Universidade do Estado do Rio de Janeiro
Centro Biomédico
Faculdade de Ciências Médicas

Caio Leal Leidersnaider

Análise comparativa entre exame físico, ultrassonografia e ressonância magnética nos punhos e mãos no estudo das manifestações clínicas musculoesqueléticas da febre Chikungunya crônica

Rio de Janeiro
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Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-Graduação em Ciências Médicas, da Universidade do Estado do Rio de Janeiro.

Orientador: Prof. Dr. Roberto Mogami

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DEDICATÓRIA

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O médico que só sabe de medicina, nem de medicina sabe.

Abel de Lima Salazar (1889-1946).

RESUMO

LEIDERSNAIDER, Caio Leal. *Análise comparativa entre exame físico, ultrassonografia e ressonância magnética nos punhos e mãos no estudo das manifestações clínicas musculoesqueléticas da febre Chikungunya crônica.* 2021. 99f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2021.

A febre Chikungunya (FC) é uma doença arboviral transmitida por mosquitos *Aedes* infectados pelo vírus Chikungunya (VCHIK). Ela é epidêmica em vários países ao redor do mundo. A doença causa artrite crônica e incapacitante por até cinco anos após a infecção, e atinge grande parte da população economicamente ativa. O estudo um descreve, por meio de dados clínicos, laboratoriais, ultrassonográficos (US) e de ressonância magnética (RM) como um homem de 49 anos desenvolveu artrite psoriásica (AP) após infecção pela FC. O quadro de sinovite e tenossinovite clássicas secundárias à FC, a persistência de doença inflamatória com sinais de entesite e dactilite na US e RM, a história familiar positiva e o aparecimento de lesões cutâneas no couro cabeludo sugere fortemente AP pós-FC, segundo os critérios do Colégio Americano de Reumatologia. O estudo dois teve como objetivo analisar as alterações musculoesqueléticas de punhos e mãos por meio do exame físico (EF), US e RM. Trinta pacientes com diagnóstico laboratorial comprovado de FC foram avaliados na fase crônica da doença. Houve predominância do sexo feminino e a média da idade foi de 54,7 anos. Os locais analisados foram as regiões interfalângica (IF), metacarpofalângica (MCF) e articulações do punho/mediocarpal (PMC). O intervalo entre o EF e os exames de imagens foi de sete dias, e o intervalo entre a US e RM foi de no máximo dois dias. O coeficiente *kappa* foi calculado para estimar a concordância entre os achados de EF, US e RM. Foi observada concordância significativa entre EF e US no diagnóstico de sinovites. A única concordância estatisticamente significativa (grau moderado) entre US e RM foi o achado de tenossinovite flexora. A US tem potencial para confirmação diagnóstica na suspeita de sinovite, com base na uma positividade do EF. A limitada concordância entre US e RM para outros achados, por sua vez, pode sugerir um papel complementar destes métodos.

Palavras-chave: Febre Chikungunya. Exame físico. Ultrassonografia. Ressonância Magnética. Musculoesquelético.

ABSTRACT

LEIDERSNAIDER, Caio Leal. *Comparative analysis between physical examination, ultrasound, and magnetic resonance imaging of the wrists and hands in the study of clinical musculoskeletal manifestations of chronic Chikungunya fever.* 2021. 99f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2021.

Chikungunya fever (CF) is an arboviral disease transmitted by Aedes mosquitoes infected with the Chikungunya virus (VCHIK). It is an epidemic in several countries around the world. The disease causes chronic and disabling arthritis for up to five years after infection and affects many of the economically active population. Study one describes, through clinical, laboratory, ultrasound (US), and magnetic resonance (MRI) data, how a 49-year-old man developed psoriatic arthritis (PA) after CF infection. The clinical picture of classic synovitis and tenosynovitis secondary to CF, the persistence of inflammatory disease with signs of enthesitis and dactylitis on US and MRI, positive family history, and the appearance of skin lesions on the scalp strongly suggested post-CF PA, according to the criteria of the American College of Rheumatology. Study two aimed to analyze the musculoskeletal changes in the wrists and hands through physical examination (PE), US, and MRI. Thirty patients with a proven laboratory diagnosis of CF were evaluated in the chronic phase of the disease. There was a predominance of females, and the average age was 54.7 years. The analyzed sites were the interphalangeal (IF), metacarpophalangeal (MCF), and wrist/midcarpal joints. The interval between PE and imaging exams was seven days, and the interval between US and MRI was at most two days. The kappa coefficient was calculated to estimate the agreement between the PE, US, and MR findings. A significant agreement was observed between PE and US in diagnosing synovitis. The only statistically significant (moderate agreement) between US and MRI was the finding of flexor tenosynovitis. US has potential for diagnostic confirmation of suspected synovitis based on positivity of the PE. The limited agreement between US and MRI for other findings, in turn, may suggest a complementary role for these methods.

Keywords: Chikungunya fever. Physical examation. Ultrasound. Magnetic Resonance Imaging. Musculoskeletal.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS E SIGLAS

ACR	*American College of Rheumatology*
Anti-CCP	*Cyclic citrullinated peptide antibodies*
AP	Artrite psoriásica
AR	Artrite reumatoide
CAAE	Certificado de apresentação para apreciação ética
CDC	*Center for Disease Control and Prevention*
CEDI	Centro Estadual de Diagnóstico por Imagem
DMD	Drogas modificadoras de doença
DNA	*Deoxyribonucleic acid*
DP	Desvio padrão
DPr	Densidade protônica
EA	Espondilite anquilosante
EF	Exame físico
ELISA	*Enzyme-linked immunosorbent assay*
EMO	Edema de medula óssea
ERV	*Endogenous retrovirus*
EUA	Estados Unidos da América
FC	Febre Chikungunya
FCEV	Fator de crescimento endoteliar vascular
FOV	*Field of view*
FR	Fator reumatoide
HIV 1	*Human immunodeficiency virus 1*
HLA	*Human leukocyte antigen*
HUGG	Hospital Universitário Graffé e Guinle
HUPE	Hospital Universitário Pedro Ernesto
IF	Interfalângica
IFI	Ensaio de imunofluorescência indireta
IgG	Imunoglobulina G
IgM	Imunoglobulina M
IJCRI	*International Journal of Case Reports and Images*

JUM	*Journal of Ultrasound in Medicine*
LES	Lúpus eritematoso sistêmico
MCF	Metacarpofalângica
OMERACT	*Outcome Measures in Rheumatology*
PCR	Proteína C reativa
PIC	Pressão intracraniana
PMC	Punho/mediocarpal
POCT	*Point-of-care testing*
PPC	Policlínica Piquet Carneiro
PRF	*Pulse repetition frequency*
RM	Ressonância magnética
RNA	*Ribonucleic acid*
RT-PCR	*Reverse-transcriptase polymerase chain reaction*
STC	Síndrome do túnel do carpo
STIR	*Short tau inversion recovery*
TCLE	Termo de consentimento livre e esclarecido
US	Ultrassonografia
VCHIK	Virus Chikungunya
VEB	Vírus Epstein-Barr
VHS	Velocidade de hemossedimentação
VZIK	Vírus Zika

LISTA DE SÍMBOLOS

%	Porcentagem
<	Menor que
±	Mais ou menos
3D	Tridimensional
cm	Centímetro
cm^2	Centímetros quadrados
cm^3	Centímetros cúbicos
Hz	Hertz
K	*Kappa*
MHz	Megahertz
mm	Milímetros
mm^2	Milímetros quadrados
T	Tesla

SUMÁRIO

INTRODUÇÃO

Febre Chikungunya – Definição e Diagnóstico

A febre Chikungunya (FC) é uma doença viral transmitida pelos mosquitos da família Togaviridae e do gênero *Alphavirus* (1-4), cuja transmissão ocorre pela picada de fêmeas dos mosquitos *Aedes aegypti* e *Aedes albopictus* infectadas pelo vírus Chikungunya (VCHIK) (2,3). A intensidade da dor deu à doença o nome "chikungunya", que significa "aqueles que se dobram" na língua Makonde (falada pela tribo que vive no sudeste da Tanzânia e norte de Moçambique), descrevendo a aparência encurvada das pessoas que sofrem com artralgia característica nos pés e tornozelos (5). O *Aedes albopictus* também transmite o vírus da dengue, febre amarela, zika e suspeita-se ser o vetor do vírus da encefalite equina venezuelana (6,7). Excepcionalmente, pode haver transmissão vertical durante o parto em gestantes virêmicas, o que pode provocar infecção neonatal grave (8). No entanto, não se tem conhecimento do aumento da frequência de malformações (8,9). Contaminações transfusionais são raras, se os protocolos de segurança forem executados (9). Entre os diagnósticos diferenciais, podemos citar: dengue (na fase aguda), malária, leptospirose, febre reumática, artrite séptica, zika e Mayaro (6).

Existem duas formas de diagnóstico laboratorial da FC: teste sorológico (também conhecido como teste indireto), e teste molecular (conhecido como teste direto) (5,10). O principal teste molecular é o RT-PCR (reação em cadeia da polimerase com transcrição reversa em tempo real) (11), que proporciona um diagnóstico rápido e sensível, por meio da detecção do RNA viral até o oitavo dia após o aparecimento dos sintomas (11,12). Para a pesquisa de anticorpos específicos, as principais técnicas disponíveis são: o *enzyme-linked immunosorbent assay* (ELISA), imunofluorescência indireta e o teste imunocromatográfico do tipo *point-of-care* (POCT) (13). Os testes sorológicos permitem a detecção de anticorpos específicos do tipo IgM, que podem ser identificados a partir do segundo dia após o aparecimento dos sintomas e do tipo IgG a partir do 15º dia. Em geral, a FC não costuma ter reação cruzada com as demais arboviroses (14).

Febre Chikungunya – Aspectos Epidemiológicos

Globalmente, a doença foi descrita pela primeira vez durante um surto ao sul da Tanzânia em 1952 (15). Após um período com número menor de casos desde a sua descoberta, o VCHIK reemergiu durante a segunda metade do século XX e foi responsável por grandes epidemias na África e na Ásia (16). A partir de 2005, ele se espalhou rapidamente pelas ilhas do sudoeste do Oceano Índico e no final de 2013 emergiu na região das Américas (16). Em 2014, mais de um milhão de casos foram notificados nas três Américas e no Caribe (17). No Brasil, a transmissão autóctone foi confirmada no segundo semestre de 2014, primeiramente nos estados do Amapá e da Bahia (18,19). Desde então, todos os demais estados registraram ocorrência de casos autóctones (19).

A alta densidade do vetor, a presença de indivíduos susceptíveis e a intensa circulação de pessoas em áreas endêmicas são alguns dos fatores que contribuem para a transmissão (20). Ao contrário do *Aedes aegypti*, que existe em áreas tropicais e subtropicais (16), o *Aedes albopictus* também pode prosperar em regiões temperadas, com o potencial de introduzir o VCHIK em novos nichos ecológicos (21). Há relatos de casos autóctones na Itália (22), França (23) e EUA (24). Não há tratamento antiviral efetivo até o momento e a profilaxia é feita por meio do controle do vetor, o único elo vulnerável na cadeia de transmissão da doença (15,17,20). Vários testes clínicos para a criação de vacina têm sido realizados (25), embora nenhum tenha sido aprovado para uso na população geral. As estratégias incluem vacinas com vírus completo inativado (26), vírus vivo atenuado (27,28), vacinas de DNA (29) e vacinas de partículas virais (30,31).

Febre Chikungunya – Aspectos Clínicos

Clinicamente, podemos dividir o curso da doença em fase aguda e crônica (3,4,32). A fase aguda começa cerca de três a sete dias após a inoculação do vírus pela picada da fêmea infectada e é caracterizada por febre, exantema, alterações gastrointestinais, cefaleia e artralgia (2,4). A fase crônica, presente em 30-50% dos casos, ocorre quando a adoença tem duração maior que três meses a partir do início dos primeiros sintomas (2,3,5). Os achados mais comuns são artralgia (manifestação mais frequente e de caráter simétrico e bilateral),

artrite e impotência funcional, o que acarreta incapacidade moderada a grave vários meses após a infecção aguda (1,3,4).

A literatura sugere que até 60% (33) dos infectados pelo VCHIK têm chance de desenvolver artrite crônica (34,35) e a incapacidade motora pode persistir por até cinco anos após a infecção (33). A doença também tem o potencial para desenvolver sequelas permanentes e irreversíveis (36).

Febre Chikungunya como uma doença reumatológica - Aspectos de gravidade e/ou cronicidade

Os fatores de risco clínico-epidemiológicos que predispõem à cronicidade da doença são idade acima de 45 anos, sexo feminino, envolvimento genético e existência de doenças ou lesões musculoesqueléticas anteriores (37,38).

Alguns estudos apontam que os sintomas clássicos e graves da FC durante a fase aguda se devem ao tropismo do VCHIK por fibroblastos (39), de forma semelhante ao que ocorre em outras alphaviroses (40,41). Também foi descoberto RNA do VCHIK em células musculares satélites humanas três meses após a infecção (42). A longa duração da presença de anticorpos IgM anti-VCHIK também pode indicar a persistência do VCHIK em certas células ou tecidos hospedeiros (43).

Malvy e cols. (44) relataram o caso de um paciente que desenvolveu artrite erosiva progressiva acompanhada de entesopatias por 24 meses após a infecção pelo VCHIK. Este paciente não apresentava positividade para marcadores de autoimunidade, notadamente anti-peptídeo citrulinado cíclico (anti-CCP), anticorpos antinucleares ou crioglobulinemia. Entretanto, havia aumento na contagem de células T CD4, persistência de anticorpos IgM específicos e positividade para o gene HLA B27. A genotipagem do sistema HLA classe II revelou genótipo HLA-DRB1, apesar de que nenhuma manifestação reumatológica clínica tenha sido observada antes da infecção pelo VCHIK.

Sissoko e cols. (45) avaliaram 147 pacientes com diagnóstico de FC e relataram que 57% dos pacientes mantiveram artrite crônica por mais de 15 meses após o diagnóstico inicial da infecção viral. Este dado é importante porque sugere que as manifestações reumáticas do VCHIK, a longo prazo, podem ser uma condição subjacente pós-epidêmica frequente. Portanto, a identificação de fatores que possam auxiliar no reconhecimento e tratamento

precoce de pacientes com maior risco de apresentar doença prolongada pode ser útil no desenvolvimento de estratégias futuras de prevenção e cuidados para essa infecção viral emergente.

FEBRE CHIKUNGUNYA E SUA RELAÇÃO COM OUTRAS DOENÇAS

Febre Chikungunya e Artrite Reumatoide – Uma possível associação

A artrite reumatoide (AR) é uma doença inflamatória crônica que cursa com poliartrite periférica e simétrica de pequenas articulações. A doença tem prevalência de 1% na população mundial e predomina em mulheres (proporção de três mulheres para um homem), com idade entre 33 e 55 anos (46). O curso é intermitente e há um processo contínuo de lesão tecidual que afeta, especialmente, membranas sinoviais e as cartilagens articulares que revestem diartroses (articulações livremente móveis, compostas de superfície articular, cartilagem articular, cápsula articular e ligamentos) (47).

Foi relatada alta incidência de AR em pessoas previamente infectadas pelo VCHIK quando comparadas à população em geral (48). A associação entre FC e AR tem sido descrita tanto na semelhança dos sintomas quanto na possibilidade de evolução de FC para AR, de acordo com os critérios do *American College of Rheumatology* (ACR) (49). Estudos recentes sugerem que uma pequena parcela dos pacientes com FC e formas poliarticulares graves podem evoluir para a AR e/ou agravar quadros de AR preexistentes (48,50,51). Supõe-se que o estímulo inflamatório provocado pela FC possa funcionar como um gatilho para o desenvolvimento de AR em pessoas com predisposição genética para a doença (4,52,53).

Um estudo realizado numa ilha do Oceano Índico relatou 21 casos de AR de acordo com os critérios da ACR (49) após infecção por FC confirmada por anticorpos IgM e/ou IgG. Entre estes, 12 pacientes (57,1%) eram positivos para o fator reumatoide (FR), mas apenas seis (28,6%) desenvolveram anticorpos anti-CCP (54). Em outro estudo, Manimuda e cols. (55) acompanharam 203 pacientes com FC crônica, e cerca de 36% preencheram critérios para AR, segundo o ACR. Da mesma forma que a AR, a FC manifesta-se com sinovite simétrica e bilateral, tenossivite, tendinopatia, artropatia erosiva, edema de medula óssea (EMO) e erosão óssea (9,15).

Febre Chikungunya e outras formas de artrites

Além da AR, há relatos de pacientes que desencadearam artrite psoriásica (AP), lúpus eritematoso sistêmico (LES) e espondilite anquilosante (EA) após infecção por FC (56,57). A artrite psoriásica é uma doença autoimune, presente em cerca de 30% dos pacientes com psoríase (58). Leidersnaider e cols. descreveram o caso de um paciente com FC, sem histórico de doença reumatológica que evoluiu para AP (Artigo 1) (59). A FC pode ser não apenas um fator desencadeante para AP, como também um fator de exacerbação da doença, visto que ambos os vírus compartilham a mesma patogênese de envolvimento de células T e citocinas (58,60).

O LES é uma doença crônica multissistêmica de caráter autoimune e inflamatório, cuja etiologia ainda não está completamente elucidada. Há uma ampla gama de manifestações e o envolvimento musculoesquelético está presente em mais de 90% dos casos (61,62). Estudos demonstram que alguns tipos de vírus podem induzir o aparecimento do LES, como o vírus Epstein-Barr (VEB), parvovírus B19, retrovírus exógenos (HIV-1) e retrovírus endógenos (ERVs) (63).

Métodos de imagem no diagnóstico das alterações musculoesqueléticas na febre Chikungunya

Embora a primeira etapa para a avaliação musculoesquelética seja anamnese e exame físico (EF) completos, sabe-se que a sensibilidade da US e da RM são maiores que a do EF para o diagnóstico de lesões reumatológicas (64,65) como sinovites e entesopatias (66).

Mesmo que a US tenha limitação para avaliação óssea, ela se apresenta como um excelente método no acompanhamento de doenças inflamatórias com alto potencial para complicações musculoesqueléticas crônicas (67,68) e apresenta vantagens em relação à RM por ser um método mais acessível, de menor custo e com boa aceitação geral pelos pacientes (69,70).

A partir de 2017, uma série de publicações de Mogami e cols. (51-53) destacou a importância da sinovite e tenossinovite no quadro clínico dos pacientes com FC e sugeriu que

algumas formas de apresentação radiológica poderiam estar associadas a quadros clínicos mais graves da doença (51).

Na série de estudos dos autores supracitados, foram avaliados ultrassonograficamente punhos e mãos de 50 pacientes com FC crônica, cujos achados, em ordem decrescente de frequência, foram: sinovite de pequenas articulações, principalmente metacarpofalângicas, derrame e/ou espessamento sinovial mediocarpal/radiocarpal/radiulnar, tenossinovite dos tendões flexores dos dedos, celulite, tenossinovite de extensores do punho e espessamento do nervo mediano (52).

O *Doppler* é uma ferramenta útil na detecção de inflamação aguda, especialmente o *power Doppler*, que possui resultados comparáveis aos da RM (69,71). A maior dificuldade para o emprego do *power Doppler* como ferramenta na detecção de atividade inflamatória está na padronização do ganho de sinal. O uso de ganho excessivo pode superestimar fluxos sanguíneos normais, ao passo que um ganho pouco intenso pode reduzir a sensibilidade do método e subdimensionar uma atividade inflamatória (51).

A síndrome do túnel do carpo (STC) ocorre quando há aumento da pressão do interstício intracarpal, o que leva à redução do fluxo sanguíneo normal para o nervo mediano (72). Geralmente, a STC está associada a várias condições clínicas, como obesidade, AR, diabetes, LES, hipotireoidismo e esclerose sistêmica (72,73). Os sintomas associados à STC incluem dor, parestesia, alteração sensorial ou uma combinação destes (74). Durante a fase crônica da FC foram observadas manifestações decorrentes da STC, representadas por dor, parestesia e perda de força no território de sensibilidade do nervo mediano (75). O diagnóstico da STC é feito por estudos de condução do nervo mediano e/ou por US e RM. A vantagem do uso de um método de imagem no estudo de pacientes com a STC é a possibilidade de avaliar as estruturas adjacentes do nervo mediano, o que pode fornecer dados quanto à etiologia da doença (76).

Processos inflamatórios em articulações periféricas (derrames, espessamentos sinoviais ou tenossinovite), assim como lesões estruturais (condropatias, erosões da cortical óssea e rupturas de tendões) são mais bem avaliados pela RM (28,70). Outras vantagens em relação aos demais métodos de imagem são a possibilidade de visualizar lesões em três planos ortogonais e a avaliação do osso medular (70), o que permite a identificação do edema de medula óssea (EMO) (70). Entre as desvantagens estão a baixa disponibilidade, maior custo, tempo longo de exame e desconforto do paciente devido ao posicionamento para aquisição das imagens (70).

O EMO é um indicador precoce de inflamação, pois sua presença correlaciona-se a níveis aumentados de reagentes de fase aguda, tais como velocidade de hemossedimentação (VHS) e proteína C-reativa (PCR) (77,78), e integra escalas para avaliação clínica-laboratorial de atividade de doença (67,68). No caso da AR, este achado sugere possível evolução para erosões ósseas (47,70,77), uma vez que a literatura demonstra que o risco de erosão é seis vezes maior em áreas nas quais o EMO é identificado pela RM (70).

1 JUSTIFICATIVA

Apesar da FC ser conhecida há quase 70 anos, pouco foi descrito na literatura sobre as alterações em exames de imagens em pacientes que evoluíram com manifestações musculoesqueléticas decorrentes da infecção por este vírus. Os seguimentos dos punhos e mãos foram escolhidos por serem as regiões anatômicas mais acometidas pela doença, com significativo impacto na qualidade de vida dos pacientes.

A carência destas informações torna-se ainda mais relevante visto que a FC assemelha-se, do ponto de vista radiológico, a outras doenças reumatológicas. Neste contexto, o presente estudo é importante para a compreensão das alterações articulares determinadas pela doença, bem como a comparação entre o EF com a US e RM, devido a ausência de publicações sobre o tema até o presente momento. A relevância desta análise comparativa entre os métodos reside no fato de serem dois exames com perfis muito diferentes de realização e custo.

2 OBJETIVOS

2.1 Objetivo Geral

Caracterizar, por meio do EF, US e RM, as complicações musculoesqueléticas de punhos e mãos de pacientes com diagnóstico de febre Chikungunya crônica.

2.2 Objetivo Específico

Determinar o grau de concordância da positividade do EF com os achados de exames de imagens (US e RM) dos punhos e mãos, e entre a US e RM.

3 METODOLOGIA

3.1 Aspectos Éticos

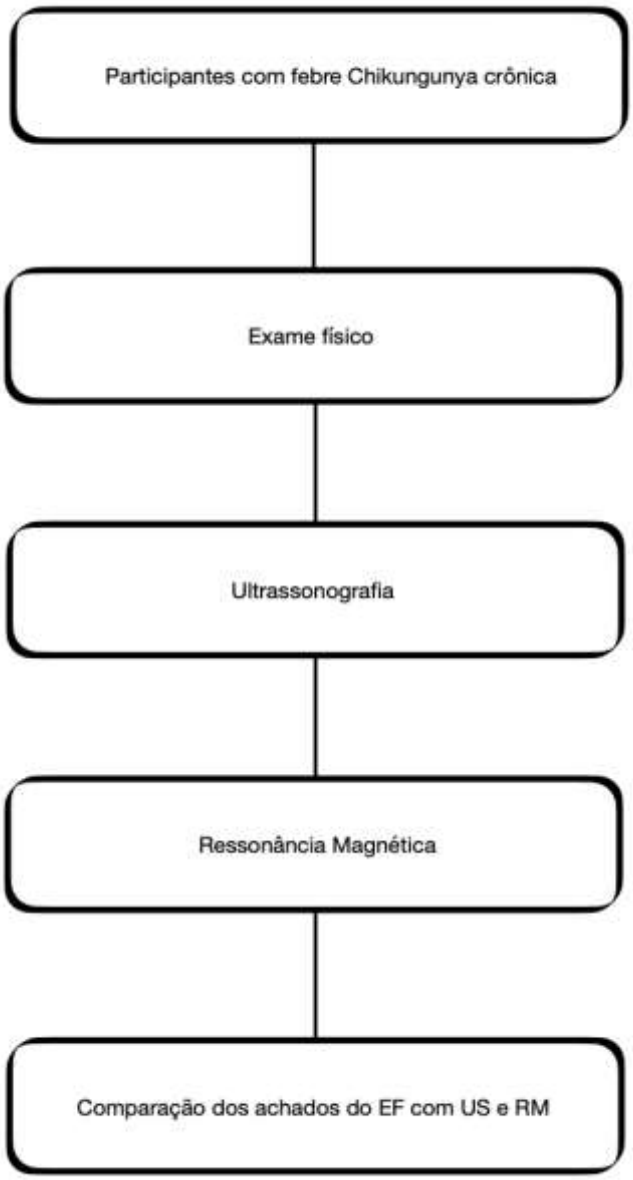
Todos os pacientes foram previamente informados da pesquisa e consentiram na realização do trabalho por meio da assinatura do termo de consentimento livre e esclarecido (TCLE) (Anexo I), que foi apresentado ao Comitê de Ética em Pesquisa (CEP) do HUPE. O TCLE informa o tipo de pesquisa, seus objetivos e esclarece que a inserção do participante é voluntária, não prevê qualquer ressarcimento e que tanto sua presença quanto a não concordância em participar do estudo não acarretará prejuízo de qualquer tipo. Nele, também se estabelece um compromisso com a privacidade de cada um e a utilização confidencial e sigilosa dos dados colhidos.

Este estudo foi avaliado e aprovado pelo Comitê de Ética em Pesquisa do HUPE (CEP- HUPE) (CAAE: 04179118.8.0000.5259), sob o número de comprovante do parecer 3.113.111. Não houve conflitos de interesse por parte do autor na realização deste trabalho.

3.2 Locais do Estudo

Estes pacientes foram recrutados no ambulatório de Reumatologia do Hospital Universitário Graffée e Guinle (HUGG) e da Policlínica Piquet Carneiro (PPC), da Universidade do Estado do Rio de Janeiro (UERJ), em primeira consulta ou em consulta de retorno, de janeiro de 2018 a março de 2020, desde que cumprissem os critérios de elegibilidade. Os participantes realizaram exame físico na unidade ambulatorial de origem e posteriormente foram encaminhados para o Serviço de Radiologia do HUPE, onde realizaram a US, admitindo-se um intervalo máximo de sete dias entre o exame físico e a US. Em seguida, estes pacientes realizaram RM no Centro Estadual de Diagnóstico por Imagem (CEDI), como demostrado no fluxograma a seguir (figura 1), admitindo-se um intervalo máximo de dois dias entre a US e RM.

Figura 1 - Fluxograma do estudo



Fonte: O autor.

3.3 **Desenho do Estudo**

Trata-se de um estudo transversal observacional em um grupo de 30 pacientes, com diagnóstico clínico-laboratorial de FC na fase crônica da doença. O fluxo de encaminhamento de pacientes do ambulatório para realização dos exames de imagem ocorreu por meio do enquadramento nos critérios de inclusão e exclusão, independentemente da extensão ou da

gravidade clínica do comprometimento articular, com objetivo de evitar o viés de seleção. Todos os pacientes foram submetidos a um questionário clínico-epidemiológico, incluindo dados demográficos e duração da doença (Apêndice B).

3.4 Critérios de Inclusão e Exclusão

Critério de Inclusão

a) Pacientes com diagnóstico clínico e laboratorial (sorologia reagente para anticorpos IgM e/ou IgG e/ou por detecção por RT-PCR indicando a presença do vírus) de febre Chikungunya em fase crônica, de ambos sexos, com idade superior a 18 e inferior a 70.

Critérios de Exclusão

a) Pacientes com FC durante a fase aguda da doença;
b) Pacientes que se recusaram a responder o questionário e/ou recusaram fazer algum dos exames do protocolo da pesquisa;
c) Pacientes que, por qualquer motivo, não conseguiram realizar completamente o exame de RM;
d) Pacientes com diagnóstico prévio de artrite reumatoide, espondiloartropatias, gota, artrite séptica ou de qualquer outra doença articular com dano estrutural prévio;
e) Pacientes com fraturas antigas ou atuais de mão ou punho;
f) Pacientes que tiveram reação alérgica ao meio de contraste gadolínio;
g) Pacientes que possuíam contraindicações absolutas à realização do exame de RM, como: portadores de bomba de infusão de insulina, de clipe de aneurisma cerebral ferromagnético (inserido anteriormente a 1995), de desfibrilador implantável, de fio-guia intravascular, de fixador ortopédico externo metálico

não removível, de implante dentário magnético, de marca-passo implantado antes de 1998, temporário ou definitivo com cabos epicárdicos ou implantados há menos de quatro semanas, de monitor de pressão intracraniana (PIC), de neuroestimuladores e moduladores (espinhais/medulares, intestinais, vesicais e outros) ou de implantes cocleares não compatíveis com a máquina utilizada na pesquisa.

3.5 **Análise Estatística**

No artigo 1, não houve análise estatística por se tratar de um relato de caso.

No artigo 2, a fidedignidade intermétodos foi avaliada pelo coeficiente de *Kappa*, uma medida utilizada para indicar o nível de concordância. O objetivo desta medida é comparar a proporção de acertos entre os dois examinadores com a proporção que poderíamos obter se os resultados entre eles fossem independentes.

Quanto mais próximo de um (1), mais forte (ou perfeita) é a concordância entre os métodos, ou seja, os métodos se assemelham sob o aspecto qualitativo da avaliação. Por outro lado, quanto mais próximo de zero (0), maior é indicativo de que a concordância é puramente aleatória e não há nível de reprodutibilidade entre os conjuntos de dados. A interpretação da magnitude dos estimadores de concordância *Kappa* deve ser convencionada de acordo com Landis e cols. (79), como: 0-0,19 (pobre), 0,20-0,39 (fraca), 0,40-0,59 (moderada), 0,60-0,79 (substancial), e ≥ 0,80 (quase completa). O critério de determinação de significância adotado foi o nível de 5%. A análise estatística foi processada pelo *software* estatístico SAS® System, versão 6.11 (SAS Institute, Inc., Cary, North Carolina).

O cálculo da amostra foi realizado para a verificação da significância do coeficiente *kappa*. Considerou-se um nível de Confiança de 95%, o que equivale a assumir uma significância de 5% para o teste.

Utilizando-se uma prevalência de 74% (baseado no estudo de Mogami e cols. do artigo “Ultrassonografia de mãos e punhos no diagnóstico de complicações da febre

Chikungunya"), obteve-se que a quantidade de 30 pacientes para identificar um *kappa* de 0,5 como significativo geraria um Poder[1] de 78,5%.

Calculou-se também o tamanho amostral necessário para identificar como significante um *kappa* de 0,4, de 0,5 e de 0,6, conforme a fórmula a seguir.

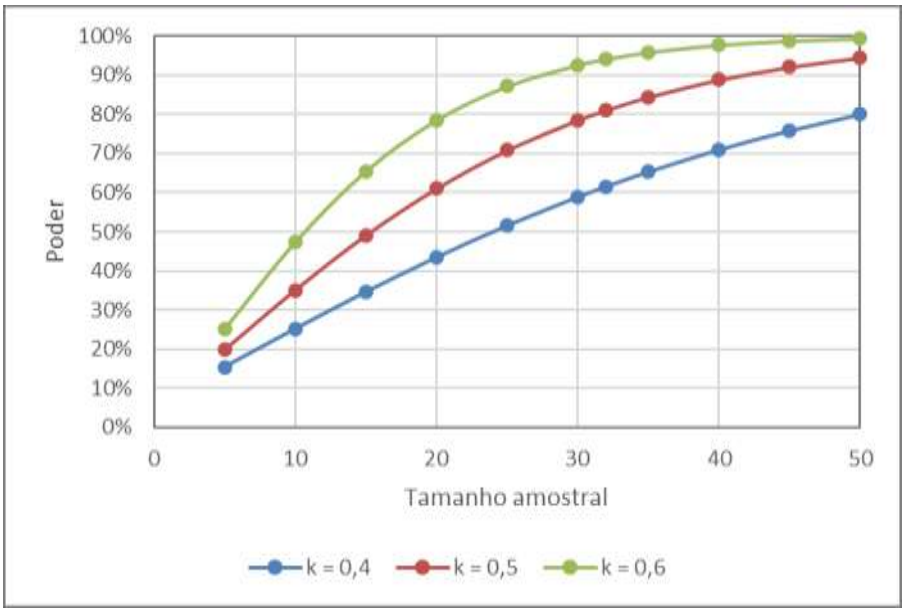
$$n = \left(\frac{sd_0.z^2_{(1-\alpha)} + sd_1.z^2_{(1-\beta)}}{\kappa_1 - \kappa_0} \right)^2$$

Onde:

a) n: tamanho da amostral;
b) sd_0: desvio padrão do *kappa* sob a hipótese nula;
c) sd_1: desvio padrão do *kappa* sob a hipótese de teste;
d) α: nível de significância;
e) 1- β: poder;
f) z: percentil da distribuição Normal.

No gráfico 1 e na tabela 1 apresentamos diversos valores para o cálculo do tamanho amostral versus o poder.

Gráfico 1 - Poderes e tamanho amostral para teste de significância de *kappa*



Fonte: O autor, 2021.

[1] Poder do teste é a chance de encontrarmos diferença significativa na comparação, caso essa realmente exista. Um poder considerado bom é próximo ou acima de 80%. Testes com poder baixo podem não ser conclusivos, principalmente se não houver diferença significativa, quando não se poderá afirmar que os grupos sejam iguais.

Tabela 1 - Poderes e tamanho amostral para teste de significância de kappa

n	k = 0,4	k = 0,5	k = 0,6
5	15,4%	19,8%	25,0%
10	25,2%	35,1%	47,3%
15	34,6%	49,1%	65,4%
20	43,4%	61,0%	78,5%
25	51,6%	70,8%	87,2%
30	58,8%	78,5%	92,6%
32	61,5%	81,1%	94,1%
35	65,3%	84,4%	95,8%
0	70,9%	88,8%	97,7%
45	75,8%	92,1%	98,8%
50	79,9%	94,5%	99,4%

Fonte: O autor, 2021.

3.6 **Cálculo do Tamanho da Amostra Considerando *kappa***

O tamanho de amostra para o estudo foi calculado para a verificação da significância do coeficiente *kappa* através do respectivo teste.

Assumiu-se uma significância de 5% e um poder do teste de 80% para o cálculo.

Foram considerados 30 pacientes no estudo final, quantidade que levou um poder de 78,5%, o qual foi considerado aceitável para o estudo.

4 AVALIAÇÃO DOS PUNHOS E MÃOS PELO EXAME FÍSICO

4.1 Técnica Exame Físico

Foi realizado anamnese, exame físico (EF) e um questionário de autoavaliação da dor no qual ilustramos duas mãos esquemáticas, em frente e verso, para que o paciente marcasse com "X" o local da queixa álgica (apêndice C). Foi realizado o seguinte protocolo:

a) A ectoscopia foi realizada sob inspeção do contorno, posição, formato e integridade dos dedos;

b) A palpação de cada articulação da mão e punhos.

O EF foi realizado por um reumatologista com 25 anos de experiência. Nosso protocolo foi baseado num estudo de Almoallim e cols. (80), cujo objetivo foi avaliar o padrão para doença reumatológica em punhos e mãos com foco em achados relacionados à artrites (edema e sensibilidade e/ou nas articulações). Desta forma, foi subdivido nos seguintes sítios anatômicos: interfalângicas proximais e distais (IF), metacarpofalângicas (MCF) e punho/mediocarpal (PMC). Estes segmentos foram escolhidos porque eles são locais frequentemente mais acometidos, de acordo com estudos anteriores (81).

O EF foi baseado numa avaliação dicotômica (positiva ou negativa), isto é, não foi avaliado o aspecto quantitativo.

Durante a inspeção dos punhos e mãos dos pacientes, o reumatologista buscou a presença de dor, sensibilidade e edema. Na palpação, três técnicas foram aplicadas para detectar a positividade nas articulações:

a) técnica de tesoura para articulações MCF, conforme descrito na Figura 2;

b) técnica de quatro dedos para articulações IF, conforme descrito na Figura 3, e;

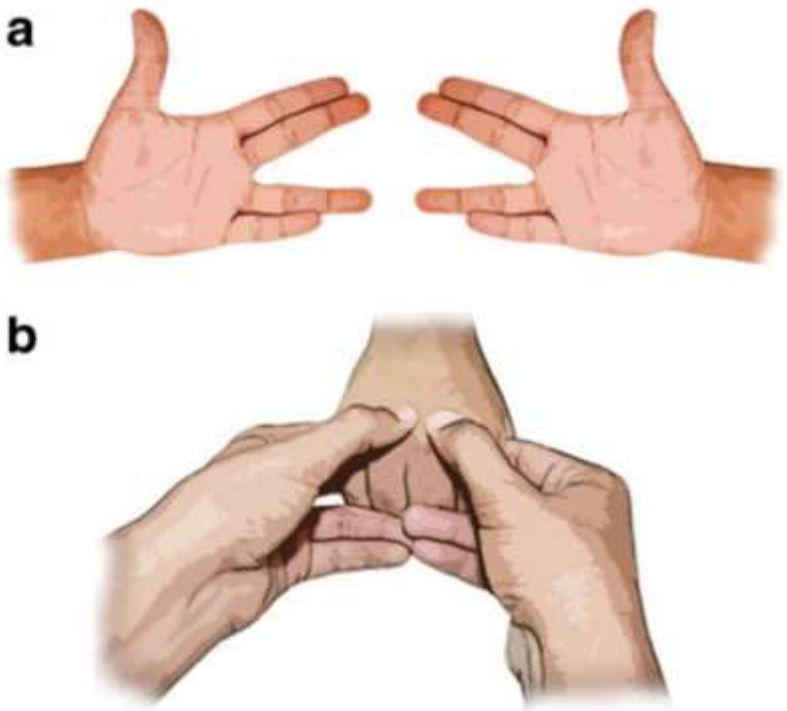
c) técnica de dois polegares para articulação do punho/mediocarpal.

As articulações IF foram palpadas com o polegar e o dedo indicador do médico posicionado para avaliar a articulação na vertical e planos transversais, alternando entre esses planos. A palpação nas articulações MCF também foi realizada entre o polegar e o indicador do médico, mas o do reumatologista as mãos estavam na posição de tesoura (dedo anelar e mínimo separados dos dedos médio e indicador pelos dedos do paciente). Nas articulações

PMC, a palpação foi realizada colocando os polegares no lado dorsal e os dedos indicadores na parte ventral da articulação examinada.

O examinador determinou o edema caso houvesse fluido percebido à palpação.

Figura 2 - Palpação das regiões metacarpofalângicas por meio da técnica de tesoura



Fonte: Almoallim, H., Attar, S., Jannoudi, N. et al. *Sensitivity of standardised musculoskeletal examination of the hand and wrist joints in detecting arthritis in comparison to ultrasound findings in patients attending rheumatology clinics. Clin Rheumatol* 31, 1309–17 (2012).

Figura 3 - Palpação das regiões interfalângicas por meio da técnica de quatro dedos

Fonte: Almoallim, H., Attar, S., Jannoudi, N. et al. *Sensitivity of standardised musculoskeletal examination of the hand and wrist joints in detecting arthritis in comparison to ultrasound findings in patients attending rheumatology clinics. Clin Rheumatol* 31, 1309–17 (2012).

5 AVALIAÇÃO DOS PUNHOS E MÃOS PELA US

5.1 Aquisição de Imagens

Os exames de US de todos os pacientes foram realizados em um aparelho Toshiba Aplio XG US (fabricado em 2013, Toshiba Medical Systems; Otawara, Japão) com uma sonda multifrequencial de 7 a 18 MHz, no modo B e com *power Doppler* (frequência de repetição de pulso de 750 Hz, filtro de parede baixa e ganho ajustado logo abaixo da aparência dos artefatos).

5.2 Técnica de Exame

Os sítios anatômicos avaliados por meio da US foram adaptados pelos autores deste estudo da diretriz desenvolvida por Backhaus e cols. (81): articulações interfalângicas (IF) proximal e distal; articulações metacarpofalângicas (MCF); articulações punho/mediocarpal (PMP) (recessos radiocarpais, radioulnares distais e carpalproximal); bainhas extensoras; bainhas flexoras; tecido subcutâneo; nervo mediano; erosão do osso subcondral (que também pode ser um sinal de sinovite); e locais com aumento do fluxo vascular nas imagens de power Doppler.

A área do nervo mediano também foi estimada em todos os pacientes. A técnica utilizada foi a partir da imagem captada no plano transverso, cujos pontos de referência foram os ossos pisiforme e escafoide. Uma medida normal da área do nervo mediano foi definida como até 10 mm^2 (83), e seu espessamento foi definido como uma área maior que 10 mm^2.

Em todos os pacientes foi aplicado o *power Doppler*, principalmente nas regiões anatômicas com sinais de suspeita de inflamação (derrame sinovial, tenossinovite e/ou espessamento sinovial).

5.3 **Definição dos Achados**

O critério da definição dos achados na US foi de acordo com o O*utcome Measures in Rheumatology* (OMERACT) em suas definições atualizadas (83) cujas descrições são listadas a seguir.

Sinovite foi definida como presença de hipertrofia sinovial hipoecoica em modo B, independentemente da presença de derrame ou de qualquer aumento do fluxo vascular ao *Doppler*.

Tenossinovite foi definida como espessamento anecoico e/ou hipoecoico da bainha do tendão, com ou sem líquido em sua bainha sinovial. O sinal *Doppler* pode ser considerado se visto em dois planos perpendiculares, dentro da bainha sinovial peritendínea, excluindo os vasos normais.

Erosão óssea foi definida como descontinuidade intra e/ou extra-articular da superfície óssea (visível em dois planos perpendiculares).

Celulite foi definida como espessamento e hiperecogenicidade do tecido subcutâneo.

6 AVALIAÇÃO DOS PUNHOS E MÃOS PELA RM

6.1 Aquisição de Imagens

Os exames de ressonância magnética foram realizados em um equipamento Siemens Magnetom Avanto 1.5 T de alto campo (fabricado em 2003, Munique, Alemanha). O meio de contraste intravenoso (gadolínio) foi administrado em todos os pacientes.

Quarenta e um pacientes foram incluídos na pesquisa, porém 11 não conseguiram concluir o exame de RM, a saber: nove devido à dor articular pela posição; um não coube na máquina devido à obesidade mórbida e outra devido à claustrofobia.

6.2 Técnica de Exame

Os exames de RM foram realizados com bobina tipo flexível de uso geral (tipo *flex*), devido a indisponibilidade de bobina específica no CEDI.

Os pacientes posicionaram-se em decúbito ventral, com o braço sobre a cabeça, conhecida como posição "do nadador" ou do "super-homem". A aquisição de volume tridimensional (3D) com a utilização de imagens com gradiente eco permite a obtenção de cortes muito finos (2 mm), úteis para a boa identificação dos ligamentos.

O FOV (*field of view*; campo de visão) variou de acordo com o tamanho do paciente. Para isso, foi compartimentalizado o exame em: punho (rádio distal, ulna distal, ossos do carpo e metacarpos) e mão (metacarpos e dedos).

Foram obtidas imagens dos punhos e mãos nos planos axiais, sagitais e coronais nas sequências pesadas em densidade protônica (DPr) com supressão de gordura, T1 com e sem supressão de gordura antes e após administração endovenosa de gadolínio e T2 com supressão de gordura.

Todas essas sequências foram adquiridas primeiro do lado direito, e depois esquerdo. Foram realizadas as sequências em ambos os punhos e mãos em todos os pacientes. Os sítios anatômicos estudados foram divididos nos mesmos grandes grupos que foram usados para US: articulações IF (proximal e distal); articulações MCF; Articulações PMC (recessos

radiocarpais, radioulnares distais e mediocarpais); extensor de bainhas; bainhas flexoras; tecido subcutâneo; nervo mediano, e; ossos.

6.3 **Definição dos Achados**

O critério de definição dos achados na RM foi de acordo com o O*utcome Measures in Rheumatology* (OMERACT) em suas definições atualizadas (84), cujas descrições são a seguir.

Sinovite foi definida como área no compartimento sinovial que mostra realce pós-gadolínio acima do normal com uma espessura maior do que a largura da sinóvia normal.

Tenossinovite foi definida com presença de líquido na bainha tendínea, espessamento da bainha e realce após injeção de contraste intravenoso visto em dois cortes axiais consecutivos.

Edema de medula óssea (EMO), também chamado de osteíte, foi definido por aumento do sinal dentro do osso trabecular na sequência T2 com saturação de gordura. É uma lesão dentro do osso trabecular, com margens mal definidas e características de sinal consistentes com aumento do conteúdo de água.

Erosões ósseas são visualizadas como uma descontinuidade óssea cortical. Devem ser visualizadas em pelo menos dois planos com baixa intensidade de sinal em imagens ponderadas em T1 e alta intensidade de sinal em imagens ponderadas em T2.

Celulite na RM é observada como aumento do sinal nas imagens ponderadas em T2 e realce nas imagens pós-contraste do tecido adiposo intra ou extracapsular.

Na STC, a RM pode demonstrar abaulamento do retináculo dos flexores, alargamento do nervo mediano no nível do pisiforme e achatamento do nervo mediano no nível do gancho do hamato (85). Devido à falta de uma definição objetiva da dimensão da área do nervo mediano na RM, os critérios adotados para espessamento do nervo foi o aumento da intensidade de sinal na seqüência ponderada em T2 (86).

7 RESULTADOS E DISCUSSÃO

Esta tese resultou em dois artigos científicos.

O primeiro artigo foi publicado na International Journal of Case Reports and Images (IJCRI), periódico revisado por pares, estrato Qualis A3, em 2021, com base de um paciente da amostra que evoluiu de FC para AR, e encontra-se aqui em Word e no APÊNDICE D, na forma como foi publicado.

O segundo artigo foi publicado no Journal of Ultrasound in Medicine (JUM), periódico revisado por pares, estrato Qualis A4, em 2021, e também se encontra aqui em Word e no APÊNDICE E, na forma como foi publicado.

7.1 Artigo 1 - Multimodal Imaging of Psoriatic Arthritis Triggered by Chikungunya fever

Title: Multimodal imaging of psoriatic arthritis triggered by Chikungunya fever

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ABSTRACT

Chikungunya fever (CF), caused by the Chikungunya virus (CHIKV), is an arboviral disease transmitted by infected Aedes mosquitoes found worldwide. Although CF may trigger chronic arthritis, there are still few reports of patients who have progressed to psoriatic arthritis (PsA). We describe the clinical and ultrasound (US) and magnetic resonance imaging (MRI) findings of the wrist and hands of a 49-year-old man who had peripheral PsA triggered by CHIKV. He had scaly, itchy scalp lesions three months after the diagnosis of CF. The patient had classic synovitis and tenosynovitis secondary to CF. The persistence of inflammatory disease with signs of enthesitis and dactylitis on magnetic resonance imaging (MRI) and US, family history and appearance of skin lesions on the scalp strongly suggest post-CF PsA. Viral infections can be a triggering factor for several diseases with chronic arthritis, such as PsA. Imaging exams are essential methods for both diagnosis and the monitoring of treatment.

INTRODUCTION

Chikungunya fever (CF) is a viral disease whose transmission occurs through vector females of Aedes aegypti and Aedes albopictus mosquitoes infected by the Chikungunya virus (CHIKV). There are reports of outbreaks in Europe, the Americas, Asia, Africa, and Oceania [1].

Approximately 60% of patients with CHIKV infection progress to chronic arthritis [2]. In these cases, joint limitations can persist for up to five years after infection [3] and are associated with permanent sequelae [4]. After an incubation period of three to seven days, patients may experience fever, skin rash, myalgia, and arthralgia. The disease becomes chronic when the arthralgias persist for more than three months. The literature shows that a small portion of patients with chronic CF and severe polyarticular forms develop rheumatoid arthritis (RA) [5] or other forms of arthritis, including psoriatic arthritis (PsA) [6].

Conventional radiology is still a first-line exam in the investigation of rheumatological diseases. However, the method is not as sensitive as MRI or US in showing early bone and soft tissue changes. Although US has limitations in bone evaluation, together with Doppler it can identify early signs of enthesitis or organ-enthesis involvement [7]. Conventional MRI, in turn, is useful for diagnosing bone complications such as marrow edema and erosions as well as soft tissue involvement [8].

The pattern of involvement of the hands and wrists by CF is very similar to that found in RA, and it is characterized by symmetrical and bilateral involvement of the

metacarpophalangeal and proximal interphalangeal joints, tenosynovitis, subcutaneous edema, and bone changes, such as marrow edema and erosions [9].

Although there have been several reports of developing RA, to our knowledge, there are few descriptions of postCF PsA. Mathew et al. [5] investigated 1396 individuals with CF and concluded that only 2.5% of patients developed PsA. Thus, our report is valuable due to the scarcity of cases, and it features an imaging presentation typical of peripheral spondyloarthropathy secondary to arbovirus infection.

CASE REPORT

A 49-year-old man had a fever (101.30°F/38.5°C) for approximately ten days and exhibited persistent signs of polymyalgia and polyarthralgia. He used dipyrone and oral hydration to reduce the fever, and his musculoskeletal symptoms partially improved. Serologies for CHIKV were positive for IgM (51; normal value: 9). Subsequently, a skin rash appeared, and polyarthralgia associated with edema of the hands, wrists (Figure 1), elbows, knees, and feet worsened. Two months later, he was evaluated in an outpatient rheumatology clinic at a university hospital in Rio de Janeiro, Brazil. He continued to experience polyarthralgia and edema in the metacarpophalangeal and interphalangeal joints, especially of the left hand. Erythematous scaling and itchy skin lesions were also noted in the anterior medial region of the scalp on physical examination. At the time, the patient was not taking any known medication that could precipitate psoriasis. He also denied any preceding emotional stress (at least two months prior to the appearance of the skin lesion). The patient had never had any episode of psoriatic skin lesions. The patient was hypertensive, using enalapril 20 mg/day, and was an abstainer, nonsmoker, and physically active. He denied allergies and blood transfusions and had an up-to-date vaccination schedule. His father had PsA. One maternal aunt had multiple sclerosis, and another had ankylosing spondylitis.

The rheumatologists prescribed meloxicam 15 mg/day and prednisone 20 mg/day after discussing the case. The patient returned the following month with little clinical improvement, and methotrexate 15 mg and folic acid 5 mg were started after verification of the laboratory tests.

After starting the medication, he was followed up on an outpatient basis and remained asymptomatic. However, the patient stopped medication on his own, and after two years and four months he returned to the outpatient clinic with symptom recrudescence. After that, the

joint pain returned, but the psoriatic skin lesions did not. He was re-evaluated with US and MRI.

Written consent was obtained from the patient to be evaluated at the rheumatology outpatient clinic and the radiology department of a university hospital in the city of Rio de Janeiro, Brazil.

There were no changes in the patient's complete blood count: C-reactive protein 13 mg/L (normal index: up to 3 mg/L), fibrinogen 340 mg/dL (normal index: 200– 400 mg/dL), and normal levels of transaminases and electrolytes (sodium and potassium). The nonreactive immunological tests included the following: antinuclear factor (ANA), antibodies against citrullinated peptides (ACPA), rheumatoid factor (RF), and cytoplasmic antineutrophil antibodies (ANCA). Serological tests for HIV and hepatitis B and C were nonreactive; CHIKV IgM and IgG were reactive; and HLA-B27 was negative.

The equipment used was a Toshiba US, model Aplio XG, with a 7–18 MHz multifrequency probe, in B mode and with power Doppler (pulse repetition frequency 750 Hz, low wall filter and gain adjusted just below the appearance of the artifacts).

The MRI scans were performed in a Siemens model Avanto, 1.5 T high-field scanner. The image acquisition protocol had the following sequences: protonic density (PD) with fat saturation in the axial, sagittal, and coronal planes and T1 pre- and post-contrast fat saturation in the axial plane.

The US and MRI scans showed signs of arthritis in the wrist and metacarpophalangeal joints of both hands. There was also tenosynovitis of all extensor compartments, digital flexor tenosynovitis (Figures 2 and 3), and signs of classical enthesitis due to thickening of the digital extensor entheses and functional enthesitis (Figures 4–6) due to peritendinous extensor thickenings. Vascular hyperflow was observed by power Doppler (Figure 4) at several sites of inflammation, paramagnetic contrast enhancement of the distended sheaths, and functional enthesitis sites. Focal bone edema was identified as an indirect sign of enthesitis at the base of the left third metacarpal associated with signs of inflammation of the extensor carpi radialis brevis.

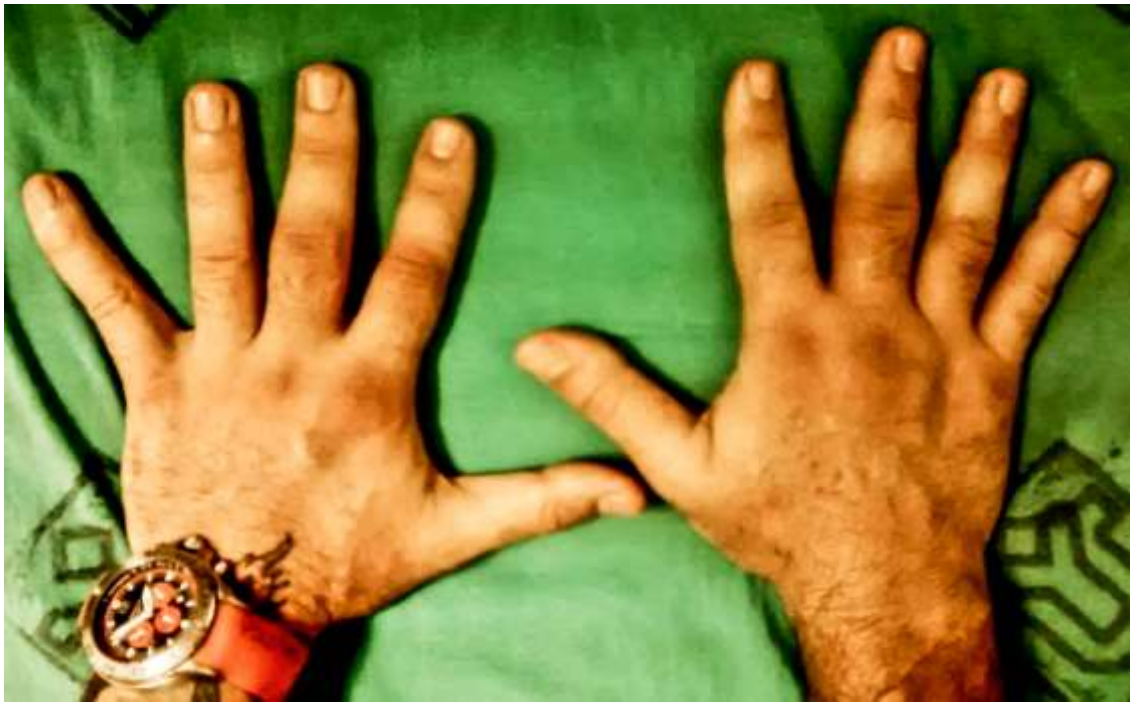

Figure 1. 49-year-old man with chronic Chikungunya fever. Panoramic view of both hands with metacarpophalangeal and interphalangeal oedema.

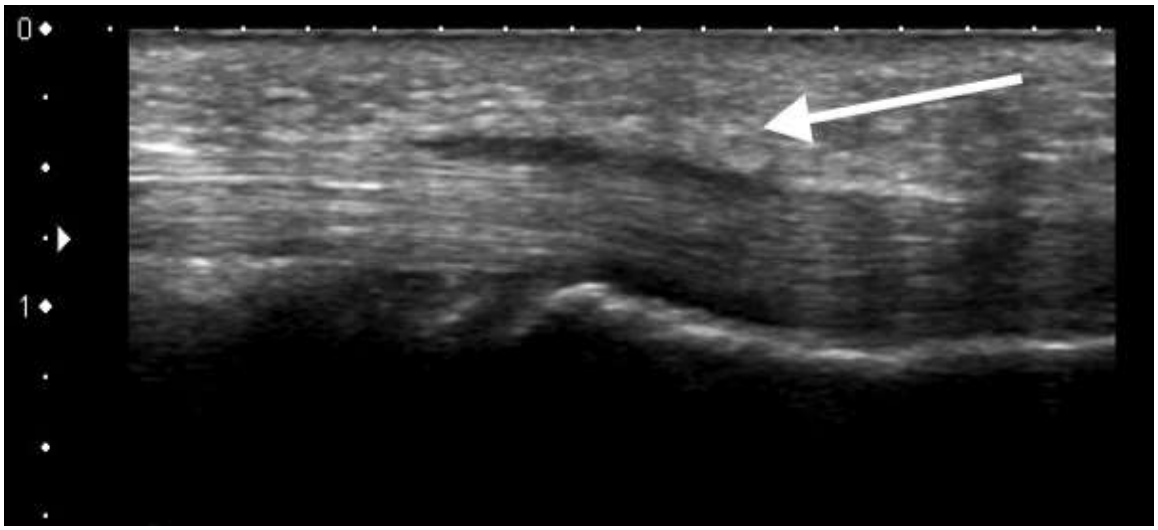

Figure 2. B-mode ultrasound in the sagittal plane of the second right digit. Note the flexor tendon sheath distention.

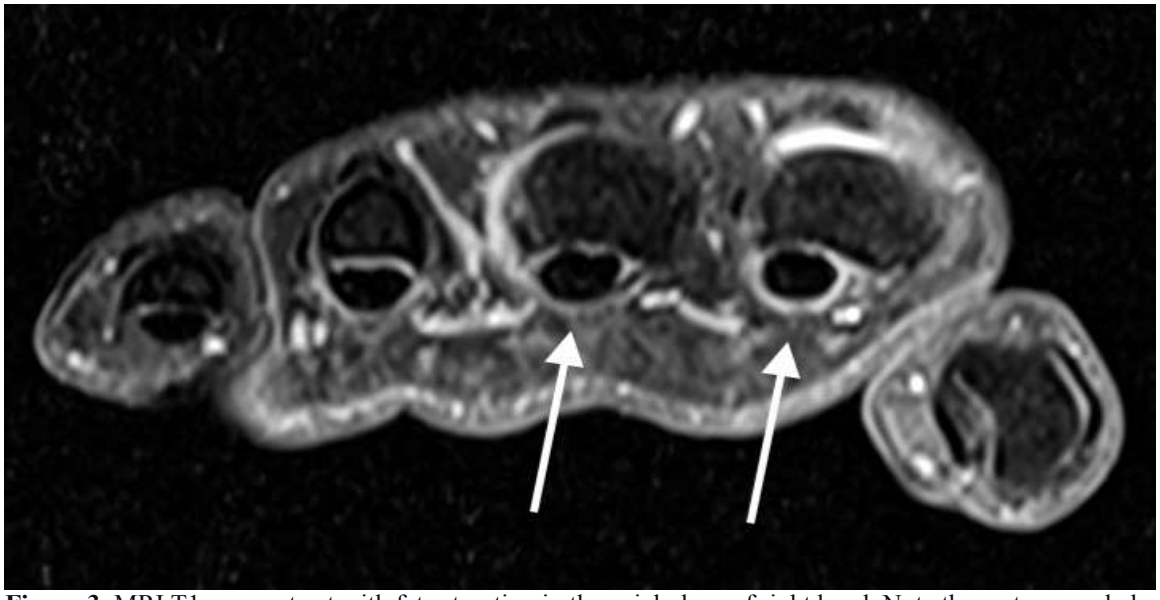

Figure 3. MRI T1 pre-contrast with fat saturation in the axial plane of right hand. Note the metacarpophalangeal synovitis and flexor tenosynovitis of the second and third digits (arrows).

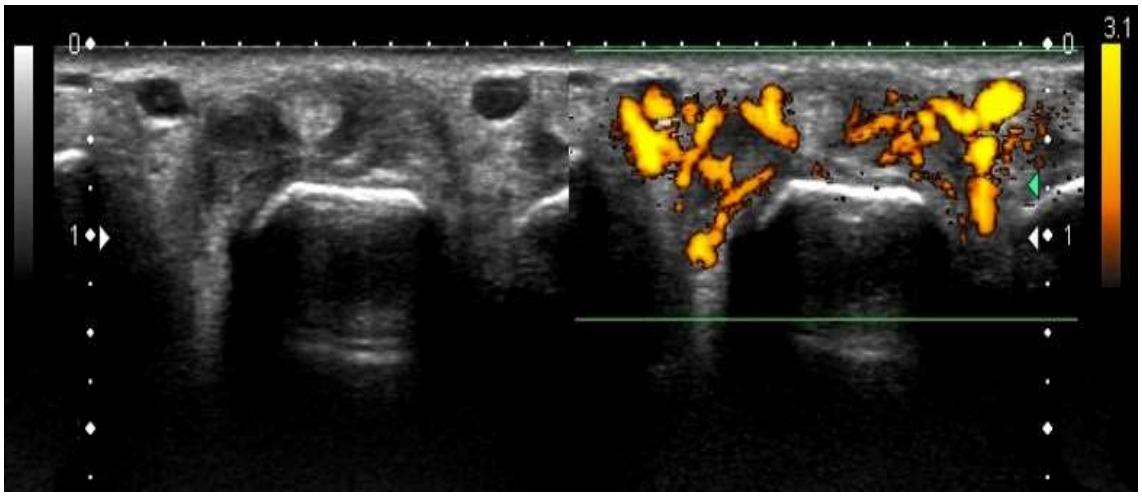

Figure 4. 49-year-old man with chronic Chikungunya fever. B-mode and power Doppler ultrasound of the left fourth digit in the axial plane. Note the extensive peritendinous extensor thickening with vascular hyperflow at the level of the metacarpophalangeal joint, indicating functional enthesitis. **Note**: This image had already been presented at the 2017 European Congress of Radiology in electronic poster (EPOS) mode, DOI: 10.1594/ecr2017/C 0384 (https://dx.doi.org/10.1594/ecr2017/C-0384). According to the congressional ethics committee, the authors have the right to use it.

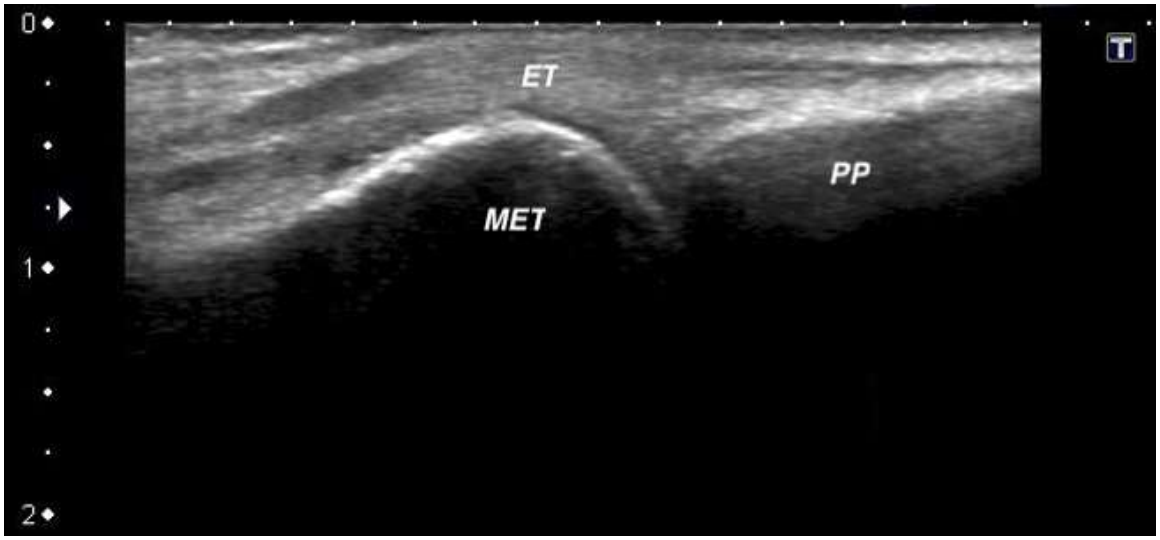

Figure 5. B-mode ultrasound in the sagittal plane of the left fourth digit at the metacarpophalangeal level. Note the soft tissue peritendinous extensor thickening, indicating functional enthesitis.

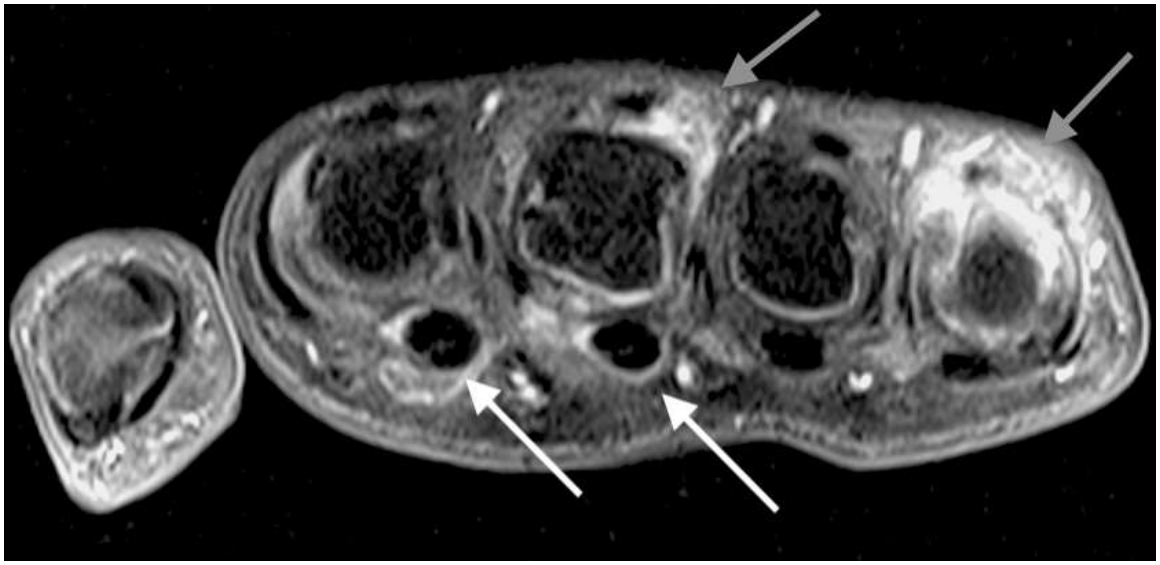

Figure 6. MRI of the left-hand show T1 postcontrast with fat saturation. Note the enhancement of the flexor sheaths of the second and third digits (white arrows) and of the extensor peritendinous soft tissue of the third and fifth digits (grey arrows).

DISCUSSION

The authors present an unusual complication of CF suggested by clinical and imaging findings. US and MRI were also essential during the treatment follow-up.

According to the Classification Criteria for Psoriatic Arthritis (CASPAR) [10], to confirm the diagnosis of PsA, it is necessary to have an inflammatory joint disease and at least a three-point score in the other categories. The patient had a five-point score due to scalp psoriasis (two points), family history (one point), negative RF (one point), and dactylitis (one

point). As reported in other literature cases, these signs and symptoms appeared immediately after CF infection, and the disease regressed with methotrexate therapy [5].

The patient's age and gender profiles disagree with the literature, which describes a predominance in women over 45 years old who are at risk for musculoskeletal complications in CF [11]. Among the usual manifestations of CF, the presentation of only fever, polymyalgia, polyarthralgia, and skin rash and the high levels of C-reactive protein are in accordance with the literature [12].

The US and MRI scans showed several signs of involvement, with characteristics of spondyloarthropathy: dactylitis due to flexor tenosynovitis, classic enthesitis in distal extensor insertions, functional enthesitis due to peritendinous extensor thickening adjacent to the metacarpophalangeal and interphalangeal joints, and metacarpal marrow edema adjacent to the insertion of an extensor tendon.

After the 2015–2016 CF outbreak in Rio de Janeiro, Brazil, our group [9, 13] reported wrist/hand and ankle ultrasound changes. The authors highlighted bilateral synovitis and tenosynovitis as relevant findings for the diagnosis of musculoskeletal complications. However, in this case report, the existence of several signs of very intense enthesitis and flexor tenosynovitis in the imaging exams raised the suspicion of some other disease associated with CF.

There are two types of entheses according to function and location: fibrous and fibrocartilage. The most common fibrocartilage is found in the apophyses and epiphyses of long bones, short bones of the hands and feet, and several ligaments in the spine. Fibrous entheses are found in the metaphyses and diaphyses of long bones. Fibrocartilaginous entheses are those affected in spondyloarthropathies and altered in the US and MRI exams of the reported case [14,15].

Functional enthesis is another essential concept to understanding our imaging findings. In specific locations where the tendon deflects or rubs against a bone surface, there are sesamoid (tendinous) and periosteal fibrocartilages. This patient had intense digital peritendinous extensor inflammatory thickenings, which are explained by these functional enthesis impairments [16,17].

Dactylitis is one of the main features of psoriatic arthritis and is present in 40% of cases. The main finding is digital flexor tenosynovitis, that is, distention of the fibrous sheaths, which also existed in the reported case [18].

Clinical recognition of early-stage PsA is challenging when the disease affects only the peripheral joints. Despite the efficiency of CASPAR in identifying patients with less than

one year of symptom onset (early psoriatic arthritis) [19], peripheral PsA remains a challenge for rheumatologists [20]. In our case, imaging helped detect the entheseal manifestations of the disease, suggesting alternative diagnoses in CF patients.

CONCLUSION

With the resurgence of CF epidemics worldwide, managing chronic arthritis has become an enormous challenge for rheumatologists. It is essential to follow these chronic cases and to identify the progression to other forms of arthritis, such as PsA. Imaging exams have become indispensable for the diagnosis and management of these complications.

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João Luiz Pereira Vaz – Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Flávio Roberto Sztajnbok – Acquisition of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Marcelo Torres Gonçalves – Acquisition of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Roberto Mogami – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

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Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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7.2 Artigo 2 – Chikungunya fever: Comparison Study of Synovitis and Tenosynovitis of the Hands and Wrists Using Physical Examination, Ultrasound and MRI Findings

Title: Chikungunya fever: Comparison Study of Synovitis and Tenosynovitis of the Hands and Wrists Using Physical Examination, Ultrasound and MRI Findings

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Abbreviations

ACR, American College of Rheumatology; CF, Chikungunya fever; CHIKV, Chikungunya virus; DRUJ, distal radioulnar joints; EULAR, European League Against Rheumatism; IP, interphalangeal; MCP, metacarpophalangeal; MRI, magnetic resonance imaging; PE, physical examination; RA, rheumatoid arthritis; US, ultrasound; WMC, wrist/mediocarpal

doi: 10.1002/jum.15766

ABSTRACT

Objectives—To compare musculoskeletal changes on a physical examination (PE), ultrasound (US) and magnetic resonance imaging (MRI) of the hands and wrists of patients with Chikungunya fever (CF).

Methods—The sample consisted of 30 patients in the chronic phase of CF. The sites analyzed were the interphalangeal (IP), metacarpophalangeal (MCP) and wrist/mediocarpal (WMC) joints and periarticular soft tissue. The interval between the PE and imaging tests was 7 days, and the interval between US and MRI was 2 days. The kappa coefficient was calculated to estimate the agreement between the PE and US and MRI findings and between the US and MRI findings.

Results—Significant agreement was observed between PE and US in the diagnosis of synovitis. The only statistically significant agreement between US and MRI was the finding of flexor tenosynovitis; the agreement was moderate.

Conclusions—US has great potential for use in diagnosing synovitis suspected based on a PE. The limited agreement observed between US and MRI, in turn, may suggest a complementary role of these methods.

Key Words—arthritis; Chikungunya fever; magnetic resonance imaging; musculoskeletal; physical examination; ultrasound

Short Running Title: Imaging findings in Chikungunya fever

Chikungunya fever (CF) is a viral disease transmitted through the bite of female Aedes aegypti and Aedes albopictus mosquitoes infected with the Chikungunya virus (CHIKV).[1] Outbreaks have been reported on all continents except Antarctica.[2] An effective antiviral treatment is currently unavailable, and prophylaxis is performed by vector control.[3] Clinically, the disease has acute and chronic phases.[4] The chronic phase is characterized by a symptom duration longer than 3 months. Patients may present with arthralgia (bilateral and symmetrical) or arthritis and functional impotence.[4] Approximately 60%[5] of those infected with CHIKV have a chance of developing chronic arthritis.[6] In these cases, motor disability

may persist for up to 5 years after infection[5] and is associated with permanent and irreversible sequelae.[7]

According to recent studies, a small portion of patients with CF and severe polyarticular involvement may progress to rheumatoid arthritis (RA) or aggravated pre-existing RA.[7] Similar to RA, CF manifests as erosive arthropathy, and imaging findings include bone erosion, joint effusion, bone marrow edema, synovial thickening, tenosynovitis and tendinopathy[8]. Sissoko et al.[9] investigated 147 patients diagnosed with CF and reported that 57% maintained rheumatic pain for more than 15 months after the initial diagnosis of viral infection. Mogami et al.[10,11] notedthat some radiological presentations of CF are potentially associated with more severe clinical manifestations of the disease.[10] In the hands and wrists, the authors observed synovitis of small joints, especially the metacarpophalangeal (MCP) joints, isolated effusion or synovitis in the wrist, flexor and extensor tenosynovitis, cellulitis, and median nerve thickening.[12]

Points of intersection have been identified between CF and RA due to both the similarity of symptoms and the possibility of progression from CF to RA according to the criteria of the American College of Rheumatology (ACR).[13]

The sensitivity of ultrasound (US) and magnetic resonance imaging (MRI) is higher than that of PE for the diagnosis of rheumatic lesions,[14] and those techniques enable the identification of treatable inflammatory lesions, such as synovitis and enthesopathy.[15] Although US has limitations for bone evaluation, it has the following advantages over MRI in the follow-up of chronic musculoskeletal inflammatory diseases[16]: wide availability, lower cost, good general acceptance by patients and its use as a quick guide for various types of interventions at the level of the wrists and hands (eg, aspiration, injection and biopsy).[17]

The lack of documentation of CHIKV-induced musculoskeletal complications in imaging tests is surprising because the profile of the disease is similar to that of other rheumatic diseases.[10]

Considering the clinical-epidemiological relevance of CF, the need to better understand musculoskeletal lesions/disorders and the lack of studies comparing physical examination (PE) results with US and MRI findings in patients with chronic CF, the objective of this study was to evaluate the agreement between a PE of the hands and wrists and imaging findings and to determine the agreement between US and MRI findings in the hands and wrists.

Materials and Methods

Study Population

This study was approved by the Research Ethics Committee of the Pedro Ernesto University Hospital, State University of Rio de Janeiro (Number 04179118.8.0000.5259). All participants signed an informed consent form. This cross-sectional study was conducted on patients with a clinical and laboratory diagnosis of CF in the chronic phase of the disease who had inflammatory symptoms in their hands and/or wrists at the time they underwent imaging tests.

All consecutively treated men and women with a chronological age >18 years who had a clinical and laboratory diagnosis (IgM and/or IgG and/or PCR) of CF and were in the chronic disease phase were included. The following patients were excluded: those with a previous or current diagnosis of RA (all patients were negative for rheumatoid factor and cyclic citrullinated peptide antibodies and none of them fulfilled the criteria for RA established by the ACR and European League Against Rheumatism (EULAR)[18] or any other joint disease with structural damage; those with old or current hand or wrist fractures; those who, for any reason, were unable to undergo any of the imaging tests; those with an absolute contraindication to MRI (such as patients with an insulin infusion pump, ferromagnetic intracerebral aneurysm clip [inserted before 1995] or cardiac pacemaker not compatible with MRI; electrostimulators not compatible with MRI; intracranial aneurysm clips not compatible with MRI; intraocular metallic material; Triggerfish contact lenses; cochlear implants not compatible with MRI; or a nonremovable metallic orthopedic external fixator not compatible with MRI).

Forty-one patients met the inclusion criteria. However, 11 patients were excluded (9 due to an inability to remain on the MRI table due to joint pain; 1 due to size, since the patient was morbidly obese; and another due to claustrophobia). The 30 patients who participated in the study were treated at the Rheumatology Outpatient Clinic of the Rio de Janeiro State University and were attending their first visit or a return visit between January 2018 and March 2020. The sample was selected by consecutive sampling of patients with symptoms of the hands and wrists during outpatient care.

Physical Examination

A qualitative and subjective analysis of joint involvement was performed by ectoscopy and palpation and observations of redness, heat, swelling and pain in the interphalangeal

joints = (IP), MCP and radiocarpal and distal radioulnar joints (DRUJ) and mediocarpal joint. The last 3 joints belong to the wrist/ mediocarpal (WMC) region.

Ultrasound

The US examinations of all patients were performedusing a Toshiba Aplio XG US machine (Toshiba Medical Systems; Otawara, Japan) with a 7- to 18-MHz multifrequency probe in B mode and with power Doppler (750-Hz pulse repetition frequency, low wall filter and gain adjusted just below the appearance of artifacts). Power Doppler was used for sites with suspected inflammation (effusion, tenosyn- ovitis and synovial thickening). The median nerve area was also estimated based on an image captured in the transverse plane, whose reference points were the pisiform and scaphoid bones. A normal median nerve area measurement was defined as <10 mm2[19]. Nine sites or parameters based on the guideline developed by Backhaus et al.[20] were adapted and investigated by the authors of this study: IP joints (proximal and distal); MCP joints; WMC joints (radiocarpal, distal radioulnar and mediocarpal recesses); extensor sheaths; flexor sheaths; subcutane- ous tissue; median nerve; subchondral bone erosion (which may also be a sign of synovitis); and sites with increased vascular flow on power Doppler images. The parameters used to define joint impairment were fluid distension of the joint capsule, synovial thickening and the presence of increased vascular flow on power Doppler images. The authors did not use classifications to estimate the degree of synovitis.

Magnetic Resonance Imaging

The MRI exams were performed in a high-field Siemens Magnetom Avanto 1.5 T instrument (manufactured in 2003, Munich, Germany), and intravenous contrast medium (gadolinium) was administered to all patients. The following sequences were used: proton density with fat saturation in the axial, sagittal and coronal planes; T1 with pre- and postcontrast fat saturation in the axial and coronal planes; and T2 with fat saturation in the coronal plane. All of these sequences were acquired first on one side and then on the other. The studied anatomical sites were divided into the same large groups that were used for US: IP joints (proximal and distal); MCP joints; WMC joints (radiocarpal, distal radioulnar and mediocarpal recesses); extensor sheaths; flexor sheaths; subcutaneous tissue; median nerve; and bone. The criteria adopted for abnormalities were fluid distension of the joint capsules, syno- vial thickening, contrast medium impregnation, bone edema characterized by an

increased signal in the T2 sequence with fat saturation, median nerve hypersignal in the same sequence and cortical bone discontinuity (erosion).

Ultrasound and Magnetic Resonance Imaging

The US examinations were independently evaluated by 2 examiners: 1 with 20 years of experience in musculoskeletal US and another with 10 years of experience. Two other radiologists analyzed all MRI examinations; the first had 15 years of experience in musculoskeletal imaging, and the second had 8 years of experience. None of the examiners had prior knowledge of any test results. The reports for both modalities were issued by consensus. The patients underwent US first, followed by MRI. The interval between the PE and imaging tests was 7 days for all patients, and a maximum interval of 48 hours was allowed between the performance of the 2 imaging tests.

Statistical Analysis

The primary analysis was descriptive. Continuous/interval variables are reported as measures of central tendency and dispersion, and categorical variables are presented as absolute and relative frequencies.

The kappa coefficient was calculated to estimate the agreement between the PE and the US and MRI findings and between US and MRI findings.

The level of statistical significance adopted for the comparisons was 5%. Statistical analyses were performed using SPSS version 26 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY).

Results

Sample Characterization

The authors studied 30 patients, 26 of whom were women (86.7%). The age of the participants ranged from 32 to 73 years, with a mean ± standard deviation (SD) of 54.7± 10.0 years.

All patients were in the chronic phase of the disease, and the mean elapsed time between the diagnosis and US examination was 336.1 ± 251.7 days, ranging from 53 to 911 days. For MRI, the mean elapsed time was 337.5 ± 251.7 days, ranging from 54 to 913 days.

The most frequent symptoms, in decreasing order of frequency, were joint pain in 30 patients (100%), par- esthesia in 23 patients (76.7%), pruritus in 19 patients (63.3%) and edema in 22 patients (73.3%).

Regarding treatment, the sample was divided as follows: 8 patients (26.7%) were not taking any medication; among the 22 patients who were on continuous medication, 12 (40%) used corticosteroids. Seven (23.3%) used steroids in combination with immune suppressants, 2 (6.7%) used only nonsteroidal anti-inflammatory drugs and 1 (3.3%) used only immunosuppressants.

Laboratory Tests

The presence of other autoimmune diseases in both clinical and laboratory tests was excluded in all patients enrolled in the study.

Laboratory confirmation was obtained by IgG serology in 23 patients (76.7%), IgM and IgG serology in 3 (10%), IgM serology alone in 2 (6.6%) and PCR in 2 (6.6%).

Regarding the laboratory measurements of inflammation, 20 patients (66.6%) had abnormal values for both tests (C-reactive protein and erythrocyte sedimentation rate), 4 (13.3%) had only abnormal C-reactive protein levels and 4 (13.3%) had only an abnormal erythrocyte sedimentation rate. Two patients (6.6%) did not undergo these tests.

Physical Examination

In the examination of signs of inflammation and pain on palpation, 27 patients presented with sensitivity in the MCP region (90%), 19 (63.3%) had sensitivity in the WMC and 17 (56.7%) had sensitivity in the IP region.

Table 1 shows the PE, US and MRI results for IP and MCP involvement and joint recesses, as well as the kappa coefficients and respective p-values.

Moderate agreement was observed between PE and US for the IP (kappa = 0.49; P = 0.026) and MCP (kappa = 0.429; P = 0.064) findings. Substantial agreement was also observed between PE and US for the involvement of the radiocarpal, distal radioulnar and mediocarpal recesses (kappa = 0.661; $P < 0.0001$).

The agreement between MRI and PE was very low (approximately 0), and none of the results reached statistical significance. Kappa values equal to zero indicate that the agreement between the methods was not higher than that expected by chance.

Site of Involvement: US And MRI

Table 2 shows the frequency of the sites of involvement identified by US and MRI.

In descending order of frequency, the US identified sites of involvement with effusion or synovial thickening were MCP in 25 patients (83.3%) (Figure 1), extensor sheaths in 18 patients (60%), flexor sheaths in 18 (60%) (Figure 2), radiocarpal/ DRUJ/proximal carpal joints in 16 (53.3%) (Figure 3) and IP in 12 (40%). The other changes included increased vascular flow on power Doppler images in 8 patients (26.7%), median nerve thicken- ing in 7 (23.3%), subcutaneous edema in 5 (16.7%) and bone erosion in 1 (3.3%).

The MRI sites of involvement, in decreasing order of frequency, were fluid distension of the exten- sor sheaths in 19 patients (63.3%), synovitis of the MCP joints and radiocarpal/DRUJ/proximal carpal recesses in 17 (56.7%), fluid distension of the flexor sheaths in 12 (40%) and IP joints in 8 (26.6%).

Other associated findings were signs of bone marrow edema in 11 patients (36.7%), bone erosion in 8 (26.2%) and subcutaneous edema in 5 (16.7%). No change in the median nerve signal was observed in any patient.

Table 1. Kappa agreement between the PE and US and MRI results by anatomical location.

INTERPHALANGEAL			
Physical examination	***Ultrasound***		***Kappa (p-value)***
	+	-	
+	10	7	0.416 (0.026)
-	2	11	
Physical examination	***Magnetic resonance imaging***		***Kappa (p-value)***
	+	-	
+	4	13	
-	4	9	-0.067 (0.69)
METACARPOPHALANGEAL			
Physical examination	***Ultrasound***		***Kappa (p-value)***
	+	-	
+	24	3	
-	1	2	0.429 (0.064)
Physical examination	***Magnetic resonance imaging***		***Kappa (p-value)***
	+	-	
+	16	11	
-	1	2	0.104 (0.56)
RECESSES			
Physical examination	***Ultrasound***		***Kappa (p-value)***
	+	-	
+	15	4	
-	1	10	0.661 (< 0.0001)
Physical examination	***Magnetic resonance imaging***		***Kappa (p-value)***
	+	-	
+	10	9	
-	7	4	-0.106 (0.70)

US revealed a higher frequency of MCP synovitis (83.3%), flexor tenosynovitis (60.0%), IP synovitis (40.0%) and median nerve changes (23.3%) than MRI.

MRI showed a higher frequency of extensor tenosynovitis (63.3%), radiocarpal/DRUJ/mediocarpal synovitis (56.7%) and erosions (26.7%) than US.

Analysis of the Agreement between US and MRI Findings

Table 2 shows the frequency (n) and percentage (%) of 8 US and MRI findings. In addition to these data, the table shows the number of positive findings in terms of agreement between US and MRI, as well as the respective kappa coefficients and P-values.

Significant but moderate agreement was observed between the 2 methods for only the flexor tenosynovitis finding (kappa = 0.49; P = 0.003).

Table 2. Frequency of findings at sites and agreement between US and MRI in 30 patients with CF.

Finding	***US***	***MRI***	***No. of agreements***	***Kappa***	***p-value***
	n (%)	***n (%)***			
Interphalangeal	12 (40.0)	8 (26.7)	4	0.12	0.5
Metacarpophalangeal	25 (88.3)	17 (56.7)	16	0.27	0.069
Proximal carpal/wrist	16 (53.3)	17 (56.7)	10	0.13	0.49
Extensor tenosynovitis	18 (60.0)	19 (63.3)	11	-0.06	0.76
Flexor tenosynovitis	18 (60.0)	12 (40.0)	11	0.49	0.003
Cellulitis	5 (16.7)	5 (16.7)	0	-0.2	0.27
Median nerve change	7 (23.3)	0 (0)	0	0	0.99
Erosions	1 (3.3)	8 (26.7)	0	-0.06	0.54

US: ultrasound; MRI: magnetic resonance imaging; Kappa: kappa coefficient of agreement; No. of agreements: Number of patients whose findings were detected using both methods.

Figure 1. A, US images in the sagittal plane of the right radiocarpal and mediocarpal recesses that are distended (stars). **B,** MRI of the right wrist in the axial plane (T1-weighted imaging with fat saturation post contrast) shows the same distention as the radiocarpal recess (stars).

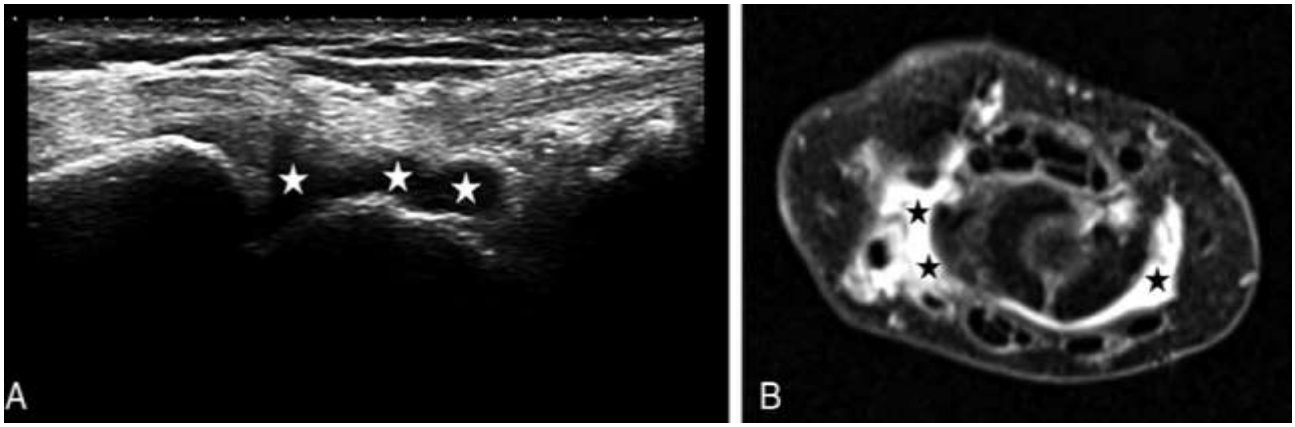


Figure 2. A, US and power Doppler images of the components of the fifth extensor compartment (extensor digit minimi) of the right wrist. Signs of tenosynovitis are characterized by increased vascular flow and distension of

the peritendinous sheath. **B,** MRI of the right wrist in the axial plane (T1-weighted imaging with fat saturation post contrast) shows distension of the sheath of the fifth extensor compartment (arrow).

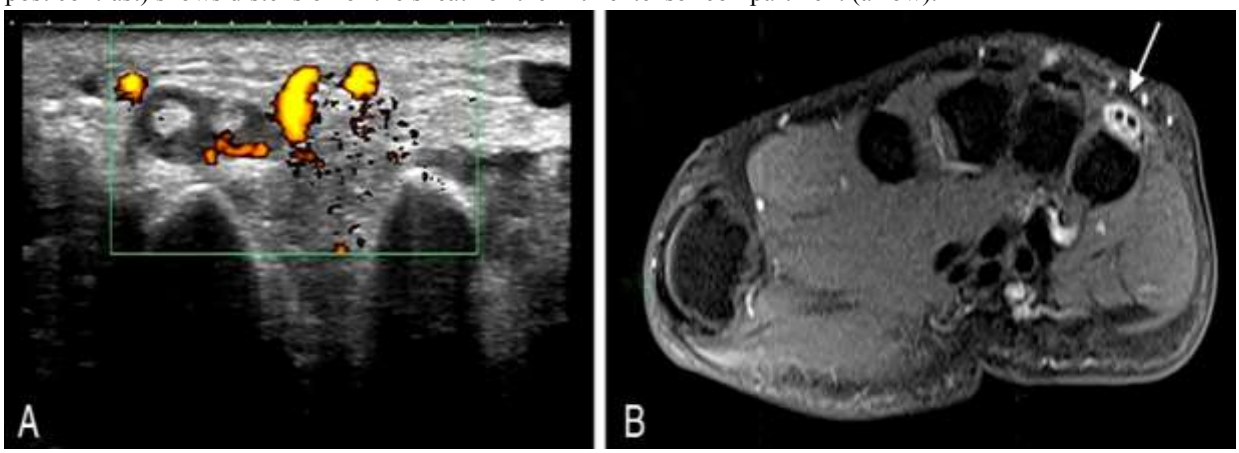
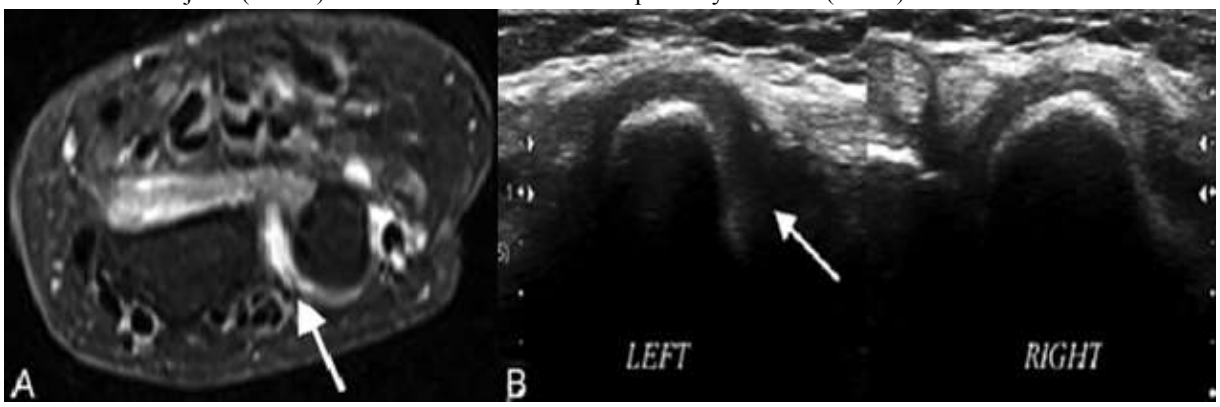


Figure 3. A, MRI of the left wrist in the axial plane (proton density-weighted imaging with fat suppression) showing distension of the capsule by effusion (arrow). **B,** Comparative US images showing the axial plane of the distal radioulnar joint (DRUJ) with distension of the left capsule by effusion (arrow).



Discussion

The sample studied included a predominance of women and a mean age of 54.7 years, consistent with the characteristics described in the literature.[9,12]

This study is the first to analyze musculoskeletal complications of CF and compare 2 different imaging modalities with PE to the best of our knowledge. In a previous study examining wrist/hand US findings in patients with CF, Mogami et al. only reported some frequencies of PE alterations and the corresponding US findings. They did not use any statistical tests to validate the comparisons.

Although thorough anamnesis and a complete PE are the starting points for a patient evaluation, limitations such as pain on maneuvers, obesity and injuries that are inaccessible to

touch may explain the lower accuracy of the PE. In these situations, imaging tests can clarify the sites of involvement with greateraccuracy. This outcome was true for the finding of tenosynovitis, for instance, which was not detected only by palpating the fingers to search for painful points. However, both imaging modalities detected tenosynovitis, and it was the only parameter with significant agreement between US and MR. As the frequency of tenosynovitis was high in US and MR (varying between 40 and 63.3%), complementary imaging is justified to better characterize CF complications. Furthermore, US and MR were also complimentary because power Doppler information was exclusive to US, and the detection of bone edema was exclusive to MR. In addition, median nerve abnormalities were detected only by US, which is another finding that may be difficult to evaluate using a PE alone. Mogami et al.[12] also reported a high frequency of median nerve thickening using US (36%), which was higher than the value reported in our sample (23.3%). US evaluates the median nerve in both a static and dynamic manner. MRI, in addition to being less sensitive for median nerve abnormalities, does not allow a dynamic evaluation either. US measurements of the median nerve have a sensitivity of 89% and a specificity of 83% for the diagnosis of carpal tunnel syndrome, suggesting that this method is an important tool for the rapid diagnosis of this complication; however, its use still must be evaluated in future prospective studies on patients with CF.[21]

The involvement of the hands and wrists follows a pattern very similar to that observed in studies of RA and in other studies of CF,[10,12] with synovitis in several joints (predominantly proximal), tenosynovitis, median nerve thickening, cellulitis and bone changes characterized by edema and erosions; in addition, CF and RA share the same symmetrical and bilateral characters.[22]

The results in Table 1 show that US revealed a pattern of detection of joint abnormalities closer to that of PE compared to MRI. This new information is relevant to the choice of which imaging modality would be better to complement PE. Therefore, in this sample, the use of US may be more advantageous than MRI. In addition to the lower financial cost and greater accessibility and quicker completion of US, it is more compatible with the outpatient clinical evaluation of these patients.

Unlike US, MRI detects bone marrow edema (osteitis), which has been established as an important prognostic marker of arthritis due to other causes.[23] Hypothetically, this marker might also be useful for monitoring CF. Further studies are needed to evalu- ate the importance of osteitis in the follow-up of patients with CF.

The frequency of bone marrow edema findings (36.7%) was similar to that reported by Manimunda et al.(35%).[22] Bone erosion, in turn, was detected at a frequency of 26.5% in our

study and 20% in their study. MRI was superior to US (3.3%) at detecting this complication. Mogami et al. did not report bone erosions in their study of patients with CF using wrist/hand US.

Some limitations of the study deserve to be highlighted. First, our sample was small. Second, the absence of medication use, as well the duration of medication use, may have influenced the existence or absence of inflammatory changes, which mainly influ- ences color Doppler findings. Finally, some changes in the imaging tests were evaluated exclusively using US or MRI due to technical issues.

In conclusion, our results showed significant agreement between PE and US in the diagnosis of synovitis of large joints (radiocarpal/distal radioulnar/mediocarpal) and the MCP and IP joints. In addition, US and MR detected a significant prevalence of tenosynovitis, and both methods showed substantial agreement. Therefore, these findings may support the routine recommendation of US examination, as it is noninvasive and accessible and can be performed during consultations. For at least mild or moderate cases, US potentially represents a relevant tool to confirm PE findings and to detect tenosynovitis and median nerve thickening, as reported in other studies.[10,12] MRI might be indicated for severe cases because it has superior performance for detecting bone abnormalities such as marrow edema and subchondral erosions. Its use would be similar to the recommendations for RA and the screening of worse prognostic parameters (osteitis) and structural injuries (erosions).[24]

Moderate agreement was observed between US and MRI only for flexor tenosynovitis. This dissociation between the methods indicates the need for studies with larger samples to obtain a more reliable comparison but may also suggest a complementary role of the 2 methods.

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CONCLUSÕES

a) O diagnóstico de tenossinovite teve pouca positividade ao EF, mas apareceu com frequência na US e RM, o que evidencia o papel limitado do EF na identificação deste achado;
b) O EF teve boa concordância com a US no diagnóstico de sinovites de grandes articulações, mostrando-se confiável para confirmação diagnóstica na suspeita clínica;
c) Somente o achado de tenossinovite flexora teve concordância estatisticamente significativa entre US e RM;
d) A US detectou espessamento do nervo mediano em um maior número de pacientes do que a RM, o que possivelmente está relacionado às tenossinovites flexoras encontradas em pacientes com FC;
e) A limitada concordância entre US e RM para outros achados pode sugerir um papel complementar destes métodos.

Considerações Finais

A presente Tese, reforçada pelas publicações de dois artigos apresentados anteriormente, mostrou que a FC determina alterações sobre o sistema musculoesquelético capaz de causar lesões anatômicas e funcionais nos pacientes. Ainda que o exame físico tenha o poder de direcionar a investigação da causa da dor, ele é incapaz de determinar o diagnóstico por si só, sendo necessário o auxílio de métodos por imagem. Acreditamos que nossos resultados indicam que a associação dos métodos deve ser realizada como ponto de partida na investigação destes pacientes. A RM justifica-se para investigar presença de EMO com a finalidade de evitar evolução para erosão óssea por meio da terapêutica adequada. A partir de então, o uso da US pode ser usada como um acompanhamento em pacientes estáveis e que não apresentam riscos de evolução para erosão óssea.

Além disso, os resultados deste estudo podem servir como embasamento teórico para futuros protocolos de recomendação de métodos de imagens a serem realizados nestes pacientes. Estes protocolos podem ser especialmente úteis em países subdesenvolvidos, onde a doença é invariavelmente endêmica e há limitações de acesso a exames como a RM.

Espera-se que os resultados aqui apresentados possam contribuir para aprofundar o entendimento das repercussões da FC sobre o sistema musculoesquelético, e principalmente, o uso racional dos métodos de imagem.

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ANEXO – Aprovação do Comitê de Ética em Pesquisa

UERJ - HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO/ UNIVERSIDADE DO

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Correlação entre Ultrassonografia e Ressonância Magnética no Estudo das Complicações Musculoesqueléticas da Febre Chikungunya

Pesquisador: CAIO LEAL LEIDERSNAIDER

Área Temática:

Versão: 1

CAAE: 04179118.8.0000.5259

Instituição Proponente:

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.113.111

Apresentação do Projeto:

A evolução das complicações musculoesqueleticas em pacientes que tiveram infecção por arborvírus é imprevisível e pode variar desde quadros leves cuja resolução se faz em dias a outros cujas evoluções são crônicas e podem ser resistentes aos anti-inflamatórios e/ou corticoides. A US e a RM podem ter um papel importante na definição de padrões de acometimento que estejam associados a cada um desses tipos de evolução e desfecho.

Objetivo da Pesquisa:

Avaliar por meio de ultrassonografia (US) e ressonância magnética (RM) de mão e punhos, pacientes com diagnóstico de febre chikungunya encaminhados pelo ambulatório de reumatologia

Avaliação dos Riscos e Benefícios:

Para a realização de ressonância magnética os pacientes deverão utilizar contraste endovenoso. Os pacientes são devidamente informados sobre esta necessidade no termo de consentimento. Por outro lado, os exames propostos podem identificar alterações osteomusculares associadas ao quadro infeccioso.

Comentários e Considerações sobre a Pesquisa:

O projeto está claro o suficiente para permitir a análise ética. A pesquisa está bem estruturada e o referencial teórico e metodológico estão explicitados, demonstrando aprofundamento e conhecimento necessários para sua realização. As referências estão adequadas e a pesquisa é

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exequível.

Considerações sobre os Termos de apresentação obrigatória:

Todos os documentos de apresentação obrigatória foram enviados a este Comitê, estando dentro das boas práticas e apresentando todas dados necessários para apreciação ética. Foram avaliadas as informações contidas na Plataforma Brasil e as mesmas se encontram dentro das normas vigentes e sem riscos eminentes aos participantes envolvidos de pesquisa.

Recomendações:

Solicitamos que as páginas do TCLE sejam numeradas e que se coloque um espaço que que as partes envolvidas (paciente e pesquisador) possam rubricas todas as folhas

Conclusões ou Pendências e Lista de Inadequações:

O projeto pode ser realizado da forma como está apresentado. Diante do exposto e à luz da Resolução CNS nº466/2012, o projeto pode ser enquadrado na categoria – APROVADO.

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente, o CEP recomenda ao Pesquisador: Comunicar toda e qualquer alteração co projeto e no termo de consentimento livre e esclarecido, para análise das mudanças; Informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa; O Comitê de Ética solicita a V. Sª., que encaminhe relatórios parciais de andamento a cada 06 (seis) Meses da pesquisa e ao término, encaminhe a esta comissão um sumáro dos resultados do projeto; Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1228437.pdf	12/11/2018 21:01:37		Aceito
Projeto Detalhado / Brochura Investigador	Projeto.pdf	12/11/2018 18:07:53	CAIO LEAL LEIDERSNAIDER	Aceito
Brochura Pesquisa	Brochura.doc	19/10/2018 14:57:37	CAIO LEAL LEIDERSNAIDER	Aceito
Declaração de Instituição e Infraestrutura	Declaracao.pdf	17/10/2018 15:52:41	CAIO LEAL LEIDERSNAIDER	Aceito
Folha de Rosto	FR.pdf	17/10/2018 15:51:57	CAIO LEAL LEIDERSNAIDER	Aceito

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Continuação do Parecer: 3.113.111

Cronograma	Cronograma.pdf	17/10/2018 15:49:23	CAIO LEAL LEIDERSNAIDER	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	01/10/2018 19:56:02	CAIO LEAL LEIDERSNAIDER	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

RIO DE JANEIRO, 15 de Janeiro de 2019

Assinado por:
DENIZAR VIANNA ARAÚJO
(Coordenador(a))

Endereço: Avenida 28 de Setembro 77 - Térreo
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APÊNDICE A - Termo de Consentimento Livre e Esclarecido

Número e iniciais do (a) paciente:_____/_____

TERMO DE CONSENTIMENTO INFORMADO LIVRE E ESCLARECIDO

Estudo: Análise comparativa entre exame físico, ultrassonografia e ressonância magnética nos punhos e mãos no estudo das manifestações clínicas musculoesqueléticas da febre Chikungunya crônica

Coordenador: Caio Leal Leidersnaider

Endereço: Serviço de Radiologia e Diagnóstico por Imagem do Hospital Universitário Pedro Ernesto (HUPE)

Av. 28 de Setembro, 77

20551-030 Rio de Janeiro/RJ

Telefone: (24) 99952-9740

INTRODUÇÃO E CONVITE PARA PARTICIPAR:

O(A) Sr.(a) está sendo convidado para participar de uma pesquisa. Antes de concordar em participar desta pesquisa, é importante que o (a) Sr.(a) leia e entenda as explicações. Esta declaração descreve o objetivo, as consultas e exames, benefícios, riscos, desconfortos e cuidados associados à pesquisa.

Ela descreve também o seu direito de sair da pesquisa a qualquer momento.

O(A) Sr.(a) está sendo convidado(a) a participar desta pesquisa para estudar as possíveis lesões musculoesqueléticas, provocadas pela febre Chikungunya, doença que o (a) sr.(a) já tem o diagnóstico clínico e laboratorial.

OBJETIVO DO ESTUDO:

O objetivo deste estudo é por meio do exame físico, ultrassonografia e ressonância magnética de punhos/mãos para definir as principais lesões musculoesqueléticas secundárias à infecção pelo vírus Chikungunya.

CONSULTAS E EXAMES DO ESTUDO:

Haverá um período de seleção e um período de realização dos exames de ultrassonografia e ressonância magnética de punhos/mãos.

Depois que o (a) Sr(a) concordar em participar e assinar este termo de consentimento livre e esclarecido, serão feitos os seguintes exames:

- exames de rotina, como exame físico e história médica;
- preenchimento de alguns questionários;
- ultrassonografia articular com *Doppler*;
- ressonância magnética com uso de contraste endovenoso.

Durante todo o período de participação neste estudo o senhor(a) continuará sendo atendido no ambulatório de reumatologia do hospital de origem.

Os exames de ultrassonografia dos punhos e mãos serão realizados no Serviço de Radiologia do Hospital Universitário Pedro Ernesto e os exames de ressonância magnética dos punhos e mãos serão realizados no Centro Estadual de Diagnóstico por Imagem (Rio Imagem), conforme marcação.

SUAS RESPONSABILIDADES:

O Sr.(a) deverá vir realizar os exames programados de ultrassonografia e ressonância magnética.

RISCOS RELACIONADOS AO ESTUDO:

Este estudo requer que seja feita uma ultrassonografia articular, exame comum, que não expõe o (a) Sr.(a) à radiação. Posteriormente, será realizado ressonância magnética com contraste dos mesmos segmentos. Esses exames são importantes para o acompanhamento da sua doença e podem ser solicitados mesmo sem a participação no estudo. Nos exames de ressonância magnética, será necessário o uso de contraste paramagnético endovenoso, considerado seguro em pacientes sem doença renal conhecida e naqueles que não submeteram a transplante hepático.

BENEFÍCIOS:

O Sr.(a) não obterá nenhum benefício direto ao participar desta pesquisa.

RESSARCIMENTO DE DESPESAS:

Não haverá nenhum tipo de compensação financeira para os participantes da pesquisa.

CONFIDENCIALIDADE:

Seu médico do estudo irá coletar informações a seu respeito. Em todos esses registros um código substituirá seu nome. Todos os dados coletados serão mantidos de forma confidencial e serão usados para avaliação do estudo. Os dados podem ser submetidos às autoridades de saúde, do Comitê de Ética em Pesquisa ou outras pessoas exigidas por lei podem revisar os dados fornecidos.

Estes dados podem ser usados em publicações médicas sobre os resultados do estudo. Todavia, sua identidade não será revelada em qualquer relatório do estudo ou publicações médicas.

PARTICIPAÇÃO VOLUNTÁRIA / RETIRADA:

Sua participação neste estudo é completamente voluntária. Cabe ao (a) Sr.(a) decidir se quer participar ou não. Mesmo se decidir participar, o (a) Sr.(a) é livre para desistir do estudo a qualquer momento sem dar um motivo ou explicação. Isto não afetará seu cuidado médico futuro de qualquer forma.

ANUÊNCIA PARA FAZER PARTE DO ESTUDO:

Assinando este documento você concorda que:

- Você teve chance para fazer perguntas.

- Você é voluntário(a) para participar deste estudo.

EU CONCORDO LIVREMENTE EM PARTICIPAR DESTE ESTUDO

_____ _____

Assinatura do paciente **Data (dia/mês/ano)**

_____

Nome por escrito do paciente

_____ _____

Assinatura da pessoa que explicou o consentimento **Data (dia/mês/ano)**

_____

Nome e título da pessoa que explicou o consentimento

APÊNDICE B – Questionário epidemiológico e sociodemográfico

Questionário epidemiológico e sociodemográfico para pacientes da pesquisa "Análise comparativa entre exame físico, ultrassonografia e ressonância magnética nos punhos e mãos no estudo das manifestações clínicas musculoesqueléticas da febre Chikungunya crônica"

Nome: **Sexo:**

Data de Nascimento: **Telefone:**

Etnia:

1. **Confirmação laboratorial:**
   ( ) IgM ( ) IgG ( ) RT-PCR

2. **Sintomas:**
   ( ) Dor Articular ( ) Edema
   ( ) Parestesia ( ) Outro (s): _____

3. **Data início dos sintomas**:_____

4. **Data do diagnóstico laboratorial**:_____

5. **Data início uso da medicação**:_____

6. **Local de dor além de punhos e mãos:**

( ) Cotovelo ( ) Ombro ( ) Joelho

( ) Tornozelo ( ) Pés ( ) Outro (s):_____

7. **Região onde reside:**

( ) Zona Norte ( ) Zona Oeste

( ) Zona Sul ( ) Região Metropolitana

8. **Escolaridade:**

( ) Ensino Fundamental

( ) Ensino Médio

( ) Ensino Superior

( ) Pós Graduação

9. **Ocupação:**

10. **Houve afastamento do trabalho/atividades?:**

( ) Sim ( ) Não

11. **Se sim, quantos dias?**

12. **Classe dos medicamentos em uso (preenchido pelo pesquisador)**

( ) AINH

( ) Esteroides

( ) Imunossupressores

( ) Esteroides + Imunossupressores

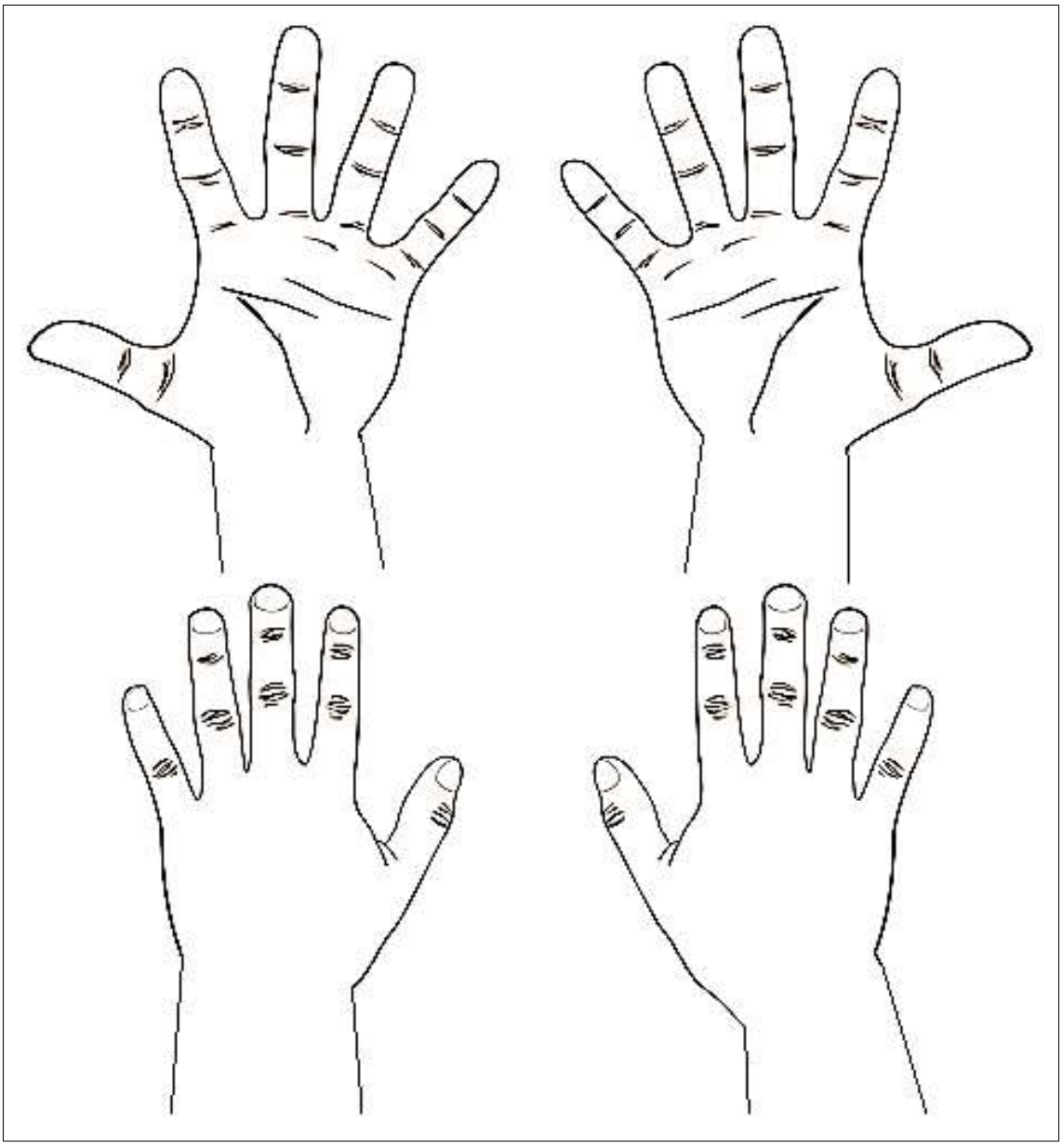
( ) Sem uso regular de medicação

Apêndice C – Esquematização para preenchimento do local de dor

Esquema topográfico para autoavaliação da dor em pacientes da pesquisa "Análise comparativa entre exame físico, ultrassonografia e ressonância magnética nos punhos e mãos no estudo das manifestações clínicas musculoesqueléticas da febre Chikungunya crônica"

Por favor, marquem com um "X" onde o (a) sr (a) sente dor ou qualquer outra queixa nas topografias da ilustração dos punhos e mãos, abaixo:

ESQUERDA **DIREITA**



APÊNDICE D – Artigo 1

Int J Case Rep Images 2021;12:101229Z01CL2021.
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CASE REPORT PEER REVIEWED | OPEN ACCESS

Multimodal imaging of psoriatic arthritis triggered by Chikungunya fever

Caio Leal Leidersnaider, João Luiz Pereira Vaz, Flávio Roberto Sztajnbok, Marcelo Torres Gonçalves, Roberto Mogami

ABSTRACT

Chikungunya fever (CF), caused by the Chikungunya virus (CHIKV), is an arboviral disease transmitted by infected Aedes mosquitoes found worldwide. Although CF may trigger chronic arthritis, there are still few reports of patients who have progressed to psoriatic arthritis (PsA). We describe the clinical and ultrasound (US) and magnetic resonance imaging (MRI) findings of the wrist and hands of a 49-year-old man who had peripheral PsA triggered by CHIKV. He had scaly, itchy scalp lesions three months after the diagnosis of CF. The patient had classic synovitis and tenosynovitis secondary to CF. The persistence of inflammatory disease with signs of enthesitis and dactylitis on magnetic resonance imaging (MRI) and US, family history and appearance of skin lesions on the scalp strongly suggest post-CF PsA. Viral infections can be a triggering factor for several diseases with chronic arthritis, such as PsA. Imaging exams are essential methods for both diagnosis and the monitoring of treatment.

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Keywords: Arthritis, Chikungunya fever, Magnetic resonance imaging, Psoriatic, Ultrasonography

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Article ID: 101229Z01CL2021

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doi: 10.5348/101229Z01CL2021CR

INTRODUCTION

Chikungunya fever (CF) is a viral disease whose transmission occurs through vector females of *Aedes aegypti* and *Aedes albopictus* mosquitoes infected by the Chikungunya virus (CHIKV). There are reports of outbreaks in Europe, the Americas, Asia, Africa, and Oceania [1].

Approximately 60% of patients with CHIKV infection progress to chronic arthritis [2]. In these cases, joint limitations can persist for up to five years after infection [3] and are associated with permanent sequelae [4]. After an incubation period of three to seven days, patients may experience fever, skin rash, myalgia, and arthralgia. The disease becomes chronic when the arthralgias persist for more than three months. The literature shows that a small portion of patients with chronic CF and severe polyarticular forms develop rheumatoid arthritis (RA) [5] or other forms of arthritis, including psoriatic arthritis (PsA) [6].

Conventional radiology is still a first-line exam in the investigation of rheumatological diseases. However, the method is not as sensitive as MRI or US in showing early bone and soft tissue changes. Although US has limitations in bone evaluation, together with Doppler it can identify

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early signs of enthesitis or organ-enthesis involvement [7]. Conventional MRI, in turn, is useful for diagnosing bone complications such as marrow edema and erosions as well as soft tissue involvement [8].

The pattern of involvement of the hands and wrists by CF is very similar to that found in RA, and it is characterized by symmetrical and bilateral involvement of the metacarpophalangeal and proximal interphalangeal joints, tenosynovitis, subcutaneous edema, and bone changes, such as marrow edema and erosions [9].

Although there have been several reports of developing RA, to our knowledge, there are few descriptions of post-CF PsA. Mathew et al. [5] investigated 1396 individuals with CF and concluded that only 2.5% of patients developed PsA. Thus, our report is valuable due to the scarcity of cases, and it features an imaging presentation typical of peripheral spondyloarthropathy secondary to arbovirus infection.

CASE REPORT

A 49-year-old man had a fever (101.30°F/38.5°C) for approximately ten days and exhibited persistent signs of polymyalgia and polyarthralgia. He used dipyrone and oral hydration to reduce the fever, and his musculoskeletal symptoms partially improved. Serologies for CHIKV were positive for IgM (51; normal value: 9). Subsequently, a skin rash appeared, and polyarthralgia associated with edema of the hands, wrists (Figure 1), elbows, knees, and feet worsened. Two months later, he was evaluated in an outpatient rheumatology clinic at a university hospital in Rio de Janeiro, Brazil. He continued to experience polyarthralgia and edema in the metacarpophalangeal and interphalangeal joints, especially of the left hand. Erythematous scaling and itchy skin lesions were also noted in the anterior medial region of the scalp on physical examination. At the time, the patient was not taking any known medication that could precipitate psoriasis. He also denied any preceding emotional stress (at least two months prior to the appearance of the skin lesion). The patient had never had any episode of psoriatic skin lesions. The patient was hypertensive, using enalapril 20 mg/day, and was an abstainer, nonsmoker, and physically active. He denied allergies and blood transfusions and had an up-to-date vaccination schedule. His father had PsA. One maternal aunt had multiple sclerosis, and another had ankylosing spondylitis.

The rheumatologists prescribed meloxicam 15 mg/day and prednisone 20 mg/day after discussing the case. The patient returned the following month with little clinical improvement, and methotrexate 15 mg and folic acid 5 mg were started after verification of the laboratory tests.

After starting the medication, he was followed up on an outpatient basis and remained asymptomatic. However, the patient stopped medication on his own, and after two years and four months he returned to the outpatient clinic with symptom recrudescence. After that, the joint pain returned, but the psoriatic skin lesions did not. He was re-evaluated with US and MRI.

Written consent was obtained from the patient to be evaluated at the rheumatology outpatient clinic and the radiology department of a university hospital in the city of Rio de Janeiro, Brazil.

There were no changes in the patient's complete blood count: C-reactive protein 13 mg/L (normal index: up to 3 mg/L), fibrinogen 340 mg/dL (normal index: 200–400 mg/dL), and normal levels of transaminases and electrolytes (sodium and potassium). The nonreactive immunological tests included the following: antinuclear factor (ANA), antibodies against citrullinated peptides (ACPA), rheumatoid factor (RF), and cytoplasmic antineutrophil antibodies (ANCA). Serological tests for HIV and hepatitis B and C were nonreactive; CHIKV IgM and IgG were reactive; and HLA-B27 was negative.

The equipment used was a Toshiba US, model Aplio XG, with a 7–18 MHz multifrequency probe, in B mode and with power Doppler (pulse repetition frequency 750 Hz, low wall filter and gain adjusted just below the appearance of the artifacts).

The MRI scans were performed in a Siemens model Avanto, 1.5 T high-field scanner. The image acquisition protocol had the following sequences: protonic density (PD) with fat saturation in the axial, sagittal, and coronal planes and T1 pre- and post-contrast fat saturation in the axial plane.

The US and MRI scans showed signs of arthritis in the wrist and metacarpophalangeal joints of both hands. There was also tenosynovitis of all extensor compartments, digital flexor tenosynovitis (Figures 2 and 3), and signs of classical enthesitis due to thickening of the digital extensor entheses and functional enthesitis (Figures 4–6) due to peritendinous extensor thickenings. Vascular hyperflow was observed by power Doppler (Figure 4) at several sites of inflammation, paramagnetic contrast enhancement of the distended sheaths, and functional enthesitis sites. Focal bone edema was identified as an indirect sign of enthesitis at the base of the left third metacarpal associated with signs of inflammation of the extensor carpi radialis brevis.

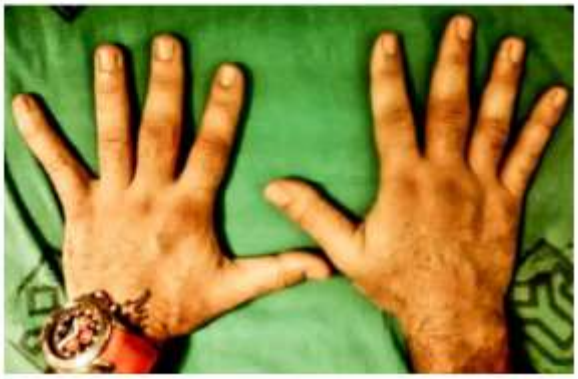

Figure 1: 49-year-old man with chronic Chikungunya fever. Panoramic view of both hands with metacarpophalangeal and interphalangeal edema.

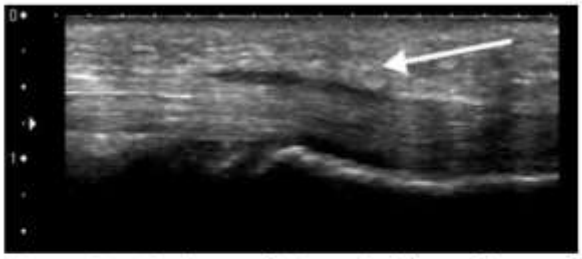

Figure 2: B-mode ultrasound in the sagittal plane of the second right digit. Note the flexor tendon sheath distention.

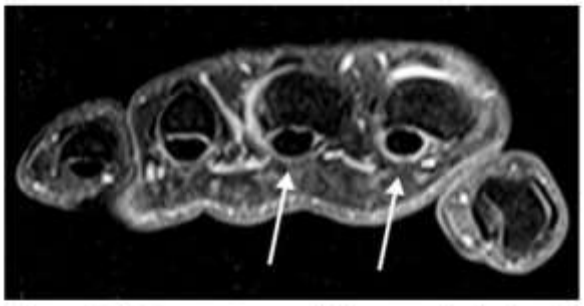

Figure 3: MRI T1 pre-contrast with fat saturation in the axial plane of right hand. Note the metacarpophalangeal synovitis and flexor tenosynovitis of the second and third digits (arrows).

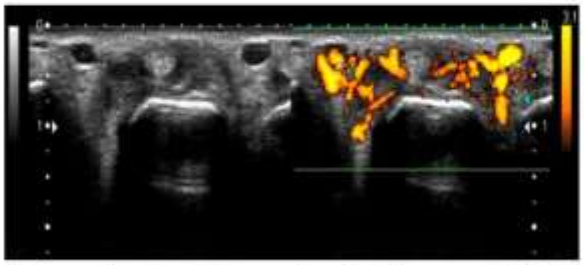

Figure 4: B-mode and power Doppler ultrasound of the left fourth digit in the axial plane. Note the extensive peritendinous extensor thickening with vascular hyperflow at the level of the metacarpophalangeal joint, indicating functional enthesitis.
Note: This image had already been presented at the 2017 European Congress of Radiology in electronic poster (EPOS) mode, (https://dx.doi.org/10.1594/ecr2017/C-0384). According to the congressional ethics committee, the authors have the right to use it.

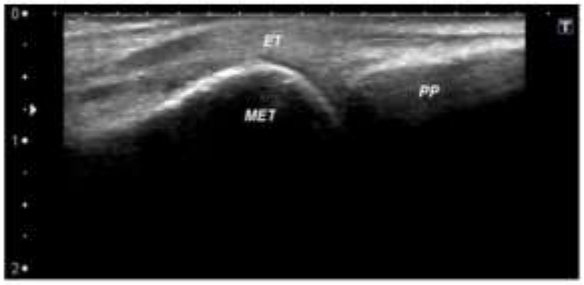

Figure 5: B-mode ultrasound in the sagittal plane of the left fourth digit at the metacarpophalangeal level. Note the soft tissue peritendinous extensor thickening, indicating functional enthesitis.

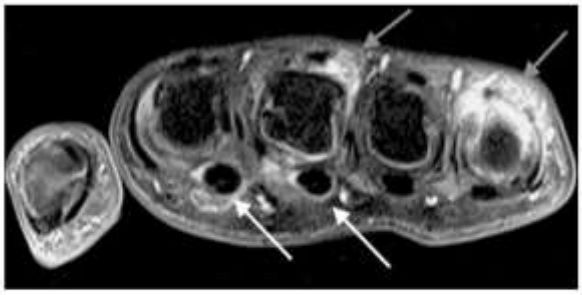

Figure 6: MRI of the left-hand shows T1 post-contrast with fat saturation. Note the enhancement of the flexor sheaths of the second and third digits (white arrows) and of the extensor peritendinous soft tissue of the third and fifth digits (gray arrows).

DISCUSSION

The authors present an unusual complication of CF suggested by clinical and imaging findings. US and MRI were also essential during the treatment follow-up.

According to the Classification Criteria for Psoriatic Arthritis (CASPAR) [10], to confirm the diagnosis of PsA, it is necessary to have an inflammatory joint disease and at least a three-point score in the other categories. The patient had a five-point score due to scalp psoriasis (two points), family history (one point), negative RF (one point), and dactylitis (one point). As reported in other literature cases, these signs and symptoms appeared immediately after CF infection, and the disease regressed with methotrexate therapy [5].

The patient's age and gender profiles disagree with the literature, which describes a predominance in women over 45 years old who are at risk for musculoskeletal complications in CF [11]. Among the usual manifestations of CF, the presentation of only fever, polymyalgia, polyarthralgia, and skin rash and the high levels of C-reactive protein are in accordance with the literature [12].

The US and MRI scans showed several signs of involvement, with characteristics of spondyloarthropathy: dactylitis due to flexor tenosynovitis, classic enthesitis in distal extensor insertions, functional enthesitis due to peritendinous extensor thickening adjacent to the metacarpophalangeal and interphalangeal joints, and metacarpal marrow edema adjacent to the insertion of an extensor tendon.

After the 2015–2016 CF outbreak in Rio de Janeiro, Brazil, our group [9, 13] reported wrist/hand and ankle ultrasound changes. The authors highlighted bilateral synovitis and tenosynovitis as relevant findings for the diagnosis of musculoskeletal complications. However, in this case report, the existence of several signs of very intense enthesitis and flexor tenosynovitis in the imaging exams raised the suspicion of some other disease associated with CF.

There are two types of entheses according to function and location: fibrous and fibrocartilage. The most common fibrocartilage is found in the apophyses and epiphyses of long bones, short bones of the hands and feet, and several ligaments in the spine. Fibrous entheses are found in the metaphyses and diaphyses of long bones. Fibrocartilaginous entheses are those affected in spondyloarthropathies and altered in the US and MRI exams of the reported case [14, 15].

Functional enthesis is another essential concept to understanding our imaging findings. In specific locations where the tendon deflects or rubs against a bone surface, there are sesamoid (tendinous) and periosteal fibrocartilages. This patient had intense digital peritendinous extensor inflammatory thickenings, which are explained by these functional enthesis impairments [16, 17].

Dactylitis is one of the main features of psoriatic arthritis and is present in 40% of cases. The main finding is digital flexor tenosynovitis, that is, distention of the fibrous sheaths, which also existed in the reported case [18].

Clinical recognition of early-stage PsA is challenging when the disease affects only the peripheral joints. Despite the efficiency of CASPAR in identifying patients with less than one year of symptom onset (early psoriatic arthritis) [19], peripheral PsA remains a challenge for rheumatologists [20]. In our case, imaging helped detect the entheseal manifestations of the disease, suggesting alternative diagnoses in CF patients.

CONCLUSION

With the resurgence of CF epidemics worldwide, managing chronic arthritis has become an enormous challenge for rheumatologists. It is essential to follow these chronic cases and to identify the progression to other forms of arthritis, such as PsA. Imaging exams have become indispensable for the diagnosis and management of these complications.

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Author Contributions

Caio Leal Leidersnaider – Conception of the work, Design of the work, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

João Luiz Pereira Vaz – Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Flávio Roberto Sztajnbok – Acquisition of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Marcelo Torres Gonçalves – Acquisition of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Roberto Mogami – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

Copyright

APÊNDICE E – Artigo 2

ORIGINAL RESEARCH

Chikungunya Fever

Comparison Study of Synovitis and Tenosynovitis of the Hands and Wrists Using Physical Examination, Ultrasound and MRI Findings

Caio Leal Leidersnaider, MD, Flávio Roberto Sztajnbok, MD, PhD, Evandro Silva Freire Coutinho, MD, PhD, João Luiz Pereira Vaz, MD, PhD, Marina Porangaba, MD, Paulo Cesar Hamdan, MD, MSc, Pedro Henrique Martins, MD, Carolina Pesce Lamas Constantino, MD, MSc, Roger Vinicius Ancillotti, MD, MSc, Alexandre Malta Messeder, MD, Débora Guimarães Monteiro, MS, Mayara Malta Folly, MS, Roberto Mogami, MD, PhD

Objectives—To compare musculoskeletal changes on a physical examination (PE), ultrasound (US) and magnetic resonance imaging (MRI) of the hands and wrists of patients with Chikungunya fever (CF).

Methods—The sample consisted of 30 patients in the chronic phase of CF. The sites analyzed were the interphalangeal (IP), metacarpophalangeal (MCP) and wrist/mediocarpal (WMC) joints and periarticular soft tissue. The interval between the PE and imaging tests was 7 days, and the interval between US and MRI was 2 days. The kappa coefficient was calculated to estimate the agreement between the PE and US and MRI findings and between the US and MRI findings.

Results—Significant agreement was observed between PE and US in the diagnosis of synovitis. The only statistically significant agreement between US and MRI was the finding of flexor tenosynovitis; the agreement was moderate.

Conclusions—US has great potential for use in diagnosing synovitis suspected based on a PE. The limited agreement observed between US and MRI, in turn, may suggest a complementary role of these methods.

Key Words—arthritis; Chikungunya fever; magnetic resonance imaging; musculoskeletal; physical examination; ultrasound

Chikungunya fever (CF) is a viral disease transmitted through the bite of female *Aedes aegypti* and *Aedes albopictus* mosquitoes infected with the Chikungunya virus (CHIKV).[1] Outbreaks have been reported on all continents except Antarctica.[2] An effective antiviral treatment is currently unavailable, and prophylaxis is performed by vector control.[3] Clinically, the disease has acute and chronic phases.[4] The chronic phase is characterized by a symptom duration longer than 3 months. Patients may present with arthralgia (bilateral and symmetrical) or arthritis and functional impotence.[4] Approximately 60%[5] of those infected with CHIKV have a chance of developing chronic arthritis.[6] In these cases, motor disability may persist for up to 5 years after infection[5] and is associated with permanent and irreversible sequelae.[7]

Received March 24, 2021, from the Department of Radiology, Rio de Janeiro State University, Rio de Janeiro, Brazil (C.L.L., M.P., A.M.M., D.G.M., M.M.F., R.M.); Department of Pediatrics, Rio de Janeiro State University, Rio de Janeiro, Brazil (F.R.S.); Department of Epidemiology, Rio de Janeiro State University, Rio de Janeiro, Brazil (E.S.F.C.); Department of Rheumatology, Federal University of the State of Rio de Janeiro, Brazil (J.L.P.V.); Department of Rheumatology, Rio de Janeiro Federal University, Rio de Janeiro, Brazil (P.C.H.); and Rio de Janeiro State Center for Diagnostic Imaging, Rio de Janeiro, Brazil (P.H.M., C.P.L.C., R.V.A.). Manuscript accepted for publication May 31, 2021.

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Abbreviations

ACR, American College of Rheumatology; CF, Chikungunya fever; CHIKV, Chikungunya virus; DRUJ, distal radioulnar joints; EULAR, European League Against Rheumatism; IP, interphalangeal; MCP, metacarpophalangeal; MRI, magnetic resonance imaging; PE, physical examination; RA, rheumatoid arthritis; US, ultrasound; WMC, wrist/mediocarpal

doi:10.1002/jum.15766

According to recent studies, a small portion of patients with CF and severe polyarticular involvement may progress to rheumatoid arthritis (RA) or aggravated pre-existing RA.[7] Similar to RA, CF manifests as erosive arthropathy, and imaging findings include bone erosion, joint effusion, bone marrow edema, synovial thickening, tenosynovitis and tendinopathy.[8] Sissoko et al[9] investigated 147 patients diagnosed with CF and reported that 57% maintained rheumatic pain for more than 15 months after the initial diagnosis of viral infection. Mogami et al[10,11] noted that some radiological presentations of CF are potentially associated with more severe clinical manifestations of the disease.[10] In the hands and wrists, the authors observed synovitis of small joints, especially the metacarpophalangeal (MCP) joints, isolated effusion or synovitis in the wrist, flexor and extensor tenosynovitis, cellulitis, and median nerve thickening.[12]

Points of intersection have been identified between CF and RA due to both the similarity of symptoms and the possibility of progression from CF to RA according to the criteria of the American College of Rheumatology (ACR).[13]

The sensitivity of ultrasound (US) and magnetic resonance imaging (MRI) is higher than that of PE for the diagnosis of rheumatic lesions,[14] and those techniques enable the identification of treatable inflammatory lesions, such as synovitis and enthesopathy.[15] Although US has limitations for bone evaluation, it has the following advantages over MRI in the follow-up of chronic musculoskeletal inflammatory diseases[16]: wide availability, lower cost, good general acceptance by patients and its use as a quick guide for various types of interventions at the level of the wrists and hands (eg, aspiration, injection and biopsy).[17]

The lack of documentation of CHIKV-induced musculoskeletal complications in imaging tests is surprising because the profile of the disease is similar to that of other rheumatic diseases.[10]

Considering the clinical-epidemiological relevance of CF, the need to better understand musculoskeletal lesions/disorders and the lack of studies comparing physical examination (PE) results with US and MRI findings in patients with chronic CF, the objective of this study was to evaluate the agreement between a PE of the hands and wrists and imaging findings and to determine the agreement between US and MRI findings in the hands and wrists.

Materials and Methods

Study Population

This study was approved by the Research Ethics Committee of the Pedro Ernesto University Hospital, State University of Rio de Janeiro (Number 04179118.8.0000.5259). All participants signed an informed consent form. This cross-sectional study was conducted on patients with a clinical and laboratory diagnosis of CF in the chronic phase of the disease who had inflammatory symptoms in their hands and/or wrists at the time they underwent imaging tests.

All consecutively treated men and women with a chronological age >18 years who had a clinical and laboratory diagnosis (IgM and/or IgG and/or PCR) of CF and were in the chronic disease phase were included. The following patients were excluded: those with a previous or current diagnosis of RA (all patients were negative for rheumatoid factor and cyclic citrullinated peptide antibodies and none of them fulfilled the criteria for RA established by the ACR and European League Against Rheumatism (EULAR)[18] or any other joint disease with structural damage; those with old or current hand or wrist fractures; those who, for any reason, were unable to undergo any of the imaging tests; those with an absolute contraindication to MRI (such as patients with an insulin infusion pump, ferromagnetic intracerebral aneurysm clip [inserted before 1995] or cardiac pacemaker not compatible with MRI; electrostimulators not compatible with MRI; intracranial aneurysm clips not compatible with MRI; intraocular metallic material; Triggerfish contact lenses; cochlear implants not compatible with MRI; or a nonremovable metallic orthopedic external fixator not compatible with MRI).

Forty-one patients met the inclusion criteria. However, 11 patients were excluded (9 due to an inability to remain on the MRI table due to joint pain; 1 due to size, since the patient was morbidly obese; and another due to claustrophobia). The 30 patients who participated in the study were treated

at the Rheumatology Outpatient Clinic of the Rio de Janeiro State University and were attending their first visit or a return visit between January 2018 and March 2020. The sample was selected by consecutive sampling of patients with symptoms of the hands and wrists during outpatient care.

Physical Examination

A qualitative and subjective analysis of joint involvement was performed by ectoscopy and palpation and observations of redness, heat, swelling and pain in the interphalangeal joints (IP), MCP and radiocarpal and distal radioulnar joints (DRUJ) and mediocarpal joint. The last 3 joints belong to the wrist/mediocarpal (WMC) region.

Ultrasound

The US examinations of all patients were performed using a Toshiba Aplio XG US machine (Toshiba Medical Systems; Otawara, Japan) with a 7- to 18-MHz multifrequency probe in B mode and with power Doppler (750-Hz pulse repetition frequency, low wall filter and gain adjusted just below the appearance of artifacts). Power Doppler was used for sites with suspected inflammation (effusion, tenosynovitis and synovial thickening). The median nerve area was also estimated based on an image captured in the transverse plane, whose reference points were the pisiform and scaphoid bones. A normal median nerve area measurement was defined as $<10\ mm^2$.[19] Nine sites or parameters based on the guideline developed by Backhaus et al[20] were adapted and investigated by the authors of this study: IP joints (proximal and distal); MCP joints; WMC joints (radiocarpal, distal radioulnar and mediocarpal recesses); extensor sheaths; flexor sheaths; subcutaneous tissue; median nerve; subchondral bone erosion (which may also be a sign of synovitis); and sites with increased vascular flow on power Doppler images. The parameters used to define joint impairment were fluid distension of the joint capsule, synovial thickening and the presence of increased vascular flow on power Doppler images. The authors did not use classifications to estimate the degree of synovitis.

Magnetic Resonance Imaging

The MRI exams were performed in a high-field Siemens Magnetom Avanto 1.5 T instrument (manufactured in 2003, Munich, Germany), and intravenous contrast medium (gadolinium) was administered to all patients. The following sequences were used: proton density with fat saturation in the axial, sagittal and coronal planes; T1 with pre- and postcontrast fat saturation in the axial and coronal planes; and T2 with fat saturation in the coronal plane. All of these sequences were acquired first on one side and then on the other. The studied anatomical sites were divided into the same large groups that were used for US: IP joints (proximal and distal); MCP joints; WMC joints (radiocarpal, distal radioulnar and mediocarpal recesses); extensor sheaths; flexor sheaths; subcutaneous tissue; median nerve; and bone. The criteria adopted for abnormalities were fluid distension of the joint capsules, synovial thickening, contrast medium impregnation, bone edema characterized by an increased signal in the T2 sequence with fat saturation, median nerve hypersignal in the same sequence and cortical bone discontinuity (erosion).

Ultrasound and Magnetic Resonance Imaging

The US examinations were independently evaluated by 2 examiners: 1 with 20 years of experience in musculoskeletal US and another with 10 years of experience. Two other radiologists analyzed all MRI examinations; the first had 15 years of experience in musculoskeletal imaging, and the second had 8 years of experience. None of the examiners had prior knowledge of any test results. The reports for both modalities were issued by consensus. The patients underwent US first, followed by MRI. The interval between the PE and imaging tests was 7 days for all patients, and a maximum interval of 48 hours was allowed between the performance of the 2 imaging tests.

Statistical Analysis

The primary analysis was descriptive. Continuous/interval variables are reported as measures of central tendency and dispersion, and categorical variables are presented as absolute and relative frequencies.

The kappa coefficient was calculated to estimate the agreement between the PE and the US and MRI findings and between US and MRI findings.

The level of statistical significance adopted for the comparisons was 5%. Statistical analyses were

performed using SPSS version 26 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY).

Results

Sample Characterization

The authors studied 30 patients, 26 of whom were women (86.7%). The age of the participants ranged from 32 to 73 years, with a mean ± standard deviation (SD) of 54.7 ± 10.0 years.

All patients were in the chronic phase of the disease, and the mean elapsed time between the diagnosis and US examination was 336.1 ± 251.7 days, ranging from 53 to 911 days. For MRI, the mean elapsed time was 337.5 ± 251.7 days, ranging from 54 to 913 days.

The most frequent symptoms, in decreasing order of frequency, were joint pain in 30 patients (100%), paresthesia in 23 patients (76.7%), pruritus in 19 patients (63.3%) and edema in 22 patients (73.3%).

Regarding treatment, the sample was divided as follows: 8 patients (26.7%) were not taking any medication; among the 22 patients who were on continuous medication, 12 (40%) used corticosteroids. Seven (23.3%) used steroids in combination with immunosuppressants, 2 (6.7%) used only nonsteroidal anti-inflammatory drugs and 1 (3.3%) used only immunosuppressants.

Laboratory Tests

The presence of other autoimmune diseases in both clinical and laboratory tests was excluded in all patients enrolled in the study.

Laboratory confirmation was obtained by IgG serology in 23 patients (76.7%), IgM and IgG serology in 3 (10%), IgM serology alone in 2 (6.6%) and PCR in 2 (6.6%).

Regarding the laboratory measurements of inflammation, 20 patients (66.6%) had abnormal values for both tests (C-reactive protein and erythrocyte sedimentation rate), 4 (13.3%) had only abnormal C-reactive protein levels and 4 (13.3%) had only an abnormal erythrocyte sedimentation rate. Two patients (6.6%) did not undergo these tests.

Physical Examination

In the examination of signs of inflammation and pain on palpation, 27 patients presented with sensitivity in the MCP region (90%), 19 (63.3%) had sensitivity in the WMC and 17 (56.7%) had sensitivity in the IP region.

Table 1 shows the PE, US and MRI results for IP and MCP involvement and joint recesses, as well as the kappa coefficients and respective p-values.

Moderate agreement was observed between PE and US for the IP (kappa = 0.49; $P = 0.026$) and MCP (kappa = 0.429; $P = 0.064$) findings. Substantial agreement was also observed between PE and US for the involvement of the radiocarpal, distal radioulnar and mediocarpal recesses (kappa = 0.661; $P < 0.0001$).

The agreement between MRI and PE was very low (approximately 0), and none of the results reached statistical significance. Kappa values equal to zero indicate that the agreement between the methods was not higher than that expected by chance.

Site of Involvement: US And MRI

Table 2 shows the frequency of the sites of involvement identified by US and MRI.

In descending order of frequency, the US-identified sites of involvement with effusion or synovial thickening were MCP in 25 patients (83.3%) (Figure 1), extensor sheaths in 18 patients (60%), flexor sheaths in 18 (60%) (Figure 2), radiocarpal/DRUJ/proximal carpal joints in 16 (53.3%) (Figure 3) and IP in 12 (40%). The other changes included increased vascular flow on power Doppler images in 8 patients (26.7%), median nerve thickening in 7 (23.3%), subcutaneous edema in 5 (16.7%) and bone erosion in 1 (3.3%).

The MRI sites of involvement, in decreasing order of frequency, were fluid distension of the extensor sheaths in 19 patients (63.3%), synovitis of the MCP joints and radiocarpal/DRUJ/proximal carpal recesses in 17 (56.7%), fluid distension of the flexor sheaths in 12 (40%) and IP joints in 8 (26.6%).

Other associated findings were signs of bone marrow edema in 11 patients (36.7%), bone erosion in 8 (26.2%) and subcutaneous edema in 5 (16.7%). No change in the median nerve signal was observed in any patient.

Table 1. Kappa Agreement Between the Physical Examination and Ultrasound and Magnetic Resonance Imaging Results by Anatomical Location

Interphalangeal			
Physical examination	*Ultrasound*		*Kappa (P-value)*
	+	−	
+	10	7	0.416 (.026)
−	2	11	
Physical examination	*Magnetic resonance imaging*		*Kappa (P-value)*
	+	−	
+	4	13	
−	4	9	−0.067 (.69)
Metacarpophalangeal			
Physical examination	*Ultrasound*		*Kappa (P-value)*
	+	−	
+	24	3	
−	1	2	0.429 (.064)
Physical examination	*Magnetic resonance imaging*		*Kappa (P-value)*
	+	−	
+	16	11	
−	1	2	0.104 (.56)
Recesses			
Physical examination	*Ultrasound*		*Kappa (P-value)*
	+	−	
+	15	4	
−	1	10	0.661 (<.0001)
Physical examination	*Magnetic resonance imaging*		*Kappa (P-value)*
	+	−	
+	10	9	
−	7	4	−0.106 (.70)

US revealed a higher frequency of MCP synovitis (83.3%), flexor tenosynovitis (60.0%), IP synovitis (40.0%) and median nerve changes (23.3%) than MRI.

MRI showed a higher frequency of extensor tenosynovitis (63.3%), radiocarpal/DRUJ/mediocarpal synovitis (56.7%) and erosions (26.7%) than US.

Analysis of the Agreement between US and MRI Findings

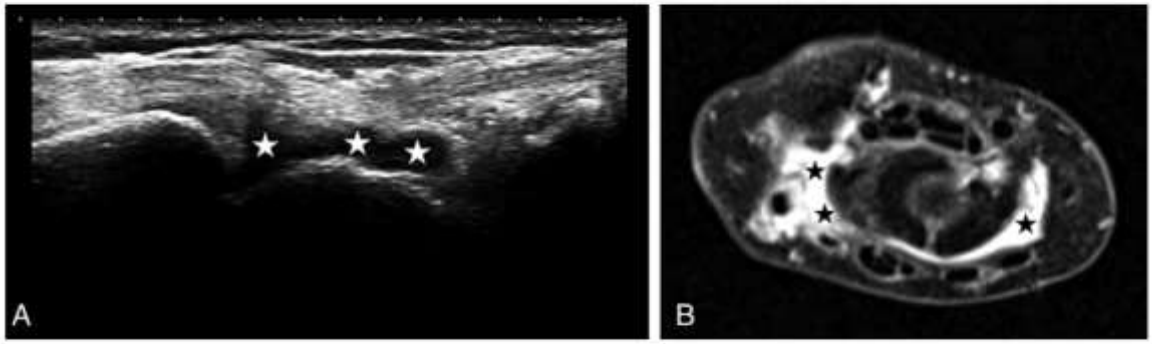
Table 2 shows the frequency (n) and percentage (%) of 8 US and MRI findings. In addition to these data, the table shows the number of positive findings in terms of agreement between US and MRI,

Table 2. Frequency of Findings at Aites and Agreement Between US and MRI in 30 Patients with CF

Finding	US, n (%)	MRI, n (%)	No. of Agreements	Kappa	*P*-value
Interphalangeal	12 (40.0)	8 (26.7)	4	0.12	0.5
Metacarpophalangeal	25 (88.3)	17 (56.7)	16	0.27	0.069
Proximal carpal/wrist	16 (53.3)	17 (56.7)	10	0.13	0.49
Extensor tenosynovitis	18 (60.0)	19 (63.3)	11	−0.06	0.76
Flexor tenosynovitis	18 (60.0)	12 (40.0)	11	0.49	0.003
Cellulitis	5 (16.7)	5 (16.7)	0	−0.2	0.27
Median nerve change	7 (23.3)	0 (0)	0	0	0.99
Erosions	1 (3.3)	8 (26.7)	0	−0.06	0.54

US, ultrasound; MRI, magnetic resonance imaging; Kappa, kappa coefficient of agreement; No. of agreements, number of patients whose findings were detected using both methods.

Figure 1. A, US images in the sagittal plane of the right radiocarpal and mediocarpal recesses that are distended (stars). **B**, MRI of the right wrist in the axial plane (T1-weighted imaging with fat saturation post contrast) shows the same distention as the radiocarpal recess (stars).



as well as the respective kappa coefficients and *P*-values.

Significant but moderate agreement was observed between the 2 methods for only the flexor tenosynovitis finding (kappa = 0.49; $P = 0.003$).

Discussion

The sample studied included a predominance of women and a mean age of 54.7 years, consistent with the characteristics described in the literature.[9,12]

This study is the first to analyze musculoskeletal complications of CF and compare 2 different imaging modalities with PE to the best of our knowledge. In a previous study examining wrist/hand US findings in patients with CF, Mogami et al only reported some frequencies of PE alterations and the corresponding US findings. They did not use any statistical tests to validate the comparisons.

Although thorough anamnesis and a complete PE are the starting points for a patient evaluation, limitations such as pain on maneuvers, obesity and injuries that are inaccessible to touch may explain the lower accuracy of the PE. In these situations, imaging tests can clarify the sites of involvement with greater accuracy. This outcome was true for the finding of tenosynovitis, for instance, which was not detected only by palpating the fingers to search for painful points. However, both imaging modalities detected tenosynovitis, and it was the only parameter with significant agreement between US and MR. As the frequency of tenosynovitis was high in US and MR (varying between 40 and 63.3%), complementary

Figure 2. A, US and power Doppler images of the components of the fifth extensor compartment (extensor digit minimi) of the right wrist. Signs of tenosynovitis are characterized by increased vascular flow and distension of the peritendinous sheath. **B**, MRI of the right wrist in the axial plane (T1-weighted imaging with fat saturation post contrast) shows distension of the sheath of the fifth extensor compartment (arrow).

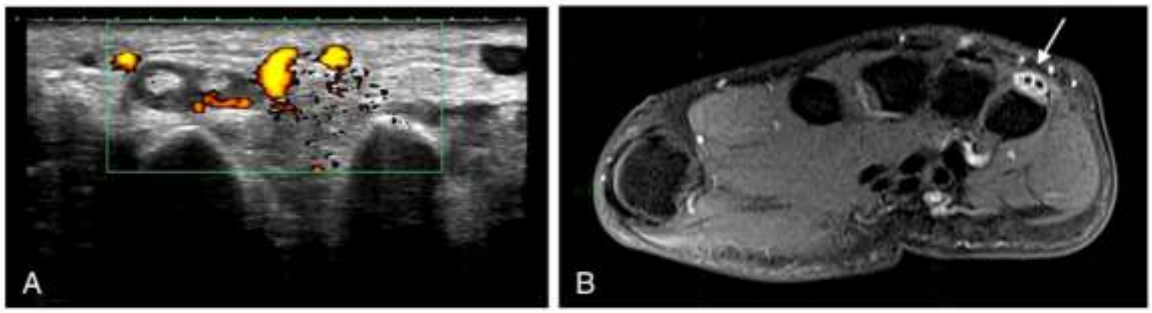
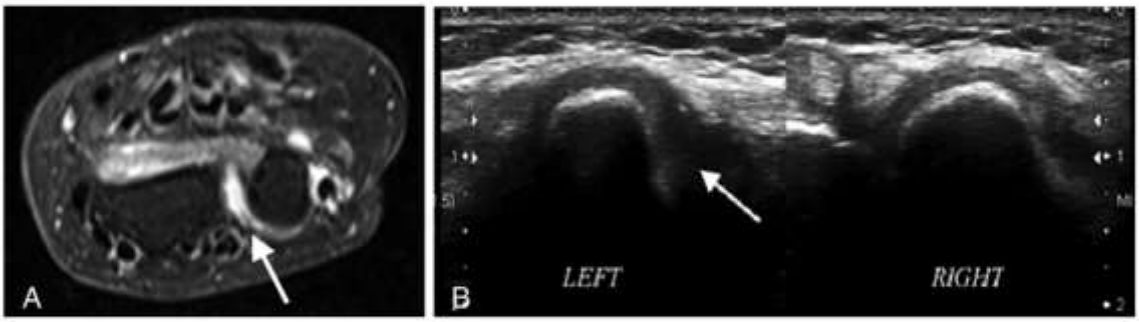


Figure 3. **A**, MRI of the left wrist in the axial plane (proton density-weighted imaging with fat suppression) showing distension of the capsule by effusion (arrow). **B**, Comparative US images showing the axial plane of the distal radioulnar joint (DRUJ) with distension of the left capsule by effusion (arrow).



imaging is justified to better characterize CF complications. Furthermore, US and MR were also complimentary because power Doppler information was exclusive to US, and the detection of bone edema was exclusive to MR. In addition, median nerve abnormalities were detected only by US, which is another finding that may be difficult to evaluate using a PE alone. Mogami et al[12] also reported a high frequency of median nerve thickening using US (36%), which was higher than the value reported in our sample (23.3%). US evaluates the median nerve in both a static and dynamic manner. MRI, in addition to being less sensitive for median nerve abnormalities, does not allow a dynamic evaluation either. US measurements of the median nerve have a sensitivity of 89% and a specificity of 83% for the diagnosis of carpal tunnel syndrome, suggesting that this method is an important tool for the rapid diagnosis of this complication; however, its use still must be evaluated in future prospective studies on patients with CF.[21]

The involvement of the hands and wrists follows a pattern very similar to that observed in studies of RA and in other studies of CF,[10,12] with synovitis in several joints (predominantly proximal), tenosynovitis, median nerve thickening, cellulitis and bone changes characterized by edema and erosions; in addition, CF and RA share the same symmetrical and bilateral characters.[22]

The results in Table 1 show that US revealed a pattern of detection of joint abnormalities closer to that of PE compared to MRI. This new information is relevant to the choice of which imaging modality would be better to complement PE. Therefore, in this sample, the use of US may be more advantageous than MRI. In addition to the lower financial cost and greater accessibility and quicker completion of US, it is more compatible with the outpatient clinical evaluation of these patients.

Unlike US, MRI detects bone marrow edema (osteitis), which has been established as an important prognostic marker of arthritis due to other causes.[23] Hypothetically, this marker might also be useful for monitoring CF. Further studies are needed to evaluate the importance of osteitis in the follow-up of patients with CF.

The frequency of bone marrow edema findings (36.7%) was similar to that reported by Manimunda et al (35%).[22] Bone erosion, in turn, was detected at a frequency of 26.5% in our study and 20% in their study. MRI was superior to US (3.3%) at detecting this complication. Mogami et al did not report bone erosions in their study of patients with CF using wrist/hand US.

Some limitations of the study deserve to be highlighted. First, our sample was small. Second, the absence of medication use, as well the duration of medication use, may have influenced the existence or absence of inflammatory changes, which mainly influences color Doppler findings. Finally, some changes in the imaging tests were evaluated exclusively using US or MRI due to technical issues.

In conclusion, our results showed significant agreement between PE and US in the diagnosis of synovitis of large joints (radiocarpal/distal

radioulnar/mediocarpal) and the MCP and IP joints. In addition, US and MR detected a significant prevalence of tenosynovitis, and both methods showed substantial agreement. Therefore, these findings may support the routine recommendation of US examination, as it is noninvasive and accessible and can be performed during consultations. For at least mild or moderate cases, US potentially represents a relevant tool to confirm PE findings and to detect tenosynovitis and median nerve thickening, as reported in other studies.[10,12] MRI might be indicated for severe cases because it has superior performance for detecting bone abnormalities such as marrow edema and subchondral erosions. Its use would be similar to the recommendations for RA and the screening of worse prognostic parameters (osteitis) and structural injuries (erosions).[24]

Moderate agreement was observed between US and MRI only for flexor tenosynovitis. This dissociation between the methods indicates the need for studies with larger samples to obtain a more reliable comparison but may also suggest a complementary role of the 2 methods.

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