の浸潤を病変局所において認められるものの、関与しているThサブセットは異なっている事が示唆された。さらにMDでは血清IgG4値とIL-4、IL-10、foxp3との間に正の相関を認めた。免疫組織化学染色におけるIgG4陽性細胞率とIL-4では相関は認められなかったが、IL-10とFoxp3においては正の相関が認められた。

Q. B細胞とT細胞のcontactはin situで行われるか、リンパ節で行われるか?
A. 検討中である。
Q. CCR4の局在は?
A. SSでは導管周囲、MDでは胚中心～瀰漫性に存在。T-regも瀰漫性。

2）IgG4包括診断基準に対するIgG4+MOLPSからの提案　(研究分担者：梅原久範)

○梅原久範　(金沢医科大学 血液免疫制御学)

IgG4 セカンドミーテーィングで IgG4 の統一名称として、IgG4-related disease, IgG4 関連疾患と呼ぶこととなった。IgG4 関連疾患は全身性疾患であり、ミクリッツ病, IgG4 関連自己免疫性膵炎, IgG4 関連腎症, 後腹膜線維症, IgG4 関連橋本病, IgG4 関連下垂体腺腫は、IgG4 が関係している。

当研究班は、各領域の医師で構成され、総勢 53 名となっている。倫理委員会承認施設は 23 施設あり、症例登録は 73 例である。

2010 年 2 月 11 日、IgG4 セカンドミーテーィングで IgG4 の統一名称として、IgG4-related disease, IgG4 関連疾患と呼ぶこととなった。IgG4 関連疾患の診断基準として、1. 血清 IgG4 > 135mg/dl、2. 組織で IgG4+ 形質細胞浸潤 (IgG4+/IgG+ 形質細胞>40%) を大前提とし、3. 病理像・著明な線維化または硬化像・閉塞性静脈炎をどのようにして加えるかが課題であった。

2010 年 11 月 21 日、梅原班と岡崎班の診断基準作成ワーキンググループが行われた。IgG4 関連疾患包括診断基準の日本語版ができあがり、今英文を作成している。IgG4 関連疾患診断のフローチャートがあり、確定例や疑診例はそれぞれの疾患の診断基準と照らし合わせるようにしている。

日本腎臓学会にて「IgG4 関連疾患ワーキンググループ」を立ち上げ、「IgG4 関連腎症の診断基準」 作成への取り組みが行われている。IgG4 関連腎症診断のためのフローチャート案もできてきている。IgG4 関連呼吸器疾患の診断の手引きも作成中である。
以上が当研究班からの報告である。

【病因病態解明のための遺伝子、免疫学的解析】

プロジェクト4　接着制御分子破綻による自己免疫発症の機構

(プロジェクトリーダー：木梨達雄)

IgG4 関連全身硬化性疾患患者における RASSF5C、MST1 遺伝子のメチル化解析 (研究分担者：木梨達雄)

木梨達雄、○富山尚、植田祥啓、安田鐘樹　(関西医科大学　分子遺伝学講座)

接着制御因子 RAPL, Mst1 を欠損したマウスは加齢とともに自己免疫様症状を呈する。健常人の DNA を材料に RAPL, Mst1 プロモーター領域の sodium bisulfite 法によるメチル化マッピングを行った。同様の手法で IgG4 関連疾患自己免疫性膵炎患者検体を解析した。その結果、RAPL 遺伝子で IgG4 値とメチル化が相関する部位が見出された。

IgG4 関連疾患で RAPL 遺伝子のメチル化が亢進していることから、病態に何らかの影響を及ぼしている可能性がある。Mst1 は有意差がでなかったが、今後検体数を増やして解析を行う予定である。

プロジェクト5　IgG4関連疾患の疾患感受性遺伝子の解析

(プロジェクトリーダー：川　茂幸)

全ゲノム網羅的SNPを用いた自己免疫性膵炎の感受性遺伝子の解析（研究分担者：川　茂幸）

川　茂幸、○大田正穂、伊藤哲也、浜野英明、目黒　明、猪子英俊
（信州大学健康安全センター、法医学教室、消化器内科学教室、医療情報部、東海大学医学部分子生命科学教室）

自己免疫性疾患は遺伝的要因と環境要因が背景に存在する多因子疾患である。本疾患の病態に関連する遺伝的要因解明の目的で、Affimetrix社製SNPチップ、GeneChip Human Mapping 500k Array Setを用いて、自己免疫性膵炎88検体の全ゲノム網羅的な相関解析（genome-wide association study: GWAS）を行った。

コントロールのタイピングデータは健常人766例分をもちいた。SNPのquality controlとして、call rate 95%以上、Hardy-Weinberg equilibrium P 値が 0.001 以上、MAF (minor allele frequency)が 5% 以上で選択し、322,091SNPsが統計解析に用いられた。P<0.0001で疾患と相関したSNPsをLead SNPsとして連鎖不平衡下にある遺伝子を拾い出すと14種類の染色体上に、25種類の遺伝子が感受性遺伝子として候補にあがった。

現在、これらの遺伝子について、さらにその遺伝子内に設けたSNPを用いて、fine mapping を行い、確認解析を行っている。

プロジェクト6　ゲノム解析の手法を用いた疾患関連遺伝子の探索

（プロジェクトリーダー：松田文彦）

「IgG4関連疾患・自己免疫性膵炎における疾患関連遺伝子の解析」に関わる現在の進捗状況

岡崎和一、○内田一茂　（研究班事務局）

事務局より現在の進捗状況につき報告した。

プロジェクト7　プロテオミクス解析による新規診断マーカーの開発

（プロジェクトリーダー：坪内博仁）

プロテオミクス解析による自己免疫性膵炎診断マーカーの探索（研究分担者：坪内博仁）

坪内博仁、○嵜山敏男、宇都浩文、前田拓郎、船川慶太、井戸章雄
（鹿児島大学大学院医歯学総合研究科　消化器疾患・生活習慣病学）

ClinProtシステムとMALDI-TOF/MSを用いたプロテオミクス解析と二次元電気泳動法によるプロテオミクス解析を行いました。

まず、ClinProtシステムとMALDI-TOF/MSを用いたプロテオミクス解析では特発性膵炎群とステロイド加療歴のないAIP群を比較したところAIP群において4963m/zピーク蛋白が有意に高く、また2560m/zピーク蛋白も高い傾向であった。それぞれのタンパクの同定を試みましたが同定は困難でした。しかし、この二つの蛋白はアルコール性慢性膵炎患者群でも上昇しているため疾患特異性は乏しい可能性があります。

ステロイド治療前後のAIP患者血清の比較では5900m/z, 3224m/z, 2660m/z等のピーク蛋白は治療後に低下し、2953m/z等のピーク蛋白は治療後の上昇が認められました。今後これらの蛋白を同定することができるかが課題であります。

二次元電気泳動法によるプロテオミクス解析ではApolipoprotein EとTransthyretinとamyloid-P componentがステロイド加療前後の患者血清比較から有意差のある蛋白として同定されました。Apolipoprotein Eは治療後に低下し、Transthyretinとamyloid-P componentは治療後に上昇しました。今後ELISA法でも検討し再現性の有無や疾患特異性の評価を行っていきたいと思います。

プロジェクト8　IgG4における自然免疫系と獲得免疫系の関係に関する研究

（プロジェクトリーダー：千葉　勉）

IgG4 産生に関わる自然免疫反応の解明（研究分担者：千葉　勉）

千葉　勉、○渡邊智裕　（京都大学 消化器内科学講座）

自然免疫に関するレセプターとして TLR は有名ですが最近 NOD が注目されています。NOD1 はヘリコバクタピロリ感染に関与し、NOD2 はクローン病に関与することがすでにわかっています。今回我々は AIP における NOD を中心とした自然免疫反応について研究しました。

NOD2 は CD14 陽性単球細胞内に存在するレセプターでリガンドは MDP です。主にグラム陽性、または一部のグラム陰性菌の細胞膜に存在すると言われています。

前回までの研究で健常人において CD14 陽性の単球は NOD2 が活性化し BAFF を産生し、それが CD19 陽性の B 細胞に作用して IgG4 を産生することがわかりました。またこの IgG4 の産生の機序には T 細胞は関与していませんでした。

今回 IgG4 関連疾患患者でどのようになっているか調べました。

患者 10 例の末梢血より PBMC を採取し NOD や TLR のリガンドで刺激したとろ、ほぼすべてにおいて健常人より患者群で IgG1, IgG4 ともに産生が亢進していました。同時に BAFF の産生についても調べましたが IgG4 と同じように産生が亢進していました。またサイトカインについても測定しましたが INF-γの産生が抑制され Th1 反応が減弱していました。

健常人の B 細胞に健常人、あるいは患者の単球を反応させたところ健常人の単球は IgG4 の産生は増加しないが患者の単球を反応させると IgG4 の産生が増加しました。逆に患者の B 細胞に健常人、あるいは患者の単球を反応させるといずれも IgG4 の産生は亢進していました。つまり単球の種類に依存することなく、末梢ですでに B 細胞のクラススイッチが行われているのではないかと考えました。

結論ですが、健常人では NOD2 のリガンド刺激でのみ BAFF の産生が亢進していたのに対し、患者では NOD だけでなく TLR の刺激を介しても BAFF の産生が行われていることが分かりました。

仮説ですが IgG4 へのクラススイッチは骨髄のレベルで行われているのかもしれません。

質問「BAFF の産生が直接 IgG のクラススイッチに関与しているのですか」
⇒「B 細胞は活性化しているがクラススイッチに関与しているかは不明です。」
質問「実際 BAFF は疾患にどのように作用しているのか」
⇒「まだ不明です。」
質問「主にどの TLR に反応するのですか」
⇒「TLR7,9以外はほぼすべての TLR に反応します。」

プロジェクト9　IgG4関連疾患における標的抗原と免疫制御に関する研究

（プロジェクトリーダー：岡崎和一）

悪性腫瘍（膵癌、胆管癌）における IgG4 陽性形質細胞および CD163 陽性マクロファージの検討

（研究協力者：能登原憲司）

○能登原憲司　（倉敷中央病院　病理検査科）

LPSP において CD163 陽性細胞と線維芽細胞が storiform fibrosis を形成することを報告してきました。今回我々は癌における CD163 陽性細胞について調べました。

膵癌においては膵実質の残存しているところに CD163 陽性細胞が集簇し、強拡で確認すると同部位に好中球の浸潤も認められました。また小葉構造が破壊されているところでも CD163 陽性細胞が集簇していました。

胆管癌においては小葉内の辺縁部に好中球浸潤が認められました。このような所見は IDCP でも類似した所見が観察されます。CD163 陽性細胞も認められますが線維芽細胞がそれほど多くないため LPSP のような storiform fibrosisi の形成は認められませんでした。

また、胆管癌において IgG4 陽性細胞はそれほど多く認められませんでした。つまり IgG4 と IgG の比率を確

認すればLPSP と癌の鑑別がつくのではないかと考えられます。ただし1視野だけで判断すると focal にCD163 細胞が集簇している可能性があるのでいくつかの視野で確認する必要があるかと思われます。

LPSP においてCD163 陽性細胞と IgG4 陽性細胞と両方が多数認められることが特徴と考えられます。癌の場合はさまざまな形態があり特徴ある所見は見当たりませんでした。ただしLPSP に類似した所見を呈する癌は極めてまれであり、多くの症例はCD163 と IgG4 を注意深く観察することで鑑別可能と思われます。

結論ですが膵癌、胆管癌で見られる CD163 陽性マクロファージの分布は多くの場合、IDCP で見られる分布に類似し、実質の破壊に対する反応である可能性がある。CD163 陽性マクロファージと IgG4 陽性形質細胞の数は必ずしも相関しない。真にLPSP に類似するような反応をきたす膵癌、胆管癌は極めて稀で、特殊なケースと考えられる。

質問「M2 マクロファージへの反応は自然免疫でも確認されますか」
⇒「NOD を刺激しM2 のマーカーをいくつか測ってみましたがいずれも上昇は確認できませんでした。」

質問「LPSP と IDCP の病理学的な特徴は」
⇒「LPSP では脂肪組織の周囲に storiform fibrosis を形成し、IDCP では好中球の浸潤と浮腫が特徴です。マクロファージを染色し比較すれば鑑別可能ではないか。」

2）自己免疫性膵炎におけるLPSP と IDCP の免疫学的相違　　(研究分担者：岡崎和一)

岡崎和一、○内田一茂、楠田武生、福井由理、吉田勝紀、坂口雄沢、福井寿朗、西尾彰功
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IDCP は欧米では多く報告されているが、本邦での報告は極めて少ない。そこで今回当院で経験した IDCP 症例と好中球病変を伴ったAIP with GEL について臨床的、免疫組織額的に検討をおこなった。画像上はいずれの症例も膵管は途絶しており、いわゆる自己免疫性膵炎に特徴的な狭細像はみとめられなかった。免疫組織学的には、いずれの症例も IgG4 陽性細胞の浸潤はLPSP に比較して少なく、制御性T 細胞のマーカーであるFoxp3 陽性細胞も同様にLPSP に比較し少なかった。これらの症例は術前膵癌との鑑別はつかず自己免疫性膵炎とは診断できなかった。日本では IDCP 症例は少なく、今後膵癌との鑑別を含めてどう診断していくのかが課題であると考えられた。

X. 研究成果の刊行物・別刷

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Comparison of steroid pulse therapy and conventional oral steroid therapy as initial treatment for autoimmune pancreatitis

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Abstract
Background The efficacy of oral steroid therapy for autoimmune pancreatitis (AIP) is well known, and oral prednisolone treatment is most usually commenced at 30–40 mg/day, but there have been few reports about comparative studies of oral steroid therapy and steroid pulse therapy as the initial treatment for AIP. We studied the clinical course and image findings to estimate the utility of steroid pulse therapy for AIP, comparing it with oral steroid therapy.
Methods Laboratory and image findings were assessed retrospectively in 11 patients who received steroid pulse therapy, and the findings were compared to those in 10 patients who received conventional oral steroid therapy.
Results Change in pancreatic size showed no significant difference between the therapies after 2 weeks of treatment. Significant improvement of lower bile duct strictures after 2 weeks of treatment and that of immunoglobulin values within 6 months were shown with both therapies. However, steroid pulse therapy showed significant improvement of γ-guanosine triphosphate (GTP) in 2 weeks and of alanine aminotransferase (ALT) in 2 and 8 weeks, compared with oral steroid therapy. Moreover, there was one patient in whom the lower bile duct stricture was not improved by oral steroid therapy, but it did show improvement with steroid pulse therapy.
Conclusions Initial steroid pulse therapy is a beneficial alternative to oral steroid therapy for the improvement of bile duct lesions. In future, the accumulation of a larger number of patients receiving steroid pulse therapy is needed, and prospective studies will be required.

Keywords Autoimmune pancreatitis (AIP) · Steroid pulse therapy · Bile duct stricture · Diabetes mellitus · Pancreatic cancer

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Introduction

Sarles et al. [1] reported a case of chronic pancreatitis with hypergammaglobulinemia, but the clinical entity was not confirmed thereafter. Autoimmune pancreatitis (AIP), which was first proposed as a clinical entity by Yoshida et al. [2] from Japan, is now generally accepted as a distinctive type of pancreatitis [1]. AIP is characterized by diffuse irregular narrowing of the main pancreatic duct, sausage-like diffuse swelling of the pancreas, high serum levels of IgG or IgG4, and steroid responsiveness [3–6]. Since the fibroinflammatory process of AIP responds well to steroids, autoimmune mechanisms are thought to be involved in the development of AIP. A recent large Japanese study of AIP and guidelines for treatment recommend standard oral steroid therapy with an initial dose of 0.5–0.6 mg/kg/day [7, 8].

While steroid responsiveness as a diagnostic component is not included in the revised Japanese criteria, it is included in the Korean criteria, Mayo Clinic HISORt (Histology, Imaging, Serology, Other organ involvement, and Response to steroids) criteria, and recently proposed Asian criteria [8–11]. The most important issue in AIP management is making the diagnosis of AIP, especially the

mass-forming type, differentiating it from pancreatic or biliary cancers [12–15], although some cases of pancreatic cancer are accompanied by AIP [16–19]. In some tumor-forming AIP cases, the efficacy of a steroid trial has been reported as useful in diagnosing AIP by criteria other than the Japanese diagnostic criteria [20]. Moreover, Korean investigators have reported the usefulness of a 2 weeks' trial of oral steroids in differentiating AIP from malignancy, with continuing administration if AIP is diagnosed [20]. However, it has not yet been established whether or not withdrawal of steroids in reconsidering malignancy presents a risk of postoperative adrenal insufficiency [21–23]. Therefore, it is desirable to have an alternative to the discontinuation of steroid administration immediately after surgery.

Steroid pulse therapy is widely used to initiate treatment in patients with rapidly progressive and immunologically mediated disorders such as acute graft rejection, Graves ophthalmopathy, pemphigus, and severe systemic lupus erythematosus [24–27]. Moreover, high doses of systemic steroid can be given with comparative safety within a period of 1 week [28]. We therefore evaluated the efficacy of short-term steroid pulse therapy, in comparison with oral steroid therapy, in patients with AIP.

Methods

Patients and treatment

For this study, we retrospectively examined the records of all 21 AIP patients treated in our hospitals from November 2004 to May 2009. All patients were diagnosed with AIP according to the clinical diagnostic criteria for AIP proposed by the Research Committee of Intractable Diseases of the Pancreas supported by the Japanese Ministry of Health, Labor, and Welfare, and the Japan Pancreas Society. Following diagnosis, 20 patients with AIP were randomly distributed to two treatment groups by their attending physicians. One patient (case 10) was referred to our hospital after the withdrawal of oral steroid for AIP because his bile duct lesion had not responded to the treatment. Eleven patients (cases 1–11; 5 male and 6 female; aged 47–80 years, with a mean age of 66 years, named the "pulse group") (Table 1) received steroid pulse therapy, and ten patients (cases 12–21; 8 male and 2 female, aged 49–72 years, with a mean age of 69 years, named the "oral group") (Table 2) received oral steroid therapy. For the pulse group, the initial dose of methylprednisolone was 500 mg/day for 3 days each week as 1 course, and we treated them with 2 weekly courses. Then oral prednisolone at 20 mg/day was prescribed as maintenance therapy and the dose was tapered off. For the oral group, ten patients commenced oral prednisolone at 30–40 mg/day. Two weeks after the start of the treatment, oral prednisolone at 20 mg/day was prescribed, and the dose was tapered off. This study was approved by the Kansai Medical University ethics committee.

Serological study

We analyzed immunological findings for the following: IgG, IgG4, antinuclear antibodies (ANA), rheumatoid factor (RF), antimitochondrial antibodies (AMA), myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA), anti-Sjögren's syndrome A antibodies (SS-A), anti-Sjögren's syndrome B antibodies (SS-B), anti-thyroid peroxidase antibodies (TPOAb), and anti-thyroglobulin antibodies (TgAb). To compare liver and endocrine function in both groups, we evaluated the serum levels of γ-guanosine triphosphate (GTP) and alanine aminotransferase (ALT) on day 0 (data just before the treatment), and at weeks 2 and 8 after therapy, and checked glycosylated hemoglobin values (HbA1c) at months 1, 3, and 7 after therapy, which closely reflected glucose tolerance at months 0, 2, and 6, respectively. In each evaluation, patients who did not show abnormal values during the clinical course were excluded in order to evaluate the therapeutic effect strictly.

Radiological study

All the patients were examined by contrast-enhanced helical computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic retrograde cholangiopancreatography (ERCP) and underwent liver function tests, combined with bile duct drainage and pathological tests as necessary.

For morphological changes, CT, MRI, and ERCP were studied. The width of the pancreas along its longest axis was measured on CT or MRI images and compared with the transverse diameter of the vertebral body according to the method of Heuck et al. [29]. The pancreas size on the first image was defined as 100%.

Cases showing lower bile duct stricture were classified as follows: 0 = absent, 1 = <0–25%, 2 = <25–50%, 3 = <50–75%, and 4 = <75–100%, according to the method of Craig et al. [30]. Using the method described above, pancreas size was evaluated after 2 weeks on steroids, and stricture of the distal third of the common bile duct was measured after 2 weeks and after 8 weeks.

Statistical analysis

Statistical analysis was performed using the Mann–Whitney *U*-test, Wilcoxon signed-ranks test, paired *t*-test, and

Table 1 Background of AIP patients who received steroid pulse therapy

Patient ID	Age (years)/ sex	Symptoms	IgG <1,700 (mg/dl)	IgG 4 <135 (mg/dl)	Amy <130 (IU/L)	T-Bil <0.9 (mg/dl)	ALT <30 (IU/L)	γ-GTP <35 (IU/L)	ANA	PFD <73.4 (%)	DM	Extrapancreatic lesion	Stenosis on ERCP	Morphological change of the pancreas
1	80/F	Jaundice	2,604	1,230	52	0.9	43	260	−	52.1	−	Sialoadenitis	Head, CBD	FS in head
2	63/M	Epigastralgia	1,714	354	66	0.9	56	222	−	29.7	−	Warthin tumor	Head, CBD	DS
3	54/F	Epigastralgia	1,828	324	561	1.0	100	403	−	NT	−	Hypothyroidism	Body, CBD	DS
4	71/F	None	1,916	295	78	0.6	60	101	−	97.9	−	Sialoadenitis, mediastinum LNS	Head	FS in head
5	66/F	Nausea	1,535	235	77	2.2	118	1,311	−	NT	−	Hypothyroidism, retroperitoneal fibrosis	Head to tail, CBD	FS in head
6	66/M	Epigastralgia, jaundice	2,695	1,790	164	12.5	98	137	−	58.1	+	None	Body, CBD	DS
7	47/F	Jaundice	2,453	629	15	1.0	190	65	−	NT	−	None	Head, body to tail, CBD	DS
8	72/M	Epigastralgia	1,692	452	66	1.3	721	1,352	+	30.9	+	None	Head to tail CBD	FS in head
9	72/M	Epigastralgia, jaundice	1,513	411	32	14.1	114	352	−	NT	+	None	Head, CBD	DS
10	63/M	Malaise	1,514	394	76	0.5	20	82	−	NT	−	None	Head to tail, CBD	FS in head
11	73/F	Epigastralgia	1,598	373	55	0.6	33	588	−	59.7	+	None	Head to tail, CBD	FS in head

AIP autoimmune pancreatitis, *T Bil* total bilirubin, *ALT* alanine aminotransferase, *ID* identification, *γ-GTP* γ-guanosine triphosphate, *Amy* amylase, *ANA* antinuclear antibody, *PFD* pancreatic functional diagnostic test, *DM* diabetes mellitus, *ERCP* endoscopic retrograde cholangiopancreatography, *CBD* common bile duct, *FS* focal swelling, *DS* diffuse swelling, *NT* not tested, *LNS* lymph node swelling

Table 2 Background of AIP patients treated with oral prednisolone

Patient ID	Age (years)/sex	Symptoms	IgG <1,700 (mg/dl)	IgG4 <135 (mg/dl)	Amy <130 (IU/L)	T-Bil <0.9 (mg/dl)	ALT <30 (IU/L)	γ-GTP <35 (IU/L)	ANA	PFD <73.4 (%)	DM	Extrapancreatic lesion	Stenosis on ERCP	Morphological change of the pancreas
12	71/M	Jaundice	3,274	1,870	58	1.0	24	76	−	32.7	−	Mediastinum LNS	Head to tail, CBD	DS
13	66/M	Thirst	4,060	1,170	64	0.4	18	116	−	65.8	−	Sialoadenitis, mediastinum LNS	Tail, CBD	DS
14	58/F	Epigastralgia	2,754	1,110	95	0.9	13	10	−	NT	−	Thyroiditis, mediastinum LNS	Body to tail	FS in head
15	52/F	None	2,190	661	435	0.6	15	15	−	69.7	−	Interstitial pneumonia, Mikulicz tumor	Tail	FS in tail
16	68/M	Fever	1,622	407	34	0.6	30	30	−	73.4	−	Thyroiditis	Head, body, CBD	DS
17	72/M	Vomiting	2,010	773	51	0.3	34	67	+	NT	−	None	Head	FS in head
18	55/M	Epigastralgia	1,461	659	53	0.6	178	240	−	17.9	+	None	Head to tail, CBD	DS
19	63/M	Jaundice	2,073	487	41	1.1	52	149	−	NT	+	None	Head, CBD	FS in head
20	49/M	Jaundice	2,065	479	62	0.9	52	503	−	35.7	−	None	Body, tail, CBD	DS
21	66/M	Malaise	1,607	200	47	1.0	41	189	−	77.9	+	None	Head, CBD	FS in head

Amy amylase, *ANA* antinuclear antibody, *PFD* pancreatic functional diagnostic test, *DM* diabetes mellitus, *ERCP* endoscopic retrograde cholangiopancreatography, *LNS* lymph node swelling, *CBD* common bile duct, *DS* diffuse swelling, *NT* not tested, *FS* focal swelling

Student's t-test. In all tests, corrected P values of < 0.05 were considered statistically significant.

Results

Clinical manifestations

After 6 months' treatment, oral prednisolone had been administered to 19 patients in both groups [pulse group: 9 of 11 vs. oral group: 10 of 10; difference not significant (N.S.)], and the median dosage of prednisolone in each group was 10 mg/day (pulse group: 2.5–12.5 vs. oral group: 5–12.5; N.S.). Two patients in the pulse group dropped out of the maintenance therapy. Neither group showed severe or lethal complications.

In both groups, extrapancreatic lesions other than the bile duct lesions were observed in 10 patients (pulse group: 5 of 11 vs. oral group: 5 of 10; N.S.) (Tables 1, 2). No exacerbation of the extrapancreatic lesions was found following either of the treatments (data not shown). Laboratory findings including immunoglobulin, autoantibody, and exocrine function at the treatment start are listed in Tables 1 and 2.

Immunoglobulin

At the beginning of treatment, in both groups, abnormal serum immunoglobulin-G4 (IgG4) values were observed in all patients (Tables 1, 2), and abnormal serum immunoglobulin-G (IgG) values were observed in 13 patients (pulse group: 6 of 11 vs. oral group: 7 of 10; N.S.) (Tables 1, 2). Normalization of the IgG value was shown in all these patients within 6 months (data not shown).

Liver function

At the beginning of treatment, abnormal γ-GTP values were revealed in both groups, in a total of 18 patients (pulse group: 11 of 11 vs. oral group: 7 of 10; N.S.). In the pulse group, the median γ-GTP levels fell, from 222 IU/L (range 65–1,352) at the beginning of treatment to 92 IU/L (22–679) ($P < 0.01$) after 2 weeks of pulse therapy (Fig. 1a), and to 36 IU/L (19–556) ($P < 0.01$) after 8 weeks of pulse therapy (Fig. 1a). In the oral group, however, the median γ-GTP fell insignificantly after 2 weeks of prednisolone treatment, from 149 IU/L (range 67–380) at the beginning of treatment to 125 IU/L (63–274) ($P = 0.083$) (Fig. 1b), although the level fell significantly to 72 IU/L (29–114) ($P = 0.027$) after 8 weeks of prednisolone treatment (Fig. 1b). When limiting results to the patients who showed diffuse pancreatic swelling, γ-GTP was significantly improved in the pulse group after 2 weeks ($P = 0.043$) and 8 weeks ($P = 0.043$) of pulse therapy (Fig. 1c), whereas the improvement in the γ-GTP level was insignificant in the oral group after 2 weeks ($P = 0.27$) and 8 weeks ($P = 0.27$) of prednisolone treatment (Fig. 1d).

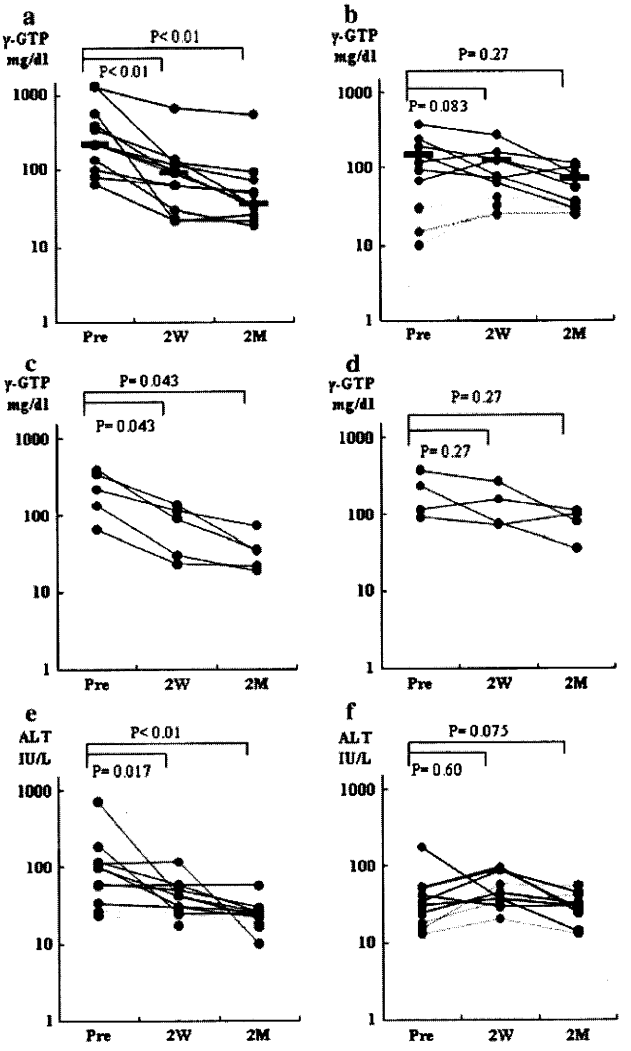

Fig. 1 γ-Guanosine triphosphate (γ-*GTP*) and alanine aminotransferase (*ALT*) changes after steroids. The serum levels of γ-GTP after steroid pulse therapy (**a**), after oral steroid therapy (**b**), those of ALT after steroid pulse therapy (**e**) and those after oral steroid therapy (**f**) were monitored on day 0 (*Pre*), and 2 weeks (*W*) and 8 weeks after therapy. To evaluate the therapeutic effect strictly, the patients (*dotted lines*) who did not show an abnormal value during the clinical course were excluded from this analysis. The serum levels of γ-GTP after 2 weeks on steroids and those of ALT after 2 and 8 weeks on steroids were significantly improved in the pulse group, compared with the oral group. When limiting the patients to those who showed diffuse pancreatic swelling, the serum level of γ-GTP was significantly improved in the pulse group after 2 and 8 weeks of pulse therapy (**c**), compared with the oral group (**d**). *M* Months

At the beginning of treatment, abnormal ALT values were revealed in both groups, in a total of 16 patients

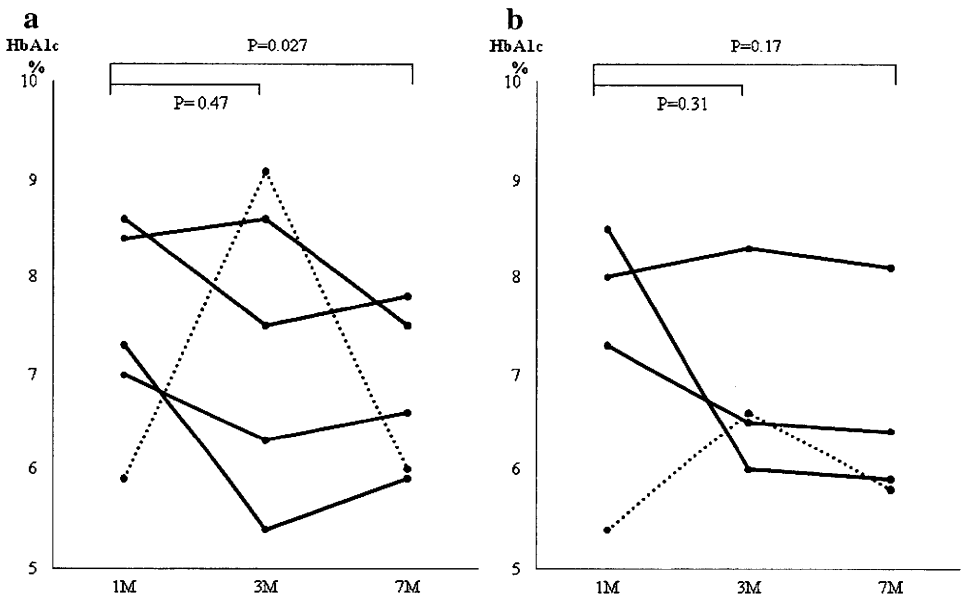

Fig. 2 Glycosylated hemoglobin (*HbA1C*) changes after steroid therapy. The levels of HbA1c after steroid pulse therapy (**a**) and oral steroid therapy (**b**) were monitored at months 1, 3, and 7 after therapy, which closely reflect glucose tolerance at months 0, 2, and 6, respectively. To evaluate the therapeutic effect strictly, patients who did not show abnormal values during the clinical course were excluded from this analysis. *Dotted lines* represent the patients who developed glucose intolerance after 2 months of steroid therapy. The level of HbA1c at month 7 on steroids tended to be improved in the pulse group, compared with the oral group

(pulse group: 10 of 11 vs. oral group: 6 of 10; N.S.). In the pulse group, the median ALT level fell from 100 IU/L (range 33–721) at the beginning of treatment to 41 IU/L (24–117) ($P = 0.017$) after 2 weeks of pulse therapy (Fig. 1e), and to 25 IU/L (10–57) ($P < 0.01$) after 8 weeks of pulse therapy (Fig. 1e). In the oral group, however, the median ALT rose transiently from 46.5 IU/L (range 30–178) at the beginning of treatment to 62 IU/L (29–96) ($P = 0.60$) after 2 weeks of prednisolone (Fig. 1f), but improved to 28 IU/L (14–44) ($P = 0.075$) after 8 weeks of prednisolone treatment (Fig. 1f).

Endocrine function

Before steroid treatment, diabetes mellitus was seen in 7 patients (pulse group: 4 of 11 vs. oral group: 3 of 10; N.S.) (Tables 1, 2). One patient in each group developed glucose intolerance after 2 months of steroid therapy. Including these patients, all the patients with impaired glucose tolerance were treated with dietary measures and received medical therapy while the steroid therapy was maintained. Neither group showed significant improvement in glucose tolerance after 2 months, but at 6 months, the pulse group had improved significantly ($P = 0.027$), whereas the oral group had not ($P = 0.17$) (Fig. 2).

Pancreas size

Both groups evidenced pancreatic swelling: diffuse pancreatic swelling was observed in 10 patients (pulse group: 5 of 11 vs. oral group: 5 of 10; N.S.) and focal swelling was observed in 11 patients (pulse group: 6 of 11 vs. oral group: 5 of 10; N.S.) (Tables 1, 2). The change in pancreas size

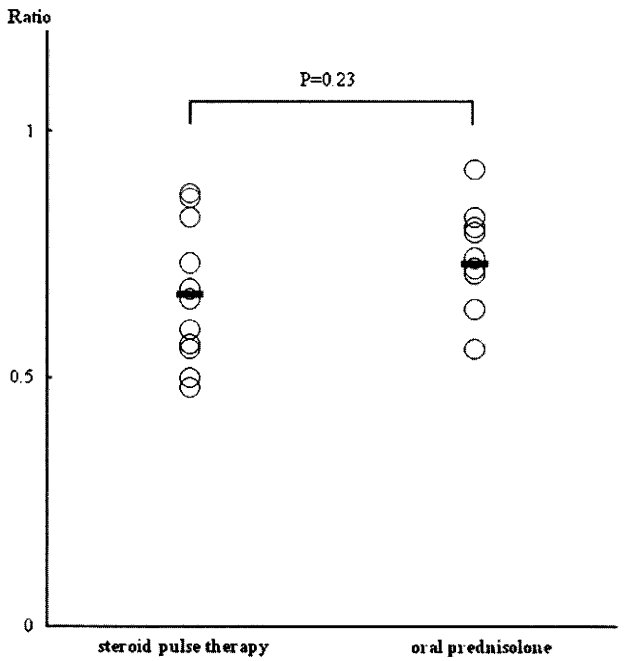

Fig. 3 Pancreas morphology changes after 2 weeks on steroids. Morphological changes of the pancreas after 2 weeks of steroid pulse therapy (*left*) and oral steroid therapy (*right*) were scored. The width of the pancreas along its longest axis was measured on computed tomography (CT) or magnetic resonance imaging (MRI) and compared with the transverse diameter of the vertebral body, referred to in the method of Heuck et al. [29]. The pancreas size on the first image was defined as 100%, and the ratio after 2 weeks with each treatment was measured in the same manner. The *black bars* represent the mean in each group. The two groups showed no significant difference in morphological change of the pancreas after 2 weeks

after 2 weeks showed no significant difference between the groups after treatment (pulse group: 67% vs. oral group: 73.4%, $P = 0.23$) (Fig. 3).

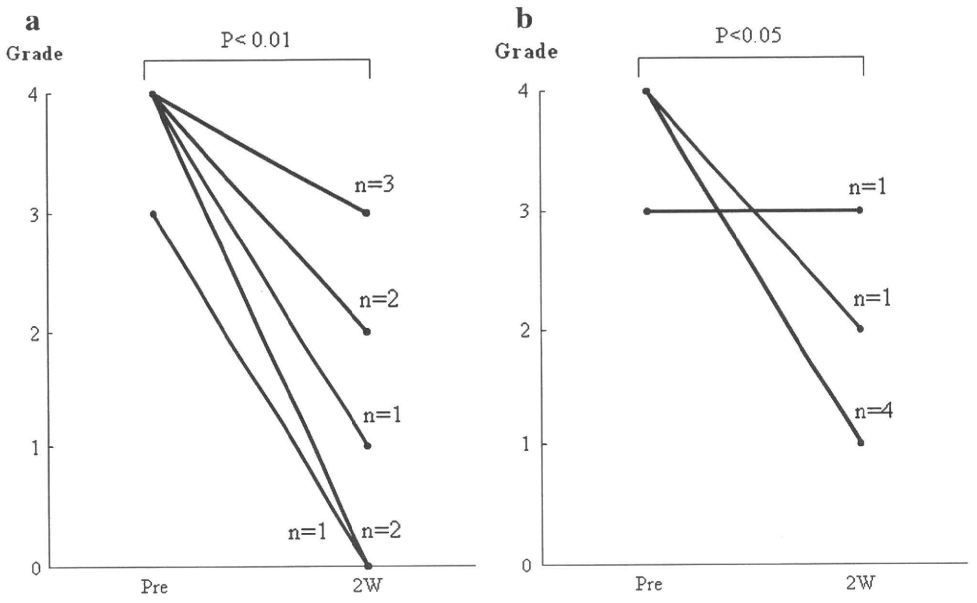

Fig. 4 Lower bile duct stricture changes after steroids. The changes in lower bile duct stricture in the pulse group (**a**) and the oral group (**b**) on day 0 and 2 weeks after therapy were scored as follows: 0 = absent, 1 = <0–25%, 2 = <25–50%, 3 = <50–75%, 4 = <75–100%, referred to in the method of Craig et al. [30]. Bile duct stenosis in the distal third part was significantly improved after 2 weeks in each group

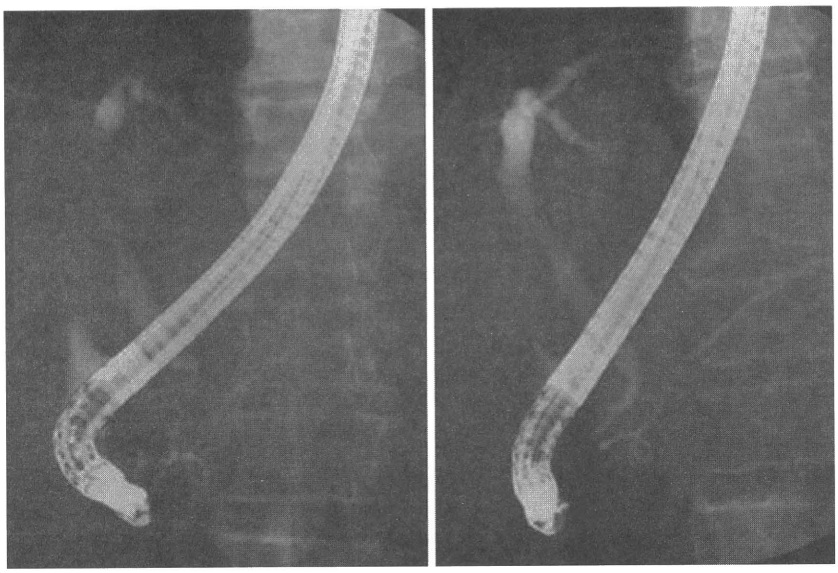

Fig. 5 Endoscopic retrograde cholangiopancreatography (ERCP) images of the impact of steroid pulse therapy on refractory autoimmune pancreatitis (AIP). Although oral prednisolone was commenced, it had had no effect on the biliary stenosis (*left*). Two courses of steroid pulse therapy ameliorated the stenosis dramatically (*right*) (Case 10; reference [31])

Bile duct lesion

After 2 weeks on steroids, significant improvement of lower bile duct stricture was shown in both groups (pulse group: $P < 0.01$, and oral group: $P < 0.05$) (Fig. 4). However, there was one patient (case 10) whose lower bile duct stricture did not improve following oral prednisone treatment, but showed definite improvement with steroid pulse therapy [31] (Fig. 5).

Discussion

Several cases have been reported of pancreatic cancer or bile duct cancer concurrent with AIP [16–19]; because the image findings of AIP often mimic pancreatobiliary malignancies, it is extremely crucial to distinguish AIP from cancers, although this can be difficult [12–15].

In the Asian diagnostic criteria proposed by the Japan-Korea symposium on autoimmune pancreatitis [11], the use of steroids as diagnostic treatment was allowed only when the imaging findings were compatible with AIP and only after there was a negative result for malignancy work-up. Cases of diagnostic treatment using steroids will doubtless increase in future. The usefulness of a 2-week conventional oral steroid diagnostic treatment was also proposed by Moon et al. [20]. However, oral steroid therapy requires a long period for drug tapering, because any patient who has received a glucocorticoid in doses equivalent to at least 20 mg a day of prednisone for >5 days is at risk of

secondary adrenal insufficiency due to hypothalamic–pituitary–adrenal suppression [21–23]. Diagnostic treatment with an oral steroid may cause an undesirable effect when surgical resection is required. Although one article reported that azathioprine was used for refractory AIP [32], it is causative of acute pancreatitis [33]. Therefore, a safe and simple alternative to oral steroid treatment is needed for refractory AIP [34].

Steroid pulse therapy is a well known alternative to oral steroid treatment for autoimmune disorders; it requires no drug tapering [28], and we have already reported cases where steroid pulse therapy was effective for AIP [35], although comparative studies of conventional oral steroid therapy and steroid pulse therapy have not been reported. Here we report that steroid pulse therapy is an effective alternative to oral steroid for the initial treatment of AIP.

The efficacy of oral steroid therapy for AIP is well known, and the improvement of AIP in patients treated with steroids for 2 weeks can be shown in radiographic findings [5, 20, 36]. Our data on pancreas size after 2 weeks did not show a significant difference between oral steroid and pulse therapy. Both therapies were effective for alleviating lower bile duct stricture in the short term and for resolving abnormal IgG values. However, the short-term change in γ-GTP showed significant improvement in the steroid pulse therapy group, but not in the oral steroid group. In one patient, lower bile duct stricture was improved by steroid pulse therapy, although it had not been improved by oral steroids. These findings suggest that steroid pulse therapy may prevent patients from having unnecessary major operations for benign bile duct lesions which do not respond to oral steroid treatment.

Steroid therapy is reported to be effective in approximately half of AIP patients with accompanying diabetes mellitus [37, 38]. The mechanism of steroid action in the recovery of endocrine function in patients with AIP is unclear, but Tanaka et al. [39] have suggested that steroids can suppress the release of cytokines produced by inflammatory cells, and enable islet regeneration and eventual restoration of insulin secretion. However, we have reported that conventional oral steroids did not improve diabetes mellitus in the long term [40]. Although the accumulation of a larger numbers of cases is needed, our study of glycosylated hemoglobin values showed that steroid pulse therapy tended to be more effective than oral steroids for improving glucose tolerance after 6 months of treatment. In our protocol, there was a decisive difference between the two therapies just for the initial 2 weeks, because 20 mg/day of oral prednisolone was prescribed as maintenance therapy after the 2 weeks of steroid pulse therapy. We presume that the steroid pulse therapy was better than the oral steroid therapy for improving glucose tolerance because of its stronger cytokine suppression.

In summary, steroid pulse therapy is an effective alternative initial treatment for AIP, and surpasses conventional oral steroid therapy in the improvement of bile duct lesions. When a differential diagnosis between AIP and pancreatic cancer is difficult clinically or when bile duct lesions do not respond to oral steroid treatment, we recommend steroid pulse therapy as an alternative to oral steroid therapy. In future, the accumulation of a larger number of patients receiving steroid pulse therapy is needed, and prospective studies will be required.

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Recent Concepts of Autoimmune Pancreatitis and IgG4-Related Disease

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Abstract Recent studies suggested the existence of two subtypes of autoimmune pancreatitis (AIP): type 1 related with IgG4 (lymphoplasmacytic sclerosing pancreatitis; LPSP) and type 2 related with a granulocytic epithelial lesion (idiopathic duct-centric chronic pancreatitis; IDCP). Apart from type 2 AIP, the pathological features of type 1 AIP with increased serum IgG4/IgE levels, abundant infiltration of IgG4+ plasmacytes and lymphocytes, fibrosis, and steroid responsiveness are suggestive of abnormal immunity such as allergy or autoimmunity. Moreover, the patients with type 1 AIP often have extrapancreatic lesions such as sclerosing cholangitis, sclerosing sialadenitis, or retroperitoneal fibrosis showing similar pathological features. Based on these findings, many synonyms have been proposed for these conditions, such as "multifocal idiopathic fibrosclerosis", "IgG4-related autoimmune disease", "IgG4-related sclerosing disease", "IgG4-related plasmacytic disease", and "IgG4-related multiorgan lymphoproliferative syndrome", all of which may refer to the same conditions. Therefore, the Japanese Research Committee for "Systemic IgG4-related Sclerosing Disease" proposed a disease concept and clinical diagnostic criteria based on the concept of multifocal fibrosclerosis in 2009, in which the term "IgG4-related disease" was appointed as a minimal consensus on these conditions. Although the significance of IgG4 in the development of "IgG4-related disease" remains unclear, we have proposed a hypothesis for the development of type 1 AIP, one of the IgG4-related disease. The concept and diagnostic criteria of "IgG4-related disease" will be changed in accordance with future studies.

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Keywords IgG4 · IgG4-related disease · Autoimmune pancreatitis · Mikulicz disease · Regulatory T cell (Treg)

Abbreviations

AIP	Autoimmune pancreatitis
ANA	Anti-nuclear antibody
CA-II	Carbonic anhydrase-II
CTLA-4	Cytotoxic T lymphocyte antigen-4
ERCP	Endoscopic retrograde cholangiopancreatography
FCRL	Fc-receptor-like
IFN-γ	Interferon-γ
IL-4	Interleukin-4
LF	Lactoferrin
LPSP	Lymphoplasmacytic sclerosing pancreatitis
MD	Mikulicz disease
MHC	Major histocompatibility complex
MOLPS	Multiorgan lymphoproliferative disease
PBP	Plasminogen-binding protein
SjS	Sjögren's syndrome
PSC	Primary sclerosing cholangitis
RF	Rheumatoid factor
SIPS	IgG4-systemic plasmacytic syndrome
SLE	Systemic lupus erythematosus
Treg	Regulatory T cell
UBR2	Ubiquitin-protein ligase E3 component n-recognin 2

Introduction

In 1961, Sarles et al. first observed a case of particular pancreatitis with hypergammaglobulinemia [1]. Yoshida et al. first proposed the concept of autoimmune pancreatitis (AIP) [2]. Hamano et al. reported the increased serum levels of IgG4 in Japanese patients with AIP [3]. Thereafter, many studies of AIP have been reported, mainly by

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Japanese investigators. The histopathological findings of AIP are characterized by the periductal localization of predominantly CD4-positive T cells, IgG4-positive plasma cells, storiform fibrosis with acinar cell atrophy frequently resulting in stenosis of the main pancreatic duct, and obliterative fibrosis [4–6], which is also called lymphoplasmacytic sclerosing pancreatitis (LPSP) [7]. In 2003, Kamisawa et al. [8] suggested that AIP is a systemic sclerosing disease based on the findings that the pancreas and other involved organs have fibrosis with abundant infiltration of IgG4-positive plasma cells, which is similar to the concept of multifocal fibrosclerosis proposed by Comings et al. [9]. Further, histological and clinical profiling of patients with "AIP" reveals two distinct subtypes, type 1 and type 2 AIP [10]. Type 1 AIP is classified as a pancreatic manifestation of IgG4-related disease, probably a systemic disease with an autoimmune process, whereas type 2 AIP is supposed to be a specific pancreatic disease with occasional coexistence with ulcerative colitis.

On the other hand, patients with Mikulicz's disease (MD), classified as an atypical type of Sjögren's syndrome, who usually have bilateral, painless, and symmetrical swelling of the lachrymal, parotid, and submandibular glands [11], show elevated serum levels of IgG4, infiltration of IgG4-positive plasma cells into the glands, and recovery of secretion with steroid treatment. Similar to AIP, these patients often show other systemic organ involvement such as AIP, sclerosing cholangitis, retroperitoneal fibrosis, enlarged celiac and hilar lymph nodes, chronic thyroiditis, interstitial nephritis, and so on [4–6, 12]. Recently, MD has been considered to be completely different from Sjögren's syndrome because of lacking anti-SS-A/Ro or anti-SS-B/La antibodies and showing steroid responsiveness [2–6]. The steroid responses and the prognoses of AIP patients with sclerosing cholangitis differ from patients with primary sclerosing cholangitis (PSC), which suggests different pathological conditions. These findings led us to the concept of "IgG4-related disease" such as IgG4-related systemic sclerosing disease [8, 13], systemic IgG4-related plasmacytic syndrome (SIPS) [14], or IgG4-positive multiorgan lymphoproliferative syndrome (IgG4-MOLPS) [15]. Although pathogenesis or pathophysiology remains unclear, we will discuss the most recent advances in the concept of AIP and a novel concept of "IgG4-related disease."

Recent Concepts of AIP: Subtypes

Recent studies have revealed that "AIP" manifests two distinct subtypes, type 1 and type 2 AIP [10] (Table 1). In type 1 AIP, whose histologic description is called LPSP, the pancreatic histopathology shows the following characteristic features: (a) abundant infiltration of plasma cells (IgG4+ cells; >10/hpf, 40% > IgG4/IgG cells) and lymphocytes, (b) peculiar storiform or swirling fibrosis, and (c) perivenular infiltration with lymphocytes and plasma cells often leading to obliterative phlebitis. Clinically, type 1 AIP seems to be the pancreatic manifestation of the recently proposed IgG4-related disease, characterized by swelling of the pancreas, elevated serum IgG4 levels, and extrapancreatic

Table 1 Subtypes of autoimmune pancreatitis

Subtype of AIP	Type 1	Type 2
Other nomenclatures	AIP without GEL	AIP with GEL
	IgG4-related	IgG4-unrelated
	LPSP	IDCP
Prevalence	Asia>USA, EU	EU>USA>Asia
Age	High aged	Younger
Gender	Male ≫ female	Male=female (NS)
Symptoms	Obstructive jaundice, rare abdominal pain	Often obstructive jaundice abdominal pain like acute pancreatitis
Pancreas images	Swelling (diffuse/segmental/focal)/mass forming	Swelling (diffuse/segmental/focal)/mass forming
Serology	High serum IgG, IgG4, autoAbs (+)	Normal IgG, normal IgG4, autoAbs (−)
OOI	Sclerosing cholangitis	Unrelated with OOI
	Sclerosing sialadenitis	
	Reteroperitoneal fibrosis	
	Others	
Ulcerative colitis	Rare	Often
Steroid	Responsive	Responsive
Relapse	High rate	Rare

OOI other organ involvement

lesions (e.g., sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis) associated with infiltration of abundant IgG4+ plasma cells (Figs. 1 and 2). Patients with type 1 AIP often have obstructive jaundice in elderly males, and the pancreatic and extrapancreatic manifestations respond to steroid therapy.

On the other hand, type 2 AIP was proposed from histological examination of the resected pancreata of patients with chronic non-alcoholic pancreatitis by American and European pathologists, who reported another histopathological pattern named as idiopathic duct-centric pancreatitis (IDCP) or AIP with granulocytic epithelial lesion (GEL) [16, 17]. The most characteristic feature of type 2 AIP is the GEL often with destruction and obliteration of the pancreatic duct (Fig. 3). Type 2 AIP has swelling of the pancreas, but none or very few IgG4-positive plasma cells, and clinical features show a distinctly different profile associated with no serum IgG4, IgG elevation, presence of autoantibodies, or other organ involvement except for inflammatory bowel disease (approximately 30%). Although it is still in debate as to whether type 2 AIP should be classified as an autoimmune disease or not, the nomenclature of the two subtypes is generally accepted in the meeting of the International Association of Pancreatology held at Fukuoka in 2010.

Extrapancreatic Lesions

A variety of extrapancreatic lesions in patients with AIP have been noted, including lachrymal and salivary gland lesions [18], pulmonary lesions including hilar lymphadenopathy [19], sclerosing cholangitis [20, 21], retroperitoneal fibrosis [22], and tubulointerstitial nephritis [23, 24]. Associations were also reported with hypophysitis [25], chronic thyroiditis [26], and prostatitis [27]. Other extrapancreatic involvements have been reported in a few cases [28–30]. Though it is not certain that all of them have a relation with AIP, extrapancreatic lesions are prevalent in the systemic organs (Table 2) [24–36], suggesting that type 1 AIP, but not type 2 AIP, may be a pancreatic manifestation of IgG4-related disease. The extrapancreatic lesions appear synchronously or metachronously with the pancreatic lesion(s), share the same pathological conditions, and show favorable response to steroid therapy; these characteristics suggest a common pathophysiological background. The lesions are usually detected by imaging and blood tests (CT, MRI, gallium scintigraphy, FDG-PET, and IgG4); however, these should be confirmed by histological findings. Extrapancreatic lesions sometimes mimic, or are misdiagnosed as, primary lesions of the corresponding organs: lachrymal and salivary gland lesions for Sjögren's syndrome, respiratory lesions for sarcoidosis, and sclerosing cholangitis for PSC. Therefore, it is necessary to differentiate between IgG4-related diseases and inherent diseases of the corresponding organs. The patients with IgG4-related sialodacryoadenitis, synonymous with IgG4-related Mikulicz's disease [11, 36], have usually symmetrical enlargement of salivary and lacrimal glands. The IgG4-related central nervous system lesions include infundibulohypophysitis, hypertrophic pachymeningitis, intracranial inflammatory pseudotumor, and orbital pseudotumor [18–36].

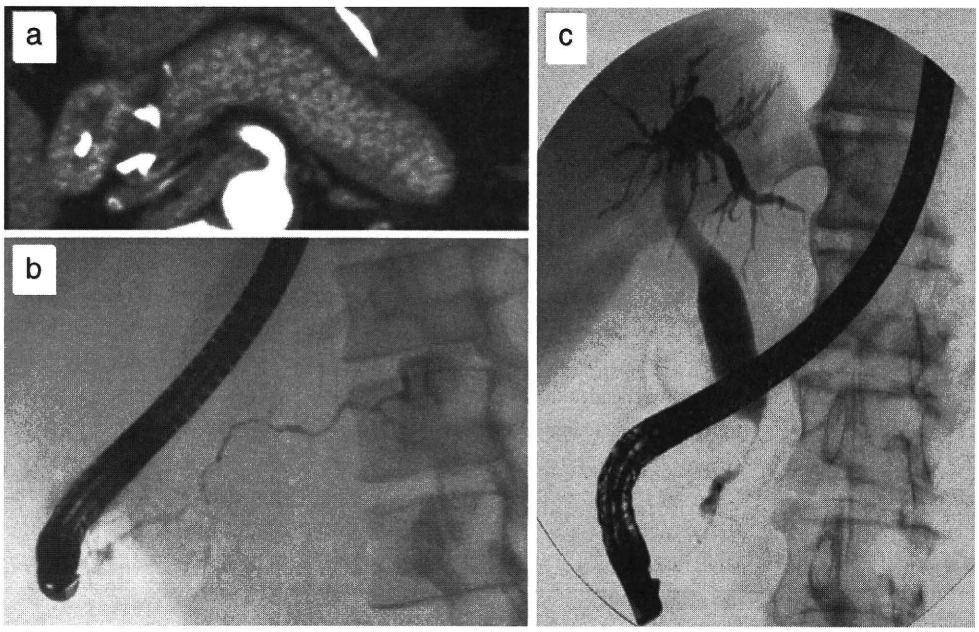

Fig. 1 Pancreas images of type 1 AIP. **a** Swelling of the pancreas with hepatic phase enhancement and low-density capsule like rim. **b** Pancreatogram shows diffusely irregular narrowing of the main pancreatic duct. **c** Cholangiogram shows stenosis of the biliary duct

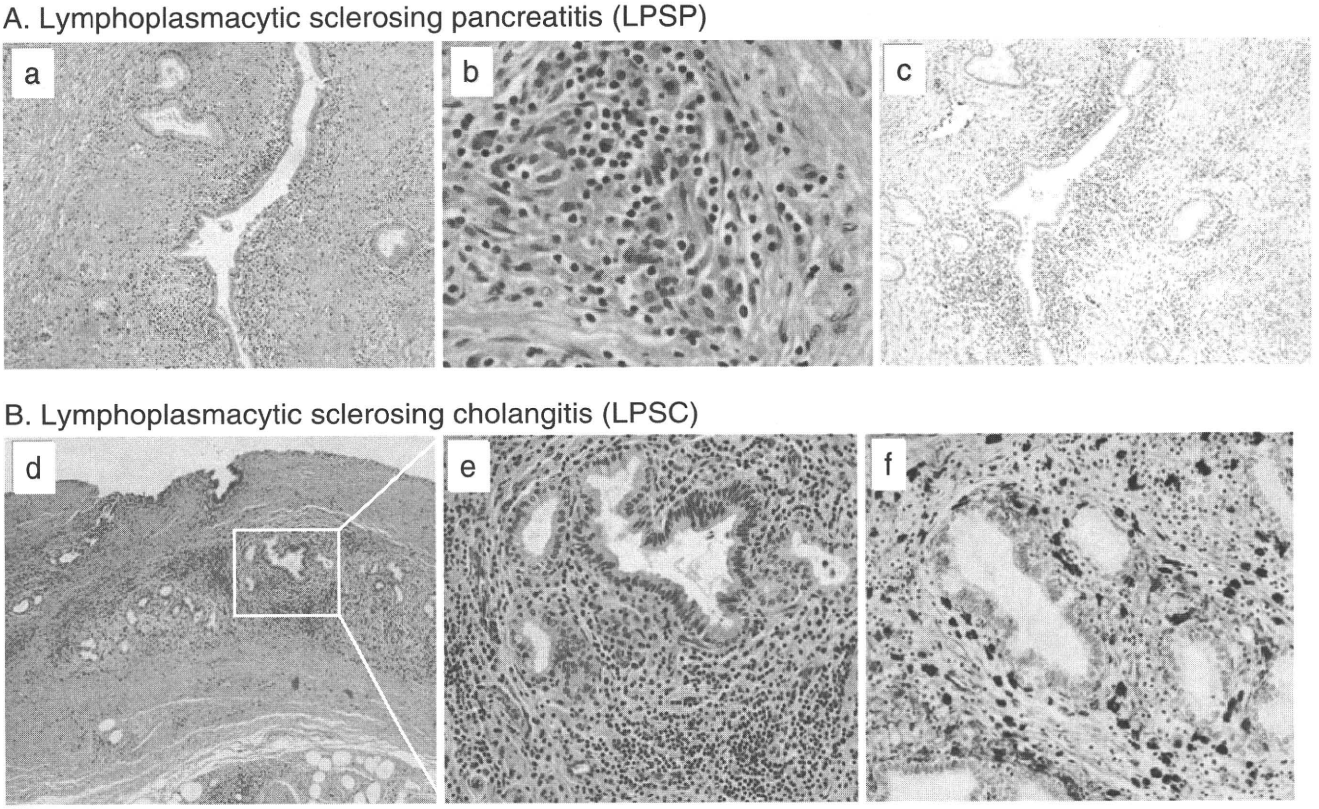

Fig. 2 Histopathology of type 1 AIP. **a** Lymphoplasmacytic sclerosing pancreatitis (*LPSP*). Histopathological findings show abundant infiltration of plasmacytes and lymphocytes mainly around the pancreatic duct and fibrosis (**a**) and obliterative phlebitis (**b**). Immunohistological findings show abundant infiltration of IgG4-positive plasma cells (**c**). **b** Lymphoplasmacytic sclerosing cholangitis (*LPSC*). Histopathological findings show abundant infiltration of infiltration of plasmacytes and lymphocytes and fibrosis (**a**, **b**). Immunohistological findings show abundant infiltration of IgG4-positive plasma cells (**c**)

The Concept of IgG4-Related Disease and Proposal of the Clinical Diagnostic Criteria

The patients with IgG4-related disease show diffuse/focal organ enlargement, mass forming, or nodular/thickened lesions in various organs, synchronously or metachronously, due to the prominent infiltration of lymphocytes and plasmacytes with fibrosis [18–36]; however, the causes of the disease are still not clear. The organs known to be affected include the central nervous system, lacrimal/salivary glands, thyroid gland, lungs, pancreas, biliary duct, liver, gastrointestinal tracts, kidneys, prostate gland, retroperitoneum, lymph nodes, and so on [18–36]. Clinical symptoms vary depending on the organ in which the lesions are located, but many cases are treated effectively by steroid therapy [18–36]. The prognosis is not clear; however, some patients develop serious complications such as obstructive jaundice due to hepatic, gallbladder, or pancreatic lesions, hydronephrosis due to retroperitoneal fibrosis, or respiratory symptoms due to pulmonary lesions [13–16, 21–24]. Although the infiltration of IgG4-positive cells and increased serum levels of IgG4 are characteristic in IgG4-related disease, the severity of fibrosis seems to be different among the individual involved organs. These conditions are quite similar to multifocal idiopathic fibrosclerosis (MIF) [9].

In addition to MIF, there are many synonyms, such as IgG4-related autoimmune disease [8], "IgG4-related sclerosing disease" [13], SIPS [14], and "IgG4+MOLPS" [15], all of which may refer to the same conditions. It has been debated which term is the most appropriate or not. Storiform fibrosis and obliterative phlebitis are characteristic in the pancreatic and biliary tract lesions, but the degree varies depending on the individual organs, e.g. very seldom in lacrimal/salivary gland lesions or lymph node lesions. Then, the nomenclature of "IgG4-related sclerosing disease" is mainly based on the fibrous swollen organs, whereas those of "IgG4-SIPS" and "IgG4+MOLPS" are based on lymphoplasmacytic proliferation and swollen lymph nodes without fibrosis.

Although most patients have multiorgan lesions synchronously or metachronously, about 10–20% of the patients show a solitary organ involved without confirming other organ involvement. Therefore, it is unclear whether the pathogenetic mechanism is same among individual organs or not. Based on these findings, the members of the

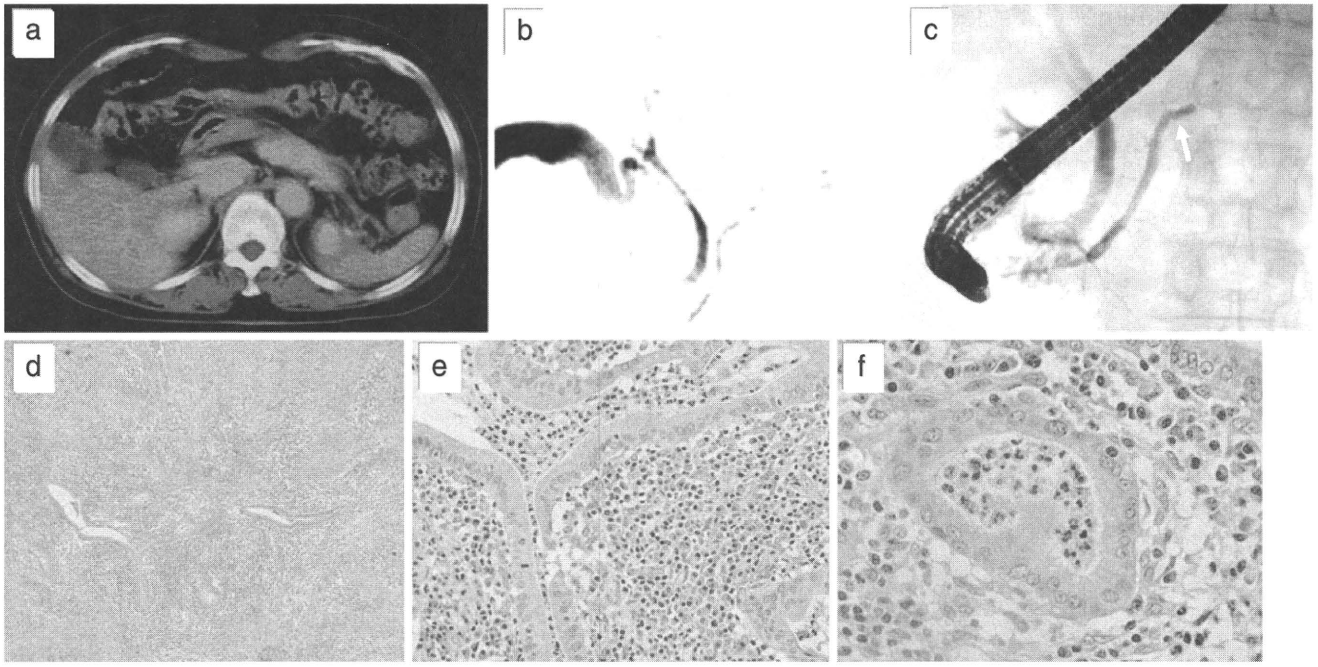

Fig. 3 Pancreas images and histopathology of type 2 AIP CT shows swelling of the pancreas (**a**). MRCP (**b**) and ERCP (**c**) show obstruction of the main pancreatic duct. Histopathological findings show fibrosis, abundant infiltration with granulocytes (**d–f**) cited from ref. [88]

Japanese Research Committees for "systemic IgG4-related sclerosing disease" (chaired by Prof. Okazaki K) [35] and "IgG4-MOLPS" (chaired by Prof. Umehara H) [36], both of which were supported by the "Research for Intractable Disease Program from the Ministry of Health, Labor and Welfare of Japan", have agreed that the term "IgG4-related disease" is appointed as minimally accepting these conditions at this moment. To study these conditions, the Japanese Research Committee for "systemic IgG4-related sclerosing disease" (chaired by Prof. Okazaki K) proposed a disease concept and clinical diagnostic criteria of "systemic IgG4-related sclerosing disease" in 2009 (Table 3) [35]. However, the concept and diagnostic criteria should be changed in accordance with the findings of the future studies.

Pathogenesis and Pathophysiology of AIP and "IgG4-Related Disease"

The pathogenesis and pathophysiology of AIP have been studied mainly from immunological approaches and focused mainly on IgG4-related type 1 AIP because few evidences of abnormal immunity have been reported in type 2 AIP.

Immunogenetic Factors

Immunogenetic factors have been present in a few series of AIP, but not conclusive. Susceptibility to AIP may be

Table 2 Extrapancreatic lesions complicated with autoimmune pancreatitis (from [31])

Close association
Lachrymal gland inflammation
Sialoadenitis
Hilar lymphadenopathy
Interstitial pneumonitis
Sclerosing cholangitis
Retroperitoneal fibrosis
Tubulointerstitial nephritis
Possible association
Hypophysitis
Autoimmune neurosensory hearing loss
Uveitis
Chronic thyroiditis
Pseudotumor (breast, lung, liver)
Gastric ulcer
Swelling of papilla of Vater
IgG4 hepatopathy
Aortitis
Prostatitis
Schonlein–Henoch purpura
Autoimmune thrombocytopenia

Table 3 Clinical diagnostic criteria 2009 for "IgG4-Related Disease" (proposed by the Japanese Research Committee for "Systemic IgG4-related Sclerosing Disease"; [35])

1. Clinically, diffuse/focal enlargement, or mass forming, nodular/thickened lesions in one or more organs
2. Elevated levels of serum IgG4 (>135 mg/dl)
3. Histopathological findings
① Prominent infiltration and fibrosis of lymphocytes and plasmacytes, but no neutrophilic infiltration
② Abundant infiltration of IgG4-positive plasmacytes (>10/hpf) and/or the ratio of IgG4/IgG-positive cells (>40%)
③ Storiform/swirling fibrosis
④ Obliterative phlebitis

Diagnosis of IgG4-related disease: 1+2, 1+3 ①②, 2+3 ①②, or 3 ①②③④

The following cases must be excluded from the diagnosis: malignant tumors developed in organs (e.g., cancers, malignant lymphomas) or similar diseases (e.g., Sjögren's syndrome, primary sclerosing cholangitis), bronchial asthma, and Castleman's disease

associated with immunogenetic factors such as the class II antigen of the major histocompatibility complex (MHC), polymorphism of nuclear factor-κB and Fc-receptor-like (FCRL) 3 genes expressed on B cells [37, 38]. Two studies of HLA association with AIP have been reported from the Japanese [37] and Korean groups [38]. In the Japanese patients with AIP, HLA haplotype DRB1*0405-DQB1*0401 (class II), and ABCF1 proximal to C3-2-11, telomeric of HLA-E (class I), are susceptible to AIP [37], but not so with the Korean patients [38]. However, substitution of aspartic acid to nonaspartic acid at DQβ1 may be a predictive factor for the relapse of AIP in Korean patients [38]. FCRL3 polymorphisms are linked to various autoimmune diseases, such as rheumatoid arthritis, autoimmune thyroid disease, and systemic lupus erythematosus (SLE) in the Japanese population [39, 40]. However, Fc-receptor-like 3 gene polymorphisms are not correlated with the DRB1*0405-DQB1*0401 haplotype, suggesting that while both are related to AIP susceptibility in the Japanese population, they are part of the distinct underlying mechanisms of disease development [39, 40].

A few immunogenetic studies for innate or acquired immunity have been reported. Innate immunity is important in the development of acquired immunity or autoimmune diseases. Although polymorphisms in the toll-like receptor-4 gene have been linked with several autoimmune and allergic diseases, this gene seems not to play an important role in the development of AIP [41]. On the other hand, an inhibitory molecule, cytotoxic T lymphocyte antigen-4 (*CTLA-4*; CD152), expressed on the activated memory T cells and $CD4^{+}CD25^{+}$ regulatory T cells (Tregs), was independently reported as a susceptibility factor for AIP in the Taiwanese [42] and Japanese population [43]. CTLA-4 acts as a negative regulator of T cell responses by competing with the CD28 molecule for engagement with the B7 molecules CD80 and CD86 on antigen-presenting cells [43]. Umemura et al. [43] reported that the 3′ untranslated region of *CTLA-4*+6230 SNP plays a pivotal role in both susceptibility (+6230G/G genotype) to and protection (haplotype of the +6230A allele) from AIP, while exon 1+49 SNP is not associated with AIP in the Japanese patients. They also found that +49A/A or +6230A/A genotypes may be associated with recurrence of the disease, which is observed in Graves' disease, type 1 diabetes, and clearance of hepatitis B virus [44]. On the other hand, Chan et al. [43] have reported that *CTLA-4* SNPs have shown significantly higher frequencies of the +49G allele in patients with AIP than in controls, but not with other subtypes of chronic pancreatitis. Chan et al. also reported that tumor necrosis factor (TNF)-alpha promoter 863A was associated with a significantly higher risk of AIP. Racial and geographical differences may be associated with SNPs of the different locus of CTLA-4 [42]. The soluble isoform of CTLA4 (sCTLA4) is reported to be elevated in patients with autoimmune diseases, such as autoimmune thyroid disease, SLE, and myasthenia gravis [43]. Therefore, the sCLTA4 molecule may have a dual role of maintaining self-tolerance and enhancing immune responses by blocking the interaction of CD80 on antigen-presenting cells and CTLA4 on T cells.

Immunoglobulin Subclasses and IgG4

In healthy subjects, IgG1 usually accounts for most of the total IgG [45]. Generally, the amount of IgG4 does not vary with sex or age, and the quantity of IgG4 as well as the IgG4/total IgG ratio tends to remain constant [45]. The ratios for each IgG subclass are 65% of IgG1, 25% of IgG2, 6% of IgG3, and 4% of IgG4 [45]. In IgG4-related diseases, total IgG, IgG1, IgG2, IgG4, and IgE are usually increased compared with healthy subjects, while IgM, IgA, and the ratios of IgG to IgM or IgA are decreased compared with normal or other control diseases [3, 14, 15, 46] (Table 4). Ratios of IgG subclasses other than IgG4 are somewhat different among individual diseases; in AIP, all subclasses (IgG1–G4) of IgG increased compared with other types of pancreatitis. In contrast, IgG_1 and IgG_3 in MD are