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〔ガイドライン〕

報告　自己免疫性膵炎臨床診断基準 2011

日本膵臓学会・厚生労働省難治性膵疾患に関する調査研究班

新しい自己免疫性膵炎（autoimmune pancreatitis：AIP）の概念として，lymphoplasmacytic sclerosing pancreatitis（LPSP）を1型（type1 AIP），idiopathic duct-centric chronic pancreatitis（IDCP）を2型（type2 AIP）とする国際コンセンサス診断基準（International Consensus Diagnostic Criteria：ICDC）が提唱され，それぞれ臨床的に診断可能になるとともに，初めて国際的な比較検討ができるようになった．しかしながら，ICDCは専門家が使用するには極めて有用と思われるものの，専門家だけでなく一般医も使用することを前提とするわが国の診断基準にはやや煩雑であること，またわが国では極めてまれな2型AIPの実態が不明であることより，日本膵臓学会と厚生労働省難治性膵疾患調査研究班では，ICDCの精神を尊重しつつ，わが国の実状に即して1型AIPを対象とする改定診断基準を作成した．

I. 診断基準改定の経緯

自己免疫性膵炎（autoimmune pancreatitis：AIP）は，1995年にYoshidaら[1]により提唱された後，IgG4関連病変としての位置づけ，さらには疾患亜分類など疾患概念の変遷を経て，現在国際的にも確立されつつある新しい疾患である[2]．臨床的にはステロイドに反応する膵の腫大・腫瘤あるいは合併する胆管病変により，しばしば閉塞性黄疸を認めることより，膵癌や胆管癌などとの鑑別が最も重要である．わが国におけるAIPの診断には，日本膵臓学会より提唱された「自己免疫性膵炎診断基準2002」[3]の改定版である厚生労働省難治性膵疾患調査研究班・日本膵臓学会による「自己免疫性膵炎臨床診断基準2006」[4]やアジア基準[5]が主に使用されている[6]．わが国のAIPのほとんどは，病理組織でリンパ球やIgG4陽性形質細胞浸潤，閉塞性静脈炎，線維化を特徴とするlymphoplasmacytic sclerosing pancreatitis（LPSP）であり，近年IgG4関連疾患の膵病変として注目されている[2,6]．一方，欧米でしばしばAIPとして報告されている好中球上皮病変（granulocytic epithelial lesion：GEL）を特徴とするidiopathic duct-centric chronic pancreatitis（IDCP）はわが国では極めてまれであり[6]，その実態や病態像は不明である．2010年，LPSPを1型（type1 AIP），IDCPを2型（type2 AIP）とした亜分類を包括した新しい概念と国際コンセンサス診断基準（International Consensus Diagnostic Criteria：ICDC）が提唱された[2]．ICDCにより1型と2型AIPがそれぞれ臨床的に診断可能になるとともに，初めて国際的な比較検討ができるようになった．しかしながら，ICDCは専門家が使用するには極めて有用と思われるものの，専門家だけでなく一般医も使用することを前提とするわが国の診断基準には，やや煩雑であること，わが国では極めてまれな2型AIPの実態が不明であることより，日本膵臓学会自己免疫性膵炎診断基準委員会では，ICDCの精神を尊重しつつわが国の実状に即した診断基準の改定作業を行うことが決定された（平成22年7月13日，於福岡国際会議場）．

実際の改定作業のために，日本膵臓学会の診断基準委員会と厚生労働省難治性膵疾患に関する調査研究班（研究代表者：下瀬川徹教授）の診断基準改定ワーキンググループによる合同委員会（表1）が組織された．合同委員会では第1回（平成22年10月15日，於横浜ランドマークタワー），第2回（平成23年5月14日，於京王プラザホテル），第3回（平成23年1月21日，於東京コンファレンス），第4回（平成23年7月29日，於弘前市ホテルニューキャッスル）の議論を経て，自己免疫性膵炎臨床診断基準

表1　自己免疫性膵炎臨床診断基準改定合同委員会
「自己免疫性膵炎臨床診断基準」改定作成委員（所属は2010年当時）

日本膵臓学会自己免疫性膵炎診断基準委員会委員：
委員長：岡崎和一（関西医科大学内科学第三講座（消化器肝臓内科））
副委員長：下瀬川徹（東北大学大学院医学系研究科消化器病態学分野）
委　員（50音順）：
・内科系
伊藤鉄英（九州大学大学院医学研究院病態制御内科学）
乾　和郎（藤田保健衛生大学・坂文種報徳會病院消化器内科）
内田一茂（関西医科大学内科学第三講座（消化器肝臓内科））
大原弘隆（名古屋市立大学大学院地域医療教育学）
神澤輝実（がん・感染症センター東京都立駒込病院内科）
川　茂幸（信州大学健康安全センター）
清水京子（東京女子医科大学消化器内科）
多田　稔（東京大学医学部附属病院消化器内科）
西野博一（慈恵医科大学消化器肝臓内科）
西森　功（西森医院，高知大学消化器内科）
廣岡芳樹（名古屋大学医学附属病院光学医療診療部・消化器内科）
水野伸匡（愛知癌センター中央病院消化器内科部）
山口武人（千葉県立癌センター内科）
・外科系
杉山政則（杏林大学外科）
山口幸二（産業医科大学第一外科）
・病理系
能登原憲司（倉敷中央病院病理検査科）
諸星利男（昭和大学病理学）

厚生労働省難治性膵疾患に関する調査研究班（研究代表者：下瀬川徹）
自己免疫性膵炎診断基準改定案作成ワーキンググループ（WG）
（*日本膵臓学会自己免疫性膵炎診断基準委員会委員併任）
委員長：*岡崎和一（関西医科大学内科学第三講座（消化器肝臓内科））
委　員（50音順）：
*伊藤鉄英（九州大学病態制御内科・肝膵胆道内科）
*乾　和郎（藤田保健衛生大学・坂文種報徳會病院消化器内科）
入澤篤志（福島県立医科大学内科学第二講座）
*大原弘隆（名古屋市立大学大学院地域医療教育学）
*川　茂幸（信州大学総合健康安全センター）
*神澤輝実（がん・感染症センター東京都立駒込病院内科）
洪　繁（名古屋大学消化器内科，現 国立長寿医療研究センター・消化機能診療科）
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須田耕一（東京西徳洲会病院病理科）
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浜野英明（信州大学医学部附属病院医療情報部，消化器内科）

（改定案）を作成した．第42回日本膵臓学会会期中の公聴会（平成23年7月30日）と日本膵臓学会ホームページでのパブリックコメント（平成23年8月7日～9月8日）を経て，第5回委員会（平成23年10月21日，於マリンメッセ福岡）において改定診断基準の最終案（表2）が作成された．

表 2　自己免疫性膵炎臨床診断基準 2011
（日本膵臓学会・厚生労働省難治性膵疾患に関する調査研究班）

【疾患概念】

わが国で多く報告されている自己免疫性膵炎は，その発症に自己免疫機序の関与が疑われる膵炎であるが，IgG4 関連疾患の膵病変である可能性が高い．中高年の男性に多く，膵の腫大や腫瘤とともに，しばしば閉塞性黄疸を認めるため，膵癌や胆管癌などとの鑑別が必要である．高γグロブリン血症，高 IgG 血症，高 IgG4 血症，あるいは自己抗体陽性を高頻度に認め，しばしば硬化性胆管炎，硬化性唾液腺炎，後腹膜線維症などの膵外病変を合併する．病理組織学的には，著明なリンパ球や IgG4 陽性形質細胞の浸潤，花筵状線維化（storiform fibrosis），閉塞性静脈炎を特徴とする lymphoplasmacytic sclerosing pancreatitis（LPSP）を呈する．ステロイドが奏功するが，長期予後は不明であり，再燃しやすく膵石合併の報告もある．

一方，欧米では IgG4 関連の膵炎以外にも，臨床症状や膵画像所見は類似するものの，血液免疫学的異常所見に乏しく，病理組織学的に好中球上皮病変（granulocytic epithelial lesion；GEL）を特徴とする idiopathic duct-centric chronic pancreatitis（IDCP）が自己免疫性膵炎として報告されている．男女差はなく，比較的若年者にもみられ，時に炎症性腸疾患を伴う．ステロイドが奏功し，再燃はまれである．国際的には IgG4 関連の膵炎（LPSP）を 1 型，GEL を特徴とする膵炎（IDCP）を 2 型自己免疫性膵炎として分類し，国際コンセンサス基準（International Consensus of Diagnostic Criteria（ICDC）for autoimmune pancreatitis）が提唱されている．しかしながら，わが国では 2 型は極めてまれであるため，本診断基準ではわが国に多い 1 型を対象とし，2 型は参照として記載するに留めた．

【診断基準】

A. 診断項目

Ⅰ．膵腫大：
- a. びまん性腫大（diffuse）
- b. 限局性腫大（segmental/focal）

Ⅱ．主膵管の不整狭細像：ERP

Ⅲ．血清学的所見
- 高 IgG4 血症（≧135mg/dl）

Ⅳ．病理所見：以下の①～④の所見のうち，
- a. 3 つ以上を認める．
- b. 2 つを認める．
- ①高度のリンパ球，形質細胞の浸潤と，線維化
- ②強拡 1 視野当たり 10 個を超える IgG4 陽性形質細胞浸潤
- ③花筵状線維化（storiform fibrosis）
- ④閉塞性静脈炎（obliterative phlebitis）

Ⅴ．膵外病変：硬化性胆管炎，硬化性涙腺炎・唾液腺炎，後腹膜線維症
- a. 臨床的病変
  臨床所見および画像所見において，膵外胆管の硬化性胆管炎，硬化性涙腺炎・唾液腺炎（Mikulicz 病）あるいは後腹膜線維症と診断できる．
- b. 病理学的病変
  硬化性胆管炎，硬化性涙腺炎・唾液腺炎，後腹膜線維症の特徴的な病理所見を認める．

＜オプション＞ステロイド治療の効果

専門施設においては，膵癌や胆管癌を除外後に，ステロイドによる治療効果を診断項目に含むこともできる．悪性疾患の鑑別が難しい場合は超音波内視鏡下穿刺吸引（EUS-FNA）細胞診まで行っておくことが望ましいが，病理学的な悪性腫瘍の除外診断なく，ステロイド投与による安易な治療的診断は避けるべきである．

B. 診　　断

Ⅰ．確診
- ①びまん型
  Ia＋＜Ⅲ/Ⅳb/Ⅴ(a/b)＞
- ②限局型
  Ib＋Ⅱ＋＜Ⅲ/Ⅳb/Ⅴ(a/b)＞の 2 つ以上
  または
  Ib＋Ⅱ＋＜Ⅲ/Ⅳb/Ⅴ(a/b)＞＋オプション
- ③病理組織学的確診
  Ⅳa

Ⅱ．準確診
- 限局型：Ib＋Ⅱ＋＜Ⅲ/Ⅳb/Ⅴ(a/b)＞

Ⅲ．疑診*
- びまん型：Ia＋Ⅱ＋オプション
- 限局型：Ib＋Ⅱ＋オプション

自己免疫性膵炎を示唆する限局性膵腫大を呈する例で ERP 像が得られなかった場合，EUS-FNA で膵癌が除外され，Ⅲ/Ⅳb/Ⅴ（a/b）の 1 つ以上を満たせば，疑診とする．さらに，オプション所見が追加されれば準確診とする．

疑診*：わが国では極めてまれな 2 型の可能性もある．

＋；かつ，／；または

（続く）

【解　説】

I.　膵腫大

“ソーセージ様”を呈する膵のびまん性（diffuse）腫大は本症に特異性の高い所見である．しかし限局性（segmental/focal）腫大では膵癌との鑑別が問題となる．膵腫大の定義に関しては Haaga 基準「膵頭部で1椎体以上，膵体尾部で2/3椎体以上を膵腫大」（およそ頭部 3cm，体尾部 2cm）を使う施設が多い．年齢による影響もあり，厳密な定義は難しく，ステロイドにより膵の大きさが縮小する場合には膵腫大と捉えることもできる．びまん性，限局性の定義に厳密なものはないが，慢性膵炎における ERP 像の Cambridge 分類（2/3＜diffuse，1/3＜segmental＜2/3，focal＜1/3）に準ずる場合が多い．

1)　腹部超音波検査：腫大部の低エコー像に高エコースポットが散在することが多い．

2)　腹部 CT：ダイナミック CT では遅延性増強パターンと被膜様構造（capsule-like rim）が特徴的である．

3)　腹部 MRI：T1 強調像での低信号，ダイナミック MRI での遅延性増強パターンと被膜様構造（capsule-like rim）が特徴的である．

4)　FDG-PET：活動性病変にしばしば異常集積を認めるが，ステロイド治療により集積像の陰性化を認める．

II.　主膵管の不整狭細像：主膵管にびまん性，限局性に不整狭細像を認める．

1)　狭細像とは閉塞像や狭窄像と異なり，ある程度広い範囲におよび，膵管径が通常より細くかつ不整を伴っている像を意味する．典型例では狭細像が全膵管長の3分の1以上（5cm）を占めるが，限局性の病変でも，狭細部より上流側の主膵管には著しい拡張を認めないことが多い．短い膵管狭細像（およそ 3cm 未満）の場合には膵癌との鑑別が困難である．主膵管の狭細部からの分枝の派生（side branch arising from narrowed portion of the main pancreatic duct）や非連続性の複数の主膵管狭細像（skip lesions）は，膵癌との鑑別に有用である．

2)　膵管像は基本的に ERP など直接膵管造影が必要である．MRCP は現段階では主膵管の狭細像の正確な評価はできないが，主膵管が非連続に描出される場合には，診断の参考になる．

3)　上記の膵画像所見は診断時から過去にさかのぼって認めることもある．

III.　血清学的所見

1)　血清γグロブリン，IgG または IgG4 の上昇，自己抗体を認めることが多い．高 IgG 血症（1800mg/dl 以上），高 IgG4 血症（135mg/dl 以上）が一つの基準である．本診断基準に用いられるのは IgG4 のみであるが，IgG4 高値は他臓器の IgG4 関連疾患を含む他疾患（アトピー性皮膚炎，天疱瘡，喘息など）にも認められるため，本疾患に必ずしも特異的ではない．IgG4 は膵癌との鑑別において，感度，特異度ともに最も優れた血清マーカーであるが，膵癌や胆管癌の一部でも高値を示す例や，AIP に合併する膵癌例もあり，注意が必要である．今のところ，病因や病態生理における IgG4 高値の意義は不明である．

2)　自己抗体では時に抗核抗体，リウマチ因子などが陽性になることがあり，本疾患の存在を疑うことができる．

IV.　病理所見

本疾患は LPSP と呼ばれる特徴的な病理像を示し，以下はその代表的な所見である．

1)　高度のリンパ球，形質細胞の浸潤と，線維化を認める．好酸球浸潤をしばしば伴うが，好中球浸潤は欠くことが多い．リンパ濾胞形成のみられることもある．炎症所見は小葉内，小葉間，膵周囲脂肪組織，膵管上皮周囲で著しいが，膵管上皮内への炎症細胞浸潤は殆ど認めない．

2)　著しい IgG4 陽性形質細胞浸潤が特徴的であり，切除膵による検討では殆どの症例で，強拡（400倍）1視野当たり 50個以上の陽性形質細胞を認める．しかしながら，サンプルの小さい膵針生検組織でも診断を可能にするため，国際的に強拡1視野当たり 10個以上の基準が用いられている．本診断基準もそれに従ったが，AIP 以外の炎症性病変や腫瘍でもこの基準を満たすことはあり，病理診断項目①②の所見のみで AIP の確定診断とはできない．

3)　花筵状線維化（storiform　fibrosis）は，炎症細胞（リンパ球，形質細胞）浸潤と紡錘形細胞の増生からなる病変で，花筵状と表現される特徴的な錯綜配列を示し，さまざまな程度の線維化を伴う．膵辺縁および周囲脂肪組織に出現しやすい．

4)　閉塞性静脈炎（obliterative phlebitis）とは，小葉間，膵周囲脂肪組織におけるリンパ球，形質細胞の浸潤と線維化よりなる病変が静脈内に進展し，これを狭窄あるいは閉塞する所見である．

診断に用いられる材料は，切除膵，膵生検のいずれでも構わない．EUS-FNA 細胞診は，悪性腫瘍との鑑別に極めて有用な検査であるが，AIP の診断には有用でない．また EUS-FNA 生検も，検体量が十分でなく，AIP の確定診断に至らないことが多い．EUS-core　biopsy は，AIP の診断に有用と報告されている．膵癌では内部や周辺部に多数の IgG4 陽性形質細胞を認めたり，まれには LPSP 類似の組織所見を認めることがあるため，生検材料で自己免疫性膵炎を診断する際には注意を要する．

【参照】2型自己免疫性膵炎（IDCP）について

小葉間膵管の内腔あるいは上皮内への好中球浸潤を特徴とする原因不明の膵炎で，LPSP と同様，臨床的に膵癌との鑑別が問題になる．膵管上皮の周囲にリンパ球・形質細胞浸潤と線維化を伴う点は LPSP に類似するため，かつては LPSP と同じ範疇の疾患と認識されていた．現状では画像や臨床所見では診断できず，診断のためには病理組織学的検索が必須である．しかも，切除膵や剖検膵など大きな標本では確診できるが，生検膵組織での確診は困難なことが多い．典型的な AIP の膵画像所見を認めるものの，血液学的な異常所見を欠く場合には，1型，2型いずれの自己免疫性膵炎の可能性も考えられる．2型自己免疫性膵炎では臨床症状や画像所見が膵癌と類似しているものがあり，膵癌との鑑別が極めて困難である．

（続く）

V. 膵外病変（Other organ involvement：OOI）

1) 自己免疫性膵炎に認められる膵外病変とは1型に合併するIgG4関連病変を意味する.

2) 膵以外の罹患臓器には，中枢神経系，涙腺・唾液腺，甲状腺，肺，胆管，肝臓，消化管，胆嚢，腎臓，前立腺，後腹膜腔，リンパ節などの報告がある．しかしながら，リンパ節や唾液腺では線維化に乏しく，これらすべての臓器病変の概念が確立されているわけではない．明確な根拠は存在しないが，以下の条件が満たされれば自己免疫性膵炎との密接な関連が推測できる.

①多数例の調査・報告で自己免疫性膵炎に合併することが多い.

②病理組織所見でリンパ球浸潤と線維化，閉塞性静脈炎，IgG4陽性形質細胞の病変局所への浸潤を認める.

③ステロイド治療により改善する．または膵病変と当該病変の治療による出現と消褪が同期している.

④各臓器の対応疾患との鑑別点が明確である.

上記の条件を比較的満たしているものとして，硬化性胆管炎，硬化性涙腺炎・唾液腺炎（Mikulicz病），後腹膜線維症，呼吸器病変，尿細管間質性腎炎などがある．現状では，コンセンサスの得られている硬化性胆管炎，硬化性涙腺・唾液腺炎，後腹膜線維症にとどめる.

3) 硬化性胆管炎

①自己免疫性膵炎に合併する硬化性胆管炎は胆管系に広範に病変を認め，下部胆管の狭窄は膵癌または下部胆管癌との，肝内・肝門部胆管狭窄は原発性硬化性胆管炎（primary sclerosing cholangitis：PSC）や胆管癌との鑑別を要する．胆管像のみならず，超音波内視鏡（EUS），管腔内超音波（IDUS），細胞診，組織診などにより総合的に慎重に鑑別する必要がある.

②PSCと本症にみられる硬化性胆管炎はステロイドに対する反応・予後が異なり，別の病態である．PSCでは帯状狭窄（band-like stricture，1～2mmの短い帯状狭窄），数珠状所見（beaded appearance短い狭窄と拡張を交互に繰り返す所見），剪定状所見（pruned tree appearance；剪定したように肝内胆管の分枝が減少している所見），憩室様所見（diverticulum-like outpouching）が特徴的である.

③IgG4関連硬化性胆管炎に下部胆管狭窄のみの症例を含めるか，膵病変の一部として捉えるかは専門家の間でも議論が分かれるところである．自己免疫性膵炎を診断するために有用な胆管病変は肝内や肝門部胆管の狭窄，上中部胆管の硬化像や壁肥厚である.

④病理学的には，胆管壁は多くの場合肥厚し，全層性に高度のリンパ球，形質細胞の浸潤と線維化がみられる．病巣内には多数のIgG4陽性形質細胞が認められる．胆管上皮は正常に保たれていることが多い．花筵状線維化や閉塞性静脈炎も認められる.

4) 頻度は少ないものの腫大した十二指腸乳頭部生検のIgG4染色は補助診断として有用である．しかし，あくまでも膵頭部病変の波及によるものであり，膵外病変の範疇には入らない.

5) 硬化性涙腺炎・唾液腺炎

①自己免疫性膵炎に合併する涙腺炎・唾液腺炎では涙腺分泌機能低下に起因する乾燥性角結膜炎症状や口腔乾燥症状は認めないか，認めても軽度のことが多い．耳下腺腫大の多いシェーグレン症候群と異なり，自己免疫性膵炎にみられる唾液腺炎は顎下腺が多く，ステロイド治療に良好に反応する．涙腺・唾液腺の腫脹の多くは左右対称性であり，唾液腺腫脹は耳下腺，顎下腺，舌下腺，小唾液腺の一部であることが多い．涙腺炎・唾液腺炎のほとんどは抗SS-A抗体，抗SS-B抗体陰性であり，シェーグレン症候群と異なる．臓器診断基準（IgG4関連Mikulicz病の診断基準，日本シェーグレン症候群研究会，2008年）により診断できるが，IgG4陽性形質細胞の著明な浸潤が認められれば，口唇腺生検により診断できることもある.

②病理学的には，小葉内において腺房細胞の消失，高度のリンパ球，形質細胞浸潤，リンパ濾胞形成をきたし，小葉間には線維化がみられる．小葉の構築が破壊され，高度のリンパ球・形質細胞の浸潤と線維化よりなる病変がびまん性に形成されることもある．形質細胞の多くはIgG4陽性である．花筵状線維化や閉塞性静脈炎を認めることがあるが，自己免疫性膵炎に比較するとその頻度は低い.

6) 後腹膜線維症

①後腹膜を中心とする線維性結合織のび慢性増殖と炎症により，腹部CT/MRI画像で腹部大動脈周囲の軟部影や腫瘤がみられる．尿管閉塞を来し水腎症が診断契機のこともある．また，腹部大動脈の拡張病変を伴い，炎症性腹部大動脈瘤と呼ばれる病態を示すことがあるが，他の原因による大動脈瘤との鑑別は困難である.

②病理学的には，高度のリンパ球，形質細胞の浸潤と線維化よりなる腫瘤状病変が形成される．病巣内には多数のIgG4陽性形質細胞が認められる．花筵状線維化や閉塞性静脈炎も高頻度に認められる.

VI. オプション：ステロイド治療の効果

画像で評価可能な病変が対象であり，臨床症状や血液所見は効果評価の対象としない．2週間以内に効果不十分の場合には再精査が必要である．できる限り病理組織を採取する努力をすべきであり，ステロイドによる安易な診断的治療は厳に慎むべきである．悪性リンパ腫ではステロイド投与により改善する可能性がある.

VII. 膵内外分泌機能

典型的な自己免疫性膵炎では，膵外分泌機能障害および糖尿病を認めることが多い．ステロイド投与により膵内外分泌機能障害の改善を認めることも少なくない.

II. 改定診断基準の基本コンセプト

わが国で汎用されてきた診断基準2002，2006やアジア基準は，一般消化器内科医を含む一般医家も使用できること，膵胆道系悪性腫瘍との鑑別を重視することを前提に作成されてきており，従来の前提とICDCのコンセプトを尊重しつつ，わが国の実状にあった改定をすることとなった．とくにわが国では2型症例の経験が極めて少なく，その臨床像や実態が不明であることより，1型AIPを対象とした診断基準とした．

1. 診断項目の検討

診断項目では，①ICDCの膵実質画像による病変の範囲分類（びまん性，限局性），②ICDCの診断項目のLevel 1，2分類の単純化，③血液所見はIgG4のみ，④病理所見はLPSPのみ，⑤膵外病変（OOI），⑥ステロイド効果をオプションとして採用した．

①膵画像

a）膵実質像と膵管像の分離

最近，典型的な膵癌の確定診はERCPよりも，EUS-FNAでなされる施設が増加しており，膵画像所見はCT/MRIによる実質像とERPによる膵管像を分離して別項目とした．

b）MRCPは治療の評価や経過観察に有用なことがあるが，満足な解像度の得られない現状では，診断項目から除外した．

②血液所見

1型AIPを対象としたことより，高γグロブリン血症，高IgG4血症，抗核抗体などの非特異的項目は除外し，高IgG4血症のみを診断項目とした．また作成委員の施設からAIP 717例，膵癌577例，計1294例よりカットオフ値の再評価を行い，現行のカットオフ値（135mg/dl）の妥当性が確認された（図1A，B）．

③病理組織所見

1型AIPが対象であるため，病理組織の診断項目としてLPSPの病理所見であるa)高度のリンパ球，形質細胞の浸潤と，線維化，b）強拡1視野当たり10個を超えるIgG4陽性形質細胞浸潤，c）花筵状線維化（storiform fibrosis），d）閉塞性静脈炎（obliterative phlebitis）を採用した．IgG4陽性形質細胞浸潤について，IgG4関連疾患の抱括診断基準[7]ではより詳細に規定されており，IgG4陽性形質細胞浸潤数＞10個/強拡大視野，かつIgG4/IgG陽性細胞比40％以上が必要とされている．しかし，膵針生検組織ではサンプルが小さく，IgG4/IgG陽性細胞比40％以上の所見を得るのは困難なことが多いことより，前者のみが採用された．

④膵外病変（other organ involvement：OOI）

現行の診断基準2006やアジア基準では（OOI）は含まれていないが，病理所見以外でも理学所見や画像などにより臨床的診断の可能な硬化性唾液腺炎，硬化性胆管炎，後腹膜線維症をOOIとして採用した．

a）硬化性胆管炎

肝内胆管や上部～中部肝外胆管狭窄については，狭窄や壁肥厚所見はIgG4関連硬化性胆管炎としてほぼコンセンサスが得られているが，下部胆管では膵腫大による狭窄と胆管自体の病変による場合が混在しており，その定義に関しては意見の一致をみていない．したがって，ここでいう硬化性胆管炎は自己免疫性膵炎の診断に有用な肝内・上部～中部肝外胆管病変を意味する用語とした．

b）十二指腸乳頭部病変は，生検材料のIgG4陽性細胞浸潤は診断の参考になるものの，膵炎症の波及によるものが多いため，OOIの定義から除外した．

c）各臓器病変はそれぞれの診断基準が作成されると将来的にOOIとして追加する可能性が高い．

⑤ステロイドオプション

アジア診断基準と同様に診断項目とは別に専門施設でのみ可能なオプションとして採用した．

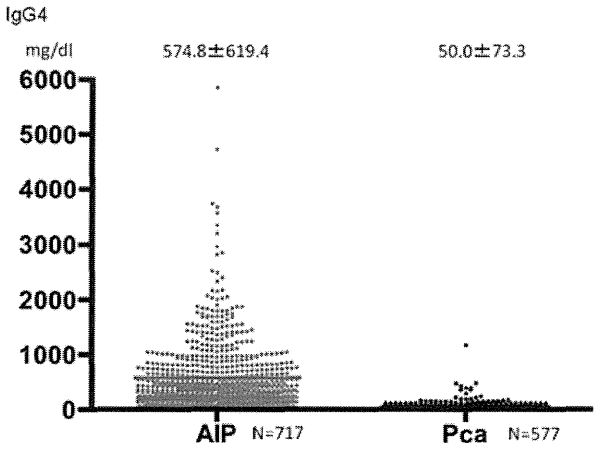

図 1A　自己免疫性膵炎と膵癌における血中 IgG4 値

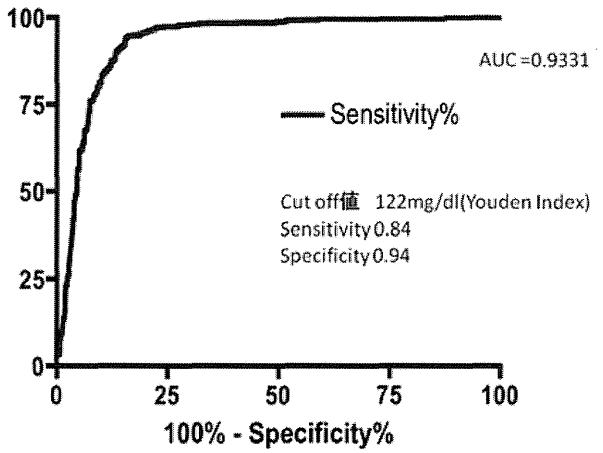

図 1B　自己免疫性膵炎と膵癌における血中 IgG4 値の ROC 曲線

2. 診　　断

診断については ICDC との齟齬がないように，現行診断基準と異なり，上記診断項目の組み合わせによる確診，準確診，疑診が採用された．血中 IgG4 値正常例で，典型的な膵画像とステロイド効果を認めるも，病理組織の得られない場合は疑診と診断されるが，わが国では極めて稀とされる 2 型の可能性のあることに留意する必要がある．また，自己免疫性膵炎を示唆する限局性膵腫大を呈する例で ERP 像が得られない場合には，EUS-FNA で膵癌が除外され，＜III/IVb/V(a/b)＞の 1 つ以上を満たせば疑診とし，さらにステロイド効果が見られれば準確診として，ICDC との整合性をできるだけ保った．

本診断基準の作成は日本膵臓学会と，厚生労働省難治性疾患克服研究事業によってなされた．

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Clinical Diagnostic Criteria for Autoimmune Pancreatitis 2011 (Proposal) (The Japan Pancreas Society, the Ministry of Health and Welfare Investigation Research Team for Intractable Pancreatic Disease)

Autoimmune pancreatitis (AIP) is worldwide accepted as distinct pancreatitis with steroid response. The Japan Pancreas Society (JPS) first proposed the diagnostic criteria of AIP in 2002 (Suizo 2002；17：587) and the revised one in 2006 (J Gastroenterology 2006；40：626–31). The most important issue in diagnosing AIP is how to distinguish it from pancreatic or biliary cancer. The Japanese clinical criteria have been proposed for the practical use and the minimum consensus features of AIP in order to avoid the misdiagnosis of malignancy as far as possible. Internationally, two subtypes of AIP have been proposed in the International Consensus of Diagnostic Criteria (ICDC) for AIP in 2011 (Pancreas 2011；40：352–358)：type 1 related with IgG4 (lymphoplasmacytic sclerosing pancreatitis：LPSP), and type 2 with granulocytic epithelial lesions (idiopathic duct–centric pancreatitis：IDCP). As the ICDC are still complicated for the practical use, The Research Committee of Intractable Diseases of the Pancreas supported by the Japanese Ministry of Health, Labor and Welfare and the JPS have proposed the revised diagnostic criteria in 2011. Since type 2 is extremely rare in Japan, the diagnostic criteria described here are intended to cover type 1, commonly seen in Japan, with type 2 noted only as reference.

【Diagnostic criteria】

A. Diagnostic items

I. Enlargement of the pancreas：
   a. Diffuse enlargement
   b. Segmental/focal enlargement

II. ERP (Endoscopic Retrograde Pancreatography) shows irregular narrowing of the main pancreatic duct

III. Serological findings
   Elevated levels of serum IgG4 (≥135mg/dl)

IV. Pathological findings：among ①～④ listed below,
   a. three or more are observed
   b. two are observed
   ①Prominent infiltration of lymphocytes and plasmacytes and fibrosis
   ②More than 10 IgG4–positive plasmacytes per high–power microscope field
   ③Storiform fibrosis
   ④Obliterative phlebitis

V. Extra–pancreatic lesions：sclerosing cholangitis, sclerosing dacryoadenitis/sialoadenitis, retroperitoneal fibrosis
   a. Clinical lesions
      Extra–pancreatic sclerosing cholangitis, sclerosing dacryoadenitis/sialoadenitis (Mikulicz disease), or retroperitoneal fibrosis can be diagnosed with clinical and image findings.
   b. Pathological lesions
      Pathological examination shows characteristic features of sclerosing cholangitis, sclerosing dacryoadenitis/sialoadenitis, or retroperitoneal fibrosis.

＜Option＞ Effectiveness of steroid therapy

A specialized facility may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or bile duct cancers have been ruled out. When it is difficult to differentiate from malignant conditions, it is desirable to perform cytological examination using an endoscopic ultrasound–guided fine needle aspiration (EUS–FNA). Facile therapeutic diagnosis by steroids should be avoided unless the possibility of malignant tumor has been ruled

out by pathological diagnosis.

B. Diagnosis

I. Definite diagnosis
①Diffuse type
I a + III/IVb/V (a/b)
②Segmental/focal type
I b + II + two or more of ＜III/IVb/V (a/b)＞
or
I b + II + ＜III/IVb/V (a/b)＞ + Option
③Definite diagnosis by histopathological study
IV a

II. Probable diagnosis
Segmental/focal type : I b + II + ＜III/IVb/V (a/b)＞

III. Possible diagnosis*
Diffuse type : I a + II + Option
Segmental/focal type : I b + II + Option

When a patient with a focal/segmental image of AIP on CT/MRI without ERCP findings fulfill more than one of III, IVb and V (a/b) ERP criteria, he/she can be diagnosed as probable AIP only after the negative workup for malignancy by EUS-FNA, and confirmed as definitive one by an optional steroid response.
Possible diagnosis* : A case may possibly be type 2, although it is extremely rare in Japan.
"+" refers to "and", and "/" refers to "or".

Risk of Cancer in Patients With Autoimmune Pancreatitis

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

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

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

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

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

Am J Gastroenterol 2013; 108:610–617; doi:10.1038/ajg.2012.465; published online 15 January 2013

INTRODUCTION

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

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

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Received 23 April 2012; accepted 18 December 2012

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

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

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

METHODS

Patients

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

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

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

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

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

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

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

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

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

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

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

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

Calculation of relative risk of cancer in AIP patients and controls

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

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

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

Immunohistochemical study

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

Statistical analysis

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

RESULTS

Proportion and sites of cancers in AIP patients

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

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

SIRs of cancer in AIP patients

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

Time period between the diagnosis of cancer and AIP

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

Relative risk of cancer at diagnosis of AIP

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

Table 2. **SIRs of cancer in patients with AIP**

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

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

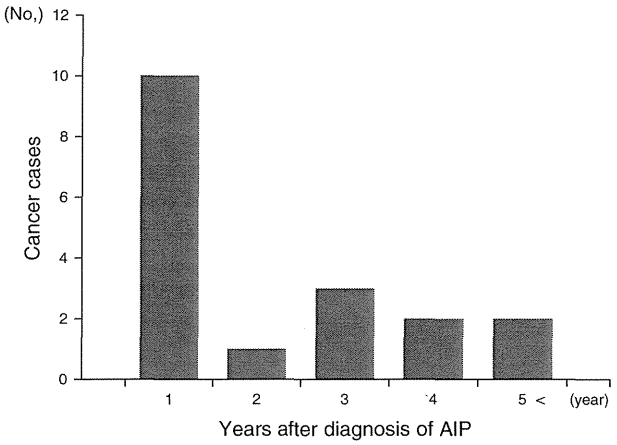

Figure 1. Time of cancer diagnosis in patients with AIP. Blue columns show the number of cancers diagnosed each year after the diagnosis of AIP. Ten cancers were diagnosed at or within 1 year after AIP diagnosis (eight cancers at the time of the diagnosis of AIP). AIP, autoimmune pancreatitis; no., number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

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

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

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

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

Clinicopathological characteristics of AIP patients with cancer

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

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

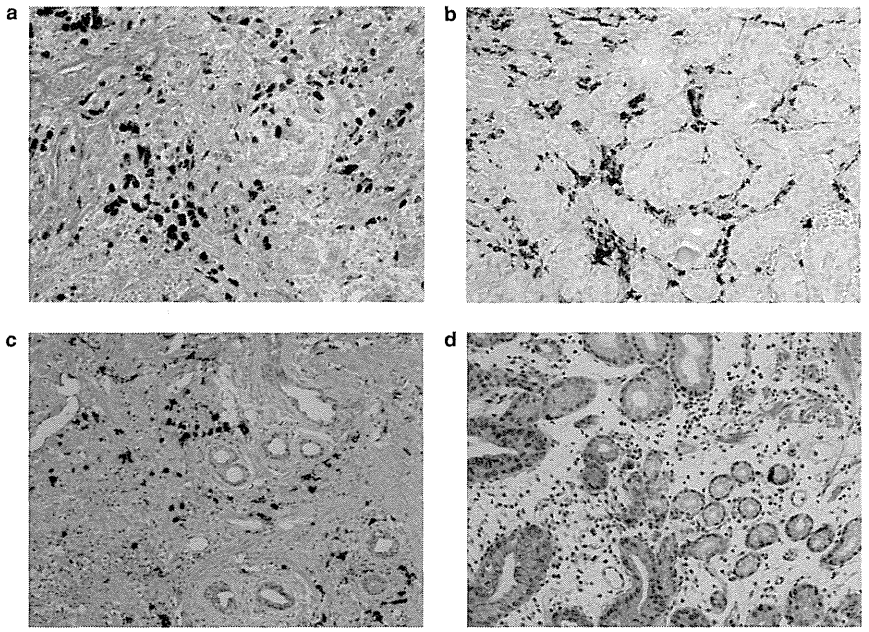

Figure 2. Infiltration of IgG4-positive plasma cells around the cancer before corticosteroid therapy. Representative cases of bile duct cancer (**a**), thyroid cancer (**b**), and prostate cancer (**c**) coexisting with AIP show abundant infiltration of IgG4-positive plasma cells before corticosteroid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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ACKNOWLEDGMENTS

This work was supported in part by the Health and Labour Sciences Research Grants for research on intractable diseases (Research on IgG4-related disease) from Ministry of Health, Labour and Welfare of Japan.

CONFLICT OF INTEREST

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

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

Competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

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

WHAT IS NEW HERE

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

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Nationwide Epidemiological Survey of Autoimmune Pancreatitis in Japan

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Objectives: To clarify the clinicoepidemiological features of autoimmune pancreatitis (AIP) in Japan, the nationwide survey was conducted.
Methods: Patients with AIP who had visited the selected hospitals in 2007 were surveyed. Autoimmune pancreatitis was diagnosed according to the Japanese clinical diagnostic criteria 2006. The study consisted of 2-stage surveys: the number of patients with AIP was estimated by the first questionnaire and their clinical features were assessed by the second questionnaire.
Results: The estimated total number of AIP patients in 2007 was 2790 (95% confidence interval, 2540–3040), with an overall prevalence rate of 2.2 per 100,000 populations. The number of patients, who were newly diagnosed as AIP, was estimated to be 1120 (95% confidence interval, 1000–1240), with an annual incidence rate of 0.9 per 100,000 populations. Sex ratio (male to female) was 3.7, and the mean (SD) age was 63.0 (11.4) years. Among the 546 patients whose clinical information was obtained, 87.6% of the patients presented high serum immunoglobulin G4 levels (≥135 mg/dL), and 83% received steroid therapy.
Conclusions: The data represent the current clinical features of AIP in Japan. From the results, most AIP patients in Japan can be categorized to type 1 AIP according to the recent classification of AIP.

Key Words: pancreatitis, IgG4, steroid, sclerosing cholangitis, epidemiology

Abbreviations: AIP - autoimmune pancreatitis, CI - confidence interval, IgG - immunoglobulin G, MPD - main pancreatic duct

(*Pancreas* 2012;41: 835–839)

Autoimmune pancreatitis (AIP) is a unique form of pancreatitis in which autoimmune mechanisms are suspected to be involved in the pathogenesis. Characteristic clinical, radiological, serological, and histopathological features of AIP patients have been described as follows: (i) elderly male preponderance; (ii) radiological findings of irregular narrowing of the main pancreatic duct (MPD) and enlargement of the pancreas; (iii) serological findings of elevation of serum γ-globulin, immunoglobulin G (IgG), or IgG4 levels, along with the presence of some autoantibodies; (iv) histopathological findings of dense lymphoplasmacytic infiltration with fibrosis and obliterative phlebitis in the pancreas; and (v) a favorable response to steroid therapy.[1–8] Because AIP is a relatively new disease concept, many controversies concerning the epidemiology, pathology, and treatment methods remain to be solved.

The first nationwide survey of AIP in Japan was carried out in 2002 by the Research Committee of Intractable Pancreatic Diseases, supported by the Ministry of Health, Labour, and Welfare of Japan.[9] In the survey, the number of patients with AIP who visited hospitals in Japan in 2002 was estimated to be approximately 900, with an overall prevalence rate of 0.9 per 100,000 populations. However, these results might not represent the actual number of patients with AIP, because the patients were, in that survey, diagnosed according to the Japanese clinical diagnostic criteria of AIP 2002,[10] which could not pick up cases with localized pancreatic enlargement. In 2006, the Japanese criteria were revised (Japanese clinical diagnostic criteria of AIP 2006)[11] to correct the drawback in the 2002 criteria. In addition, the disease concept of AIP has been rapidly spreading in Japan in recent years. To estimate the precise number of AIP patients in Japan and to elucidate their clinical features, we undertook the second nationwide epidemiological survey.

MATERIALS AND METHODS

We conducted a 2-staged postal survey. The first survey aimed to estimate the number of patients with AIP, and the second survey aimed to elucidate the clinicoepidemiological characteristics of AIP. This study was approved by the Ethics Committee of Tohoku University School of Medicine (article no. 2008-177).

Diagnosis of AIP

In this study, AIP was diagnosed according to the Japanese clinical diagnostic criteria of AIP 2006.[11] The diagnostic criteria consisted of characteristic radiological findings (diffuse or segmental irregular narrowing of the MPD and enlargement of the pancreas) as an essential factor in combination with serological findings (elevated serum γ-globulin [≥2.0 g/dL], IgG [≥1800 mg/dL], IgG4 [≥135 mg/dL] or the presence of autoantibodies, such as anti–nuclear antibodies [≥80-folds] and rheumatoid factor [≥20 IU/mL]) and/or histopathological findings (marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas).

First-Stage Survey

Our target subjects were patients diagnosed as AIP between January 1 and December 31, 2007, in Japan. The list of hospitals for the survey was prepared from the "Listing of Japanese Hospitals 2003–2004," which was compiled by the Committee

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This work was supported in part by the Research Committee on Intractable Pancreatic Diseases, supported by the Ministry of Health, Labour, and Welfare of Japan.
The authors declare no conflict of interest.