資 料

自己免疫性膵炎とIgG4関連硬化性胆管炎の診断における内視鏡の役割

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要 旨

自己免疫性膵炎（AIP）は膵臓癌と，IgG4関連硬化性胆管炎（IgG4-SC）は胆管癌や原発性硬化性胆管炎（PSC）との鑑別を要する．主膵管の長い狭細像，狭細部の上流主膵管の軽度拡張，スキップした狭細像，狭細部からの分枝膵管の派生などの膵管像は，膵臓癌よりAIPを示唆する．短い狭窄（band-like stricture），数珠状変化（beaded appearance），肝内胆管の減少（pruned-tree appearance）や憩室様突出（diverticulum-like outpouching）などのPSCで見られる特徴的な胆管像の変化は，IgG4-SCではほとんど見られない．一方，胆管の長い狭窄後の拡張所見はIgG4-SCに良く見られる．胆管狭窄部の経乳頭的生検は，胆管癌を否定し，IgG4免疫染色によりIgG4-SCの補助診断に有用である．主乳頭からの生検組織のIgG4免疫染色は，AIPの診断を補助する．造影超音波内視鏡（EUS）と超音波内視鏡下エラストグラフィーは，病変の組織学的本質を予測する可能性を持つ．管腔内超音波検査による胆管造影で狭窄のない胆管における胆管壁の肥厚所見は，IgG4-SCを胆管癌と鑑別するのに有用である．超音波内視鏡下穿刺吸引法（EUS-FNA）は，膵臓癌を否定するために広く使われている．AIPの組織学的診断に足りうるだけの十分な量の組織を採取するには，EUS下のTru-cut生検や19ゲージの穿刺針を用いたEUS-FNAが推奨される．しかし，22ゲージの穿刺針を用いたEUS-FNAでも，取集後の注意深い検体処理と膵臓内でのFNA針の素早い動作により十分な量の組織を採取することができる．内視鏡所見の検証と内視鏡的に採取した組織による診断能を高める新しい技術やデバイスの開発が求められる．

Key words 自己免疫性膵炎／慢性膵炎／内視鏡科穿刺吸引法（EUS-FNA）／免疫グロブリンG4／硬化性胆管炎

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I はじめに

自己免疫性膵炎（AIP）とIgG4関連硬化性胆管炎（IgG4-SC）は，IgG4関連疾患の膵胆道病変として最近認知されている[1),2)]．AIPとIgG4-SCは膵胆道の悪性腫瘍より稀な疾患であるが，臨床的には悪性腫瘍と類似した所見を呈する．AIPは，

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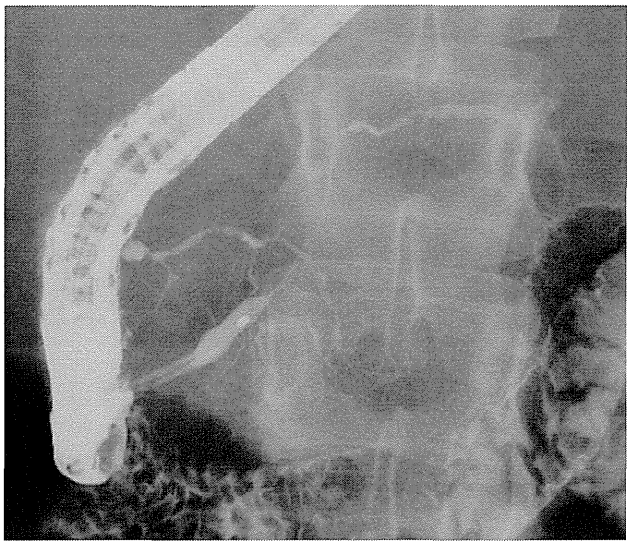

Figure 1　AIP 患者における主膵管狭細像を示す ERP 像．副膵管が狭細部から派生し，狭細部の上流の膵管の拡張は軽度である．

膵臓癌との鑑別が必要である．肝内および肝門部胆管の IgG4-SC は，肝門部胆管癌や原発性硬化性胆管炎（PSC）と鑑別しなければならない．両疾患ともステロイドが劇的に奏効するので，不要な手術を避けるためにも適切な診断が重要である[1),3),4)]．

内視鏡医は，両疾患の評価と治療において重要な役割を果たす．内視鏡的逆行性膵胆管造影（ERCP）は，胆道ステントによる胆汁うっ滞の解除，造影や生検の目的でしばしば施行される．超音波内視鏡下穿刺吸引法（EUS-FNA）は，確定診断と悪性の否定において重要な役割をなす．

第 86 回日本消化器内視鏡学会総会（藤田直孝会長）中に，「IgG4 関連疾患と内視鏡」の国際セッションが行われた．AIP と IgG4-SC の診断における内視鏡の役割に関していくつかの重要なトピックスが議論された．AIP と IgG4-SC の診断における内視鏡に役割に関するこの総説は，そのセッションの司会者 2 名とパネリスト 3 名により共同執筆された．

Ⅱ　内視鏡的逆行性膵胆管造影（ERCP）

主膵管の不整狭細像は，AIP の特徴的な膵管像である．び漫性の主膵管の不整狭細像は AIP にかなり特異的な所見であるが，限局性の主膵管の狭細像は膵臓癌によって生じる主膵管の狭窄との鑑別がしばしば困難である．膵臓癌の典型的な膵管像は，上流膵管の著明な拡張を伴う主膵管の 1 カ所に限局した狭窄である．一方，主膵管の非閉塞，主膵管全体の三分の一以上の長い狭細像，上流膵管の拡張が 5 mm 未満，スキップして存在する主膵管狭細像，狭細部からの分枝膵管の派生などは，AIP により良く見られる所見である（Figure 1）[5)~7)]．AIP では，リンパ球と形質細胞の浸潤は基本的に膵管の上皮下に生じて，膵管上皮は通常保たれているが，典型的な膵癌は膵管上皮に浸潤して破壊して，膵管閉塞を起こす．これらの膵管周囲における病理組織学的な所見の違いにより，AIP と膵癌における膵管像の差違が説明できると思われる[5)~7)]．AIP と膵臓癌の鑑別における有用性より，膵管像所見は AIP の国際コンセンサス診断基準（ICDC）[8)] と本邦の診断基準 2011[9)] において重要な役割を果たしている．しかし，CT で後期相での造影効果を示すび漫性の膵腫大の典型的所見を呈する例においては，カプセル様リムの所見の有無にかかわらず，内視鏡的逆行性膵管造影（ERP）から得られる追加の所見は少ないので，これらの診断基準では ERP は不要としている．ブラッシングの有無にかかわらず，膵液細胞診は AIP と膵臓癌との鑑別に有用である．

IgG4-SC は，AIP に最も高頻度に認められる他臓器病変である[1)]．AIP に合併した IgG4-SC の多くは下部胆管狭窄を呈するが，狭窄は胆管のどの部位にも起こりうる．特徴的な胆管像は，IgG4-SC と PSC の鑑別に役立つと思われる．短い狭窄（band-like stricture），数珠状変化（beaded appearance），肝内胆管の減少（pruned-tree appearance）や憩室様突出（diverticulum-like outpouching）などの PSC で見られる胆管像の変化は，IgG4-SC ではほとんど見られない．一方，胆管の長い狭窄後の拡張所見は IgG4-SC に良く見られる[4),10),11)]．胆管像では，IgG4-SC と肝門部胆管癌との鑑別は困難である．ERCP の際に胆管狭窄に対して経乳頭的生検が行われるが，採取される組織が小さいのでその評価は難しい．IgG4 免疫染色は，IgG4-SC の組織学的診断を補助する．経乳頭的生検組織の IgG4 免疫染色による IgG4-SC と悪性との鑑別の感度は 18-88％と報告されているが[12)~15)]，多数の IgG4 陽性形質細胞浸潤を胆管癌[13)] と PSC[15)] 各 1 例の胆管生検組織において認めた．肝門部胆管癌における経乳頭的生検の胆管狭窄部の診断能は 53％と報告されており[16)]，生検は

IgG4-SCから胆管癌を除外するのに有用と思われる．IgG4-SC患者における最も高頻度にみられる経口胆道鏡所見は，拡張蛇行した血管を認める点と，部分的に太くなった血管がない所見であり，経口胆道鏡はIgG4-SCとPSCや胆管癌との鑑別に有用である[17]．

Ⅲ 主乳頭からの生検組織のIgG4染色

十二指腸主乳頭は，解剖学的に総胆管と主膵管の合流する部位に存在するので，主乳頭は膵頭部の炎症が波及することにより，しばしばAIPの病巣に含まれる．主乳頭は，AIP患者の41-65%で腫大すると報告されている[18)~20)]．主乳頭から生検された組織におけるIgG4陽性形質細胞の密な浸潤は，AIP患者の53-80%において認められたと報告されている[19)~22)]．主乳頭の組織のIgG4免疫染色の陽性所見は他の膵胆道疾患ではほとんど見られないので，主乳頭からの生検組織のIgG4免疫染色は，AIPの診断の補助になりうる[19)~22)]．主乳頭の内視鏡的生検は，簡便で安全な方法として，ICDC[8)]でも推奨されている．

Ⅳ 超音波内視鏡検査（EUS），造影超音波内視鏡検査（造影EUS），超音波内視鏡下エラストグラフィー（EUS下エラストグラフィー）

AIPの典型的な超音波内視鏡（EUS）像は，びまん性の膵腫大を示し，内部は均一な低エコーで線状または網状高エコーを伴う[23)~27)]．多くの症例では，主膵管の拡張はみられない．一方，慢性膵炎でみられる膵実質の不均一構造，分葉状の辺縁像，石灰化および高輝度の膵管像などの所見がみられることは少ない[26),28)]．

AIPでは，線状または網状高エコーを伴う限局性の低エコー腫瘤像を示すことがある．その腫瘤内を膵管が貫通する所見（duct penetrating sign）は膵癌との鑑別に有用である[26)]．Hokiら[28)]は，びまん性膵腫大，びまん性の低エコー所見，胆管壁の肥厚および膵辺縁の低エコー帯は膵癌に比較してAIPにより高頻度に認められ，限局性の膵腫大や限局的な低エコー所見はAIPより膵癌に多くみられると報告している．しかし，時折AIPにおいて，膵癌を含む他の膵疾患でみられる所見を認めることがあり，鑑別診断に苦慮する[23),25)]．そのため，AIPの診断をより正確かつ確実にするために，最近では造影超音波内視鏡検査や超音波内視鏡下エラストグラフィーなどの新たなEUSの診断技術が応用されている[25),29),30)]．

造影EUSにより，正常または病的組織における血管分布と血流に関するより多くの情報を得ることができる[30)~32)]．造影剤によりドップラー信号が増強し，微細血管が可視化されるため，造影EUSは種々の膵疾患の鑑別診断において，通常のEUSに比較してより高い有効性を示すことが報告されている[25),29),31)~33)]．造影EUSでは，AIPは膵辺縁に血管に富む多血性の所見を呈するが，膵癌は血管に乏しい乏血性の所見を示す[31),33)]．

エラストグラフィーは，組織の硬さを画像化してその違いを明らかにする技術であり，正常または病的な組織の評価を容易にする[29),34)~36)]．膵腫瘤の診断におけるEUS下エラストグラフィーの正診率を検討した報告では，感度は85～100%，特異度は33～93%とされている[29),32),34)~37)]．膵の良性腫瘤と悪性の腫瘤との鑑別診断に関するメタ解析では，EUS下エラストグラフィーの感度，特異度および診断オッズ比は，それぞれ0.95（95% confidence interval〔CI〕，0.94-0.97），0.67（95% CI，0.61-0.73），42.28（95% CI，0.94-0.97）であった[38)]．Dietrichら[34)]は，AIPにおけるEUS下エラストグラフィーの特徴的な所見として，硬化性変化が膵腫瘤だけではなく，腫瘤周辺の膵実質にも認められることを挙げており，膵癌ではこのような所見はみられないと報告している．しかし，EUS下エラストグラフィーの限局的なAIPと小膵癌との鑑別診断における有用性については，今後さらなる検討が必要である．

Ⅴ 管腔内超音波検査（IDUS）

IgG4-SCは，CTで造影効果を伴う胆管壁の肥厚がみられることや，胆管造影検査において多彩な胆管像を示すことにより，胆管癌との鑑別が容易ではない[13),14),26),39),40)]．特に，AIPを合併しないIgG4-SCの診断は困難である[41)~43)]．胆管壁層構造の高分解能画像を描出することができる管腔内超音波検査（IDUS）は，胆管壁の肥厚を評価する信頼性の高い検査手技であり，ERCPと同時に行うことができる[13)]．内視鏡的胆道ドレナージはしばしば胆管壁の肥厚を引き起こすため，IDUS

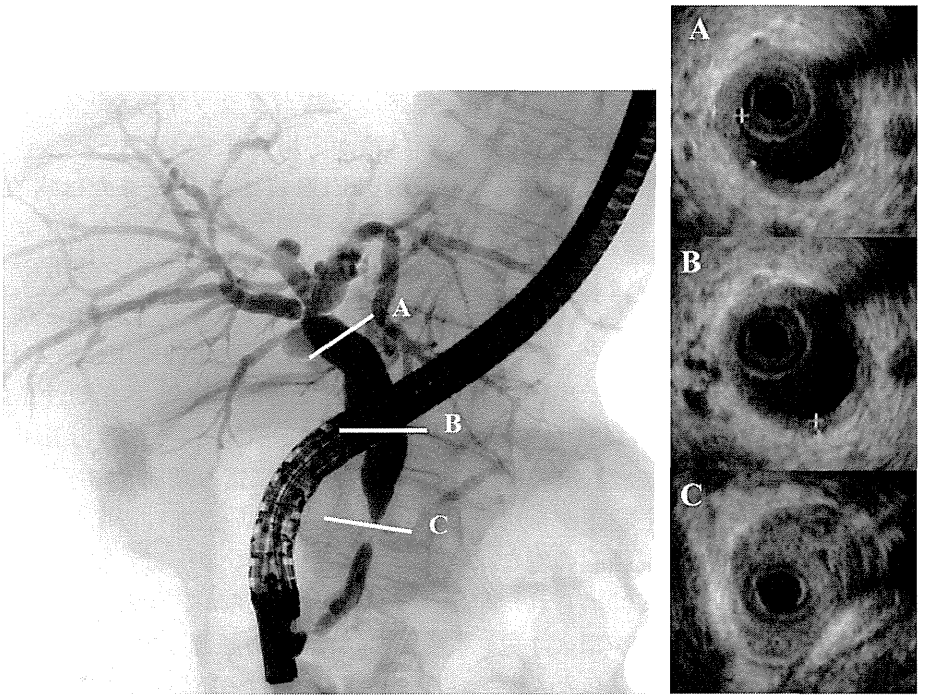

Figure 2　下部総胆管に狭窄を有する IgG4-SC 症例の管腔内超音波検査（IDUS）所見.
IDUS では，狭窄を認める下部総胆管（C）に全周性，対称性の壁肥厚像（3.0mm）がみられるとともに，胆管造影にて狭窄がない部位（A，B）においても胆管壁の肥厚（1.0-1.2mm）を認めた．また，総胆管狭窄部の内側縁，外側縁は平滑で，壁内部は均一なエコー像を示した．

による観察はドレナージの前に行う必要がある[44].

IgG4-SC の胆管狭窄部における IDUS 所見は，全周性，対称性の壁肥厚像を呈することが多く，内側縁，外側縁は平滑で，内部は均一なエコーを示す（Figure 2）[13),26),27),40)]．一方，胆管癌では全周性であるが非対称な壁肥厚が多く，内側縁，外側縁は不整で，内部エコーは不均一を呈することが多い[13),26),45)]．Hyodo ら[40)]は，IgG4-SC の肥厚した胆管は，レボビスト®（Bayer, Leverkusen, Germany）を用いた IDUS において著明な造影効果を示すと報告している.

IgG4-SC における最も特徴的な IDUS 所見は，胆管像の非狭窄部位にも壁の肥厚を認めることである（Figure 2）[13),26),27),39),46)]．膵内胆管に狭窄を有する症例では，狭窄部からその上流胆管に連続的に胆管壁の肥厚が認められる．IDUS の特徴的な所見は，IgG4-SC と胆管癌の鑑別に有用である．Naitoh ら[13)]は，胆管像の非狭窄部位の胆管壁が 0.8mm を超える場合，IgG4-SC を強く疑うべきであると報告している（感度 95%，特異度 90.9%，正診率 93.5%）.

Ⅵ　自己免疫性膵炎の診断における超音波内視鏡下穿刺吸引法の役割

ICDC[8)]に基づいた AIP の診断における病理組織学的検索は，極めて重要である．EUS-FNA は，膵疾患の診断に広く用いられるようになった．ICDC によると，評価に十分な組織標本を得ることが難しいため，EUS-FNA は AIP の病理組織学的診断には薦められていない[47)]．EUS 下の Trucut 生検（TCB）による組織採取のみが，AIP の病理組織学的診断に適していると考えられている[25),48),49)]．19 ゲージの穿刺針を用いた EUS-FNA も AIP の診断に有用であると報告されている[50)]．しかし，EUS-TCB や太い穿刺針を用いた EUS-FNA は，合併症の危険性や取扱いの難しさが問題である[51),52)]．Kanno ら[53)]は，AIP の病理組織学的診断における 22 ゲージ針を用いた EUS-FNA の有用性を報告した．22 ゲージ針を用いた EUS-FNA は組織学的評価に十分な組織を得ることが可能で，ICDC の病理組織学的診断基準に基づくと 80%以上の症例で AIP と診断出来ると報告された[53)]．閉塞性静脈炎も 40%に認められた．彼ら

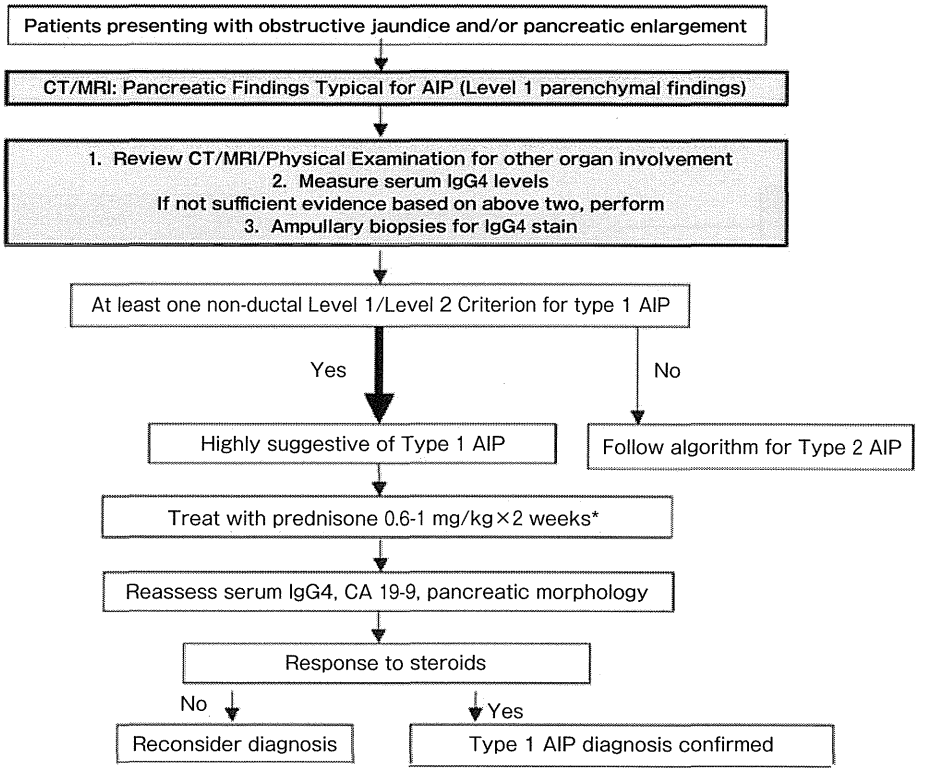

Figure 3 ICDC による AIP1 型の診断のアルゴリズム[8].
閉塞性黄疸や膵腫大を呈する AIP1 型の診断のアルゴリズム．CT ないし MRI 画像において典型的なび漫性膵腫大（レベル 1 膵実質所見）を呈する AIP1 型の診断過程．IgG, immunoglobulin G

は，EUS-FNA により十分な組織を採取するために，組織採取後の注意深い検体処理と，膵内で FNA 穿刺針を素早く動かすことを強調している．スライドグラス上に組織を押し出した後，血液の中からイトミミズ状の組織片を取り出し，ホルマリンを満たした皿の中に移す．このイトミミズ状の組織片は，赤い凝血塊と白い膵組織を含んでいる．この膵組織は 18 ゲージ disposable 注射針を用いて切り取られ，ホルマリンを満たしたコンテナーの中に移されてから，検査のために病理医へ提出する．十分な組織検体を得るためのもう一つの重要なポイントは，針の穿刺スピード，すなわち，いかに早く膵内で穿刺針を動かせるかである．穿刺の充分なスピードを手動で得ることは難しいため，彼らは内部にばねの組み込まれた穿刺針の使用を薦めている．いくつかの新しい EUS-FNA 用の穿刺針により，膵臓の組織採取の改善が期待されている．EUS-FNA は，AIP の病理組織学的診断の改善により ICDC に基づいた AIP 診断の強力な道具になり得る．

Ⅶ 内視鏡を用いた診断のアルゴリズム

5 つの主な診断基準（ICDC[8]，日本の診断基準 2011[9]，アジア診断基準[54]，HISORt 診断基準改訂版[55]，韓国診断基準[56]）の中で，AIP の診断に関して最も感度が良い ICDC では，診断のアルゴリズム（Figure 3）は地域における専門性に従って，それぞれの施設で調整できるとしている．日本の診断基準 2011[9] も，ICDC に従って，レベル 1 とレベル 2 の分類はないが，ICDC と同様の診断項目（CT/MRI による膵画像，膵管像，血清学的所見，他臓器病変，ステロイドの反応性）を採用した．IgG4-SC の診断基準[4] でも同様な診断項目（胆管像，血清学的所見，他臓器病変，ステロイドの反応性）が用いられている．MRCP は，IgG4-SC の診断においては採用されているが，AIP の診断においては ERCP に比べた解像度の低さより，多発の膵管閉塞像とステロイド治療後の変化以外は，用いられていない．診断的 ERCP は，日本と韓国と違って西洋ではほとんど行われない[8]．自己免疫性膵炎の日本の診断基準 2011[9] と

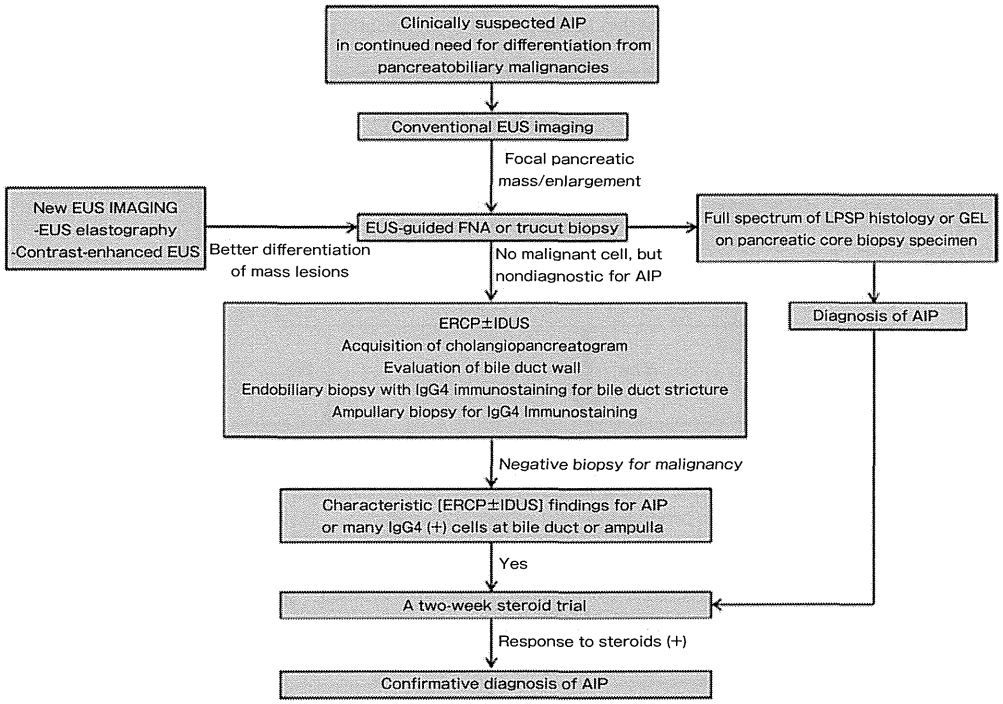

Figure 4　韓国の AIP と膵胆道癌との内視鏡的鑑別方法[27].
ERCP, endoscopic retrograde cholangiopancreatography ; EUS, endoscopic ultrasonography ; FNA, fine-needle aspiration ; GEL, granulocytic epithelial lesion ; IDUS, intraductal ultrasonography ; LPSP, lymphoplasmacytic sclerosing pancreatitis
LPSP, lymphoplasmacytic sclerosing pancreatitis ; GEL, granulocytic epithelial lesion

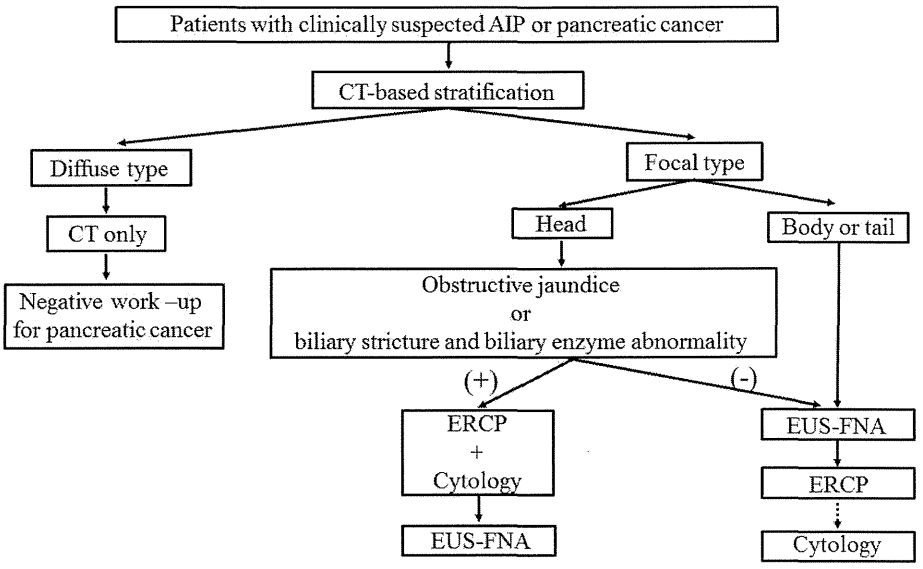

Figure 5　日本の診断基準 2011 に基づく診断アルゴリズムの修正版[64].
AIP, autoimmune pancreatitis ; CT, computed tomography ; ERCP, endoscopic retrograde cholangiopancreatography ; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration

韓国の診断アルゴリズム[27),56)]（Figure 4）と日本のIgG4-SCの診断基準では，ERCPは非典型例（区域性/限局性）のAIPやIgG4-SCにおいては基本的に必須であるが，典型的なび漫性のAIPの診断には必須ではない．AIPと膵臓癌の両方で通常認められる膵内胆管の狭窄と違って，IgG4-SCの合併を示唆する肝内/肝門部胆管狭窄は，AIPの診断において重要な役割を果たす[10),57)]．しかし，肝内/肝門部胆管狭窄を示すIgG4-SCは，PSCと肝門部胆管癌と鑑別しなければならない[10),57)]．

管腔像に加えて，膵液や胆汁のブラッシング細胞診，生検，IgG4免疫染色を加えたEUS-FNA/TCBは，AIPやIgG4-SCの診断をするに足る量を採取することはできないが，有用である．EUS-FNAの膵腫瘤の診断における正診率は，ブラッシング細胞診より優れているが[47),50),52),58)~63)]，胆管病変に関しては必ずしも優れていない．日本では，EUS-FNAができる施設は増えているが[47),50),59),60)]，ERCPはEUS-FNA/TCBより一般的に行われている．従って，日本の診断基準2011[9)]では，分節型/腫瘤型のAIPを含めた膵腫瘤においては，最初のCT/MRIによる膵実質像の評価に続いてERCPを行うことを推奨している，しかし典型的なび漫性のAIPでは必須ではない．西洋と同様に，膵体尾部腫瘤や閉塞性黄疸のない膵頭部腫瘤においてERCPの先にEUS-FNA/TCBを行うことを推奨する報告[64)]が最近日本からもなされた（Figure 5）．この報告では，閉塞性黄疸や胆道系酵素の上昇を伴う膵頭部腫瘤においては最初に診断的および治療的ERCPを行うことを推奨している．ERCP施行時にルチーンにIgG4免疫染色を加えた主乳頭生検[21)]やIDUSを行う事が，AIPやIgG4-SCの診断の補助として推奨される．

Ⅷ 将来の展望

IgG4-SCの定義と疾患領域

AIPとIgG4-SCの診断における内視鏡のコンセプトや役割は，発展し続けている．膵内に限局した下部胆管狭窄をIgG4-SCに入れるかに関しては現在も論議があるが，IgG4-SCの疫学的特徴に差違が生じないためにも，はっきりした定義のコンセンサスを得ることが重要である．膵内に限局した下部胆管狭窄は，AIPの腫大した炎症性の膵臓からの圧排や進展による結果なのか，真のIgG4-SCなのか．

一部のPSC患者で血中IgG4値が上昇することと，PSC患者から切除された肝臓に多数のIgG4陽性細胞が存在することが最近報告された[65)]．血中や組織中のIgG4の上昇を認めるPSCとIgG4-SCは，同じ疾患の異なる最終形なのか，別の臨床的疾患なのかまだ明らかでない[66)]．

診断的モダリティー

胆管造影はPSCの診断のゴールドスタンダードである．MRCは，非侵襲的であり，非電離放射線を使用し，胆管閉塞があっても胆道全体の解剖を表すことができるので，PSCの診断においては最初に行われるモダリティーと思われる[67)]．しかし，ERCPには組織を採取できるというMRCPにない利点がある．MRPは解像度の低さよりERPに代ることは認められていないが，MRCはIgG4-SCが疑われた患者において胆道系の評価の第一選択肢になりうる．ERCPは，非典型的な胆管像を呈したり，内視鏡的胆管生検が必要な患者に備える役割かもしれない．そして，内視鏡的な組織採取の診断能を高める新しい技術やデバイスの開発が必要である[27)]．

Ⅸ 結　語

AIPとIgG4-SCの診療において内視鏡医は重要な役割を果たす．ERCPとEUSは両疾患の診断おいて中心となる手技である．内視鏡的所見の検証と内視鏡的に採取した組織による診断能を高める新しい技術やデバイスの開発が求められる．

本論文内容に関連する著者の利益相反：なし

文　献

1. Kamisawa T, Takuma K, Egawa N et al. Autoimmune pancreatitis and IgG4-related sclerosing disease. Nat Rev Gastroenterol Hepatol 2010；7：401-9.
2. Stone JH, Khosroshahi A, Deshpande V et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis Rheum 2012；64：3061-7.
3. Kamisawa T, Chari ST, Lerch MM et al. Recent advances in autoimmune pancreatitis：type 1 and type 2. Gut 2013；62：1373-80.
4. Ohara H, Okazaki K, Tsubouchi H et al. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci 2012；19：536-42.

5. Kamisawa T, Imai M, Chen PY et al. Strategy for differentiating autoimmune pancreatitis from pancreatic cancer. Pancreas 2008 ; 37 : e62-7.
6. Sugumar A, Levy MJ, Kamisawa T et al. Endoscopic retrograde pancreatography criteria to diagnose autoimmune pancreatitis : an international multicenter study. Gut 2011 ; 60 : 666-70.
7. Takuma K, Kamisawa T, Tableata T et al. Utility of pancreatography for diagnosing autoimmune pancreatitis. World J Gastroenterol 2011 ; 17 : 2332-7.
8. Shimosegawa T, Chari ST, Frulloni L et al. International consensus diagnostic criteria for autoimmune pancreatitis : guidelines of the International Association of Pancretology. Pancreas 2011 ; 40 : 352-8.
9. Shimosegawa T. Working Group Members of the Japan Pancreas Society ; Research Committee for Intractable Pancreatic Disease by the Ministry of Labor, Health and Welfare of Japan. The amendment of the Clinical Diagnostic Criteria in Japan (JPS2011) in response to the proposal of the International Consensus of Diagnostic Criteria (ICDC) for autoimmune pancreatitis. Pancreas 2012 ; 41 : 1341-2.
10. Nakazawa T, Ohara H, Sano H et al. Cholangiography can discriminate sclerosing cholangitis with autoimmune pancreatitis from primary sclerosing cholangitis. Gastrointest Endosc 2004 ; 60 : 937-44.
11. Kamisawa T, Takuma K, Anjiki H et al. Sclerosing cholangitis associated with autoimmune pancreatitis differs from primary sclerosing cholangitis. World J Gastroenterol 2009 ; 15 : 2357-60.
12. Ghazale A, Chari ST, Zhang L et al. Immunoglobulin G4-associated cholangitis : clinical profile and response to therapy. Gastroenterology 2008 ; 134 : 706-15.
13. Naitoh I, Nakazawa T, Ohara H et al. Endoscopic traspapillary intraductal ultrasonography and biopsy in the diagnosis of IgG4-related sclerosing cholangitis. J Gastroenterol 2009 ; 44 : 1147-55.
14. Oh HC, Kim MY, Lee KT et al. Clinical clues to suspicion of IgG4-associated sclerosing cholangitis disguised as primary sclerosing cholangitis or hilar cholangiocarcinoma. J Gastroenterol Hepatol 2010 ; 25 : 1831-7.
15. Kawakami H, Zen Y, Kuwatani M et al. IgG4-related sclerosing cholangitis and autoimmune pancreatitis : histological assessment of biopsies from Vater's ampulla and the bile duct. J Gastroenterol Hepatol 2010 ; 25 : 1648-55.
16. Weber A, von Weyhern C, Frnd F et al. Endoscopic transpapillary brush cytology and forceps biopsy in patients with hilar cholangiocarcinoma. World J Gastroenterol 2008 ; 14 : 1097-101.
17. Itoi T, Kamisawa T, Igarashi Y et al. The role of peroral video cholangioscopy in patients with IgG4-related sclerosing cholangitis. J Gastroenterol 2013 ; 48 : 504-14.
18. Unno H, Saegusa H, Fukushima M et al. Usefulness of endoscopic observation of the main duodenal papilla in the diagnosis of sclerosing pancreatitis. Gastrointest Endosc 2002 ; 56 : 880-4.
19. Kubota K, Iida H, Fujisawa T et al. Clinical significance of swollen duodenal papilla in autoimmune pancreatitis. Pancreas 2007 ; 35 : e51-60.
20. Kim MH, Moon SH, Kamisawa T. Major duodenal papilla in autoimmune pancreatitis. Dig Surg 2010 ; 27 : 110-4.
21. Kamisawa T, Tu Y, Egawa N et al. A new diagnostic endoscopic tool for autoimmune pancreatitis. Gastrointes Endosc 2008 ; 68 : 358-61.
22. Hirano K, Fukushima N, Tada M et al. Diagnostic utility of biopsy specimens for autoimmune pancreatitis. J Gastroenterol 2009 ; 44 : 765-73.
23. Farrell JJ, Garber J, Sahani D et al. EUS findings in patients with autoimmune pancreatitis. Gastrointest Endosc 2004 ; 60 : 927-36.
24. Sahani DV, Kalva SP, Farrell J et al. Autoimmune pancreatitis : imaging features. Radiology 2004 ; 233 : 345-52.
25. Levy MJ, Wiersema MJ, Chari ST. Chronic pancreatitis : focal pancreatitis or cancer? Is there a role for FNA/biopsy? Autoimmune pancreatitis. Endoscopy 2006 ; 38(suppl 1) : S30-5.
26. Kawa S, Okazaki K, Kamisawa T et al. Japanese consensus guidelines for management of autoimmune pancreatitis : Ⅱ. Extrapancreatic lesions, differential diagnosis. J Gastroenterol 2010 ; 45 : 355-69.
27. Moon SH, Kim MH. The role of endoscopy in the diagnosis of autoimmune pancreatitis. Gastrointest Endosc 2012 ; 76 : 645-56.
28. Hoki N, Mizuno N, Sawaki A et al. Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography. J Gastroenterol 2009 ; 44 : 154-9.
29. Hirooka Y, Itoh A, Kawashima H et al. Diagnosis of pancreatic disorders using contrast-enhanced endoscopic ultrasonography and endoscopic elastography. Clin Gastroenterol Hepatol 2009 ; 7 : S63-7.
30. Fusaroli P, Saftoiu A, Mancino MG et al. Techniques of image enhancement in EUS (with videos). Gastrointest Endosc 2011 ; 74 : 645-55.
31. Hocke M, Ignee A, Dietrich CF. Contrast-enhanced endoscopic ultrasound in the diagnosis of autoimmune pancreatitis. Endoscopy 2011 ; 43 : 163-5.
32. Saftoiu A, Iordache SA, Gheonea DI et al. Combined contrast-enhanced power Doppler and real-time sonoelastography performed during EUS, used in the differential diagnosis of focal pancreatic masses (with videos). Gastrointest Endosc 2010 ; 72 : 739-47.
33. Hocke M, Schulze E, Gottschalk P et al. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. World J Gastroenterol 2006 ; 12 : 246-50.
34. Dietrich CF, Hirche TO, Ott M et al. Real-time tissue elastography in the diagnosis of autoimmune pancreatitis. Endoscopy 2009 ; 41 : 718-20.
35. Janssen J, Schlorer E, Greiner L. EUS elastography of the pancreas : feasibility and pattern description of the normal pancreas, chronic pancreatitis, and focal

pancreatic lesions. Gastrointest Endosc 2007 ; 65 : 971-8.
36. Zhang MM, Yang H, Jin ZD et al. Differential diagnosis of pancreatic cancer from normal tissue with digital imaging processing and pattern recognition based on a support vector machine of EUS images. Gastrointest Endosc 2010 ; 72 : 978-85.
37. Iglesias-Garcia J, Larino-Noia J, Abdulkader I et al. Quantitative endoscopic ultrasound elastography : an accurate method for the differentiation of solid pancreatic masses. Gastroenterology 2010 ; 139 : 1172-80.
38. Mei M, Ni J, Liu D et al. EUS elastography for diagnosis of solid pancreatic masses : a meta-analysis. Gastrointest Endosc 2013 ; 77 : 578-89.
39. Hirano K, Tada M, Isayama H et al. Endoscopic evaluation of factors contributing to intrapancreatic biliary stricture in autoimmune pancreatitis. Gastrointest Endosc 2010 ; 71 : 85-90.
40. Hyodo N, Hyodo T. Ultrasonographic evaluation in patients with autoimmune-related pancreatitis. J Gastroenterol 2003 ; 38 : 1155-61.
41. Nakazawa T, Ohara H, Sano H et al. Difficulty in diagnosing autoimmune pancreatitis by imaging findings. Gastrointest Endosc 2007 ; 65 : 99-108.
42. Hamano H, Kawa S, Uehara T et al. Immunoglobulin G4-related lymphoplasmacytic sclerosing cholangitis that mimics infiltrating hilar cholangiocarcinoma : part of a spectrum of autoimmune pancreatitis? Gastrointest Endosc 2005 ; 62 : 152-7.
43. Hayashi K, Nakazawa T, Ohara H et al. Autoimmune sclerosing cholangiopancreatitis with little pancreatic involvements by imaging findings. Hepatogastroenterology 2007 ; 54 : 2146-51.
44. Tamada K, Tomiyama T, Oohashi A et al. Bile duct wall thickness measured by intraductal US in patients who have not undergone previous biliary drainage. Gastrointest Endosc 1999 ; 49 : 199-203.
45. Pavey DA, Gress FG. The role of EUS-guided FNA for the evaluation of biliary strictures. Gastrointest Endosc 2006 ; 64 : 334-7.
46. Inui K, Yoshino J, Miyoshi H. Differential diagnosis and treatment of biliary strictures. Clin Gastroenterol Hepatol 2009 ; 7 : S79-83.
47. Imai K, Matsubayashi H, Fukutomi A et al. Endoscopic ultrasonography-guided fine needle aspiration biopsy using 22-gauge needle in diagnosis of autoimmune pancreatitis. Dig Liver Dis 2011 ; 43 : 869-74.
48. Mizuno N, Bhatia V, Hosoda W et al. Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy : a comparison study with EUS-FNA. J Gastroenterol 2009 ; 44 : 742-50.
49. Levy MJ, Reddy RP, Wiersema MJ et al. EUS-guided trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. Gastrointest Endosc 2005 ; 61 : 467-72.
50. Iwashita T, Yasuda I, Doi S et al. Use of samples from endoscopic, ultrasound-guided, 19-gauge, fine-needle aspiration in diagnosis of autoimmune pancreatitis. Clin Gastroenterol Hepatol 2012 ; 10 : 316-22.
51. Binmoeller KF, Jabusch HC, Seifert H et al. Endosonography-guided fine-needle biopsy of indurated pancreatic lesions using an automated biopsy device. Endoscopy 1997 ; 29 : 384-8.
52. Varadarajulu S, Fraig M, Schmulewitz N et al. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. Endoscopy 2004 ; 36 : 397-401.
53. Kanno A, Ishida K, Hamada S et al. Diagnosis of autoimmune pancreatitis by EUS-FNA by using a 22-gauge needle based on the International Consensus Diagnostic Criteria. Gastrointest Endosc 2012 ; 76 : 594-602.
54. Otsuki M, Chung JB, Okazaki K et al. Asian diagnostic criteria for autoimmune pancreatitis : consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. J Gastroenterol 2008 ; 43 : 403-8.
55. Chari ST, Smyrk TC, Levy MJ et al. Diagnosis of autoimmune pancreatitis : the Mayo Clinic experience. Clin Gastroenterol Hepatol 2006 ; 4 : 1010-6.
56. Kim KP, Kim MH, Kim JC et al. Diagnostic criteria for autoimmune chronic pancreatitis revisited. World J Gastroenterol 2006 ; 12 : 2487-96.
57. Nakazawa T, Ohara H, Sano H et al. Schematic classification of sclerosing cholangitis with autoimmune pancreatitis by cholangiography. Pancreas 2006 ; 32 : 229.
58. Deshpande V, Mino-Kenudson M, Brugge WR et al. Endoscopic ultrasound guided fine needle aspiration biopsy of autoimmune pancreatitis : diagnostic criteria and pitfalls. Am J Surg Pathol 2005 ; 29 : 1464-71.
59. Uchida N, Kamada H, Tsutsui K et al. Utility of pancreatic duct brushing for diagnosis of pancreatic carcinoma. J Gastroenterol 2007 ; 42 : 657-62.
60. Takahashi K, Yamao K, Okubo K et al. Differential diagnosis of pancreatic cancer and focal pancreatitis by using EUS-guided FNA. Gastrointest Endosc 2005 ; 61 : 76-9.
61. Raut CP, Grau AM, Staerkel GA et al. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration in patients with presumed pancreatic cancer. J Gastrointest Surg 2003 ; 7 : 118-26.
62. Tadic M, Kujundzic M, Stoos-Veic T et al. Role of repeated endoscopic ultrasound-guided fine needle aspiration in small solid pancreatic masses with previous indeterminate and negative cytological findings. Dig Dis 2008 ; 26 : 377-82.
63. Möller K, Papanikolaou IS, Toermer T et al. EUS-guided FNA of solid pancreatic masses : high yield of 2 passes with combined histologic-cytologic analysis. Gastrointest Endosc 2009 ; 70 : 60-9.
64. Sumimoto K, Uchida K, Mitsuyama T et al. A proposal of a diagnostic algorithm with validation of International Consensus Diagnostic Criteria for autoimmune pancreatitis in a Japanese cohort. Pancreatology 2013 ; 13 : 230-7.

65. Zhang L, Lewis JT, Abraham SC et al. IgG4+ plasma cell infiltrates in liver explants with primary sclerosing cholangitis. Am J Surg Pathol 2010 ; 34 : 88-94.
66. Chapman R, Fevery J, Kalloo A et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology 2010 ; 51 : 660-78.
67. Culver EL, Chapman RW. Systematic review : management options for primary sclerosing cholangitis and its variant forms -IgG4-associated cholangitis and overlap with autoimmune hepatitis. Aliment Pharmacol Ther 2011 ; 33 : 1273-91.

ROLE OF ENDOSCOPY IN THE DIAGNOSIS OF AUTOIMMUNE PANCREATITIS AND IMMUNOGLOBULIN G4-RELATED SCLEROSING CHOLANGITIS

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Autoimmune pancreatitis (AIP) must be differentiated from pancreatic carcinoma, and immunoglobulin (Ig) G4-related sclerosing cholangitis (SC) from cholangiocarcinoma and primary sclerosing cholangitis (PSC). Pancreatographic findings such as a long narrowing of the main pancreatic duct, lack of upstream dilatation, skipped narrowed lesions, and side branches arising from the narrowed portion suggest AIP rather than pancreatic carcinoma. Cholangiographic findings for PSC, including band-like stricture, beaded or pruned-tree appearance, or diverticulum-like outpouching are rarely observed in IgG4-SC patients, whereas dilatation after a long stricture of the bile duct is common in IgG4-SC. Transpapillary biopsy for bile duct stricture is useful to rule out cholangiocarcinoma and to support the diagnosis of IgG4-SC with IgG4-immunostaining. IgG4-immunostaining of biopsy specimens from the major papilla advances a diagnosis of AIP. Contrastenhanced endoscopic ultrasonography (EUS) and EUS elastography have the potential to predict the histological nature of the lesions. Intraductal ultrasonographic finding of wall thickening in the non-stenotic bile duct on cholangiography is useful for distinguishing IgG4-SC from cholangiocarcinoma. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is widely used to exclude pancreatic carcinoma. To obtain adequate tissue samples for the histological diagnosis of AIP, EUS-Tru-cut biopsy or EUS-FNA using a 19-gauge needle is recommended, but EUS-FNA with a 22-gauge needle can also provide sufficient histological samples with careful sample processing after collection and rapid motion of the FNA needles within the pancreas. Validation of endoscopic imaging criteria and new techniques or devices to increase the diagnostic yield of endoscopic tissue sampling should be developed.

IgG4-related disease

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

Introduction

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

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

Epidemiology

Understanding of the epidemiology of IgG4-related disease is hampered by insufficient awareness of the diagnosis, because the disease did not appear in medical publications until 2003.[5,6] Definitive diagnosis generally necessitates a biopsy, insightful interpretation of the pathology, and rigorous clinicopathological correlation. Although the overall prevalence of type 1 (IgG4-related) autoimmune pancreatitis in Japan has been estimated as 2·2 cases per 100 000 population,[7] the pancreas is only one of more than a dozen organs affected by IgG4-related disease. Therefore, this is surely a substantial underestimate of the true prevalence, especially because the study from which this estimate was derived was done early in the development of knowledge about IgG4-related disease. The prevalence of various organ manifestations also remains unclear, but autoimmune pancreatitis, sialadenitis (particularly of the submandibular gland), dacryoadenitis, and IgG4-related retroperitoneal fibrosis are the most common disease features.

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

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

Search strategy and selection criteria

Data for this Review were identified by searches of Medline, PubMed, and references from relevant articles with the search terms "IgG4", "IgG4-related", and "autoimmune pancreatitis". We focused on publications since the year 2000, since the multiorgan nature of IgG4-related disease was not recognised until 2003. We also cited other important publications from earlier years pertaining to conditions now recognised as part of the IgG4-related disease spectrum.

Pathology

Histology features

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

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

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

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

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

Panel 1: Conditions once regarded as individual disorders now recognised to be part of IgG4-related disease

- Autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis)
- Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
- Fibrosing mediastinitis
- Hypertrophic pachymeningitis
- Idiopathic hypocomplementaemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
- Inflammatory pseudotumour (affecting the orbits, lungs, kidneys, and other organs)
- Küttner's tumour (affecting the submandibular glands)
- Mikulicz's disease (affecting the salivary and lacrimal glands)
- Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
- Periaortitis and periarteritis
- Inflammatory aortic aneurysm
- Retroperitoneal fibrosis (Ormond's disease)
- Riedel's thyroiditis
- Sclerosing mesenteritis

Immunostaining

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

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

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

Morphological change of affected organs

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

See Online for appendix

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

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

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

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

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

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

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

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

Lungs
- Malignancy (adenocarcinoma or bronchioloalveolar carcinoma)
- Inflammatory myofibroblastic tumour
- Sarcoidosis
- Granulomatosis with polyangiitis
- Castleman's disease
- Lymphomatoid granulomatosis
- Idiopathic interstitial pneumonitis
- Erdheim-Chester disease

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

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

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

Pancreas
- Pancreatic cancer

Biliary tree
- Pancreatic cancer
- Cholangiocarcinoma
- Primary sclerosing cholangitis

Liver
- Cholangiocarcinoma
- Hepatocellular carcinoma
- Primary sclerosing cholangitis

Prostate
- Benign prostatic hypertrophy

Skin
- Cutaneous lymphoma

Pathophysiology

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

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

process called Fab-arm exchange within the endosomal compartment of endothelial cells.[20] In this process, the heavy-chain dimers of an IgG4 molecule dissociate and each hemi-molecule associates with another, different, hemi-IgG4 protein. Most secreted IgG4 is therefore functionally monovalent and cannot crosslink antigens to form the lattice structure found in immune complexes. As a result, IgG4 antibodies do not directly fix complement, they bind poorly to activating Fc receptors, and they are generally thought to be non-inflammatory. IgG4 concentrations are also known to rise after IgE concentrations decline in allergic disorders. For these reasons, one possible view of IgG4 is that it perhaps evolved as a non-inflammatory antigen sink that is largely monovalent, the purpose of which is to mop up antigen in an attempt to attenuate inflammatory processes. In theory, however, IgG4 could be pathogenic and could perhaps collaborate with circulating lectins to activate complement in disease lesions. However, no evidence to support such a view is available.

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

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

One plausible model of pathogenesis is that in genetically susceptible individuals, generally older men, some environmental insult, possibly an encounter with a specific microbe, triggers tissue damage and a break in immunological tolerance. A self-antigen-driven, polarised CD4-positive T-helper response would induce a fibrotic pathological process at one or several sites. The reasons for the targeting of particular organs remain unclear. Within these organs, increased CD4-positive T cells would

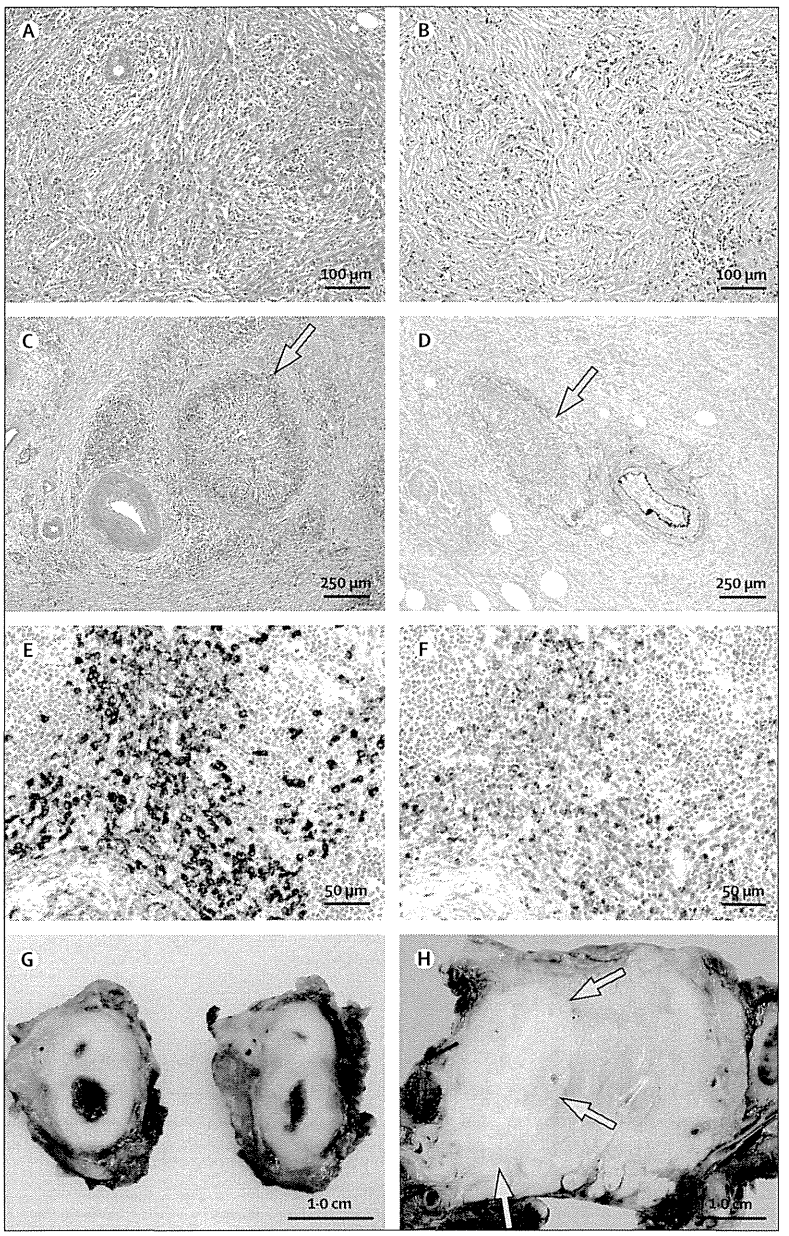

Figure 1: **Pathological features of IgG4-related disease**
(A) Submandibular gland affected by a fibroinflammatory process; the inflammatory-cell infiltrate consists mainly of lymphocytes and plasma cells, and whorls of fibrosis are evident throughout the tissue. (B) Storiform fibrosis is apparent in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

activate innate immune cells that secrete other cytokines and drive the pathology. The memory CD4-positive T cells that orchestrate the disease are presumably sustained by antigen-presenting B cells, which would explain the clinical improvement after B-cell depletion.[27,28] Either the same antigen or some event triggered by fibrosis could trigger a parallel T-follicular helper response that would induce the development of germinal centres within lymph nodes and the generation of IgG4-secreting plasmablasts and long-lived plasma cells. The existence of these cells can be inferred because rituximab does not completely attenuate IgG4 concentrations in treated patients.

Diagnosis

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

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

Differentiation of IgG4-related disease from malignant tumours is crucial. Common mimics of multi-organ IgG4-related disease are Sjögren's syndrome, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome), sarcoidosis, and multicentric Castleman's disease. Single-organ diseases such as primary sclerosing cholangitis must also be excluded (panel 2).

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

Serology

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

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

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

Organ involvement

Constitutional and musculoskeletal symptoms

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

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

Orbits

The typical ophthalmic presentation involves swelling within the ocular region or frank proptosis, generally

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

Salivary glands

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

Ears, nose, and throat

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

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

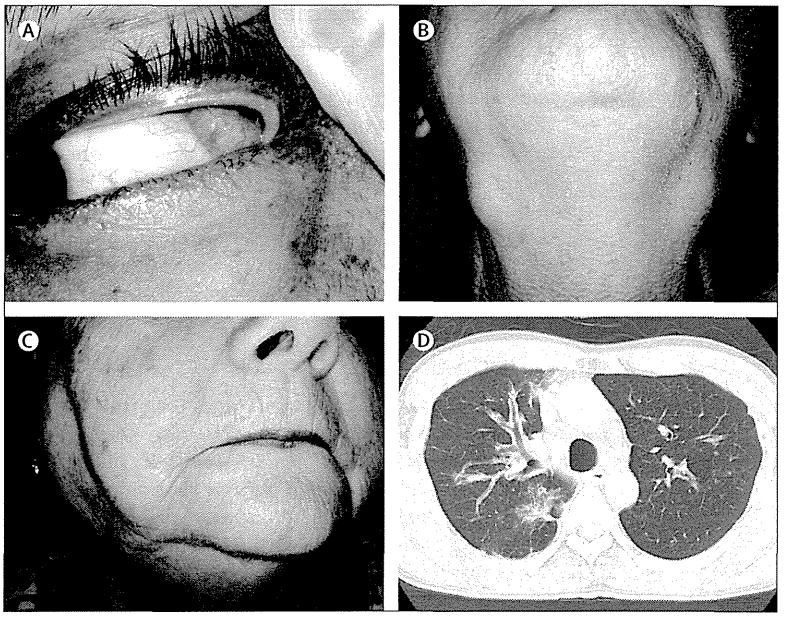

Figure 2: **Clinical features**
(A) Dacryoadenitis; the typical ophthalmic presentation of IgG4-related disease involves some swelling within the ocular region or proptosis, generally caused by lacrimal-gland enlargement. (B) Submandibular gland enlargement in a patient who had previously undergone a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

Thyroid gland

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

Lymphadenopathy

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

Thoracic aorta, branches of the aorta, and coronary lesions

IgG4-related aortitis can lead to aneurysms or dissections in the thoracic aorta.[63–65] This feature, commonly an incidental radiological finding, is also

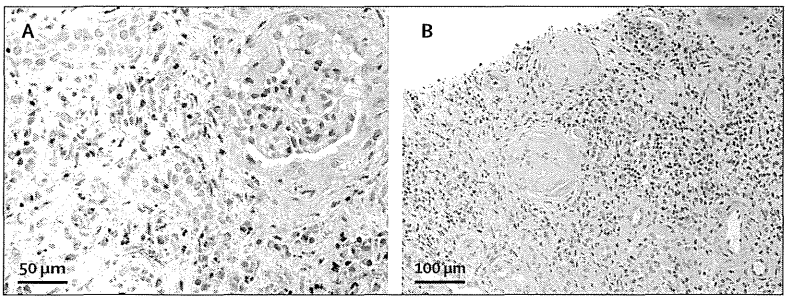

Figure 3: **IgG4-related disease in the kidney**
(A) Tubulointerstitial nephritis in the setting of IgG4-related disease shows the histopathology found in other organs: a lymphoplasmacytic infiltrate (with an IgG4 predominance among plasma cells), storiform fibrosis, and moderate tissue eosinophilia.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

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

Chronic periaortitis and retroperitoneal fibrosis

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

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

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

Lungs

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

Kidneys

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

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

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

Pancreas

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

basis of histological features of neutrophilic infiltration into the epithelium of the pancreatic duct.[79–81]

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

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

IgG4-related sclerosing cholangitis and cholecystitis

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

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

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

Other organs

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

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

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

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

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

Treatment

Glucocorticoids

Most clinical manifestations of IgG4-related disease respond to glucocorticoids. These agents are the first-line, standard-of-care approach for most patients.[43,99] However, no randomised treatment trials have been done, and few large retrospective examinations have been reported. One treatment approach uses a starting prednisolone dose of

0·6–1·0 mg/kg daily.[30,43] After 2–4 weeks, the dose is tapered by 5 mg every 1–2 weeks according to clinical responses (eg, clinical manifestations, blood tests, and follow-up imaging studies). Practice varies as to whether the prednisolone is discontinued entirely after 2 or 3 months or maintained at a low dose. A single-group trial of prednisolone in Japan showed complete remissions in only 61% of patients at 1 year despite continuation of maintenance doses of prednisone in all patients.[100]

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

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

Conventional steroid-sparing agents

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

B-cell depletion

Rituximab was used initially in patients who did not respond to glucocorticoids, conventional steroid-sparing agents, or both, under the assumption that B-cell depletion might ameliorate the condition putatively mediated by high serum concentrations of IgG4.[27,48,106] The fundamental assumption underlying this approach now seems incorrect or at least not entirely true, but careful mechanistic studies of patients with IgG4-related disease treated with rituximab have led to several important observations and novel insights about the pathophysiology of this disorder. First, B-cell depletion targets the subset of plasma cells that produce IgG4 in IgG4-related disease.[27,28] They seem to achieve this action by depleting all circulating CD20-positive cells (ie, B cells), which interferes in turn with the repletion of short-lived plasma cells making IgG4. In other words, the plasma cells generating IgG4 in IgG4-related disease are mainly of the short-lived type that naturally undergo apoptosis within weeks. Once these cells disappear as programmed, they cannot be repleted after rituximab administration because their precursors—CD20-positive B cells—are not available.

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

Future perspectives

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

Contributors

All the authors contributed equally to the literature search, planning, writing, and editing of the Review and all have approved the submission of this version.

Declaration of interests

JHS is the principal investigator in a Genentech-funded trial of rituximab in IgG4-related disease and has consulted for Genentech on this disease. The other authors declare no competing interests.

References

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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