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Aprisionamento Aéreo na Pneumonia Intersticial Usual: Caracterização Diagnóstica e Prognóstica

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Sumário

Lista de abreviaturas utilizadas

TC-AR: tomografia computadorizada de alta resolução.

TC: tomografia computadorizada.

PIU: Pneumonia Intersticial Usual.

PII: Pneumonias Intersticiais Idiopáticas.

FPI: Fibrose Pulmonar Idiopática.

PH: Pneumonia de Hipersensibilidade.

MLDexp: Volume Pulmonar Médio na expiração.

MLDinsp: Volume Pulmonar Médio na Inspiração.

ATIexp: Volume de Aprisionamento Aéreo na Expiração.

UH: Unidades Hounsfield.

ATS: American Thoracic Society.

ERS: European Respiratory Society.

Resumo da Dissertação

Introdução: A Tomografia Computadorizada de Tórax de Alta Resolução (TC-AR) consiste no exame diagnóstico mais acessível da Pneumonia Intersticial Usual (PIU) e, consequentemente, Fibrose Pulmonar Idiopática (FPI). O aprisionamento aéreo quando presente afasta este diagnóstico, levando a necessidade de biópsia pulmonar cirúrgica.

Objetivo: caracterizar o aprisionamento aéreo em portadores de PIU e FPI na TC-AR e avaliar o impacto da sua presença sobre a mortalidade.

Material e Métodos: Foram incluídos pacientes que realizaram TC-AR com laudo de PIU. O diagnóstico de FPI foi estabelecido pela biópsia pulmonar ou discussão multidisciplinar. Duas medidas quantitativas do aprisionamento aéreo foram feitas, a primeira quantificou a densidade pulmonar ao término da expiração (ATIexp) e a segunda considerou a relação entre expiração e inspiração da densidade pulmonar média (relação E/IMLD). O óbito ou o transplante pulmonar foram os desfechos.

Resultados: Dos 75 pacientes, 67% tinham FPI e 33% apresentaram PIU por causas definidas, com sobrevida média de 3 (IC95%: 2,5–3,5) e 4,2 anos (IC95%: 3,6–4,7), respectivamente. Óbito ocorreu em 40% dos casos, destes, 3 foram transplantados. Considerando a variável ATIexp, o aprisionamento aéreo não teve influencia sobre a mortalidade (p=0.137), o que também foi observado na relação E/IMLD (p=0,06). Quando estratificada a amostra pelo aprisionamento aéreo o tempo médio de sobrevida da FPI foi menor em relação aos portadores de PIU por causas definidas tanto para os pacientes sem aprisionamento aéreo (ATIexp, p<0,013 e E/I, p<0,005) quanto com presença deste achado (ATIexp, p<0,038 e E/I, p<0,05).

Conclusão: O aprisionamento aéreo não influenciou a mortalidade dos pacientes, sugerindo que este achado não possuiu relevância significativa quando presente, podendo afastar a necessidade de biópsia pulmonar cirúrgica para diagnóstico de PIU/FPI.

Palavras-Chave: Pneumonia Intersticial Usual, Aprisionamento aéreo, Tomografia de Tórax de Alta Resolução, Fibrose Pulmonar Idiopática.

1. Introdução

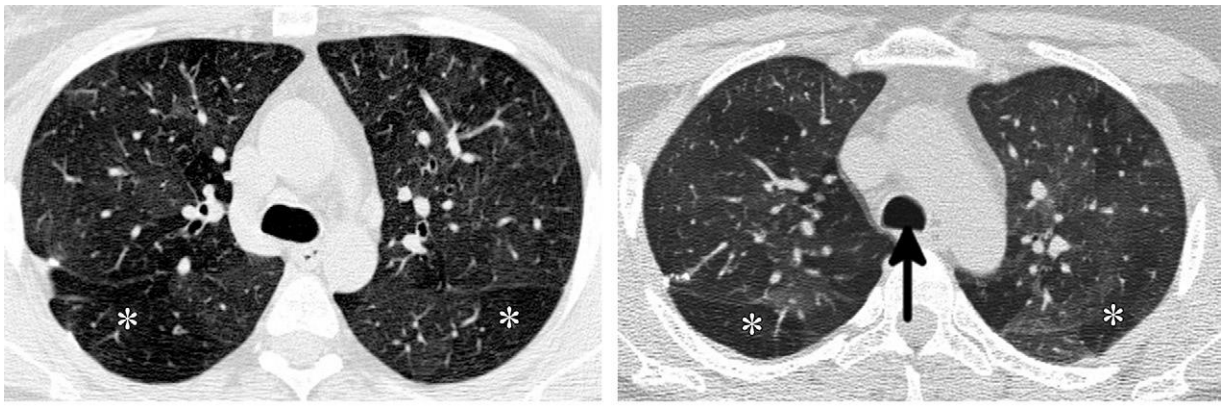
1.1 Aprisionamento Aéreo

Em radiologia, o termo aprisionamento aéreo indica retenção de ar inspirado durante a expiração, detectado na Tomografia Computadorizada (TC) de Tórax. Patologicamente representa a obstrução de pequenas vias aéreas pulmonares, que corresponde às vias não cartilaginosas, com diâmetro interno menor ou igual a 2 milímetros, que envolve os bronquíolos terminais e bronquíolos respiratórios (Burgel e Cols, 2013).

O aprisionamento aéreo foi inicialmente descrito em 1993 por Webb, quando pacientes realizaram a Tomografia de Tórax prendendo a respiração ao término da expiração. Os pesquisadores notaram que certos pacientes apresentaram diminuição da atenuação ao nível dos lóbulos pulmonares secundários, em diferentes graus de intensidade (Webb e Cols, 1993). Na presença de doenças das pequenas vias aéreas, o ar não pode escapar facilmente nas regiões onde tais vias estão obstruídas. Consequentemente, a atenuação do parênquima pulmonar nestes segmentos envolvidos permanece relativamente inalterada em comparação com suas mesmas imagens obtidas em inspiração. Isso gera um contraste com segmentos pulmonares mais sadios, que em expiração apresentam aumento da atenuação parenquimatosa (Kligerman e cols, 2015).

O aprisionamento aéreo pode ser detectado a olho nu, pelo médico radiologista, principalmente quando se apresenta na forma de pavimentação em mosaico, sendo este um padrão de imagem definido como atenuação pulmonar variável resultando em uma aparência heterogênea do parênquima (Figura 1). No

entanto, até 20% de pacientes sem doenças pulmonares podem apresentar atenuação em mosaico ao realizarem a TC de tórax, mesmo em inspiração (Park e cols, 1997) e algumas doenças vasculares também levam à presença deste achado. Além disto, o aprisionamento aéreo envolvendo um segmento pulmonar pode ocasionalmente ser detectado em pacientes normais, sendo ainda mais comum em idosos e fumantes (Figura 2) (Webb e cols, 1993; Pipavath e cols, 2005).



a. b.

Figura 1: Aprisionamento aéreo em mulher de 45 anos protadora de artrite reumatóide. (a) TC em corte axial, ao nível da carina, mostra atenuação em mosaico, com áreas de diminuição da atenuação (*) adjacentes ao pulmão normal. (b) Imagem obtida em expiração à um nível similar mostra que as áreas de hipoatenuação não se alteraram, isso ocorre devido ao aprisionamento aéreo (*****).A curvatura da parede posterior da traquéia (seta) significa bom efeito expiratório produzido pela paciente (Kligerman e cols, 2015).

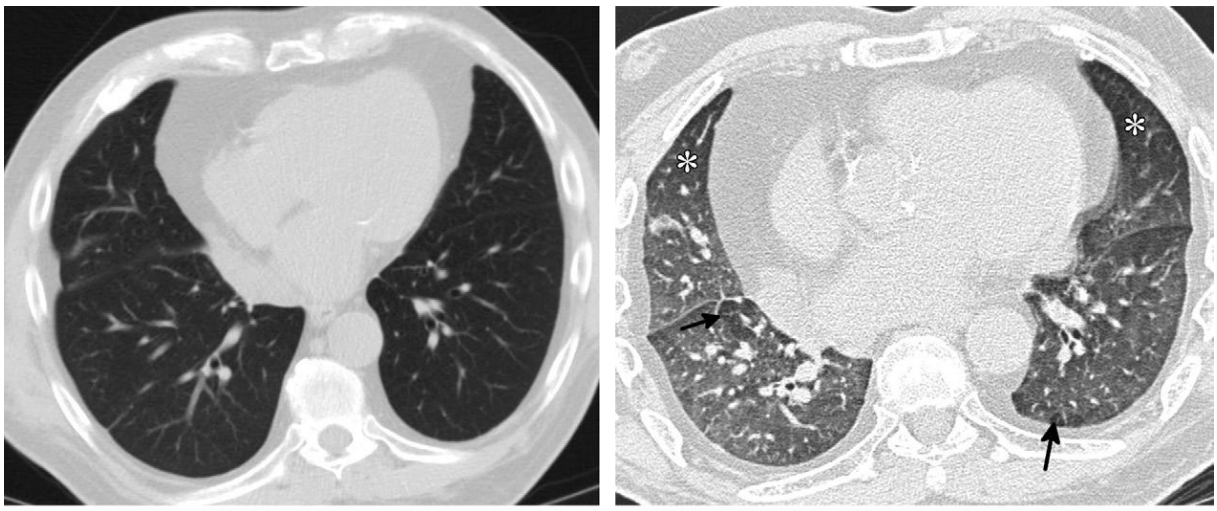


Figura 2: Variação normal da atenuação pulmonar em mulher de 73 anos. (a) Imagem da TC em inspiração mostra atenuação pulmonar normal. (b) Tomografia de Tórax de Alta resolução (TC-AR) durante a expiração mostra o gradiente fisiológico normal, com a porção anterior do pulmão (*) apresentando menor atenuação em relação à posterior. A imagem demonstra parênquima pulmonar heterogêneo na expiração, embora quase todo o pulmão tenha aumentado sua atenuação. Além disso, alguns lóbulos permanecem radiolucentes, indicando aprisionamento aéreo (setas). Esta variação durante a expiração é vista em uma grande quantidade de pacientes, não sendo considerada patológica (Kligerman e cols, 2015).

Portanto, vários graus de atenuação em mosaico e aprisionamento aéreo podem ser uma descoberta incidental e não relacionada a sintomas subjacentes que levaram o paciente a realizar a TC. Em geral, estes achados, quando envolvem mais que um segmento pulmonar, tem frequentemente uma patologia subjacente para a qual uma causa deve ser procurada.

A adequada mensuração da obstrução de vias aéreas, de maneira objetiva e quantitativa, é feita com o uso de softwares que calculam a área de baixa atenuação, em Unidade Hounsfield (UH), e avalia sua extensão total no parênquima

pulmonar. A Densidade Pulmonar Média também é calculada, tanto na expiração quanto na inspiração, e a respectiva relação entre tais valores foi considerada válida para mensuração do aprisionamento aéreo (Bommart e Cols, 2014), embora ainda não haja um valor de corte estabelecido para tal medida que defina a normalidade em relação ao aprisionamento. De maneira geral, quanto maior a relação entre as densidades, maior é o aprisionamento (Mets e Cols, 2012).

Quanto à etiologia, o aprisionamento aéreo, resultante das doenças de pequenas vias aéreas, pode ser consequência de uma desordem primária, como bronquiolite obliterante e bronquiolite constritiva, ou pode fazer parte de alguma forma de doença pulmonar intersticial (DPI), como a Pneumonia de Hipersensibilidade, e também ser consequência da doença de grandes vias aéreas, como as bronquiectasias e asma (Ryu e cols, 2003). Uma série de casos demonstrou que 31% dos pacientes com aprisionamento aéreo eram portadores de alguma forma de DPI (Wallace e Cols, 2014). Entre estas doenças, a sarcoidose, Pneumonia de Hipersensibilidade e Pneumonia Idiopática não Específica são as mais prevalentes. Existem poucos dados na literatura que descrevem este achado em outras formas de DPI, incluindo o padrão de Pneumonia Intersticial Usual (PIU) e Fibrose Pulmonar Idiopática (FPI).

1.2 Doenças Pulmonares Intersticiais

As Doenças Pulmonares Intersticiais agregam uma grande variedade de patologias pulmonares que apresentam características clínicas, fisiológicas, radiográficas e patológicas comuns. O acometimento parenquimatoso é preferencial,

porém há preenchimento alveolar, envolvimento das vias aéreas distais e comprometimento vascular pulmonar.

Estas numerosas entidades patológicas são subdivididas em quatro grupos, sendo estes os das doenças intersticiais de causas conhecidas, as Pneumonias Intersticiais Idiopáticas (PII), doenças granulomatosas e o conjunto de outras doenças que podem levar ao acometimento intersticial (linfangioleiomiomatose, histiocitose). O grupo mais abrangente corresponde ao das PII, onde várias classificações para categoriza-las foram propostas. O esquema mais amplamente aceito foi desenvolvido pela American Thoracic Society/European Respiratory Society (ATS/ERS) em 2002, com uma atualização publicada em 2013 (Travis e Cols, 2013). Esta atualização recente separa os PII em quatro grupos: PII fibrosantes crônicas (Fibrose Pulmonar Idiopática [FPI] e Pneumonia Intersticial não Específica [PINE]), PII agudas ou subagudas (Pneumonia Intersticial Aguda [PIA] e Pneumonia em Organização Criptogênica [POC]), PII relacionadas ao tabagismo (Pneumonia Intersticial Descamativa [PID] e Bronquiolite Respiratória com Doença Pulmonar Intersticial [BR-DPI]) e PII raras (Pneumonia Intersticial Linfocítica [PIL] e Fibroelastosa Pleuroparenquimatosa Idiopática) (Travis e Cols, 2013). Dentre todas as doenças expostas, destaca-se a Fibrose Pulmonar Idiopática (FPI), principal foco deste estudo, sendo esta a mais prevalente (American Thoracic Society, 2000).

Considerando que as DPI constituem-se em mais de 150 entidades patológicas distintas e baseando-se nas publicações recentes, para individualizar estas diversas patologias a estratégia diagnóstica recomenda caracterizar o tempo de sintomas (aguda, subaguda, crônica), a causa (conhecida ou não) e o contexto de apresentação da doença (presença de manifestações extrapulmonares) (American Thoracic Society/European Respiratory Society ,2002). A conduta frente

ao quadro sugestivo de DPI leva à necessidade da realização de uma Tomografia de tórax Computadorizada de Alta Resolução (TC-AR). Paralelo à análise dos exames de imagem, a abordagem diagnóstica deve também estabelecer a intensidade dos sintomas. O mais importante, no entanto, é identificar fatores de risco conhecidos, sendo necessário uma anamnese detalhada sobre funções laborativas, condições e hábitos de vida, uso de medicações, exposições habituais com outras atividades, presença de doenças sistêmicas e histórico de doenças familiares (Zanon e Cols, 2017). Com a identificação de uma causa estabelecida para a DPI, faz-se necessário o controle da mesma, seja este medicamentoso ou comportamental, o que tende a melhorar o prognóstico da doença (Raghu e Cols, 2011).

1.3 Fibrose Pulmonar Idiopática

A Fibrose Pulmonar Idiopática (FPI) é a expressão clínica do diagnóstico histopatológico de Pneumonia Intersticial Usual (PIU), definida pela infiltração crônica e progressiva limitada ao interstício pulmonar, por um processo colagênico, de causa desconhecida, que acompanha a piora gradual do quadro clínico levando a um prognóstico reservado (Raghu e Cols, 2011), com sobrevida média de 2,5 a 3,5 anos (Ley e Cols, 2011). Esta condição ocorre principalmente em idosos, sendo limitada aos pulmões e deve ser supeitada, portanto, em todos os pacientes adultos, em geral na sexta ou sétima décadas de vida, com dispnéia crônica aos esforços, sem causa aparente, geralmente com tosse seca associada. Achados no exame físico incluem creptações pulmonares em bases durante a inspiração e baqueteamento digital (Gribbin e Cols 2006).

A predominância pelo sexo masculino foi relatada na maioria dos estudos prévios, e embora a causa seja desconhecida, muitos pacientes tem histórico de tabagismo (Iwai e Cols, 1994). Testes de função pulmonar mostram um padrão restritivo com volumes pulmonares reduzidos e comprometimento na troca gasosa (Martinez e Cols, 2006). A patogênese da FPI é desconhecida. Estudos atuais sugerem causas multifatoriais, entre elas a senescência parenquimatosa pulmonar acelerada consequente a fatores de predisposição genética e disfunção da telomerase, que em conjunto com exposições ambientais, como o tabagismo, podem comprometer gravemente o potencial regenerativo de células tronco parenquimatosas (Chilosi e Cols, 2010 ; Wolters e Cols, 2014). Esses diversos fatores levam à microagressões repetitivas em pulmões geneticamente suscetíveis, ocasionando lesão de pneumócitos tipo I e ruptura de sua membrana basal celular, com consequente liberação de fatores responsáveis pela migração de fibroblastos e produção exagerada de matriz extracelular pelos focos fibroblásticos, o que resulta na destruição do parênquima pulmonar (Galvin e Cols, 2010 ; King e Cols, 2011). O fato da FPI ocasionalmente afetar familiares próximos e irmãos gêmeos, reforça a evidência para a predisposição genética desta DPI (Leslie e Cols, 2012).

1.4 Pneumonia Intersticial Usual

A Pneumonia Interticial Usual (PIU) é um diagnóstico histológico, pertencente ao grupo das DPI, caracterizada microscopicamente por uma aparência heterogênea irregular, do parênquima pulmonar, em que áreas de faveolamento e fibrose se intercalam com tecido pulmonar normal em meio a focos de fibroblastos (Larsen e

Cols, 2012). Na macroscopia, estas lesões predominam nas regiões pulmonares subpleurais, parasseptais e basais. Fisiopatologicamente, a PIU pode apresentar causas conhecidas que levaram à injúria dos pneumócitos tipo I e ao consequente processo colagênico ocasionando a fibrose progressiva. Portanto, em pacientes com PIU já estabelecida por critérios histológicos ou tomográficos, o diagnóstico de FPI exige a exclusão de outras causas conhecidas de doença pulmonar intersticial, como exposições ambientais domésticas e ocupacionais, doença do tecido conjuntivo e toxicidade medicamentosa (Raghu e Cols, 2011).

No que diz respeito a etiologias estabelecidas para o padrão de PIU, com o constante surgimento de novos medicamentos e aumento da possibilidade de interações medicamentosas, tem merecido atenção especial o diagnóstico das pneumopatias induzidas por fármacos (Cooper e Cols, 1986). Medicamentos como quimioterápicos, antimicrobianos, drogas ilícitas, fármacos cardiovasculares e uma miscelânea de outros medicamentos podem provocar alterações pulmonares, entre elas a própria PIU (Cooper e Cols, 1986). Doenças do tecido conjuntivo e artrites soropositivas comprometem o aparelho respiratório em dois terços dos casos, sobretudo o Lúpus Eritematoso Sistêmico, a Artrite reumatóide e a Esclerose Sistêmica, nas quais, principalmente o pulmão se encontra envolvido (Lamblin e Cols, 2001). Em relação às vasculites (angiites) sistêmicas, as que mais frequentemente comprometem o pulmão são as vasculites de pequenos vasos associadas a anticorpo citoplasmático antineutrófilo (ANCA): granulomatose de Wegener, Granulomatose de Churg-Strauss e Poliangiite microscópica, cujas apresentações clínicas, radiológicas e achados histológicos, em conjunto, devem ser avaliados para diagnóstico de possível causa de PIU (Queluz e Cols, 2005). Por fim, as doenças pulmonares ocupacionais ocorrem após inalação de substâncias e

microorganismos sensibilizantes eventualmente presentes no ambiente de trabalho, embora certos agressores, como poeiras, gases ou vapores, possam estar presentes também no domicílio (Mohr, 2004). O espectro de lesões resultantes é amplo, entre elas destacam-se as DPI e pneumoconioses (Algranti e Cols, 1995; Lido e Cols, 2008).

Excluídas todas as diversas possíveis causas da PIU, o diagnóstico mais provável passa a ser a FPI. Quando a doença parenquimatosa é identificada através da história clínica e dos exames de imagem e há, portanto, forte suspeita de FPI, três perguntas devem orientar a investigação subsequente: Há uma causa conhecida? Se não há causa, o padrão clínico e tomográfico encontrado é de FPI? Se o padrão não é de FPI, está recomendada uma biópsia pulmonar?

1.5 Diagnóstico

Durante vários anos, o diagnóstico das diversas formas de DPI era feito somente através da biópsia pulmonar cirúrgica, demonstrando o padrão histológico específico. Este achado anatomopatológico, quando associado ao quadro clínico e radiológico condizente, fechava o diagnóstico final da DPI em questão. Para o diagnóstico definitivo da FPI é necessário o padrão histológico corresponde à PIU associado aos 3 demais critérios clínicos: (1) Exclusão de outras causas de doenças pulmonares intersticiais; (2) Testes de função pulmonar anormais ou alteração na troca gasosa; e (3) imagens condizentes com o diagnóstico.

Na última década, após a declaração internacional ATS / ERS / JRS / ALAT sobre FPI publicada em 2011 (Raghu e Cols, 2011) ficou estabelecido que um diagnóstico de PIU pudesse ser feito com a adequada interpretação da TC-AR, por

radiologista experiente, evitando assim a biópsia pulmonar. Em pacientes com achados característicos de PIU na TC-AR ou na biópsia, quando realizada, o diagnóstico de FPI exige inicialmente a exclusão de outras causas conhecidas de doença pulmonar intersticial, como exposições ambientais domésticas ou ocupacionais, doença do tecido conjuntivo, vasculites e toxicidade por medicamentos, haja vista que nesses casos o diagnóstico seria de PIU secundária à etiologia estabelecida, o que muda a conduta terapêutica e o prognóstico do paciente (Raghu e Cols, 2011). Consequentemente, com a interpretação correta da TC-AR, poucos pacientes provavelmente portadores de FPI necessitam de biópsia pulmonar cirúrgica para confirmação diagnóstica quando a tomografia é condizente com PIU somada à adequada apresentação clínica (Olson e Cols, 2012).

Mesmo com a interpretação da TC-AR e das apresentações anatomopatológicas, a abordagem diagnóstica multidisciplinar é essencial para estabelecer o diagnóstico final de FPI (Baddini-Martinez e Cols, 2015; Raghu e Cols, 2011). Sabe-se que a acurácia diagnóstica da FPI aumenta quando realizada em conjunto a avaliação clínica, radiológica e histológica (Flaherty e Cols, 2004) por melhorar a concordância entre observadores e evitar possíveis procedimentos diagnósticos sujeitos à riscos, como a biópsia pulmonar cirúrgica (Mikolasch e Cols 2016). Em um estudo com 58 casos consecutivos de PII, Flaherty e cols (2004) forneceram diversas informações para pneumologistas, radiologistas e patologistas experientes sobre casos de DPI e posteriormente permitiram a discussão entre os especialistas para estabelecerem um diagnóstico definitivo, em grupo. Conforme novas informações foram fornecidas e as discussões multidisciplinares ocorreram, o nível de concordância diagnóstica melhorou para as DPI. Atualmente, centros especializados em FPI possuem melhor acurácia diagnóstica em comparação com

os demais (Hunninghake e Cols, 2001). Por razões não totalmente estabelecidas, o encaminhamento precoce para centros de referência melhora a sobrevida de pacientes com FPI (Lamas e Cols, 2011).

1.6 Padrões de Imagem na Tomografia Computadorizada de Tórax

Entre os achados tomográficos definitivos de PIU incluem-se o predomínio basal (subpleural) da doença, anormalidades reticulares, faveolamento com ou sem bronquiectasias de tração e ausência de fatores inconsistentes com padrão de Pneumonia Intersticial Usual (International ATS; ERS Multidisciplinary Consensus, 2001). Entre os achados radiográficos supracitados, o mais comum na FPI, descrito em aproximadamente 80% dos pacientes que tem a doença comprovada por biópsia (evidenciando padrão de PIU), consiste nas opacidades lineares bilaterais, irregulares, levando ao padrão reticular (Carrington e Cols, 1978; Grenier e Cols, 1994), que em 60% a 80% dos casos acometem predominantemente as zonas pulmonares inferiores (Müller e Cols, 1987; Grenier e Cols, 1991). Com a progressão da fibrose, o padrão reticular torna-se mais grosseiro, e há perda progressiva do volume pulmonar com posterior aparecimento de faveolamento.

As anormalidades reticulares constituem o critério inicial necessário para o diagnóstico de PIU na tomografia, definido como uma coleção de inúmeras pequenas opacidades lineares que produzem uma aparência semelhante a uma rede (Figura 3) (Hansell e Cols, 2008). Os componentes do padrão reticular são melhores visualizados na TC-AR, onde são geralmente caracterizadas como pertencentes a um dos três seguintes padrões: (a) espessamento de septos interlobulares, (b) faveolamento, e (c) espessamento intersticial intralobular, que às

vezes podem ser vistos juntos. Os dois primeiros achados geralmente estão associado às DPI, mas também à congestão pulmonar e infecções (por exemplo, viral) sendo estas os principais diagnósticos diferenciais (Hansell e Cols, 2008). O espessamento do interstício intralobular é mais inespecífico, não sendo tão característico das DPI, portanto.

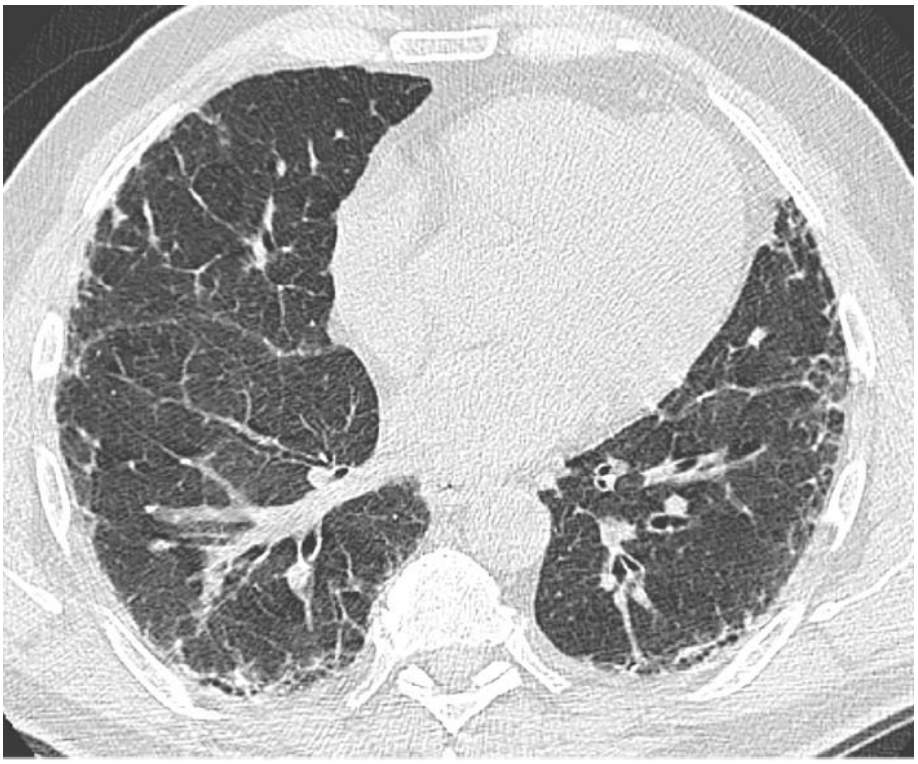


Figura 3: TC de tórax de um homem de 61 anos de idade com FPI. Existem diversas áreas de espessamento difuso dos septos interlobulares, predominantemente nas zonas pulmonares corticais (Webb e Cols, 2015).

A apresentação característica em rede ocorre devido ao espessamento dos septos interlobulares, que delimitam o lóbulo pulmonar secundário, a menor unidade pulmonar margeada por estes septos conjuntivos, que mede de 1 a 2,5 cm de diâmetro e apresentam-se na TC-AR com forma poligonal (Figura 4). Os lóbulos

secundários são facilmente visíveis na superfície do pulmão em especial quando esses septos estão espessados, como na PIU e em demais DPI (Webb e Cols, 2006).

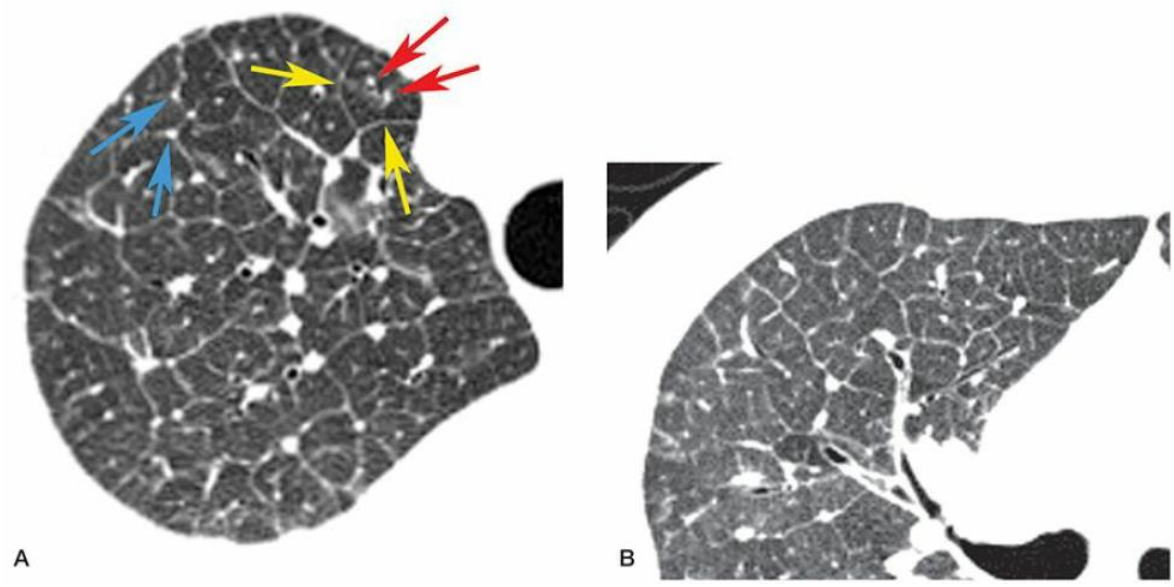


Figura 4: Espessamento septal interlobular na TC de dois pacientes com edema pulmonar. (a) O espessamento é reconhecido devido às linhas delimitando lóbulos pulmonares secundários reconhecíveis (flechas amarelas), todas estas unidades possuem uma artéria lobular central (flechas vermelhas). Pequenas opacidades nodulares vistas junto aos septos espessados representam ramos da veia pulmonar (flechas azuis). (b) numerosos septos interlobulares visíveis no lobo pulmonar superior. Leve espessamento peribroncovascular também é visível, sendo comumente relacionado ao espessamento septal (Webb e Cols, 2015).

O faveolamento é um importante critério tomográfico, que quando presente fecha o diagnóstico de fibrose pulmonar, sendo muito indicativo de PIU (Akira e Cols, 1993; Raghu e Cols, 2011). É definido patologicamente pela presença de

pequenos espaços císticos contendo ar, geralmente alinhados por epitélio bronquiolar e com paredes espessass compostas por tecido fibroso denso. Na TC-AR produz imagens císticas caracteríticas, geralmente de 3 milímetros à 1 centímetro de diâmetro e com paredes espessas (1 a 3mm) (Sakai e Cols, 2003; Raghu e Cols, 2011). Estes cistos são preenchidos com ar, apresentando-se mais radioluscentes em relação ao parênquima pulmonar normal (Figura 5). Outras características importantes incluem a localização imediatamente subpleural dos cistos e sua disposição agregada em múltiplas camadas.

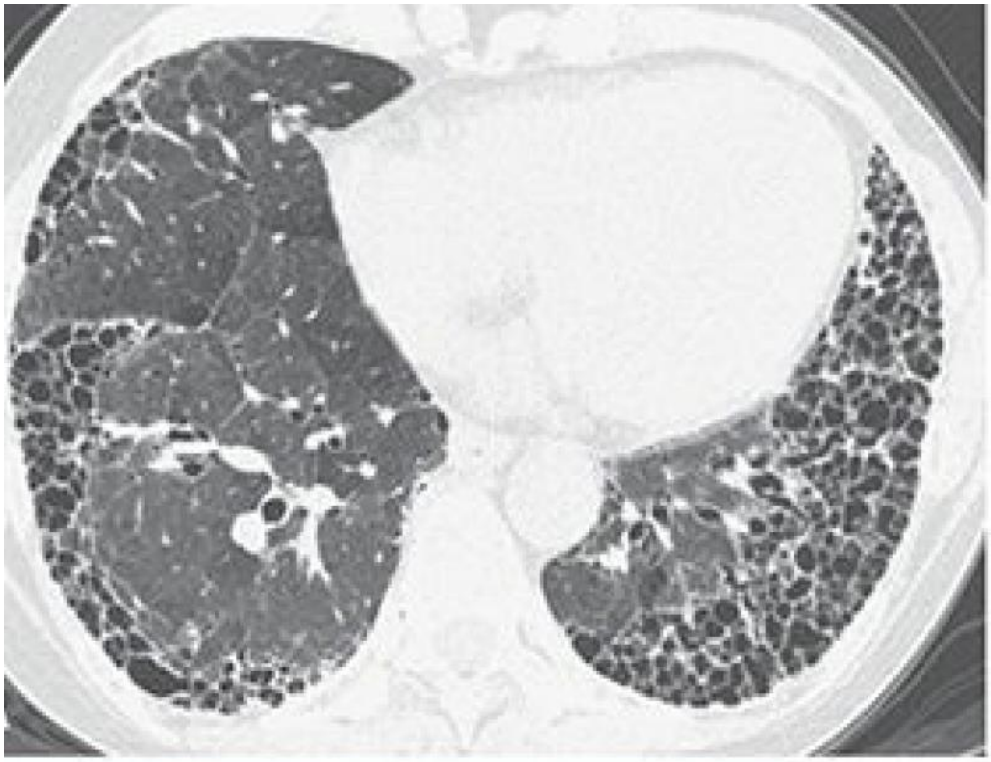


Figura 5: TC-AR demosntrando faveolamento nas regiões periféricas e subpleurais. Notar a presença de cistos preenchidos por ar, menores que 1cm de diâmetro com paredes espessas e facilmente reconhecíveis (Webb e Cols, 2015).

A combinação dos 4 achados citados para PIU prevê o diagnóstico patológico em 95 a 100% das situações. No entanto, nem todos os casos de PIU atenderão a esses critérios. Quando o faveolamento não esta presente, mas a TC-AR apresenta anormalidades reticulares, predomínio subpleural e basal e ausência de fatores inconsistentes com PIU, tem-se a definição de PIU provável. Nessa situação, o acompanhamento clínico e radiológico deve ser mantido, haja vista a possibilidade da progressão de uma eventual fibrose pulmonar com posterior surgimento do faveolamento (American Thoracic Society, 2000). Em fases iniciais de fibrose, apenas alguns cistos subpleurais característicos de faveolamento podem ser visíveis, mas é aconselhado reservar o diagnóstico deste achado somente quando a TC-AR mostra agrupamentos ou linhas agregadas claramente definidas, dotadas destes cistos subpleurais com parede espessa. Portanto, geralmente é uma boa idéia ser conservador ao descrever este achado, pois significa que a fibrose pulmonar está presente, sendo o faveolamento um critério essencial no diagnóstico de PIU e FPI (Hansell e Cols, 2008; Raghu e Cols, 2011).

Outro termo citado, correspondente à uma alteração pulmonar também presente no padrão de PIU, e detectada na TC-AR, consiste nas bronquiectasias de tração que representam dilatações irregulares das vias aéreas (Figura 6). No caso da PIU, este achado é melhor explicado como resultado da proliferação bronquiolar associada à tração mecânica exercida pelo parênquima pulmonar em fibrose progressiva (Piciucchi e Cols, 2016). Estudos recentes sugeriram que bronquiectasia de tração e faveolamento são partes de um espectro da apresentação pertencentes a um processo único e contínuo de displasia bronquiolar proliferativa que ocorre na fisiopatologia da PIU (Piciucchi e Cols, 2016).

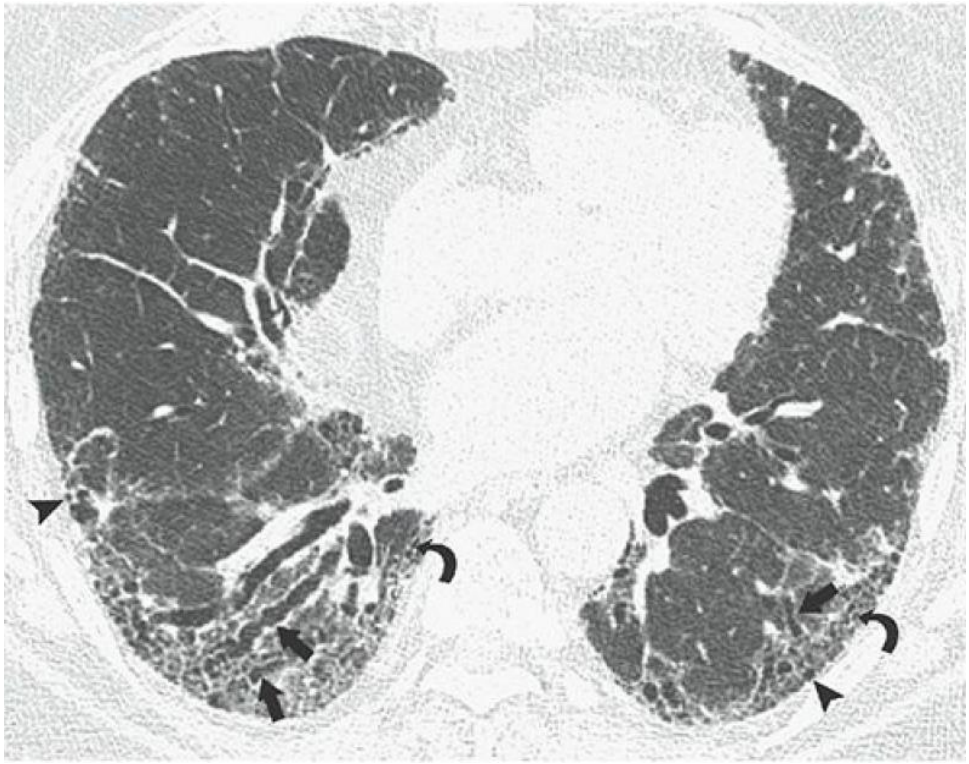


Figura 6: Bronquiectasias de tração em um paciente, masculino, com 75anos de idade diagnosticado com FPI. TC-AR demonstra padrão reticular periférico predominando nas regiões dorsais dos lobos inferiores. Os Brônquios entre as áreas de reticulação estão dilatados e distorcidos (bronquiectasias de tração) (flechas), sendo também visíveis próximos à superfície pleural (flechas curvas). Há presença de faveolamento (*setas*) adjacente à pleura (Webb e Cols, 2015).

Conforme exposto, o padrão reticular, faveolamento e bronquiectasias de tração, quando predominam nas bases pulmonares, sugerem o diagnóstico de PIU por serem as apresentações mais comuns na TC-AR destes pacientes. No entanto é de fundamental importância que os radiologistas estejam familiarizados com os achados tomográficos inconsistentes com o padrão de PIU. Entre estes achados, está incluído o Aprisionamento Aéreo ou a evidência de perfusão em mosaico quando bilateral, em três ou mais lóbulos, que uma vez presente, o foco diagnóstico

passa a ser principalmente a Pneumonia de Hipersensibilidade (PH) (Visscher e Cols, 2006), por ser esta a DPI que possui o aprisionamento aéreo como um dos principais achados tomográficos (Figura 7) (Chung e Cols, 2001). Em certas formas de PH crônicas, a TC-AR é igual ao padrão de PIU, por também apresentar redução do volume pulmonar, presença de opacidades lineares e faveolamento (Lynch e Cols, 1995). Alterações como cistos e predomínio do acometimento nas regiões superiores do pulmão auxiliam a diferenciar a PH crônica da PIU (Silva e Cols, 2008).

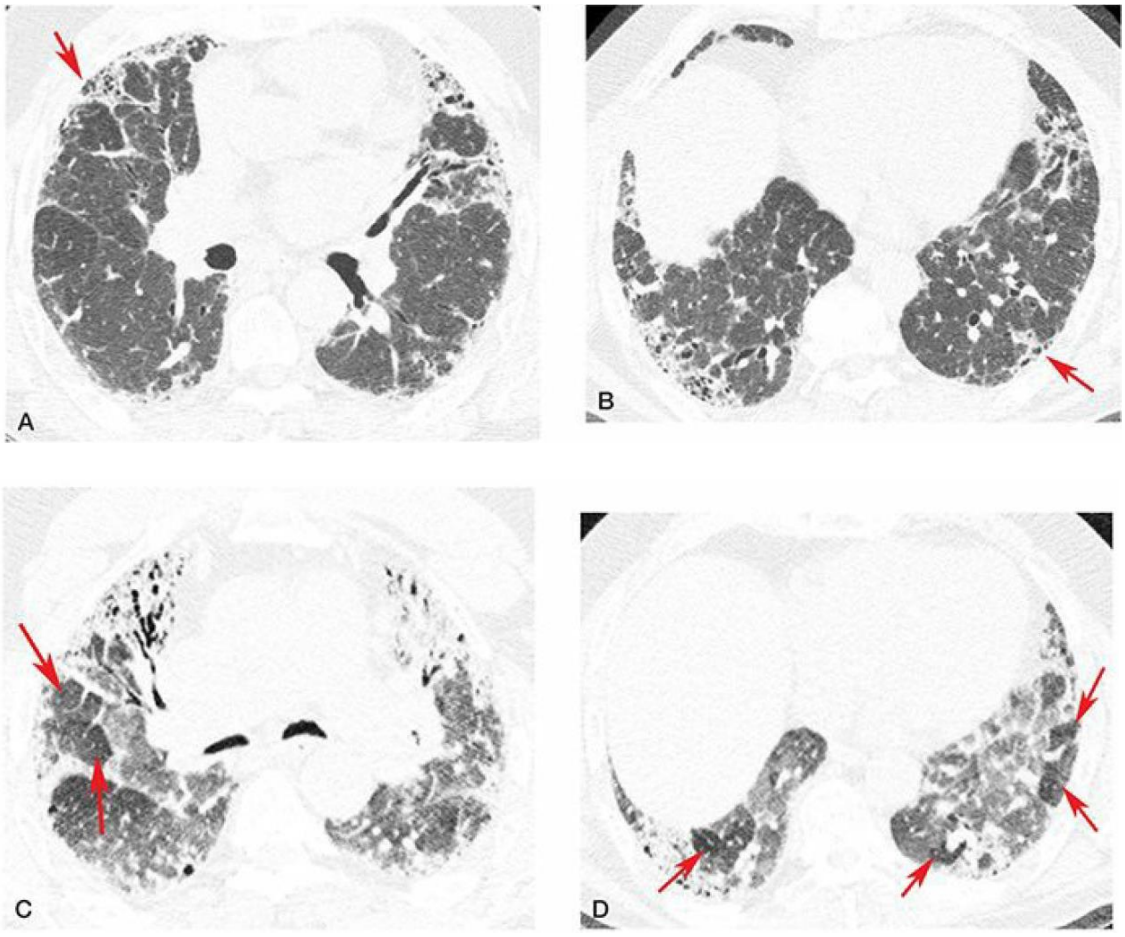


Figura 7: TC-AR inconsistente com PIU em paciente com PH crônica e faveolamento.(a) e (b) Imagens em inspiração revelam anormalidade reticular, bronquiectasias de tração e faveolamento (flechas). (c) e (d) imagens obtidas na expiração mostram aprisionamento aéreo em múltiplos lóbulos (flechas), um achado inconsistente com PIU.

Outros demais achados, considerados inconsistentes com PIU incluem o predomínio em zonas pulmonares médias ou superiores, predomínio peribroncovascular do acometimento pulmonar, presença de consolidações, opacidades extensas em vidro-fosco, micronódulos difusos e cistos discretos (múltiplos, bilaterais, sem característica de faveolamento) (Raghu e Cols, 2011**).** A tabela abaixo sumariza os achados diagnósticos da PIU na TC-AR (American Thoracic Society, 2000). Cada um destes achados é típico de uma DPI diferente da PIU, ou de uma outra forma de doença pulmonar.

Tabela 1: Critérios na TC-AR para o diagnóstico de PIU.

Padrão de PIU	**Possível padrão PIU**	**Inconsistente com padrão PIU**
Predomínio subpleural, basal	Os mesmos critérios para padrão PIU definido, mas faveolamento não está presente	predomínio em zonas pulmonares médias ou superiores
Anormalidade reticular		predomínio peribroncovascular do acometimento pulmonar
Faveolamento com ou sem bronquiectasias de tração		opacidades extensas em vidro-fosco (mais extensas em relação ao acometimento reticular)
Ausência de fatores inconsistentes com padrão de PIU		Micronódulos difusos
		Cistos discretos
		Atenuação em mosaico difusa ou aprisionamento aéreo (bilateral, em 3 ou mais lobos)
		Consolidações em segmentos pulmonares ou lobos
* Todos os 4 critérios devem estar presentes † Qualquer um dos 6 critérios pode estar presente Adaptado de Raghu e Cols, 2011		

Em casos onde as características na TC-AR estão ausentes, ou quando há a presença de critérios inconsistentes com o padrão de PIU, a biópsia pulmonar cirúrgica é necessária para confirmação diagnóstica definitiva, constituindo ainda o padrão áureo para o diagnóstico das DPI (Raghu e Cols, 2011). No entanto, este procedimento apresenta algumas limitações, principalmente pelo fato de ser invasivo e proporcionar acesso somente a uma pequena parte do pulmão visível durante a cirurgia. Consequentemente, a amostra coletada pode não ser representativa do pulmão como um todo e a presença de inflamação e possível fibrose pode ser perdidas por não terem sido biopsiadas, haja vista que diferentes lobos pulmonares apresentam graus variados de acometimento pela doença. Ademais, diferentes lobos podem apresentar diferentes formas de acometimento intersticial (Flaherty e Cols, 2001). O fato de ser um procedimento invasivo justifica a relutância dos clínicos para sua indicação, haja vista que os pacientes acometidos por alguma forma de DPI não diagnosticada tendem a apresentar riscos quando submetidos à biópsia devido à própria doença de base. A taxa de mortalidade varia de 3-4% e complicações ocorrem em cerca de 16% dos casos (Kaarteenaho e Cols, 2013), em internações que duram em média 2 – 4 dias (Monaghan e Cols, 2004). Atualmente, com a utilização adequada dos critérios da ATS/ERS de 2011, cerca de dois terços dos pacientes são diagnosticados como portadores de FPI com base na associação clínica e radiológica (Raghu e Cols, 1999).

Este estudo foi desenvolvido com intuito de identificar e descrever a frequência de aprisionamento aéreo nos pacientes com padrão de PIU na TC-AR e correlacionar sua presença com o desfecho clínico, haja vista que recentemente tem se observado este achado em tais pacientes, o que trouxe o questionamento sobre seu significado como critério de exclusão para verdadeiro padrão de PIU na

tomografia de tórax. Esta é uma questão relevante, visto que a análise radiológica previa é de fundamental importância no diagnóstico, podendo poupar o paciente da biópsia pulmonar cirúrgica.

1.7 Referências Bibliográficas

Burgel PR, Bergeron A, de Blic J, et al. Small airways diseases, excluding asthma and COPD: an overview. Eur Respir Ver 2013;22(128):131–147.

Kligerman, S.J., Henry, T., Lin, C.T. et al*,* Mosaic attenuation: etiology, methods of differentiation, and pitfalls. Radiographics*.* 2015;35:1360–1380.

Park CS, Müller NL, Worthy SA, Kim JS, Awadh N, Fitzgerald M. Airway obstruction in asthmatic and healthy individuals: inspiratory and expiratory thin- section CT findings. Radiology 1997;203(2):361–367.

Webb WR, Stern EJ, Kanth N, Gamsu G. Dynamic pulmonary CT: findings in healthy adult men. Radiology. 1993;186(1):117-24.

Pipavath SJ, Lynch DA, Cool C, Brown KK, Newell JD. Radiologic and pathologic features of bronchiolitis. AJR Am J Roentgenol 2005;185(2):354–363.

Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. Am J Respir Crit Care Med 2003;168(11):1277–1292.

S. Bommart et al. Relationship between CT air trapping criteria and lung function in small airway impairment quantification, BMC Pulmonary Medicine 2014: 10.1186/1471-2466-14-29.

Mets OM, Zanen P, Lammers JW, et al. Early identification of small airways disease on lung cancer screening CT: comparison of current air trapping measures. Lung 2012; 190: 629–633.

Wallace T. Miller, Jr, Jonathan Chatzkel, Michael G. Hewitt. Expiratory Air Trapping on Thoracic CT: A Diagnostic Subclassification, ATS 2014: 201311-390.

Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013;188(6):733–748.

American Thoracic Society. Idiopathic pulmonar fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the Eurpean Respiratory Society (ERS) Am J Resp Crit Care Med. 2000.

American Thoracic Society/European Respiratory Society internation multidisciplinar consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002.

Zanon M, Hochhegger B, Marchiori E, et al. Imaging in idiopathic pulmonary fibrosis: diagnosis and mimics. Clinics, 2017, 0225.R1, in press.

Raghu G, Collard HR, Egan JJ, et al. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. *Am J Respir Crit Care Med* [Internet] 2011;183(6):788–824.

Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011 Feb 15;183(4):431-40. doi: 10.1164/rccm.201006-0894CI.

Gribbin J, Hubbard RB, Le Jeune I, Smith CJ, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax 2006;61:980–985.

Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis: epidemiologic approaches to occupational exposure. Am J Respir Crit Care Med 1994;150:670–675.

Martinez FJ, Flaherty K. Pulmonary function testing in idiopathic interstitial pneumonias. *Proc Am Thorac Soc* 2006;3(4):315–321.

Chilosi M, Doglioni C, Murer B, Poletti V. Epithelial stem cell exhaustion in the pathogenesis of idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2010;27(1):7-18

Wolters PJ, Collard HR, Jones KD. Pathogenesis of idiopathic pulmonar fibrosis. Annu Rev Pathol. 2014;9:157-79

Galvin JR, Frazier AA, Franks TJ. Collaborative radiologic and histopathologic assessment of fibrotic lung disease. *Radiology* 2010;255(3):692–706.

King TE Jr, Pardo A, Selman M. Idiopathic pulmonary fibrosis. *Lancet* 2011;378(9807):1949–1961.

Leslie KO, Cool CD, Sporn TA, et al. Familial idiopathic interstitial pneumonia: histopathology and survival in 30 patients. *Arch Pathol Lab Med* 2012;136(11):1366–1376.

Larsen BT, Colby TV. Update for pathologists on idiopathic interstitial pneumonias. *Arch Pathol Lab Med* 2012;136(10):1234–1241.

Cooper JA Jr, White DA, Matthay RA. Drug-induced pulmonary disease. Part 1: cytotoxic drugs. Am Rev Respir Dis. 1986;133(2):321-40.

Cooper JA Jr, White DA, Matthay RA. Drug-induced pulmonary disease. Part 2: Noncytotoxic drugs. Am Rev Respir Dis. 1986;133(3):488-505.

Lamblin C, Bergoin C, Saelens T, Wallaert B. Interstitial lung diseases in collagen vascular diseases. Eur Respir J Suppl. 2001;32:69s-80s.

Queluz TT, Yoo HHB. Vasculites pulmonares: novas visões de uma velha conhecida. J Bras Pneumolo. 2005;31(supl 1):s1-3.

Mohr LC. Hypersensitivity pneumonitis. Curr Opin Pulm Med. 2004;10(5):401-11.

Algranti E, Souza Filho AJ de, Mendonça EMC de, Silva RCC da, Alice SH. Pneumoconiose de mineiros de carvão: dados epidemiológicos de minas da bacia carbonífera brasileira. J Pneumol. 1995;21(3):168-72.

Lido AV, Kitamura S, Oliveira JI, Lucca SR de, Azevedo VAZ de, Bagatin E. Exposição ocupacional e ocorrência de pneumoconioses na região de Campinas (SP) Brasil, 1978 – 2003. J Bras Pneumol. 2008;34(6):367-72.

AL. Olson, et al. Idiopathic Pulmonary Fibrosis: Diagnosis and Epidemiology; Clin Chest Med 33 (1), 41- 50.3 2012.

Baddini-Martinez J, Baldi BG, Costa CH, Jezler S, Lima MS, Rufino R. Update on diagnosis and treatment of idiopathic pulmonar fibrosis. J Bras Pneumol. 2015;41(5):456-466.

Flaherty KR, King TE, Raghu G, Lynch JP, Colby TV, Travis WD, Gross BH, Kazerooni EA, Toews GB, Long Q, Murray S, Lama VN, Gay SE, Martinez FJ: Idiopathic interstitial pneumonia: what is the effect of a multidisciplinar approach to diagnosis?. Am J Respir Crit Care Med. 2004, 170: 904-910.10.1164/rccm 200402 – 147OC.

TA Mikolasch, HS Garthwaite, JC Porter. Update in diagnosis and management of interstitial lung disease, Clinical Medicine 2016 Vol 16, No 6: s71–s78.

Hunninghake GW, Zimmerman MB, Schwartz DA, et al. Utility of a lung biopsy for the diagnosis of Idiopathic pulmonar fibrosis. Am J Resp Crit Care Med 2001;164: 193-6.

Lamas Dj, Kawut SM, Bagliella E, et al. Delayed access and survival in idiopathic pulmonar fibrosis: a cohort study. Am J Resp Crit Care Med 2011; 184(7):842 – 7

International ATS; ERS Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the ATS and ERS was adopted by the ATS board of directors, June 2001 and ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2001; 165:277 – 304.

Carrington CB, Gaensler EA, Coute RE, et al. Natural history and treated course of usual and desquamative interstitial pneumonia. *N Engl J Med* 1978;298:801–809.

Grenier P, Chevret S, Beigelman C, et al. Chronic diffuse infiltrative lung disease: determination of the diagnostic value of clinical data, chest radiography, and CT with Bayesian analysis. *Radiology* 1994;191:383–390.

Müller NL, Guerry-Force ML, Staples CA, et al. Differential diagnosis of bronchiolitis obliterans with organizing pneumonia and usual interstitial pneumonia: clinical, functional, and radiologic findings. *Radiology* 1987;162:151–156.

Grenier P, Valeyre D, Cluzel P, et al. Chronic diffuse interstitial lung disease: diagnostic value of chest radiography and highresolution CT. *Radiology* 1991;179:123–132.

Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722.

Webb WR. Thin-section CT of the secondary pulmonary lobule: anatomy and the image – the 2004 Fleischner lecture. Radiology. 2006;239 (2):322-38.

Webb W, Müller N, Naidich D. *High-resolution CT of the lung*. 5th Edition. Philadelphia. Wolters Kluwer Health, 2015.

Akira M, Sakatani M, Ueda E. Idiopathic pulmonary fibrosis: progression of honeycombing at thin-section CT. *Radiology* 1993;189:687–691.

Sakai S, Ono M, Nishio T, et al. Lung cancer associated with diffuse pulmonary fibrosis: CT-pathologic correlation. *J Thorac Imaging* 2003;18(2):67–71.

Hansell DM, Bankier AA, MacMahon H, et al. Fleischner society: glossary of terms for thoracic imaging. *Radiology* 2008;246:697–722

Piciucchi S, Tomassetti S, Ravaglia C, et al. From "traction bronchiectasis" to honeycombing in idiopathic pulmonary fibrosis: A spectrum of bronchiolar remodeling also in radiology? BMC Pulm Med. 2016;16(1):87.

Visscher DW, Myers JL. Histologic spectrum of idiopathic interstitial pneumonias. Proc Am Thorac Soc 2006;3:322–329.

Chung MH, Edinburgh KJ, Webb EM, McCowin M, Webb WR. Mixed infiltrative and obstructive disease on high-resolution CT: differential diagnosis and functional correlates in a consecutive series. J Thorac Imaging. 2001 Apr;16(2):69-75.

Lynch DA, Newell JD, Logan PM, et al. Can CT distinguish hypersensitivity pneumonitis from idiopathic pulmonar fibrosis? AJR Am J Roentgenol 1995: 165:807-11

Silva CIS, Muller NL, Lynch DA et al. Chronic hypersensitivity pneumonits: differentiation from idiopathic pulmonar fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology 2008; 246:288-97

Flaherty KR, Travis WD, Colby TV, et al. Histopathologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med* 2001;164(9):1722–1727.

Kaarteenaho R. The current position of surgical lung biopsy in the diagnosis of idiopathic pulmonary fibrosis . *Respir Res* 2013 ; 14 : 43.

Monaghan H, Well Au et al. Prognostic implications of histologic patterns in multiple surgical lung biopsies from patients with idiopathic interstitial pneumonias, Chest 2004; 125:522 – 6.

Raghu G et al. The accuracy of the clinical diagnosis of new-onset idiophatic pulmonar fibrosis and other interstitial lung disease: a prospective study. Chest 1999, 116:1168 – 1174. 10.1378/chest 116.5.1168.

2. Objetivos

2.1 Objetivo Geral

Identificar e caracterizar o aprisionamento aéreo na Tomografia de Tórax de Alta Resolução em pacientes portadores de Fibrose Pulmonar Idiopática (FPI) e Pneumonia Intersticial Usual (PIU) e avaliar o impacto deste achado sobre a mortalidade.

2.2 Objetivos secundários

Avaliar a necessidade de biópsia pulmonar cirúrgica para o diagnóstico de Pneumonia Intersticial Usual em casos onde o aprisionamento aéreo está presente.

Quantificar o grau de aprisionamento aéreo nos pacientes portadores de FPI e PIU com etiologia definida.

3. Artigo científico Redigido em Inglês

Air trapping in the Usual Interstitial Pneumonia pattern: diagnostic characterization and prognosis

Short tittle: Air trapping in Usual Interstitial Pneumonia

Enviado para publicação na revista: Respiratory Medicine

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Background: Our purpose was to evaluate the frequency of air trapping in patients with usual interstitial pneumonia (UIP) pattern on a high-resolution computed tomography (HRCT) and access the impact of this finding on mortality.

Methods*:* The current study included 74 patients with UIP pattern on HCRT. Idiopathic pulmonary fibrosis (IPF) was diagnosed by surgical lung biopsy or multidisciplinary team approach. Air trapping on HCRT was defined as the percentage of lung voxels in expiratory CT images with attenuation between below -856HU (ATIexp) >6% or expiratory to inspiratory ratio of mean lung density (E/I-ratio) >0.87. Survival analysis was performed. Death and lung transplantation were the outcomes.

Results*:* In 74 patients with radiological findings of UIP, 50 (67.5%) had IPF and 24 (32.5%) UIP secondary to known causes with an average survival of 3 years (CI95% 2.5–3.5) and 4.2 years (CI95%: 3.6–4.7) respectively. Outcome was confirmed in 28 subjects (25 deaths and 3 unilateral lung transplantations).

Air trapping was found in 30 patients (40.5%) by the ATIexp and 29 patients (39.2%) by the E/I-ratio. In the multivariate analysis, presence of air trapping was not associated with the death or transplantation, and diagnosis of IPF (HR 3.57; CI 95% 1.41 – 9.02; p = 0.007) was the only individual factor associated with a higher hazard of the outcome.

Conclusion*:* Air trapping on HCRT had no impact on mortality of patients with IPF or UIP of known etiology, suggesting that the presence of this finding may not require surgical lung biopsy to establish the diagnosis of UIP/IFP.

Introduction

In radiology, air trapping is defined as retention of air during expiration on high-resolution computed tomography (HRCT) and represents the obstruction of small airways. [1] Its proper quantification by software-assisted CT was found to be feasible and reproducible in the literature, [2,3] as pulmonary function tests are not accurate enough to identify this obstruction. [4] Recently, it has been demonstrated that 31% of patients with air trapping have some form of Interstitial Lung Disease (ILD), of which 4% had Idiopathic pulmonary fibrosis (IPF).[2] However, there is little data on the literature describing this finding in usual interstitial pneumonia (UIP).

Idiopathic pulmonary fibrosis is the most common of the ILD, representing the clinical expression of the histopathological and radiological pattern of UIP of unknown cause and carries the worst prognosis. [5,6] Other ILD, such as chronic hypersensitivity pneumonitis (CHP) and connective tissue disease related, can be radiologically expressed as UIP, but must be differentiate from IPF according to their etiological nature as they have different therapeutic and prognostic implications. [5,7,8] According to the current guidelines,[5] the finding of UIP on a HRCT in the absence of any identifiable cause of another ILD is sufficient to the diagnosis of IPF, which spares a patient from the need of a surgical lung biopsy (SLB). The presence of air trapping on HCRT is considered an inconsistent finding of UIP, since it favors CHP as a differential, in which case SLB may be necessary. [5] However, this approach in patients with ILD is associated with substantial hospitalization and mortality rates. [9]

Considering that air trapping was recently associated with UIP and IPF, it is reasonable to question if this CT finding should in fact be considered a criteria of incompatibility of IPF, which could spare patients from SLB. Our goal was to describe

the frequency of air trapping in patients with UIP on the HRCT and correlate these findings with clinical outcome.

Material and Methods

Participants

We retrospectively identified 95 patients with the diagnosis of IUP on HCRT between July 2011 and July 2016. Medical records were reviewed to identify important clinical information, need for SLB, final diagnosis and follow-up of the patient. After the record analysis, 18 patients were excluded for lack of follow-up with a pulmonologist after the initial scan or inadequate medical recording, and other 3 because the initial CT could initially suggest UIP pattern but the hypothesis was rejected after evaluation by another radiologist. As a result, 74 patients were included in the analysis. Patients were divided into two groups according to diagnosis: IPF or UIP with a known etiology. All imaging exams and histological samples were revised. All cases were discussed by a multidisciplinary group (composed by pulmonologist, rheumatologist, radiologist, pathologist) to provide a final diagnosis. The retrospective review of clinical data was approved by the local institutional review board with waiver of consent.

CT protocols

All subjects underwent a paired inspiratory and expiratory chest CT with 16 x 1.25 mm collimation (Advantage Workstation 4.6, GE Healthcare). Scans were performed cranio-caudally using a helical acquisition. Images were reconstructed with a slice thickness and interval of 1.0 mm to achieve near-isotropic voxels. Inspiratory images were acquired at 200 mAs and expiratory images were acquired

at 50 mAs. All images were acquired at 120kVP tube potential, using a pitch of 1.375. A standard reconstruction kernel was used to achieve medium-smooth images. A data matrix of 512 x 512 and a FOV of 35-45 cm^2 were used. No CT dose modulation or intravenous contrast agent was used for this study.

Imaging analysis – variable gauging

Inspiratory and expiratory CT images were evaluated using software designed for the assessment of segmented images from the chest wall, mediastinum, diaphragm, and airways. Automated segmentation of the right and left lungs from the chest wall and mediastinum was performed. Two chest radiologists, each with more than 8 years of experience, independently assessed the CT images blinded to the clinical information. Images were analyzed according to criteria defined in the ATS/ERS 2011.[5] Total lung volume (TLV) and attenuation of all voxels included in the lung segmentation were obtained. The air-trapping index (ATIexp) was calculated as the percentage of lung voxels in expiratory CT images with attenuation between below -856 HU. [10] The mean lung density (MLD) histograms in expiration (MLDexp) and inspiration (MLDinsp) histograms were created for each subject, so the ratio of MLD on expiration and inspiration (E/I-ratio) could be calculated.[11,12] Significant air trapping was defined as ATIexp >6% or E/I-ratio >0.87 according to previous findings in the literature.[12,13] We did not consider the presence of air trapping significant if it was described on the CT only based on the radiologist's observation. All examinations were analyzed in an Advantage Workstation (Advantage Workstation 4.6, GE Healthcare) from one PACS system.

Statistical analysis

Data was presented as frequency and percentage or mean ± standard deviation (SD). Shapiro-Wilk test was used to test for normality. Continuous variables were compared using the independent Student's *t* test. Kaplan-Meier curves compared with log-rank tests were used for cumulative survival analysis. A p-value <0.05 level was considered significant. Survival analysis was performed using Cox proportional hazard regression models: (i) Events were defined as the time to death or unilateral pulmonary transplantation; (ii) censored data was used when the event did not occur at the end of the follow up period. All parameters at a significance level of p-value less than 0.15 in the univariate analysis were included in a multivariate model and considered statistically significant if the overall p-value was less than 0.05.[14] Models were adjusted for all variables. The analysis supported the assumption of proportional hazard. Data were analyzed using Stata software, version 13 (StataCorp, College Station, TX, USA).

Results

Subjects

Baseline characteristics of the study subjects are described in Table 1. The study sample consisted of 74 patients, of which most were male, with a mean age of 66.9 years, and did not have air trapping by either index. Of the 74 patients with radiological diagnosis of IUP, 50 (67.5%) were diagnosed with IPF – 40 of them by multidisciplinary group discussion and the other 10 by surgical lung biopsy. In the group with confirmed etiology, 9 patients had rheumatoid arthritis, 6 conjunctive tissue diseases, 3 microscopic polyangiitis, 3 chronic HP, 1 Wegener's Granulomatosis, 1 pneumoconiosis and 1 amiodarone pulmonary toxicity. Mean ATIexp in the IFP group was 9,47 (95% CI: 6.66 – 12.29), whereas in the non-IFP it

was 5.83 (95% CI: 3.59 – 8.06). Moreover, mean E/I-ratio was 0.84 (95% CI: 0.82 – 0.87) in the IFP group and 0.84 (95% CI: 0.81 – 0.88) in non-IFP group. Figure 1 represents a patient with UIP pattern on HRCT associated with significant air trapping by both index.

Survival analysis by UIP etiology

Death was confirmed in 25 patients and 3 underwent unilateral lung transplantation during follow-up. Mean survival time for IPF was 3 years (IC95%: 2.5–3.5), significantly shorter than patients with IUP by defined etiology (4.2 years; IC95%: 3,6–4,7) (p<0,04). Event-free survival (Figure 2a) was 88% at 1 year, 49% at 3 years, and 15% at 5 years for the IPF group. Survival for the non-IPF group was 96%, 83% and 47% at the same time points (p<0.004).

Survival analysis by air trapping

Air trapping was found in 30 patients (40.5%) by the ATIexp and in 29 patients (39.2%) by the E/I-ratio. The presence of air trapping by either measurement had no significant impact over mortality in patients with UPI considered altogether (Figure 2b and 2c). Survival in patients with IFP remained lower than non-IFP even after stratifying for the presence of air trapping (ATIexp, p<0,038; E/I-ratio, p<0,05). Similar results were found comparing the etiologies in subjects with no evidence of air trapping (ATIexp, p<0,013 e E/I-ratio, p<0,005).

We created regression models to assess the impact of the variables investigated in the all-cause mortality or pulmonary transplantation risk of our cohort (Table 2). In the univariate analysis, diagnosis of IPF was the only variable associated with a significant increased risk of the event (HR 3.57; CI 95% 1.41 –

9.02; p = 0.007). Age and air trapping showed a slight trend to increased risk of the event, although not reaching significance. In the multivariate models, the hazard ratio for IPF remained the only parameter significantly increased with the event, even after adjusting for air trapping and age. Air trapping, either by ATIexp or E/I-ratio, and age were not associated with the event in the final models.

Discussion

We have shown that air trapping is not an infrequent finding in patients with IFP; moreover, there was no difference in the degree of air trapping between IFP and patients with UIP due to other etiology by either index. Moreover, the presence of air trapping had no significant impact in prognosis of patients with UIP on the HCRT. In our multivariate analysis, the diagnosis of IFP was the only individual predictor of mortality in patients with UIP on HCRT, which is consistent with the literature. [5]

The differential clinical diagnosis of radiological UIP is challenging, as there are several conditions other than IPF that must be distinguish by clinical and radiological grounds. Imaging in some cases may be assimilated to non-specific interstitial pneumonia, CPH or sarcoidosis, which may lead to initial difficulty in diagnosis, especially when considered only the imaging exam.[15] The latest ATS/ERS guidelines (2011) emphasized the importance of the multidisciplinary discussion between radiologists, pulmonologists and pathological for the diagnosis of IPF to increase inter-observer agreement.[5,16] In our cohort, cases of typical UIP pattern on HRCT, but associated with air trapping had a multidisciplinary workout to establish the final diagnosis. As a result, SLB was performed only when judged necessary by consensus to spare patients from an unnecessary invasive procedure.[17] The higher

mortality outcome in patients with IFP compared to other types of UIP indicates that diagnoses were made appropriately in our study population.

Small airways obstruction with subsequent air trapping is a common finding in several pulmonary conditions, such as obstructive diseases, bronchiectasis and different ILD.[2,18] The best method currently recommend to measure air trapping is the E/I-ratio,[19] although there is no clear established cutoff value that defines normality. In our study, we have used the cutoff of 0.87, which was found to be the optimal cutoff to depict air trapping in previous studies.[19] In general, the greater the ratio, greater the trapping. [19] Among the ILD, CHP has air trapping as one of the main tomographic findings. [15] In certain types of CPH, HRCT may demonstrate the same pattern of UIP, associated with reduction in pulmonary volume, presence of linear opacities, reticular opacities and honeycombing.[20] The presence of centrilobular nodules, lobular areas with decrease attenuation and predominance for superior areas of lung tend to differentiate CHP from IPF. [21,22] However, these findings were not detected in our sample of 3 patients with chronic HP and the air trapping considering the ATIexp index and the E/I-ratio ratio was not significant either.

Since it is a more invasive procedure, surgical lung biopsy is recommended when it is not possible to establish an appropriate diagnosis using HRCT and other clinical and laboratorial criteria. Its association with a higher risk of morbidity and mortality limits the indication only for patients who may have the clinical course changed depending on the result of histological analysis.[17,23] The mortality rates range from 3 to 4% of cases and complications of this procedure are report in up to 16% of cases.[9] These drawbacks justify a great reluctance of physicians to indicate this procedure.

Often biopsy-proven IPF cases may present as a probable or inconsistent finding of UIP on the HRCT, so that SLB may be necessary.[15,24] Possibly, some of these cases could have been spared from the comorbidities related to SLB. Our study supports the fact that the presence of air trapping alone should not be considered inconsistent the UIP pattern, as it has shown to be a not so infrequent finding in our population of patients with IPF. Moreover, air trapping has shown to not change the prognosis of these patients.

Our study has some limitations. First is the numeric difference between the two groups. Second is the fact that the research is conducted in just one center. Our institution is a local reference center for diagnosis and management of ILD, especially IPF, fact that may justify the greater prevalence of this diseases compared to UIP due to other causes. For this reason, the sample selection may not represent the reality of other populations, although the clinical outcome of our cohort resembles previous findings in the literature.[25]

Conclusion

The degree of air trapping, measured by currently recommended objective methods, did not have any significant impact in the outcome of patients with IPF or UIP secondary to a known etiology. Surgical lung biopsy may not be necessary to establish the final diagnosis in patients with typical UIP pattern on HRCT but associated with air trapping.

Table 1

Table 1. Baseline characteristics.

Parameter	N=74
Male	41 (55.4)
Age in years	66.7±11.5
IPF	50 (67.5)
ATIexp	
> 6.000	30 (40.5)
TLVinsp	3319.94±1168.82
MLDexp	-619.76±74.45
MLDinsp	-732.68±56.71
E/I-ratioMLD, > 0.87	29 (39.2)
Follow-up in years	2,55±1.27
Death or Transplantation	28 (37.8)

All Variables are expressed as frequency (%) or mean ±SD. IPF, xxx;

Table 2

Table 2. Cox regression analysis for all-cause mortality or unilateral lung transplantation

Parameter	Univariate analysis		Multivariate analysis for ATIexp		Multivariate analysis for E/I-ratioMLD	
	HR (95% CI)	*P*[a]	HR (95% CI)	*P*[b]	HR (95% CI)	*P*[b]
Male	1.16 (0.56–2.38)	.683	-	-	-	-
Age, years	1.03 (0.99–1.08)	.094	1.01 (0.99–1.08)	.482	1.01 (0.97–1.05)	.094
IPF	3.57 (1.41–9.02)	.007	3.98 (1.54–10.2)	.004	4.02 (1.57–10.2)	.004
ATIexp, > 6.000	1.73 (0.83–3.60)	.141	1.39 (0.64–3.03)	.403	-	.-
E/I-ratioMLD, > 0.87	1.99 (0.63–4.14)	.063	-	-	1.84 (0.88–3.81)	.100

Note: IPF, Idiopathic pulmonary fibrosis; HR, hazard ratio; CI, confidence interval.

[a] Parameter associated with the event (*P* less than 0.15) in the univariate analysis were included in a multivariate model.

[b] All multivariate models were adjusted for all variables.

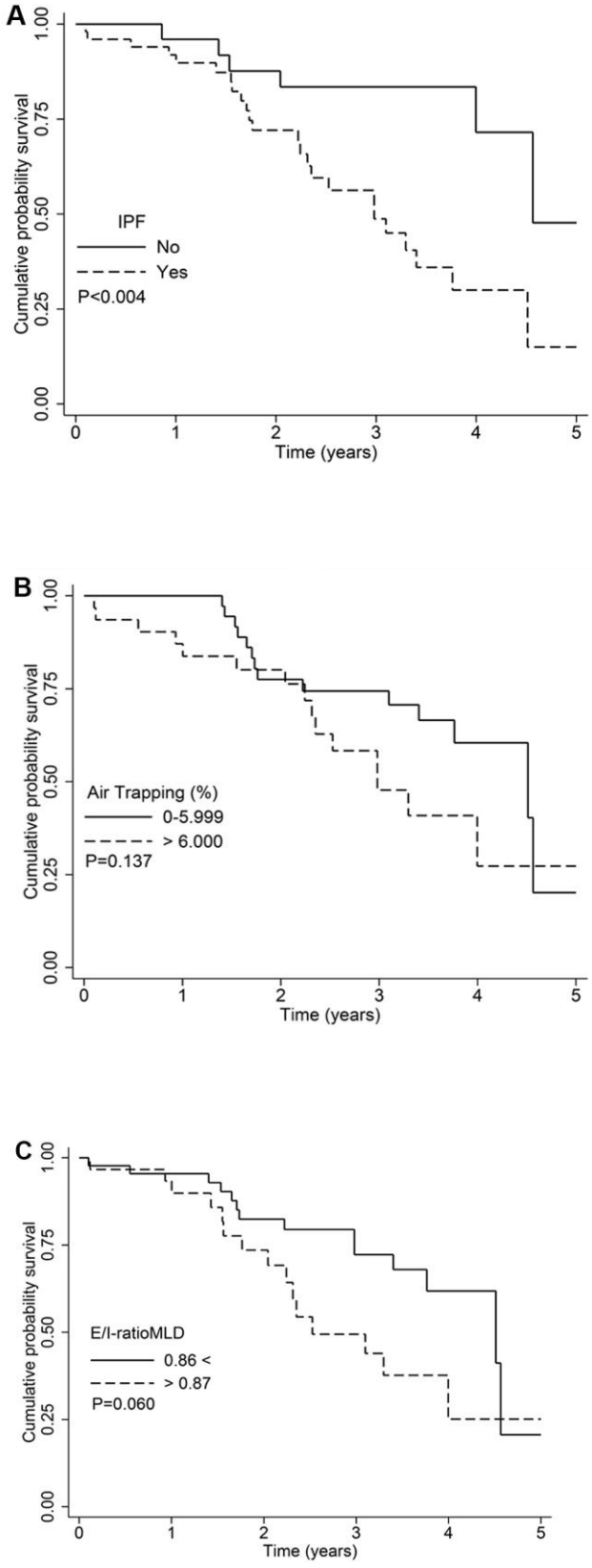

Figure Legends

Fig. 1. Kaplan-Meier survival analysis according to etiology and presence of air trapping.

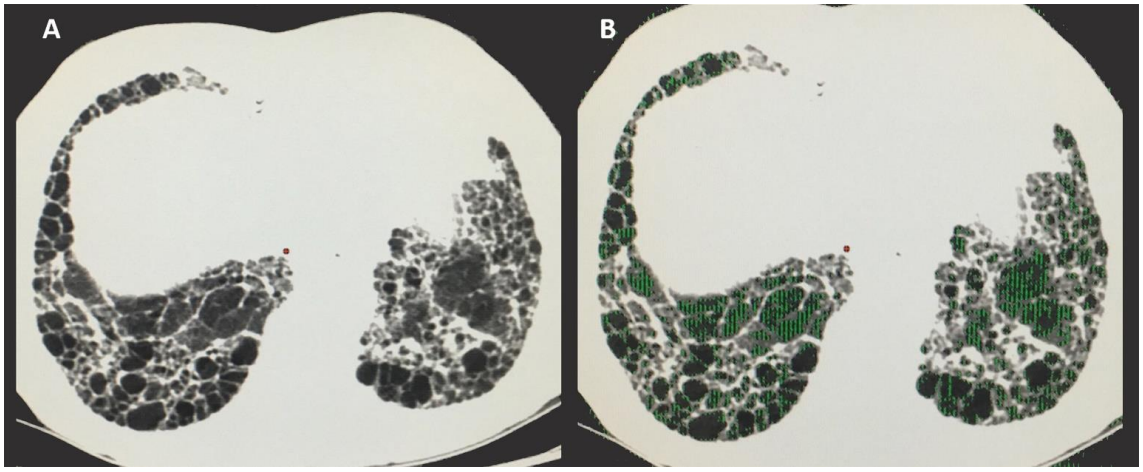

Fig. 2. Expiratory HRCT from a subject with UIP pattern associated with air trapping.

83-year-old patient diagnosed with IFP. (A) Chest CT demonstrates extensive areas of honeycombing in the cortical of the inferior lobes, suggestive of UIP pattern. (B) Same CT slice demonstrating the air trapping regions colored in green (ATIexp = 31.6%, E/I-ratio of 0.91).

REFERENCES

1. Webb WR, Stern EJ, Kanth N, Gamsu G. Dynamic pulmonary CT: findings in healthy adult men. *Radiology* [Internet] 1993;186(1):117–124. Available from: http://pubs.rsna.org/doi/10.1148/radiology.186.1.8416550
2. Miller WT, Chatzkel J, Hewitt MG. Expiratory Air Trapping on Thoracic Computed Tomography. A Diagnostic Subclassification. *Ann Am Thorac Soc* [Internet] 2014;11(6):874–881. Available from: http://www.atsjournals.org/doi/abs/10.1513/AnnalsATS.201311-390OC
3. Bommart S, Marin G, Bourdin A, et al. Relationship between CT air trapping criteria and lung function in small airway impairment quantification. *BMC Pulm Med* [Internet] 2014;14(1):29. Available from: http://bmcpulmmed.biomedcentral.com/articles/10.1186/1471-2466-14-29
4. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* [Internet] 2005;26(5):948–68. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16264058
5. Raghu G, Collard HR, Egan JJ, et al. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. *Am J Respir Crit Care Med* [Internet] 2011;183(6):788–824. Available from: http://www.atsjournals.org/doi/abs/10.1164/rccm.2009-040GL
6. Ley B, Collard HR, King TE. Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* [Internet] 2011;183(4):431–440. Available from: http://www.atsjournals.org/doi/abs/10.1164/rccm.201006-0894CI
7. Morell F, Villar A, Montero M-Á, et al. Chronic hypersensitivity pneumonitis in

patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med* [Internet] 2013;1(9):685–694. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2213260013701917

8. Wuyts WA, Cavazza A, Rossi G, Bonella F, Sverzellati N, Spagnolo P. Differential diagnosis of usual interstitial pneumonia: when is it truly idiopathic? *Eur Respir Rev* [Internet] 2014;23(133):308–319. Available from: http://err.ersjournals.com/cgi/doi/10.1183/09059180.00004914
9. Kaarteenaho R. The current position of surgical lung biopsy in the diagnosis of idiopathic pulmonary fibrosis. *Respir Res* [Internet] 2013;14(1):43. Available from: http://respiratory-research.com/content/14/1/43
10. Busacker A, Newell JD, Keefe T, et al. A Multivariate Analysis of Risk Factors for the Air-Trapping Asthmatic Phenotype as Measured by Quantitative CT Analysis. *Chest* [Internet] 2009;135(1):48–56. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0012369209600660
11. Eda S, Kubo K, Fujimoto K, Matsuzawa Y, Sekiguchi M, Sakai F. The relations between expiratory chest CT using helical CT and pulmonary function tests in emphysema. *Am J Respir Crit Care Med* [Internet] 1997;155(4):1290–1294. Available from: http://www.atsjournals.org/doi/abs/10.1164/ajrccm.155.4.9105069
12. Mets OM, Isgum I, Mol CP, et al. Variation in quantitative CT air trapping in heavy smokers on repeat CT examinations. *Eur Radiol* [Internet] 2012;22(12):2710–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22696157
13. Lee KW, Chung SY, Yang I, Lee Y, Ko EY, Park MJ. Correlation of aging and smoking with air trapping at thin-section CT of the lung in asymptomatic

subjects. *Radiology* 2000;214(3):831–836.

14. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med* [Internet] 2008;3(1):17. Available from: http://scfbm.biomedcentral.com/articles/10.1186/1751-0473-3-17
15. Sverzellati N, Wells AU, Tomassetti S, et al. Biopsy-proved idiopathic pulmonary fibrosis: spectrum of nondiagnostic thin-section CT diagnoses. *Radiology* [Internet] 2010;254(3):957–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20177106
16. Flaherty KR, King TE, Raghu G, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med* [Internet] 2004;170(8):904–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15256390
17. Mikolasch TA, Garthwaite HS, Porter JC. Update in diagnosis and management of interstitial lung disease . *Clin Med* [Internet] 2017;17(2):146–153. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28365626
18. Arakawa H, Webb WR. Air trapping on expiratory high-resolution CT scans in the absence of inspiratory scan abnormalities: correlation with pulmonary function tests and differential diagnosis. *Am J Roentgenol* [Internet] 1998;170(5):1349–1353. Available from: http://www.ajronline.org/doi/10.2214/ajr.170.5.9574614
19. Mets OM, Zanen P, Lammers J-WJ, et al. Early Identification of Small Airways Disease on Lung Cancer Screening CT: Comparison of Current Air Trapping Measures. *Lung* 2012;629–633.
20. Chung MH, Edinburgh KJ, Webb EM, McCowin M, Webb WR. Mixed infiltrative

and obstructive disease on high-resolution CT: differential diagnosis and functional correlates in a consecutive series. *J Thorac Imaging* [Internet] 2001;16(2):69–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11292207

21. Silva CIS, Müller NL, Lynch DA, et al. Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. *Radiology* [Internet] 2008;246(1):288–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18096541
22. Lynch DA, Newell JD, Logan PM, King TE, Müller NL. Can CT distinguish hypersensitivity pneumonitis from idiopathic pulmonary fibrosis? *Am J Roentgenol* [Internet] 1995;165(4):807–811. Available from: http://www.ajronline.org/doi/10.2214/ajr.165.4.7676971
23. Chechani V, Landreneau RJ, Shaikh SS. Open lung biopsy for diffuse infiltrative lung disease. *Ann Thorac Surg* [Internet] 1992;54(2):296–300. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1637223
24. Chung JH, Chawla A, Peljto AL, et al. CT Scan Findings of Probable Usual Interstitial Pneumonitis Have a High Predictive Value for Histologic Usual Interstitial Pneumonitis. *Chest* [Internet] 2015;147(2):450–459. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0012369215301793
25. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (E. *Am J Respir Crit Care Med* [Internet] 2002;165(2):277–304. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11790668

4. Considerações Finais

O estudo foi aprovado pelo Comitê de Ética e Pesquisa, na Plataforma Brasil (CAAE 60976716.9.0000.5335), sendo um estudo longitudinal, descritivo e retrospectivo (coorte histórica) com intuito de analisar a sobrevida dos pacientes selecionados. Por ser um estudo retrospectivo observacional, não foi necessária a aplicação de nenhum termo de consentimento. A identidade dos pacientes foi preservada. A revisão da literatura para a elaboração da introdução dessa dissertação utilizou como base teórica outro artigo, apresentado no anexo 5 (Imaging in idiopathic pulmonary fibrosis: diagnosis and mimics), ainda em análise para publicação, submetido para o jornal Clinics pertencente ao Hospital de Clínicas da Faculdade de Medicina da Universidade de São Paulo, no primeiro trimestre de 2017, tendo como grande área a radiologia torácica. No momento, ainda não há outros trabalhos em desenvolvimento partindo deste mestrado.

Ao término do trabalho, concluímos que a mortalidade foi maior nos indivíduos diagnosticados com FPI, reforçando que o diagnóstico histopatológico e a análise multidisciplinar em nossa instituição são feitos de maneira adequada e confiável. O grau de aprisionamento aéreo não influenciou a sobrevida dos pacientes, sugerindo que este achado não possuiu relevância significativa quando presente, mesmo sendo este um critério tomográfico considerado incompatível com o diagnóstico de PIU. Consequentemente, a presença do aprisionamento aéreo pode afastar a necessidade de biópsia pulmonar cirúrgica para diagnóstico e manejo da PIU/FPI em casos onde os demais achados tomográficos são compatíveis com PIU.

O artigo elaborado nesse mestrado é composto por pacientes que realizaram Tomografia de Tórax de Alta Resolução (TC-AR) somente em nossa instituição,

considerada um centro de referência local para diagnóstico e manejo das DPI. A maioria destes pacientes apresenta vínculo, por vezes já de longa data, com nossa equipe multidisciplinar, também responsável pelos cuidados e controle da sua patologia.

Este é um estudo unicêntrico, portanto, a seleção da amostra pode não refletir a realidade de diferentes populações, embora o desfecho encontrado assemelha-se à literatura atual e o esperado para estas patologias. A conclusão deste trabalho abre perspectivas para um estudo com um maior número de pacientes, idealmente conduzido em diferentes regiões do nosso país, com intuito de questionar o verdadeiro impacto do aprisionamento aéreo como critério incompatível para o diagnóstico de Pneumonia Intersticial Usual na TC-AR.

5. Anexos

5.1 Imaging in idiopathic pulmonar fibrosis: diagnosis and mimics

Bruno Hochhegger, Edson Marchiori, Matheus Zanon, Adalberto Sperb Rubin, Renata Fragomeri, Carlos Roberto Ribeiro Carvalho, Bruno Guedes Baldi.

Abstract

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown etiology, generally with a chronic and progressive course, often resulting in a fatal outcome. IPF occurs mainly in patients over their sixth decades of life, with a higher prevalence in male and smokers or former smokers, affecting exclusively the lungs. Main symptoms in IPF are often nonspecific, including progressive dyspnea and dry cough. Chest high-resolution CT has a central role in the initial evaluation of patients with suspected IPF and may influence considerably on subsequent management decisions. CT primary role is to distinguish chronic fibrosing lung diseases with a usual interstitial pneumonia (UIP) pattern from those presenting a non-UIP pattern, suggesting an alternative diagnosis when possible. A UIP pattern is characterized by the presence of the following four features: subpleural and basal predominance, reticular abnormality predominance, honeycombing with or without traction bronchiectasis, and absence of features inconsistent with UIP pattern. IPF can be diagnosed by clinical and radiologic criteria in about two-thirds of cases. The confirmation of IPF diagnosis is challenging, requiring the exclusion of pulmonary fibrosis with known causes, such as asbestosis, connective tissue diseases, drug exposure, chronic

hypersensitivity pneumonitis, and other forms of idiopathic interstitial pneumonitis. The histopathologic hallmark of UIP is a heterogeneous appearance, characterized by areas of fibrosis with scarring and honeycomb alternating with areas of less affected or normal parenchyma. The aim of this article was to review the clinical, radiological and pathological features of IPF and diseases that might mimic IPF presentation.

Keywords

Differential diagnosis; idiopathic pulmonary fibrosis; radiology; pathology; interstitial lung diseases.

1. Introduction and history

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown etiology, generally with a chronic and progressive course, often resulting in a fatal outcome. Although IPF has been described extensively in literature, controversy exists as to the history of the disease. IPF is usually considered to be first described by Hamman & Rich in 1933 as a new clinical and pathological entity (1). However, several reports in German had been previously published, describing autopsy findings consistent with IPF (2). Patients presented progressively worsening cough and dyspnea and autopsies usually revealed hypertrophied right ventricles and small, stiff lungs with widened and thickened bronchioli and an increased amount of interstitial tissue but no pleural adhesions (2). In these German reports, different terms were proposed to describe these interstitial changes, such as cirrhosis cystica pulmonum and lymphangitis reticularis pulmonum (2).

2. Clinical and laboratory assessment

A detailed clinical assessment is essential for the diagnostic work-up of patients with interstitial lung diseases (ILDs), and for the diagnostic confirmation of IPF. A detailed search for exposure, such as mold, birds and drugs, should be investigated. Evidence of extrapulmonary manifestations, such as arthralgia, Raynaud phenomenon, dry mouth and dry eyes, and skin lesions, are essential in the approach of ILDs, as they can be helpful to establish the diagnosis of connective tissue diseases (CTDs), conditions that may also present a usual interstitial pneumonia (UIP) pattern. The investigation of family history of lung disorders is also recommended, because CTDs and hereditary diseases are potential etiologies of ILDs (3-5).

IPF occurs mainly in patients in their sixth and seventh decades of life, with a higher prevalence in male and smokers or former smokers, affecting exclusively the lungs (3). Gastroesophageal reflux is a common association (3, 6).

Main symptoms in IPF are often nonspecific, including progressive dyspnea and dry cough (6). Frequent signs on physical examination include presence of bilateral inspiratory crackles (velcro-like) predominantly in the lower lung zones, and digital clubbing (3, 5). Pulmonary function tests (PFTs) in IPF are characterized by a restrictive pattern combined with decreased diffusing capacity. Diminished exercise performance and hypoxemia at rest or during exercise may be found (7).

Serologic testing, including rheumatoid factor (RF), anti-cyclic citrullinated peptide and anti-nuclear antibody (ANA) should be performed in patients with a

suspicion of IPF, because UIP pattern can also be found in CTDs (7, 8). In addition, patients with IPF may have mildly positive ANA and/or RF serology (5).

3. Computed tomography signs (definition, accuracy, interobserver agreement and differential diagnosis)

Ground-glass opacities, reticular pattern, traction bronchiectasis and honeycombing are among the most common features on high-resolution CT (HRCT) for ILDs and physicians should be familiar with their definitions, accuracies, and differential diagnosis for the diagnostic work-up.

3.1 Ground glass

On CT scans, ground-glass opacity (GGO) present as hazy increased opacity areas within the lungs, with preservation of bronchial and vascular margins (Figure 1A) (9). Ground-glass opacity is less opaque than consolidation, in which bronchovascular margins are obscured. GGO can be due to partial filling of airspaces, interstitial thickening (due to fluid, cells, and/or fibrosis), partial collapse of alveoli, increased capillary blood volume, or a combination of these, whereas all are related to common partial displacement of air (9). Good inter-observer agreement (kappa value, 0.78-0.90) has been reported in the detection of ground-glass opacities (10).

3.2. Reticular pattern

Reticular pattern is defined as a collection of innumerable small linear opacities that produce an appearance similar to a net (Figure 1B) (9). The

constituents of a reticular pattern are more clearly seen at thin-section CT, whether they are interlobular septal thickening, intralobular lines, or the cyst walls of honeycombing. This finding usually is associated to ILDs, but also congestion and infections (e.g. viral) are important differential diagnosis (9).

3.3. Honeycombing

Honeycombing is defined as clustered cystic air spaces, typically with diameters ranging from 3–10 mm, but occasionally as large as 2.5 cm. Honeycombing is usually subpleural and is characterized by well-defined walls (Figure 1C) (9). As honeycombing is often considered specific for pulmonar fibrosis and an important criterion in UIP diagnosis, the term should be used carefully, as it may influence directly on patient care (11). Centrilobular emphysema, traction bronchiectasis and cystic lung disease should be included in the differential diagnosis. Interobserver agreement for honeycombing is moderate (kappa = 0.59 ± 0.12). In a study by Watadani et al., there was disagreement on identification of honeycombing in 29% of cases due to co-existence of traction bronchiectasis, large cysts, and superimposed pulmonary emphysema (12).

3.4. Traction bronchiectasis

Traction bronchiectasis and traction bronchiolectasis represent irregular bronchial and bronchiolar dilatation, respectively (Figure 1A) (9). Dilated airways can also present as cysts (bronchi) or microcysts (bronchioles in the lung periphery). In IPF, traction bronchiectasis is better explained as a result from bronchiolar proliferation instead of utter mechanical traction (13). Recent studies have suggested

traction bronchiectasis and honeycombing as parts of a spectrum of presentation of a unique and continuous process of bronchiolar dysplastic proliferation in IPF (13,14). On the other hand, in nonspecific interstitial pneumonia (NSIP), bronchocentricity is predominant, and traction bronchiectasis is completely surrounded by the fibrotic tissue, characteristics that suggest the mechanical traction as the main component in the development of traction bronchiectasis in NSIP (13,14). Interobserver agreement for traction bronchiectasis is moderate, with kappa values ranging from 0.24 to 0.42 (11).

4. Idiopathic pulmonary fibrosis

4.1. Computed tomography diagnostic criteria (usual interstitial pneumonia)

Chest HRCT has a central role in the initial evaluation of patients with suspected IPF and may influence considerably on subsequent management decisions. The primary role of HRCT is to distinguish chronic fibrosing lung diseases with an UIP pattern from those presenting a non-UIP pattern, suggesting an alternative diagnosis when possible. The most common HRCT protocol used to evaluate diffuse lung diseases is a volumetric acquisition of thin sections (usually ≤1·5 mm), combined with a high spatial frequency reconstruction algorithm (15). The 2011 International HRCT criteria for UIP patterns (6) proposed three diagnostic categories: (a) UIP, (b) possible UIP, and (c) inconsistent with UIP (Table 1). HRCT criteria for UIP diagnosis include presence of honeycombing in a basal and subpleural distribution, without features considered incompatible with diagnosis of IPF (Figure 2) (6). Although GGO are common in UIP, to be characterized as an UIP pattern, they must be less extensive than the reticulation (6). Another common

feature on HRCT is mediastinal and hilar lymph node enlargement, present in up to 70% to 86% of patients with a UIP pattern (typically <15 mm) (16).

IPF can be diagnosed by clinical and radiologic criteria in about two-thirds of cases (17). Morbidity and mortality associated with lung biopsies in patients with fibrosis are high, around 3%–4% in most studies (18). Some recent papers suggest surgical lung biopsy sampling as not necessary to reach IPF diagnosis in some cases of patients with possible UIP pattern on HRCT, in the appropriate clinical setting at specialized centers (19). A confident diagnosis of UIP based on HRCT is correct in 80% to 95% of cases using pathology as a reference (20). In multiple studies assessing CT accuracy for IPF diagnosis, pathology was considered a gold standard. However, there is substantial interobserver variation among pathologists in the assessment of nonneoplastic lung disease (21). An interobserver variation over 50% has been reported for the pathology diagnosis of nonspecific interstitial pneumonia (NSIP) and its distinction from UIP (21).

4.2. Histopathology diagnostic criteria (usual interstitial pneumonia)

The histopathologic hallmark and chief diagnostic criterion of UIP is a heterogeneous appearance at low magnification, characterized by areas of fibrosis with scarring and honeycomb alternating with areas of less affected or normal parenchyma (Table 2) (Figure 2C) (22). These histopathologic changes often affect more severely the subpleural and paraseptal parenchyma. Inflammation is usually absent or mild and consists of a patchy interstitial infiltrate of lymphocytes and plasma cells associated with hyperplasia of type 2 pneumocytes and bronchiolar epithelium. The fibrotic zones are composed mainly of dense collagen, but scattered

convex subepithelial foci of proliferating fibroblasts and myofibroblasts (so-called fibroblast foci) are consistent findings. These foci must be distinguished from fibroblastic alveolar plugs of organizing pneumonia. A true fibroblastic focus should be interstitial-based and never a formed polypoid intrusion into the alveolar space. Areas of honeycombing change are composed of cystic fibrotic airspaces that are frequently lined by bronchiolar epithelium and filled with mucus and inflammatory cells (22).

4.3. Pathogenesis

The pathogenesis of IPF has been debated for several years, and one of the most accepted views is that initial inflammatory events might initiate a dysregulated fibroblast-mediated wound-healing response, that can be sustained due to several factors, leading to lung fibrosis (23). One of the most accepted models is the “alveolar stem cell exhaustion” that suggest that an accelerated parenchymal senescence determined by predisposition factors, such as genetic mutations or variations, telomerase dysfunction, together with environmental exposures, like tobacco smoking, could severely compromise the regenerative potential of parenchymal epithelial stem cells (13, 24, 25). This epithelial damage to the airway wall could lead to alveolar collapse, what could trigger a fibroproliferation process and promote destruction of airways, eventually leading to severe and irreversible functional impairment (24-26).

Mai et al. 2016 recently used micro-computed tomography to analyze the geometric progression of lung changes caused by IPF associating concomitantly histopathological and CT findings and encountered evidence to suggest that the

disease starts preferentially at the periphery of secondary pulmonary lobules, gradually extending toward the centrilobular region, finally replacing the entire lobule (26). The sequence of lung changes at CT in patients with IPF starts with areas of GGO that turn into areas of reticulation and end with cystic changes (26, 27). The so-called “microscopic honeycombing” represent the formation of these cystic spaces. They should be differentiated from honeycombing visualized in CT scans, as the former is present in most cases and is not necessarily specific for a UIP diagnosis, while the latter is highly specific for UIP and is associated with a poor prognosis (26, 28).

4.4. When is biopsy necessary?

Surgical lung biopsy (SLB) is the diagnostic method of choice for patients whose imaging findings are not definitive for UIP, which includes the possible UIP and inconsistent with UIP patterns on HRCT. Hence, an integrated multidisciplinary approach assessing both imaging and pathologic features is essential to establish final diagnosis (3, 6).

Tissue samples should be obtained from more than one site within the lungs due to a high degree of variability in the distribution and morphology of abnormalities. Evaluating carefully the presence of potential risks before performing SLB is essential, as risks associated with the procedure can outweigh benefits of determining the diagnosis, especially in older patients, or those with severe impairment in PFTs or with coexistence of comorbidities, such as pulmonary hypertension and severe heartfailure (6, 29). Recent evidence suggests cryobiopsy

as a promising less-invasive method to replace SLB to obtain lung samples to confirm IPF diagnosis (30).

5. Mimics of idiopathic pulmonary fibrosis

5.1. Clinical mimics

The confirmation of IPF diagnosis is challenging, requiring the exclusion of pulmonary fibrosis with known causes, such as asbestosis, CTDs, drug exposure, chronic hypersensitivity pneumonitis (HP), and other forms of idiopathic interstitial pneumonitis (3, 5, 6). Although these entities have similarities with IPF, such as progressive dyspnea, dry cough, and a restrictive pattern with decreased diffusing capacity in PFTs, they are associated with better prognosis and more responsiveness to immunosuppressive drugs (7).

5.1.1. Connective tissue diseases

These disorders often affect young women, and rheumatoid arthritis and systemic sclerosis are the most common CTDs associated with the UIP pattern. Extrapulmonary manifestations, such as arthralgia, Sicca symptoms, Raynaud phenomenon and esophageal manifestations, are commonly identified in ILD associated with CTD. However, interstitial lung changes can be the sole manifestation of CTD. Presence of serological abnormalities is an important finding in CTDs (7). Interstitial lung disease is also associated with interstitial pneumonia with autoimmune features, which should be included in the differential diagnosis of IPF (31, 32).

5.1.2. Hypersensitivity pneumonitis

Hypersensitivity pneumonitis is an inflammatory syndrome associated with an exposure history to suspected antigens, such as mold, birds and drugs. Hence, potential exposures should be investigated in patients with pulmonary fibrosis. Fatigue, fever, and weight loss may be found in patients with acute and subacute HP and rarely in those with chronic forms. Progressive dyspnea is the main symptom in chronic HP, inspiratory squeaks on pulmonary auscultation and digital clubbing may be identified. If the responsible inhaled antigen can be identified, the most effective therapy is complete avoidance (5, 29). Acute disease commonly remits without specific therapy. Corticosteroid therapy may be indicated for acute symptomatic relief and may accelerate the initial recovery in patients with severe disease. However long-term efficacy has not been proved in prospective clinical trials (33).

5.1.3. Idiopathic nonspecific interstitial pneumonia

In comparison with IPF, idiopathic NSIP occurs predominantly in younger women and may be associated with systemic manifestations, such as fever, fatigue and weight loss, and features suggestive of CTD (4, 7, 34).

5.1.4. Asbestosis

The main feature to distinguish asbestosis from IPF is a history of occupational exposure to asbestos, such as asbestos mining, shipbuilding and welding. It is essential to establish a temporal relationship between the exposure and the occurrence of symptoms (7).

5.1.5. Drug-induced lung diseases

In the assessment of patients with a suspicion of IPF, it is essential to investigate the exposure to drugs that can induce ILD, such as bleomycin, amiodarone, nitrofurantoin, methotrexate and cyclophosphamide. It is also necessary to determine a temporal association between the exposure to the potential drug and the occurrence of respiratory manifestations (5).

5.2. Radiological mimics

NSIP accounts for most of the disagreements among observers for idiopathic interstitial pneumonias. HRCT findings that favor NSIP rather than UIP include presence of GGOs, which is found in most cases. Subpleural sparing is highly suggestive of NSIP, present in 64% of patients with NSIP, in 11% with chronic HP, and in 4% with IPF (34). The features that best differentiate chronic HP from IPF and NSIP are lobular areas with decreased attenuation, presence of centrilobular nodules, and a lack of lower zone predominance of the abnormalities. The former has been a finding reported in 80% of patients with chronic HP, 43% of patients with IPF and in 34% with NSIP (34). UIP pattern on HRCT in patients with CTDs or fibrotic HP is similar to that found in idiopathic UIP and this should be distinguished on a clinical basis. However, radiologists may contribute to such differentiation based on additional findings such as esophageal dilatation, and pleural or pericardial effusion or thickening. Asbestosis typically has a histologic and HRCT pattern of UIP, and pleural plaque usually aids in diagnosis. Fibrotic sarcoidosis can be distinguished from UIP by the upper lobe and peribronchial predominant distribution and by some

additional HRCT findings, including pulmonary nodules and lymph node enlargement and calcifications.

5.3. Histopathological mimics

The pathologist goal while examining a biopsy of a patient with ILDs is to differentiate UIP from other diseases that may simulate this pattern, such as CTDs, chronic HP, pneumoconiosis and NSIP (7,35).

5.3.1. Connective tissue diseases

CTDs are a heterogeneous group of diseases, with different patterns in biopsy. Although the most common is a NSIP pattern, frequently UIP can be observed. Presence of an exuberant lymphocytic infiltrate, forming germinal centers and follicular bronchiolitis can be helpful features towards CTDs diagnosis in these situations. In addition, presence of pleural fibrosis is more characteristic of CTDs (7,35).

5.3.2. Chronic hypersensitivity pneumonitis

In chronic HP, fibrosis is predominantly airway-centered, but occasionally can manifest as UIP. Features that might suggest a diagnosis of a chronic HP are the predominance of upper lobes and presence of interstitial granulomas, mainly peribronchiolar, and bronchiolitis with peribronchiolar metaplasia (7,35). Recent studies focusing on genetic factors associated with chronic HP have suggested a common pathobiology with IPF. MUC5B rs35705950 single-nucleotide polymorphism

and short telomere length, as seen in sporadic and familial forms of IPF, can predispose patients with HP to lung remodeling and fibrosis (Ley 2017).

5.3.3. Asbestosis

Asbestosis is histopathologically characterized by presence of interstitial fibrosis, predominantly subpleural, similar to UIP. However, in early cases fibrosis can be more prominent around bronchioles. Other helpful features in the differential diagnosis with UIP are collagen fibrosis with absence of fibroblastic foci and mild inflammatory infiltrate. To confirm the histologic diagnosis, asbestos bodies must be present (36).

5.3.4. Nonspecific Interstitial Pneumonia

NSIP is a type of chronic interstitial pneumonia characterized by a relative spatial homogeneity in the involvement of lung parenchyma, differently from the typical patchy pattern of UIP where regions of normal lung are interspersed with affected parenchyma. In addition, NSIP is characterized by temporal homogeneity of lesions (inflammation and/or fibrosis), in contrast to temporal heterogeneity in UIP (co-existence of recent and old injury) (7, 35, 37-40). Some other features of UIP are not found in most cases of NSIP, such as smooth muscle hyperplasia, fibroblastic foci, and aggregation of elastic fibers (38). In addition, peripheral accentuation is absent or inconspicuous (40).

6. Conclusions

Although the UIP pattern may be observed in several ILD, there are relevant clinical, tomographic and histopathological features that contribute to differentiate them from IPF. The diagnosis of IPF is challenging and a multidisciplinary discussion with ILD experts, including clinicians, radiologists and pathologists, improves the accuracy of the diagnosis, which is essential to establish the appropriate management.

References

1. Hamman L, Rich AR. Clinical pathologic conference. Int Clin. 1933;1:196-231.

2. Homolka J. Idiopathic pulmonary fibrosis: a historical review. CMAJ. 1987;137(11):1003–1005.

3. Baddini-Martinez J, Baldi BG, Costa CH, Jezler S, Lima MS, Rufino R. Update on diagnosis and treatment of idiopathic pulmonar fibrosis. J Bras Pneumol. 2015;41(5):454-466.

4. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med.
2013;188(6):733-748.

5. Wuyts WA, Cavazza A, Rossi G, Bonella F, Sverzellati N, Spagnolo P. Differential diagnosis of usual interstitial pneumonia: when is it truly idiopathic? Eur Respir Rev. 2014;23(133):308-319.

6. Raghu G, Collard H, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An oficial ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidencebased guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824.

7. King TE Jr. Idiopathic pulmonary fibrosis. In: Schwarz MI, King TE Jr (eds). Interstitial Lung Disease, 5th ed. Shelton: People's Medical Publishing House-USA; 2011. p 895.

8. Moua T, Maldonado F, Decker PA, Daniels CE, Ryu JH. Frequency and implication of autoimmune serologies in idiopathic pulmonary fibrosis. Mayo Clin Proc. 2014;89(3):319-26.

9. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722.

10. Sergiacomi G, Ciccio C, Boi L, Velari L, Crusco S, Orlacchio A, et al. Ground-glass opacity: high-resolution computed tomography and 64-multislice computed tomography findings comparison. Eur J Radiol. 2010;74(3):479-483.

11. Walsh SL, Calandriello L, Sverzellati N, Wells AU, Hansell DM, UIP Observer Consort. Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT. Thorax. 2016;71(1):45-51.

12. Watadani T, Sakai F, Johkoh T, Noma S, Akira M, Fujimoto K, et al. Interobserver variability in the CT assessment of honeycombing in the lungs. Radiology. 2013;266(3):936-944.

13. Piciucchi S, Tomassetti S, Ravaglia C, et al. From "traction bronchiectasis" to honeycombing in idiopathic pulmonary fibrosis: A spectrum of bronchiolar remodeling also in radiology? BMC Pulm Med. 2016;16(1):87.

14. Walsh SL, Wells AU, Sverzellati N, et al. Relationship between fibroblastic foci profusion and high resolution CT morphology in fibrotic lung disease. BMC Med. 2015;13:241

15. Kusmirek JE, Martin MD, Kanne JP. Imaging of Idiopathic Pulmonary Fibrosis. Radiol Clin North Am. 2016;54(6):997-1014.

16. Jung JI, Kim HH, Jung YJ, Park SH, Lee JM, Hahn ST. Mediastinal lymphadenopathy in pulmonary fibrosis: correlation with disease severity. J Comput Assist Tomogr. 2000;24(5):706–710.

17. Raghu G, Mageto YN, Lockhart D, Schmidt RA, Wood DE, Godwin JD. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: a prospective study. Chest. 1999;116(5):1168–1174.

18. Kaarteenaho R. The current position of surgical lung biopsy in the diagnosis of idiopathic pulmonary fibrosis. Respir Res. 2013;14(1):43.

19. Raghu G, Lynch D, Godwin JD, Webb R, Colby TV, Leslie KO, et al. Diagnosis of idiopathic pulmonary fibrosis with high-resolution CT in patients with little or no radiological evidence of honeycombing: secondary analysis of a randomised, controlled trial. Lancet Respir Med. 2014;2(4):277-284.

20. Nicholson AG, Addis BJ, Bharucha H, Clelland CA, Corrin B, Gibbs AR, et al. Interobserver variation between pathologists in diffuse parenchymal lung disease. Thorax. 2004;59(6):500–505.

21. Flaherty KR, King TE Jr, Raghu G, Lynch JP 3rd, Colby TV, Travis WD, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinar approach to diagnosis? Am J Respir Crit Care Med. 2004;170(8):904–910.

22. Martinez FJ, Chisholm A, Collard HR, Flaherty KR, Myers J, Raghu G, et al. The diagnosis of idiopathic pulmonary fibrosis: current and future approaches. Lancet Respir Med. 2017; 5(1):61-71.

23. Wilson MS, Wynn TA. Pulmonary fibrosis: pathogenesis, etiology and regulation. Mucosal Immunol. 2009; 2(2):103-21.

24. Wolters PJ, Collard HR, Jones KD. Pathogenesis of idiopathic pulmonar fibrosis. Annu Rev Pathol. 2014;9:157-79.

25. Chilosi M, Doglioni C, Murer B, Poletti V. Epithelial stem cell exhaustion in the pathogenesis of idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2010;27(1):7-18.

26. Mai C, Verleden SE, McDonough JE. Thin-Section CT Features of Idiopathic Pulmonary Fibrosis Correlated with Micro-CT and Histologic Analysis. Radiology. 2017;283(1):252-263.

27. Akira M, Sakatani M, Ueda E. Idiopathic pulmonary fibrosis: progression of honeycombing at thin-section CT. Radiology 1993;189(3):687–691.

28. Chung JH, Chawla A, Peljto AL, et al. CT scan findings of probable usual interstitial pneumonitis have a high predictive value for histologic usual interstitial pneumonitis. Chest. 2015;147(2):450-459.

29. Hodnett PA, Naidich DP. Fibrosing interstitial lung disease: a practical highresolution computed tomography-based approach to diagnosis and management and a review of the literature. Am J Respir Crit Care Med. 2013;188(2):141-149.

30. Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, et al. Bronchoscopic lung cryobiopsy increases diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2016;193(7):745-752.

31. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J. 2015;46(4):976-987.

32. Pereira DAS, Dias OM, Almeida GE, Araujo MS, Kawano-Dourado LB, Baldi BG, et al. Lung-dominant connective tissue disease among patients with interstitial lung disease: prevalence, functional stability, and common extrathoracic features. J Bras Pneumol. 2015;41(2):151-160.

33. Selman M, Pardo A, King TE Jr. Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. Am J Respir Crit Care Med. 2012;186(4):314-324.

34. Silva CI, Muller NL, Lynch DA, Curran-Everett D, Brown KK, Lee KS, et al. Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonar fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology. 2008;246(1):288-297.

35. Smith M, Dalurzo M, Panse P, Parish J, Leslie K. Usual interstitial pneumonia-pattern fibrosis in surgical lung biopsies. Clinical, radiological and histopathological clues to aetiology. J Clin Pathol. 2013;66(10): 896–903.

36. Roggli VL, Gibbs AR, Attanoos R, Churg A, Popper H, Cagle P, et al. Pathology of Asbestosis - An Update of the Diagnostic Criteria: Report of the Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society. Arch Pathol Lab Med. 2010;134(3):462-480.

37. Larsen BT, Colby TV. Update for pathologists on idiopathic interstitial pneumonias. Arch Pathol Lab Med. 2012;136(10):1234-41.

38. Hashisako M, Fukuoka J. Pathology of Idiopathic Interstitial Pneumonias. Clin Med Insights Circ Respir Pulm Med. 2016;9(Suppl 1):123-33.

39. Visscher DW, Myers JL. Histologic spectrum of idiopathic interstitial pneumonias. Proc Am Thorac Soc. 2006;3(4):322-9.

40. Flaherty KR, Travis WD, Colby TV, Toews GB, Kazerooni EA, Gross BH, et al. Histopathologic Variability in Usual and Nonspecific Interstitial Pneumonias. Am J Respir Crit Care Med. 2001;164(9):1722–1727.

Tables

Table 1. High-resolution CT criteria for UIP pattern

UIP Pattern*	Possible UIP Pattern	Inconsistent with UIP Pattern†
● Subpleural, basal predominance	● Same UIP, but without honeycombing	● Other than subpleural/ basal predominance
● Reticular abnormality		● Extensive GGO (extension > reticular abnormality)
● Honeycombing with or without traction bronchiectasis		● Profuse micronodules (bilateral, predominantly upper lobes)
● Absence of features listed as inconsistent with UIP pattern		● Discrete cysts (multiple, bilateral, away from areas of honeycombing)
		● Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes)
		● Consolidation in bronchopulmonary segment(s) / lobe(s)

CT, computed tomography; GGO, ground-glass opacity; UIP, usual interstitial pneumonia.
* All the 4 criteria listed must be present
† Any of the 6 criteria listed can be present
Adapted from *Raghu et al.* [6]

Table 2. Histopathological Criteria for UIP Pattern

UIP Pattern*	**Probable UIP Pattern†**	**Possible UIP Pattern‡**	**Not UIP Pattern§**
1. Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution	**1.** Evidence of marked fibrosis/ architectural distortion, ± honeycombing	**1.** Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation	**1.** Hyaline membranes
2. Patchy involvement of lung parenchyma by fibrosis	**2A.** Patchy involvement of lung parenchyma by fibrosis OR **2B.** Fibroblast foci	**2.** Absence of other criteria for UIP *(see 1st column)*	**2.** Organizing pneumonia
3. Fibroblast foci	**3.** Absence of features listed as not UIP pattern (*see 4th column*)	**3.** Absence of features listed as not UIP pattern (*see 4th column*)	**3.** Granulomas
4. Absence of features listed as not UIP pattern *(see 4th column)*	OR		**4.** Marked interstitial inflammatory cell infiltrate away from honeycombing
	S. Honeycomb changes exclusively		**5.** Predominant airway centered changes
			6. Other features suggestive of an alternate diagnosis

Note. - UIP = usual interstitial pneumonia
* - All 4 criteria listed must be present
† - All 3 criteria listed must be present **OR** "S" only
‡ - All 3 criteria listed must be present
§ - Any of the 6 criteria listed can be present
Adapted from *Raghu et al.* [6]

Figure Captions

Fig 1. Common features on high-resolution computed tomography in interstitial lung diseases. **(a)** Images from a 63-year-old female presenting a nonspecific interstitial pneumonia pattern. There are predominant areas of ground-glass opacities, with some traction bronchiectasis and cortical interlobular septal thickening. **(b)** Images from a 61-year-old male with idiopathic pulmonary
fibrosis. There are diffuse areas of interlobular septal thickening, predominantly in the cortical lung zones. **(c)** Images from a 56-year-old female with idiopathic pulmonary fibrosis. There are extensive areas of honeycombing, with some interlobular septal thickening.

Fig 2. Images from a 53-year-old male with idiopathic pulmonary fibrosis. **(a)** Axial and **(b)** coronal computed tomography images demonstrating areas of honeycombing, reticulation and subpleural predominance. **(c)** Histopathology images demonstrating areas of marked fibrosis, with architectural distortion and fibroblast foci, alternating with areas of normal parenchyma.

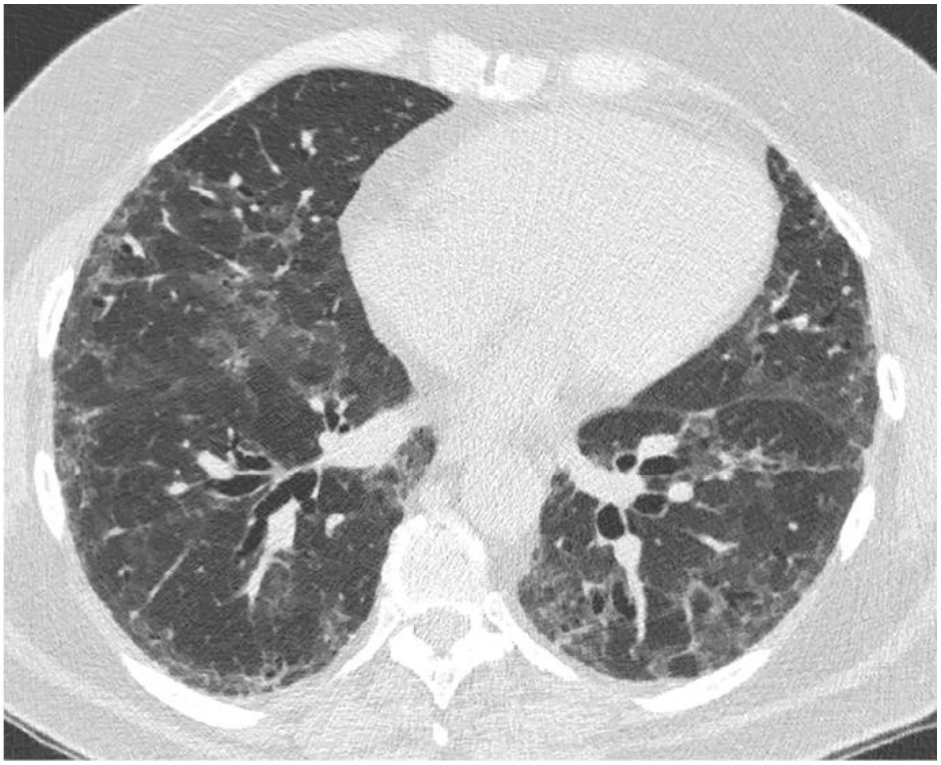

Fig 1A
10 X 12,36 cm

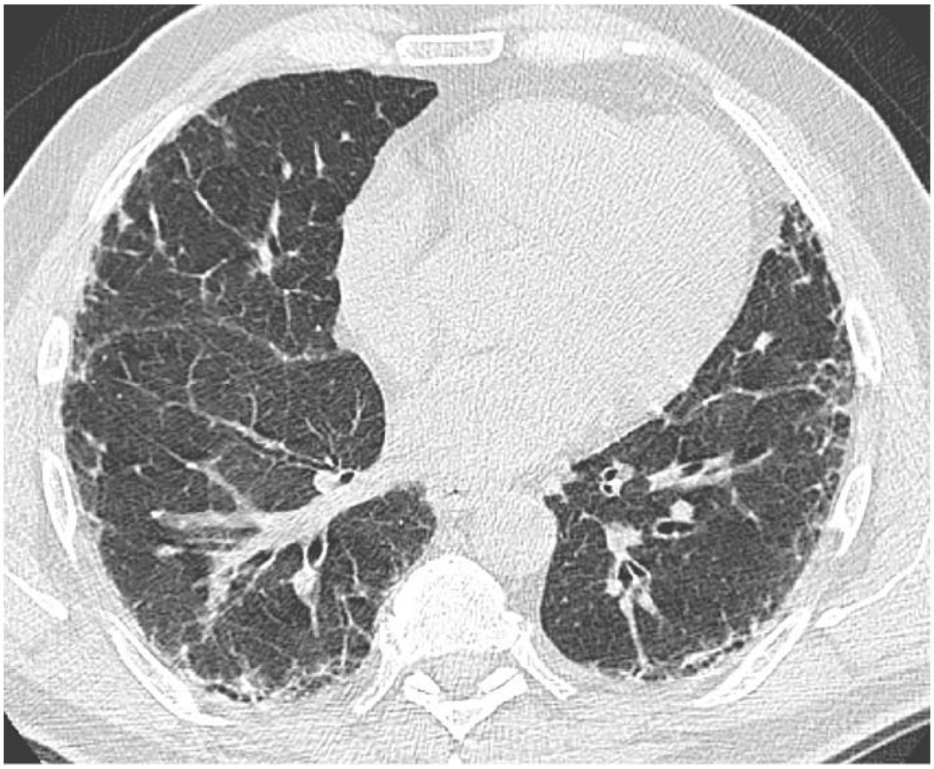

Fig 1B
10,08 X 12,36mm

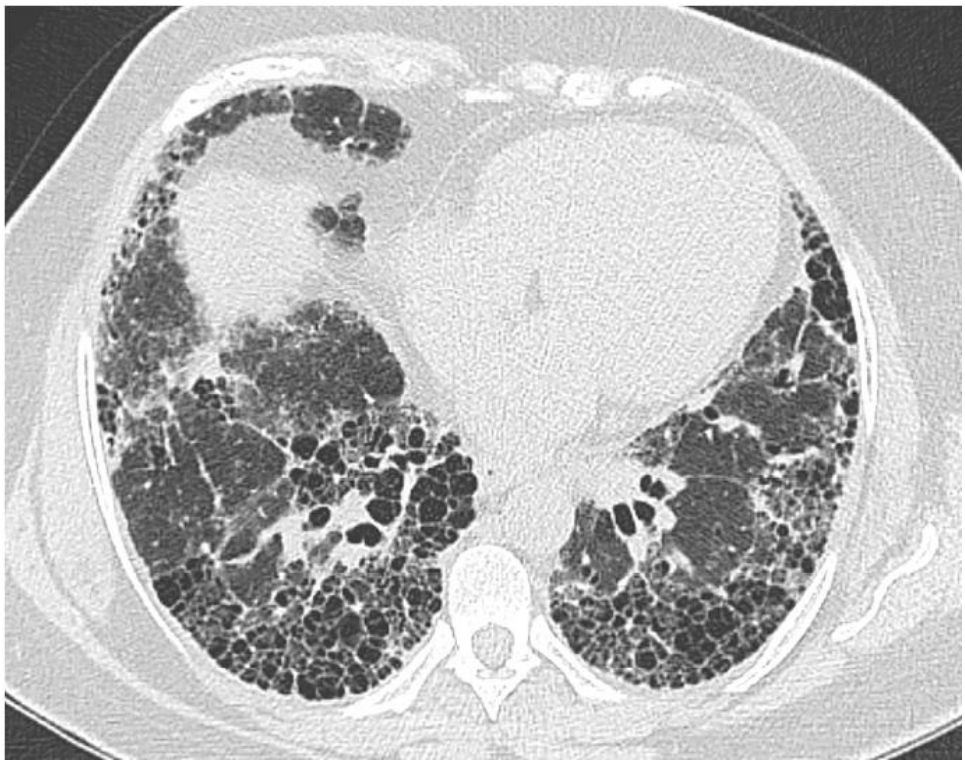

Fig 1C
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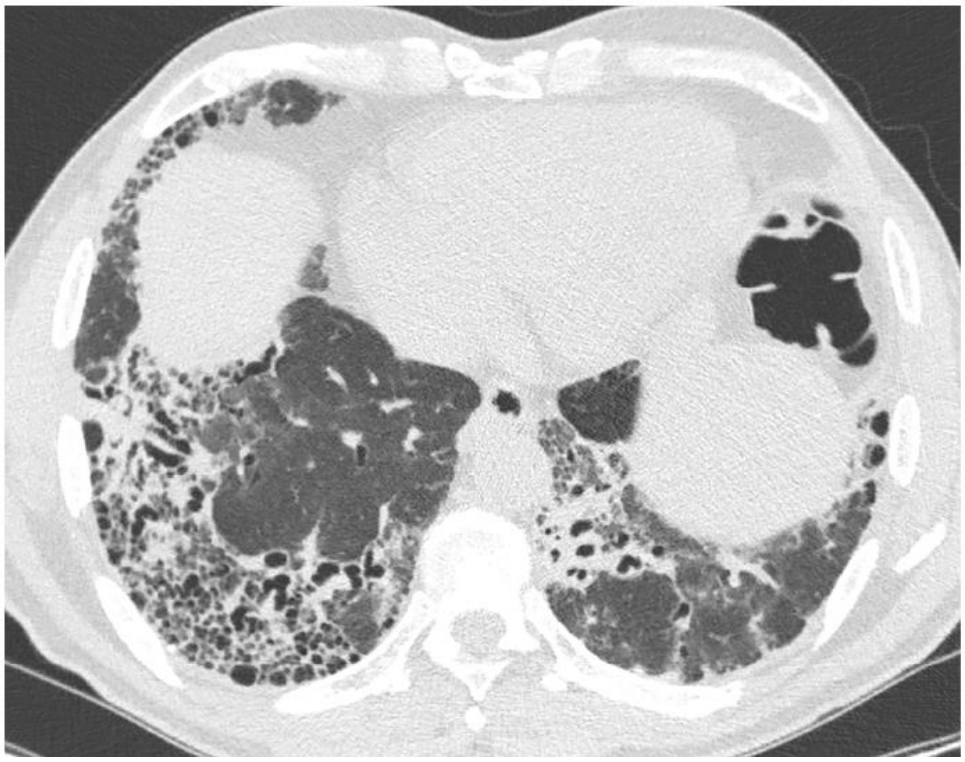

Fig 2A
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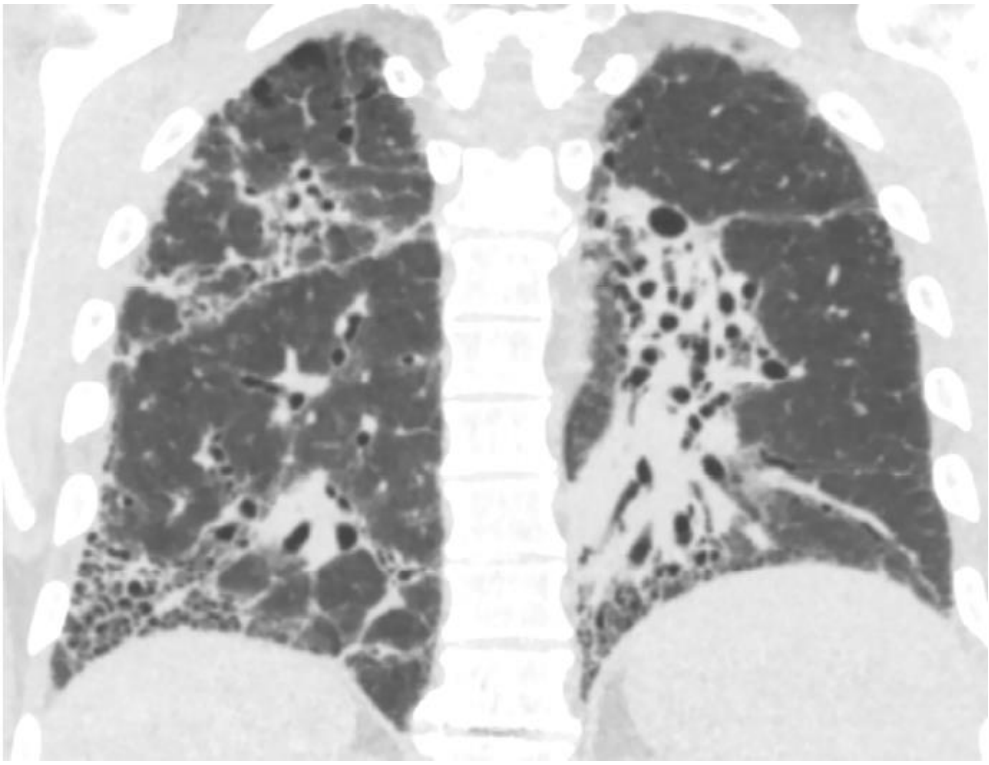

Fig 2B
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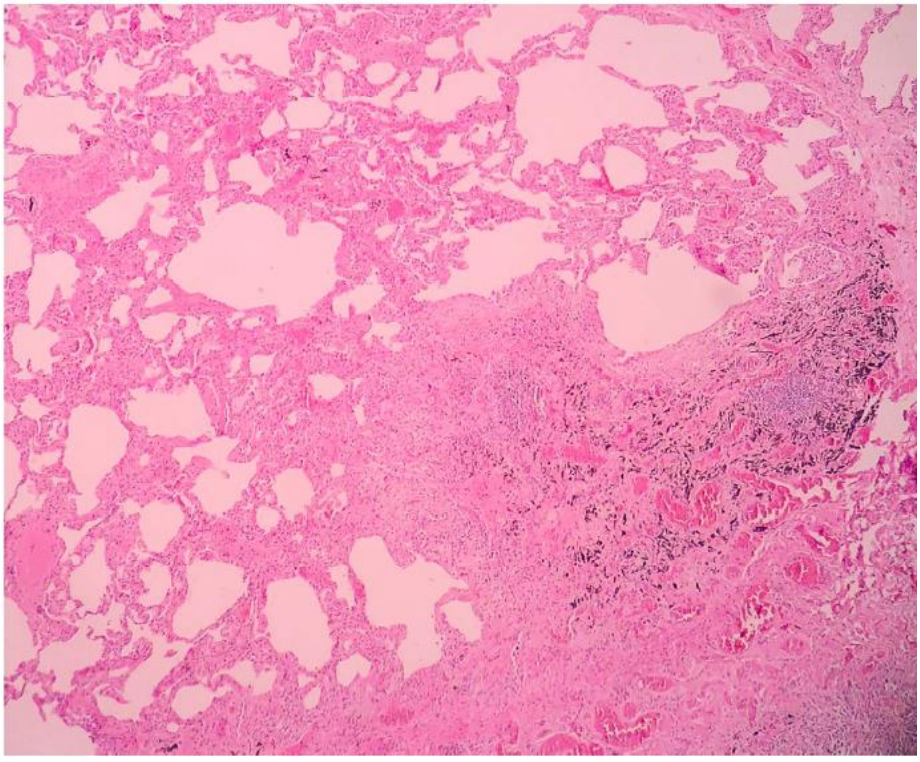

Fig 2C
10 X 12,1 cm