Epidemiology

Understanding of the epidemiology of IgG4-related disease is hampered by insufficient awareness of the diagnosis, because the disease did not appear in medical publications until 2003.[5,6] Definitive diagnosis generally necessitates a biopsy, insightful interpretation of the pathology, and rigorous clinicopathological correlation. Although the overall prevalence of type 1 (IgG4-related) autoimmune pancreatitis in Japan has been estimated as 2·2 cases per 100000 population,[7] the pancreas is only one of more than a dozen organs affected by IgG4-related disease. Therefore, this is surely a substantial underestimate of the true prevalence, especially because the study from which this estimate was derived was done early in the development of knowledge about IgG4-related disease. The prevalence of various organ manifestations also remains unclear, but autoimmune pancreatitis, sialadenitis (particularly of the submandibular gland), dacryoadenitis, and IgG4-related retroperitoneal fibrosis are the most common disease features.

The typical patient with IgG4-related disease is a middle-aged to elderly man.[7,8] For autoimmune pancreatitis, the mean age at diagnosis is 67 years and the male to female ratio is three to one.[7] The male predilection contrasts strikingly with classic autoimmune diseases, for which female patients can outnumber male cases by nine to one. For organs of the head and neck, however—the orbits, salivary glands, and sinuses—the proportions of male and female patients are roughly equal.[9] The reasons for differential organ expression in the two sexes are unclear.

We know of no reports of familial cases of IgG4-related disease. More extensive studies of patients from several ethnic backgrounds are needed before any conclusions can be drawn about genetic susceptibility.[10-13]

Pathology
Histology features

Histopathology is the key to diagnosis of IgG4-related disease. Three central pathology features are lymphoplasmacytic infiltration, obliterative phlebitis, and storiform fibrosis (figure 1).[14] The lymphocytes and plasma cells are polyclonal. Eosinophils are also commonly present and extreme examples can resemble eosinophilic organopathy, but neutrophilic infiltration is

rare in IgG4-related disease. Necrosis, discrete granulomata, and xanthogranulomatous changes are atypical and, when present, suggest other diagnoses.[9,14]

Fibrosis is a histological prerequisite for the diagnosis. Some fibrosis is present in all cases, even in patients who present shortly after symptom onset. Storiform fibrosis, characterised by radially arranged collagen fibres that seem to weave through the tissue, typifies the unique pattern associated with IgG4-related disease (figure 1).[9,14] Because of its typically patchy distribution, however, storiform fibrosis sometimes escapes detection through sampling error, especially if the tissue is obtained by needle biopsy. Acellular, keloidal fibrosis is not characteristic of IgG4-related disease.

The characteristic venous lesion, obliterative phlebitis, is defined as the partial or complete obliteration of medium-sized veins.[9,14] This finding should be distinguished from fibrous venous occlusion with no inflammation, which is known to occur in other conditions (eg, primary sclerosing cholangitis). Obliterated veins commonly appear as an inflammatory nodule next to a patent artery (figure 1) and sometimes can be identified as veins only through elastin staining (figure 1).

See Online for appendix

The histological appearance is similar for all organs. Some more organ-specific changes, however, are noteworthy. Both obliterative arteritis and focal neutrophilic infiltration, rare in other organs, can occur in the lungs. Obliterative arteritis lacks the vascular-wall necrosis typical of many systemic vasculitides. The neutrophilic infiltration in IgG4-related pulmonary disease is typically seen in alveolar spaces.[15] Other minor pathological differences between organs include the absence of storiform fibrosis within lacrimal glands and lymph nodes, and the lower frequency of obliterative phlebitis in salivary glands, lacrimal glands, lymph nodes, and kidneys.[9,14] The rarity of fibrosis in lymph nodes means that the diagnosis of IgG4-related disease is difficult on the basis of lymph-node pathology alone.

Immunostaining

High numbers of IgG4-positive plasma cells at tissue sites are a disease hallmark, even when serum IgG4 concentrations are normal. The finding of IgG4-positive plasma cells is helpful in differentiating IgG4-related disease from other plasma-cell-rich disorders, such as primary sclerosing cholangitis and multicentric Castleman's disease.[16,17]

In interpretation of tissue IgG4 stains, several caveats must be borne in mind.[14] First, IgG4-positive plasma cells are generally present diffusely throughout lesions of IgG4-related disease. Focal aggregations of IgG4-positive cells are atypical. Second, the absolute number of IgG4-positive plasma cells must be interpreted according to the specific tissue. An international pathology consensus statement proposed, for example, that for sialadenitis the cutoff value should be at least 100 cells per high-power field, but that in the pancreas more than 50 cells per high-power field is compatible with a diagnosis of autoimmune pancreatitis.[14] Third, the ratio of IgG4 to IgG-positive plasma cells must be at least 40% (it is typically 70% or higher) (figure 1). Finally, and most importantly, IgG4-related disease cannot be diagnosed on the basis of infiltration by IgG4-positive cells alone, because these plasma cells can be present in other inflammatory and neoplastic disorders.[18]

Fibrosis commonly predominates over a long disease course, and the histological features can become less specific in patients with longstanding disease. Thus, some undiagnosed or untreated cases of IgG4-related disease are consigned to categories such as so-called idiopathic end-stage diseases—for example, chronic pancreatitis, cryptogenic cirrhosis, or honeycomb lung. Review of biopsy samples taken earlier in the course, however, could document the progression of IgG4-related disease from a lymphoplasmacytic infiltrate to one characterised mainly by fibrosis.

Morphological change of affected organs

Transformations in the gross pathology of affected organs occur. The pancreas and kidneys become diffusely enlarged (appendix). By contrast, ductal organs (eg, bile duct, bronchus) assume the appearance of a pipe stem, with diffuse wall-thickening (figure 1).[19] In IgG4-related disease, discrete small nodules within an otherwise unremarkable organ are seen occasionally, indicating site-selective immune reactions. The background tissue is histologically not inflamed, even though its tissue constituents are the same as those of affected regions (figure 1). This feature contrasts with those of classic autoimmune disorders such as autoimmune hepatitis and Graves' disease, in which the organs are diffusely inflamed and the cells targeted are injured non-selectively.

Panel 2: Differential diagnosis of IgG4-related disease, by organ system

Orbits and periorbital tissues
- Lymphoma
- Graves' orbitopathy
- Granulomatosis with polyangiitis
- Sarcoidosis

Ears, nose, and sinuses
- Allergic disease
- Churg-Strauss syndrome
- Granulomatosis with polyangiitis
- Sarcoma
- Chronic infection

Salivary glands
- Lymphoma
- Sjögren's syndrome
- Sarcoidosis
- Sialodocholithiasis

Meninges
- Idiopathic hypertrophic pachymeningitis
- Inflammatory myofibroblastic tumour
- Lymphoma
- Granulomatosis with polyangiitis
- Giant-cell arteritis
- Langerhans-cell histiocytosis
- Sarcoidosis

Pituitary
- Neoplasms
- Histiocytosis
- Primary hypophysitis
- Secondary hypophysitis (sarcoidosis, ipilimumab-induced)

Lymph nodes
- Multicentric Castleman's disease
- Lymphoma
- Sarcoidosis
- Systemic lupus erythematosus

Thyroid gland
- Thyroid lymphoma
- Differentiated thyroid carcinoma (papillary variant)
- Other malignant disease

Lungs
- Malignancy (adenocarcinoma or bronchioloalveolar carcinoma)
- Inflammatory myofibroblastic tumour

- Sarcoidosis
- Granulomatosis with polyangiitis
- Castleman's disease
- Lymphomatoid granulomatosis
- Idiopathic interstitial pneumonitis
- Erdheim-Chester disease

Aorta
- Primary large-vessel vasculitis (giant-cell or Takayasu's arteritis)
- Sarcoidosis
- Erdheim-Chester disease
- Histiocytosis
- Lymphoma
- Infectious aortitis

Retroperitoneum
- Lymphoma
- Sarcoma
- Methysergide-induced retroperitoneal fibrosis
- Idiopathic retroperitoneal fibrosis

Kidney
- Lymphoma
- Renal-cell carcinoma
- Drug-induced tubulointerstitial nephritis
- Idiopathic membranous glomerulonephritis
- Pauci-immune, necrotising glomerulonephritis
- Sarcoidosis
- Sjögren's syndrome
- Systemic lupus erythematosus (membranous nephropathy)

Pancreas
- Pancreatic cancer

Biliary tree
- Pancreatic cancer
- Cholangiocarcinoma
- Primary sclerosing cholangitis

Liver
- Cholangiocarcinoma
- Hepatocellular carcinoma
- Primary sclerosing cholangitis

Prostate
- Benign prostatic hypertrophy

Skin
- Cutaneous lymphoma

Pathophysiology

Two parallel processes could underlie the observed pathological features in IgG4-related disease. The first is the induction of a polarised CD4-positive T-cell population, yet to be conclusively characterised, which activates innate immune cells, including macrophages, myofibroblasts, and fibroblasts to drive fibrosis. This process could involve the collaboration of activated B-lineage cells, possibly expanded plasmablasts that enter the damaged tissue along with activated CD4-positive T cells. The second is a feedback negative regulatory process, which might involve the generation of IgG4-secreting plasmablasts, plasma cells, and IgG4 antibodies.

Several reasons lead us to believe that IgG4 itself is not a driver of pathogenesis. IgG4 antibodies undergo a

process called Fab-arm exchange within the endosomal compartment of endothelial cells.[20] In this process, the heavy-chain dimers of an IgG4 molecule dissociate and

Figure 1: Pathological features of IgG4-related disease
(A) Submandibular gland affected by a fibroinflammatory process; the inflammatory-cell infiltrate consists mainly of lymphocytes and plasma cells, and whorls of fibrosis are evident throughout the tissue. (B) Storiform fibrosis is apparent in a sclerotic area of the bile duct in this patient with IgG4-related sclerosing cholangitis. (C) In obliterative phlebitis, an obliterated vein creates an inflammatory nodule (arrow) next to a patent artery (from a patient with type 1 [IgG4-related] autoimmune pancreatitis). (D) Van Gieson stain (for elastin) shows obliterative phlebitis (arrow); the adjacent artery is intact. (E) and (F): Immunostaining for IgG4 shows many IgG4-positive plasma cells in (E) a lacrimal-gland biopsy sample; (F) the IgG-stained section shows that the ratio of IgG4 to IgG-positive plasma cells is above 80%. (G) Transection of the bile duct with IgG4-related sclerosing cholangitis shows diffuse wall thickening. (H) A well circumscribed nodule (arrows) is formed in the pancreatic head of this patient with type 1 (IgG4-related) autoimmune pancreatitis; the background pancreas is unremarkable.

each hemi-molecule associates with another, different, hemi-IgG4 protein. Most secreted IgG4 is therefore functionally monovalent and cannot crosslink antigens to form the lattice structure found in immune complexes. As a result, IgG4 antibodies do not directly fix complement, they bind poorly to activating Fc receptors, and they are generally thought to be non-inflammatory. IgG4 concentrations are also known to rise after IgE concentrations decline in allergic disorders. For these reasons, one possible view of IgG4 is that it perhaps evolved as a non-inflammatory antigen sink that is largely monovalent, the purpose of which is to mop up antigen in an attempt to attenuate inflammatory processes. In theory, however, IgG4 could be pathogenic and could perhaps collaborate with circulating lectins to activate complement in disease lesions. However, no evidence to support such a view is available.

T cells are implicated in the disease pathogenesis for several reasons, the most obvious of which is the observation that many CD4-positive T cells are present at sites of inflammation in IgG4-related disease. The finding of a linkage to HLA class II in a Japanese population indirectly supports a role for CD4-positive T cells.[12] Although Th2 cells that secrete interleukins 4, 5, and 13 are commonly implicated in the pathogenesis of fibrosis, many diseases, including tuberculosis and Crohn's disease, have a more dominant Th1 phenotype that is linked to fibrosis. Indeed, in IgG4-related disease, conflicting reports have implicated Th1 cells and Th2 cells in disease pathophysiology.[21,22] Studies published this year suggest that circulating Th2 memory cells do accumulate in a proportion of people with IgG4-related disease but only if they have concomitant atopic disease.[23,24] The precise nature of the disease-causing CD4-positive T cells remains to be resolved.

The molecular mechanisms that drive the IgG4 class switch remain unknown, but roles for interleukins 4 and 10 have been suggested.[25] Although a link between Th2 cells and both the IgG4 class switch and the disease process is tempting, our understanding of the role of T cells in isotype switching has evolved. Class switching to IgE is driven by T-follicular helper cells that make interleukin 4, not by Th2 cells themselves.[26] Therefore, some polarised T cells, perhaps Th1 or Th2 cells or those of a yet to be identified phenotype, could drive the storiform fibrosis and obliterative phlebitis. A separate T-follicular helper cell response might bring about generation of the IgG4 phenotype that helps define the disease.

One plausible model of pathogenesis is that in genetically susceptible individuals, generally older men, some environmental insult, possibly an encounter with a specific microbe, triggers tissue damage and a break in immunological tolerance. A self-antigen-driven, polarised CD4-positive T-helper response would induce a fibrotic pathological process at one or several sites. The reasons for the targeting of particular organs remain unclear. Within these organs, increased CD4-positive T cells would
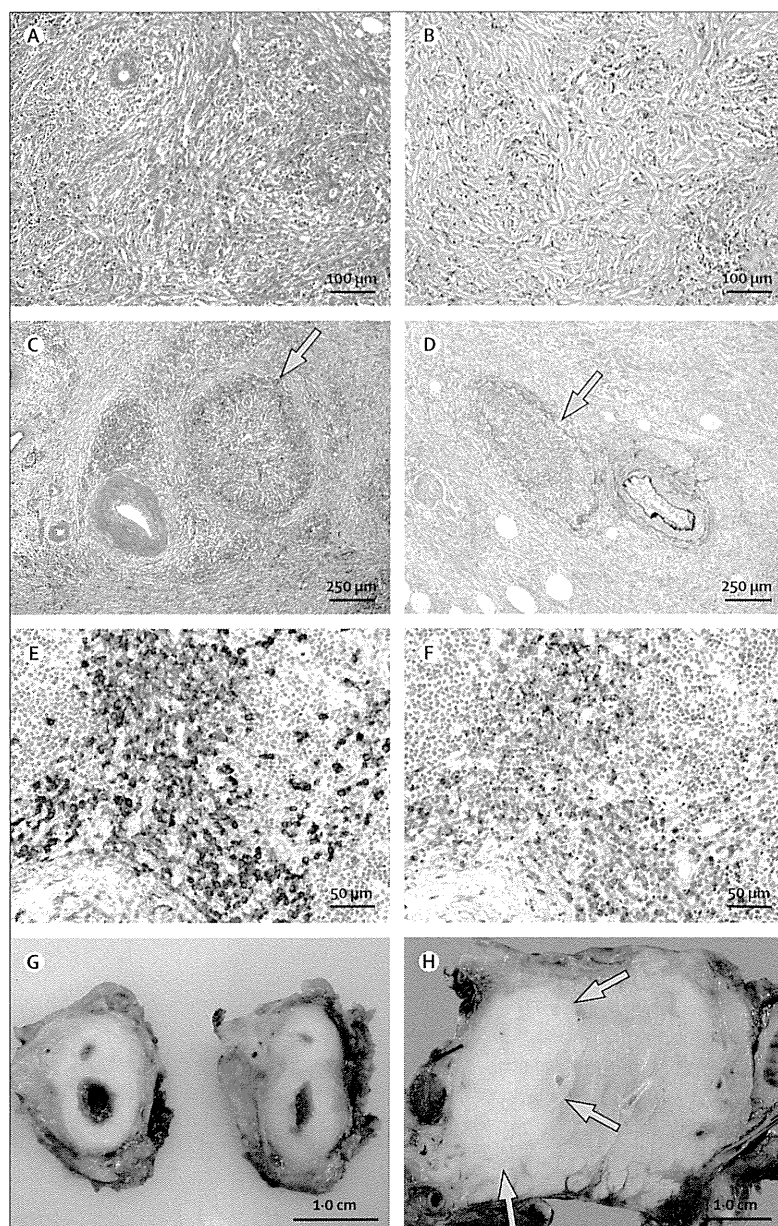
activate innate immune cells that secrete other cytokines and drive the pathology. The memory CD4-positive T cells that orchestrate the disease are presumably sustained by antigen-presenting B cells, which would explain the clinical improvement after B-cell depletion.[27,28] Either the same antigen or some event triggered by fibrosis could trigger a parallel T-follicular helper response that would induce the development of germinal centres within lymph nodes and the generation of IgG4-secreting plasmablasts and long-lived plasma cells. The existence of these cells can be inferred because rituximab does not completely attenuate IgG4 concentrations in treated patients.

Diagnosis

Tissue biopsy is the gold standard for diagnosis in most settings. Review of archived pathology samples can confirm the diagnosis of IgG4-related disease on histological findings alone, if large specimens such as submandibular gland resections are available. Even with supporting histopathological evidence, however, clinicopathological correlation is needed to confirm the diagnosis.

Imaging is an important part of the diagnostic approach in many organs. Under some circumstances, the imaging findings in autoimmune pancreatitis (appendix) can be regarded as diagnostic, provided that the clinical presentation is also straightforward. Because imaging findings elsewhere in the body are less specific, tissue diagnosis is important for patients with no pancreatic involvement. Several samples or repeat biopsy procedures might be needed. PET can help to define the extent of organ involvement and can also be helpful in monitoring disease activity after treatment.[29]

Differentiation of IgG4-related disease from malignant tumours is crucial. Common mimics of multi-organ IgG4-related disease are Sjögren's syndrome, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome), sarcoidosis, and multicentric Castleman's disease. Single-organ diseases such as primary sclerosing cholangitis must also be excluded (table).

Four sets of diagnostic criteria for specific organs have been devised.[30–33] Comprehensive diagnostic criteria for IgG4-related disease have been proposed for practical use by non-specialists.[34]

Serology

High serum IgG4 concentrations are neither sufficiently sensitive nor specific for diagnosis. Serum IgG4 concentrations are useful for screening but are unreliable as a single diagnostic marker. About 20% of patients with type 1 autoimmune pancreatitis have normal serum IgG4 concentrations at presentation.[35,36] The proportion with normal concentrations can be somewhat lower among patients with multi-organ disease,[37] but many diagnoses can be associated with high serum IgG4 concentrations. In one study, 22% of patients who did not have IgG4-related disease had serum IgG4 concentrations higher than twice normal.[37] Other studies have shown that 4–10% of both healthy and disease controls, including patients with pancreatic cancer, have high serum IgG4 concentrations.[36,38,39] Increased ratios of IgG4 to total IgG (>10%) or IgG1 (>24%) increase diagnostic specificity, especially when IgG4 concentrations are only slightly raised.[40] The identification of high numbers of plasmablasts within blood by flow cytometry is more sensitive than serum IgG4 concentrations,[41,42] but such assays are not yet widely available.

Monitoring of serum IgG4 concentrations seems useful in assessment of disease activity in some patients, but this measurement should never be used as the sole determinant in treatment decisions. The serum IgG4 concentration declines substantially after glucocorticoid treatment in most patients, but in one study did not return to the normal range in 115 (63%) of 182 patients.[43] Clinical relapses occurred in 10% of patients who had persistently normal IgG4 concentrations.[43]

Nephelometry assays for IgG4 are prone to error in the presence of large antigen excess, potentially leading to gross underestimates of the serum IgG4 concentration because flocculation does not occur. This effect, known as the prozone phenomenon, can lead to false reports of normal serum IgG4 concentrations and has been observed frequently in patients with IgG4-related disease with serum IgG4 concentrations many times higher than the upper limit of normal.[44] Appropriate dilution of the serum sample during the assay process prevents the prozone effect.

Organ involvement
Constitutional and musculoskeletal symptoms
The presentation of IgG4-related disease is typically subacute, with symptoms and organ dysfunction evident for months or even years before diagnosis. Disease can progress haltingly, with occasional spontaneous improvements (generally temporary) or long plateaus of disease quiescence in a specific organ. In such cases, disease recurrence in an organ known to be affected or the emergence of new organ involvement can lead to diagnosis.

Weight loss of 5–10 kg can occur over months, but fevers and hectic presentations are unusual. Fatigue commonly accompanies IgG4-related disease, especially when the disease affects several organ systems. We have observed a diffuse array of musculoskeletal symptoms, including arthralgias and enthesopathy (inflammation in the site at which a tendon inserts into a bone). To date, however, no histopathological abnormalities of synovium or tenosynovium have been confirmed.

Orbits
The typical ophthalmic presentation involves swelling within the ocular region or frank proptosis, generally
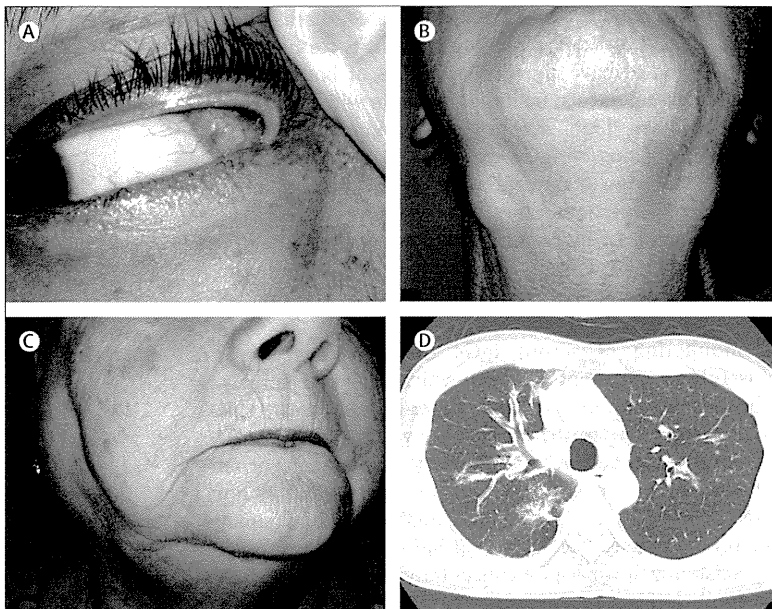
Figure 2: Clinical features
(A) Dacryoadenitis; the typical ophthalmic presentation of IgG4-related disease involves some swelling within the ocular region or proptosis, generally caused by lacrimal-gland enlargement. (B) Submandibular gland enlargement in a patient who had previously undergone a Whipple procedure for presumed pancreatic adenocarcinoma that was shown by histopathology to be type 1 (IgG4-related) autoimmune pancreatitis. (C) Parotid disease in a 70-year-old woman who had a classic case of what used to be called Mikulicz disease, the triad of parotid, lacrimal, and submandibular gland enlargement. (D) Chest CT shows thickening of the bronchovascular bundle in the right lung as well as a posterior ground-glass infiltrate.

Ears, nose, and throat

Allergic features occur in a substantial subset of patients with IgG4-related disease and in many cases are most prominent in the ears, nose, and throat (eg, allergic rhinitis, nasal polyps, chronic sinusitis, nasal obstruction, and rhinorrhea). Many patients have longstanding histories of allergy (rhinitis, nasal polyps, asthma, mild eosinophilia) before the full IgG4-related disease phenotype emerges. Mild to moderate peripheral eosinophilia, sometimes up to 20% or more of the leucocyte count, is common. High serum IgE concentrations, sometimes higher than ten times the upper limit of normal, are also common. However, most patients with IgG4-related disease are not atopic.[24] A subset of non-atopic individuals has peripheral-blood eosinophilia and high concentrations of IgE, which suggests that processes inherent to IgG4-related disease itself rather than atopy contribute to the eosinophilia and high IgE concentrations.

IgG4-related disease can lead to diffuse inflammation in the pharynx, hypopharynx, and Waldeyer's ring, frequently associated with mass lesions.[55] Tracheal inflammation and vocal-cord involvement have also been described. Further studies are needed of the potential relation between IgG4-related disease and so-called idiopathic subglottic stenosis or isolated tracheal inflammation. Mass lesions can occur in the sinuses, and destructive lesions in the middle ear and facial bones have been reported.[56,57]

Thyroid gland

Riedel's thyroiditis (appendix) has been linked convincingly to IgG4-related disease.[58] Fibrosing Hashimoto's thyroiditis also seems to be in the range of IgG4-related disease pathology.[59,60] More controversial is the assertion that a substantial proportion of patients with Hashimoto's thyroiditis also have an IgG4-related disorder. A form of thyroid disease referred to as IgG4-related thyroiditis, distinct from Hashimoto's thyroiditis, is purported,[61] but further study is needed.

Lymphadenopathy

The lymphadenopathy associated with IgG4-related disease is typically either generalised or localised disease adjacent to an affected organ.[62] The affected lymph nodes are generally 1–3 cm in diameter and non-tender. Involvement of the cervical, supraclavicular, submandibular, axillary, hilar, mediastinal, para-aortic, retroperitoneal, and inguinal nodes has been described. Diagnosis of IgG4-related disease through lymph-node biopsy is difficult because lymph nodes are unlikely to show the degree of fibrosis seen in other organs.

Thoracic aorta, branches of the aorta, and coronary lesions

IgG4-related aortitis can lead to aneurysms or dissections in the thoracic aorta.[63–65] This feature, commonly an incidental radiological finding, is also sometimes an unexpected finding at surgery. In contrast to giant-cell and

caused by lacrimal-gland enlargement (dacryoadenitis; figure 2).[45] Proptosis can also result from orbital pseudotumours that do not affect the lacrimal gland, from involvement of extraocular muscles (orbital myositis), and from combinations of these abnormalities. Less common ophthalmic manifestations of IgG4-related disease are scleritis, disease of the nasolacrimal duct (obstruction), and compression of peripheral nerves in the area of the orbit, particularly the trigeminal and infra-orbital nerves.[46–49]

Salivary glands

Both major and minor salivary glands can be affected by IgG4-related disease.[50–52] A disorder known for more than 100 years as Mikulicz's disease, consisting of dacryoadenitis and enlargement of the parotid and submandibular glands, is now recognised as a classic IgG4-related condition.[53,54] Isolated enlargement of the submandibular glands (figure 2) is a common finding in IgG4-related disease. By contrast, in Sjögren's syndrome parotid enlargement predominates. Parotid disease in IgG4-related disease can also be extensive, however (figure 2), as can sublingual-gland enlargement. Xerostomia commonly accompanies IgG4-related disease, but it is generally less severe than in Sjögren's syndrome and, in contrast to Sjögren's syndrome, can improve with immunosuppression.

Takayasu's arteritis, which mainly affect the primary aortic branches, especially the subclavian arteries, IgG4-related disease tends to spare these vessels, at least in terms of clinical manifestations. No definitive histopathological investigations of primary aortic branch vessels have been undertaken, but small case series substantiate the concept that medium-sized blood vessels can also be affected by IgG4-related disease.[66,67] Coronary artery lesions in IgG4-related disease are rare but documented.[68]

Chronic periaortitis and retroperitoneal fibrosis

So-called idiopathic retroperitoneal fibrosis, known for decades as Ormond's disease,[69] is now classified within a larger disease grouping known as chronic periaortitis (appendix). The three major components of chronic periaortitis are IgG4-related retroperitoneal fibrosis, IgG4-related abdominal aortitis, and IgG4-related perianeurysmal fibrosis.[65,70]

The presentations of IgG4-related chronic periaortitis can be subtle and non-specific, leading to diagnostic delay. Common presentations are: a poorly localised pain in the back, flanks, lower abdomen, or thighs; leg oedema; and hydronephrosis from ureteral involvement. The disease targets three sites: periaortic/arterial regions, involving connective tissue around the abdominal aorta or its first branches (appendix); periureteral areas, tending to cause ureteral obstruction and hydronephrosis; and a plaque-like mass that broadly involves the retroperitoneum.

IgG4-related disease is the cause of up to two-thirds of cases of idiopathic retroperitoneal fibrosis.[69,70] In advanced disease, the ratio of IgG4-positive plasma cells to the total number of plasma cells in tissue can be more helpful diagnostically than the overall number of IgG4-positive plasma cells per high-power field. Even if the classic lymphoplasmacytic infiltrate is not evident in longstanding cases, both storiform fibrosis and obliterative phlebitis are commonly identified (appendix)

Lungs

The greatest diversity of clinical and radiological presentations is seen in the lungs.[71] Thickening of the bronchovascular bundle, best shown by CT, is a characteristic lesion (figure 2); it shows the tendency of IgG4-related disease to track along bronchi and blood vessels, which course together.[15] Other radiological features of IgG4-related disease include pulmonary nodules, ground-glass opacities, pleural thickening, and interstitial lung disease. The last of these, which mimics non-specific interstitial pneumonitis and other forms of interstitial fibrosis, emphasises the fibrotic tendencies of IgG4-related disease.

Kidneys

The most characteristic form of IgG4-related renal disease is tubulointerstitial nephritis, which has the same histopathology as in other organs: lymphoplasmacytic infiltrate with IgG4 predominance among plasma cells;
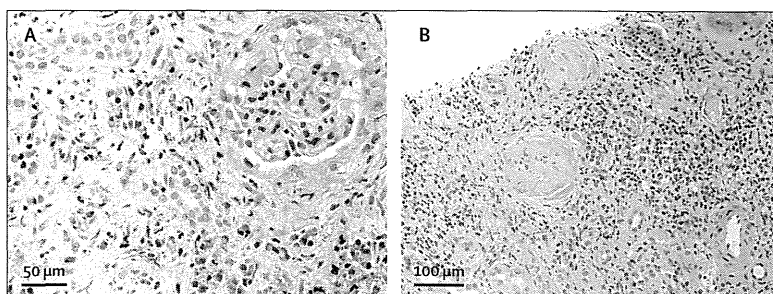

Figure 3: IgG4-related disease in the kidney
(A) Tubulointerstitial nephritis in the setting of IgG4-related disease shows the histopathology found in other organs: a lymphoplasmacytic infiltrate (with an IgG4 predominance among plasma cells), storiform fibrosis, and moderate tissue eosinophilia. (B) Obsolescent glomeruli.

storiform fibrosis; and moderate tissue eosinophilia (figure 3).[72] IgG4-related tubulointerstitial nephritis is distinguished from many other forms of organ involvement by profoundly low concentrations of complement. The basis of this feature remains poorly understood but is unlikely to be explained by IgG4 itself, because this molecule does not bind complement effectively. One plausible explanation is that hypocomplementaemia in IgG4-related disease results from the formation of immune complexes that contain IgG1 or IgG3, subclasses that are raised to a lesser degree in many cases and bind complement more effectively.

Many patients with IgG4-related tubulointerstitial nephritis have substantial enlargements of the kidney and hypodense lesions evident on CT (appendix). Patients with this disorder can experience advanced renal dysfunction and even end-stage renal disease. Substantial proteinuria can develop, but concentrations are generally subnephrotic. Kidneys affected by IgG4-related disease can undergo atrophy, even in the setting of good clinical responses to therapy.[73]

Membranous glomerulonephropathy also occurs in IgG4-related disease.[74] Although the antibody to PLA2 receptor linked to idiopathic membranous glomerulonephritis is primarily of the IgG4 subclass,[75] this specific antibody is not associated with IgG4-related membranous glomerulonephropathy.[76]

Pancreas

The pancreas was the first organ recognised to be associated with high serum IgG4 concentrations.[5,6,77] Two subtypes of autoimmune pancreatitis are known, only one of which (type 1) is associated with IgG4-related disease.[3,78] Type 1 autoimmune pancreatitis, the more common form worldwide, is characterised by the classic histopathological findings of lymphoplasmacytic sclerosing pancreatitis. Type 2, by contrast, has no relation to IgG4-related disease and is identified on the basis of histological features of neutrophilic infiltration into the epithelium of the pancreatic duct.[79–81]

The most common clinical presentation of autoimmune pancreatitis is obstructive jaundice, induced by

concomitant IgG4-related sclerosing cholangitis. Secondary diabetes mellitus occurs in about half of cases, which makes treatment with glucocorticoids difficult in many patients. Differentiation of autoimmune pancreatitis from pancreatic cancer is crucial to avoid unnecessary surgery. The nearly diagnostic CT features of autoimmune pancreatitis include diffuse pancreatic enlargement with delayed enhancement and a capsule-like low-density rim (appendix).[80,81] Diffuse, irregular narrowing of the main pancreatic duct on endoscopic retrograde and magnetic resonance cholangiopancreatography is also highly specific for autoimmune pancreatitis. In cases of segmental autoimmune pancreatitis, skipped narrowed lesions, side-branch derivation from the narrowed portion, and relatively less upstream dilatation on pancreatography suggest autoimmune pancreatitis rather than pancreatic cancer (appendix).[81,82] In PET studies, uptake of fluoro-deoxyglucose in organs other than the pancreas known to be affected by IgG4-related disease suggests autoimmune pancreatitis.[29,83]

International consensus diagnostic criteria for autoimmune pancreatitis were proposed in 2011.[30] Under these criteria, the diagnosis can be made by a combination of parenchymal and ductal imaging, serum IgG4 concentrations, pancreatic histology, extra-pancreatic disease, and glucocorticoid responsiveness. Endoscopic ultrasonography-guided fine-needle aspiration is a useful diagnostic approach to exclude pancreatic cancer and should be attempted before any empirical trial of glucocorticoid treatment is undertaken. Several cases of pancreatic cancer have been reported in patients with type 1 autoimmune pancreatitis.[84,85] Pancreatic stones occur with increased frequency among these patients.[79,86]

IgG4-related sclerosing cholangitis and cholecystitis

Type 1 autoimmune pancreatitis is commonly accompanied by IgG4-related sclerosing cholangitis.[19] Whether the limited intrapancreatic bile-duct stricture associated with autoimmune pancreatitis should be regarded as a biliary manifestation of IgG4-related disease is controversial, because such stenoses can be induced by compression from the swollen pancreas.[87] The histology of IgG4-related sclerosing cholangitis includes obliterative phlebitis and transmural fibrosis with dense infiltration of IgG4-positive plasma cells and T cells.

IgG4-related sclerosing cholangitis must be differentiated from both primary sclerosing cholangitis and hilar cholangiocarcinoma. Neither serum IgG4 concentrations nor cholangiographic or cholangioscopic findings differentiate these disorders clearly.[88–91] Thus, endoscopic transpapillary biopsy is generally needed. Although cholangiocarcinoma can be excluded by endoscopic biopsy, the superficial nature of samples obtained by this procedure limits their usefulness for diagnosis of IgG4-related sclerosing cholangitis.[92]

IgG4-related cholecystitis can occur with sclerosing cholangitis. Thickening of the gallbladder wall is detected on imaging, but it is asymptomatic in most cases.[81]

Other organs

IgG4-related disease seldom, if ever, affects the brain parenchyma but it is one of the most common causes of hypertrophic pachymeningitis.[93] IgG4-related disease is also an unheralded cause of hypophysitis. IgG4-related hypophysitis can lead to hormone deficiencies from both the anterior and posterior pituitary.[94] MRI shows sellar enlargement and thickening of the pituitary stalk.

Sclerosing lesions of both the mediastinum and mesentery have been described.[95,96] In fibrosing mediastinitis, compression of vital mediastinal structures can result from proliferation of invasive fibrous tissue within the mediastinum. A review of 15 patients with fibrosing mediastinitis showed that a substantial proportion of cases are within the IgG4-related disease spectrum.[95] The relation between these cases and antecedent infections with histoplasma, if any, remains unclear.

The inflammatory process in sclerosing mesenteritis seems to originate at the mesenteric root.[96] The ensuing process merges imperceptibly with retroperitoneal fibrosis and can evolve in a devastating manner, encasing vital organs and obviating any attempt at surgical resection.

Several clinical presentations of IgG4-related skin disease have been reported. The most common is the presence of erythematous papules. These lesions typically affect the head and neck but have also been described on the trunk and limbs.[97] Among individuals with darkly pigmented skin, hyperpigmented lesions have been observed. Peripheral-nerve lesions typically consist of perineural masses, up to 3 cm in diameter. These are commonly seen on MRI in the absence of overt clinical manifestations.[48]

The diagnosis of IgG4-related prostate disease is commonly made presumptively when the initiation of treatment for IgG4-related disease in other organs mediates abrupt symptomatic relief of apparently benign prostatic hypertrophy. Both radiological demonstration of prostatic enlargement and biopsy-proven IgG4-related prostatic disease have been reported.[98]

Treatment

Glucocorticoids

Most clinical manifestations of IgG4-related disease respond to glucocorticoids. These agents are the first-line, standard-of-care approach for most patients.[43,99] However, no randomised treatment trials have been done, and few large retrospective examinations have been reported. One treatment approach uses a starting prednisolone dose of 0·6–1·0 mg/kg daily.[30,43] After 2–4 weeks, the dose is tapered by 5 mg every 1–2 weeks according to clinical responses (eg, clinical mani-festations, blood tests, and follow-up imaging studies).

Practice varies as to whether the prednisolone is discontinued entirely after 2 or 3 months or maintained at a low dose. A single-group trial of prednisolone in Japan showed complete remissions in only 61% of patients at 1 year despite continuation of maintenance doses of prednisone in all patients.[100]

Clinical improvement after the start of glucocorticoid therapy is rapid, and a follow-up serological assessment should be done about 2 weeks after treatment initiation. Follow-up radiological assessment is also appropriate for some types of organ involvement, such as the pancreas, biliary tree, lungs, and kidneys. PET with fluorodeoxyglucose is useful to assess treatment response.[29] A swift response to glucocorticoids is reassuring and provides further diagnostic confirmation if a tissue diagnosis was not possible before the start of therapy. A poor response to glucocorticoids, however, should raise the possibility of other diagnoses, particularly cancer.

The response to glucocorticoids varies according to the affected organs and the degree of fibrosis.[8] Both endocrine and exocrine pancreatic function can improve in autoimmune pancreatitis, and salivary secretion in IgG4-related sialadenitis is more likely to improve after glucocorticoid therapy than is the glandular function of Sjögren's syndrome.[100–103] By contrast, retroperitoneal fibrosis, sclerosing mesenteritis, and fibrosing mediastinitis are less amenable to therapy with glucocorticoids, underscoring the importance of early diagnosis and treatment.[104]

Conventional steroid-sparing agents

Drugs such as azathioprine, mycophenolate mofetil, and methotrexate, all used widely in gastroenterology, rheumatology, and transplant medicine as means of achieving additional immunosuppression and sparing patients the effects of long-term glucocorticoids, are commonly chosen for this purpose in IgG4-related disease.[79,105] However, none has been tested in prospective, controlled studies, and evidence for their efficacy beyond that offered by concomitant glucocorticoid therapy is scarce. Rigorous assessment of these treatments in IgG4-related disease is needed.

B-cell depletion

Rituximab was used initially in patients who did not respond to glucocorticoids, conventional steroid-sparing agents, or both, under the assumption that B-cell depletion might ameliorate the condition putatively mediated by high serum concentrations of IgG4.[27,48,106] The fundamental assumption underlying this approach now seems incorrect or at least not entirely true, but careful mechanistic studies of patients with IgG4-related disease treated with rituximab have led to several important observations and novel insights about the pathophysiology of this disorder. First, B-cell depletion targets the subset of plasma cells that produce IgG4 in IgG4-related disease.[27,28] They seem to achieve this action by depleting all circulating

CD20-positive cells (ie, B cells), which interferes in turn with the repletion of short-lived plasma cells making IgG4. In other words, the plasma cells generating IgG4 in IgG4-related disease are mainly of the short-lived type that naturally undergo apoptosis within weeks. Once these cells disappear as programmed, they cannot be repleted after rituximab administration because their precursors—CD20-positive B cells—are not available.

Second, IgG4-positive plasmablasts (positive for IgG4, CD38, CD37, and CD19lo cells) seem to be a good biomarker for IgG4-related disease and are probably superior to serum IgG4 concentrations for diagnosis and monitoring of disease activity.[41,42] We have seen patients with substantially raised numbers of IgG4-positive plasmablasts whose serum IgG4 concentrations were normal in the setting of active disease. These plasmablasts decline quickly after B-cell depletion and can be useful in identifying when to readminister rituximab in some patients, but this question needs further study.

Future perspectives

In only 10 years since the recognition of extrapancreatic features in patients with autoimmune pancreatitis signalled a systemic, multi-organ disease, substantial progress has been achieved in IgG4-related disease. The disease has been identified in nearly every organ system and most of its clinical features have been mapped. Nomenclature has been standardised, and a consensus has been achieved about the major and minor pathological manifestations.[3,14] Effective treatments have been identified and important advances have been made in understanding of disease pathophysiology through mechanistic studies of B-cell depletion. Greater awareness in the medical community of this protean disease is needed to ensure earlier diagnoses, which can prevent severe organ damage, disabling tissue fibrosis, and death. The epidemiology of IgG4-related disease remains poorly understood, mainly because of challenges in recognition and differentiation from the many disorders it mimics. Blood-based diagnostic tests through serology or flow cytometry would be a step forward in case identification. Greater understanding of the immunopathology of IgG4-related disease promises new insights into human immunology and interactions between various T-cell pathways, as well as the possibility of new mechanisms of disease centred around novel T-cell phenotypes. Identification of specific antigens and T-cell clones that drive the disease will be crucial steps in elucidating the pathogenesis of IgG4-related disease.

References

1   Mahajan VS, Mattoo H, Deshpande V, Pillai SS, Stone JH. IgG4-related disease. *Annu Rev Pathol* 2014; **9**: 315–47.

2   Umehara H, Okazaki K, Masaki Y, et al, and the Research Program for Intractable Disease by Ministry of Health, Labor and Welfare (MHLW) Japan G4 team. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. *Mod Rheumatol* 2012; **22**: 1–14.

3   Stone JH, Khosroshahi A, Deshpande V, et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. *Arthritis Rheum* 2012; **64**: 3061–67.

4   Kawa S, Kawano M. IgG4-related disease: an overview. In: Umehara H, Okazaki K, Stone JH, Kawa S, Kawano M, eds. IgG4-related disease. Berlin: Springer, 2013.

5   Kamisawa T, Egawa N, Nakajima H. Autoimmune pancreatitis is a systemic autoimmune disease. *Am J Gastroenterol* 2003; **98**: 2811–12.

6   Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; **38**: 982–84.

7   Kanno A, Nishimori I, Masamune A, et al, and the Research Committee on Intractable Diseases of Pancreas. Nationwide epidemiological survey of autoimmune pancreatitis in Japan. *Pancreas* 2012; **41**: 835–39.

8   Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012; **366**: 539–51.

9   Zen Y, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. *Am J Surg Pathol* 2010; **34**: 1812–19.

10   Ota M, Ito T, Umemura T, et al. Polymorphism in the KCNA3 gene is associated with susceptibility to autoimmune pancreatitis in the Japanese population. *Dis Markers* 2011; **31**: 223–29.

11   Umemura T, Ota M, Hamano H, et al. Association of autoimmune pancreatitis with cytotoxic T-lymphocyte antigen 4 gene polymorphisms in Japanese patients. *Am J Gastroenterol* 2008; **103**: 588–94.

12   Ota M, Katsuyama Y, Hamano H, et al. Two critical genes (HLA-DRB1 and ABCF1)in the HLA region are associated with the susceptibility to autoimmune pancreatitis. *Immunogenetics* 2007; **59**: 45–52.

13   Umemura T, Ota M, Hamano H, Katsuyama Y, Kiyosawa K, Kawa S. Genetic association of Fc receptor-like 3 polymorphisms with autoimmune pancreatitis in Japanese patients. *Gut* 2006; **55**: 1367–68.

14   Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012; **25**: 1181–92.

15   Zen Y, Inoue D, Kitao A, et al. IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. *Am J Surg Pathol* 2009; **33**: 1886–93.

16   Hamano H, Kawa S, Ochi Y, et al. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet* 2002; **359**: 1403–04.

17   Kamisawa T, Funata N, Hayashi Y, et al. Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. *Gut* 2003; **52**: 683–87.

18   Strehl JD, Hartmann A, Agaimy A. Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. *J Clin Pathol* 2011; **64**: 237–43.

19   Zen Y, Harada K, Sasaki M, et al. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? *Am J Surg Pathol* 2004; **28**: 1193–203.

20   Aalberse RC, Stapel SO, Schuurman J, Rispens T. Immunoglobulin G4: an odd antibody. *Clin Exp Allergy* 2009; **39**: 469–77.

21   Okazaki K, Uchida K, Ohana M, et al. Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2-type cellular immune response. *Gastroenterology* 2000; **118**: 573–81.

22   Zen Y, Fujii T, Harada K, et al. Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. *Hepatology* 2007; **45**: 1538–46.

23   Mattoo H, Della-Torre E, Mahajan VS, Stone JH, Pillai S. Circulating Th2 memory cells in IgG4-related disease are restricted to a defined subset of subjects with atopy. *Allergy* 2014; **69**: 399–402.

24   Della Torre E, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. *Allergy* 2014; **69**: 269–72.

25   Tsuboi H, Matsuo N, Iizuka M, et al. Analysis of IgG4 class switch-related molecules in IgG4-related disease. *Arthritis Res Ther* 2012; **14**: R171.

26   King C, Tangye SG, Mackay CR. T follicular helper (TFH) cells in normal and dysregulated immune responses. *Annu Rev Immunol* 2008; **26**: 741–66.

27   Khosroshahi A, Bloch DB, Deshpande V, Stone JH. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum* 2010; **62**: 1755–62.

28   Khosroshahi A, Carruthers MN, Deshpande V, Unizony S, Bloch DB, Stone JH. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. *Medicine (Baltimore)* 2012; **91**: 57–66.

29   Ebbo M, Grados A, Guedj E, et al. Usefulness of 2-[18F]-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography for staging and evaluation of treatment response in IgG4-related disease: a retrospective multicenter study. *Arthritis Care Res (Hoboken)* 2014; **66**: 86–96.

30   Shimosegawa T, Chari ST, Frulloni L, et al, and the International Association of Pancreatology. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011; **40**: 352–58.

31   Ohara H, Okazaki K, Tsubouchi H, et al, and the Research Committee of IgG4-related Diseases, and the Research Committee of Intractable Diseases of Liver and Biliary Tract, and the Ministry of Health, Labor and Welfare, Japan, and the Japan Biliary Association. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. *J Hepatobiliary Pancreat Sci* 2012; **19**: 536–42.

32   Kawano M, Saeki T, Nakashima H, et al. Proposal for diagnostic criteria for IgG4-related kidney disease. *Clin Exp Nephrol* 2011; **15**: 615–26.

33   Masaki Y, Sugai S, Umehara H. IgG4-related diseases including Mikulicz's disease and sclerosing pancreatitis: diagnostic insights. *J Rheumatol* 2010; **37**: 1380–85.

34   Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012; **22**: 21–30.

35   Sah RP, Chari ST. Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. *Curr Opin Rheumatol* 2011; **23**: 108–13.

36   Tabata T, Kamisawa T, Takuma K, et al. Serum IgG4 concentrations and IgG4-related sclerosing disease. *Clin Chim Acta* 2009; **408**: 25–28.

37   Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in patients with potential IgG4-related disease. *Ann Rheum Dis* 2014; published online March 20. DOI:10.1136/annrheumdis-2013-204907.

38   Ghazale A, Chari ST, Smyrk TC, et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. *Am J Gastroenterol* 2007; **102**: 1646–53.

39   Sadler R, Chapman RW, Simpson D, et al. The diagnostic significance of serum IgG4 levels in patients with autoimmune pancreatitis: a UK study. *Eur J Gastroenterol Hepatol* 2011; **23**: 139–45.

40   Boonstra K, Culver EL, de Buy Wenniger LM, et al. Serum IgG4 and IgG1 for distinguishing IgG4-associated cholangitis from primary sclerosing cholangitis. *Hepatology* 2014; **59**: 1954–63.

41   Wallace ZS, Mattoo H, Carruthers MN, et al. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. *Ann Rheum Dis* 2014; published online May 9. DOI:10.1136/annrheumdis-2014-205233.rint.

42   Mattoo H, Mahajan VS, Della Torre E, et al. De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4-related disease. *J Allergy Clin Immunol* 2014; published online May 6. DOI:10.1016/j.jaci.2014.03.034.

43   Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. *Gut* 2009; **58**: 1504–07.

44   Khosroshahi A, Cheryk LA, Carruthers MN, Edwards JA, Bloch DB, Stone JH. Brief Report: spuriously low serum IgG4 concentrations caused by the prozone phenomenon in patients with IgG4-related disease. *Arthritis Rheum (Munch)* 2014; **66**: 213–17.

−218−

45   Wallace ZS, Deshpande V, Stone JH. Ophthalmic manifestations of IgG4-related disease: single-center experience and literature review. *Semin Arthritis Rheum* 2013; **43**: 806–17.

46   Ohno K, Sato Y, Ohshima K, et al. IgG4-related disease involving the sclera. *Mod Rheumatol* 2014; **24**: 195–98.

47   Wallace ZS, Khosroshahi A, Jakobiec FA, et al. IgG4-related systemic disease as a cause of "idiopathic" orbital inflammation, including orbital myositis, and trigeminal nerve involvement. *Surv Ophthalmol* 2012; **57**: 26–33.

48   Inoue D, Zen Y, Sato Y, et al. IgG4-related perineural disease. *Int J Rheumatol* 2012; **29**: 212–18.

49   Takahira M, Ozawa Y, Kawano M, et al. Clinical aspects of IgG4-related orbital inflammation in a case series of ocular adnexal lymphoproliferative disorders. *Int J Rheumatol* 2012; published online April 2. DOI:10.1155/2012/635473.

50   Baer AN, Gourin CG, Westra WH, Cox DP, Greenspan JS, Daniels TE, and the Sjögren's International Collaborative Alliance. Rare diagnosis of IgG4-related systemic disease by lip biopsy in an international Sjögren syndrome registry. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013; **115**: e34–39.

51   Hermet M, André M, Kémény JL, et al. Is IgG4-related disease a cause of xerostomia? A cohort study of 60 patients. *Int J Rheumatol* 2012; published online Oct 16. DOI:10.1155/2012/303506.

52   Geyer JT, Ferry JA, Harris NL, et al. Chronic sclerosing sialadenitis (Küttner tumor) is an IgG4-associated disease. *Am J Surg Pathol* 2010; **34**: 202–10.

53   Yao Q, Wu G, Hoschar A. IgG4-related Mikulicz's disease is a multiorgan lymphoproliferative disease distinct from Sjögren's syndrome: a Caucasian patient and literature review. *Clin Exp Rheumatol* 2013; **31**: 289–94.

54   Himi T, Takano K, Yamamoto M, Naishiro Y, Takahashi H. A novel concept of Mikulicz's disease as IgG4-related disease. *Auris Nasus Larynx* 2012; **39**: 9–17.

55   Fatemi G, Fang MA. IgG4-related pharyngitis-an addition to the nomenclature of IgG4-related disease: comment on the article by Stone et al. *Arthritis Rheum* 2013; **65**: 2217.

56   Hu EK, Parrish C, Wrobel B, Deshpande V, Stone JH. Immunoglobulin G4-related disease presenting as an ethmoid and maxillary mass. *Ann Allergy Asthma Immunol* 2013; **111**: 75–77.

57   Schiffenbauer AI, Gahl WA, Pittaluga S, et al. IgG4-related disease presenting as recurrent mastoiditis. *Laryngoscope* 2012; **122**: 681–84.

58   Dahlgren M, Khosroshahi A, Nielsen GP, Deshpande V, Stone JH. Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. *Arthritis Care Res (Hoboken)* 2010; **62**: 1312–18.

59   Deshpande V, Huck A, Ooi E, Stone JH, Faquin WC, Nielsen GP. Fibrosing variant of Hashimoto thyroiditis is an IgG4 related disease. *J Clin Pathol* 2012; **65**: 725–28.

60   Pusztaszeri M, Triponez F, Pache JC, Bongiovanni M. Riedel's thyroiditis with increased IgG4 plasma cells: evidence for an underlying IgG4-related sclerosing disease? *Thyroid* 2012; **22**: 964–68.

61   Watanabe T, Maruyama M, Ito T, et al. Clinical features of a new disease concept, IgG4-related thyroiditis. *Scand J Rheumatol* 2013; **42**: 325–30.

62   Cheuk W, Chan JK. Lymphadenopathy of IgG4-related disease: an underdiagnosed and overdiagnosed entity. *Semin Diagn Pathol* 2012; **29**: 226–34.

63   Kasashima S, Zen Y, Kawashima A, et al. A clinicopathologic study of immunoglobulin G4-related sclerosing disease of the thoracic aorta. *J Vasc Surg* 2010; **52**: 1587–95.

64   Stone JH, Patel VI, Oliveira GR, Stone JR. Case records of the Massachusetts General Hospital: case 38-2012, a 60-year-old man with abdominal pain and aortic aneurysms. *N Engl J Med* 2012; **367**: 2335–46.

65   Zen Y, Kasashima S, Inoue D. Retroperitoneal and aortic manifestations of immunoglobulin G4-related disease. *Semin Diagn Pathol* 2012; **29**: 212–18.

66   Stone JR. Aortitis, periaortitis, and retroperitoneal fibrosis, as manifestations of IgG4-related systemic disease. *Curr Opin Rheumatol* 2011; **23**: 88–94.

67   Inoue D, Zen Y, Abo H, et al. Immunoglobulin G4-related periaortitis and periarteritis: CT findings in 17 patients. *Radiology* 2011; **261**: 625–33.

68   Inokuchi G, Hayakawa M, Kishimoto T, Makino Y, Iwase H. A suspected case of coronary periarteritis due to IgG4-related disease as a cause of ischemic heart disease. *Forensic Sci Med Pathol* 2014; **10**: 103–08.

69   Khosroshahi A, Carruthers MN, Stone JH, et al. Rethinking Ormond's disease: "idiopathic" retroperitoneal fibrosis in the era of IgG4-related disease. *Medicine (Baltimore)* 2013; **92**: 82–91.

70   Zen Y, Onodera M, Inoue D, et al. Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. *Am J Surg Pathol* 2009; **33**: 1833–39.

71   Inoue D, Zen Y, Abo H, et al. Immunoglobulin G4-related lung disease: CT findings with pathologic correlations. *Radiology* 2009; **251**: 260–70.

72   Saeki T, Nishi S, Imai N, et al. Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. *Kidney Int* 2010; **78**: 1016–23.

73   Saeki T, Kawano M, Mizushima I, et al. The clinical course of patients with IgG4-related kidney disease. *Kidney Int* 2013; **84**: 826–33.

74   Alexander MP, Larsen CP, Gibson IW, et al. Membranous glomerulonephritis is a manifestation of IgG4-related disease. *Kidney Int* 2013; **83**: 455–62.

75   Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; **361**: 11–21.

76   Khosroshahi A, Ayalon R, Beck LH Jr, Salant DJ, Bloch DB, Stone JH. IgG4-related disease is not associated with antibody to the phospholipase A2 receptor. *Int J Rheumatol* 2012; published online May 10. DOI:10.1155/2012/139409.

77   Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; **344**: 732–38.

78   Sah RP, Chari ST, Pannala R, et al. Differences in clinical profile and relapse rate of type 1 versus Type 2 autoimmune pancreatitis. *Gastroenterology* 2010; **139**: 140–48, quiz e12–13.

79   Hart PA, Kamisawa T, Brugge WR, et al. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. *Gut* 2013; **62**: 1771–76.

80   Kamisawa T, Chari ST, Lerch MM, Kim MH, Gress TM, Shimosegawa T. Recent advances in autoimmune pancreatitis: type 1 and Type 2. *Gut* 2013; **62**: 1373–80.

81   Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T. Autoimmune pancreatitis and IgG4-related sclerosing disease. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 401–09.

82   Sugumar A, Levy MJ, Kamisawa T, et al. Endoscopic retrograde pancreatography criteria to diagnose autoimmune pancreatitis: an international multicentre study. *Gut* 2011; **60**: 666–70.

83   Ozaki Y, Oguchi K, Hamano H, et al. Differentiation of autoimmune pancreatitis from suspected pancreatic cancer by fluorine-18 fluorodeoxyglucose positron emission tomography. *J Gastroenterol* 2008; **43**: 144–51.

84   Pezzilli R, Vecchiarelli S, Di Marco MC, et al. Pancreatic ductal adenocarcinoma associated with autoimmune pancreatitis. *Case Rep Gastroenterol* 2011; **5**: 378–85.

85   Gupta R, Khosroshahi A, Shinagare S, et al. Does autoimmune pancreatitis increase the risk of pancreatic carcinoma?: a retrospective analysis of pancreatic resections. *Pancreas* 2013; **42**: 506–10.

86   Maruyama M, Arakura N, Ozaki Y, et al. Type 1 autoimmune pancreatitis can transform into chronic pancreatitis: a long-term follow-up study of 73 Japanese patients. *Int J Rheumatol* 2013; published online May 16. DOI:10.1155/2013/272595.

87   Hirano K, Tada M, Isayama H, et al. Endoscopic evaluation of factors contributing to intrapancreatic biliary stricture in autoimmune pancreatitis. *Gastrointest Endosc* 2010; **71**: 85–90.

88   Mendes FD, Jorgensen R, Keach J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. *Am J Gastroenterol* 2006; **101**: 2070–75.

89   Oseini AM, Chaiteerakij R, Shire AM, et al. Utility of serum immunoglobulin G4 in distinguishing immunoglobulin G4-associated cholangitis from cholangiocarcinoma. *Hepatology* 2011; **54**: 940–48.

90   Kalaitzakis E, Levy M, Kamisawa T, et al. Endoscopic retrograde cholangiography does not reliably distinguish IgG4-associated cholangitis from primary sclerosing cholangitis or cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2011; **9**: 800–03, e2.

—219—

91 Itoi T, Kamisawa T, Igarashi Y, et al. The role of peroral video cholangioscopy in patients with IgG4-related sclerosing cholangitis. *J Gastroenterol* 2013; **48**: 504–14.

92 Nakazawa T, Ando T, Hayashi K, Naitoh I, Ohara H, Joh T. Diagnostic procedures for IgG4-related sclerosing cholangitis. *J Hepatobiliary Pancreat Sci* 2011; **18**: 127–36.

93 Wallace ZS, Carruthers MN, Khosroshahi A, et al. IgG4-related disease and hypertrophic pachymeningitis. *Medicine (Baltimore)* 2013; **92**: 206–16.

94 Leporati P, Landek-Salgado MA, Lupi I, Chiovato L, Caturegli P. IgG4-related hypophysitis: a new addition to the hypophysitis spectrum. *J Clin Endocrinol Metab* 2011; **96**: 1971–80.

95 Peikert T, Shrestha B, Aubry MC, et al. Histopathologic overlap between fibrosing mediastinitis and IgG4-related disease. *Int J Rheumatol* 2012; published online May 10. DOI:10.1155/2012/207056.

96 Salvarani C, Valli R, Boiardi L, Pipitone N, Nicoli F, Muratore F. IgG4-associated sclerosing mesenteritis. *Clin Exp Rheumatol* 2011; **29** (suppl 64): S79–80.

97 Ikeda T, Oka M, Shimizu H, et al. IgG4-related skin manifestations in patients with IgG4-related disease. *Eur J Dermatol* 2013; **23**: 241–45.

98 Hart PA, Smyrk TC, Chari ST. IgG4-related prostatitis: a rare cause of steroid-responsive obstructive urinary symptoms. *Int J Urol* 2013; **20**: 132–34.

99 Kamisawa T, Okazaki K, Kawa S, Shimosegawa T, Tanaka M, and the Research Committee for Intractable Pancreatic Disease and Japan Pancreas Society. Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP. *J Gastroenterol* 2010; **45**: 471–77.

100 Masaki Y, for the All-Japan Team for the Prospective Treatment Study of IgG4-RD. A trial of corticosteroids for IgG4-related disease. Second International Symposium on IgG4-related Disease & Associated Conditions, Honolulu, HA, USA, February 16–19, 2014.

101 Kamisawa T, Egawa N, Inokuma S, et al. Pancreatic endocrine and exocrine function and salivary gland function in autoimmune pancreatitis before and after steroid therapy. *Pancreas* 2003; **27**: 235–38.

102 Ito T, Kawabe K, Arita Y, et al. Evaluation of pancreatic endocrine and exocrine function in patients with autoimmune pancreatitis. *Pancreas* 2007; **34**: 254–59.

103 Ko SB, Mizuno N, Yatabe Y, et al. Corticosteroids correct aberrant CFTR localization in the duct and regenerate acinar cells in autoimmune pancreatitis. *Gastroenterology* 2010; **138**: 1988–96.

104 Shimizu Y, Yamamoto M, Naishiro Y, et al. Necessity of early intervention for IgG4-related disease–delayed treatment induces fibrosis progression. *Rheumatology (Oxford)* 2013; **52**: 679–83.

105 Hart PA, Topazian MD, Witzig TE, et al. Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. *Gut* 2013; **62**: 1607–15.

106 Carruthers MN, Khosroshahi A, Topazian M, et al. Rituximab for IgG4-related disease: a prospective treatment trial. *Arthritis Rheum* 2013; **10**: 2649.

●短　報

第 54 回日本呼吸器学会学術講演会　シンポジウム報告

IgG4 関連呼吸器疾患の診断基準

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要旨：IgG4 関連呼吸器疾患の診断基準を，厚生労働省難治性疾患克服研究事業研究班より提案し，第 54 回日本呼吸器学会学術講演会シンポジウムにて討議した．診断項目は，画像所見・血液検査所見・病理所見・胸郭外臓器病変の存在，の 4 項目とし，診断を，確定診断群 (definite)・準確診群 (probable)・疑診群 (possible) の 3 つに分類した．また解説とアルゴリズムを付記した．本診断基準の普及が望まれる．

キーワード：IgG4 関連疾患，IgG4 関連呼吸器疾患，診断基準

IgG4-related disease, IgG4-related respiratory disease, Diagnostic criteria

診断基準作成までの経緯

IgG4 関連疾患は，高 IgG4 血症および病変部への IgG4 陽性形質細胞浸潤と線維化を特徴とする新しい全身性疾患である．2011 年，厚生労働省難治性疾患克服研究事業研究班（厚労班）から，IgG4 関連疾患包括診断基準が提唱され，現在では広く認知されている[1][2]．

包括診断基準は，多臓器の共通所見をまとめた利便性の高い診断基準である．しかし医療が専門化・細分化されている現況から，厚労班では，各臓器病変の特異性に着目した「臓器別診断基準」の必要性も検討されており，すでに膵臓，腎臓などの臓器別診断基準が公表されている[3][4]．

以上の経過から，厚労班呼吸器分科会では，呼吸器病変の診断基準作成を試みた．それを第 54 回日本呼吸器学会学術講演会（2014 年 4 月，河野修興会長）のシンポジウムにおいて議論し，出席した会員との意見交換後，全員の同意を得て最終的な診断基準を作成したので，ここに報告する．

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IgG4 関連呼吸器疾患の診療指針

1. 呼吸器病変の疾患名称

2011 年にボストンで開催された国際シンポジウムにおいて，IgG4 関連疾患の呼吸器病変は，「IgG4 関連肺疾患 (IgG4-related lung disease)」と「IgG4 関連胸膜疾患 (IgG4-related pleural disease)」という 2 つの個別の名称が採択された[5]．しかしその後，呼吸器病変は広義間質病変であることが報告されたため[6]，厚労班では，胸郭内の呼吸器および附属器の病変を包括して「IgG4 関連呼吸器疾患 (IgG4-related respiratory disease)」と呼称することとした．

2. IgG4 関連呼吸器疾患の診断基準

呼吸器疾患の診断基準を表 1 に示した．

この診断基準の画像所見，臨床/検査所見，病理所見の把握のために，解説を付記した（表 2）．

また，診断へ至る過程を具体的に示すためのアルゴリズムも作成した（図 1）．

ま と め

IgG4 関連呼吸器疾患の診断基準を報告した．今後は，本基準の普及が望まれる．