たCD163(＋) Mφとよく似た形態をとっている。HEでもなかなかそういう物の同定が困難である点も膵臓のLPSPと全く同じである。

CD68なんですが、実は陽性に染まってくる細胞が少し違ってきておりまして、両方とも染まってくる細胞もきっとあるんだろうと思うんでけども、CD68が、例えばリンパ濾胞の周りにこのように非常にたくさん陽性の細胞がこの様に割と大き目の細胞があるのですが、そういう細胞はCD163では認識できないという事とちょっと下の方になるのですがリンパ濾胞の中のMφ、このようなCD68しか染まってまいりません。リンパ節なんかもいくつか染色しるんですけど、そのように一致して認められるのはCD68、germinal cellの中のMφはD68しか染まってこない。CD163では染まらないということで結果は一定しております。小葉の辺縁が崩れてまいりますと、小葉の間にもこのような炎症の広がりがあって、これはLPSPにみられる所見と非常によく似たものであります。この間の中にもCD163(＋) 細胞のMφが一緒にたくさんみられる。ただ、こういうものが唾液腺の周囲の結合組織の炎症とつながってみられる所見があるので、そういうものがLPSPとの違いになってくる。

この繊維化を伴っていない小葉病変、辺縁にみられる所見でありますけども、そういう所にやはりCD163(＋) 細胞のMφが非常にたくさんみられる。同じような紡錘形であるということ。ちなみに、こういう所をIgG4を染めてみると多数の陽性細胞が出てきますので、繊維化があろうがなかろうが基本的には同じような硬化性唾液腺炎というのは適切ではないのかもしれませんが、同じ様な所見が起こっているんだろうという風に考えております。辺縁はこの通り明瞭であって周囲の脂肪組織と炎症はあったとしても極めて軽度であって、ここら辺でLPSPとの違いということになる。

これはコントロールで検討しました唾石症の患者さんですけれども、基本的には細かい結合組織が小葉の間に入っているんですが、そういう所に一致して紡錘形のMφがいるという事で実質の中に染み入るように多数増生して結節状になっていくのは、唾石症では通常見られません。ただ、1例だけ実質でかなり破壊された所にCD163(＋) Mφが集族するような形で見られ、実際この部分ではCD68とも対応いたしましたが、だいたいCD68(+)細胞はCD163(＋)細胞より非常に弱いんですが、ここでもCD68(+)細胞は非常に少なくてCD163(＋)細胞より弱い。こういうものが出てくることがありました。これは形態的には鑑別は可能であろうという風に思うんですけども。おそらく何か違った機序でMφの増生を起こすんではないかなという風に考えております。

という事で、結論なんですけども

(小括)

IgG4-SSにおいては、CD163陽性紡錘形のマクロファージが小葉内を主体に著明に増生し、この像は唾石症にみられる散在性の分布とは異なっていたという事がわかりました。

CD163 陽性紡錘形マクロファージの小葉内増生は、線維化を伴わない小葉病変においても認められたという事で、繊維化のあるなしに関わらず共通して起こしている異常な病変ではないのかな、あるいは非常に早期に起こっている病変なのかもしれない。

IgG4-SSとLPSPの小葉病変は組織学的によく類似していて、組織学的な所見が最初違うと言っていたのですが、基本的には同じ事が唾液腺でも膵臓でも起こっているのではないのかなという風に思っています。ただ、IgG4-SS の方においてはリンパ濾胞の形成が顕著である点、線維化のない病変を伴う点が異なっていて、この違いが何で起こるものなのかはよくわからない。

CD163 陽性紡錘形マクロファージの増生は、唾液腺でも認められたという事で、諸臓器の IgG4 関連硬化性疾患に共通してみられる異常である可能性がある。

（質問）

繊維化といっていたが、繊維化のある臓器とない臓器との違いがこの埋める様な答えはないようですが。

AIP の患者で腺房細胞の完全に脱落して、消化酵素機能の低下しているのですが、唾液腺炎でもほとんど腺房細胞が脱落して機能低下しているんでしょうか？

そうだと思います。唾液腺機能の低下、ひょっとするとあまり腫脹ではなくて形態学的に高率な Mφ増生が起こっていると思っている。

膵臓の方は幹細胞の研究では HE ではわからないですが形態学的に異常がある

上皮に異常が無いと言った訳ではなくて、異常があるのは小葉管・膵管の話でありまして、抹消の膵管では恐らく起こっていると思います。小葉の中で激しくリモルディングが起こっているだと思います。全く起こっているのではなくて、小さいレベルでは形態学的変化は起こっている。形態学的に区別するのは困難。

（質問）

Up to date されたで、CD80・86 の免疫染色はいかがでしょうか？

それがパラフィンで染色される抗体がない。非常に興味深いものだとは思う。残念ながら現時点では難しい。class2 は陽染化しております。

周囲に形質細胞がいるとか、局在とか？Tcell はたくさん浸潤している。

リンパ濾胞については？検討しときます。

CD14 については、Mφの一部が陽性であると確認していますが、CD163 よりに比べると陽性細胞は非常に少ない。これはかなり BREAK THROUGH すのでは。

ＣＲＰなんかは関係している？ CD？ サプレッシブな Th2 に向かわせるという話があるんですけど、抑制系になんか働くという風のはある？

これから検討しようとしてますが、パラフィン切片の限界がある。

２）自己免疫性膵炎における IgG4 と制御性 T 細胞の関係（研究分担者：岡崎和一）

岡崎和一、○内田一茂、小藪雅紀、楠田武生、吉田勝紀、坂口雄沢、福井寿朗、西尾彰功（関西医科大学内科学第三講座）

先ほど渡辺先生は IL-10 はたぶん候補にあがらないだろうと言われていましたが、我々は IgG4 関係において積極的に IL-10 が関与しているんじゃないか仮設をたてて、抹消血と膵臓の組織と肝臓についての繊維組織の比較検討をしました。

抹消血については、CD25high の Treg、CD45RA+の naïve Treg を検討しますと自己免疫性膵炎の患者さんで、ステロイドの投与に関係なく健常者・アルコール疾患・特発性慢性膵炎に比べると抹消血で増えていました。一方、CD45RA+の naïve Treg では他の群に比べると優位に抹消血で低いという事がわかりました。

IL-10 を産生する Treg と IgG4 値の相関をみますと、Treg の数と IgG4 の数とみますと正の相関が認められて、IL-10 産生 Treg と IgG4 との関係をみると、同様に正の相関が認められました。自己免疫性膵炎の膵臓のではどうなっているかという事を検討しました。緑が CD4+ IgG4

で、赤が Foxp3 (+)。上の段が自己免疫性膵炎の患者さんの膵臓で、下の段がアルコール性膵炎の患者さんの膵臓です。自己免疫性膵炎の患者さんでは、Foxp3 (+)の Treg、同様に IgG4(+)形質細胞も見られますけれども。アルコール性膵炎の患者さんでは、それらは認められませんでした。

浸潤しているリンパ球のサブセットを見ますと、CD3+細胞も CD4+細胞も CD79+細胞もアルコール性膵炎の患者さんとは変わりませんでした。

一方、Foxp3 (+)細胞は自己免疫性膵炎の患者さんで優位に高く、IgG4+細胞も自己免疫性膵炎の患者さんで優位に高いことがわかりました。

続いて膵外病変である肝臓について検討しました。上は自己免疫性膵炎に伴った硬化性胆管炎で、下は PSC の患者さんです。左半分が IgG4 陽性細胞、右半分が IgG1 の免疫染色です。PSC の IgG4 より AIP-SC の IgG4 の方が多いことがわかります。

これを数えますと、IgG1+形質細胞では AIP も PSC でも変わりませんでした。IgG4+細胞は AIP の患者さんで浸潤していることがわかりました。IgG4+/IgG1+の形質細胞の比をとりますと、自己免疫性膵炎の患者さんの多く、PSC の患者さんは IgG1+細胞の方が多く浸潤していることがわかりました。

上の段は自己免疫性膵炎の患者さんの肝臓で、下の段は PSC の患者さんの肝臓です。Foxp3 (+)細胞をみますと、自己免疫性膵炎の患者さんにだけ浸潤していることがわかりました。PSC の患者さんにはほとんど浸潤していないことがわかりました。数えますと、このグラフになりまして、自己免疫性膵炎の患者さんの方が多きことがわかります。Foxp3 (+)細胞の浸潤している数と IgG4+細胞をみますと、やはり肝臓でも正の相関が見られました。

以上、まとめますと

末梢血において、CD4+CD25highTreg は AIP において増加しており、CD4+CD25+CD45RA+(naïve) Treg は減少していた。

CD4+CD25highTreg と血清 IgG4 値には正の 相関を認めた。さらに IL-10 産生 Treg と血清 IgG4 値には正の相関を認めた。

自己免疫性膵炎の膵臓においてはアルコール性膵炎と比較して、CD3、CD4、CD79 陽性細胞の浸潤については差を認めなかったが、Foxp3 (+)細胞と IgG4(+)形質細胞が増加していることがわかりました。

自己免疫性膵炎の患者さんの肝組織においては、浸潤している IgG4/IgG1 陽性形質細胞の比は、PSC に比し高値であった。肝組織中 Treg と IgG4 陽性形質細胞数には正の相関を認めました。

以上をまとめますと、

(小括)

自己免疫性膵炎の患者さんは、たぶん naïve Treg が下がってしまうことで、発症にこれが関わっていると考えられる。一方で、抗原に暴露されて Treg が増加することで IL-10 が増えて血中 IgG4 が増えるのではないか、組織の浸潤性・IgG4 が増えるのではないかと考えられる。

(コメント)

九州大学の中村 Dr の所では、同じ様なデータで、恐らく制御性 T 細胞が局所で誘導されて IL-10 を介する IgG4 の増加はあるんではないかと思われますが、先ほど渡辺 Dr が言われたようにそれだけでは説明がつかないのではないかと、そんな気もしております。まだまだやらな

いといけない事がてんこ盛りにあるような気がします。

総合討論

総合討論として、IgG4 関連全身硬化性疾患の診断基準、試案（岡崎班）として提示させて頂きました。本日提示させてもらうのが、Version3 でございます。疾患概念についてはその通りになっております。診断基準に関しましては、梅原班が、最終的に梅原班でも MOLPS の観点から診断基準を作られるとお聞きしておりますが、現在 MOLPS 班では血中 IgG４値、病理組織と二つを満たすものをと診断されておりまして。梅原班と動向を合わせる形で、違うのは１）の臨床的な所を少し入れてあります。自己免疫性膵炎とか、あるいは下垂体とか臓器によってはなかなか組織が取れない部位がございますので、そういった所をどうやって診断するのか、一つの方法として臨床的な最近の画像診断も発達しておりますのでそういったものも含めた。自己免疫性膵炎でもそういったものとして相違が無いようにして提案しております。血清学的なところは同じです。３）の病理の事に関しましては、今日お話があったように能登原 Dr がお話になったような CD163(+)Mφが非常に共通点で、そういったものも恐らくは、この班が将来的に続けば病理の所に入って来るんではないかと今思っておりますが。硬化性疾患と MOLPS と一応その違う立場で病気、同じ病気ではないかもしれないという事で厚労省の理解を得て二つの班が並列して走っている背景がございます。これ梅原班と岡崎班がですね。競い合ってやっている訳ではなくて喧嘩をしている訳ではなくて十分ディスカッションしてやっている訳です。私どもの班に梅原 Dr にも入って頂き、梅原 Dr の班に私も入っている訳でございます。それから川 Dr、神澤 Dr、下瀬川 Dr・膵臓班長の指名で個人的にではなくて膵臓グループとして入っておりますので。違う病気かもしれないと診断基準にもそういった所も盛り込まないといけない。病理所見に関しましては梅原班では３）②ですが IgG4 形質細胞浸潤が 50%以上ということですが、病理の方で 40%以上の論文がありますので 40%とさせて頂きました。３）組織の①と③④は自己免疫性膵炎の観点から添加。結果的には、こういった診断基準にしておりますが、梅原班も岡崎班も IgG４が一つのキーワードで全身の疾患・病体であることは間違いない。個々の臓器によって組織が違ったり、抗原が違うのかもしれません。わが国から IgG4 関連全身硬化性疾患という概念を発信していきたい。将来的には大きな班になればなと思っています。

IgG4 という研究は膵臓班の先生方が発見されて、重々認識しております。ただ、岡崎 Dr と討論してきました。繊維化という方向に向かい、我々はリンパ増殖性疾患の血液疾患という概念の方に進んでいったということで。岡崎 Dr と相談していなければ、研究班に参加し、お互いを理解できたように思います。

【概念】

IgG4 関連全身硬化性疾患とは、リンパ球と IgG4 陽性形質細胞の著しい浸潤を伴う線維化により、同時性あるいは異時性に全身各臓器の腫大や結節・肥厚性病変などを認める原因不明の疾患である。罹患臓器としては中枢神経系、涙腺・唾液腺、甲状腺、肺、胆管、胃、膵臓、肝臓、腎臓、前立腺、後腹膜腔、などが知られている。多巣性線維硬化症（multifocal fibrosclerosis）との異同は不明であるが、本症である可能性がある。臨床的には各臓器病変により異なった症状を呈するが、ステロイド治療の有効なことが多い。予後は不明であるが、

肝・胆・膵病変における閉塞性黄疸、後腹膜病変における水腎症、肺病変における呼吸器症状など、時に重篤な合併症を伴うことがある。

【診断基準】

1) 臨床的に単一または複数臓器にびまん性腫大あるいは腫瘤、結節、肥厚性病変を認める。

2) 血液学的に高 IgG4 血症（135 mg/dl 以上）を認める。

3) 病理組織学的に以下の所見を認める。

①組織所見

著明なリンパ球、形質細胞の浸潤と線維化を認め、好中球浸潤を欠く。

②IgG4 陽性形質細胞浸潤

10/HPF 以上、かつ IgG4/IgG 陽性細胞比 40%以上

③花筵様線維化（storiform fibrosis）

④閉塞性静脈炎（obliterative phlebitis）

上記のうち、1)＋2)、1)＋3)①②、2)＋３）①②、または 3)①②③④を満たすものを確診とする。

【付記】

・ IgG4 関連中枢神経系病変では漏斗下垂体炎、肥厚性硬膜炎、脳内炎症性偽腫瘍、眼窩偽腫瘍などが知られている。

・ IgG4 関連涙腺・唾液腺炎は IgG4 関連 Mikulicz 病と同義で、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。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。時に、口唇腺生検により診断できることもある。

・ IgG4 関連膵炎は自己免疫性膵炎と同義で、臓器診断基準（自己免疫性膵炎の臨床診断基準 2006、厚生労働省・日本膵臓学会、2006 年）により診断できる。膵病変の画像は、診断基準 2006 の画像所見を満たすことが必要である。

・ 花筵様線維化(storiform fibrosis),閉塞性静脈炎(obliterative phlebitis)は臓器によりその程度は異なる。殆どの膵・胆管病変に認められるが、涙腺・唾液腺病変やリンパ節病変では殆ど認められない。臓器毎に IgG4 関連病変の成立機序の異なる可能性がある。

・ 各臓器の悪性腫瘍（癌、悪性リンパ腫など）や類似疾患（Sjogren 症候群、原発性硬化性胆管炎(Primary sclerosing cholangitis:PSC)、気管支喘息、Castleman 症候群など）を除外することが必要である。

X. 研究成果の刊行物・別刷

Japanese Clinical Guidelines for Autoimmune Pancreatitis

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Objectives: As the patients with autoimmune pancreatitis (AIP) are increasing in Japan, the practical guideline for managing AIP is required to be established.

Methods: Three committees (the professional committee for making clinical questions [CQs] and statements by Japanese specialists, the expert panelist committee for rating statements by the modified Delphi method, and the evaluating committee by moderators) were organized. Fifteen specialists for AIP extracted the specific clinical statements from a total of 871 literatures by PubMed search (~1963–2008) and from a secondary database and made the CQs and statements. The expert panelists individually rated these clinical statements using a modified Delphi approach, in which a clinical statement receiving a median score greater than 7 on a 9-point scale from the panel was regarded as valid.

Results: The professional committee made 13, 6, 6, and 11 CQs and statements for the concept and diagnosis, extrapancreatic lesions, differential diagnosis, and treatment, respectively. The expert panelists regarded them as valid after a 2-round modified Delphi approach.

Conclusions: After evaluation by the moderators, the Japanese clinical guideline for AIP has been established. Further studies for the international guideline are needed after international consensus for diagnosis and treatment.

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Received for publication June 7, 2009; accepted July 8, 2009.

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This study was supported by the grant-in-aid for the Intractable Pancreatic Diseases, supported by the Ministry of Health, Labor, and Welfare of Japan.

Key Words: autoimmune pancreatitis, guideline, diagnosis, treatment, Delphi method

(*Pancreas* 2009;38: 849–866)

Autoimmune pancreatitis (AIP) is accepted worldwide as a distinctive type of pancreatitis.[1–4] It is suspected that the pathogenesis of AIP involves autoimmune mechanisms. In addition to pancreatitis, patients with AIP often accompany extrapancreatic lesions such as biliary lesions, sialadenitis, retroperitoneal fibrosis, enlarged celiac and hilar lymph nodes, chronic thyroiditis, and interstitial nephritis, suggesting that AIP may be a systemic disorder.[5–7] Although the pathogenesis still remains unclear, the most important issue in the management of AIP is to differentiate it from pancreas and biliary malignancy. Recently, various diagnostic criteria for AIP have been proposed, including those of Japan,[8] Korea,[9,10] Mayo,[11] and Asia.[12] Because systemic corticosteroid is usually effective, steroid effect is included in the diagnostic criteria proposed by Korea and Mayo. In Japan, facile therapeutic use of steroid, however, is not recommended. Although the numbers of patients with AIP are increasing in Japan, clinical evidence is limited. Therefore, practical guidelines for managing AIP are required. The modified Delphi approach, developed at RAND in the 1950s as a tool to predict the future and applied to political-military, technological, and economics topics,[13] is a consensus method that involves the administration of 2 or more rounds of questionnaires.[13,14] Unlike the original Delphi method, the modified Delphi method provides panelists with the opportunity to discuss their judgments between the ratings' rounds. It has also been used in various areas of medicine to develop consensus.[14,15] This method ensures anonymity, and hence, more reliable and unbiased expert opinions can be obtained. When clinical evidence is lacking and management of the disease relies mostly on expert opinion, this method is suitable for the development of guideline statements. The objective of this study was to develop consensus-based practice guidelines for the diagnosis and management of AIP in Japan.

AN OVERVIEW OF THE STUDY

To establish the present guideline, 3 committees (the professional committee for making clinical questions [CQs] and statements by Japanese specialists for AIP, the expert panelist committee for rating statements by the modified Delphi method, and the evaluating committee by moderators) were organized. The study consists of 4 phases. In brief, during the first phase, 15 specialists (11 pancreatologists, 2 radiologists, 1 expert in the respiratory system, and 1 pathologist), who were selected from the members of the Research Committee of the Intractable

Pancreatic Diseases, supported by the Ministry of Health, Labor, and Welfare of Japan, extracted the specific clinical statements from 871 literatures by PubMed search (~1963–2008) and a secondary database and made the 36 CQs and statements for (I) concept and diagnosis (13 CQS), (II) extrapancreatic lesions (6 CQs), (III) differential diagnosis (6 CQs), and (IV) treatment (11 CQs). In the second phase, the expert panelists individually rated these clinical statements for appropriateness and discussed areas of disagreement and uncertainty. Ratings of appropriate methods for management of AIP were developed using a modified Delphi approach.[13–15] For the present study, a 10-member panel of pancreatologists was established. In the third phase, the specialist revised some of the clinical statements after discussion with expert panelists. During the third phase, the revised clinical statements were rated again. In addition to the specialist and expert panel, the moderators comprised 1 pancreatologist, 1 surgeon, 1 pathologist, and 1 internist who were also familiar with epidemiology and the modified Delphi approach. The moderators searched and reviewed the literature, collected clinical statements from the literature as well as from the professional group's survey, facilitated the panelist meetings, and analyzed the data obtained using the modified Delphi approach.

MODIFIED DELPHI APPROACH[13–15]

Panelists were asked to rate the appropriateness of the clinical statements regarding the diagnosis and management of AIP. Rating was on a 9-point scale, with 1 being highly inappropriate and 9 being highly appropriate. A clinical statement receiving a median score greater than 7 from the panel was regarded as valid. A clinical statement with a median score of 7 and a range (maximum score to minimum score) of 4 or less was regarded as possibly valid, pending panelist discussion. Clinical statements with a median score of 7 and a range of 5 or more, or a median of 6 to 6.5, were also discussed by the panelists. After the first round of rating, panelists met to discuss areas of disagreement and to clarify areas of uncertainty. The clinical statements to be discussed were determined according to the criteria previously mentioned. After discussion, the list of clinical statements was revised. Revised clinical statements were sent to the panelists for a second round of ratings. The panelists were also informed of the results of the first round of ratings. On the basis of the 2-round modified Delphi approach, guideline statements for diagnosis and management of AIP were developed. Because available clinical evidence regarding diagnosis and management of AIP is limited, we could not set a suitable recommendation level for some clinical statements. In the present consensus-based guideline, the statements for clinical practice receiving score of 9 and less than 9 were evaluated as strongly recommendable (level A) and ordinarily recommendable (level B), respectively.

CLINICAL QUESTIONS AND STATEMENTS

(I) Concept and Diagnosis

CQ-I-1) What is "Autoimmune Pancreatitis (AIP)"?

- It is a unique form of pancreatitis that shows evidence of possible involvement of autoimmune mechanisms such as hypergammaglobulinemia, increased serum levels of immunoglobulin G (IgG), increased serum levels of IgG4, or presence of autoantibodies, and effective response to steroid therapy.
- Autoimmune pancreatitis, as commonly observed in Japan, shows symptoms of lymphoplasmacytic sclerosing pancreatitis (LPSP) characterized by pronounced infiltration of lymphocytes and plasmacytes, infiltration of IgG4-positive plasmacytes, storiform fibrosis, and obliterative phlebitis.
- However, idiopathic duct-centric chronic pancreatitis (IDCP) or granulocyte epithelial lesions, commonly seen in Europe and the United States, show neutrophilic lesions and are therefore different conditions from AIP.
- Autoimmune pancreatitis may be a systemic disorder associated with pancreatic lesions because the following disease concepts have also been proposed: IgG4-related sclerosing disorders, systemic IgG4-related plasmacytic syndrome, or IgG4-positive multiorgan lymphoproliferative syndrome.

Description

Autoimmune pancreatitis is a concept of disease originally proposed in Japan.[1] Because its characteristics are associated with evidence of possible involvement of autoimmune mechanisms such as hypergammaglobulinemia, increased serum levels of IgG, increased levels of IgG4 or presence of autoantibodies, and effective response to steroid therapy, the disease is defined as a pancreatitis whose pathogenesis could possibly involve autoimmune mechanisms.[1–4] In Japan, it is commonly observed in elderly males and is comparable to LPSP, which is characterized by histopathological findings of pronounced infiltration of lymphocytes and plasmacytes, infiltration of IgG4-positive plasmacytes, storiform fibrosis, and obstructive phlebitis.[8,16] Cases in young patients associated with ulcerative colitis, commonly reported in Europe and the United States, show pathological neutrophilic lesions and are called IDCP[17] or granulocyte epithelial lesions.[18] Although their image findings are similar to those of AIP, seronegative and pathological conditions are different from AIP showing LPSP.[16,17,19] Because most cases in Japan show a diffusely enlarged pancreas and narrowing of the main pancreatic duct, it is believed that typical AIP lesions spread to more than one-third of the pancreas; however, there are also cases of focal, segmental, or mass-forming types.[2–8] Autoimmune pancreatitis is occasionally associated with extrapancreatic lesions (sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis, enlarged celiac and hilar lymph nodes, chronic thyroiditis, interstitial nephritis, etc), suggesting that it might be a systemic disorder such as IgG4-related systemic sclerosing disease,[5] systemic IgG4-related plasmacytic syndrome,[6] or IgG4-positive multiorgan lymphoproliferative syndrome.[7] Autoimmune pancreatitis is considered to be different from typical Sjögren syndrome because sialadenitis, in most cases, is found negative for both the anti-SS-A/Ro antibody and anti-SS-B/La antibody distinctive to Sjögren syndrome,[2–4] and the histopathological images show pronounced infiltration of IgG4-positive plasmacytes seen in Mikulicz disease and Küttner tumor. Because sclerosing cholangitis-like lesions seen in patients with AIP show different responses to steroids and different prognoses than with primary sclerosing cholangitis (PSC), and further because AIP is characterized by the infiltration of IgG4-producing plasmacytes, the 2 diseases are considered to be different pathological conditions.

CQ-I-2) Are There Characteristic Clinical Symptoms in AIP?

- There are no specific symptoms seen in patients with AIP. However, in many cases, the patients show minor to no abdominal pain, obstructive jaundice, symptoms of diabetes mellitus, or accompanying extrapancreatic lesions.

Description

Although most patients show mild or no abdominal pain,[2,20–23] a few cases of acute or severe pancreatitis have been reported.[24] One-third to one-half of the patients show

obstructive jaundice or mild abdominal pain, and 15% have shown back pain or weight loss.[20,24,25] More than half of the cases are associated with sclerosing cholangitis, diabetes mellitus, sclerosing sialoadenitis/dacryoadenitis, or retroperitoneal fibrosis, showing, in some cases, obstructive jaundice, polydipsia/polyuria or malaise, xerostomia/xerophthalmia, or hydronephrosis, respectively.[25]

CQ-I-3) How Is AIP Found?

- In many cases, patients go to see physicians with complaints such as minor abdominal pain, general malaise, jaundice, or dry mouth.
- In many cases, AIP is found when patients showing increased levels of biliary enzymes, obstructive jaundice, or diabetes mellitus are tested for pancreatic or biliary duct cancers in a differential diagnosis.
- In many cases, an enlarged pancreas demonstrated by abdominal ultrasonography (US) leads to the detection of AIP.

Description

In many cases, AIP is found in the course of a differential diagnosis against pancreatic or biliary cancers.[1–4,20–22] Autoimmune pancreatitis is also found during the close examination of extrapancreatic lesions; for example, during the differential diagnosis against PSC; in examination in suspicion of Sjögren syndrome by a head/neck otolaryngologist, ophthalmologist, or collagen disease-rheumatologist; or in examination for retroperitoneal fibrosis by a urologist.

CQ-I-4) What Are the Characteristic Blood-Biochemical or Immunological Findings in AIP?

- Although there are no disease-specific blood-biochemical findings, increased serum levels of pancreatic enzymes, biliary enzymes and total bilirubin are commonly observed in AIP.
- Serum levels of IgG4 have the highest diagnostic value as a single serological diagnostic method among all the available ones; however, it is not disease-specific.
- The combination of nonspecific antibodies, such as serum IgG, antinuclear antibodies, or rheumatoid factor, shows sensitivity and specificity equivalent to IgG4.

Description

Abnormal biliary findings are observed in many cases; 60% to 82% of cases exhibit an increase in biliary enzymes; 39% to 62% of cases exhibit an increase in total bilirubin, and so on.[17,18,20,21] Compared with acute pancreatitis or acute exacerbation of chronic pancreatitis, the occurrence rate of abnormal levels of serum pancreatic enzymes is lower, between 36% and 64%.[25,26] There have been reports of increased levels of peripheral eosinophil granulocytes[25] and activated T-lymphocytes (CD4-positive, CD8-positive).[26]

Immunological examinations show high incidences of hypergammaglobulinemia (43%), increased levels of serum IgG (62%–80%), increased levels of serum IgG4 (68%–92%),[2,25–28] antinuclear antibodies (40%–64%), rheumatoid factor (25%), and so on,[25,26] although these are not disease-specific. Some reports have shown the presence of autoantibodies, such as anti–carbonic anhydrase II antibodies (55%) or antilactoferrin antibodies (75%), in patients with AIP in high frequency, although they generally cannot be tested.[26] Anti–SSA/B antibodies or antimitochondrial antibodies, on the other hand, are rarely seen.[25,26] Among all serological diagnostic methods, increased level of serum IgG4 has the highest diagnostic value as a single method because of its sensitivity (80%) and its specificity (98%) in differentiating from pancreatic cancer[28]; however, it is not disease-specific. The sensitivity and specificity of serum IgG are 70% and 75%, respectively, and the positive ratios of antinuclear antibodies and rheumatoid factor are 60% and 20% to 30%, respectively.[28] Even when IgG is combined with antinuclear antibodies or rheumatoid factor, the sensitivity is 91% but the specificity is 61%; the specificity is lower than that for IgG4; however, the sensitivity is equivalent to that for IgG4[28] (refer to CQ-II-2).

CQ-I-5) Are There Pancreatic Exocrine and Endocrine Dysfunctions?

- Autoimmune pancreatitis is often associated with pancreatic exocrine and endocrine dysfunctions (diabetes mellitus); occurrence ratios are approximately 80% and 70%, respectively.

Description

There are some cases where both pancreatic exocrine and endocrine dysfunction are improved by steroid treatment; however, because not all cases improved, it can be stated that medical conditions that have progressed far enough to cause some degree of organic change cannot be reversed (refer to CQ-IV-9). Pancreatic exocrine dysfunction are associated in 83% to 88% of the cases, and diabetes mellitus is associated in 42% to 78%.[25,28–31] By the national survey of the Japanese Research Committee, 66.5% of AIP cases were associated with diabetes mellitus; of those, 33.3% had diabetes mellitus before the onset of AIP and 51.6% started developing diabetes mellitus around the same time as the onset of pancreatitis. Among those patients having diabetes mellitus, 14% developed diabetes after steroid treatment,[25,27] suggesting that such diabetes may be caused by long-term steroid treatment.

In AIP, the mechanism of pancreatic exocrine dysfunction is assumed to involve the following: decreased secretion of pancreatic enzymes associated with collapsed acinar cells caused by pronounced cellular infiltration mainly of plasmacytes and fibrosis and obstructed flow of pancreatic juice due to inflammatory cell infiltration around the pancreatic ducts and subsequent narrowing of pancreatic ducts.[30–32] In contrast, the mechanism of diabetes mellitus is assumed to be affected by impaired blood flow of islets glands[31,32] and damaged function of islets of Langerhans due to fibrosis and inflammation,[2,33] although further studies are necessary.[34]

CQ-I-6) What Are the Characteristic Findings of Abdominal US in AIP?

- Abdominal US is effective for the diagnosis of AIP. (Level of recommendation: A)
- Ultrasonic findings in patients with AIP are characterized by a diffusely or locally enlarged pancreas with low echo; a diffusely enlarged pancreas is called a "sausage-like" pancreas. (Level of recommendation: A)

Description

In many cases, abdominal US, which is the initial tool to diagnose AIP, shows diffusely enlarged low-echoic pancreas (Fig. 1) with scattered high-echo spots giving a so-called sausage-like appearance.[35] Cases of the locally enlarged pancreas should be distinguished from pancreatic cancer or mass-forming pancreatitis. Although dilatation of the main pancreatic duct is not visible in most cases, some patients may show minor dilation, which makes the differential diagnosis difficult. Conversely, if the main duct is found to penetrate through the mass (duct-penetration sign), it may be useful for differential diagnosis against pancreatic cancer.[34] In some cases, the thickened wall extends from the extrahepatic bile duct to the intrahepatic bile duct or gallbladder.[36] Some recent studies

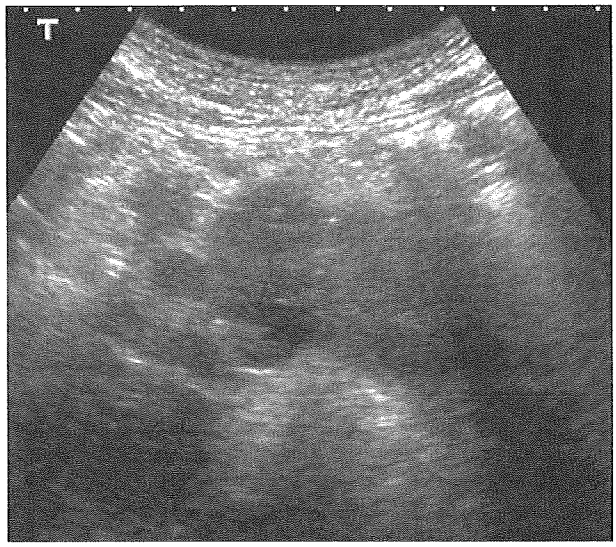

FIGURE 1. Abdominal US in AIP. Sonogram shows the diffusely enlarged low-echoic pancreas with scattered high-echo spots in a so-called sausage-like appearance.

have reported the usefulness of contrast-enhanced US in the differential diagnosis of AIP from pancreatic cancer.[37,38]

CQ-I-7) What Are the Characteristic Findings of Abdominal Computed Tomography (CT) in AIP?

- Abdominal CT images of patients with AIP show a diffusely or locally enlarged pancreas. The dynamic CT shows a distinctive delayed enhancement pattern with various images depending on the activity or stages of the disease. (Level of recommendation: A)
- If a capsule-like rim is observed, the patient is highly suspected of having AIP. (Level of recommendation: A)

Description

Dynamic CT is useful for the diagnosis of AIP. Diffusely enlarged pancreas with slow and delayed enhancement on the dynamic CT is the typical image of AIP (Fig. 2).[2–4,39] A "capsule-like rim," which may indicate fibrotic changes of the peripancreatic area, is a distinctive and specific CT feature of AIP.[39,40] Because CT images of AIP are heterogeneous, it is noted that AIP without typical CT images may exist.[39]

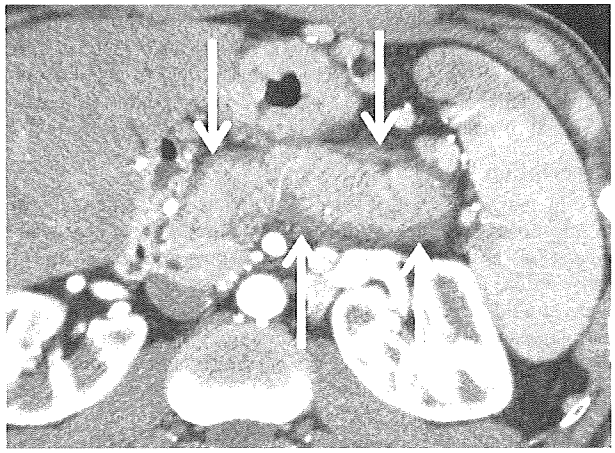

FIGURE 2. Abdominal CT in AIP. Diffusely enlarged pancreas with slow and delayed enhancement and capsule-like rim on the dynamic CT scan are the typical images of AIP.

CQ-I-8) What Are the Characteristic Findings of Magnetic Resonance Imaging (MRI) in AIP?

- Magnetic resonance images of AIP show a diffusely enlarged pancreas with distinctive characteristic, such as a low signal on T1-weighted images and a delayed enhancement pattern on dynamic MRIs. (Level of recommendation: A)
- A capsule-like rim reflects strong fibrosis of the peripancreatic lesion, which is highly specific for AIP. (Level of recommendation: A)
- At this moment, magnetic resonance cholangiopancreatography (MRCP) is not recommended for the accurate evaluation of the narrowing of the main pancreatic duct. (Level of recommendation: B)

Description

Magnetic resonance images of AIP show a diffusely or locally enlarged pancreas, like other images.[2–4,39,40] On T1-weighted images, the pancreas in AIP shows lower signals than the liver, whereas the normal pancreas shows higher signals than the liver. However, because a low signal is also observed in pancreatic cancer or chronic pancreatitis, it is not a characteristic finding of AIP.[36] The T2-weighted images may show a slightly lower signal in strong fibrosis and a slightly higher signal in weak fibrosis.[39,40] A capsule-like rim as a low signal on T2-weighted images, which seems to reflect strong fibrosis, and a delayed enhancement pattern are often observed.[38,39]

It is currently difficult to use MRCP pancreatic images for the diagnosis of AIP.[2–4] Because further image quality improvement can be expected for MRCP with the introduction of 3-T MRI technology, it is possible that MRCP will be used to evaluate the therapeutic effect or monitor the progress of AIP in the future (Fig. 3).[39,40]

CQ-I-9) What Are the Characteristic Findings of Positron Emission Tomography (PET) and Gallium Scintigram in AIP?

- Patients with AIP show accumulation of Ga-67 and fluorodeoxyglucose (FDG) in the pancreatic and extrapancreatic lesions, which disappear shortly after steroid treatment. The characteristic accumulation pattern and kinetics in the pancreatic and extrapancreatic lesions after the steroid treatment can be used for the diagnosis of the disease. (Level of recommendation: B)

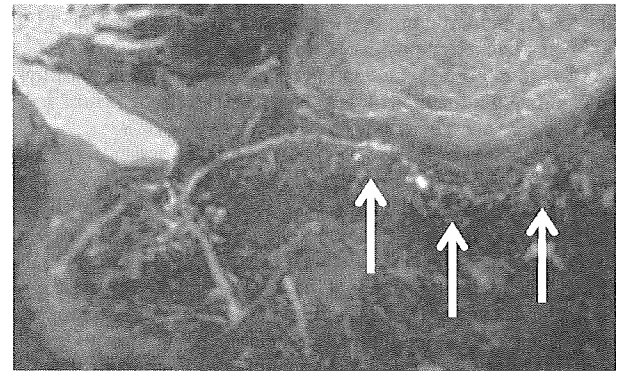

FIGURE 3. Magnetic resonance cholangiopancreatography image in AIP. Three-dimensional MRCP shows irregular narrowing of the main pancreatic duct (tail).

Description

Gallium scintigraphy and fluorine-18 FDG-PET show accumulation of gallium citrate (Ga-67) or FDG in the pancreatic or extrapancreatic lesions of AIP, respectively.[41–48] The accumulation of Ga-67[41] or FDG[42–47] is positive at approximately 70% or 90% for pancreatic lesions and hilar lymph nodes and approximately 20% for lachrymal/salivary glands. The accumulation reflects high disease activity and disappears quickly after steroid treatment.[41,45] It is not clear at this point whether the disappearance of FDG after steroid treatment can be used as a differential diagnostic criterion because there have been no reports on pancreatic cancer in this regard.

CQ-I-10) What Are the Characteristic Findings of Endoscopic Retrograde Cholangiopancreatography (ERCP) in AIP?

- Endoscopic retrograde cholangiopancreatography shows narrowing of the main pancreatic duct characteristic to AIP. (Level of recommendation: A)
- Autoimmune pancreatitis may be associated with stenosis of the bile duct. (Level of recommendation: A)

Description

The narrowing of the pancreatic duct is defined as being: "unlike the obstruction or stenosis, the narrowing extends to certain degree and the duct is narrower than normal, with some irregularities"[2–4,48–55] (Figs. 4A–C). The Clinical Diagnostic Criteria of Autoimmune Pancreatitis 2006 states that diagnosis of the disease requires pancreatic images showing "the distinctive narrowing of the main pancreatic duct," where the narrowing may be diffuse or local. In a typical case, the narrowing extends more than one third of the entire pancreatic duct. Even when the narrowing is localized to less than one third of the entire duct, in most cases, no significant dilatation is observed above the narrowed area upstream of the main duct.[48,51] If the narrowing is localized, it is necessary to consider differentiating the disease from pancreatic cancer.[8,51–58] Approximately 80% of patients with AIP show stenosis of the bile duct.[49–60] Although most of the stenosis is found in the lower bile duct, it can also be detected in the extrahepatic or intrahepatic bile ducts.[49–60]

CQ-I-11) What Are the Characteristic Histopathological Findings in AIP?

- Histopathological findings of AIP are characterized by the fibrosis with strong lymphoplasmacytic infiltration, which gives rise to distinctive inflammatory findings, such as circumferential inflammation around duct epithelium and obstructive phlebitis. (Level of recommendation: A)
- A number of infiltrations of IgG4-positive plasma cells are observed in the lesions. (Level of recommendation: A)

Description

The histological feature of AIP is called as LPSP (Figs. 5A–D).[16–18,61–65] Immunohistochemistry shows prominent infiltration of IgG4-positive plasma cells[63,64,66,67] and high ratio of IgG4- to IgG- or IgG1-positive plasma cells. However, it has not been established yet as to how many or what percentage of IgG4-positive plasma cells must be observed for

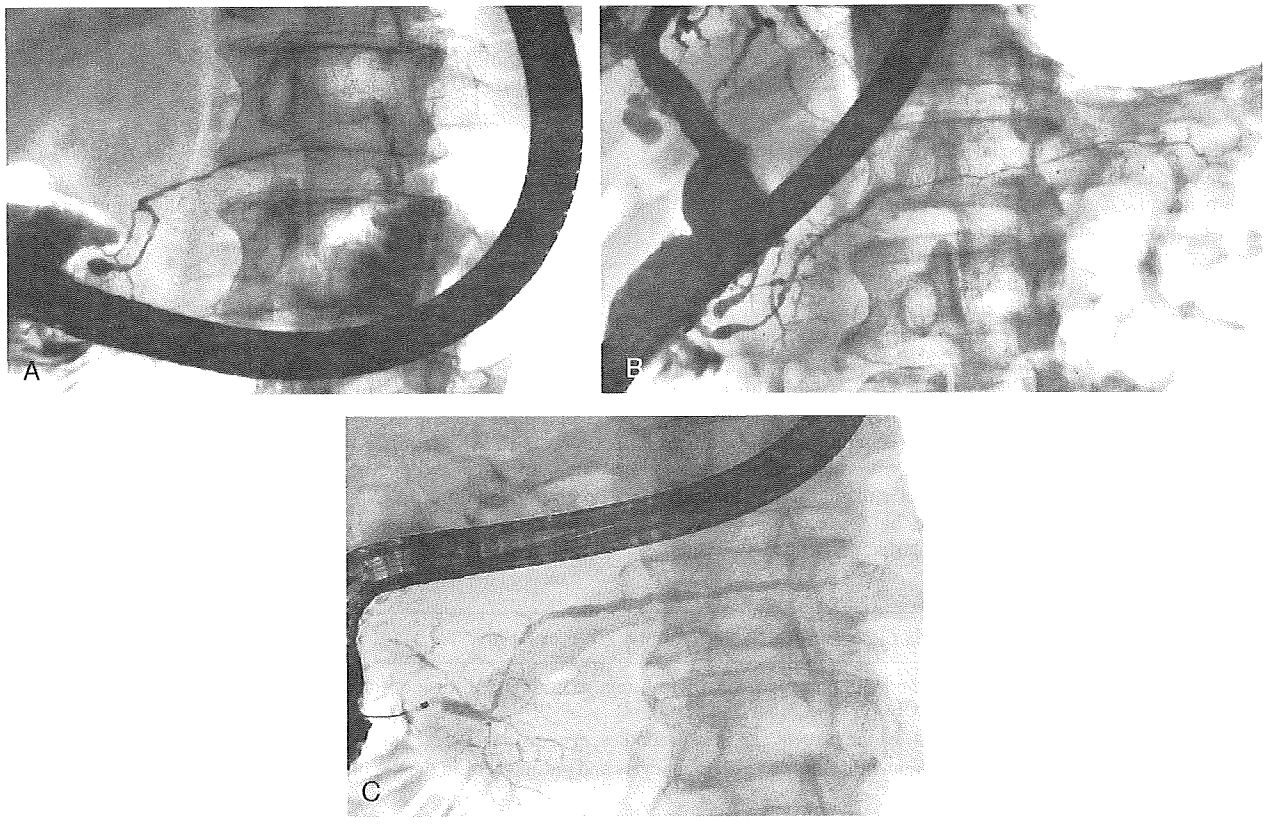

FIGURE 4. Endoscopic retrograde cholangiopancreatography images in AIP. A, Diffusely irregular narrowing of the main pancreatic duct. B, Segmental irregular narrowing of the main pancreatic duct (body to tail). C, Focal irregular narrowing of the main pancreatic duct (head).

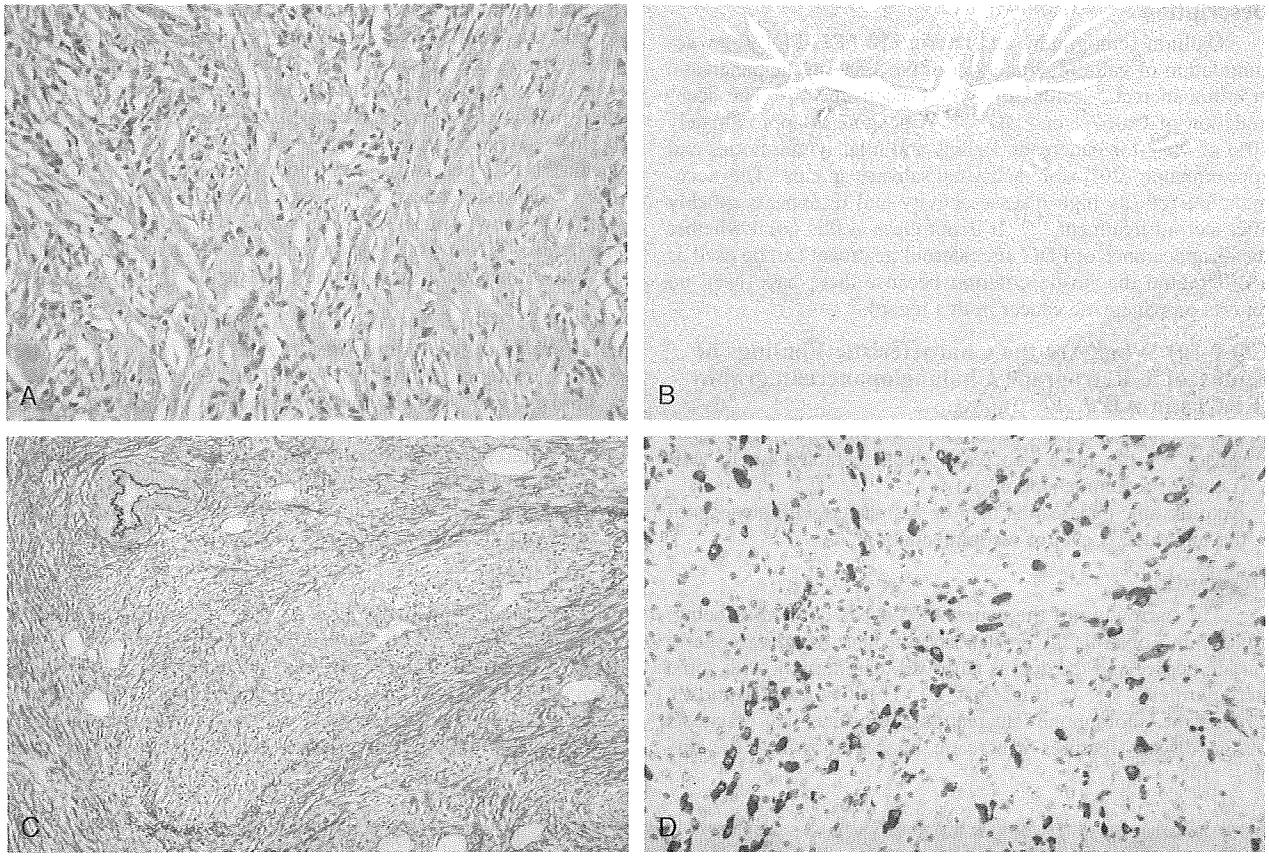

FIGURE 5. Histopathological findings in AIP: LPSP (A), circumferential inflammation of LPSP around duct epithelium (B), obliterative phlebitis (C), and numerous IgG4-positive cells in LPSP (D).

the diagnosis of AIP. Because there have been some cases reported where IgG4-positive plasma cells appear in patients with pancreatic cancer or alcoholic pancreatitis, the presence of IgG4-positive plasma cells cannot be used as the sole basis for the diagnosis of AIP.[64,67] In Europe and in the United States, another type of idiopathic pancreatitis called as IDCP or autoimmune pancreatitis with granulocytic epithelial lesions characterized by the infiltration of neutrophils into the duct epithelium has been reported.[17,18,61,64,65] A number of pathologists in Europe and in the United States believe that this type of pancreatitis should be included in AIP. However, because patients with such pancreatitis is not uncommon in younger patients or in female, can be associated with inflammatory bowel disease, and lack elevated serum level and immunohistochemical finding of IgG4, it is conceivable that this entity is different from LPSP. Thus, the diagnostic standards proposed by the Mayo Clinic clearly define that only LPSP is the AIP,[11,67] and the same concept is also adopted in Japan.[8] Further discussion is necessary to clarify the significance of this idiopathic pancreatitis with infiltration of neutrophils.

CQ-I-12) How to Diagnose AIP?

- A comprehensive diagnosis must be performed based on pancreatic image findings, serological findings, and histopathological findings. In Japan, as defined by the Clinical Diagnostic Criteria of Autoimmune Pancreatitis 2006, the diagnosis of AIP requires specific image findings, along with hematological and/or histopathological evidences. (Level of recommendation: A)
- The presence of extrapancreatic lesions may suggest the possibility of AIP. (Level of recommendation: A)

TABLE 1. Clinical Diagnostic Criteria of Autoimmune Pancreatitis 2006 in Japan

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas by imaging studies, such as abdominal US, CT, and MRI.
2. High-serum γ-globulin, IgG or IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor.
3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas.

For diagnosis, criterion 1 must be present, together with criterion 2 and/or 3.

Diagnosis of AIP is established when criterion 1, together with criterion 2 and/or 3, is fulfilled.

However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancers.

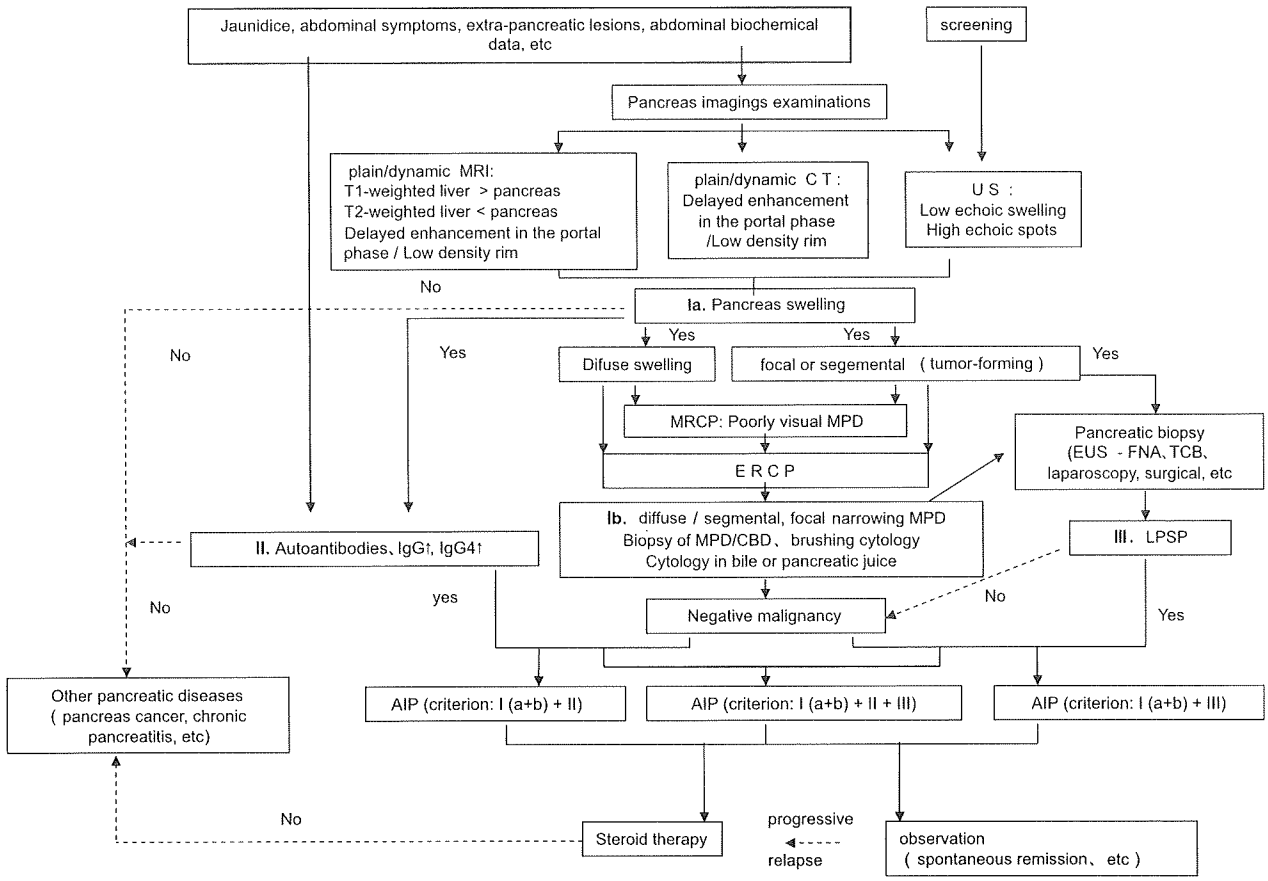

FIGURE 6. Algorithm of diagnosis and management of AIP by the Japanese diagnostic criteria 2006.

Description

The Japan Pancreas Society proposed the world's first clinical diagnostic criteria for AIP in 2002,[68] which was then revised in 2006 by the joint efforts of the Research Committee of the Intractable Pancreatic Diseases, supported by the Ministry of Health, Labor, and Welfare of Japan and the Japan Pancreas Society[2–4,8] (Table 1 and Fig. 6). The basic concepts were established on the basis of the following minimal consensus: (1) the criteria apply to the diagnosis performed by not only the pancreatic disorder specialists or gastroenterology specialists but also the general clinicians; (2) the criteria are used to distinguish and exclude malignant disorders such as pancreatic cancer or bile duct cancer as much as possible; (3) in pathology, the criteria are applied to clinical cases showing evidence of LPSP; (4) the criteria are used to diagnose pancreatic lesions, although the disease could be systemic; and (5) diagnostic trial of steroid therapy is not recommended. The decision tree for the diagnosis is based on (1) specific image findings (a mandatory requirement), along with (2) hematological and/or (3) histopathological evidence.[2–4,8,11,69]

According to the Clinical Diagnostic Criteria of Autoimmune Pancreatitis 2006, the pancreatic images specific to AIP can be confirmed retrospectively from the time of diagnosis.[8] Although some patients with pancreatic cancer show high levels of IgG4, patients with AIP show significantly higher levels of serum IgG4 with much higher rates; the diagnostic capability of IgG4 levels for AIP is high.[12,27,28,34] The diagnostic criteria for AIP have also been proposed by Korea[10] and by the Mayo Clinic of the United States.[11] The Asian diagnostic criteria were proposed jointly by researchers in Japan and Korea[12] (Table 2 and Fig. 7). Use of the response to steroid treatment as a diagnostic option is allowed to specialists only; in Japan, it is recommended that the diagnosis is performed based on the Japanese diagnostic

TABLE 2. Asian Diagnostic Criteria for AIP

Criterion I. Imaging (both required)
Imaging of pancreatic parenchyma;
Diffusely/segmentally/focally enlarged gland, occasionally with mass and/or hypoattenuation rim
Imaging of pancreatobiliary ducts
Diffuse/segmental/focal pancreatic ductal narrowing, often with the stenosis of bile duct
Criterion II. Serology (one required)
Elevated level of serum IgG or IgG4
Detected autoantibodies
Criterion III. Histopathology of pancreatic biopsy lesion
Lymphoplasmacytic infiltration in fibrosis, common with abundant IgG4-positive cell infiltration
*Option: Response to steroids
Diagnostic trial of steroid therapy could be done carefully in patients fulfilling criterion I alone with a negative workup for pancreatobiliary cancer by experts.
Diagnosis of AIP is made when any 2 criteria including criterion I are satisfied or histologic diagnosis of LPSP is present in the resected pancreas.

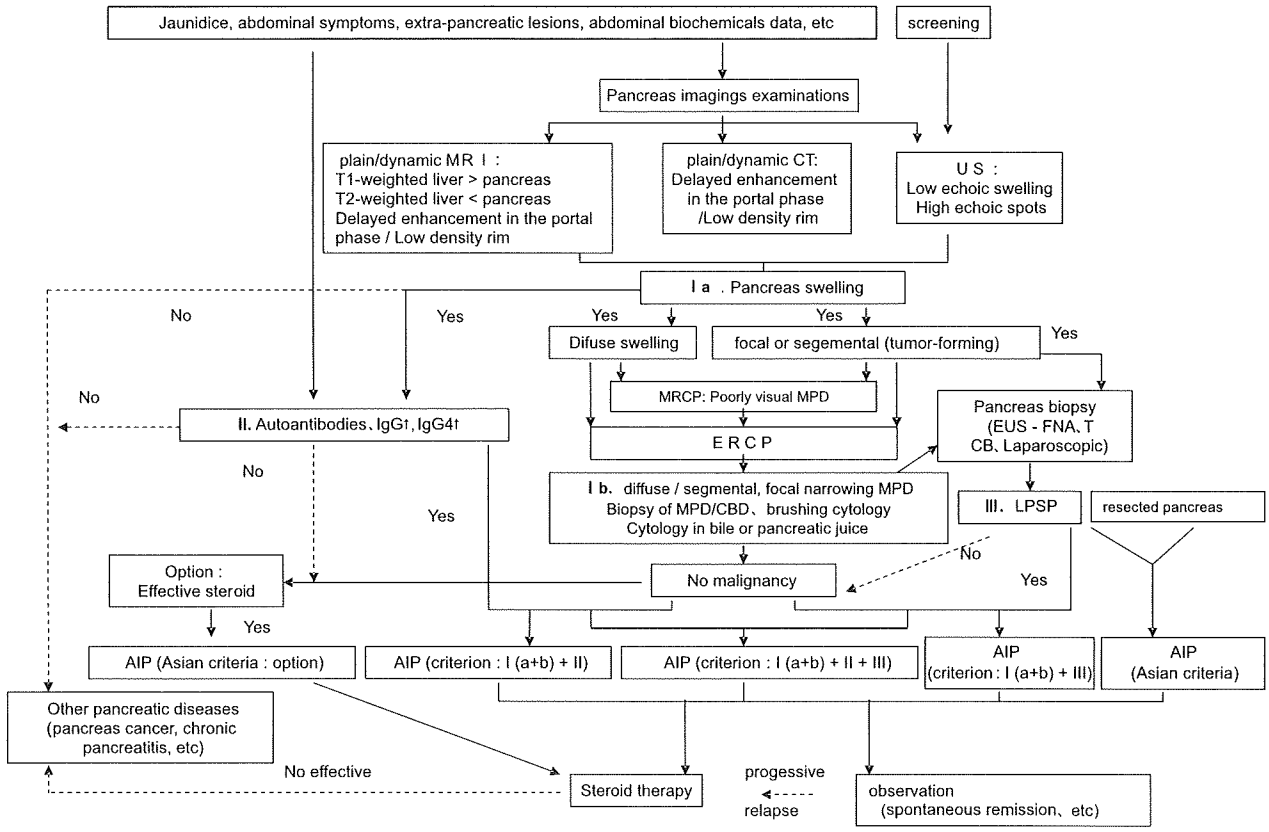

FIGURE 7. Algorithm of diagnosis and management of AIP by the Asian diagnostic criteria.

criteria 2006.[8] The differences between Japan and western countries with regard to the diagnosis of AIP are in considering the observation of ERCP images, response to steroid treatment, and extrapancreatic lesions. Although the presence of extrapancreatic lesions is not listed as a diagnostic tool in the Japanese diagnostic criteria 2006 or the Asian Diagnostic Criteria, a complete examination is important because the presence of extrapancreatic lesions may be indicative of AIP. There has been a report showing that if infiltration of IgG4-positive plasmacytes is observed in the biopsy of the duodenal papillary mucosa, the chance of the patient having AIP is high.[70]

CQ-I-13) Can the Response to Steroid Therapy Used for Diagnosis?

- If a patient responds to steroid treatment, it indicates that he/she may have AIP. However, because response to steroid treatment does not exclude the possibility of the patient having pancreatic cancer, facile diagnostic treatment is not recommended. (Level of recommendation: B)

Description

In the Japanese criteria, steroid effects on pancreatic and extrapancreatic lesions are excluded from AIP diagnosis based on the following reasons: (i) the effect of steroid treatment as diagnostic criteria for autoimmune diseases is not used except for autoimmune hepatitis; (ii) the disease that needs to be differentiated from autoimmune hepatitis is chronic hepatitis of other pathogenesis; the clinical importance of such case is different from that of AIP which needs to be differentiated from pancreatic cancer or bile duct cancer; (iii) no evidence exists to show that the use of steroids does not affect the outcome of surgery or the long-term prognosis; (iv) there is a danger that easy steroid trial may be used as an easy solution to differentiate AIP from malignant tumors such as pancreatic cancer; (v) the standards were established not only for pancreas specialists but also for general gastrointestinal internists or general practitioners; (vi) in Japan, the objective of the diagnostic criteria is not so much as to find AIP but rather to eliminate the misdiagnosis of diseases with malignant tumors as often as possible; and (vii) there have been reports of AIP associated with pancreatic cancer.[2] However, the Asian diagnostic criteria proposed by Japanese and Korean specialists in 2008[11] state that if the possibility of pancreatic cancer is excluded by a reliable exclusive-diagnosis using endoscopic US (EUS)–guided fine needle aspiration (EUS-guided FNA) or the like, the effect of steroid treatment may be used as optional diagnostic criteria. Meanwhile, there have been reports of pancreatic cancers associated with AIP (refer to treatment, prognosis CQ-IV-10 and -11). Therefore, if a patient responds to steroid treatment, it may suggest that he/she has AIP; however, it does not exclude coexistence of malignant tumors such as pancreatic cancer or biliary cancer.[2–4,69]

(II) Extrapancreatic Lesions

CQ-II-1) What Kind of Extrapancreatic Lesions Are Complicated With AIP?

- A variety of extrapancreatic lesions are reported to be complicated with AIP. Among them, a close association with lachrymal and salivary gland lesions, hilar lymphadenopathy, interstitial pneumonitis, sclerosing cholangitis, retroperitoneal fibrosis, and tubulointerstitial nephritis has been cited.

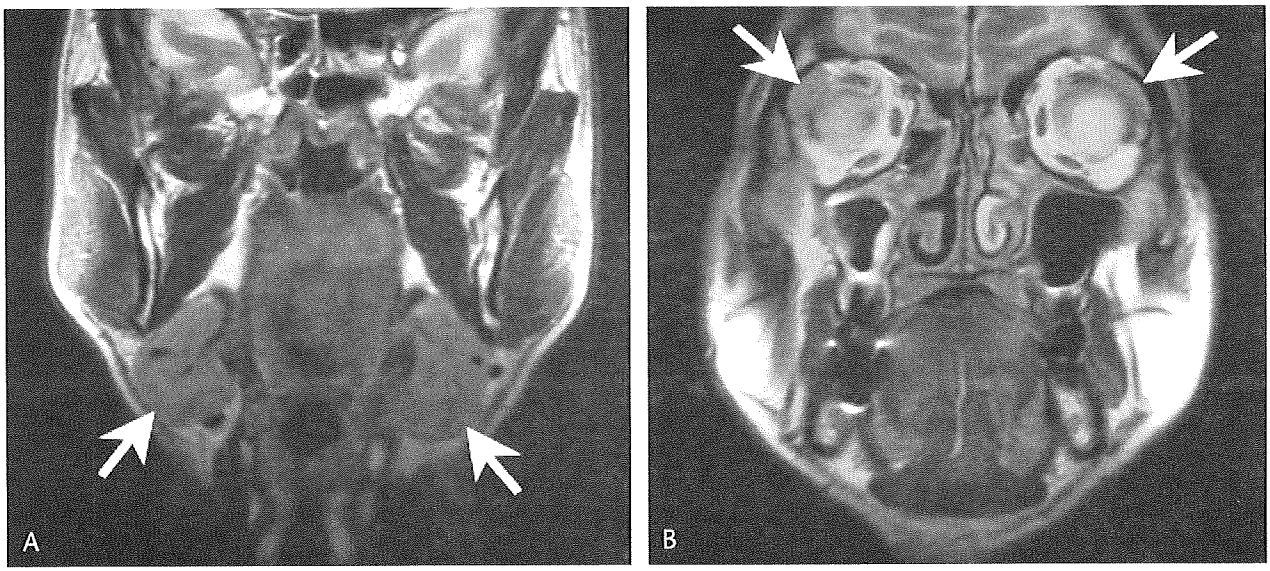

FIGURE 8. T2-weighted MRI images of the salivary gland (submandibular gland; A) and lachrymal gland (B) swellings. Arrows indicate swollen salivary and lachrymal glands. Homogeneous signal was shown in swollen submandibular gland, although vessels are recognized in it.

Description

A variety of extrapancreatic lesions are reported to be complicated with AIP, and a close association was pointed out with lachrymal and salivary gland lesions (Fig. 8),[51] hilar lymphadenopathy,[41] sclerosing cholangitis,[71,72] retroperitoneal fibrosis,[73] and tubulointerstitial nephritis.[74] These extrapancreatic lesions share the same pathological conditions and showed favorable response to corticosteroid therapy, indicating the presence of a common pathophysiological background. Furthermore, the prevalence of extrapancreatic lesions seems to extend to systemic organs (Table 3),[69,75–79] suggesting that AIP may be a member of IgG4-related systemic disease. Extrapancreatic lesions sometimes precede or occur after AIP, mimicking or being misdiagnosed with the lesions of corresponding organs. However, recognition of these extrapancreatic lesions should also aid in the correct diagnosis of AIP.

CQ-II-2) How to Diagnose Extrapancreatic Lesion?

- The diagnosis of extrapancreatic lesions complicated with AIP is based on clinical findings, which suggest close association, characteristic pathological findings, favorable response to corticosteroid therapy, and distinct differentiation from the lesions of the corresponding organ. (Level of recommendation: B)

Description

The evidences to support the association between extrapancreatic lesions and AIP are the following: (i) many reports indicating frequent or intimate co-occurrence; (ii) the pathological finding indicating severe lymphoplasmacytic infiltration and fibrosis, numerous IgG4-positive plasma cell infiltration, and obliterative phlebitis; (iii) a favorable response to corticosteroid therapy or synchronous response to therapies; and (iv) the distinct differentiation from the lesions of the corresponding organ, such as salivary gland lesion from Sjögren syndrome. Among many possible extrapancreatic lesions listed in Table 3, lachrymal and salivary gland lesion (Fig. 8), respiratory lesion (Fig. 9), sclerosing cholangitis, retroperitoneal fibrosis, and tubulointerstitial nephritis substantially fulfill these criteria.

CQ-II-3) What Are the Differences Between Lachrymal and Salivary Gland Lesions Associated With AIP and Those of Sjögren Syndrome?

- Compared with Sjögren syndrome, lachrymal and salivary gland lesions associated with AIP show normal or slightly

TABLE 3. Extrapancreatic Lesions Complicated With AIP

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
Schönlein-Henoch purpura
Autoimmune thrombocytopenia

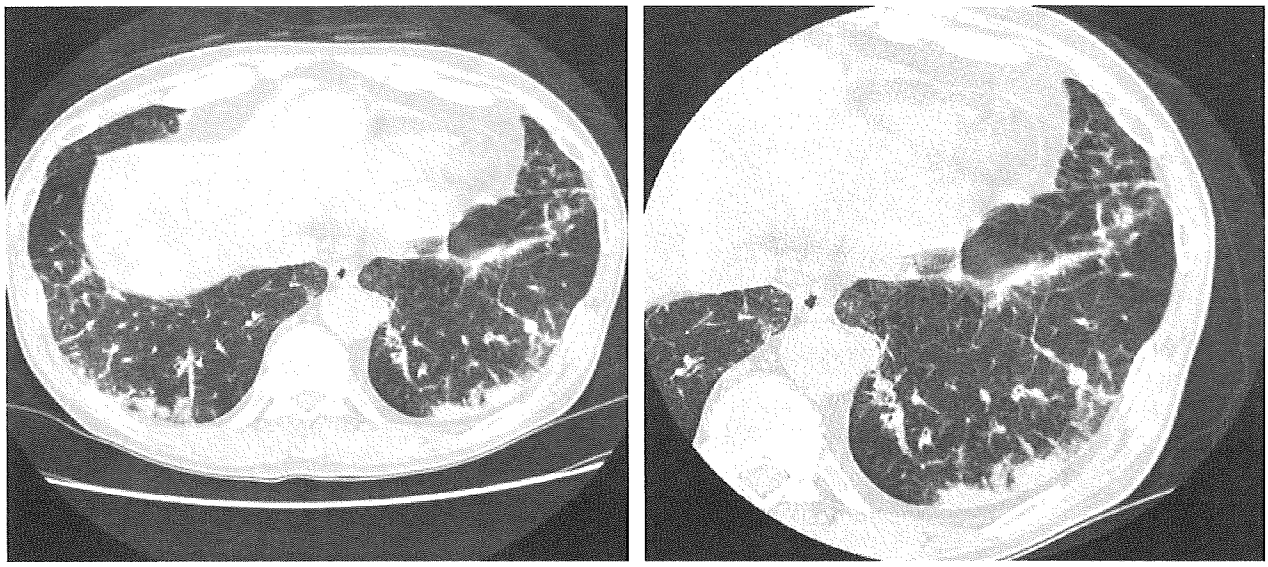

FIGURE 9. Computed tomographic scan showing various lung lesions associated with AIP, bronchial wall thickening, nodule, interlobular thickening, and infiltration.

impaired exocrine function, presenting as slight or no dry eye and mouth. (Level of recommendation: B)
- Salivary gland lesions associated with AIP show preponderance to the submandibular gland, whereas those with Sjögren syndrome were frequently seen in the parotid gland. (Level of recommendation: B)
- Compared with Sjögren syndrome, lachrymal and salivary gland lesions associated with AIP show negative results for SS-A/Ro 60 and SS-B/La autoantibodies. (Level of recommendation: B)
- Compared with Sjögren syndrome, lachrymal and salivary gland lesions associated with AIP show favorable response to corticosteroid therapy. (Level of recommendation: B)

Description

Symmetrical lachrymal and salivary gland lesions were found in approximately 14% to 39% of patients with AIP (Fig. 8)[69,78,79] and were thought to correspond to Mikulicz disease or Küttner tumor (chronic sclerosing sialadenitis).[80,81] For correct diagnosis, salivary gland biopsy is preferable, but the less-invasive lip biopsy has been substituted for the examination of small salivary gland.

CQ-II-4) What Kind of Respiratory Lesions Are Associated With AIP?

- Respiratory lesions associated with AIP include interstitial pneumonia, inflammatory pseudotumor of the lung and hilar or mediastinal lymphadenopathy. Pathological diagnosis of these lesions showed numerous IgG4-bearing plasma cell infiltration and favorable response to corticosteroid therapy and the need to be differentiated from idiopathic interstitial pneumonia, sarcoidosis, and lung tumor.

Description

Interstitial pneumonia was complicated with AIP[82–84] in approximately 8% to 13% of patients showing high serum KL-6 value and alveolar IgG4-bearing plasma cell infiltration.[83,84] Thoracic CT showed ground glass appearance in the middle and lower lung fields (Fig. 9) and honeycombing in the lower lung field. Inflammatory pseudotumor is another respiratory lesion, which corresponds to plasma cell granuloma, and is frequently misdiagnosed as lung tumor but shows favorable response to corticosteroid therapy.[85] Gallium scintigraphy disclosed hilar and mediastinal lymphadenopathy in 67%,[41] which mimic sarcoidosis but show normal serum angiotensin-converting enzyme levels.

CQ-II-5) How to Differentiate Between Sclerosing Cholangitis Associated With AIP and PSC or Biliary Malignancies?

- The differentiation between sclerosing cholangitis associated with AIP and PSC or biliary malignancies should be done carefully and based collectively on the clinical features, image tests such as cholangiography, US, EUS, intraductal ultrasonography (IDUS), CT, and MRI, and pathological findings. (Level of recommendation: A)

Description

Sclerosing cholangitis associated with AIP (SC with AIP) is widely distributed in the biliary system.[85] Lower bile duct lesions need to be differentiated from pancreatic cancer or common bile duct cancer, whereas intrahepatic and hilar bile duct lesions need to be differentiated from primary PSC and cholangiocarcinoma, respectively.

Sclerosing cholangitis associated with AIP showed preponderance among elderly males and are frequently complicated with obstructive jaundice, whereas PSC was found more commonly in young and middle-aged patients and was sometimes complicated with inflammatory bowel diseases.[21–23] Cholangiography of SC with AIP showed lower bile duct stenosis and relatively long stricture from the hilar to intrahepatic biliary systems with simple distal dilatation,[86,87] whereas those of PSC showed characteristic findings of bandlike stricture (short stricture within 1–2 mm), beaded appearance, pruned tree appearance, and diverticulum-like out-pouching (Fig. 10).[53,86,87] Ultrasonography of SC with AIP showed wall thickness of intrahepatic or extrahepatic bile ducts. Pathological findings of bile duct wall in SC with AIP showed similar findings to the pancreatic tissue.[56,66,88] Inflammatory changes were found in the whole layer of bile duct wall in SC with AIP, but those of PSC

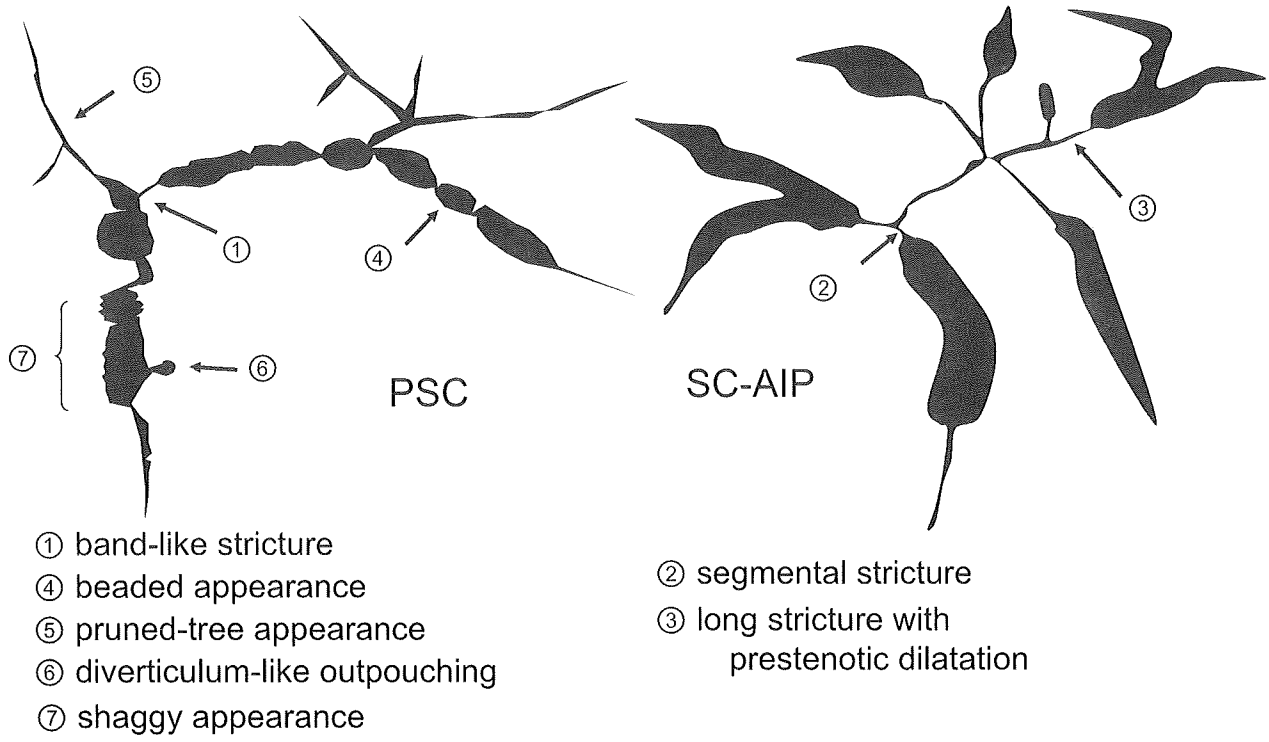

FIGURE 10. Comparison of characteristic cholangiogram between AIP and PSC.

were predominantly found at the inner portion with only slight changes at the outer portion. Liver biopsy showed numerous IgG4-bearing plasma cell infiltrations at portal area in SC with AIP, but only few in PSC.[56,66,87–89] Sclerosing cholangitis associated with AIP sometimes showed slight or no pancreatic lesions, resulting in the misdiagnosis of PSC.[90–92]

Sclerosing cholangitis associated with AIP showing localized bile duct stenosis needs to be differentiated from bile duct cancer.[93,94] IgG4-positive plasma cell infiltration found in the bile duct wall supports the diagnosis of SC with AIP.[90,91] Characteristic IDUS findings will help the differentiation between 2 conditions (refer to CQ-II-1 to -6).

CQ-II-6) What Are the Characteristic IDUS Findings of Sclerosing Cholangitis Associated With AIP?

- Lower bile duct stenosis associated with AIP is caused by 2 mechanisms: (1) extrinsic compression by swollen pancreas head and (2) wall thickness of bile duct.
- Upper bile duct changes were predominantly seen in the hilar to intrahepatic bile duct system, for which IDUS showed thickening of the inner hypoechoic zone. IDUS sometimes showed wall thickening of the bile duct whereas cholangiography showed normal findings. (Level of recommendation: B)

Description

Sclerosing cholangitis associated with AIP consists of lower and upper bile duct stenosis. Lower bile duct stenosis was caused by 2 mechanisms, namely, extrinsic compression by swollen pancreatic head and wall thickening of bile duct. In contrast with bile duct cancer, IDUS of SC with AIP showed concentric wall thickening showing delayed enhancement by levovist.[35,95] Upper bile duct changes were predominantly seen in the hilar to intrahepatic bile duct system—these changes mimic those seen in PSC, for which IDUS showed thickness of inner hypoechoic zone. Although differentiation by IDUS alone is difficult, IDUS changes seen in PSC showed slightly hyperechoic, scarce luminal dilatation, and irregular surface. In contrast with bile duct cancer, IDUS of SC with AIP commonly showed preservation of outer hyperechoic zone and sometimes showed thickening of the bile duct wall where cholangiography showed normal findings.

(III) Differential Diagnosis

CQ-III-1) What Are the Useful Clinical Symptoms or Findings in Differentiating Between AIP and Pancreatic Cancer?

- Useful clinical findings in differentiating between AIP and pancreatic cancer include abdominal pain, body weight loss, obstructive jaundice, and extrapancreatic lesions. (Level of recommendation: B)

Description

Abdominal pain in pancreatic cancer is severe, persistent, and progressive, sometimes requiring narcotics, whereas that in AIP is mild.[1,2,8,19,22,96,97] Body weight loss is frequently seen in pancreatic cancer, whereas it is rarely seen in AIP. Jaundice in pancreatic cancer is progressive, but that in AIP fluctuates or sometimes subsides spontaneously and responds well to corticosteroid therapy.[1,2,8,19,22,96,97] Various extrapancreatic lesions were complicated with AIP,[1,2,8,19,22,96,97] whereas apparent extrapancreatic lesions seen in pancreatic cancer were restricted to lower bile duct stenosis, metastatic lesions, or direct invasions.

CQ-III-2) Does High Serum IgG4 Concentration Rule Out the Possibility of Pancreatic Cancer?

- IgG4 is the best marker in sensitivity, specificity, and accuracy in differentiating between AIP and pancreatic cancer, but a few patients with pancreatic cancer have been reported to

TABLE 4. Comparison of Various Markers in the Differentiation Between AIP and Pancreatic Cancer (PC) Using Identical Sera

	Sensitivity, % (AIP n = 100)	Specificity, % (vs PC n = 80)	Accuracy, % (vs PC)
IgG4	86	96	91
IgG	69	75	72
ANA	58	79	67
RF	23	94	54
IgG4 + ANA	95	76	87
IgG + ANA	85	63	75
IgG4 + IgG + ANA	95	63	81
IgG4 + RF	90	90	90
IgG + RF	78	73	76
IgG4 + IgG + RF	91	71	82
ANA + RF	69	60	78
IgG4 + ANA + RF	97	73	86
IgG + ANA + RF	91	61	78
IgG4 + IgG + ANA + RF	97	61	81

ANA indicates antinuclear antibody; RF, rheumatoid factor.

show high serum IgG4 concentrations, suggesting that high serum IgG4 concentration cannot rule out the presence of pancreatic cancer. (Level of recommendation: B)

Description

Comparison of various markers in differentiating between AIP and pancreatic cancer using identical sera showed that the best results are obtained using IgG4, which shows 86% sensitivity, 96% specificity, and 91% accuracy (Table 4).[19] IgG4 was therefore adopted as the best marker in the Japanese diagnostic criteria 2006.[8] Furthermore, numerous IgG4-bearing plasma cell infiltrations in the pancreatic tissue is a diagnostic hallmark.[73] However, serum IgG4 elevation or numerous IgG4-bearing plasma cell infiltrations have been reported to be also found in a few patients with pancreatic cancer.[97]

CQ-III-3) What Are Useful CT and MRI Findings in Differentiating Between AIP and Pancreatic Cancer?

- Characteristic CT and MRI findings of AIP are smooth margin and capsule-like rim. (Level of recommendation: A)
- Contrast-enhanced CT often shows delayed enhancement in pancreatic lesions of both AIP and pancreatic cancer. However, contrast-enhanced images are generally homogeneous in AIP but heterogeneous in pancreatic cancer; this distinction should aid in the differentiation of these conditions. (Level of recommendation: B)
- T1-weighted MRIs of AIP showed a low signal intensity for pancreatic parenchyma lesions. (Level of recommendation: B)
- T2-weighted MRIs of AIP sometimes showed the main pancreatic duct clearly penetrating through the mass lesion (duct-penetrating sign, which was not found in the AIP-localized swelling in AIP, was sometimes difficult to differentiate from that in pancreatic cancer), but it showed marked amelioration after corticosteroid therapy. (Level of recommendation: A)

Description

One characteristic CT and MRI finding of the pancreas margin in AIP is a capsule-like rim,[39,98,99] which is prominent at the body and tail region and represents severe fibrotic changes. A CT scan and MRI of an aged pancreas showed a lobulated margin and cobblestone-like texture, whereas those of AIP showed a smooth margin probably because it is in its early stage. Contrast-enhanced CT showed delayed homogeneous enhancement in pancreatic lesions, which represented widespread loss of parenchyma and severe fibrosis. That of pancreatic cancer also showed delayed enhancement in heterogeneous pattern, reflecting necrosis or bleeding in the tumor.[98] Fat-suppressed T1-weighted MRIs of a normal pancreas showed a high signal intensity compared with those of the liver, whereas those of AIP showed decreased signal, reflecting loss of normal parenchyma. T2-weighted MRIs of AIP generally showed a high signal intensity, reflecting severe lymphoplasmacytic infiltration. T2-weighted MRIs of AIP sometimes showed the main pancreatic duct clearly penetrating through the mass lesion (duct-penetrating sign), which was useful for differentiation.[100] Like ERCP, MRCP also shows narrowing of the main pancreatic duct without distal dilatation in AIP but prominent dilatation in pancreatic cancer.

CQ-III-4) What Are Useful EUS Findings in Differentiating Between AIP and Pancreatic Cancer?

- Typical EUS findings of AIP are relatively diffuse homogeneous hypoechoic pattern and linear or reticular (tortoiseshell pattern) hyperechoic inclusions. (Level of recommendation: B)
- Compared with chronic pancreatitis, pancreatic parenchyma of AIP showed a homogeneous hypoechoic pattern, but EUS findings characteristic of chronic pancreatitis (such as heterogeneous texture, lobular out gland margin, calcification, and hyperechoic ductal margin) were scarcely found. (Level of recommendation: B)
- Localized mass of AIP also showed hypoechoic pattern and linear or reticular (tortoiseshell pattern) hyperechoic inclusions, and the duct-penetrating sign aids in the differentiation from pancreatic cancer. (Level of recommendation: B)
- Endoscopic US–FNA has a diagnostic utility in the exclusion of pancreatic cancer rather than in the final diagnosis of AIP. (Level of recommendation: B)

Description

Endoscopic US of AIP generally showed a diffuse hypoechoic pattern,[40,101–104] whereas that of chronic pancreatitis showed a heterogeneous echo pattern. Hyperechoic inclusions are found in both conditions, but those in AIP are seen less frequently and present characteristically as linear or reticular patterns against the hypoechoic background. Lobular out gland margin, hyperechoic ductal margin, calcification, and cyst were generally found in cases of chronic pancreatitis but were scarcely found in the case of AIP. A localized mass of hypoechoic pattern was found in both AIP and pancreatic cancer, but linear or reticular (tortoiseshell pattern) hyperechoic inclusions (Fig. 11A), and duct-penetrating sign (Fig. 11B) are generally found only in AIP. Although lymph node swelling or vascular invasion were observed in the case of pancreatic cancer, differentiation between the 2 conditions is sometimes difficult and needs EUS-FNA.[105] Endoscopic US–FNA has a diagnostic utility in the exclusion of pancreatic cancer.[106,107]

CQ-III-5) What Are Useful Pathological Findings for the Differentiation Between AIP and Pancreatic Cancer?

- Histological identification of carcinoma cells is a hallmark for the diagnosis of pancreatic cancer. (Level of recommendation: A)

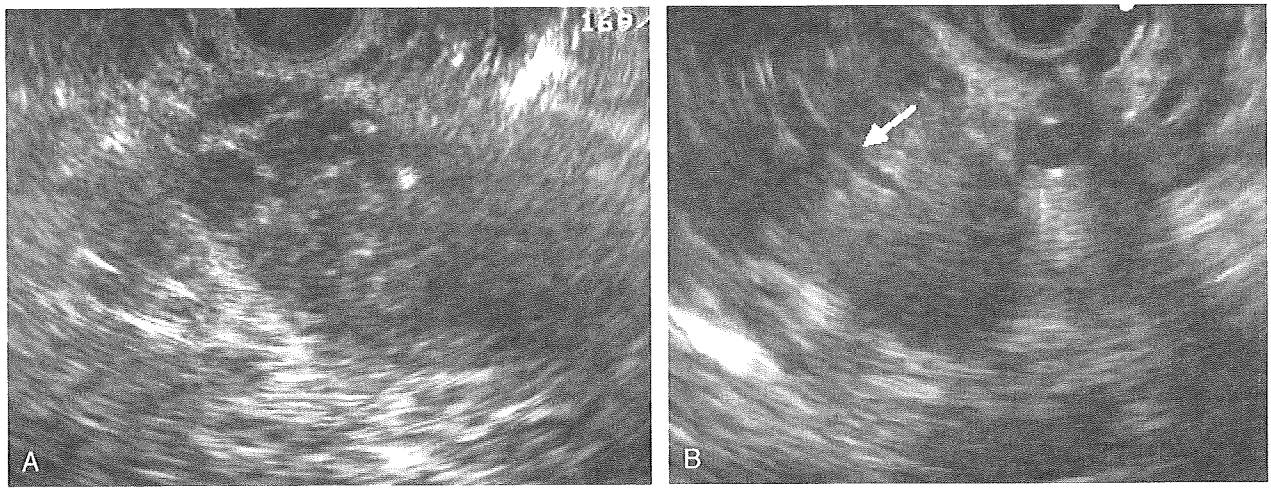

FIGURE 11. A, Endoscopic sonogram of AIP showing localized mass of hypoechoic pattern with linear or reticular (tortoiseshell pattern) hyperechoic inclusions. B, Endoscopic sonogram of AIP showing duct-penetrating sign.

- Inflammatory reactions can be commonly observed around pancreatic cancer. (Level of recommendation: A)
- Neutrophilic infiltrates, lobules with inflammatory infiltrates and edema, proliferation of plump fibroblasts, and lymphocyte-predominant infiltrates with scarce plasma cells are more common in pancreatic cancer than in AIP, and these findings should not be regarded solely as diagnostic for AIP. (Level of recommendation: B)

Description

Pathological diagnosis of pancreatic cancer can be confirmed by histological identification of carcinoma cells. This is usually easy with resected specimens. However, it is common to observe inflammatory reactions around pancreatic cancer, and interpretation of biopsy specimens with inflammatory changes should be done carefully to correctly diagnose AIP. Neutrophilic infiltrates, lobules with inflammatory infiltrates and edema, proliferation of plump fibroblasts, and lymphocyte-predominant infiltrates with scarce plasma cells are more common in pancreatic cancer than in AIP, and these findings should not be regarded solely as diagnostic for AIP. In addition, lymphoid follicles are commonly seen in both pancreatic cancer and AIP and should not be regarded as a diagnostic hallmark of AIP.[16]

CQ-III-6) Can the Histological Features That Characterize AIP Be Seen in Pancreatic Cancer?

- In rare cases, reaction around pancreatic cancer histologically resembles AIP (LPSP). (Level of recommendation: B)
- Numerous IgG4-positive plasma cells can be occasionally identified in pancreatic cancer. (Level of recommendation: B)

Description

Rare pancreatic cancers reveal histological features that resemble AIP.[108,109] In addition, numerous IgG4-positive plasma cells are occasionally identified in pancreatic cancer.[64,67,110]

(IV) Therapy and Prognosis of AIP

CQ-IV-1) Do AIP Patients Improve Spontaneously?

- Some AIP patients improve spontaneously. (Level of recommendation: B)

Description

Swelling of the pancreas or irregular narrowing of the main pancreatic duct improves spontaneously without steroid therapy in some AIP patients. It has been reported that most AIP cases that improved spontaneously did not have bile duct stenosis.[111,112] According to Kamisawa et al,[111] spontaneous improvement was detected in 2 of 21 nonjaundiced AIP patients. Kubota et al[112] compared the clinicopathological parameters in 8 AIP patients with remission in the absence of steroid therapy and 12 patients with remission after steroid therapy, and they found an association between remission in the absence of steroid therapy and seronegativity for IgG4, absence of obstructive jaundice, absence of diabetes mellitus, and the presence of focal pancreatic swelling.

CQ-IV-2) What Are the Indications for Steroid Therapy in AIP Patients?

- The indications for steroid therapy in AIP patients are symptoms such as obstructive jaundice, abdominal and back pain, and the presence of symptomatic extrapancreatic lesions. (Level of recommendation: A)

Description

Steroid therapy is effective for extrapancreatic lesions such as sclerosing cholangitis as well as the pancreatic lesion in AIP. Autoimmune pancreatitis is frequently associated with stenosis of the bile duct due to sclerosing cholangitis, and obstructive jaundice is a frequent initial symptom. Obstructive jaundice is the principal indication for steroid therapy. Patients with AIP rarely have the severe abdominal pain that occurs in acute pancreatitis, but persistent abdominal or back pain in AIP seems to be an indication for steroid therapy. Associated symptomatic extrapancreatic lesions, such as retroperitoneal fibrosis, interstitial pneumonia, tubulointerstitial nephritis, and hepatic or pulmonary pseudotumor, are indications for steroid therapy. In principle, steroid therapy should be performed for patients with a diagnosis of AIP, but a facile steroid trial to differentiate AIP from pancreatic cancer should be prohibited.[113]

CQ-IV-3) How Do We Perform Initial Steroid Therapy?

- Before steroid therapy, jaundice should be managed by biliary drainage in patients with obstructive jaundice, and blood glucose levels should be controlled in patients with diabetes mellitus. For the initial oral prednisolone dosage for induction of remission, 0.6 mg/kg per day is recommended. The initial

dose is administered for 2 to 4 weeks and is then gradually tapered. (Level of recommendation: B)

Description

Before steroid therapy, it is important to distinguish AIP from pancreatic or biliary cancer with imaging studies and endoscopic approaches.

In cases with obstructive jaundice due to bile duct stenosis, endoscopic or transhepatic biliary drainage should be performed. Cytological examination of the bile is performed repeatedly. Steroid therapy can be started without biliary drainage in cases with mild jaundice. Blood glucose levels should be controlled in patients with diabetes mellitus before steroid therapy.[31]

Because there was no correlation between the degree of morphological improvement of the pancreatic and bile ducts and the initial prednisolone dosage (30 and 40 mg/d), it is recommended that the initial oral prednisolone dosage is 0.6 mg/kg per day, and it is gradually tapered after 2 to 4 weeks of administration[114] (Fig. 12).

CQ-IV-4) How Is the Dose of Steroid Tapered?

- After 2 to 4 weeks at the initial dose, the dose is tapered by 5 mg every 1 to 2 weeks on the basis of the changes in the clinical manifestations, biochemical blood test results (such as liver enzymes and IgG or IgG4 levels), and repeated imaging findings (US, CT, MRCP, ERCP, etc). The dose is tapered to a maintenance dose during a period of 2 to 3 months. (Level of recommendation: B)

Description

The initial dose is tapered gradually to a maintenance dose, usually 5 to 10 mg/d, during a period of 2 to 3 months (Fig. 12). Because radiological improvement appears 1 to 2 weeks after the start of steroid therapy, morphological and serological evaluations for effectiveness of steroid therapy should be performed 1 to 2 weeks after starting steroid therapy. A poor response to steroid therapy should raise the possibility of pancreatic cancer and the need for rediagnosis.

CQ-IV-5) Is Maintenance Steroid Therapy Necessary?

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

Description

Autoimmune pancreatitis relapsed in 18%[115] to 32%[116] of cases treated with maintenance therapy and in 53% of cases without maintenance therapy.[90] Because anti-inflammatory and immunosuppressive effects of steroid seem to suppress the activity of AIP, maintenance steroid therapy seems to be effective in preventing AIP relapse.

CQ-IV-6) When Should Steroid Therapy Be Discontinued?

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

Description

There is no consensus about the duration of steroid therapy in AIP patients. According to Kamisawa et al,[115] steroid medication was stopped for an average of 19.5 months after the start of steroid therapy in 9 patients with complete morphological and serological resolution, and none of these patients had relapse.

Maintenance therapy is effective in preventing relapse. However, because AIP patients are typically elderly and are at high risk of developing steroid-related complications such as osteoporosis and diabetes mellitus, cessation of the medication should be tried. Stopping of maintenance therapy should be planned within at least 3 years in cases with radiological and serological improvement. After stopping medication, patients should be followed up for relapse of AIP.

CQ-IV-7) Is Early Prediction of AIP Relapse Possible?

- Conditions accompanying a relapse of AIP include pancreatic enlargement on imaging, elevated serum IgG4 levels, elevated serum hepatobiliary and pancreatic enzymes, reappearance of extrapancreatic lesions, elevated soluble interleukin 2 receptor or immune complex, and consumption of complement. (Level of recommendation: B)

Description

It is unclear whether it is possible to predict early AIP relapse based on these findings.

CQ-IV-8) How Are AIP Relapses Treated?

- Readministration or dose-up of steroid is effective for treating AIP relapses. (Level of recommendation: B)
- Remission can be effected with the same prednisolone dose as the initial dose in most relapsed AIP cases, but it may be necessary to taper more gradually. (Level of recommendation: B)

Description

Remission can be effected with readministration or dose-up of steroid in most relapsed AIP cases. According to Kamisawa et al,[5,113] 4 AIP patients who relapsed during maintenance therapy entered remission with dosage-up (30 mg/d) of steroid. Nishino et al[30] reported that bile duct stenosis relapsed in 1 patient and swelling of the salivary glands relapsed in 3 patients during steroid tapering, but they improved with dose-up steroid. They also tapered steroid more gradually in relapsed cases.[30]

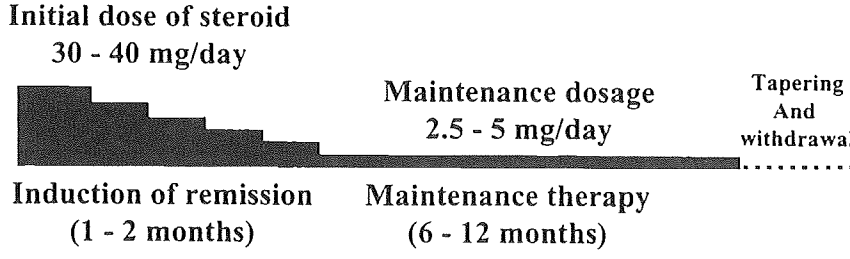

FIGURE 12. Regimen of oral steroid therapy for AIP.[30]