表 1）自己免疫性膵炎臨床診断基準 2018 （自己免疫性膵炎臨床診断基準 2011 改訂版）

日本膵臓学会・厚生労働科学研究費補助金難治性疾患等政策研究事業

「IgG4 関連疾患の診断基準ならびに治療指針の確立を目指す研究」班

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【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，IgG4 関連疾患の膵病変である．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、腎病変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 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，2 型はわが国では極めてまれであるため，本診断基準では 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：

a. ERP

b. MRCP

III. 血清学的所見

高 IgG4 血症（≧ 135mg/dl）

IV. 病理所見

a. 以下の①～④の所見のうち，3 つ以上を認める．

b. 以下の①～④の所見のうち，2 つを認める．

c. ⑤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）

⑤EUS-FNA で腫瘍細胞を認めない

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、腎病変

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）、後腹膜線維症あるいは腎病変と診断できる．

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、腎病変の特徴的な病理所見を認める．

VI. 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）細胞診は必須で（上記 IVc），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．したがって VI は IVc を包括している。

B. 診　断

I. 確診

①びまん型

Ia＋＜III/IVb/V(a/b)＞

②限局型

Ib＋IIa＋＜III/IVb/ V(a/b)＞の 2 つ以上

または

Ib＋IIa＋＜III/IVb/ V(a/b)＞＋VI

または

Ib +IIb+ <III/ V(a/b)> +IVb＋VI

③病理組織学的確診

IVa

II. 準確診

限局型：Ib＋IIa＋＜III/IVb/ V(a/b)＞

または

Ib＋IIb＋＜III/V(a/b)＞＋IVc

または

Ib＋＜III/IVb/V(a/b)＞＋VI

III.　疑診＊

びまん型：Ia＋II(a/b)＋VI

限局型：Ib＋II(a/b)＋VI

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

【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・MRI: 可能な限り造影剤急速静注によるダイナミック撮像が推奨される。膵実質相での斑点状/点状濃染（speckled/dotted enhancement），被膜様構造（capsule-like rim），後期相での均一かつ遅延性増強パターンは膵癌との鑑別に有用である。T2強調画像では被膜様構造（capsule-like rim）は低信号として描出される。また，病変内に主膵管貫通像（duct-penetrating sign）がみられることがある。

3) 自己免疫性膵炎に特徴的な所見を認めた場合も，同時に膵癌を示唆する所見（病変より上流の主膵管の著明な拡張や造影後期相での不均一な濃染，動脈の高度狭窄など）を認めた場合は，膵癌の可能性を考慮し慎重に診断を進めることが推奨される。

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（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）．

ERP所見

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．

MRCP所見

主膵管がある程度の広い範囲にわたり検出できないか狭細像を呈し、これら病変のスキップを認めることもある。病変部の上流主膵管の異常拡張は認められない。狭細部からの分枝膵管の評価は困難なことが多い。MRCP は撮像機種や条件により画像の quality に差を認め、膵管像を詳細に評価するに耐えうる画像を撮像することが必要である。

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，リウマトイド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 個を超える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．

5) EUS-FNAは癌を否定するための重要なツールであるが、癌細胞を認めないことが必ずしも癌を否定することにはならない。I -2) で述べた画像所見などにより癌との鑑別を積極的に行うことも肝要で、さらに血清学的所見、膵外病変などの所見を総合的に判断して慎重に診断を行う。

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．EUS-FNA組織診は検体量が十分採取出来れば、AIP の確定診断に至ることがある。膵癌では、内部や周辺部に多数のIgG4 陽性形質細胞を認めることや，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．壊死や肉芽腫，強い好中球浸潤，腫大した線維芽細胞増生等の所見を認めた場合，AIPとしては非典型的で，慎重な組織診断が求められる．

【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，膵癌との鑑別が臨床的に困難なことがある．

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型自己免疫性膵炎に合併する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性、すなわちIgG4関連疾患であることが推測できる．

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，腎病変などがある．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、腎病変にとどめる．これら膵外病変は自己免疫性膵炎と同時性のみならず、異時性にも認められることがある。

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．

② PSC 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．

③ IgG4 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まん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．

7) 腎病変

①自己免疫性膵炎の精査の過程で腹部造影CTを施行すると、腎実質の造影不良域を呈するIgG4関連腎臓病の合併を認めることがある。

②IgG4関連腎臓病の多くは尿細管間質性腎炎の病理所見を呈し、尿所見の異常は軽度で、低補体血症を高率に認めるが、糸球体病変を合併すると蛋白尿を認める。通常腎機能は正常もしくは軽度低下であるが、高度低下例に進展することがある。

③画像所見は特徴的で造影CTで腎実質の多発性造影不良域、単発性腎腫瘤、内腔不整を伴わない腎盂壁の肥厚病変、単純CTでびまん性腎腫大を認める。

VI. 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．

Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2018

Revision of Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2011

SUPPLEMENTAL DIGITAL CONTENT

SUPPLEMENTAL TABLE 1. Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2018: Revision of Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2011 (The Japan Pancreas Society, the Research Program on Intractable Diseases from the Ministry of Labor, Health and Welfare of Japan)

Disease Concept

Autoimmune pancreatitis (AIP), widely reported in Japan, is suspected to involve an autoimmune mechanism in its pathogenesis, which is the pancreatic lesions of IgG4-related diseases. This disease is commonly seen in middle-aged to older males. Since it is often associated with pancreatic enlargement, mass formation and obstructive jaundice, differentiation from pancreatic or bile-duct cancers becomes necessary. Laboratory data frequently shows elevated levels of serum gammaglobulin, IgG, IgG4, or the presence of positive autoantibodies, and the disease is often associated with extra-pancreatic lesions such as sclerosing cholangitis, sclerosing sialadenitis, or retroperitoneal fibrosis. Histopathological study features lymphoplasmacytic sclerosing pancreatitis (LPSP), which is characterized by prominent infiltration of lymphocytes and IgG4-positive plasmacytes, storiform fibrosis, and obliterative phlebitis. Although treated effectively by steroid therapy, its long-term prognosis is not clear; relapse occurs often, and some cases are reported to be associated with pancreatic stones.

Meanwhile, besides IgG4 related pancreatitis, the United States and Europe have reported idiopathic duct-centric pancreatitis (IDCP) as an autoimmune pancreatitis; the clinical symptoms and pancreatic image findings are similar, but abnormal immunological findings are lacking compared to IgG4-related pancreatitis, and it is characterized by granulocytic epithelial lesions (GEL). It is seen in both genders with no significant differences, also in relatively young patients, and sometimes associated with inflammatory bowel disease. Steroid therapy is effective, and relapse is rare. Internationally, two subtypes of autoimmune pancreatitis have been proposed in the International Consensus of Diagnostic Criteria (ICDC) for Autoimmune Pancreatitis: type 1 related with IgG4 (lymphoplasmacytic sclerosing pancreatitis: LPSP), and type 2 with neutrophil lesions (idiopathic duct-centric pancreatitis: IDCP). 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. Image findings showing irregular narrowing of the main pancreatic duct
- a. ERP (endoscopic retrograde pancreatography)
- b. MRCP (magnetic resonance chorangiopancreatography)

III. Serological findings

Elevated levels of serum IgG4 (≥135 mg/dl)

IV. Pathological findings: among i)~v) listed below,
- a. three or more of i)~iv) are observed
- b. two of i)~iv) are observed
- c. v) is observed

i) Prominent infiltration of lymphocytes and plasma cells along with fibrosis
ii) More than ten IgG4-positive plasma cells per high-power microscopic field
iii) Storiform fibrosis
iv) Obliterative phlebitis
v) No neoplastic cells detected by EUS-FNA (endoscopic ultrasound-guided fine needle aspiration)

V. Other organ involvement (OOI): sclerosing cholangitis, sclerosing dacryoadenitis/sialadenitis, retroperitoneal fibrosis or kidney lesion

(Continued on next page)

SUPPLEMENTAL TABLE 1. *(Continued)*

a. Clinical lesions

Extra-pancreatic sclerosing cholangitis, sclerosing dacryoadenitis/sialadenitis (Mikulicz disease), retroperitoneal fibrosis, or kidney lesion can be diagnosed with clinical and image findings.

b. Pathological lesions

Pathological examination shows characteristic features of sclerosing cholangitis, sclerosing dacryoadenitis/sialadenitis, retroperitoneal fibrosis or kidney lesion.

VI. 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 EUS-FNA (IVc). Facile therapeutic diagnosis by steroids should be avoided unless the possibility of malignant tumor has been ruled out by pathological diagnosis. Accordingly, VI includes IVc.

B. Diagnosis

I. Definite diagnosis

① Diffuse type

I a + <III/IVb/V(a/b)>

② Segmental/focal type

Ib + IIa+two or more of <III/IVb/V(a/b)>

Ib + IIa + <III/IVb/V(a/b)> +VI

Ib + IIb + <III/V(a/b)> + IVb + VI

③ Definite diagnosis by histopathological study

IVa

II. Probable diagnosis

Segmental/focal type

Ib + IIa + <III/IVb/V(a/b)>

Ib + IIb + <III/V(a/b)> + IVc

Ib + <III/IVb/V(a/b)> + VI

III. Possible diagnosis*

Diffuse type

Ia + II(a/b) + VI

Segmental type

Ib + II(a/b) + VI

*A case may be possibly type 2, although it is extremely rare in Japan.

"+" refers to "and", and "/" refers to "or".

Explanations

I. Enlarged pancreas

A diffusely enlarged pancreas with "sausage-like" appearance is highly specific to AIP. However, the problem is how to differentiate a segmentally/focally enlarged pancreas from pancreas cancer. For the definition of enlarged pancreas, many facilities use the criteria suggested by Haaga and consider the pancreas to be enlarged when "the width of the pancreatic head is more than one full transverse diameter of the vertebral body, and the width of the pancreatic tail is more than two-thirds of the transverse diameter of the vertebral body (which are approximately 3cm and 2cm for the pancreatic head and tail respectively)." Precise definition is difficult due to age-related influences; it may be considered as an enlarged pancreas if steroid therapy reduces the pancreas size.

1) Abdominal ultrasound: An enlarged pancreas often shows a hypo-echoic area with scattered hyper-echoic spots in it.
2) Abdominal CT･MRI: It is recommended to perform dynamic contrast-enhanced CT･MRI with bolus injection of contrast medium wherever possible. Useful findings for differentiation from pancreatic cancer are speckled/dotted enhancement and capsule-like rim at the parenchymal phase as well as delayed homogeneous enhancement. Capsule-like rim is seen as a band-like low intensity area on T2-weighed images. Duct-penetrating sign is another characteristic finding of focal AIP and is rarely seen.

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SUPPLEMENTAL TABLE 1. *(Continued)*

3) Even when characteristic findings for AIP can be found, careful diagnostic procedures should be conducted to exclude the possibility of pancreatic cancer if concurrent findings suggestive of cancer are present, such as upstream dilation of the main pancreatic duct, heterogeneous delayed enhancement, or severe stenosis of involved arteries.
4) FDG-PET: Abnormal intense uptake is often seen in active lesions; the uptake is reduced after steroid treatment.

II. Narrowing of the main pancreatic duct

Diffuse or segmental/focal irregular narrowing is seen in the main pancreatic duct (The pancreatic image findings described above may be observed retrospectively from the time of diagnosis).

ERP findings

Narrowing is referred to as being unlike the obstruction or stenosis, it extends to a certain degree and the duct diameter is smaller than normal, with some irregularities. In a typical case, the narrowing extends over one third (5cm) of the entire pancreatic duct; even when the lesion is segmental, no significant dilation is observed above the narrowed area upstream of the main duct. If the narrowing is short (less than about 3cm), it is difficult to differentiate from pancreatic cancer. The presence of side branches arising from narrowed portions of the main pancreatic duct or multiple skip lesions in the main pancreatic duct are effective in differentiating from pancreatic cancer.

MRCP findings

Narrowing or invisibleness of the main pancreatic duct is seen on MRCP and is extended to a certain degree, sometimes appearing as a multiple skip lesion. No significant dilation is observed above the narrowed area upstream of the main duct. It is usually difficult to evaluate side branches arising from narrowed portions of the main pancreatic duct. Although image quality of MRCP depends on the MR unit and scan parameters, it is necessary to acquire sufficient good quality images for the detailed evaluation of the pancreatic duct.

III. Hematological examination

1) Patients with AIP often show elevated levels of serum gammaglobulin, IgG, or IgG4 and autoantibodies; an elevated level of serum IgG4 (135mg/dl or higher) is one criterion for the diagnosis. Although the diagnostic criteria defined in this paper reference only IgG4, since elevated levels of IgG4 are also observed in other diseases, including IgG4-related diseases of other organs (e.g. atopic dermatitis, pemphigus, asthma), it is not necessarily specific to AIP. Serum IgG4 is the best serum marker for differentiating from pancreatic cancer in terms of both sensitivity and specificity. However, caution is advised since elevated levels are also observed in some pancreatic or bile-duct cancers, and there are cases of pancreatic cancers associated with AIP. The significance of elevated serum IgG4 in the pathogenesis and pathophysiology of AIP is still not clear.
2) Autoantibodies such as antinuclear antibodies or rheumatoid factor become positive in some cases, from which AIP presence may be suspected.

IV. Pathological findings of the pancreas

AIP shows a specific pathological image, called LPSP, whose typical features are as follows:

1) Prominent infiltration of lymphocytes and plasmacytes, and fibrosis are observed. These are often accompanied by eosinophil infiltration, but without neutrophils infiltration in most cases. Lymphoid follicle formation may also be present. Inflammation is prominent in inter- and intra-lobular regions, peripancreatic fatty tissues, and around the epithelial cells of the pancreatic duct, however, infiltration of inflammatory cells into the epithelium of the pancreatic duct is rare.
2) Prominent infiltration of IgG4-positive plasmacytes is characteristic of this disease; resected pancreatic specimens show 50 or more positive plasmacytes per high-power microscope field (x400) in most cases. In order to make diagnosis possible for small needle biopsy specimens, the criterion of more than 10 per high-power microscope field has been adopted worldwide. Although this diagnostic criteria has also adopted that guideline, since there are inflammatory lesions or tumors other than AIP which also meet this criteria, IgG4-immunostaining alone is not sufficient for making a definite diagnosis.
3) Storiform fibrosis is a lesion comprised of inflammatory cell infiltration (lymphocytes, plasmacytes) and spindle-shaped cell hyperplasia, which presents complex cell arrangements characterized by the expression "storiform", and associated with differing degrees of fibrosis. The storiform fibrosis most often appears in the pancreatic rim and peripancreatic fat tissues.

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4) Obliterative phlebitis is a finding where lesions caused by the infiltration and fibrosis of lymphocytes and plasmacytes in inter-lobular regions and peripancreatic fat tissues extends into a vein to cause venous stenosis or occlusion.
5) Although EUS-FNA is a useful tool to exclude cancer, the absence of neoplastic cells alone is insufficient; it is also important to exclude cancer using the image findings shown in I-2). Moreover, the diagnostic process should be done carefully, with comprehensive evaluation of serological findings and other organ involvement.

Either a resected or biopsied pancreatic specimen may be used for the diagnosis. EUS-FNA cytological examination is extremely effective in differentiating AIP from malignant tumors, but is not effective in diagnosing AIP. EUS-FNA histological examination can provide a definite diagnosis of AIP if sufficient sample volume is obtained. Diagnosis of AIP using biopsied specimens requires caution, since pancreatic cancer also shows a large number of IgG4-positive plasmacytes in and around the pancreas in some cases, and pathological findings similar to LPSP in some isolated cases. Careful histological diagnosis is needed when atypical findings for AIP, such as necrosis, granuloma, and abundant neutrophil infiltration, are concurrently observed.

Notes Type 2 AIP (IDCP)

IDCP is a pancreatitis of unknown cause which is characterized by the infiltration of neutrophils into the lumen or epithelium of the interlobular pancreatic ducts. As in the case of LPSP, clinical differentiation from pancreatic cancer becomes an issue. Because of its similarity to LPSP in being associated with the infiltration and fibrosis of lymphocytes/plasmacytes around the pancreatic epithelium, IDCP was once thought to be in the same category as LPSP. Currently, IDCP cannot be diagnosed by images or clinical findings, and therefore requires histopathological examinations for the diagnosis. In addition, while resected or necropsied specimens of pancreas are large enough for a definite diagnosis, biopsied specimens are so small that a definite diagnosis is difficult in many cases. If typical pancreatic images of AIP are shown without abnormal hematological evidence, the disease could be either type 1 or type 2. Some of type 2 AIP present clinical symptoms or image findings similar to those of pancreatic cancer, which makes it extremely difficult to differentiate type 2 AIP from pancreatic cancer.

V. Other organ involvement: OOI

1) Other organ involvement (OOI) observed in AIP refers to the IgG4 related lesions associated with type 1.
2) Other organs reported to be affected include the central nervous system, lacrimal/salivary glands, thyroid glands, lungs, biliary duct, liver, gastrointestinal tracts, gallbladder, kidneys, prostate glands, retroperitoneum, and lymph nodes. In the lymph nodes and lacrimal glands, however, fibrosis is scarce; not all of these organs have established concepts of their lesions. If the following conditions are met, there may be a close relation with AIP, although no clear basis is available.
    1. Investigations/reports of many cases show association with AIP.
    2. The histopathological findings feature lympoplasmacytic infiltration with fibrosis (often storiform in morphology), obliterative phlebitis, and numerous IgG4-positive plasmacytes.
    3. Steroid therapy is effective; or, the onset and offset of the effect synchronizes between pancreatic lesions and the lesions in question.
    4. There are clear points that differentiate from diseases of each organ.

Diseases that satisfy the above conditions include sclerosing cholangitis, sclerosing dacryoadenitis/sialadenitis (Mikulicz disease), retroperitoneal fibrosis, respiratory lesions, and kidney lesion (tubulo-interstitial nephritis). Currently consensus is limited to sclerosing cholangitis, sclerosing dacryoadeniti/sialadenitis retroperitoneal fibrosis and kidney lesion. These lesions could present simultaneously or in a metachronous manner with that of AIP.

3) Sclerosing cholangitis

1. The sclerosing cholangitis associated with AIP shows lesions over a wide area of the bile duct system; the stenosis of the lower bile duct caused by AIP must be differentiated from that caused by pancreatic cancer or cancer of the lower bile duct, and the stenosis of the intrahepatic and hilar bile ducts caused by AIP must be differentiated from that caused by primary sclerosing cholangitis (PSC) or bile duct cancer. It is necessary to make careful and comprehensive differentiation using not only the bile duct images but also endoscopic ultrasoundscopy (EUS), intraductal ultrasonography (IDUS), cytological and/or histological diagnosis, etc.

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SUPPLEMENTAL TABLE 1. *(Continued)*

2. PSC is a different entity from the sclerosing cholangitis seen in AIP, because their responses to steroid therapy and prognoses are different. Findings characteristic to PSC are band-like strictures (e.g. short band-like strictures of 1-2mm), a beaded appearance (e.g. alternating short strictures and dilatations), a pruned tree appearance (e.g. a reduced number of intrahepatic duct branches), and diverticulum-like outpouching.
3. It is controversial among specialists whether to include cases showing only lower bile duct stenosis within IgG4-related sclerosing cholangitis, or to view them as part of the pancreatic lesions. The findings in bile duct lesions effective in diagnosing AIP are stenosis of the intrahepatic and hilar bile ducts and the sclerosing images or wall thickening of the upper and middle bile ducts.
4. Most of the pathological studies show a thickened bile duct and prominent transmural infiltration and fibrosis of lymphocytes and plasmacytes. Many IgG4-positive plasmacytes are observed in the lesions. The epithelium of the bile duct remains normal in most cases. Storiform fibrosis and obstructive phlebitis are also observed.
5. The IgG4 immunostaining of enlarged duodenal papillary biopsy specimens may be useful as a supporting diagnosis, although this enlargement is infrequent. An enlarged duodenal papillary is considered to be spread from lesions of the pancreatic head, and therefore is not in the scope of extra-pancreatic lesions (other organ involvement).

4) Sclerosing dacryoadenitis/sialadenitis

1. Sclerosing dacryoadenitis/sialadenitis associated with AIP shows no or slight (if any) symptoms of dry eye or dry mouth caused by decreased function of the lacrimal glands. Unlike Sjögren's Syndrome which is often associated with swollen parotid glands, sialadenitis seen in AIP often demonstrates swollen submandibular glands and responds very well to steroid therapy. While most enlargement of the lacrimal and salivary glands is symmetrical, enlargement of the salivary glands is part of the enlarged submandibular, sublingual, or minor salivary glands. Dacryoadenitis/sialadenitis in most cases test negative for anti SS-A antibody and anti SS-B antibody, which is different from Sjögren's Syndrome. The disease can be diagnosed based on the diagnostic criteria of the organs (diagnostic criteria for IgG4-related Mikulicz disease, Japan Sjögren's Syndrome Study Group, 2008), however, if prominent infiltration of IgG4-positive plasmacytes are observed, it may be diagnosed by labial lip biopsy analysis.
2. Pathological findings show the disappearance of acinar cells in the lobule, prominent infiltration of lymphocytes and plasmacytes, formation of lymphoid follicles, and interlobular fibrosis. In some cases, the lobular structure may be destroyed, and prominent infiltration and fibrosis of lymphocytes and plasmacytes may form diffuse lesions. Many of the plasmacytes are IgG4 positive. Storiform fibrosis and obliterative phlebitis may be observed, although the incidence rate is lower compared with that of AIP.

5) Retroperitoneal fibrosis

1. Due to diffuse hyperplasmia and the inflammation of fibrous connective tissues on and around the retroperitoneum, abdominal CT/MRI images show soft tissue masses in the retroperitoneum, sometimes around the abdominal aorta. This can cause ureteral obstruction, and subsequent hydrophrosis occasionally provide a clue for diagnosis. In some cases, the disease is associated with dilated lesions of the abdominal aorta and the condition known as inflammatory abdominal aortic aneurysm may be present; however, it is difficult to differentiate said aortic aneurysm from those caused by other etiologies.
2. Pathological study shows mass lesions formed by prominent infiltration of lymphocytes and plasmacytes with fibrosis. Many IgG4-positive plasmacytes are seen in the lesions. Storiform fibrosis and obliterative phlebitis are also seen very frequently.

6) Kidney lesion

1. In the patients who are suspected AIP and undergo abdominal contrast-enhanced CT, decreased enhancement of renal parenchyma, suggesting IgG4-related kidney disease (IgG4-RKD), is occasionally seen.
2. IgG4-RKD usually displays histological tubulointerstitial nephritis along with mild urinary findings and hypocomplementemia, but sometimes shows proteinuria when glomerular involvement is present. Although IgG4-RKD typically exhibits normal or only slightly reduced renal function, it can also progress to an advanced stage of severe renal deficiency.

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SUPPLEMENTAL TABLE 1. *(Continued)*

3. Characteristic image findings of contrast-enhanced CT include renal parenchymal lesions seen as multiple decreased enhancement areas (small peripheral cortical nodules, round or wedge-shaped lesions), solitary mass (hypo-vasucular), or renal pelvic wall thickening without irregular lumen. Non-contrast CT may also disclose diffuse renal enlargement.

VI. Effectiveness of steroid therapy

Targets are the lesions for which image evaluation is possible; clinical conditions or hematological findings are not subject to effect evaluations. If no sufficient effect is seen within 2 weeks, reexamination is necessary. Effort should be made to take biopsies for pathological examination as much as possible, and facile diagnostic treatment with steroids should be strictly avoided. The administration of steroids may be effective in improving malignant lymphoma.

VII. Endocrine and exocrine pancreatic functions

Typical AIP shows impaired exocrine pancreatic functions and diabetes. There are quite a few cases where steroid administration is effective in improving impaired endocrine and exocrine pancreatic functions.

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