ESCOLA SUPERIOR DE CIÊNCIAS DA SANTA CASA DE MISERICORDIA
DE VITÓRIA - EMESCAM

FÁBIO FAVARATO SCOPEL

LUIZ CARLOS BARROS DE CASTRO SEGUNDO

CAQUEXIA NEUROPÁTICA DIABÉTICA ASSOCIADA A DOR ABDOMINAL: RELATO DE CASO

VITÓRIA

2015

FÁBIO FAVARATO SCOPEL

LUIZ CARLOS BARROS DE CASTRO SEGUNDO

CAQUEXIA NEUROPÁTICA DIABÉTICA ASSOCIADA A DOR ABDOMINAL: RELATO DE CASO

Trabalho de Conclusão de Curso apresentado à Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória – EMESCAM, como requisito parcial para obtenção do grau de médico.

Orientadora: Drª. Lívia Zardo Trindade

VITÓRIA

2015

FÁBIO FAVARATO SCOPEL

LUIZ CARLOS BARROS DE CASTRO SEGUNDO

CAQUEXIA NEUROPÁTICA DIABÉTICA ASSOCIADA A DOR ABDOMINAL: RELATO DE CASO

Trabalho de Conclusão de Curso apresentado ao curso de Medicina da Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória – EMESCAM, como requisito parcial para obtenção do grau de médico.

Aprovado em 26 de Março de 2015

COMISSÃO EXAMINADORA

Professora Lívia Zardo Trindade
Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória – EMESCAM
Orientadora

Professor Fabiano Quarto Martins
Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória – EMESCAM

Professora Carmen Dolores Gonçalves Brandão
Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória – EMESCAM

Dedico este trabalho aos meus pais, pelo carinho e incentivo em todos os momentos da minha vida. E a todos que participaram de alguma forma na realização e conclusão desta obra.

Fábio Favarato Scopel

Dedico este trabalho aos meus pais pela oportunidade, apoio e incentivo que me foram passados.

Luiz Carlos Barros de Castro Segundo

Agradecemos primeiramente a Deus, por iluminar nosso caminho nesta longa jornada.

À professora Drª. Lívia Zardo Trindade pela orientação e apoio e na elaboração deste trabalho.

Ao paciente que gentilmente aceitou participar deste trabalho e cedeu o direito de utilização deste caso clínico.

A todos que de alguma forma contribuíram para realização deste trabalho.

“O homem é lobo do próprio homem”

Thomas Hobbes

RESUMO

A caquexia neuropática diabética é considerada a forma mais rara da neuropatia diabética. Descrita pela primeira vez em 1974, permitiu a identificação e diagnóstico de aproximadamente 30 pacientes até hoje. De todos os sinais e sintomas, os mais frequentes na literatura englobam a perda ponderal, dor intensa (inespecífica), índices glicêmicos razoavelmente controlados, anorexia, distúrbios emocionais, neuropatia periférica e ausência de outras complicações relacionadas à diabetes. O tratamento é principalmente de suporte e sintomático. Os antidepressivos são de grande ajuda no tratamento sintomático da neuropatia e da depressão associada à síndrome. O prognóstico geralmente é bom e os pacientes geralmente recuperam seu peso, com resolução dos sintomas sensoriais dolorosos dentro de um a dois anos, embora déficits residuais possam persistir.

Palavras-chave: caquexia neuropática diabética; dor abdominal; perda de peso.

ABSTRACT

The diabetic neuropathic cachexia is considered the rarest form of diabetic neuropathy. First described in 1974, it has allowed the identification and diagnosis in approximately 30 patients until today. From all the signs and symptoms, the most frequent in the literature include weight loss, severe pain (nonspecific), glycemic index reasonably controlled, anorexia, emotional disorders, peripheral neuropathy and no other complications related to diabetes. The treatment is mainly supportive and symptomatic. The antidepressants are helpful for symptomatic treatment of neuropathy and depression associated with the syndrome. The prognosis in general is good and patients usually recover their weight with a resolution of painful sensory symptoms within one to two years, although residual deficits may persist.

Keywords: diabetic neuropathic cachexia; abdominal pain; weight loss.

SUMÁRIO

1 CAQUEXIA NEUROPÁTICA DIABÉTICA ASSOCIADA A DOR ABDOMINAL: RELATO DE CASO 10

1.1 FOLHA DE ROSTO 10

1.2 RESUMO 12

1.3 ABSTRACT 13

1.4 INTRODUÇÃO 14

1.5 RELATO DE CASO 15

1.6 DISCUSSÃO 20

1.7 CONCLUSÃO 26

1.8 AGRADECIMENTOS 27

1.9 REFERÊNCIAS 28

1.10 FIGURAS 30

2 TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO 31

3 APROVAÇÃO DO COMITÊ DE ÉTICA LOCAL 32

4 TERMOS DE RESPONSABILIDADE DE AUTORIA, DIVULGAÇÃO E TRANSFERÊNCIA DE DIREITOS AUTORAIS 35

5 NORMAS PARA PUBLICAÇÃO NO *EUROPEAN JOURNAL OF GASTROENTEROLOGY & HEPATOLOGY* 47

6 ARTIGO PUPLICADO NO *EUROPEAN JOURNAL OF GASTROENTEROLOGY & HEPATOLOGY* 63

1 CAQUEXIA NEUROPÁTICA DIABÉTICA ASSOCIADA A DOR ABDOMINAL: RELATO DE CASO

1.1 FOLHA DE ROSTO

TÍTULO COMPLETO

Caquexia neuropática diabética associada a dor abdominal: Relato de caso

Diabetic neuropathic cachexia associated with abdominal pain: Case report

TÍTULO CURTO

Caquexia neuropática diabética: Relato de caso

Diabetic neuropathic cachexia: Case report

AUTORES

Fábio Favarato Scopel

Estudante de Medicina da Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória - Vitória - Espírito Santo - Brasil

Luiz Carlos Barros de Castro Segundo

Estudante de Medicina da Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória - Vitória - Espírito Santo - Brasil

Lívia Zardo Trindade

Professora da Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória - Vitória - Espírito Santo – Brasil

LOCAL DE REALIZAÇÃO DO ESTUDO

Hospital Santa Casa de Misericórdia de Vitória - Vitória/ES

Rua Dr.João dos Santos Neves, 143. Vila Rubim, Vitória-ES CEP: 29.018-180.

CORRESPONDÊNCIA

Fábio Favarato Scopel

Rua Genserico Encarnação, 185/ apto 103. Mata da Praia, Vitória- ES CEP: 29.065-420.

Celular: (55) 27 999742108

E-mail: fabiofscopel@hotmail.com

CONFLITO DE INTERESSE

Não houve conflito de interesse.

FINANCIAMENTO

Nada a declarar.

1.2 RESUMO

A caquexia neuropática diabética é considerada a forma mais rara da neuropatia diabética. Descrita pela primeira vez em 1974, permitiu a identificação e diagnóstico de aproximadamente 30 pacientes até hoje. De todos os sinais e sintomas, os mais frequentes na literatura englobam a perda ponderal, dor intensa (inespecífica), índices glicêmicos razoavelmente controlados, anorexia, distúrbios emocionais, neuropatia periférica e ausência de outras complicações relacionadas à diabetes. O tratamento é principalmente de suporte e sintomático. Os antidepressivos são de grande ajuda no tratamento sintomático da neuropatia e da depressão associada à síndrome. O prognóstico geralmente é bom e os pacientes geralmente recuperam seu peso, com resolução dos sintomas sensoriais dolorosos dentro de um a dois anos, embora déficits residuais possam persistir.

Palavras-chave: caquexia neuropática diabética; dor abdominal; perda de peso.

1.3 ABSTRACT

The diabetic neuropathic cachexia is considered the rarest form of diabetic neuropathy. First described in 1974, it has allowed the identification and diagnosis in approximately 30 patients until today. From all the signs and symptoms, the most frequent in the literature include weight loss, severe pain (nonspecific), glycemic index reasonably controlled, anorexia, emotional disorders, peripheral neuropathy and no other complications related to diabetes. The treatment is mainly supportive and symptomatic. The antidepressants are helpful for symptomatic treatment of neuropathy and depression associated with the syndrome. The prognosis in general is good and patients usually recover their weight with a resolution of painful sensory symptoms within one to two years, although residual deficits may persist.

Keywords: diabetic neuropathic cachexia; abdominal pain; weight loss.

1.4 INTRODUÇÃO

Caquexia neuropática diabética (CND) é considerada a forma mais rara da neuropatia diabética [1]. Essa enfermidade é descrita como uma síndrome, pois apresenta um conjunto de sinais e sintomas em que os pacientes podem ter diferentes apresentações clínicas, algumas comuns e outras nem tanto. A principal característica dessa doença é a extrema perda de peso associada a dor neuropática.

Em 1974 Ellenberg descreveu a CND pela primeira vez, permitindo assim a identificação e diagnóstico de aproximadamente 30 pacientes até hoje [2]. A inconstância e a variabilidade dos sintomas torna essa doença de difícil diagnóstico a qual pode ser muitas das vezes sub diagnosticada em doentes graves [3].

Este trabalho se propõe a relatar o caso de um homem de 50 anos de idade, com caquexia neuropática diabética associada a dor abdominal recorrente. E através desse alertar a importância do diagnóstico e tratamento precoces com o objetivo de evitar o impacto iatrogênico de tratamentos específicos sobre morbidades existentes ou até mesmo inexistentes.

1.5 RELATO DE CASO

Paciente de 50 anos de idade, sexo masculino, branco, casado, pedreiro. Possuia histórico de diabetes mellitus tipo 2, diagnosticada há 5 anos, em tratamento irregular com hipoglicemiantes orais (metformina e glibenclamida) a pouco menos de 2 anos. Apresentava quadro de emagrecimento importante, cerca de 30 kg de peso em oito meses, associado a dor abdominal no mesmo período, porém com piora nos últimos três meses. Inicialmente esta dor era em andar superior do abdome, pós-prandial, de leve intensidade, progressiva, sem irradiação, que melhorava com analgésicos (Codeína 30mg de 12 em 12 horas e Hioscina 10mg de 4 em 4 horas). A dor evoluiu com extensão para todo abdome com irradiação para região lombar, contínua, de moderada a forte intensidade, sem relação com alimentação, sem melhora com analgésicos, que se intensificava com a manipulação e atividade física cotidiana. Além disso, apresentava constipação, com 2 evacuações por semana de consistência firme, sem muco, pus, sangue ou gordura. Possuía histórico de etilismo de 40g de alcool por dia durante 30 anos, negava tabagismo e uso de drogas ilícitas. Não apresentava febre, diarreia, náuseas, vômitos, disfagia, odinofagia, sudorese, palidez ou mal estar. Diante de tais sinais e sintomas o paciente procurou o ambulatório de Gastroenterologia do Hospital da Santa Casa de Misericórdia de Vitória (HSCMV), onde foi atendido e internado no dia 23/05/2014 na enfermaria Santa Luíza para investigação da dor abdominal.

Ao exame físico de admissão o paciente apresentava-se em regular estado geral, lúcido, orientado, hidratado, caquético, marcha atípica, equilíbrio estático e dinâmica preservados, coordenação motora sem alterações, peso de 52 kg,

1,75m de altura, IMC de 16,97, frequência cardíaca normal, pressão arterial e frequência respiratórias normais. Abdome escavado, ruídos hidroaéreos presentes, doloroso a palpação profunda de hipogástrio, ausência de visceromegalias.

O paciente ficou internado por 40 dias, período no qual realizou uma extensa propedêutica investigativa com realização de exames laboratoriais, exames de imagem e procedimentos diagnósticos invasivos.

Na investigação laboratorial, a glicose apresentava discreta alteração, porém as demais exames como hemograma, ionograma, função renal e função tireoideana não apresentaram nenhuma alteração. Dosagem de Peptídio C, insulina, amilase, lípase, transaminases, fosfatase alcalina, gama gt, proteína C reativa, lactato, desidrogenase láctea se apresentaram normais. Sorologias para Hepatite B, Hepatite C, Sífilis, HIV e teste para tuberculose também foram avaliados, sendo também normais, assim como as radiografias de tórax e abdome.

Na avaliação complementar, a endoscopia digestiva alta (EDA) evidenciou restos alimentares sugerindo gastroparesia, além de esofagite não erosiva com moderada gastrite enantematosa do antro**.** A colonoscopia foi normal. Na angiotomografia de abdome total, apresentava discreta falha de enchimento em ramo cólico esquerdo da artéria mesentérica superior. A arteriografia não evidenciou alterações em vaso abdominais. Na tomografia computadorizada de abdome total apresentava uma discreta redução do volume pancreático (corpo e cauda) com densidade heterogênia na cabeça do pâncreas, imagem nodular na glandula adrenal esquerda (adenoma) e cisto em polo superior de rim esquerdo**.**

Diante da dúvida diagnóstica, e com a persistência das dores abdominais, o paciente foi submetido a uma videolaparoscopia exploradora, onde não foram evidenciados ascite e/ou massa tumorais visíveis e/ou implantes tumorais em peritônio parietal, e as alças de intestino delgado e cólon eram eutróficas, de coloração atípica, com ausência de sinais macroscópicos de hipoperfusão sanguínea intestinal. Durante o procedimento foi realizado biópsia hepática, cujo laudo foi de alterações reativas leve do fígado com fibrose e ectasia ductal capsular focal.

Para tratamento da dor foram administrados tramadol (até 50mg VO de 6/6 horas) e morfina (2mg IV) de resgate caso dor refratária. Houve necessidade do uso rotineiro de morfina sem melhora do quadro, somado a episódios repetidos de insônia.

Como na tomografia de abdome havia alterações sugestivas de pancreatite crônica foi iniciado o tratamento empírico com enzimas pancreáticas, porém o mesmo não apresentou resultado clínico.

Diante da extensa investigação diagnóstica, e sem dados que evidenciassem tumor, doença infecciosa, endócrina ou digestiva, aventou-se a hipótese de dor associada a uma caquexia neuropática diabetica. Dessa forma, o paciente foi medicado com amitriptilina 25 mg/dia, com melhora gradativa da dor a medida que a mediação era ajustada para 75mg/dia, com redução também gradativa nas doses de morfina até sua suspensão, quando o paciente apresentou remissão completa da dor e da insônia.

Após a melhora da dor com o tratamento medicamentoso o paciente recebeu alta hospitalar com prescrição de 75mg de amitriptilina ao dia e insulina NPH 16 UI/dia (NPH de 10 UI / às 8 horas e 6 UI / às 18 horas). A partir de então

paciente foi orientado a fazer acompanhamento regular nos ambulatórios de Gastroenterologia e de Endocrinologia do Hospital Da Santa Casa de Misericórdia de Vitória.

Em consultas periódicas nos ambulatórios de Gatroenterologia e Endocrinologia, o paciente apresentou ganho ponderal importante de 25kg recuperando paulatinamente a massa corporal de origem, e realizou exames complementares de seguimento. Entre eles: a) uma eletroneutomiografia, onde os dados eletromiográficos e eletroneurograficos evidenciavam sinas de um processo neuropático sensitivo motor, crônico acometendo os MMII e MMSS de características axonais e mielínicas e comprometimento de intensidade moderada, revelando quadro de polineuropatia sensitivo motora crônica axonal e mielínica de intensidade moderada de predomínio sensitivo e nos MMII; b) um ecocardiograma, apresentando uma disfunção diastólica grau I e ectasia discreta do seio aórtico; c) um Raio X de tórax com pequeno nódulo de aspecto residual no terço superior do pulmão esquerdo e o restante sem alterações.

Durante as consultas de seguimento, o paciente não apresentou alterações em exames de hemograma, plaquetas, leucócitos, urina, exame parasitológico, proteínas totais, enzimas hepática, provas de função renal e tireoidiana, ionograma e sorologias para HIV, hepatite B e C e sífilis. Os controles de glicose de jejum ficaram em torno de 170mg/dL, de glicose pós-prandial em torno de 194mg/dL, a hemoglobina glicada de 7,6mg/dL e o LDL por volta de 120mg/dL.

Durante os seis meses iniciais de acompanhamento foram realizadas fotografias do paciente para comparação de ganho ponderal (Fig.1), sendo que na última consulta o mesmo apresentava 77kg (27 kg a mais desde o início do

tratamento). Nesta última consulta, fazia uso continuo de omeprazol 20mg pela manha, insulina NPH 15U pela manhã e 6U a noite, sinvastatina 20mg/dia e amtriptilina 75mg/dia.

Apesar da melhora da dor abdominal, o paciente ainda relatava diminuição de força muscular em membros, principalmente em membros inferiores, além de parestesia importante em toda região de abdome.

1.6 DISCUSSÃO

A caquexia neuropática diabética é uma doença extremamente rara, sendo relatados em torno de 35 casos no mundo desde que foi descrita pela primeira vez em 1974 por Ellenbeg. Nos casos descritos, as dores neuropáticas e a perda ponderal importante são descritos como os principais sintomas relatados [3].

Nos casos descritos na literatura, o diagnóstico de diabetes mellitus estava presente nos pacientes antes da internação, entretanto muitos realizavam tratamento e acompanhamento inadequado. Os pacientes descritos eram predominantemente de meia-idade, do sexo masculino, com diabetes do tipo 2, em uso de hipoglicemiantes orais [1,4-8]. Essas características também foram encontradas no paciente deste relato, sendo um homem de 50 anos, com diabetes tipo 2, em uso irregular de hipoglicemiantes orais.

No paciente em questão, obteve-se grande dificuldade para inserir e nos orientar nas hipóteses diagnósticas de uma possível complicação da diabetes: a neuropatia diabética. Uma vez que o paciente mesmo apresentando história de diabetes, porém sem orientação e medicação para a mesma, possuía um quadro clínico variado, com padrão de dor atípico, sendo sua principal sintomatologia a dor abdominal de forte intensidade.

A etiologia da caquexia neuropática diabética ainda permanece obscura. O catabolismo proteico exagerado devido ao pobre controle da glicemia pode ser uma das possíveis causas. Além disso, a eventual resolução dos sintomas com concomitante ganho de peso sugere um processo essencialmente metabólico [3,9-10].

Um fator complicador para a avaliação diagnóstica do paciente foi o fato dos exames laboratoriais apresentarem níveis glicêmicos acima do limite permitido, porém não o bastante para caracterizar qualquer possível complicação associada ao diabetes. Esse dado torna-se importante, pois correlaciona-se com os casos relatados na literatura com CND, onde a alteração da glicemia geralmente é leve, sendo na maioria das vezes controlada, pelo menos inicialmente, com dieta e hipoglicemiantes orais. Contudo, em alguns desses pacientes, o diabetes não consegue ser suficientemente controlado com agentes orais, sendo necessário o uso de insulina [1-2,8]. No caso relatado, a administração de insulina foi necessária a medida que o quadro de dor abdominal foi resolvendo-se e o paciente começou a ganhar peso.

Na internação hospitalar do paciente relatado, o mesmo tem como queixa principal as dores difusas em região abdominal e o emagrecimento importante de 30% de peso corporal. Tendo em vista que os sinais e sintomas de CND podem levar a uma hipótese diagnóstica de câncer oculto, as causas de perda de peso devem ser cuidadosamente investigadas, e uma terapia adequada deve ser fornecida em um tempo hábil [2,4,11]. Diante de um quadro de importante perda ponderal, de acordo com a literatura, é comum pensar-se em uma neuropatia carcinomatosa, o que foi descartado em propedêutica adequada, após a laparoscopia exploradora.

Ainda durante a investigação para a dor abdominal do paciente foi descartado o diagnóstico de síndrome da artéria mesentérica superior, pancreatite crônica e angina mesentérica após a realização de tomografia e angiografia de abdome.

Neste caso, nos deparamos com a dificuldade no diagnóstico pois o paciente apresentava dor abdominal difusa, fato que não é comumente relatado na literatura. De acordo com os estudos, as dores na CND caracteriza-se também como dor em queimação, porém com características diferentes da citada, onde o sintoma é mais predominante em região de tronco e em região proximal dos membros [1,12].

Baseado em exames iniciais de imagem, como na tomografia, e associado com a clínica de dor abdominal de forte intensidade e história de etilismo crônico, o diagnóstico de pancreatite crônica foi descartado após a introdução de enzimas pancreáticas sem melhora do quadro. Apesar desses resultados, tal ponto é de fundamental importância para gerar suposições a respeito da CND. De acordo com um estudo [13], uma série de indivíduos apresentou uma síndrome de má absorção e/ou alterações dos hábitos intestinais associada a má absorção de gordura, sendo essa característica associada a uma insuficiência pancreática, porém com mecanismos disabsortivos, não sendo muito claros, apenas pela insuficiência pancreática apresentada.

Ao excluir a pancreatite crônica como uma das causas da dor abdominal, foram solicitados exames mais específicos para a investigações de lesões em região da arterial intestinal e de possíveis alterações que pudessem mostrar qualquer alteração do trato gastrointestinal. Nesse sentido, uma angiotomografia computadorizada de abdome total e uma arteriografia dos vasos abdominais, que evidenciou discreta falha de enchimento cólico esquerdo, foram suficientes para descratar tais hipóteses já que esses exames seriam favoráveis para um possível diagnóstico de oclusão arterial como causa da dor abdominal.

Na endoscopia digestiva alta, o resultado nos mostrou um dado importante que pode ser correlacionado com os relatos dos artigos publicados sobre a CND, onde a gastroparesia grave, documentada em alguns pacientes, pode ser um fator contributivo para perda de peso e é evidenciada em pacientes que possuem diabetes porém com glicemia não controlada [3,9-10]. A colonoscopia não apresentou dados que nos ajudasse a concluir algum diagnóstico, mas foi importante na exclusão de neoplasia do intestino grosso.

O fato da dor abdominal relatada pelo paciente ser refratária ao tratamento medicamentoso com analgésicos potentes e opióides, condiz com os relatos citados na literatura em que os analgésicos opióides raramente têm benefício no tratamento da neuropatia dolorosa e, apesar de sua ampla utilização, devem ser evitadas devido ao risco de dependência [1].

Na maioria dos casos descritos, os distúrbios emocionais são graves e proeminentes. Eles, invariavelmente caminham para a depressão aguda com crises de choro, insônia, ansiedade e com marcante anorexia, sendo por isso outro fator importante para a perda de peso. A depressão parece ser uma parte integrante da síndrome como um sintoma, em vez de um fator causal independente, e sua explicação não é clara [3,6,8,11]. Dentre os sintomas acima, nosso paciente, apresentou pequenos sintomas depressivos, não evoluindo para forma grave, porém contribuindo significativamente para a hiporexia e a perda de peso do paciente.

Schipper e Poleski [12] descreveram que as dores que se restringem aos dermatomos torácicos mais baixos e lombares superiores geralmente sugerem doença visceral do abdômen. A dor atinge o auge de intensidade dentro de alguns dias do início, mas pode piorar ao longo de semanas ou meses antes

de um platô ser atingido. Raramente, a dor pode ser tão grave a ponto de sugerir a presença de abdômen agudo. Porém, quando há associação da hiporexia, perda de peso e neuropatia autonômica, como no paciente que descrevemos, não se pode descartar o diagnóstico de neuropatia autonômica. Anorexia e perda de peso acentuada frequentemente acompanham radiculopatia diabética.

Após toda a propedeutica realizada, a hipótese de CND foi aventada e o tratamento empírico da patologia foi iniciado, como nos relatos citados na literatura.

As opções de tratamento são limitadas e geralmente ineficazes em alguns pacientes, embora Gade et al. relatem uma resposta benéfica para a terapia de combinação com amitriptilina e flufenazina. Apesar disso, o prognóstico geralmente é bom e os pacientes geralmente recuperam seu peso, com resolução dos sintomas sensoriais dolorosos dentro de um a dois anos, embora déficits residuais possam persistir [1,7,10-11,14]. Com a introdução da amtriptilina no paciente do caso atual, na dose de 75mg/dia, o mesmo apresentou melhora importante da dor, podendo o tratamento ser realizado em domicilio.

De acordo com a literatura, um dos pontos principais do tratamento é o controle rigoroso da glicemia, o qual foi iniciado o uso de insulina regular.

O seguimento do paciente do caso foi realizado em consultas regulares a cada 2 meses até completar 6 meses. Durante esse período, foram realizadas consultas nos ambulatórios de gastroenterologia, para análise do peso e controle da dor abdominal, e no ambulatório de endocrinologia do HSCMV para o controle do diabetes.

Em todas as consultas, o paciente realizou exames de rotina, com enfoque para controle da diabetes, sendo este de difícil controle, principalmente pela rápida recuperação do peso. Um dos exames relatados na literatura, e também mais sensível para neuropatia diabética, seria a biópsia neural e muscular, em que demonstra atrofia neurogênica do músculo, com acentuado envolvimento das fibras mielínicas grandes e pequenas, com degeneração axonal [3,9-10,15-16]. Porém no paciente em estudo, optou-se pela realização de uma eletroneuromiografia que também pode ser usado para descrever possíveis lesões da complicação da diabetes [1]. O resultado desse exame foi a presença da polineuropatia sensitiva motora crônica axonal e mielínica de intensidade moderada de predomínio sensitivo e nos membros inferiores.

Com o seguimento adequado, observou-se a recuperação do peso, com ganho ponderal de cerca de 25kg, bem como grande melhora do estado geral, diminuição da dor abdominal, sono reparador, e melhora dos sintomas depressivos. Nos casos descritos, o controle do peso é adquirido com até 2 anos após o controle dos sintomas, entretanto em nosso paciente, o retorno ao peso habitual foi atingido em 6 meses, porém ainda apresentava desconforto abdominal e dores neuropáticas em membros inferiores, fatos esses que esperamos que regridam com a evolução do tratamento ao longo do tempo [1,7,10-11,14].

1.7 CONCLUSÃO

Por tratar-se de uma das apresentações mais raras de neuropatia diabética, a dor abdominal nem sempre é lembrada como causa de CND, por isso ainda há grandes desafios no que diz respeito ao diagnóstico adequado e o tratamento específico. A falta de diagnóstico precoce da caquexia neuropática diabética pode levar a um impacto iatrogênico de tratamentos específicos sobre morbidades existentes ou até mesmo inexistentes.

O relato deste caso visa divulgar essa entidade em meios científicos para maior conhecimento, por parte das equipes médicas, a respeito dessa doença, bem como, estimular a investigação de caquexia neuropática diabética como diagnóstico diferencial em pacientes com história de perda de peso importante associada a dor abdominal.

1.8 AGRADECIMENTOS

A Madson Macêdo Souza e Fernanda Lübe Antunes por nos auxiliarem durante o seguimento do paciente.

1.9 REFERÊNCIAS

1. Neal JM. Diabetic neuropathic cachexia: a rare manifestation of diabetic neuropathy. *South Med J* 2009;**102**:327-329.
2. Naccache DD, Nseir WB, Herskovitz MZ, Khamaisi MH. Diabetic neuropathic cachexia: a case report. *J Med Case Rep* 2014;**8**:20.
3. Ellenberg M. Diabetic neuropathic cachexia. *Diabetes* 1974;**23**:418-423.
4. Datta S, Arora R, Chitra S, Chakraborty P, Baidya A, Biswas D, et al. Diabetic neuropathic cachexia in a young female. *Indian J Endocrinol Metab* 2013;**17**(Suppl 1):S333-S334.
5. Deorchis VS, Herskovitz S, Laureta E, Heptulla RA. Neuropathic cachexia associated with type 1 diabetes in an adolescent girl. *Pediatr Neurol* 2013;**49**:282-285.
6. Weintrob N, Josefsberg Z, Galazer A, Vardi P, Karp M. Acute painful neuropathic cachexia in a young type I diabetic woman. A case report. *Diabetes Care* 1997;**20**:290-291.
7. Yuen KC, Day JL, Flannagan DW, Rayman G. Diabetic neuropathic cachexia and acute bilateral cataract formation following rapid glycaemic control in a newly diagnosed type 1 diabetic patient. *Diabet Med* 2001;**18**:854-857.
8. Massey EW. Diabetic neuropathic cachexia and diabetic amyotrophy. *Acta Diabetol Lat* 1982;**19**:91-95.

9. Al-Hajeri T, El-Gebely S, Abdella N. Profound weight loss in a type 2 diabetic patient with diabetic neuropathic cachexia: a case report. *Diabetes Metab* 2009;**35**:422-424.

10. Jackson CE, Barohn RJ. Diabetic neuropathic cachexia: report of a recurrent case. *J Neurol Neurosurg Psychiatry* 1998;**64**:785-787.

11. Godil A, Berriman D, Knapik S, Norman M, Godil F, Firek AF. Diabetic neuropathic cachexia. *West J Med* 1996;**165**:382-385.

12. Schipper HM, Poleski MH. Abdominal pain and weight loss in a patient with well controlled diabetes. *Can Med Assoc J* 1985;**133**:38-39.

13. D'Costa DF, Price DE, Burden AC. Diabetic neuropathic cachexia associated with malabsorption. *Diabet Med* 1992;**9**:203-205.

14. Gade GN, Hofeldt FD, Treece GL. Diabetic neuropathic cachexia. Beneficial response to combination therapy with amitriptyline and fluphenazine. *JAMA* 1980;**243**:1160-1161.

15. Archer AG, Watkins PJ, Thomas PK, Sharma AK, Payan J. The natural history of acute painful neuropathy in diabetes mellitus. *J Neurol Neurosurg Psychiatry* 1983;**46**:491-499.

16. Chandler PT, Singh RS, Schwetschenau RP. Diabetic neuropathic cachexia. *Acta Diabetol Lat* 1978;**15**:212-216.

1.10 FIGURAS

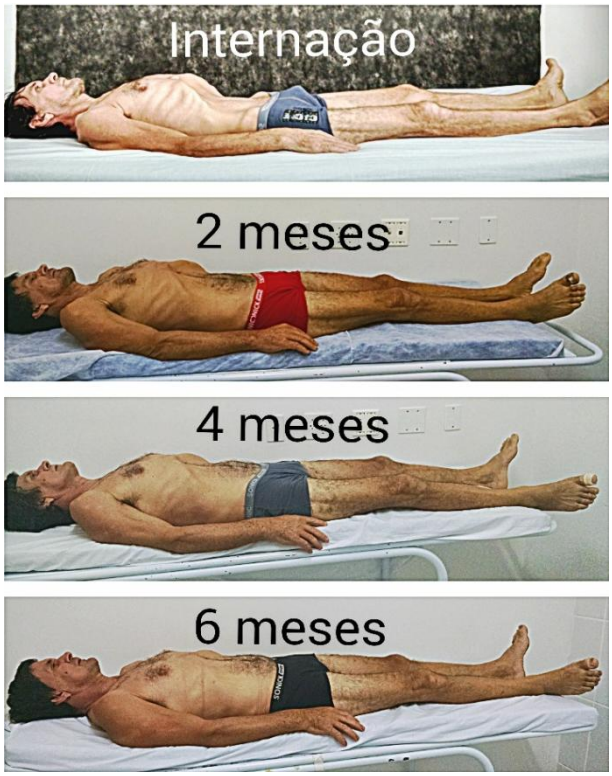


Fig.1 - Evolução do paciente da internação aos seis meses de seguimento.

2 TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Prezado paciente,

O senhor está sendo convidado a participar de um Relato de Caso. Por favor, leia este documento com bastante atenção antes de assiná-lo. Caso haja alguma palavra ou frase que o senhor não consiga entender, converse com o pesquisador responsável pelo estudo ou com um membro da equipe desta pesquisa para esclarecê-los.

O objetivo deste estudo é relatar o caso de um paciente com o diagnóstico de caquexia diabética neuropática associada a dor abdominal, para apresentação e divulgação de conhecimento científico aos profissionais da área e demais interessados.

Este estudo será realizado no Ambulatório de Gastroenterologia do Hospital Santa Casa de Misericórdia de Vitória (HSCMV) sob supervisão dos pesquisadores. O senhor foi escolhido para participar porque a Caquexia Diabética Neuropática é rara, com poucos casos relatados na literatura. Após entender e concordar em participar haverá acesso aos dados do seu prontuário, onde exames laboratoriais e de imagem assim como a história clínica serão analisados.

Não há benefício direto para o participante deste estudo. Porém contribuirá na melhoria do atendimento e aprendizado médico. A não aceitação deste termo não irá influenciar na conduta do seu tratamento nem no seu relacionamento com a equipe médica. Os resultados desta pesquisa poderão ser apresentados em reuniões e/ou publicações, contudo, sua identidade não será revelada durante essas apresentações.

Caso você tenha alguma dúvida relacionada ao estudo, poderá entrar em contato com a Pesquisadora responsável, Dra. Lívia Zardo Trindade, (Tel. 27 3212 7200) ou com os acadêmicos Fábio Favarato Scopel (Tel. 27 999742108), Fernanda Lübe Antunes Pereira (Tel. 27 992788286), Luiz Carlos Barros de Castro Segundo (Tel. 27 999530202) ou Madson Macêdo Souza (Tel. 27 998716706).

Ainda poderá recorrer ao Comitê de Ética em Pesquisa com Seres Humanos da EMESCAM (Tel. 27 3324-3586), situado na Avenida Nossa Senhora da Penha, 2190, Santa Luzia, Vitória – ES. CEP: 29045-402.

Você receberá uma cópia deste documento assinado.

Após ter lido este documento, eu _____,
RG nº:_____ / CPF nº:_____, declaro que entendi todas as informações fornecidas sobre a minha participação na pesquisa, e concordo em participar de forma voluntária.

Autorizo, também, a divulgação dos dados obtidos pela pesquisa para fins científicos, desde que respeitada a privacidade dos dados individuais.

Vitória, ____ de _____2014.

Assinatura do paciente ou responsável_____
Documento de identidade nº_____
Assinatura do pesquisador responsável_____
Documento de identidade nº _____

3 APROVAÇÃO DO COMITÊ DE ÉTICA LOCAL

ESCOLA SUPERIOR DE CIÊNCIAS DA SANTA CASA DE MISERICÓRDIA DE VITÓRIA -

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Caquexia Neuropática Diabética associada a dor abdominal recorrente - Relato de Caso

Pesquisador: Livia Zardo Trindade

Área Temática:

Versão: 1

CAAE: 36785714.0.0000.5065

Instituição Proponente: Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória -

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 848.209

Data da Relatoria: 27/10/2014

Apresentação do Projeto:

O presente projeto de pesquisa consiste no relato de caso de um paciente com caquexia neuropática diabética associada a dor abdominal recorrente que esteve internado na Santa Casa e permanece em acompanhamento no ambulatório de gastroenterologia da Santa Casa.

O projeto se justifica pois a caquexia neuropática diabética é considerada a forma mais rara da neuropatia diabética. De todos os sinais e sintomas, os mais encontrados na literatura englobam a perda ponderal, dor intensa (inespecífica), índices glicêmicos razoavelmente controlados, anorexia, distúrbios emocionais, neuropatia periférica e

ausência de outras complicações relacionadas à diabetes.

Objetivo da Pesquisa:

Objetivo primário:

- Relatar o caso de um paciente do Hospital Santa Casa de Misericórdia de Vitória (HSCMV) com o diagnóstico de Caquexia Neuropática Diabética.

Objetivo secundário:

- Alertar sobre a importância do diagnóstico e tratamento precoces com o objetivo de amenizar a evolução natural da doença e suas complicações

Endereço: EMESCAM, Av.N.S.da Penha 2190 - Centro de Pesquisa
Bairro: Bairro Santa Luzia **CEP:** 29.045-402
UF: ES **Município:** VITORIA
Telefone: (27)3334-3586 **Fax:** (27)3334-3586 **E-mail:** comite.etica@emescam.br

ESCOLA SUPERIOR DE CIÊNCIAS DA SANTA CASA DE MISERICÓRDIA DE VITÓRIA -

- Fomentar a discussão e a investigação de casos de caquexia neuropática diabética na comunidade Científica.

Avaliação dos Riscos e Benefícios:

Estudo retrospectivo que tem como base a análise de dados de prontuários, não haverá portanto interferência na conduta instituída pelo médico assistente. Os pesquisadores garantem manter a guarda adequada das informações e o anonimato do paciente.

O benefício será ampliar o conhecimento dos profissionais de saúde sobre as manifestações clínicas, possibilidades diagnósticas e tratamentos mais recomendados para os pacientes com caquexia neuropática diabética.

Comentários e Considerações sobre a Pesquisa:

Projeto com relevância científica uma vez que se propõe a relatar um caso de uma apresentação pouco usual da neuropatia diabética.

Considerações sobre os Termos de apresentação obrigatória:

apresenta folha de rosto assinada pelo coordenador de pesquisa e pós graduação da EMESCAM e carta de anuência autorizado a consulta de prontuários assinada pela diretora técnica da Santa Casa.

Apresenta TCLE em linguagem adequada.

Recomendações:

aprovar

Conclusões ou Pendências e Lista de Inadequações:

aprovar

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

O parecer do relator foi aprovado pelo CEP: projeto aprovado. Conforme a norma operacional 001/2013:

- riscos ao participante da pesquisa deverão ser comunicadas ao CEP por meio de notificação via Plataforma Brasil;

- ao final de cada semestre e ao término do projeto deverá ser enviado relatório ao CEP por meio

Endereço: EMESCAM, Av.N.S.da Penha 2190 - Centro de Pesquisa
Bairro: Bairro Santa Luzia **CEP:** 29.045-402
UF: ES **Município:** VITORIA
Telefone: (27)3334-3586 **Fax:** (27)3334-3586 **E-mail:** comite.etica@emescam.br

ESCOLA SUPERIOR DE CIÊNCIAS DA SANTA CASA DE MISERICÓRDIA DE VITÓRIA -

de notificação via Plataforma Brasil;
- mudanças metodológicas durante o desenvolvimento do projeto deverão ser comunicadas ao CEP por meio de emenda via Plataforma Brasil.

VITORIA, 28 de Outubro de 2014

Assinado por:
PATRICIA CASAGRANDE DIAS DE ALMEIDA
(Coordenador)

Endereço: EMESCAM, Av.N.S.da Penha 2190 - Centro de Pesquisa
Bairro: Bairro Santa Luzia **CEP:** 29.045-402
UF: ES **Município:** VITORIA
Telefone: (27)3334-3586 **Fax:** (27)3334-3586 **E-mail:** comite.etica@emescam.br

4 TERMOS DE RESPONSABILIDADE DE AUTORIA, DIVULGAÇÃO E TRANSFERÊNCIA DE DIREITOS AUTORAIS

Wolters Kluwer Health | Lippincott Williams & Wilkins

European Journal of Gastroenterology and Hepatology

Authorship Responsibility, Disclosure, and Copyright Transfer

Manuscript Title Diabetic neuropathic cachexia associated with abdominal pain: Case report

including all accompanying digital supplementary content, if any (the "Work")

Author Fábio Favarato Scopel

Are you the corresponding Author? ☑ Yes ☐ No

Corresponding Author's Name Fábio Favarato Scopel

Mailing Address Rua Genserico Encarnação, 185/ apto 103. Mata da Praia, Vitória- ES CEP: 29.065-420.

Telephone (+55) 27 999742108

Fax Number (+55) 27 33256636

Email Address fabiofscopel@hotmail.com

Instructions

Each author must read and provide the information requested in the form, and sign the following statements; this document must be distributed and completed by each co-author for their original electronic or ink signature. For instructions to electronically sign this document, please see instructions at the bottom of the form below the Signature field.

DISCLOSURES/CONFLICT OF INTEREST: All questions in this section MUST be answered by each author. To verify this, the author must click the "Check for Required" fields button at the bottom of the form before signing it.

Completed forms must be submitted online through Editorial Manager along with the article in order for your submission to be sent for peer review. Any relevant current or past conflicts of interest or sources of funding listed on this form must also be included on the Title page of the manuscript (as indicated in the Instructions for Authors). Submissions which do not comply with these instructions will be returned to the author for correction prior to review.

Conditions of Submission

RETAINED RIGHTS: Except for copyright, other proprietary rights related to the Work (e.g., patent or other rights to any process or procedure) shall be retained by the author. To reproduce any text, figures, tables, or illustrations from this Work in future works of their own, the author must obtain written permission from Lippincott Williams & Wilkins (LWW); such permission cannot be unreasonably withheld by LWW.

ORIGINALITY: Each author warrants that his or her submission to the Work is original, does not infringe upon, violate, or misappropriate any copyright or other intellectual property rights, or any other proprietary right, contract or other right or interest of any third party, and that he or she has full power to enter into this agreement. Neither this Work nor a similar work has been published nor shall be submitted for publication elsewhere while under consideration by this Publication.

AUTHORSHIP RESPONSIBILITY: Each author warrants that he or she has participated sufficiently in the intellectual content, the analysis of data, if applicable, and the writing of the Work to take public responsibility for it. Each has reviewed the final version of the Work, believes it represents valid work, and approves it for publication. Moreover, should the editors of the Publication request the data upon which the work is based, they shall produce it.

PREPRINTS: Upon acceptance of the article for publication, each author warrants that he/she will promptly remove any prior versions of this Work (normally a preprint) that may have been posted to an electronic server.

DISCLAIMER: Each author warrants that this Work contains no libelous or unlawful statements and does not infringe any or violate the publicity or privacy rights of any third party, libel or slander any third party, contain any scandalous, obscene, or negligently prepared information, or infringe or violate other personal or proprietary right of others, nor contains any fraudulent, plagiarized or incorrectly attributed material. Each author warrants that all statements contained in the work purporting to be facts are true, and any formula or instruction contained in the work will not, if followed accurately, cause any injury, illness, or damage to the user. If excerpts (e.g., text, figures, tables, illustrations, or audio/video files) from copyrighted works are included, a written release will be secured by the author prior to submission, and credit to the original publication will be properly acknowledged. Each author further warrants that he or she has obtained, prior to submission, written releases from patients whose names or likenesses are submitted as part of the Work. Should the Editor or LWW request copies of such written releases, the author shall provide them in a timely manner.

DISCLOSURES/CONFLICT OF INTEREST

Each author must identify any financial interests or affiliations with institutions, organizations, or companies relevant to the manuscript by completing the form below. Additionally, any financial associations involving spouse or partner or children must be disclosed as well.

Note: Items 1, 2, and 3 listed below come from the ICMJE Uniform Disclosure Form for Potential Conflicts of Interest at http://www.icmje.org/update.html (dated July 2010), except for the columns in numbers 1 and 2 that ask whether the relationship is current, ongoing, or past.

1. The work under consideration for publication

Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information.

Type	No	Money Paid to you	Money to Your Institution*	Name of Entity	Is the relationship current (C), ongoing (O), or past (P)?	Comments**	

* This means money that your institution received for your efforts on this study. ** Use this section to provide any needed explanation.

2. Relevant financial activities outside the submitted work

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Type	No	Money Paid to you	Money to Your Institution*	Name of Entity	Is the relationship current (C), ongoing (O), or past (P)?	Comments**	

* This means money that your institution received for your efforts. ** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

3. Other Relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☑ No other relationships/conditions/circumstances that present potential conflict of interest

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

Explanation

At the time of manuscript acceptance, journals will ask the author to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask the author to disclose further information about reported relationships.

Transfer of Copyright

AUTHOR's OWN WORK: In consideration of LWW's publication of the Work, the author hereby transfers, assigns, and otherwise conveys all his/her copyright ownership worldwide, in all languages, and in all forms of media now or hereafter known, including electronic media such as CD-ROM, Internet, and Intranet, to LWW. If LWW should decide for any reason not to publish the Work, LWW shall give prompt notice of its decision to the corresponding author, this agreement shall terminate, and neither the author nor LWW shall be under any further liability or obligation. Each author grants LWW the rights to use his or her name and biographical data (including professional affiliation) in the Work and in its or the journal's promotion. Notwithstanding the foregoing, this paragraph shall not apply, and any transfer made pursuant to this paragraph shall be null and void if (i) the work has been accepted by LWW for publication, and (ii) the author chooses to have the work published by LWW as an open access publication.

WORK MADE FOR HIRE: If this Work or any element thereof has been commissioned by another person or organization, or if it has been written as part of the duties of an employee, an authorized representative of the commissioning organization or employer must also sign this form stating his or her title in the organization.

GOVERNMENT EMPLOYEES: If the Work or a portion of it has been created in the course of any author's employment by the United States Government, check the "Government" box at the end of this form. A work prepared by a government employee as part of his or her official duties is called a "work of the U.S. Government" and is not subject to copyright. If it is not prepared as part of the employee's official duties, it may be subject to copyright.

INSTITUTIONAL REVIEW BOARD/ANIMAL CARE COMMITTEE APPROVAL: Each author warrants that his or her institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

WARRANTIES: Each author warranty made in this form is for the benefit of LWW and the Editor; each author agrees to defend, indemnify, and hold harmless those parties for any breach of such warranties.

Author(s) Posting of Articles to an Institutional Repository

European Journal of Gastroenterology and Hepatology will permit the author(s) to deposit for display a "final peer-reviewed manuscript" (the final manuscript after peer-review and acceptance for publication but prior to the publisher's copyediting, design, formatting, and other services) 12 months after publication of the final article on his/her personal web site, university's institutional repository or employer's intranet, subject to the following:

* *You may only deposit the final peer-reviewed manuscript.*
* *You may not update the final peer-reviewed manuscript text or replace it with a proof or with the final published version.*
* *You may not include the final peer-reviewed manuscript or any other version of the article in any commercial site or in any repository owned or operated by* any third party. For authors of articles based on research funded by NIH, Welcome Trust, HHMI, or other funding agency, see below for the services that LWW will provide on your behalf to comply with "Public Access Policy" guidelines.
* You may not display the final peer-reviewed manuscript until twelve months after publication of the final article.
* You must attach the following notice to the final peer-reviewed manuscript: "This is a non-final version of an article published in final form in (provide complete journal citation)".
* You shall provide a link in the final peer-reviewed manuscript to the *European Journal of Gastroenterology and Hepatology* website.

"Public Access Policy" Funding Disclosure

Please disclose below if you have received funding for research on which your article is based from any of the following organizations:

☐ National Institutes of Health (NIH)	☐ Wellcome Trust	☐ Howard Hughes Medical Institute (HHMI)
☐ Research Councils UK (RCUK)	☐ Other	Please List:

Compliance with NIH and Other Research Funding Agency Accessibility Requirements

A number of research funding agencies now require or request the author to submit the final peer-reviewed manuscript (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. Within medical research, three funding agencies in particular have announced such policies:

* The U.S. National Institutes of Health (NIH) requires the author to deposit the final peer-reviewed manuscript based on NIH-funded research in its repository PubMed Central (PMC) within twelve months after publication of the final article in the journal.
* The Howard Hughes Medical Institute (HHMI) requires as a condition of research grants, deposit in PMC, but in its case within six months after publication of the final article.
* The Wellcome Trust requires, as a condition of research grants, deposit in UK PubMed Central within six months after publication of the final article.

As a service to our authors, LWW will identify to National Library of Medicine (NLM) articles that require deposit. This Copyright Transfer Agreement provides the mechanism for identifying such articles.

LWW will transmit the final peer-reviewed manuscript of an article based on research funded in whole or in part by one or more of these three agencies to Pub Med Central.

Upon NIH request, it remains the legal responsibility of the author to confirm with NIH the provenance of his/her manuscript for purposes of deposit. Author will not deposit articles his/herself. Author will not alter the final peer-reviewed manuscript already transmitted to NIH.

Author will not authorize the display of the final peer-reviewed manuscript prior to:

(a) 12 months following publication of the final article, in the case of NIH,

(b) 6 months following publication of the final article, in the case of Welcome Trust and HHMI

Compliance with RCUK and Wellcome Trust Open Access Policies

Both the Research Councils UK (RCUK) and the Wellcome Trust have adopted policies regarding Open Access to articles that have been funded by grants from the RCUK or the Wellcome Trust. If either "Wellcome Trust" or "Research Councils UK (RCUK)" has been selected above, and the authors of the applicable article choose to have the article published as an open access publication, the following policies will apply:

* If the article is to be published pursuant to the "Gold" route of Open Access, both the RCUK and the Wellcome Trust require that LWW make the article freely available immediately pursuant to the Attribution 3.0 Creative Commons License, currently found at http://creativecommons.org/licenses/by/3.0/legalcode (the "CC BY License"). The CC BY License is the most accommodating of the Creative Commons licenses and allows others to distribute, remix, tweak, and build upon the article, even commercially, as long as they credit the authors for the original creation.
* If the article is to be published pursuant to the "Green" route of Open Access, both the RCUK and the Wellcome Trust require that LWW make the article freely available within six months pursuant to the Attribution-NonCommerical 3.0 Creative Commons License, currently found at http://creativecommons.org/licenses/by-nc/3.0/legalcode (the "CC BY-NC License"). The CC BY-NC License allows others to remix, tweak, and build upon the article non-commercially, and although their new works must also acknowledge the authors for the original creation and be non-commercial, they don't have to license their derivative works on the same terms.

As a service to our authors, LWW will identify to National Library of Medicine (NLM) articles that require deposit pursuant to the RCUK and Wellcome Trust policies described in this section. This Copyright Transfer Agreement provides the mechanism for identifying such articles.

LWW will transmit the final peer-reviewed manuscript of an article based on research funded in whole or in part by either RCUK or the Wellcome Trust to Pub Med Central.

Upon NIH request, it remains the legal responsibility of the author to confirm with NIH the provenance of his/her manuscript for purposes of deposit. Author will not deposit articles him/herself. Author will not alter the final peer-reviewed manuscript already transmitted to NIH.

With respect to the "Green" route of Open Access, author will not authorize the display of the final peer-reviewed manuscript prior to 6 months following publication of the final article.

Authors of articles that have been funded from grants from the RCUK or the Wellcome Trust are required to sign the LWW Open Access License Agreement prior to publication of the applicable article. Please contact the Editorial Office of the applicable Journal to receive the Open Access License Agreement that is to be signed in connection with the publication of the article.

Show All Table Rows | Check For Required Fields

☑ Author's Own Work ☐ Work for Hire ☐ Government

Date 03/05/2015

Signature Fábio Favarato Scopel

Assinado de forma digital por Fábio Favarato Scopel
DN: cn=Fábio Favarato Scopel, o, ou, email=fabiofscopel@hotmail.com, c=BR
Dados: 2015.03.06 16:49:29 -03'00'

Important Note: Once you electronically sign this form, you will not be able to make any additional changes to it.
To electronically sign this form:
1) First click **Check For Required Fields** button above.
2) Provide any missing information highlighted in red.
3) Click the **Hide All Table Rows Checked No** button above.
4) Click the signature field above and provide the information requested in the dialog boxes.
For additional help with electronically signing this form, go to http://links.lww.com/ZUAT/A106

Wolters Kluwer Health | Lippincott Williams & Wilkins

European Journal of Gastroenterology and Hepatology

Authorship Responsibility, Disclosure, and Copyright Transfer

Manuscript Title Diabetic neuropathic cachexia associated with abdominal pain: Case report

including all accompanying digital supplementary content, if any (the "Work")

Author Luiz Carlos Barros de Castro Segundo

Are you the corresponding Author? ☐ Yes ■ No

Corresponding Author's Name Fábio Favarato Scopel

Mailing Address Rua Dom Jorge de Meneses, 50/ apto 502. Praia da Costa, Vila Velha- ES CEP: 29101-025.

Telephone (+55) 27 999530202

Fax Number (+55) 27 33392222

Email Address luizsegundo25@hotmail.com

Instructions

Each author must read and provide the information requested in the form, and sign the following statements; this document must be distributed and completed by each co-author for their original electronic or ink signature. For instructions to electronically sign this document, please see instructions at the bottom of the form below the Signature field.

DISCLOSURES/CONFLICT OF INTEREST: All questions in this section MUST be answered by each author. To verify this, the author must click the "Check for Required" fields button at the bottom of the form before signing it.

Completed forms must be submitted online through Editorial Manager along with the article in order for your submission to be sent for peer review. Any relevant current or past conflicts of interest or sources of funding listed on this form must also be included on the Title page of the manuscript (as indicated in the Instructions for Authors). Submissions which do not comply with these instructions will be returned to the author for correction prior to review.

Conditions of Submission

RETAINED RIGHTS: Except for copyright, other proprietary rights related to the Work (e.g., patent or other rights to any process or procedure) shall be retained by the author. To reproduce any text, figures, tables, or illustrations from this Work in future works of their own, the author must obtain written permission from Lippincott Williams & Wilkins (LWW); such permission cannot be unreasonably withheld by LWW.

ORIGINALITY: Each author warrants that his or her submission to the Work is original, does not infringe upon, violate, or misappropriate any copyright or other intellectual property rights, or any other proprietary right, contract or other right or interest of any third party, and that he or she has full power to enter into this agreement. Neither this Work nor a similar work has been published nor shall be submitted for publication elsewhere while under consideration by this Publication.

AUTHORSHIP RESPONSIBILITY: Each author warrants that he or she has participated sufficiently in the intellectual content, the analysis of data, if applicable, and the writing of the Work to take public responsibility for it. Each has reviewed the final version of the Work, believes it represents valid work, and approves it for publication. Moreover, should the editors of the Publication request the data upon which the work is based, they shall produce it.

PREPRINTS: Upon acceptance of the article for publication, each author warrants that he/she will promptly remove any prior versions of this Work (normally a preprint) that may have been posted to an electronic server.

DISCLAIMER: Each author warrants that this Work contains no libelous or unlawful statements and does not infringe any or violate the publicity or privacy rights of any third party, libel or slander any third party, contain any scandalous, obscene, or negligently prepared information, or infringe or violate other personal or proprietary right of others, nor contains any fraudulent, plagiarized or incorrectly attributed material. Each author warrants that all statements contained in the work purporting to be facts are true, and any formula or instruction contained in the work will not, if followed accurately, cause any injury, illness, or damage to the user. If excerpts (e.g., text, figures, tables, illustrations, or audio/video files) from copyrighted works are included, a written release will be secured by the author prior to submission, and credit to the original publication will be properly acknowledged. Each author further warrants that he or she has obtained, prior to submission, written releases from patients whose names or likenesses are submitted as part of the Work. Should the Editor or LWW request copies of such written releases, the author shall provide them in a timely manner.

DISCLOSURES/CONFLICT OF INTEREST

Each author must identify any financial interests or affiliations with institutions, organizations, or companies relevant to the manuscript by completing the form below. Additionally, any financial associations involving spouse or partner or children must be disclosed as well.

Note: Items 1, 2, and 3 listed below come from the ICMJE Uniform Disclosure Form for Potential Conflicts of Interest at http://www.icmje.org/update.html (dated July 2010), except for the columns in numbers 1 and 2 that ask whether the relationship is current, ongoing, or past.

1. The work under consideration for publication

Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information.

Type	No	Money Paid to you	Money to Your Institution*	Name of Entity	Is the relationship current (C), ongoing (O), or past (P)?	Comments**	

* This means money that your institution received for your efforts on this study. ** Use this section to provide any needed explanation.

2. Relevant financial activities outside the submitted work

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Type	No	Money Paid to you	Money to Your Institution*	Name of Entity	Is the relationship current (C), ongoing (O), or past (P)?	Comments**	

* This means money that your institution received for your efforts. ** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

3. Other Relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- [x] No other relationships/conditions/circumstances that present potential conflict of interest
- [ ] Yes, the following relationships/conditions/circumstances are present (explain below):

Explanation

At the time of manuscript acceptance, journals will ask the author to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask the author to disclose further information about reported relationships.

Transfer of Copyright

AUTHOR's OWN WORK: In consideration of LWW's publication of the Work, the author hereby transfers, assigns, and otherwise conveys all his/her copyright ownership worldwide, in all languages, and in all forms of media now or hereafter known, including electronic media such as CD-ROM, Internet, and Intranet, to LWW. If LWW should decide for any reason not to publish the Work, LWW shall give prompt notice of its decision to the corresponding author, this agreement shall terminate, and neither the author nor LWW shall be under any further liability or obligation. Each author grants LWW the rights to use his or her name and biographical data (including professional affiliation) in the Work and in its or the journal's promotion. Notwithstanding the foregoing, this paragraph shall not apply, and any transfer made pursuant to this paragraph shall be null and void if (i) the work has been accepted by LWW for publication, and (ii) the author chooses to have the work published by LWW as an open access publication.

WORK MADE FOR HIRE: If this Work or any element thereof has been commissioned by another person or organization, or if it has been written as part of the duties of an employee, an authorized representative of the commissioning organization or employer must also sign this form stating his or her title in the organization.

GOVERNMENT EMPLOYEES: If the Work or a portion of it has been created in the course of any author's employment by the United States Government, check the "Government" box at the end of this form. A work prepared by a government employee as part of his or her official duties is called a "work of the U.S. Government" and is not subject to copyright. If it is not prepared as part of the employee's official duties, it may be subject to copyright.

INSTITUTIONAL REVIEW BOARD/ANIMAL CARE COMMITTEE APPROVAL: Each author warrants that his or her institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

WARRANTIES: Each author warranty made in this form is for the benefit of LWW and the Editor; each author agrees to defend, indemnify, and hold harmless those parties for any breach of such warranties.

Author(s) Posting of Articles to an Institutional Repository

European Journal of Gastroenterology and Hepatology will permit the author(s) to deposit for display a "final peer-reviewed manuscript" (the final manuscript after peer-review and acceptance for publication but prior to the publisher's copyediting, design, formatting, and other services) 12 months after publication of the final article on his/her personal web site, university's institutional repository or employer's intranet, subject to the following:

* *You may only deposit the final peer-reviewed manuscript.*
* *You may not update the final peer-reviewed manuscript text or replace it with a proof or with the final published version.*
* *You may not include the final peer-reviewed manuscript or any other version of the article in any commercial site or in any repository owned or operated by* any third party. For authors of articles based on research funded by NIH, Welcome Trust, HHMI, or other funding agency, see below for the services that LWW will provide on your behalf to comply with "Public Access Policy" guidelines.
* You may not display the final peer-reviewed manuscript until twelve months after publication of the final article.
* You must attach the following notice to the final peer-reviewed manuscript: "This is a non-final version of an article published in final form in (provide complete journal citation)".
* You shall provide a link in the final peer-reviewed manuscript to the *European Journal of Gastroenterology and Hepatology* website.

"Public Access Policy" Funding Disclosure

Please disclose below if you have received funding for research on which your article is based from any of the following organizations:

☐ National Institutes of Health (NIH)	☐ Wellcome Trust	☐ Howard Hughes Medical Institute (HHMI)
☐ Research Councils UK (RCUK)	☐ Other	Please List:

Compliance with NIH and Other Research Funding Agency Accessibility Requirements

A number of research funding agencies now require or request the author to submit the final peer-reviewed manuscript (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. Within medical research, three funding agencies in particular have announced such policies:

* The U.S. National Institutes of Health (NIH) requires the author to deposit the final peer-reviewed manuscript based on NIH-funded research in its repository PubMed Central (PMC) within twelve months after publication of the final article in the journal.
* The Howard Hughes Medical Institute (HHMI) requires as a condition of research grants, deposit in PMC, but in its case within six months after publication of the final article.
* The Wellcome Trust requires, as a condition of research grants, deposit in UK PubMed Central within six months after publication of the final article.

As a service to our authors, LWW will identify to National Library of Medicine (NLM) articles that require deposit. This Copyright Transfer Agreement provides the mechanism for identifying such articles.

LWW will transmit the final peer-reviewed manuscript of an article based on research funded in whole or in part by one or more of these three agencies to Pub Med Central.

Upon NIH request, it remains the legal responsibility of the author to confirm with NIH the provenance of his/her manuscript for purposes of deposit. Author will not deposit articles his/herself. Author will not alter the final peer-reviewed manuscript already transmitted to NIH.

Author will not authorize the display of the final peer-reviewed manuscript prior to:

(a) 12 months following publication of the final article, in the case of NIH,

(b) 6 months following publication of the final article, in the case of Welcome Trust and HHMI

Compliance with RCUK and Wellcome Trust Open Access Policies

Both the Research Councils UK (RCUK) and the Wellcome Trust have adopted policies regarding Open Access to articles that have been funded by grants from the RCUK or the Wellcome Trust. If either "Wellcome Trust" or "Research Councils UK (RCUK)" has been selected above, and the authors of the applicable article choose to have the article published as an open access publication, the following policies will apply:

* If the article is to be published pursuant to the "Gold" route of Open Access, both the RCUK and the Wellcome Trust require that LWW make the article freely available immediately pursuant to the Attribution 3.0 Creative Commons License, currently found at http://creativecommons.org/licenses/by/3.0/legalcode (the "CC BY License"). The CC BY License is the most accommodating of the Creative Commons licenses and allows others to distribute, remix, tweak, and build upon the article, even commercially, as long as they credit the authors for the original creation.
* If the article is to be published pursuant to the "Green" route of Open Access, both the RCUK and the Wellcome Trust require that LWW make the article freely available within six months pursuant to the Attribution-NonCommerical 3.0 Creative Commons License, currently found at http://creativecommons.org/licenses/by-nc/3.0/legalcode (the "CC BY-NC License"). The CC BY-NC License allows others to remix, tweak, and build upon the article non-commercially, and although their new works must also acknowledge the authors for the original creation and be non-commercial, they don't have to license their derivative works on the same terms.

As a service to our authors, LWW will identify to National Library of Medicine (NLM) articles that require deposit pursuant to the RCUK and Wellcome Trust policies described in this section. This Copyright Transfer Agreement provides the mechanism for identifying such articles.

LWW will transmit the final peer-reviewed manuscript of an article based on research funded in whole or in part by either RCUK or the Wellcome Trust to Pub Med Central.

Upon NIH request, it remains the legal responsibility of the author to confirm with NIH the provenance of his/her manuscript for purposes of deposit. Author will not deposit articles him/herself. Author will not alter the final peer-reviewed manuscript already transmitted to NIH.

With respect to the "Green" route of Open Access, author will not authorize the display of the final peer-reviewed manuscript prior to 6 months following publication of the final article.

Authors of articles that have been funded from grants from the RCUK or the Wellcome Trust are required to sign the LWW Open Access License Agreement prior to publication of the applicable article. Please contact the Editorial Office of the applicable Journal to receive the Open Access License Agreement that is to be signed in connection with the publication of the article.

Show All Table Rows | Check For Required Fields

☑ Author's Own Work ☐ Work for Hire ☐ Government

Date 03/05/2015

Signature Luiz Carlos Barros de Castro Segundo

Assinado de forma digital por Luiz Carlos Barros de Castro Segundo
DN: cn=Luiz Carlos Barros de Castro Segundo, o, ou, email=luizsegundo25@hotmail.com, c=BR
Dados: 2015.03.06 16:42:53 -03'00'

Important Note: Once you electronically sign this form, you will not be able to make any additional changes to it.
To electronically sign this form:
1) First click **Check For Required Fields** button above.
2) Provide any missing information highlighted in red.
3) Click the **Hide All Table Rows Checked No** button above.
4) Click the signature field above and provide the information requested in the dialog boxes.
For additional help with electronically signing this form, go to http://links.lww.com/ZUAT/A106

Wolters Kluwer Health | Lippincott Williams & Wilkins

European Journal of Gastroenterology and Hepatology

Authorship Responsibility, Disclosure, and Copyright Transfer

Manuscript Title Diabetic neuropathic cachexia associated with abdominal pain: Case report

including all accompanying digital supplementary content, if any (the "Work")

Author Lívia Zardo Trindade

Are you the corresponding Author? ☐ Yes ☒ No

Corresponding Author's Name Fábio Favarato Scopel

Mailing Address Desembargador Euripedez Queiroz do Vale Street, 550, ap 902

Telephone +55 27 999436464

Fax Number

Email Address liviaztrindade@yahoo.com.br

Instructions

Each author must read and provide the information requested in the form, and sign the following statements; this document must be distributed and completed by each co-author for their original electronic or ink signature. For instructions to electronically sign this document, please see instructions at the bottom of the form below the Signature field.

DISCLOSURES/CONFLICT OF INTEREST: All questions in this section MUST be answered by each author. To verify this, the author must click the "Check for Required" fields button at the bottom of the form before signing it.

Completed forms must be submitted online through Editorial Manager along with the article in order for your submission to be sent for peer review. Any relevant current or past conflicts of interest or sources of funding listed on this form must also be included on the Title page of the manuscript (as indicated in the Instructions for Authors). Submissions which do not comply with these instructions will be returned to the author for correction prior to review.

Conditions of Submission

RETAINED RIGHTS: Except for copyright, other proprietary rights related to the Work (e.g., patent or other rights to any process or procedure) shall be retained by the author. To reproduce any text, figures, tables, or illustrations from this Work in future works of their own, the author must obtain written permission from Lippincott Williams & Wilkins (LWW); such permission cannot be unreasonably withheld by LWW.

ORIGINALITY: Each author warrants that his or her submission to the Work is original, does not infringe upon, violate, or misappropriate any copyright or other intellectual property rights, or any other proprietary right, contract or other right or interest of any third party, and that he or she has full power to enter into this agreement. Neither this Work nor a similar work has been published nor shall be submitted for publication elsewhere while under consideration by this Publication.

AUTHORSHIP RESPONSIBILITY: Each author warrants that he or she has participated sufficiently in the intellectual content, the analysis of data, if applicable, and the writing of the Work to take public responsibility for it. Each has reviewed the final version of the Work, believes it represents valid work, and approves it for publication. Moreover, should the editors of the Publication request the data upon which the work is based, they shall produce it.

PREPRINTS: Upon acceptance of the article for publication, each author warrants that he/she will promptly remove any prior versions of this Work (normally a preprint) that may have been posted to an electronic server.

DISCLAIMER: Each author warrants that this Work contains no libelous or unlawful statements and does not infringe any or violate the publicity or privacy rights of any third party, libel or slander any third party, contain any scandalous, obscene, or negligently prepared information, or infringe or violate other personal or proprietary right of others, nor contains any fraudulent, plagiarized or incorrectly attributed material. Each author warrants that all statements contained in the work purporting to be facts are true, and any formula or instruction contained in the work will not, if followed accurately, cause any injury, illness, or damage to the user. If excerpts (e.g., text, figures, tables, illustrations, or audio/video files) from copyrighted works are included, a written release will be secured by the author prior to submission, and credit to the original publication will be properly acknowledged. Each author further warrants that he or she has obtained, prior to submission, written releases from patients whose names or likenesses are submitted as part of the Work. Should the Editor or LWW request copies of such written releases, the author shall provide them in a timely manner.

DISCLOSURES/CONFLICT OF INTEREST

Each author must identify any financial interests or affiliations with institutions, organizations, or companies relevant to the manuscript by completing the form below. Additionally, any financial associations involving spouse or partner or children must be disclosed as well.

Note: Items 1, 2, and 3 listed below come from the ICMJE Uniform Disclosure Form for Potential Conflicts of Interest at http://www.icmje.org/update.html (dated July 2010), except for the columns in numbers 1 and 2 that ask whether the relationship is current, ongoing, or past.

1. The work under consideration for publication

Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information.

Type	No	Money Paid to you	Money to Your Institution*	Name of Entity	Is the relationship current (C), ongoing (O), or past (P)?	Comments**	

* This means money that your institution received for your efforts on this study. ** Use this section to provide any needed explanation.

2. Relevant financial activities outside the submitted work

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Type	No	Money Paid to you	Money to Your Institution*	Name of Entity	Is the relationship current (C), ongoing (O), or past (P)?	Comments**	

* This means money that your institution received for your efforts. ** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

3. Other Relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

■ No other relationships/conditions/circumstances that present potential conflict of interest	☐ Yes, the following relationships/conditions/circumstances are present (explain below):

Explanation

At the time of manuscript acceptance, journals will ask the author to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask the author to disclose further information about reported relationships.

Transfer of Copyright

AUTHOR's OWN WORK: In consideration of LWW's publication of the Work, the author hereby transfers, assigns, and otherwise conveys all his/her copyright ownership worldwide, in all languages, and in all forms of media now or hereafter known, including electronic media such as CD-ROM, Internet, and Intranet, to LWW. If LWW should decide for any reason not to publish the Work, LWW shall give prompt notice of its decision to the corresponding author, this agreement shall terminate, and neither the author nor LWW shall be under any further liability or obligation. Each author grants LWW the rights to use his or her name and biographical data (including professional affiliation) in the Work and in its or the journal's promotion. Notwithstanding the foregoing, this paragraph shall not apply, and any transfer made pursuant to this paragraph shall be null and void if (i) the work has been accepted by LWW for publication, and (ii) the author chooses to have the work published by LWW as an open access publication.

WORK MADE FOR HIRE: If this Work or any element thereof has been commissioned by another person or organization, or if it has been written as part of the duties of an employee, an authorized representative of the commissioning organization or employer must also sign this form stating his or her title in the organization.

GOVERNMENT EMPLOYEES: If the Work or a portion of it has been created in the course of any author's employment by the United States Government, check the "Government" box at the end of this form. A work prepared by a government employee as part of his or her official duties is called a "work of the U.S. Government" and is not subject to copyright. If it is not prepared as part of the employee's official duties, it may be subject to copyright.

INSTITUTIONAL REVIEW BOARD/ANIMAL CARE COMMITTEE APPROVAL: Each author warrants that his or her institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

WARRANTIES: Each author warranty made in this form is for the benefit of LWW and the Editor; each author agrees to defend, indemnify, and hold harmless those parties for any breach of such warranties.

Author(s) Posting of Articles to an Institutional Repository

European Journal of Gastroenterology and Hepatology will permit the author(s) to deposit for display a "final peer-reviewed manuscript" (the final manuscript after peer-review and acceptance for publication but prior to the publisher's copyediting, design, formatting, and other services) 12 months after publication of the final article on his/her personal web site, university's institutional repository or employer's intranet, subject to the following:

* *You may only deposit the final peer-reviewed manuscript.*
* *You may not update the final peer-reviewed manuscript text or replace it with a proof or with the final published version.*
* *You may not include the final peer-reviewed manuscript or any other version of the article in any commercial site or in any repository owned or operated by* any third party. For authors of articles based on research funded by NIH, Welcome Trust, HHMI, or other funding agency, see below for the services that LWW will provide on your behalf to comply with "Public Access Policy" guidelines.
* You may not display the final peer-reviewed manuscript until twelve months after publication of the final article.
* You must attach the following notice to the final peer-reviewed manuscript: "This is a non-final version of an article published in final form in (provide complete journal citation)".
* You shall provide a link in the final peer-reviewed manuscript to the *European Journal of Gastroenterology and Hepatology* website.

"Public Access Policy" Funding Disclosure

Please disclose below if you have received funding for research on which your article is based from any of the following organizations:

☐ National Institutes of Health (NIH)	☐ Wellcome Trust	☐ Howard Hughes Medical Institute (HHMI)
☐ Research Councils UK (RCUK)	☐ Other	Please List:

Compliance with NIH and Other Research Funding Agency Accessibility Requirements

A number of research funding agencies now require or request the author to submit the final peer-reviewed manuscript (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. Within medical research, three funding agencies in particular have announced such policies:

* The U.S. National Institutes of Health (NIH) requires the author to deposit the final peer-reviewed manuscript based on NIH-funded research in its repository PubMed Central (PMC) within twelve months after publication of the final article in the journal.
* The Howard Hughes Medical Institute (HHMI) requires as a condition of research grants, deposit in PMC, but in its case within six months after publication of the final article.
* The Wellcome Trust requires, as a condition of research grants, deposit in UK PubMed Central within six months after publication of the final article.

As a service to our authors, LWW will identify to National Library of Medicine (NLM) articles that require deposit. This Copyright Transfer Agreement provides the mechanism for identifying such articles.

LWW will transmit the final peer-reviewed manuscript of an article based on research funded in whole or in part by one or more of these three agencies to Pub Med Central.

Upon NIH request, it remains the legal responsibility of the author to confirm with NIH the provenance of his/her manuscript for purposes of deposit. Author will not deposit articles his/herself. Author will not alter the final peer-reviewed manuscript already transmitted to NIH.

Author will not authorize the display of the final peer-reviewed manuscript prior to:

(a) 12 months following publication of the final article, in the case of NIH,

(b) 6 months following publication of the final article, in the case of Welcome Trust and HHMI

Compliance with RCUK and Wellcome Trust Open Access Policies

Both the Research Councils UK (RCUK) and the Wellcome Trust have adopted policies regarding Open Access to articles that have been funded by grants from the RCUK or the Wellcome Trust. If either "Wellcome Trust" or "Research Councils UK (RCUK)" has been selected above, and the authors of the applicable article choose to have the article published as an open access publication, the following policies will apply:

* If the article is to be published pursuant to the "Gold" route of Open Access, both the RCUK and the Wellcome Trust require that LWW make the article freely available immediately pursuant to the Attribution 3.0 Creative Commons License, currently found at http://creativecommons.org/licenses/by/3.0/legalcode (the "CC BY License"). The CC BY License is the most accommodating of the Creative Commons licenses and allows others to distribute, remix, tweak, and build upon the article, even commercially, as long as they credit the authors for the original creation.
* If the article is to be published pursuant to the "Green" route of Open Access, both the RCUK and the Wellcome Trust require that LWW make the article freely available within six months pursuant to the Attribution-NonCommerical 3.0 Creative Commons License, currently found at http://creativecommons.org/licenses/by-nc/3.0/legalcode (the "CC BY-NC License"). The CC BY-NC License allows others to remix, tweak, and build upon the article non-commercially, and although their new works must also acknowledge the authors for the original creation and be non-commercial, they don't have to license their derivative works on the same terms.

As a service to our authors, LWW will identify to National Library of Medicine (NLM) articles that require deposit pursuant to the RCUK and Wellcome Trust policies described in this section. This Copyright Transfer Agreement provides the mechanism for identifying such articles.

LWW will transmit the final peer-reviewed manuscript of an article based on research funded in whole or in part by either RCUK or the Wellcome Trust to Pub Med Central.

Upon NIH request, it remains the legal responsibility of the author to confirm with NIH the provenance of his/her manuscript for purposes of deposit. Author will not deposit articles him/herself. Author will not alter the final peer-reviewed manuscript already transmitted to NIH.

With respect to the "Green" route of Open Access, author will not authorize the display of the final peer-reviewed manuscript prior to 6 months following publication of the final article.

Authors of articles that have been funded from grants from the RCUK or the Wellcome Trust are required to sign the LWW Open Access License Agreement prior to publication of the applicable article. Please contact the Editorial Office of the applicable Journal to receive the Open Access License Agreement that is to be signed in connection with the publication of the article.

Show All Table Rows | Check For Required Fields

☑ Author's Own Work ☐ Work for Hire ☐ Government

Date 03/05/2015

Signature Livia Zardo Trindade

Assinado de forma digital por Livia Zardo Trindade
DN: cn=Livia Zardo Trindade, o=Emescam, ou=Emescam, email=liviaztrindade@yahoo.com.br, c=BR
Dados: 2015.03.11 23:57:44 -03'00'

Important Note: Once you electronically sign this form, you will not be able to make any additional changes to it.
To electronically sign this form:
1) First click **Check For Required Fields** button above.
2) Provide any missing information highlighted in red.
3) Click the **Hide All Table Rows Checked No** button above.
4) Click the signature field above and provide the information requested in the dialog boxes.
For additional help with electronically signing this form, go to http://links.lww.com/ZUAT/A106

5 NORMAS PARA PUBLICAÇÃO NO *EUROPEAN JOURNAL OF GASTROENTEROLOGY & HEPATOLOGY*

Guidance for Authors on the Preparation and Submission of Manuscripts to the European Journal of Gastroenterology & Hepatology

Note: These instructions comply with those formulated by the International Committee of Medical Journal Editors. For further details, authors should consult the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” at http://www.icmje.org.

The Journal is a member of the Committee on Publication Ethics (COPE) which aims to define best practice in the ethics of scientific publishing. COPE has established a number of guidelines including a Code of Conduct, and created flow charts that help editor's process cases of suspected misconduct (www.publicationethics.org).

Appeals on editorial decisions should be sent to the Editor. Complaints related to how your paper was processed during peer-review and not resolved by the Editor, should be referred to the person named as publisher in "About the Journal" under "Journal Info" contacts (http://journals.lww.com/eurojgh/), or if unsatisfied to COPE (www.publicationethics.org).

Aims and scope

The *European Journal of Gastroenterology & Hepatology* publishes papers reporting original clinical and scientific research which are of a high standard and which contribute to the advancement of knowledge in the field of gastroenterology and hepatology. The journal publishes four types of manuscripts: in-depth reviews by invitation only, original papers, case reports and letters to the Editor.

Table of contents

Points to consider before submission

Redundant or duplicate publication

Conflicts of interest

Permissions to reproduce previously published material

Patient consent forms

Ethics committee approval

Authorship

Compliance with NIH and Other Research Funding Agency Accessibility Requirements

Copyright assignment

Submissions

Presentation of Papers

- Title Page
- Abstracts
- Keywords
- Text
- Acknowledgements
- References
- Tables
- Illustrations
- Legends for illustrations
- Units of measurement
- Abbreviations and symbols
- Supplemental Digital Content
- Offprints
- Letters to the Editor

Points to consider before submission

Please think carefully about the following points and make the appropriate declarations.

Redundant or duplicate publication

We ask you to confirm that your paper has not been published in its current form or a substantially similar form (in print or electronically, including on a web site), that it has not been accepted for publication elsewhere, and that it is not under consideration by another publication. The International Committee of Medical Journal Editors has provided details of what is and what is not duplicate or redundant publication (www.icmje.org). If you are in doubt (particularly in the case of material that you have posted on a web site), we ask you to proceed with your submission but to include a copy of the relevant previously published work or work under consideration by other journals. In your covering letter to the editors, draw attention to any published work that concerns the same patients or subjects as the present paper.

Conflicts of interest

Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading “Conflicts of Interest and Source of Funding:”. For example:

Conflicts of Interest and Source of Funding: A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organization Y, and is on the speaker’s bureau for Organization X – the CME organizers for Company A. For the remaining authors none were declared.

In addition, each author must complete and submit the journal’s copyright transfer agreement, which includes a section on the disclosure of potential

conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” (www.icmje.org/update.html). The form is readily available on the manuscript submission page www.editorialmanager.com/ejgh and can be completed and submitted electronically. Please note that authors may sign the copyright transfer agreement form electronically. For additional information about electronically signing this form, go to http://links.lww.com/ZUAT/A106.

Permissions to reproduce previously published material

Authors should include with their submission copies of written permission to reproduce material published elsewhere (such as illustrations) from the copyright holder. Authors are responsible for paying any fees to reproduce material.

Patient consent forms

Patients have a right to privacy that should not be infringed without informed consent. Identifying details (written or photographic) should be omitted if they are not essential, but patient data should never be altered or falsified in an attempt to attain anonymity. Complete anonymity is difficult to achieve, and a consent form should be obtained if there is any doubt. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. When informed consent has been obtained it should be indicated in the published article.

A statement to the effect that such consent had been obtained must be included in the ‘Methods’ section of your paper and an example of the consent form you used must be uploaded with your manuscript.

Ethics committee approval

You must state clearly in your submission in the Methods section that you conducted studies on human participants must with the approval of an

appropriate named ethics committee. Please also look at the latest version of the Declaration of Helsinki. Clinical studies should be in accordance with the latest publication of ‘Good Clinical Practice’. Similarly, you must confirm that experiments involving animals adhered to ethical standards and must state the care of animal and licensing guidelines under which the study was performed.

Authorship

All authors must sign copyright forms accompanying their submission to confirm that they have read and approved the paper, that they have met the criteria for authorship as established by the International Committee of Medical Journal Editors, that they believe that the paper represents honest work, and that they are able to verify the validity of the results reported.

Compliance with NIH and Other Research Funding Agency Accessibility Requirements

A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The Copyright Transfer Agreement provides the mechanism.

Copyright assignment

Papers are accepted for publication on the understanding that exclusive copyright in the paper is assigned to the Publisher. Authors are asked to submit signed copyright assignment form with their paper. They may use material from their paper in other works published by them after seeking formal permission.

Submissions

All manuscripts and materials must be submitted through the web-based tracking system at https://www.editorialmanager.com/ejgh/. The site contains instructions and advice on how to use the system. Authors should NOT in addition then post a hard copy submission to the editorial office, unless you are supplying artwork, letters or files that cannot be submitted electronically, or have been instructed to do so by the editorial office. For those authors who have no option but to submit by mail please contact the Editorial Office editorial.office@wolterskluwer.com. Submitted articles undergo a preliminary review by the editors. Some articles may be returned to authors without further consideration. Those being considered for publication will undergo further assessment and peer-review by the editors and those invited to do so from the board and reviewer pool.

Double spacing should be used throughout the manuscript, which should include the following sections, each starting on a separate page: title page, abstract and keywords, text, acknowledgements, references, individual tables and captions. Margins should be not less than 3 cm. Pages should be numbered consecutively, beginning with the Title Page, and the page number should be placed in the top right hand corner of each page. Abbreviations should be defined on their first appearance in the text; those not accepted by international bodies should be avoided.

Before submitting to the journal make sure you have provided:

- information whether submission contains previously published material
- conflicts of interest
- patient’s consent forms
- approval from the local Ethics Committee
- description of authors contributions to the study
- information who performed statistical analysis

Presentation of Papers

Title Page

The Title Page should carry the full title of the paper and a short title, of no more than 45 characters and spaces, to be used as a ‘running head’ (and which should be so identified). The first name, middle initial and last name of each author should appear. If the work is to be attributed to a department or institution, its full name should be included. Any disclaimers should appear on the Title Page, as should the name and address of the author responsible for correspondence concerning the manuscript and the name and address of the author to whom requests for reprints should be made. Finally, the Title Page should include a statement of conflicts of interest and source of funding, and when none state “none declared”.

Abstracts

The second page should carry a structured abstract of no more than 250 words for in-depth reviews and original papers. Case reports and letters to the editor should not have an abstract. The abstract should state the Objective(s) of the study or investigation, basic Methods (selection of study subjects or laboratory animals; observational and analytical methods), main Results (giving specific data and their statistical significance, if possible), and the principal Conclusions. It should emphasise new and important aspects of the study or observations.

Keywords

The abstract should be followed by a list of 3–10 keywords or short phrases which will assist the cross-indexing of the article and which may be published. When possible, the terms used should be from the Medical Subject Headings list of the National Library of Medicine (http://www.nlm.nih.gov/mesh/meshhome.html).

Text

Full papers of an experimental or observational nature may be divided into

sections headed Introduction, Methods (including ethical and statistical information), Results and Discussion (including a conclusion), although reviews may require a different format.

Word limit for original studies and reviews is 5000 words, case reports 3.500 words and letters 1500 words (tables and figures are not counted).

Acknowledgements

Acknowledgements should be made only to those who have made a substantial contribution to the study. Authors are responsible for obtaining written permission from people acknowledged by name in case readers infer their endorsement of data and conclusions.

References

References should be numbered consecutively in the order in which they first appear in the text. They should be assigned Arabic numerals, which should be given in brackets, e.g. [17]. References should include the names of all authors when six or fewer; when seven or more, list only the first six names and add *et al.*References should also include full title and source information. Journal names should be abbreviated as in MEDLINE (NLM Catalog, http://www.ncbi.nlm.nih.gov/nlmcatalog).

Articles in journals

Standard journal article:

Simopoulos AP. The traditional diet of Greece and cancer. *Eur J of Cancer Prev* 2004;**13**:219-230.

Tan MP, Newton JL, Chadwick TJ, Gray JC, Nath S, Parry SW. Home orthostatic training in vasovagal syncope. *Europace* 2010;**12**:240–246.

More than six authors:

Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, Schindlbeck N, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. *Hepatology* 2003;**37**:443–451.

Supplements:

Matthews G, Kronborg IJ, Dore GJ. Treatment for hepatitis C virus infection among current injection drug users in Australia. *Clin Infect Dis* 2005;**40**(Suppl 5):S325–S329

Books

Book:

Whitehead WE, Schuster MM. Gastrointestinal Disorders. *Behavioral and Physiological Basis for Treatment*. Orlando: Academic Press; 1985.

Chapter in a book:

Dancygier H, Lightdale CJ, Stevens PDDancygier H, Lightdale CJ. *Endoscopic ultrasonography of the upper gastrointestinal tract and colon. Endosonography in gastroenterology: principles, techniques, findings*. 1999 Stuttgart Thieme Verlag:13–175.

Online

Snyder CL, Young DO, Green PHR, Taylor AKPagon RA, Bird TC, Dolan CR, Stephens K. Celiac disease GeneReviews [Online, 03 July 2008]. 1993 Seattle University of Washington.

Personal communications and unpublished work should not feature in the reference list but should appear in parentheses in the text. Unpublished work accepted for publication but not yet released should be included in the reference list with the words ‘in press’ in parentheses beside the name of the journal concerned. References must be verified by the author(s) against the original documents.

Tables

Each table should be typed on a separate sheet in double spacing. Tables should not be submitted as photographs. Each table should be assigned an Arabic numeral, e.g. (Table 3) and a brief title. Vertical rules should not be used. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all non-standard abbreviations that are used in each table. Identify statistical

measures of variations, such as standard deviation and standard error of the mean.

Be sure that each table is cited in the text. If you use data from another published or unpublished source, obtain permission and acknowledge the source fully.

Illustrations

A) Creating Digital Artwork

1. Learn about the publication requirements for Digital Artwork: http://links.lww.com/ES/A42
2. Create, Scan and Save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).
3. Upload each figure to Editorial Manager in conjunction with your manuscript text and tables.

B) Digital Artwork Guideline Checklist

Here are the basics to have in place before submitting your digital artwork:

- Artwork should be saved as TIFF, EPS, or MS Office (DOC, PPT, XLS) files. High resolution PDF files are also acceptable.
- Crop out any white or black space surrounding the image.
- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi. If created in an MS Office program, send the native (DOC, PPT, XLS) file.
- Photographs, radiographs and other halftone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.

Remember:

- Cite figures consecutively in your manuscript using Arabic numerals in parentheses, e.g. (Fig. 2).
- Number figures in the figure legend in the order in which they are discussed.
- Upload figures consecutively to the Editorial Manager web site and enter figure numbers consecutively in the Description field when uploading the files.
- If hard copies are submitted they should have a label pasted to the back bearing the figure number, the title of the paper, the author's name and a mark indicating the top of the figure.
- Illustrations should be presented to a width of 82 mm or, when the illustration demands it, to a width of 166 mm.
- Photomicrographs must have internal scale markers.
- If photographs of people are used, their identities must be obscured or the picture must be accompanied by written consent to use the photograph.
- If a figure has been published before, the original source must be acknowledged and written permission from the copyright holder for both print and electronic formats should be submitted with the material. Permission is required regardless of authorship or publisher, except for documents in the public domain.
- Figures may be reduced, cropped or deleted at the discretion of the editor. Colour illustrations are acceptable but authors will be expected to cover the extra reproduction costs (for current charges, contact the publisher).

Legends for illustrations

Captions should be typed in double spacing, beginning on a separate sheet of paper. Each one should have an Arabic numeral corresponding to the illustration to which it refers. Internal scales should be explained and staining methods for photomicrographs should be identified.

Units of measurement

Measurements of length, height, weight, and volume should be reported in metric units (metre, kilogram, or litre) or their decimal multiples. Temperatures should be given in degrees Celsius. Blood pressures should be given in millimetres of mercury.

All haematologic and clinical chemistry measurements should be reported in the metric system in terms of the International System of Units (SI). Editors may request that alternative or non-SI units be added by the authors before publication.

Abbreviations and symbols

Use only standard abbreviations. Avoid abbreviations in the title and abstract. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

Supplemental Digital Content

Supplemental Digital Content (SDC): Authors may submit SDC via Editorial Manager to LWW journals that enhance their article's text to be considered for online posting. SDC may include standard media such as text documents, graphs, audio, video, etc. On the Attach Files page of the submission process, please select Supplemental Audio, Video, or Data for your uploaded file as the Submission Item. If an article with SDC is accepted, our production staff will create a URL with the SDC file. The URL will be placed in the call-out within the article. SDC files are not copy-edited by LWW staff, they will be presented digitally as submitted. For a list of all available file types and detailed instructions, please visit http://links.lww.com/A142.

SDC Call-outs

Supplemental Digital Content must be cited consecutively in the text of the submitted manuscript. Citations should include the type of material submitted (Audio, Figure, Table, etc.), be clearly labeled as "Supplemental Digital Content," include the sequential list number, and provide a description of the supplemental content. All descriptive text should be included in the call-out as it will not appear elsewhere in the article.

Example:
We performed many tests on the degrees of flexibility in the elbow (see Video, Supplemental Digital Content 1, which demonstrates elbow flexibility) and found our results inconclusive.

List of Supplemental Digital Content

A listing of Supplemental Digital Content must be submitted at the end of the manuscript file. Include the SDC number and file type of the Supplemental Digital Content. This text will be removed by our production staff and not be published.
Example:
Supplemental Digital Content 1.wmv

SDC File Requirements

All acceptable file types are permissible up to 10 MBs. For audio or video files greater than 10 MBs, authors should first query the journal office for approval. For a list of all available file types and detailed instructions, please visit http://links.lww.com/A142.

Offprints

Offprints may be purchased using the appropriate form that will be made

available with proofs. Orders should be sent when the proofs are returned; orders received after this time cannot be fulfilled.

Letters to the Editor

Letters commenting on papers in EJGH will be considered for publication. They should be submitted within 4 weeks of the appearance of the original item and be 300 words, or shorter. Such letters will be passed to the authors of the original paper, who will be offered an opportunity to reply.

Letters of general interest, up to 450 words long, will be peer reviewed if they contain original data. They may contain one table, or one figure and have no more than five references and up to five authors. Proofs will be sent out on acceptance.

Please include with either category of letter a declaration of conflict of interest, if any, e.g., conflict of interest: none (or declare conflict).

Open access

LWW's hybrid open access option is offered to authors whose articles have been accepted for publication. With this choice, articles are made freely available online immediately upon publication. Authors may take advantage of the open access option at the point of acceptance to ensure that this choice has no influence on the peer review and acceptance process. These articles are subject to the journal's standard peer-review process and will be accepted or rejected based on their own merit.

Authors of accepted peer-reviewed articles have the choice to pay a fee to allow perpetual unrestricted online access to their published article to readers globally, immediately upon publication. The article processing charge for *European Journal of Gastroenterology & Hepatology* is $2,000. The article processing charge for authors funded by the Research Councils UK (RCUK) is $2,540. The publication fee is charged on acceptance of the article and should be paid within 30 days by credit card by the author, funding agency or institution. Payment must be received in full for the article to be published open

access. Any additional standard publication charges, such as for color images, will also apply.

Authors retain copyright

Authors retain their copyright for all articles they opt to publish open access. Authors grant LWW a license to publish the article and identify itself as the original publisher.

Creative Commons license

Articles opting for open access will be freely available to read, download and share from the time of publication. Articles are published under the terms of the Creative Commons License Attribution-NonCommerical No Derivative 3.0 which allows readers to disseminate and reuse the article, as well as share and reuse of the scientific material. It does not permit commercial exploitation or the creation of derivative works without specific permission. To view a copy of this license visit: http://creativecommons.org/licenses/by-nc-nd/3.0.

Compliance with NIH, RCUK and other research funding agency accessibility requirements

A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW identifies to the National Library of Medicine (NLM) articles that require deposit and transmits the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The revised Copyright Transfer Agreement provides the mechanism. LWW ensures that authors can fully comply with the public access requirements of major funding bodies worldwide. Additionally, all authors who choose the open access option will have their final published article deposited into PubMed Central.

RCUK funded authors can choose to publish their paper as open access with the payment of an article process charge, or opt for their accepted manuscript to be deposited (green route) into PMC with an embargo.

With both the gold and green open access options, the author will continue to sign the Copyright Transfer Agreement (CTA) as it provides the mechanism for LWW to ensure that the author is fully compliant with the requirements. After signature of the CTA, the author will then sign a License to Publish where they will then own the copyright.

It is the responsibility of the author to inform the Editorial Office and/or LWW that they have RCUK funding. LWW will not be held responsible for retroactive deposits to PMC if the author has not completed the proper forms.

FAQ for open access

http://links.lww.com/LWW-ES/A48

6 ARTIGO PUPLICADO NO *EUROPEAN JOURNAL OF GASTROENTEROLOGY & HEPATOLOGY*

Delayed hypersensitivity reaction after initial dose of infliximab: a case report

Anna Krajcovicova, Tibor Hlavaty, Zuzana Zelinkova, Juraj Letkovsky and Martin Huorka

We report here an unusual case of delayed hypersensitivity reaction in a young woman with ulcerative colitis after the first administration of infliximab (IFX). The patient developed severe serum-sickness-like reaction, and her anti-IFX antibody titer increased rapidly after a single infusion of IFX. The possible reason for the delayed hypersensitivity reaction to a single IFX exposure might be the presensitization of the patient by murine antigens as she had been keeping mice and hamsters as pets for several years. *Eur J Gastroenterol Hepatol* **26:485–487** © **2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

European Journal of Gastroenterology & Hepatology 2014, 26:485–487

Keywords: delayed hypersensitivity reaction, infliximab, ulcerative colitis

Gastroenterology Unit, Department of Internal Medicine V., University Hospital Bratislava, Bratislava, Slovakia

Correspondence to Anna Krajcovicova, MD, Gastroenterology Unit, Department of Internal Medicine V., University Hospital Bratislava, Ruzinovska 6, SK-82606 Bratislava, Slovakia
Tel: +421 2 48 234 905; fax: +421 2 48 234 162;
e-mail: krajann@hotmail.com

Received 29 October 2013 **Accepted** 8 January 2014

Introduction

Infliximab (IFX) is a chimeric murine–human IgG1 monoclonal antibody against tumor necrosis factor-α composed of human constant and murine variable regions. It represents a valuable drug in the treatment of a variety of immune-mediated diseases including inflammatory bowel disease (IBD). As a foreign protein, it has the potential to cause acute and delayed hypersensitivity reactions. We report here a case of unusual delayed hypersensitivity reaction after IFX initialization in a 20-year-old female patient with ulcerative colitis.

Case report

A 20-year-old nonsmoking woman with steroid-dependent ulcerative pancolitis since 2001 presented at the IBD Centre of the Department of Internal Medicine, Division of Gastroenterology and Hepatology, University Hospital Bratislava. Her history revealed primary sclerosing cholangitis and seasonal allergic rhinoconjunctivitis. She did not tolerate the treatment with 5-aminosalicylates because of nausea and vomiting and developed acute pancreatitis to immune-suppressive treatment with azathioprine and cyclosporine. Because of steroid-dependent colitis, treatment with IFX was initiated. She was premedicated with 200 mg hydrocortisone and received her first IFX infusion at a dose of 5 mg/kg without acute complications. However, she was seen at the Emergency Unit 3 days later with a report of shivering, heart palpitations, nausea, vomiting, flu-like symptoms, rhinitis, and general weakness. She had no fever, headache, cough, or rash. Physical examination revealed pain in the left hypogastrium and right hemithorax. Blood tests showed modest leukocytosis (10.6×10^9/l), neutrophilia (8.3×10^9/l), elevated platelet count (565×10^9/l), and relative lymphocytopenia (10.5%). Electrolytes, liver and renal function tests, amylase, myocardial-specific markers, C-reactive protein, and hemostatic parameters were all within the normal range. Her ECG at the time of examination and the chest radiograph were unremarkable. After a few hours of monitoring, her symptoms resolved and she was discharged. Over the next 2 days, she experienced several flares of shivering lasting a few minutes that disappeared spontaneously. Ten days later, she presented at the outpatient clinic in perfect health without any complaints. On further interrogation, she mentioned that she was keeping mice and hamsters as domestic pets and suffered bites and scratches from these animals at least once a month. Two weeks after the administration of IFX, anti-IFX antibodies (ATI) of the IgG group were assessed by Q-INFLIXI ELISA Quantitative Analyses (Matriks Biotek, Ankara, Turkey) and their levels were below the detection limit, whereas the levels of IFX were at a therapeutic concentration of 7.1 μg/ml. Four weeks later the level of IFX had decreased to 2.8 μg/ml with ATI increasing to 15.2 IU/ml. Because of continuous disease activity, treatment with adalimumab was initiated. The patient did not respond to adalimumab and therefore was continued on low-dose corticosteroids.

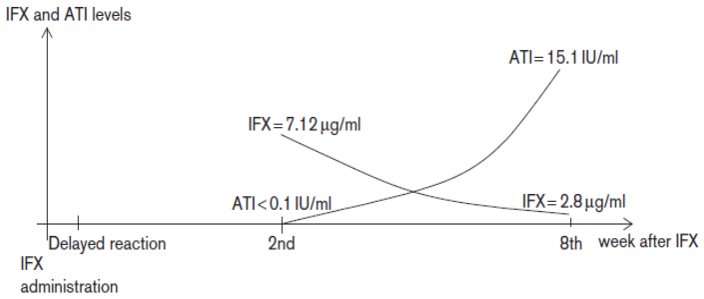
Discussion

IFX therapy has proven its efficacy in the treatment of Crohn's disease and ulcerative colitis [1–3]. To date, several large series assessing the long-term safety profile of IFX in clinical practice have reported its overall good tolerance [4–7], but hypersensitivity reactions occur in 3–13% of patients [4,6,8,9]. Infusion reactions that occur within the first 24 h are classified as acute anaphylactic-like reactions and have also been described during or after the first administration. It is assumed that these reactions are mostly non-IgE-mediated and are a result of direct degranulation and activation of mast cells [10,11]. There

0954-691X © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins

DOI: 10.1097/MEG.0000000000000049

Fig. 1



Course of first infliximab (IFX) administration and associated delayed reaction with development of antibodies to infliximab (ATI).

are case reports of anaphylactic reactions of type I hypersensitivity caused by release of histamine and other cytokines from mast cells mediated by IgE [12–14].

In contrast, delayed reactions occur 24 h to 14 days after an infusion and imitate serum sickness, a type III hypersensitivity reaction [15]. These tend to be associated with episodic therapy that predisposes to the development of antibodies to IFX (ATI) [11] and are generally reported only after repetitive treatment with IFX. So far, there has been only one case of delayed hypersensitivity reaction occurring after the first IFX infusion [16]. The pathogenesis of these delayed reactions is not fully understood, but the development of antibodies to the murine component of IFX seems to play a role. Several groups have shown that the development of antibodies to IFX correlates with increased risk of delayed hypersensitivity infusion reactions, as well as decreased drug concentration and clinical response [9,17–19]. However, the kinetics of ATI development are unexplored as trials are mainly focused on the clinical implications of antibodies to IFX.

Nonetheless, it has been shown that sera from healthy controls contain anti-animal antibodies that can arise from iatrogenic and noniatrogenic causes. These antibodies also include antibodies against murine immunoglobulins that interfere with mouse monoclonal antibody-based two-site assays causing their false-positive outcome [20]. In a recent study, Steenholdt and colleagues [21] have shown that pre-existing anti-murine antibodies reacting with the Fab region of IFX are present in healthy controls as well as in IBD patients naive to IFX. High titers of these antibodies were associated with poorer efficacy and safety responses to IFX therapy. Moreover, patients who experienced infusion reactions had significantly higher levels of anti-murine antibodies in comparison with patients with long-term remission on IFX [21].

The latter might be the case of the patient in this study who unusually developed ATI after the first exposure to IFX. This rapid immunization might result from sensitization of her immune system to murine antigens during bites and scratches and may be the underlying cause of this delayed hypersensitivity reaction occurring after IFX initialization (Fig. 1).

To the best of our knowledge, this is the first reported case of a patient who developed delayed hypersensitivity reaction after the first administration of IFX with a documented history of rearing mice. Considering the history of rearing of mice and hamsters, we hypothesize that the patient had developed anti-murine antibodies during contact with her rodent pets before the therapy administration and that these antibodies had cross-reacted with the murine part of IFX. Therefore, clinical questioning should include hamster/mouse exposure as a potential risk of immunogenicity. While considering the retreatment of patients with IFX who have had an infusion reaction, precaution should be taken to diminish the chance of infusion reaction, taking account of premedication, immunosuppressive comedication, and adjustment of the schedule and dosage of infusions.

Conclusion

Previous exposure to mice or hamsters might immunize and precondition the patient to delayed hypersensitivity reaction to IFX even after the first infusion administration.

Acknowledgements

Conflicts of interest

Zuzana Zelinkova has served as a consultant for Ferring and received speaker fees from Abbvie and MSD. For the remaining authors there are no conflicts of interest.

References

1 Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007; **369**:1641–1657.

2 Armuzzi A, Pugliese D, Danese S, Rizzo G, Felice C, Marzo M, *et al*. Infliximab in steroid-dependent ulcerative colitis: effectiveness and predictors of clinical and endoscopic remission. *Inflamm Bowel Dis* 2013; **19**:1065–1072.

3 Blonski W, Buchner AM, Lichtenstein GR. Inflammatory bowel disease therapy: current state-of-the-art. *Curr Opin Gastroenterol* 2011; **27**:346–357.
4 Zabana Y, Domenech E, Manosa M, Garcia-Planella E, Bernal I, Cabre E, *et al.* Infliximab safety profile and long-term applicability in inflammatory bowel disease: 9-year experience in clinical practice. *Aliment Pharmacol Ther* 2010; **31**:553–560.
5 Wee J, Petrof G, Jackson K, Barker J, Smith C. Infliximab for the treatment of psoriasis in the UK: 9 years' experience of infusion reactions at a single centre. *Br J Dermatol* 2012; **167**:411–416.
6 Seminerio JL, Loftus EV Jr, Colombel JF, Thapa P, Sandborn WJ. Infliximab for Crohn's disease: the first 500 patients followed up through 2009. *Dig Dis Sci* 2013; **58**:797–806.
7 Miehsler W, Novacek G, Wenzl H, Vogelsang H, Knoflach P, Kaser A, *et al.* A decade of infliximab: the Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease. *J Crohns Colitis* 2010; **4**:221–256.
8 Fidder H, Schnitzler F, Ferrante M, Noman M, Katsanos K, Segaert S, *et al.* Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009; **58**:501–508.
9 Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, *et al.* A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2007; **56**:e1–e15.
10 Steenholdt C, Svenson M, Bendtzen K, Thomsen OO, Brynskov J, Ainsworth MA. Acute and delayed hypersensitivity reactions to infliximab and adalimumab in a patient with Crohn's disease. *J Crohns Colitis* 2012; **6**:108–111.
11 Steenholdt C, Svenson M, Bendtzen K, Thomsen OO, Brynskov J, Ainsworth MA. Severe infusion reactions to infliximab: aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **34**:51–58.
12 Chavez-Lopez MA, Delgado-Villafana J, Gallaga A, Huerta-Yanez G. Severe anaphylactic reaction during the second infusion of infliximab in a patient with psoriatic arthritis. *Allergol Immunopathol (Madr)* 2005; **33**:291–292.
13 Stallmach A, Giese T, Schmidt C, Meuer SC, Zeuzem SS. Severe anaphylactic reaction to infliximab: successful treatment with adalimumab – report of a case. *Eur J Gastroenterol Hepatol* 2004; **16**:627–630.
14 Kolho KL, Ruuska T, Savilahti E. Severe adverse reactions to infliximab therapy are common in young children with inflammatory bowel disease. *Acta Paediatr* 2007; **96**:128–130.
15 Cheifetz A, Mayer L. *Monoclonal antibodies, immunogenicity, and associated infusion reactions*. New York, NY, USA: Mount Sinai Medical Center; 2005.
16 Ally MR, Betteridge JD, Veerappan GR. Delayed hypersensitivity reaction with infliximab: unusual to occur after initial dose. *Inflamm Bowel Dis* 2012; **18**:E1592–E1593.
17 Afif W, Loftus EV Jr, Faubion WA, Kane SV, Bruining DH, Hanson KA, *et al.* Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010; **105**:1133–1139.
18 Ainsworth MA, Bendtzen K, Brynskov J. Tumor necrosis factor-alpha binding capacity and anti-infliximab antibodies measured by fluid-phase radioimmunoassays as predictors of clinical efficacy of infliximab in Crohn's disease. *Am J Gastroenterol* 2008; **103**:944–948.
19 Regueiro M, Siemanowski B, Kip KE, Plevy S. Infliximab dose intensification in Crohn's disease. *Inflamm Bowel Dis* 2007; **13**:1093–1099.
20 Kricka LJ. Human anti-animal antibody interferences in immunological assays. *Clin Chem* 1999; **45**:942–956.
21 Steenholdt C, Palarasah Y, Bendtzen K, Teisner A, Brynskov J, Teisner B, *et al*. Pre existing IgG antibodies cross reacting with the Fab region of infliximab predict efficacy and safety of infliximab therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **37**:1172–1183.