9. ANEXOS

Anexo 1: Termo de Consentimento Livre e Esclarecido aprovado pelo Comitê de Ética em Pesquisa da PUCPR e Parecer CEP-PUC 53/7 de 07/03/2007

Número do prontuário:_____ Número da Ficha:_____

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Estudo de Fatores de Riscos Genéticos de Susceptibilidade do Hospedeiro à Hanseníase

A Pontifícia Universidade Católica do Paraná (PUCPR) estará realizando um estudo que irá investigar o papel da genética na susceptibilidade à hanseníase (lepra) e na gravidade da doença. Se bem sucedido, o projeto poderá facilitar o tratamento da hanseníase e melhorar a qualidade de vida dos pacientes, seus familiares e pessoas próximas. Este estudo será coordenado por Dr. Marcelo Távora Mira, professor adjunto e pesquisador do programa de Pós-Graduação em Ciências da Saúde da PUCPR.

1) Métodos

Se você concordar em participar neste estudo, você será submetido a um exame médico e coleta de uma amostra de sangue de seu antebraço, com uma agulha nova e descartável, após assepsia local (limpeza). A amostra de sangue será usada para extração de ácidos nucléicos (DNA, seu material genético). O DNA será enviado a um laboratório para um teste chamado "genotipagem" que irá permitir aos cientistas estudar as características genéticas que tornam mais fácil para alguns indivíduos e seus familiares contrair hanseníase e desenvolver os diferentes tipos clínicos da doença. Sob sua autorização, informações de prontuários clínicos também poderão ser lidas pelos cientistas e utilizadas no estudo.

2) Local do estudo

Os procedimentos descritos acima serão realizados parte na Unidade Básica de Saúde local ou no Hospital Santa Casa de Misericórdia da PUCPR, (avaliação clínica e coleta sanguínea), parte nos laboratórios da PUCPR e instituições associadas (testes laboratoriais). Colaboração entre a PUCPR e outros institutos de pesquisa deverão aumentar as chances de sucesso e o impacto do estudo. Portanto, está sendo requerida sua autorização para o uso de sua amostra em estudos da hanseníase envolvendo outras instituições. Sua autorização só valerá sob a condição de se manter o desenho, objetivos e metodologia do projeto original, além da avaliação e aprovação de eventuais alterações pelo Comitê de Ética da PUCPR.

3) Permissão para estocagem

Está sendo solicitada a sua permissão para estocagem da sua amostra de DNA na PUCPR. Se assinar esse termo de consentimento, você está autorizando estocagem de longo prazo de sua amostra de DNA. Sua amostra de DNA será mantida indefinidamente. Isto significa que sua amostra não será destruída após um determinado período de tempo, mas sim será estocada pelo tempo que ela durar. Embora pequenas quantidades

de sua amostra possam ser enviadas a instituições colaboradoras para análise, não haverá estocagem de amostras em outras instituições além da PUCPR. Amostras estocadas serão usadas exclusivamente para fins de pesquisa. Amostras estocadas poderão ser utilizadas para estudos adicionais de susceptibilidade à hanseníase. Nenhuma outra doença será investigada. O uso da sua amostra estocada terá como condição uma nova avaliação e aprovação do projeto de pesquisa pelo Comitê de Ética pertinente.

4) Riscos Físicos para Saúde/Desconfortos

Os riscos físicos para saúde de participação neste estudo são muito pequenos e limitados ao procedimento de coleta de sangue. Durante a coleta de sangue, você poderá sentir um desconforto temporário devido a introdução da agulha. A coleta de sangue poderá resultar em uma pequena lesão que quase sempre cura-se sozinha. Em raros casos, pode ocorrer infecção localizada.

5) Tratamento e Compensação por Danos

Se você desenvolver infecção localizada devido ao procedimento de coleta de sangue, o tratamento será providenciado pela PUCPR. O custo deste tratamento será totalmente coberto pelo projeto.

6) Alternativas

Se você estiver afetado por hanseníase, acesso a procedimentos médicos para diagnóstico e tratamento da doença será providenciado mesmo que não queira participar do estudo. Portanto, se você decidir não participar, ou cessar sua participação no estudo a qualquer momento, todos os procedimentos para diagnósticos e tratamento médico serão mantidos pelo Hospital Santa Casa de Misericórdia da PUCPR e instituições colaboradoras.

Se você não estiver afetado pela hanseníase, você está sendo convidado a participar do estudo como parte do grupo controle ou como familiar do afetado. Neste caso, sua decisão de participar ou não, ou de cessar sua participação a qualquer momento, não irá interferir de nenhuma forma nos procedimentos médicos para diagnóstico ou tratamento da hanseníase que você possa necessitar no futuro. Da mesma forma, sua decisão não irá refletir no acesso a procedimentos médicos necessários à algum familiar ou contato afetado pela hanseníase.

7) Custos para os participantes

No caso de você decidir participar do estudo, você não terá nenhum custo. Custos com testes laboratoriais e análises de suas amostras para propósito de pesquisa serão cobertos pelo estudo.

Número do prontuário:_____ Número da Ficha:_____

8) Benefícios

A longo prazo, os procedimentos médicos e laboratoriais aos quais você será submetido poderão facilitar a detecção de resistência ao tratamento da hanseníase, tornando possível evitar tratamentos inadequados. Além disso, espera-se que conhecimentos científicos adicionais sejam alcançados, com conseqüente melhoria do tratamento de pessoas afetadas pela hanseníase.

9) Reembolso

Você não será reembolsado por participar deste estudo.

10) Exclusividade do uso do material genético

Amostras de DNA SERÃO UTILIZADAS APENAS PARA PESQUISA DE SUSCEPTIBILIDADE À HANSENÏASE. Nenhuma outra doença será estudada. Se, devido a situações imprevistas, os pesquisadores descobrirem alguma informação relacionada a susceptibilidades que não à hanseníase, você será aconselhado a procurar seu médico para um exame completo. Você não terá acesso a nenhuma informação genética específica que nós produzirmos. Todos os resultados obtidos no estudo, após análise do conjunto completo dos dados, serão publicado em artigos científicos. Como estes dados publicados serão usados por outros investigadores é desconhecido. Importante reafirmar, o alvo de nossos estudos é a identificação do fator de risco genético à hanseníase.

11) Confidenciabilidade dos dados

A participação em projetos de pesquisa pode resultar em perda de privacidade. Além disso, a descoberta de fatores de risco genéticos para hanseníase podem expor susceptibilidades de certos grupos de pessoas, possivelmente levando a outros ou certas empresas a considerar estes grupos diferentes de uma forma negativa. Entretanto, procedimentos serão adotados pelos responsáveis por este estudo no intuito de proteger a confidencialidade das informações que você fornecer e as informações produzidas pelo projeto. Nenhuma informação genética individual será tornada pública. As informações serão codificadas e mantidas num local reservado o tempo todo. Somente os pesquisadores envolvidos neste estudo terão acesso às informações. Após o término deste estudo, as informações serão transcritas dos questionários para arquivos de computador, mantidos em local restrito com acesso premitido apenas aos mesmos pesquisadores. Os dados deste estudo poderão ser discutidos com pesquisadores de outras instituições, mas nenhuma identificação será fornecida.

Número do prontuário:_____ Número da Ficha:_____

CONSENTIMENTO

Estudo de Fatores de Riscos Genéticos de Susceptibilidade do Hospedei à Hanseníase

Você receberá uma cópia deste Termo de Consentimento para mantê-lo consigo. Se vo tiver qualquer duvida no futuro sobre a sua participação neste estudo, você pode e de utilizar os seguintes meios de contato com o pesquisador responsável:

Dr.
Marcelo Távora Mira
Telefone: (41) 3271-2618
Celular: (41) 9164-4045
E-mail: m.mira@pucpr.br

A PARTICIPAÇAO EM PESQUISA É VOLUNTARIA

Você tem o direito de não concordar em participar ou mesmo de se retirar do estu em qualquer momento que queira, sem riscos para o seu tratamento médico. Se vo desejar e concordar em participar, deve assinar ou fornecer sua impressão digital na lir apropriada abaixo.

Se você desejar participar do estudo, permitirá que seu endereço e telefone seja anotados em uma folha separada, para facilitar contato quando necessário. Como já esclarecida anteriormente, toda informação, pessoal será mantida em sigilo.

_____ _____
Assinatura ou impressão digital do voluntário Nome completo e nº do prontuário

_____ _____
Assinatura do entrevistador Nome do entrevistador

_____ _____
Assinatura testemunha 1 Assinatura testemunha 2

_____/_____/_____
Data

ANEXO 2: Declaração de doação de *M. leprae*.
"Biological Material Transfer Agreement"

Biological Material Transfer Agreement - Colorado State University (CSU)
This page is best viewed with Internet Explorer 5 or higher. Choose **File** > **Print** in browser.

Colorado State University
Knowledge to Go Places

Recipient Scientist:	Marcelo Távora Mira
Recipient Organization:	Pontifical Catholic University of Paraná
Recipient Address:	Imaculada Conceição, 1155; CCBS – PPGCS; Prado Velho, Curitiba, Paraná, Brazil. CEP: 80215-901
CSU's Provider Scientist:	Patrick J. Brennan, Ph.D/ John S. Spencer, PhD
Provider's CSU Address:	Colorado State University, Dept. of Microbiology, Immunol. & Path., 1682 Campus Delivery, Ft. Collins, CO 80523-1682 U.S.A.
Regarding Biological Material identified as:	*M. leprae* Whole Cells (non-irradiated) *M. leprae* Phenolic Glycolipid-1 (PGL-1) *M. leprae* Soluble (Cytosolic) Antigen (MLSA protein) *M. leprae* Membrane Antigen (MLMA protein) *M. leprae* Cell Wall Antigen (MLCwA protein)
Biological Material to be used for:	- affinity column; - immunization of rabbits; - electrophoresis; - Western blotting; - MDM and PBMC "in vitro" challenge for functional assays (cytokine, nitric oxide production, phagocytosis).

In response to **RECIPIENT'S** request for the above-identified Biological Material from Colorado State University (CSU), **RECIPIENT ORGANIZATION** agrees to the following terms in consideration of receipt of the Biological Material:

1. The above Biological Material is the property of CSU and is made available as a service to the Research community. Biological Material shall mean the above-referenced biological material plus progeny, unmodified derivatives, and any accompanying know-how or data.

2. The Biological Material will not be further distributed to others not affiliated with the **RECIPIENT SCIENTIST'S** laboratory without the written permission of CSU. CSU reserves the right to make the Biological Material available to others, both profit and non-profit.

3. It is understood that no right to any license of the Biological Material is given or implied by this Agreement. CSU's name will be used for no endorsements.

4. The Biological Material will be used for research purposes only.

5. If **RECIPIENT SCIENTIST** or **RECIPIENT ORGANIZATION** wishes to patent or commercialize the Biological Material or modifications, they will contact CSU prior to such use to negotiate CSU's ownership interests. Ownership will be negotiated in good faith by the parties hereto depending upon a) their relative contribution to the creation of said modifications and derivatives, and b) *any* applicable laws and regulations relating to inventorship.

6. The Biological Material is experimental in nature and **IT IS PROVIDED WITHOUT ANY WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE.**

7. The **RECIPIENT SCIENTIST** agrees to use the Biological Material in compliance with all applicable Federal, State, and local statutes and regulations. The Biological Material will not be used for *in vivo* testing in human subjects.

The **RECIPIENT SCIENTIST** and the authorized representative from the **RECIPIENT ORGANIZATION** will sign **three** copies to indicate acceptance of the above terms. **Three original** signed documents should be returned to **CSU's PROVIDER SCIENTIST** for signature and routing to: Sponsored Programs, 410 USC, Colorado State University, 2002 Campus Delivery, Fort Collins, CO 80523-2002, USA, for **PROVIDER ORGANIZATION** signature.

Direct questions to 970-491-4330.

CSU's PROVIDER SCIENTIST:	Name/Title: Patrick J. Brennan Ph.D. Signature:	Date: 11-1-08
PROVIDER ORGANIZATION'S AUTHORIZED OFFICIAL:	Betty Eckert Signature:	Date: 11/8/08
RECIPIENT SCIENTIST:	Name/Title: Marcelo Tavora Mira, PhD; Associate Professor Signature:	Date: 10/Oct/2008
RECIPIENT ORGANIZATION REPRESENTATIVE:	Name/Title: Waldemiro Gremski, PhD; Director of Research Signature:	Date: 10/Oct/2008

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ANEXO 3: ARTIGO DE REVISÃO:
"ASPECTOS GENÉTICOS DA SUSCETIBILIDADE DO HOSPEDEIRO À HANSENÍASE"

Aspectos genéticos da *(de la)* suscetibilidade do hospedeiro *(del huésped)* à hanseníase *(lepra)*

Host genetics and susceptibility to leprosy

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Geovana Brotto Ramos, Graduada, candidata a mestrado, Pontifícia Universidade Católica do Paraná, Curitiba, Brasil
Vanessa Santos Sotomaior, Doutora, Pontifícia Universidade Católica do Paraná, Curitiba, Brasil
Vinicius Medeiros Fava, Graduado, candidato a doutorado, Pontifícia Universidade Católica do Paraná, Curitiba, Brasil

Abstract

Leprosy is a chronicle infectious disease that still affects approximately 215 000 individuals worldwide. Clinical and epidemiological observations suggest that only a small proportion of the population exposed to Mycobacterium leprae *develop the disease. Today, it is known that mechanisms controlling susceptibility to leprosy phenotypes strongly depend on the genetic background of the host. This review summarizes the latest advances in the field, obtained from genetic epidemiology and functional studies.*

Key words: leprosy, leprosy clinical forms, leprosy reactions, functional studies, host genetics, polymorphisms

Bibliografía completa, especialidades médicas relacionadas, producción bibliográfica y referencias profesionales del autor.

Resumo

Hanseníase é uma doença *(enfermedad)* infecciosa crônica que ainda afeta *(afecta)* aproximadamente 215 000 pessoas em todo o mundo. Observações clínicas e epidemiológicas sugerem que apenas uma pequena parcela *(parte)* de indivíduos expostos ao *(a) Mycobacterium leprae* desenvolvem *(desarrollan)* a doença. Hoje *(Hoy)*, sabe-se que mecanismos de controle da suscetibilidade a fenótipos da doença dependem, em grande parte, das características genéticas do hospedeiro. Esta revisão oferece uma síntese dos últimos avanços obtidos na *(obtenidos en el)* área a partir de estudos genéticos epidemiológicos e funcionais.

Palavras chave: hanseníase, formas clínicas, estudos funcionais, características genéticas do hospedeiro, polimorfismos

Fatores de risco *(riesgo)* genéticos de suscetibilidade à hanseníase

A hanseníase é uma doença infecciosa crônica, causada pelo *Mycobacterium leprae,* que acomete principalmente pele *(piel)* e nervos periféricos. A doença, também conhecida como lepra, tem sido *(ha sido)* um problema de saúde ancestral para populações humanas, e apesar disso, muito pouco ainda *(aún)* se conhece sobre suas bases fisiopatológicas e epidemiológicas. Atualmente, a hanseníase ainda afeta cerca de 215 000 indivíduos em todo mundo, com a maioria dos novos casos concentrados no Brasil e na India.[1] A doença apresenta um amplo espectro de manifestações clínicas que varia de acordo com a resposta imune do hospedeiro. Em um pólo desse espectro está a forma lepromatosa, sistêmica, associada com uma resposta imunológica do tipo Th2 (humoral) e no outro, a forma tuberculóide, localizada e associada com forte resposta imune do tipo Th1 (celular).[2]

Com a identificação do bacilo causador da hanseníase no século *(siglo)* XVII por Armauer Hansen,[3] confirmou-se sua natureza infecciosa e muito da investigação científica passou a se concentrar em aspectos relativos ao agente patogênico e suas propriedades, tais *(tales)* como virulência, capacidade de indução de resposta imune e resposta ao tratamento. Contudo, observações clínicas sempre indicaram que o controle da suscetibilidade a diferentes fenótipos da doença depende de características inatas ao hospedeiro, associadas a fatores ambientais e sócio-econômicos.[4] Por exemplo, a influência de fatores genéticos no controle da hanseníase *per se* (a doença independentemente de sua forma clínica) e suas formas de manifestação clínica têm sido demonstrada em estudos de agregação familial, estudos em gêmeos *(mellizos),* análises de segregação complexa e análises de associação e ligação.[5]

Em 1988, foi realizada análise de segregação complexa em uma população da ilha caribenha Desirade. A prevalência de hanseníase na ilha era de aproximadamente 30/1 000 habitantes, uma das mais elevadas do mundo na ocasião. Os resultados do estudo rejeitaram *(rechazaron)* um modelo esporádico (não familial) e indicaram uma herança mendeliana, com um gene principal co-dominante ou recessivo controlando a suscetibilidade à doença.[6] Mais recentemente, esse achado foi *(ese hallazgo ha sido)* em parte confirmado em estudo realizado por nosso grupo, envolvendo *(involucrando)* 76 *pedigrees* correspondentes à totalidade de uma população isolada *(aislada)* e hiperendêmica (128.2/1 000 hab.) para hanseníase localizada no Pará, norte do Brasil, que também resultou na rejeição *(rechazo)* de modelo predominantemente ambiental de controle da suscetibilidade à doença.[7] Importante, este estudo revelou que o efeito *(efecto)* de gene principal encontrado foi capaz de explicar integralmente a agregação familial de casos, independentemente do compartilhamento, em uma mesma família, de variáveis não-genéticas.

Embora *(Aunque)* eficientes em indicar a existência de um controle genético da suscetibilidade à hanseníase, estes estudos observacionais são limitados em seu poder de definir a exata natureza deste efeito, como por exemplo, o número e a identidade dos genes envolvidos. Para tal, estudos genético-moleculares são necessários, e vários têm sido realizados ao longo das últimas décadas [(5)]. Como resultado, diversos genes, tais como o *VDR*,[8] *NRAMP1*,[9] *TAP*,[10] *IL10*[11] e variantes da região MHC/HLA[12] foram identificados em associação ou ligação com fenótipos da hanseníase.

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m.mira@pucpr.br

Em 2001, uma primeira varredura *(barrido)* genômica para genes de suscetibilidade à hanseníase encontrou evidência de ligação entre a região cromossômica 10p13 e hanseníase paucibacilar em uma população da India.[13] O achado foi confirmado, dois anos mais tarde, em uma coleção de famílias recrutadas no Vietnam do Sul.[15] Recentemente, uma análise realizada em uma amostrar *(muestra)* da mesma população vietnamita mostrou associação significativa entre marcadores do gene *MRC1,* localizado na região 10p13, e hanseníase *per se*.[14] Esse resultado argumenta a favor do *MRC1* como um gene de suscetibilidade a hanseníase *per se;* porém *(sin embargo),* não explica o pico de ligação observado nos estudos de ligação anteriores, exclusivo para famílias contendo indivíduos portadores da forma paucibacilar da doença. Até o momento, nenhum gene candidato emergiu de estudos envolvendo a região 10p13 e hanseníase pauci-bacilar.

O resultado mais importante da varredura genômica realizada na população vietnamita,[15] com a participação de nosso grupo, foi a localização de *loci* de suscetibilidade à hanseníase *per se* nas regiões cromossômicas 6q25-q27 e 6p21.[15,16] Estudos subsequentes, de mapeamento de alta densidade, levaram *(llevaron)* à identificação de variantes dos genes *PARK2/PARCRG*[16] e *LTA,*[17] respectivamente, como importantes fatores *(factores)* de risco para a doença. Atualmente, um dos focos de nosso trabalho está na completa dissecção do forte efeito de ligação observado entre a região cromossômica 6q25-q27 e hanseníase *per se.* Nossa expectativa é de que genes candidatos adicionais, localizados neste segmento cromossômico, serão *(van a ser)* descritos.

Recentemente, uma varredura genômica de associação *(Genome-Wide Association*, ou GWA), realizada em uma população chinesa identificou variações em sete genes –*CCDC122, CD13orf31, NOD2, TNFSF15, HLA-DR, RIPK2* e *LRRK2*– associados com a suscetibilidade à hanseníase, com resultados mais evidentes para os genes *CD13orf31, NOD2, RIPK2* e *LRRK2* e hanseníase multibacilar. Na tentativa *(En el intento)* de replicar esses achados, Wong e *col.* genotiparam, em uma população africana, os mesmos marcadores associados no estudo chinês. Foi novamente observada associação significativa entre hanseníase e os genes *C13orf31* e *CCDC122,* cujas variantes têm sido descritas como fatores de risco para doença de Crohn. Curiosamente, os achados para os genes *NOD2, RIPK2, TNFSF15* e *LRRK2* não foram replicados.[18] Segundo o pesquisador Dr. Erwin Schurr, da Universidade McGill (Montreal, Canadá), o componente genético de controle da sucetibilidade a infecções em geral é complexo, heterogêneo e modulado por fatores ambientais, como determinantes da virulência microbiana. Porém, estudos do tipo GWA, que combinam o conhecimento da sequência completa do genoma humano com o da arquitetura complexa de suas variantes mais comuns, têm se mostrado uma ferramenta poderosa para se avançar na elucidação destes fatores inatos de resistência.[19]

Genética dos estados reacionais *(reaccionales)* em hanseníase

Os estados reacionais (ER) acometem cerca de 30%-50% dos pacientes que desenvolvem hanseníase[4] e são considerados os maiores causadores de sequelas neurológicas permanentes desde que a poliquimioterapia (PQT) foi implementada pela Organização Mundial da Saúde (OMS) em 1982. Estudos demonstram que de 16% a 56% dos pacientes apresentam perda *(pérdida)* ou diminuição de função neural periférica já no diagnóstico de hanseníase,[20] em sua grande maioria devido à ocorrência *(ocurrencia)* dos ER, já *(ya)* que uma parcela considerável dos diagnósticos de ER são efetuados simultaneamente ao da doença *per se*. Estudo prospectivo realizado em uma população da India demonstrou que 39.4% de novos casos multibacilares desenvolveram ER e destes, 73% desenvolveram danos neurais previamente inexistentes.[21] Os ER ocorrem com maior freqüência durante o tratamento PQT, principalmente no primeiro ano após *(luego)* o diagnóstico,[22] mas podem aparecer anos após o término do tratamento, no entanto, com menor freqüência.[23]

Os mecanismos fisiopatológicos por trás dos ER ainda permanecem obscuros. As hipóteses mais aceitas *(aceptadas)* baseiam-se *(se basan)* na ativação de um processo inflamatório de forma repentina e exacerbada nas lesões pré-existentes e/ou em novas lesões, freqüentemente envolvendo nervos periféricos, o que requer *(que requiere)* tratamento imediato, normalmente com corticóides, a fim de se evitar danos *(daños)* neurais permanentes. Os ER podem ser divididos em dois principais grupos: a reação reversa (RR), ou reação do tipo 1, e o eritema nodoso hansênico (ENH), também conhecido como reação do tipo 2. RR e ENH diferem na forma clínica, porém, podem ocorrer em um mesmo paciente em tempos distintos.[24]

Diversos estudos evidenciam níveis circulantes aumentados de citocinas Th1, tais como o TNF-alfa, INF-gamma e IL-12, em pacientes no momento do diagnóstico de RR; (rev. em[25]). Esta observação está de acordo com a hipótese de que a RR é uma reação de hipersensibilidade tardia a antígenos do *M. leprae,* causada pela reativação da resposta imune celular do tipo Th1. Pacientes que apresentam as formas *borderline* da doença[26] tem maior propensão ao desenvolvimento de RR, provavelmente devido à instabilidade no balanço *(balance)* Th1-Th2. Outros fatores como idade, índice baciloscópico e número de lesões também estão associados à patologia.[22] Quanto ao ENH, acredita-se que *(se supone que),* por motivo ainda não esclarecido, ocorra a ativação Th1 em pacientes com resposta predominantemente Th2, levando à formação de imunocomplexos que causariam inflamação nas lesões, muitas vezes de repercussão sistêmica. O ENH acomete predominantemente pacientes do pólo lepromatoso da doença,[23] em 62.5% destes, de forma crônica.[27]

Apesar dos sinais e sintomas dos ER serem bem descritos, pouco tem sido explorada e hipótese da existência de fatores genéticos que levam ao desencadeamento do processo. Variações nos genes *TLR1* e *TLR2* vêm sendo demonstradas associadas à ER. A família de receptores TLR1, 2 e 6, envolvidos na resposta imune inata, é formada por dímeros responsáveis pelo reconhecimento de antígenos, principalmente de micobactérias.[28] Estudo realizado em uma amostra populacional etíope formada por 66 casos de RR e 150 controles demonstrou associação do *single nucleotide polymorphism* (SNP) *TLR2* rs3804099 com proteção [OR = 0.34 (0.17-0.68) p = 0.002] e um microssatélite próximo ao gene com susceptibilidade à RR [OR = 5.83 (1.98-17.15) p = 0.001].[29]

Dois SNPs não-sinônimos presentes no gene *TLR1* foram descritos associados a ER: o SNP rs5743618 (I602S) foi encontrado associado com proteção à RR [OR = 0.51 (0.29-0.87) p = 0.01] em uma população do Nepal de 206 casos de RR e 603 controles;[30] o SNP rs4833095 (N248S) está associado com ENH em uma população de Bangladesh de 656 controles e apenas 11 casos de ENL [OR = 0.40 (0.16-0.99)].[31]

Recentemente, sete dos polimorfismos do gene *NOD2* investigados na mesma população nepalense utilizada no estudo do gene *TLR1* foram demonstrados associados a RR e ENL, o de maior *(mayor)* significância para RR foi o rs8044354 [OR = 0.74 (0.59-0.92) p = 0.005] e para ENL, o rs2287195 [OR = não demonstrado; p = 0.006].[32]

Apesar dos primeiros estudos sugerindo *(sugiriendo)* um controle genético em ER, há muito ainda a ser explorado. São de suma importância novas pesquisas *(investigaciones)* com o intuito *(intento)* de elucidar o mecanismo de ação dos ER, pois mesmo *(ya que aún)* em um cenário de eliminação da hanseníase, previsto pela OMS mas vista com ceticismo por muitos especialistas,[33] os ER continuarão a ser um grave problema de saúde pública. Portanto *(Por lo tanto)*, a descrição de marcadores preditivos dos ER é um dos maiores desafios em hanseníase na atualidade. Estudos funcionais, por exemplo, podem ser uma boa ferramenta *(buena herramienta)* para contribuir na escolha *(elección)* de genes e vias candidatas à susceptibilidade a ER. Em publicação recente, o grupo liderado pela Dra. Mariane Stefani, da Universidade Federal de Goiás, Brasil, comprovou alterações, previamente descritas,[34] nos níveis de expressão de diversas citocinas e quimiocinas, tanto na RR1 quanto no ENH.[35] Genes de citocinas são bons *(son buenos)* candidatos funcionais, e vários deles estão em fase avançada de investigação, em nosso laboratório, como possíveis marcadores gênicos de risco de desenvolvimento de ER.

Genética funcional da suscetibilidade à hanseníase

Entre as diversas estratégias possíveis para investigação dos mecanismos moleculares envolvidos na patogênese da hanseníase, estudos genéticos em larga escala têm produzido *(han producido)* resultados promissores. Contudo *(Sin embargo)*, para maioria desses genes, pouco se sabe sobre suas funções no contexto da infecção por *M. leprae*. Genes candidatos, como *IL10, TNFA, LTA, MRC1* e *PARK2*, vêm sendo alvo *(objetivo)* de análises funcionais cujo objetivo é entender melhor seus papéis biológicos na fisiopatologia da doença.

O gene *IL10* codifica uma citocina imunorregulatória primariamente excretada por macrófagos ativados e células T reguladoras, envolvidas *(involucradas)* no controle da imunidade inata e imunidade mediada por células, respectivamente. Análises haplotípicas ultilizando SNPs localizados na região promotora desse gene,[11,36] bem como estudo posterior caso-controle e de meta-análise, revelaram que o alelo -819T está associado com suscetibilidade à hanseníase. Consistentemente, dosagem *(medición)* de IL-10 em sobrenadantes de células mononucleares de sangue periférico de indivíduos carreadores do alelo -819T, estimuladas com antígenos *de M. leprae*, revelou menor produção da citocina quando comparado com células com o genótipo -819C.[37]

O TNF-alfa, codificado pelo gene *TNFA*, é uma citocina principalmente produzida por monócitos/macrófagos que, diferente da IL-10, tem atividade pró-inflamatória, efetora da resposta imune inata. Na hanseníase, o TNF-alfa parece estar envolvido no controle da resistência do hospedeiro ao *M. leprae*. Estudo baseado em famílias[38] e estudos subsequentes caso-controle[39,40] sugerem que o alelo -308A da região promotora do gene *TNFA* promove proteção contra hanseníase *per se*. Contudo, outros achados divergem desse resultado, e mostram o alelo -308A associado com forte resposta inflamatória contra *M. leprae*[41] e com suscetibilidade à forma multibacilar da infecção.[42] Estudo funcional indicou que portadores do alelo -308A apresentavam uma forte reação inflamatória contra antígenos do *M. leprae* em pele. Ainda, dosagens de TNF-alfa em sobrenadante de células isoladas de biópsias de pele revelaram que pacientes classificados na forma tuberculóide expressam mais essa citocina.[43] Outro estudo funcional recente demonstrou que camundongos *(ratones) knouckout* $TNF^{-/-}$ possuem menor capacidade de controlar a infecção por *M. leprae*, já que foi observado significativo aumento no número de bacilos durante nove meses de acompanhamento a partir da inoculação do microrganismo em suas patas.[44] Tais *(Tales)* achados revelam um envolvimento importante do TNF-alfa na patogênese da hanseníase; porém, o papel exato da variação -308 ainda permanece obscuro.

Outra citocina envolvida na hanseníase, a linfotoxina alfa (LT-a) é um membro da superfamília do TNF. A função da LT-a, codificada pelo gene *LTA*, é menos conhecida em comparação com o TNF-a. Sabe-se que é *(Se sabe que constituye)* uma citocina participante na ativação de inflamação crônica, através da regulação da expressão de moléculas de adesão, bem como de outras citocinas e quimicionas importantes no recrutamento de linfócitos[45] e na resposta contra patógenos intracelulares.[46] Alcaïs *e col.* relacionaram o SNP *LTA*+80 com maior risco à hanseníase, principalmente em populações de casos jovens.[17] O papel biológico deste SNP já havia sido testado *in vitro* em linhagens de células B, transfectadas para expressar os alelos *LTA* +80A ou *LTA* +80C, revelando que o primeiro é capaz de suprimir a expressão de LT-a. Outro estudo com camundongos *knouckout* $LT\text{-}a^{-/-}$ infectados com *M. leprae* mostrou uma diminuição na ativação de células T, consequentemente uma menor resposta inflamatória na fase *(en la etapa)* crônica da infecção.[44]

Mais recentemente, estudos buscaram entender o papel biológico do gene *MRC1* na hanseníase. Esse gene codifica um receptor de manose (RM), membro da família dos receptores de superfície celular de lectina tipo-1 em humanos. Apesar dos RMs não serem *(no son)* receptores intermediários da fagocitose, são expressos em células especializadas, como macrófagos e células dendríticas. Esses receptores são capazes de reconhecer e se ligar *(y se ligan)* a padrões moleculares associados a patógenos *(pathogen-associated molecular patterns* - PAMPs), como resíduos de manose, fucose e *N*-acetil-glucosamina,[47,48] evento chave *(clave)* no desencadeamento da resposta imune inata. Alter *e* col.[14] analisaram polimorfismos do éxon 7 do gene *MRC1* em amostras de famílias de indivíduos afetados por hanseníase do Vietnam e em amostras *(muestras)* caso-controle do Brasil. Os achados revelaram o haplótipo G396-A399-F407 associado a hanseníase *per se* e à doença multibacilar. Já o haplótipo S396-A399-F407 apareceu com maior frequência no grupo controle. Os mesmos pesquisadores partiram em seguida para uma abordagem *(abordaje)* funcional, realizando ensaios de associação com células recombinantes construídas para super-expressar os haplótipos citados anteriormente. Após ensaios celulares com ligantes clássicos de MR (ovoalbumina e zimosan) e ainda com *M. leprae* e *B. bovis* BCG, não verificou-se diferenças significativas entre as variantes em relação a capacidade celular de ligação e internalização. Esses achados funcionais sugerem que o efeito desses haplótipos possa ser indireto, e que o processo de internalização do *M. leprae* ou de ou-tros patógenos dependa de outras moléculas, além dos MRs.

Um dos genes de grande interesse do nosso grupo é o *PARK2*, associado ao controle da suscetibilidade à hanseníase *per se*.[16] O gene *PARK2* codifica uma enzima

altamente conservada denominada parquina, uma ubiquitina ligase (E3) de 465 aminoácidos e 52-kDa.[49,50] A parquina é expressa em vários tecidos *(tejidos)* e tipos celulares, incluindo *(que incluyen)* os neurônios dopaminérgicos presentes na *substantia nigra* do mesencéfalo e células de Schwann do sistema nervoso periférico.[16,52] Por ser uma E3, a parquina classicamente é responsável pela ubiquitinação de proteínas-alvo, dirigindoas *(dirigiéndolas)* para degradação no proteassomo.[49,50] A ubiquitinação de proteínas, além de sinalizar para a degradação, regula diversos processos celulares, como reparo de DNA recém-replicado *(recién replicado)*, endocitose, tráfego de proteínas, degradação lisossomal, apoptose, apresentação de antígeno e transcrição.[53,54] Estudos recentes utilizando diferentes modelos celulares e animais mostram que a parquina é uma proteína multifuncional, e destacam seu papel na regulação da integridade mitocondrial frente ao estresse oxidativo e fosforilação oxidativa. Variantes do gene *PARK2* são capazes que elevar o estresse oxidativo, conseqüentemente causando danos celulares indiretos e até morte celular.[55,56]

Não se sabe quais as conseqüências biológicas da presença de variações genéticas no gene *PARK2* sobre o funcionamento das células em geral, e das células-alvo do *M. leprae* em particular. Indiretamente, a inibição do proteassomo de macrófagos infectados com *M. leprae* reduz o índice de apoptose celular, além *(además)* de alterar o perfil de produção de certas citocinas.[57] É possível que variações no gene *PARK2* alteram a função normal dos macrófagos, modificando sua resposta frente ao desafio com antígenos do *M. leprae*. Este efeito poderia ser específico ao *M. leprae*, ou pode ser comum a outros microorganismos patogênicos. Estudo genético independente demonstrou associação entre aqueles polimorfismos de *PARK2/PACRG* encontrados primeiramente nos estudos com hanseníase e a febre tifóide e paratifóide, infecções causadas pelos patógenos intracelulares *Salmonella typhi* e *Salmonella paratyphi,* respectivamente.[58] Em nosso grupo, macrófagos primários contendo mutações no gene *PARK2*, e linhagens monocíticas transfectadas com RNAs de interferência para este gene vêm sendo desafiados *(están siendo provocados)* com *M. leprae;* em seguida, ensaios funcionais são aplicados, com o objetivo de se avançar *(avanzar)* no entendimento da função da proteína parquina na resposta imunológica do hospedeiro frente ao patógeno.

Considerações finais

Ao longo *(A lo largo)* dos últimos anos, um sólido corpo de evidências acumulou-se em favor de um papel crucial da genética do hospedeiro no controle da suscetibilidade à hanseníase. Porém, esses estudos não explicam na totalidade porque certos indivíduos adoecem *(se enferman)* com mais facilidade, progridem *(progresan)* para diferentes formas clínicas da doença ou desenvolvem episódios reacionais. A combinação de estudos genéticos e funcionais pode ser uma poderosa ferramenta *(herramienta poderosa)* na dissecção de vias metabólicas envolvidas na fisiopatologia da doença. Além disso os conhecimentos produzidos podem ter impacto direto sobre a saúde do paciente na forma de melhores estratégias de prevenção, diagnóstico e tratamento.

Los autores no manifiestan conflictos de interés.

Bibliografía

1. Leprosy fact sheet (revised in February 2010). Wkly Epidemiol Rec 85(6):46-8, 2009.
2. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. Int J Lepr Other Mycobact Dis 34(3):255-73, 1966.
3. Hansen GA. Spedalskhedens Arsager. Norsk Magazin for Laegevidenskaben 1874 1955:76-9.
4. Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. Clin Microbiol Rev 19(2):338-81, 2006.
5. Mira MT. Genetic host resistance and susceptibility to leprosy. Microbes Infect 8(4):1124-31, 2006.
6. Abel L, Demenais F. Detection of major genes for susceptibility to leprosy and its subtypes in a Caribbean island: Desirade island. Am J Hum Genet 42(2):256-66, 1988.
7. Lazaro FP, Werneck RI, Mackert CC, Cobat A, Prevedello FC, Pimentel RP, et al. A major gene controls leprosy susceptibility in a hyperendemic isolated population from north of Brazil. J Infect Dis 201(10):1598-605.
8. Roy S, Frodsham A, Saha B, Hazra SK, Mascie-Taylor CG, Hill AV. Association of vitamin D receptor genotype with leprosy type. J Infect Dis 179(1):187-91, 1999.
9. Meisner SJ, Mucklow S, Warner G, Sow SO, Lienhardt C, Hill AV. Association of NRAMP1 polymorphism with leprosy type but not susceptibility to leprosy per se in west Africans. Am J Trop Med Hyg 65(6):733-5, 2001.
10. Rajalingam R, Singal DP, Mehra NK. Transporter associated with antigen-processing (TAP) genes and susceptibility to tuberculoid leprosy and pulmonary tuberculosis. Tissue Antigens 49(2):168-72, 1997.
11. Moraes MO, Pacheco AG, Schonkeren JJ, Vanderborght PR, Nery JA, Santos AR, et al. Interleukin-10 promoter single-nucleotide polymorphisms as markers for disease susceptibility and disease severity in leprosy. Genes Immun 5(7):592-5, 2004.
12. Vanderborght PR, Pacheco AG, Moraes ME, Antoni G, Romero M, Verville A, et al. HLA-DRB1*04 and DRB1*10 are associated with resistance and susceptibility, respectively, in Brazilian and Vietnamese leprosy patients. Genes Immun 8(4):320-4, 2007.
13. Siddiqui MR, Meisner S, Tosh K, Balakrishnan K, Ghei S, Fisher SE, et al. A major susceptibility locus for leprosy in India maps to chromosome 10p13. Nat Genet 27(4):439-41, 2001.
14. Alter A, De Leseleuc L, Van Thuc N, Thai VH, Huong NT, Ba NN, et al. Genetic and functional analysis of common MRC1 exon 7 polymorphisms in leprosy susceptibility. Hum Genet 127(3):337-48.
15. Mira MT, Alcais A, Van Thuc N, Thai VH, Huong NT, Ba NN, et al. Chromosome 6q25 is linked to susceptibility to leprosy in a Vietnamese population. Nat Genet 33(3):412-5, 2003.
16. Mira MT, Alcais A, Nguyen VT, Moraes MO, Di Flumeri C, Vu HT, et al. Susceptibility to leprosy is associated with PARK2 and PACRG. Nature 427(6975):636-40, 2004.
17. Alcais A, Alter A, Antoni G, Orlova M, Nguyen VT, Singh M, et al. Stepwise replication identifies a low-producing lymphotoxin-alpha allele as a major risk factor for early-onset leprosy. Nat Genet Apr;39(4):517-22, 2007.
18. Wong SH, Hill AV, Vannberg FO. Genomewide association study of leprosy. N Engl J Med 362(15):1446-7; author reply 7-8.
19. Schurr E, Gros P. A common genetic fingerprint in leprosy and Crohn's disease? N Engl J Med 361(27):2666-8, 2009.
20. Britton WJ, Lockwood DN. Leprosy. Lancet 10;363(9416):1209-19, 2004.
21. Smith WC, Nicholls PG, Das L, Barkataki P, Suneetha S, Suneetha L, et al. Predicting neuropathy and reactions in leprosy at diagnosis and before incident events-results from the INFIR cohort study. PLoS Negl Trop Dis 3(8):e500, 2009.
22. Ranque B, Nguyen VT, Vu HT, Nguyen TH, Nguyen NB, Pham XK, et al. Age is an important risk factor for onset and sequelae of reversal reactions in Vietnamese patients with leprosy. Clinical Infectious Diseases 44(1):33-40, 2007.
23. Kahawita IP, Walker SL, Lockwood DNJ. Leprosy type 1 reactions and erythema nodosum leprosum. Anais Brasileiro de Dermatologia 83(1):75-82, 2008.
24. Moraes MO, Sampaio EP, Nery JA, Saraiva BC, Alvarenga FB, Sarno EN. Sequential erythema nodosum leprosum and reversal reaction with similar lesional cytokine mRNA patterns in a borderline leprosy patient. Br J Dermatol 144(1):175-81, 2001.
25. Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. Clin Microbiol Rev 19(2):338-81, 2006.
26. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. International Journal of Leprosy and others Mycobacteium Diseases 34(3):255-73, 1966.
27. Pocaterra L, Jain S, Reddy R, Muzaffarullah S, Torres O, Suneetha S, et al. Clinical course of erythema nodosum leprosum: an 11-year cohort study in Hyderabad, India. Am J Trop Med Hyg 74(5):868-79, 2006.
28. Vasselon T, Detmers PA. Toll receptors: a central element in innate immune responses. Infect Immun 70(3):1033-41, 2002.
29. Bochud PY, Hawn TR, Siddiqui MR, Saunderson P, Britton S, Abraham I, et al. Toll like receptor 2 (TLR2) polymorphisms are associated with reversal reaction in leprosy. The Journal of Infectious Diseases 197(2):253-61, 2008.

ANEXO 4: ARTIGO DE REVISÃO:
“LEPROSY AND HIV COINFECTION: A CRITICAL APPROACH ”

EXPERT REVIEWS

Leprosy and HIV coinfection: a critical approach

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An increase in leprosy among HIV patients, similar to that observed in patients with TB, was expected approximately 20 years ago. Studies conducted in the 1990s together with those reported recently seemed to indicate that a coinfection with HIV did not alter the incidence and the clinical spectrum of leprosy and that each disease progressed as a single infection. By contrast, in countries with a high seroprevalence of HIV, TB was noted to increase. Explanations may be provided by the differences in the incubation time, the biology and toxicity of *Mycobacterium leprae* and *Mycobacterium tuberculosis*. After the introduction of HAART the leprosy–HIV coinfection manifested itself as an immune reconstitution inflammatory syndrome (IRIS), typically as paucibacillary leprosy with type 1 leprosy reaction. The incidence of leprosy in HIV-infected patients has never been properly investigated. IRIS-leprosy is probably underestimated and recent data showed that the incidence of leprosy in HIV patients under HAART was higher than previously thought.

Keywords: AIDS • elimination • epidemiology • HAART • Hansen disease • HIV • immune reconstitution inflammatory syndrome • leprosy • leprosy reaction • TB

Leprosy, or Hansen disease (HD), is a chronic infectious disease caused by *Mycobacterium leprae* which is associated with inflammation that may damage the skin and the peripheral nerves [1]. Despite the claim by the WHO that it would no longer be a public health problem after the year 2000, leprosy is far from being eliminated, with more than 200,000 new cases being reported yearly during the past 5 years. Leprosy remains an important public health problem in Southeast Asia, the Americas and Africa [2].

HIV infection has altered the epidemiology of mycobacterial diseases. This has led to an increase in severe illness associated with a number of mycobacterial diseases, particularly those of the *Mycobacterium avium intracellulare* complex in the industrialized world and of TB in sub-Saharan Africa and the former Soviet Union. The interaction between TB and HIV led the WHO to declare TB a global emergency [3,4]. HIV prevalence rates are high in many countries where leprosy is still endemic.

Therefore, a similar increase was expected for *M. leprae*. It was extrapolated from animal experiments (monkeys inoculated with the Simian immunodeficiency virus and *M. leprae* that developed lepromatous leprosy) that patients with leprosy and HIV coinfection would have an increased risk of multibacillary disease, with a faster clinical evolution, and that leprosy would be more difficult to treat [3,5,6].

An outbreak of lepromatous leprosy was expected, but has not been reported to date. However, after the introduction of HAART the coinfection leprosy–HIV presented itself as immune reconstitution inflammatory syndrome (IRIS), typically as paucibacillary leprosy with type 1 reaction [7–17]. As those facts were opposite to the predictions, the interaction between *M. leprae* and HIV was defined as a paradox [4]. It appeared from the analysis of the available data that *M. leprae* behaved differently from *M. tuberculosis*. However, reinterpreting old and recent data, it appears that the interaction between *M. leprae* and HIV was not a paradox but that both HIV and leprosy progress as single and independent infections [18].

Epidemiology

According to the WHO, a country is considered endemic for leprosy when it has a prevalence rate of more than one case per 10,000 inhabitants. According to this criterion; India, Brazil, Indonesia, Bangladesh and the Democratic Republic of the Congo are the five remaining leprosy-endemic countries with a population of over 1 million. A total

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of 244,796 new cases of leprosy were diagnosed worldwide in 2009 and the registered prevalence at the beginning of 2010 was 211,903 cases [2].

HIV prevalence rates are increasing in many countries where leprosy is endemic with a clear geographical overlap. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), the number of people living with HIV worldwide continued to grow in 2008, reaching an estimated 33.4 million (31.1–35.8 million) [101].

Unfortunately, no epidemiological data on leprosy–HIV coinfected patients are available. Still, in 2010, the Weekly Epidemiological Record published by the WHO did not report data on leprosy–HIV-coinfected patients and, to our knowledge, there are no specific control programs [2]. The majority of the available data are retrieved from published papers and personal experiences. Most of the larger studies on the subject were done in the early to mid-1990s, examining the rate of HIV seropositivity among leprosy patients, but they are most likely unreliable and not suitable for a meta-analysis because of the inadequate descriptions of the methods and the analyses in most of the reports in which different inclusion criteria and designs were used together with considerable methodological limitations [3–5].

A recently published cohort study from a referral center for both diseases in Manaus (Amazonas, Brazil) reported 25 cases of *M. leprae* and HIV-coinfection out of a total of 3290 HIV-positive individuals between 1996 and June 2009. Since the prevalence of leprosy in the Amazonas State was 2.92 cases per 10,000 individuals in 2008 [102], these data clearly indicated a much higher leprosy prevalence in HIV-positive individuals than that in the general population [18]. Couppié *et al.* confirmed these data, reporting 13 per 1000 person-years in persons receiving HAART for more than 3 months versus 0.7 per 1000 person-years for persons not on HAART in French Guiana [19]. Vinay *et al.* reported an incidence of leprosy in patients on HAART of 5.22 per 1000 person-years in Pune, India [20].

Clinical manifestations & classification

Cutaneous manifestations of leprosy–HIV-coinfected patients are not different from those in conventional leprosy (Figures 1–3). The only exception is when the HIV infection is of a longer duration and the patients have a very low CD4 count; in these cases, some of the lepromatous patients may have clinical aspects similar to patients with dapsone-resistant leprosy in the 1970s who presented with histoid nodules (histiod leprosy) (Figure 4) [2,4,18]. As in leprosy, in HIV-negative subjects, the clinical manifestations are determined by a dynamic interaction process between *M. leprae* antigenic determinants and the cell-mediated immunity (CMI) in genetically and/or immunological predisposed subjects [21]. Leprosy patients can be classified into a spectrum of clinicoimmunopathological manifestations (the Ridley and Jopling classification) that include polar tuberculoid (TT) leprosy and polar lepromatous (LL) leprosy and in between borderline tuberculoid (BT), mid-borderline (BB) and borderline lepromatous (BL) leprosy. The spectrum is determined by the balance between CMI and bacilli load: high CMI results in a low number of bacilli (paucibacillary leprosy: TT and part of BT). Low CMI response goes with high number of bacilli (multibacillary leprosy: LL, BL, BB and part of BT). TT and BT patients have few asymmetric, anaesthetic lesions while BB, BL and LL have multiple, symmetric lesions with little or no sensory loss [21,22].

Leprosy reactions (called type 1 [reversal] reaction [T1R] and type 2 reaction [ENL]) are acute episodes that are common in the immunologically unstable borderline patients, and involve an upregulation of the host response to *M. leprae* antigenic determinants. T1Rs are particularly responsible for the often severe nerve damage leading to impairments and permanent disability seen in borderline patients [23,24].

According to the authors, in leprosy–HIV-coinfected patients the WHO classification based on a 'lesion counting system' (patients with up to five lesions in total are paucibacillary and those with six or more skin lesions are multibacillary) may be used for allocating patients to treatment groups, but should only be used at peripheral centers in low-resource settings. Referral centers must classify leprosy–HIV patients according to the Ridley and Jopling classification because this permits a better understanding of the disease pathology, prognosis and risk factors for neural complications. Moreover, the Ridley and Jopling classification provides standardization and comparability of different studies over time and places [25].

Histopathology

The granulomatous response in both HIV-negative and HIV-positive leprosy patients is morphologically identical. Epithelioid granulomas characterize patients with TT and BT leprosy (Figures 5 & 6), whereas macrophage granulomas with Virchow cells are typically seen in patients with BL and LL leprosy (Figure 7). Edema in the superficial dermis, edema in the granuloma with disorganization, appearance of foreign-body giant cells and large Langerhans giant cells are observed in T1R. Edema in the dermis and a neutrophilic infiltrate with background changes of pre-existing lepromatous lesions, with or without vasculitis and usually a lobular panniculitis, are observed in ENL [4,18,26,27].

Pathogenesis

AIDS is caused by a retrovirus; HIV. The virus is specifically bound to the CD4 receptor, which makes the $CD4^+$ T cells the main target. It renders the cell functionally defective. When the virus is internalized and multiplies within the lymphocyte, the cell is destroyed. As a result, during the course of an HIV infection the immune reactivity that is related to the CMI, in which $CD4^+$ cells have a major function, slowly collapses. The exact incubation time is not known, the virus can be detected after 2 weeks–12 months, depending on the initial viral load and on as yet unknown factors. The first signs of immunosuppression may be noted after 1–10 years, or not at all [28].

The leprosy pathogenesis is still not well understood, neither in HIV-negative or in HIV-positive subjects. *M. leprae* is the sole bacterium with neurotropism for the peripheral nerves. It cannot

be cultured and the exact mode of transmission is not known. There is no definite incubation time, which can vary from a few months to 20 years or more [22].

What is known is that the activity of the CMI is fundamental in the development of the immune response against *M. leprae* and, therefore, for the clinical manifestations. Subjects with a predominant Th1 immune response will develop a high degree of CMI with epithelioid granuloma formation that will destroy all the bacilli with either healing or a localized disease (TT). By contrast, individuals with a predominant Th2 response will develop a weak CMI without forming an efficacious granulomatous response, but with an increased humoral immunity. Bacilli will survive and replicate and, therefore, a systemic disease (LL) develops [21].

The T cell plays a fundamental role in the resistance to *M. leprae*, as evidenced by different experiments. TT lesions generally show $CD4^+$ lymphocytes, distributed exclusively within the epithelioid granulomas, whereas $CD8^+$ cells are found at the periphery. LL lesions show $CD8^+$ T cells distributed throughout the infiltrate rather than at the periphery. $CD4^+$ cells are primarily of a naive phenotype and the $CD8^+$ cells are predominantly of a suppressor subset. Both $CD8^+$ and $CD4^+$ T cells may function as class I- and class II-restricted cytotoxic T cells and may lyse *M. leprae*-infected macrophages [29,30].

The role of $CD4^+$ T cells in the granuloma formation in patients with leprosy and HIV infection is still controversial. Before the introduction of HAART, only few immunohistochemical studies on HIV-leprosy coinfection were conducted. Nery *et al.* reported that tuberculoid patients had a predominance of $CD4^+$ cells, whereas most lepromatous lesions showed a predominance of $CD8^+$ cells [31]. Sampaio *et al.* studied 11 patients with BT and HIV-1 coinfection and reported that, despite very low $CD4^+$ cell counts in peripheral blood, biopsies of skin lesions showed well-formed granulomas containing normal numbers of $CD4^+$ lymphocytes. Other authors also described a high frequency of $CD8^+$ T cells in the lesions of BL HIV-positive patients [32]. Naafs *et al.* reported a BT patient whose skin infiltrate consisted of 50% $CD4^+$ cells, 30–40% $CD8^+$ cells and 25% $CD68^+$ cells [33].

Recently, Talhari *et al.* reported that, in 15 HIV-leprosy patients, $CD4^+$ cells were either absent or present at a very low frequency (<1.16%). These authors also demonstrated that $CD8^+$ cells expressing a cytotoxic phenotype (TIA-1) represented the vast majority of cells within the lymphocytic infiltrates in these patients. The presence of Tregs ($FOXP3^+$) and B cells ($CD20^+$) were also observed in the large majority of the lymphocytic infiltrates that were examined [18,27]. Taflin *et al.* suggested that the presence of Tregs within granulomas may have a more preventative rather than a curative effect on the inflammatory processes [34]. Data from other authors support the hypothesis that B cells may be required for engendering optimal bacterial containment through the development and maintenance of granulomas [35]. Therefore, it is possible that cell types other than $CD4^+$ and $CD8^+$ T lymphocytes and their local production of cytokines/chemokines may play an important role in the granuloma formation and maintenance under the conditions observed for individuals with leprosy and HIV coinfection.

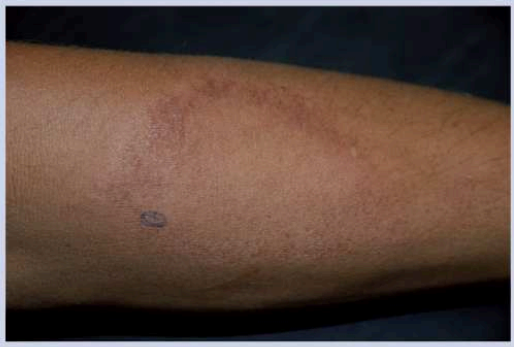

Figure 1. Borderline tuberculoid leprosy in a HIV-positive patient. Well-demarcated plaque formed by coalescence of papules with anesthesia and central resolution.
Photograph provided courtesy of Carolina Talhari, Tropical Medicine Foundation of Amazonas, Brazil.

Following the discontinuation of HIV replication after the initiation of HAART, a very rapid increase in the peripheral $CD4^+$ cell count is seen. Those cells were probably trapped in the lymphoid tissue. This increase was particularly noted in the first 3–6 months [36]. The high prevalence of BT leprosy observed among HAART-treated individuals may be a consequence of upgrading from multibacillary disease owing to the increase of $CD4^+$ T-cell counts induced by HAART [7–18,37–39]. In fact, recent reports of patients initially diagnosed with AIDS and BL, who shifted to BT leprosy following initiation of HAART/multidrug therapy (MDT), confirmed this observation [37,38]. After initiation of HAART and MDT, histopathological follow-up of coinfected patients revealed the replacement of foamy histiocytes containing numerous acid-fast bacilli by epitheliod granulomas with scanty or no acid-fast bacilli [18].

It is well accepted that TB accelerates the decline in the immune function in HIV-infected individuals [40,41], which is related to a marked pro-inflammatory cytokine production. Consequently, the inflammatory microenvironment at sites of *M. tuberculosis* infection is more favorable to the establishment and propagation of HIV infection. This is not seen in patients with leprosy. The apparent preservation of the ability to form granulomas in leprosy–HIV-coinfected patients, in clear contrast with what is reported in *M. tuberculosis*–HIV-coinfected individuals, has been named the 'granuloma paradox' [4,5,32,42].

Leprosy–HIV coinfection before the introduction of HAART therapy

Despite the absence of official regional information, epidemiological studies and global data indicated that, in contrast to the rise in the incidence of TB, there was no significant increase in leprosy and HIV co-occurrence [4]. Most of the larger studies on the subject were done in the early-to-mid-1990s, examining the rate of seroprevalence in previously established leprosy cohorts or in a series of newly diagnosed leprosy patients compared with

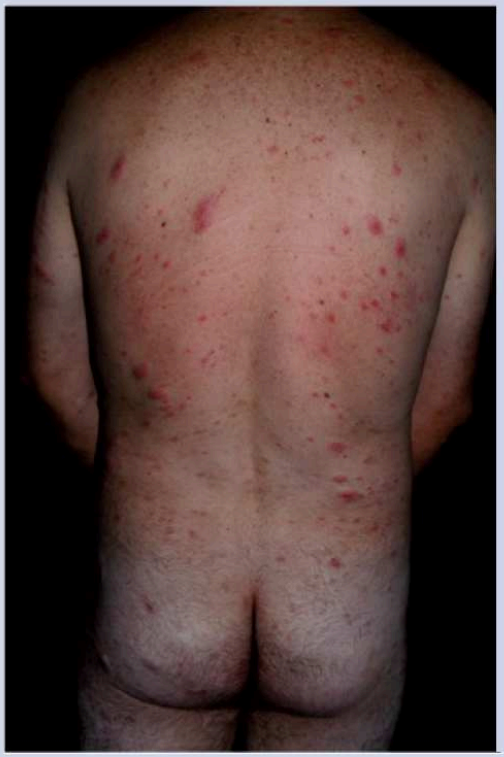

Figure 2. Borderline lepromatous leprosy manifesting as immune reconstitution inflammatory syndrome. Multiple symmetric erythematous macules, plaques and nodules distributed on the trunk and the extremities.
Photograph provided courtesy of Carolina Talhari, Tropical Medicine Foundation of Amazonas, Brazil.

control groups in some areas of India, Brazil and African countries [3–5]. Most studies reported no significant difference in HIV-1 seroprevalence between case and control groups. Only four studies demonstrated a modest increased HIV seroprevalence and another study showed a borderline trend. Peripheral blood CD4$^+$ T-cell count was considered in only a few studies and the different bias, the reliability of the diagnosis and the methodological limitations affecting these studies rendered a meta-analysis impossible and an interpretation of the data difficult [3–5]. For instance, when newly diagnosed leprosy patients were checked for HIV infection, only leprosy-infected individuals with a functional CMI showed clinical leprosy. Therefore, HIV-infected patients are under-represented in the sample. When HIV-infected individuals are clinically checked for leprosy, leprosy will be missed owing to immunodeficiency, which obliterates the analysis. In Brazil, the results of five studies led the authors to suggest that, in coinfected patients, each disease progressed as a single infection [32,42–44]. Five major pre-HAART African studies reported that the ratio of lepromatous/tuberculoid leprosy was not significantly affected by HIV coinfection in countries where both diseases are endemic [3–5].

Two reports from Haiti and Malawi showed that relapse was more common in HIV seropositive than in HIV seronegative leprosy patients [3]. There are two publications from Zambia in which it was claimed that neuritis and reactions were more serious in HIV-infected than in HIV-noninfected leprosy patients [3].

Leprosy–HIV coinfection after the introduction of HAART

HAART, widely used in countries that are endemic for both HIV infection and leprosy, suppresses HIV replication and induces a quantitative and functional restoration of the immune system [26]. During the first months of HAART, a change in the immune response occurs, leading to an exaggerated inflammatory response against pathogens, which may lead to an IRIS. This is described for many conditions among other *M. tuberculosis*, hepatitis B and C, and cytomegalovirus (CMV) infections [45].

Major criteria for the diagnosis of IRIS are: an atypical presentation of opportunistic infections or other conditions in patients responding to HAART with a decrease in viral load of at least 1 $\log_{10}$ copies/ml; the minor criteria are: an increase in CD4$^+$ cell count after HAART, an increase in immune response specific to a relevant pathogen and a spontaneous resolution of infection without specific antimicrobial therapy or another condition, that heals with the continuation of HAART [26,45].

In 2000, Opromolla *et al.*, Abels *et al.* and Pignataro *et al.* published the first case reports of leprosy and leprosy reactions presenting as an IRIS in HIV-infected patients newly started on HAART [46–48]. Since then, a surprisingly small number of similar cases (less than 100) have been reported in the English literature, particularly when compared with the numerous cases of TB. Most of the cases described are single-case reports and only a few case series [4,5,7–20,26,27,37–39,42,46–48].

Deps and Lockwood recently reviewed data of 21 published cases and reported that the mean CD4$^+$ count (pre-HAART) in these patients was 91 cells/ml. A total of 19 patients had a CD4$^+$ count at the time of diagnosis of leprosy as IRIS with a mean of 248. No apparent relationship between the development of leprosy as IRIS and any particular antiretroviral treatment was observed [26].

Although most patients developed the classic clinical and laboratory features of IRIS within 6 months after initiating HAART, periods of longer than 10 months were reported [4,6,18]. The most often observed clinical form was tuberculoid leprosy (mainly BT) with characteristic skin lesions. Besides typical cutaneous and neurological manifestations of leprosy, few coinfected patients may present with atypical hyperkeratotic eczematous and ulcerated lesions. Therefore, diagnosing leprosy may be challenging in a significant proportion of the patients with AIDS [4,6,18].

One particularly challenging aspect of leprosy–HIV coinfection is the correct diagnosis of neurological manifestations. Most IRIS–leprosy cases present with a T1R. Involvement of peripheral nerve in leprosy is well known; however, in HIV/AIDS, it may be confounded by neuropathy associated with HIV itself or with

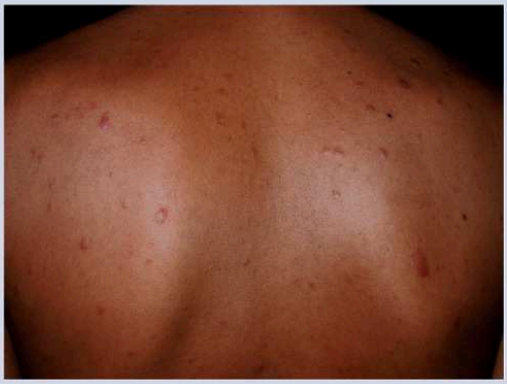

Figure 3. Borderline lepromatous leprosy in a HIV-positive patient. Multiple symmetrically distributed nodules on the back. Photograph provided courtesy of Carolina Talhari, Tropical Medicine Foundation of Amazonas, Brazil.

stavudine and other nucleoside-analogue reverse-transcriptase inhibitors [18,45,49]. Once leprosy is defined as the cause of nerve damage, an additional challenge is to differentiate between relapse, neural IRIS and silent neuropathy. In these patients, clinical findings, such as peripheral-nerve enlargement, sensory loss and muscular-force impairment, are encountered and electroneurophysiological investigations are important tools for the diagnosis of leprosy [18,45,49].

Classification for leprosy–HIV-coinfected patients

Recently, it was suggested that even though leprosy–HIV coinfections do not manifest homogenously across affected populations, immunological features seem to be shared by certain subgroups. In this context, a clinical classification of *M. leprae* and HIV/AIDS-coinfected patients was proposed by Talhari *et al.* [18] and include the following:

- *M. leprae*–HIV true coinfection: this group consists of HIV-positive individuals who do not fulfil AIDS criteria and are, therefore, not under HAART, behaving similarly to immunocompetent subjects;
- Opportunistic leprosy disease: consisting of AIDS patients not receiving HAART, presenting usually with multibacillary leprosy: this group would include individuals manifesting leprosy as an opportunistic mycobacteriosis, as expected in immunosuppressed individuals;
- HAART-related leprosy: including AIDS patients presenting all clinical forms of leprosy related or not to IRIS. Combined HAART and MDT may cause upgrading shift within the leprosy clinical spectrum, as may be revealed by long-term follow-up [18].

Deps and Lockwood proposed a classification for leprosy associated with IRIS in AIDS that include: type 1: unmasking – when patients develop leprosy or T1R after starting HAART; type 2: overlap of immune restoration (paradoxical) – when leprosy has already been diagnosed before starting HAART; type 3: undiagnosed leprosy or previously treated leprosy occurring at least 6 months before HAART; type 4: unmasking followed by overlap of immune restoration after HAART and MDT [26].

Therapy of leprosy–HIV coinfection

According to the published data, *M. leprae* and HIV-coinfected patients respond as well as immunocompetent individuals to MDT without the need for prolonged treatment courses. Most of the post-HAART reports of dually infected patients were associated with BT leprosy, usually presenting for the first time with T1R. Corticosteroid therapy (0.5–1 mg of prednisone per kilogram of bodyweight per day) should be promptly introduced in cases of IRIS/T1R in order to prevent neural damage and sequels. Moreover, coinfected patients may need prolonged steroid therapy, even after finishing MDT [4,6,18,50,51].

Genetics of leprosy–HIV coinfection

The existence of innate, host-related mechanisms controlling susceptibility to disease *per se* and clinical forms has been widely investigated in several infectious diseases, including AIDS and leprosy. The aim was to explain why disease manifestation varied

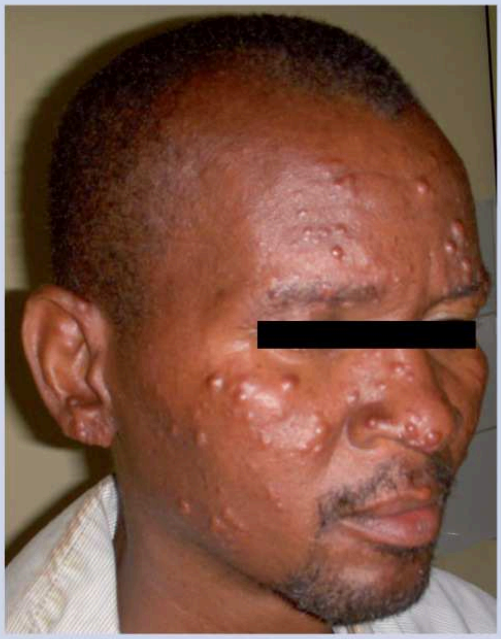

Figure 4. Lepromatous leprosy in HIV presenting with firm, dome-shaped or oval small nodules and simulating histoid leprosy.
Photograph provided courtesy of Tabor Mebratu, Regional Dermatology Training Centre (RDTC), at KCMC, Tanzania.

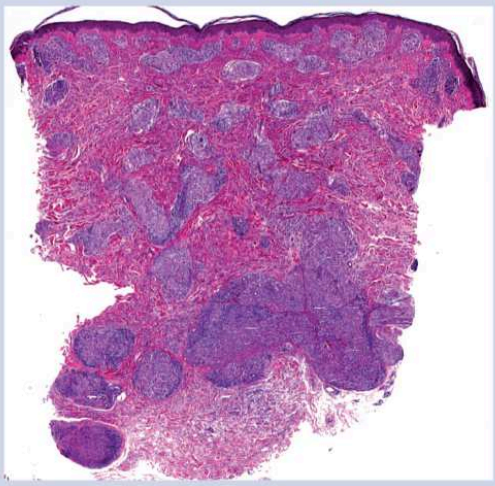

Figure 5. Borderline tuberculoid leprosy in a HIV-positive patient. Multifocal granulomatous infiltrate with epithelioid granulomas in the superficial, mid and deep dermis with periadnexal and perineural distribution.
Photograph provided courtesy of Cesare Massone, Medical University of Graz, Austria.

so greatly in individuals sharing the same environmental conditions after exposure to the same type of microbial agent. Often this variation cannot be explained only from the perspective of the pathogen. For leprosy, for example, the occurrence of different clinical forms of the disease cannot be because of the virtually

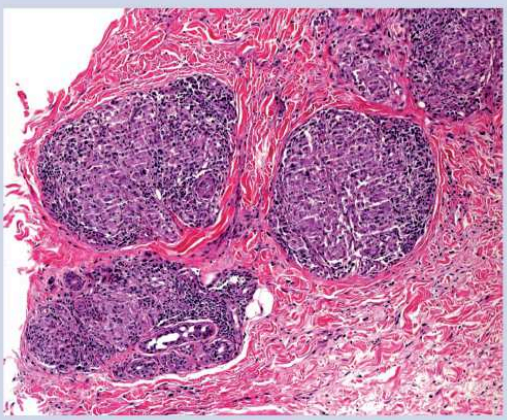

Figure 6. Borderline tuberculoid leprosy in a HIV-positive patient. Epithelioid granulomas surrounded and infiltrated by lymphocytes.
Photograph provided courtesy of Cesare Massone, Medical University of Graz, Austria.

clonal nature of the pathogen, indicating that host genetic risk factors may be crucial in defining the outcome of the complex host–pathogen interaction. The identification of genetic variants predisposing to infectious diseases has been a continuous challenge over the past decades. The task, not trivial when considering the diseases independently, becomes even more challenging in the context of coinfection.

In leprosy, over the past two decades, genes such as *VDR* [52], *NRAMP1* [53], *TAP* [54], *IL-10* [55], *MHC/HLA* variants [56], *PARK2/PACRG* [57], *LTA* [58], *TNFA* [59] and *MCR1* [60] were identified in association with leprosy phenotypes reviewed by Alter *et al.* [61]. Recently, the first leprosy genome-wide association study (GWAS), performed in a Chinese population, showed variations in seven genes – *CCDC122*, *CD13orf31*, *NOD2*, *TNFSF15*, *HLA-DRB1*, *RIPK2* and *LRRK2* – associated with susceptibility to leprosy [62]. However, few of these association signals have been replicated by independent studies; in addition, functional evidence of the underlying biological basis for the genetic effects has rarely been produced. A similar scenario is observed for HIV/AIDS: candidate-gene analysis and recent GWASs have identified several genes associated with HIV-1 acquisition and disease progression, as reviewed by An and Winkler [63]. Among the most interesting findings are genes involved in: HIV entry – *CCR5*, *CXR6*, *CCL5*, *CCR2* and *DC-SIGN*; postentry cellular viral cofactors – *TRIM5*, *CUL5* and *TSg101*; cytokines secretion – *IL-10*, *IFNG*, *IRF-1* and *CXCR1*; and HLA-linked genes – HLA class I and II variants, *HCP5* and *KIR*.

To date, no studies have addressed the molecular mechanisms controlling the susceptibility to leprosy or AIDS in the context of coinfection. However, it is interesting to note that genes such as *IL-10*, *INFG*, HLA class I and II and *KIR*, have been described in association with both leprosy and HIV/AIDS. One particularly solid example is provided by *IL-10*: case–control studies [55,64] have consistently pointed to allele-819T located at the promoter region of *IL-10* as an important variant associated with leprosy susceptibility. In HIV, Shin *et al.* reported that individuals carrying the *-592A* allele, also located at the promoter region of *IL-10* (*IL-10-5'A*), were at an increased risk for HIV-1 infection and, once infected, these patients progressed to AIDS more rapidly than individuals homozygous for the alternative *IL-10 -592 C/C* (*IL-10*$^{-/+}$) genotype, particularly in the later stages of HIV-1 infection [65]. Importantly, single gene variants associated with different diseases may reflect the existence of common, shared control pathways – in this case, human genetics could be the tool to serendipitously connect the mechanisms underlying two or more pathologies, as recently suggested for TB/sarcoidosis [66] and leprosy/Crohn's disease [62,67]. In this scenario, a more comprehensive, systems biology-based approach could help unravel these potentially critical mechanisms for disease understanding, treatment, prevention and control.

Expert commentary

The interaction between *M. leprae* and HIV seems to be fascinating and intriguing. The introduction of HAART changed the face of leprosy in HIV-infected patients. In fact, the HAART-induced

immunological changes are responsible for the occurrence of leprosy as IRIS phenomenon in HIV-infected patients.

Approximately 20 years ago, an increase in leprosy in HIV-infected patients as observed with TB was expected. It was predicted that coinfected patients would present with lepromatous disease and that the long incubation periods for leprosy may bias towards tuberculoid disease, since patients may die of AIDS-related infections before manifesting their lepromatous leprosy. It was also forecasted that leprosy patients infected with HIV not showing the disease may infect the non-HIV-infected individuals, who are able to show clinical disease due to presence of a functional immune system [3,4,6,26,33].

The studies conducted in the 1990s, as well as the recent experiences, indicated that coinfection with HIV did not alter the incidence and the clinical spectrum of leprosy and that each disease progressed as a single infection [18]. More widespread BCG vaccination, an improvement in socio–economic conditions and possibly the introduction of MDT contributed to a progressive decline in the incidence of leprosy in the last century independently of HIV infection. By contrast, TB increased in countries with high seroprevalence for HIV [3,4,6].

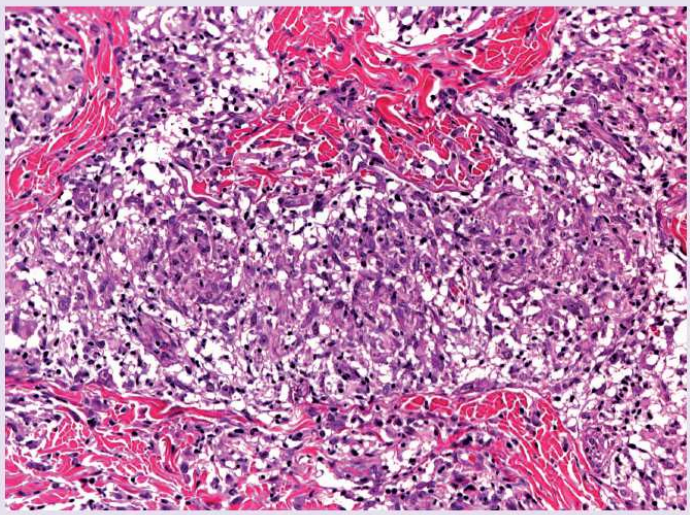

Figure 7. Borderline lepromatous leprosy in a HIV-positive patient. Macrophage granuloma with foamy macrophages, lymphocytes and plasma cells.
Photograph provided courtesy of Cesare Massone, Medical University of Graz, Austria.

There are various possible explanations for this phenomenon. In countries where leprosy and TB are both highly prevalent, it may be assumed that the HIV-infected individuals do not only run the risk of TB, but also of leprosy. TB manifests in HIV-infected patients when the CMI is unable to prevent the multiplication of the bacterium. *M. tuberculosis* multiplies faster compared with *M. leprae*. Moreover, in TB, nonrelated CMI mechanisms contribute towards the clinical symptoms. In fact, *M. leprae* and *M. tuberculosis* are different in their 'toxicity' to the human body. *M. leprae* does not cause an obvious response when inoculated in a previously uninfected individual, but *M. tuberculosis* does, mobilizing polymorphous leukocytes, causing inflammation, infiltration and sometimes ulceration. Thus, in TB, in contrast to leprosy, the clinical features are not only caused by the CMI, but also by other inflammatory mediators. *M. leprae* multiplies very slowly, it is not 'toxic' and it needs a functional CMI to develop clinical disease. Last but not least, the leprosy incubation time is longer and BCG is an effective vaccine against leprosy [3,22].

A further possible explanation is the T-helper cells. HIV infection affects the $CD4^+$ T cells, a subtype of lymphocytes considered pivotal in determining the CMI against *M. leprae*. The ability of HIV–leprosy-coinfected individuals to develop a normal granulomatous response (in contrast to TB) against *M. leprae*, even with a low number of circulating $CD4^+$ cells, has been defined as a 'paradox' [4,6]. The recent finding of a very low number of $CD4^+$ cells in leprosy granulomatous lesions in HIV–leprosy-coinfected patients together with the presence of Tregs and B cells opens the hypothesis that, in leprosy, not only T-helper cells, but also Tregs and B lymphocytes may play a role in the granuloma formation, thereby elucidating the paradox [18,27].

The exact incidence of leprosy in HIV-infected patients has never been properly estimated. Studies conducted in the 1990s examined only HIV seroprevalence in previously established leprosy cohorts or in series of newly diagnosed leprosy patients compared with control groups [3,4]. Prospective cohort studies have never been conducted and the long incubation period of leprosy has surely influenced the phenomenon. The patients reported in the literature do not reflect the incidence of leprosy–HIV-coinfected patients as most of the cases are neither described or reported in the English literature. Moreover, some cases are probably not recognized as leprosy.

These data showed that IRIS leprosy is probably underestimated. In fact, as demonstrated in Brazil, India and French Guiana, the incidence of leprosy in a HIV patient under HAART is high [18,19,20]. Some papers report an occurrence of five IRIS leprosy per 1000 patients in HAART programs, which is much higher than the prevalence of leprosy in those areas.

To complete our analysis, we must mention the impact of HIV on *M. ulcerans*, the causative agent of Buruli ulcer (BU). BU is the third most common human mycobacteriosis worldwide after TB and leprosy and is an emerging disease in humid tropical areas of Asia, Latin America and Africa (with an increasing incidence, in some regions surpassing TB and leprosy). Until now only one large serological study has been conducted and few case reports have been published. From these data, HIV had a higher prevalence (2.6%) among patients with BU than

with controls (0.6%), and in HIV-positive patients BU manifests with disseminated lesions. To our knowledge, no cases of BU manifesting as IRIS phenomenon have been reported. It should be kept in mind that the BU is not so much caused by immunological mechanisms, but is the result of the cytotoxic effect of an exotoxine, mycolactone. In summary, few data can be found regarding the interaction HIV–BU; nevertheless, it seems that HIV has a negative impact on BU (causing a disseminated disease), but similarly to leprosy and contrary to TB, an outbreak of BU in HIV patients has not been observed [68–71].

Five-year view

A detailed leprosy–HIV control program has to be implemented. A very interesting study would be to obtain nasal swabs from normal and HIV-infected patients in a leprosy-endemic area. Epidemiological studies will probably confirm that IRIS leprosy is not a rare event and that it is absolutely not a paradox.

Genetic data indicate the existence of shared immunological pathways that control the susceptibility to different infectious agents. Exploring this hypothesis may be of particular interest for leprosy–HIV coinfection. However, large sample sizes are difficult to obtain, but are mandatory to allow power analysis of such a complex study design.

Careful immunopathological follow-up of leprosy patients starting on HAART may help to elucidate the mechanisms leading to a T1R. Therefore, particular attention must be paid to leprosy-endemic areas where HAART is increasingly available.

Physicians must be aware of the possibility of the unmasking of a leprosy infection shortly after HAART initiation, particularly because leprosy in this setting manifests with T1R that may lead to irreversible neurological damage and its sequels. This group of patients has to be treated appropriately with MDT together with steroids.

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Key issues

- Despite the claim by the WHO that it would no longer be a public health problem after the year 2000, leprosy is far from being eliminated. Over the past 5 years more than 200,000 new cases were reported per year.
- HIV prevalence rates are high in many countries where leprosy is still endemic.
- Studies conducted in the 1990s, together with those reported recently, indicated that coinfection with HIV neither altered the incidence or the clinical spectrum of leprosy and that disease progression was comparable with a single infection.
- In contrast, in countries with a high seroprevalence of HIV, TB was increased. Explanations may be provided by the differences in the incubation time, biology and toxicity of *Mycobacterium leprae* and *Mycobacterium tuberculosis*.
- After the introduction of HAART, leprosy–HIV coinfection was encountered as immune reconstitution inflammatory syndrome (IRIS), typically as paucibacillary leprosy with type 1 leprosy reaction.
- The incidence of leprosy in HIV-infected patients has never been properly estimated. IRIS–leprosy is probably underestimated. In fact, the incidence of leprosy in HIV patients under HAART is high, as demonstrated in Brazil, India and French Guiana, and is not a rare event as reported by others.
- It seems in light of the old and the new data, that the interaction between *M. leprae* and HIV is not a paradox as claimed but that both HIV and leprosy progress as single and independent infections.
- Particular attention should be paid to leprosy-endemic areas where HAART is increasingly available. Physicians must be aware of the possibility of the unmasking of a leprosy infection shortly after HAART initiation, particularly because leprosy in this setting manifests with a type 1 leprosy reaction that may lead to irreversible neurological damage and its sequels.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Britton WJ, Lockwood DN. Leprosy. *Lancet* 363(9416), 1209–1219 (2004).

•• **Extensive review on leprosy covering epidemiology, pathogenesis, clinical features and therapy.**

2 Global leprosy situation, 2010. *Wkly Epidemiol. Rec.* 85(35), 337–348 (2010).

3 Naafs B. Leprosy and HIV: an analysis. *Hansen Int.* 25(1), 63–66 (2000).

4 Ustianowski AP, Lawn SD, Lockwood DN. Interactions between HIV infection and leprosy: a paradox. *Lancet Infect. Dis.* 6(6), 350–360 (2006).

• **Extensive review on leprosy–HIV coinfection.**

5 Deps PD, Lockwood DN. Leprosy occurring as immune reconstitution syndrome. *Trans. R. Soc. Trop. Med. Hyg.* 102(10), 966–968 (2008).

6 Naafs B. Some observations from the past year. *Hansen Int.* 29, 51–56 (2004).

7 Landay AL, Bettendorf D, Chan E *et al.* Evidence of immune reconstitution in anti-retroviral drug-experienced patients with advanced HIV disease. *AIDS Res. Hum. Retroviruses* 18(2), 95–102 (2002).

8 Lawn SD, Wood C, Lockwood DN. Borderline tuberculoid leprosy: an immune reconstitution phenomenon in a human immunodeficiency virus-infected person. *Clin. Infect. Dis.* 36(1), e5–e6 (2003).

9 Pignataro P, Rocha Ada S, Nery JA *et al.* Leprosy and AIDS: two cases of increasing inflammatory reactions at the start of highly active antiretroviral therapy. *Eur. J. Clin. Microbiol. Infect. Dis.* 23(5), 408–411 (2004).

10 Visco-Comandini U, Longo B, Cuzzi T, Paglia MG, Antonucci G. Tuberculoid leprosy in a patient with AIDS: a manifestation of immune restoration syndrome. *Scand. J. Infect. Dis.* 36(11–12), 881–883 (2004).

11 Trindade MA, Manini MI, Masetti JH, Leite MA, Takashashi MD, Naafs B. Leprosy and HIV co-infection in five patients. *Lepr. Rev.* 76(2), 162–166 (2005).

12 Kharkar V, Bhor UH, Mahajan S, Khopkar U. Type I lepra reaction presenting as immune reconstitution inflammatory syndrome. *Indian J. Dermatol. Venereol. Leprol.* 73(4), 253–256 (2007).

13 Batista MD, Porro AM, Maeda SM *et al.* Leprosy reversal reaction as immune reconstitution inflammatory syndrome in patients with AIDS. *Clin. Infect. Dis.* 46, e56–e60 (2008).

14 Menezes VM, Sales AM, Illarramendi X *et al.* Leprosy reaction as a manifestation of immune reconstitution inflammatory syndrome: a case series of a Brazilian cohort. *AIDS* 23(6), 641–643 (2009).

15 Couppié P, Abel S, Voinchet H *et al.* Immune reconstitution inflammatory syndrome associated with HIV and leprosy. *Arch. Dermatol.* 140(8), 997–1000 (2004).

16 Martiniuk F, Rao SD, Rea TH *et al.* Leprosy as immune reconstitution inflammatory syndrome in HIV-positive persons. *Emerg. Infect. Dis.* 13(9), 1438–1440 (2007).

17 Trindade MA, Valente NY, Manini MI *et al.* Two patients coinfected with *Mycobacterium leprae* and human immunodeficiency virus type 1 and naive for antiretroviral therapy who exhibited type 1 leprosy reactions mimicking the immune reconstitution inflammatory syndrome. *J. Clin. Microbiol.* 44(12), 4616–4618 (2006).

18 Talhari C, Mira MT, Massone C *et al.* Leprosy and HIV coinfection: a clinical, pathological, immunological, and therapeutic study of a cohort from a Brazilian referral center for infectious diseases. *J. Infect. Dis.* 202(3), 345–354 (2010).

•• **This clinical study reports the largest cohort of leprosy–HIV-coinfected patients describing a higher prevalence of leprosy in an HIV-positive population than that in the general population.**

19 Couppié P, Domergue V, Clyti E *et al.* Increased incidence of leprosy following HAART initiation: a manifestation of the immune reconstitution disease. *AIDS* 23(12), 1599–1600 (2009).

20 Vinay K, Smita J, Nikhil G, Neeta G. Human immunodeficiency virus and leprosy coinfection in Pune, India. *J. Clin. Microbiol.* 47(9), 2998–2999 (2009).

21 Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. *Int. J. Lepr. Other Mycobact. Dis.* 34(3), 255–273 (1966).

22 Nunzi E, Massone C. *Leprosy: A Practical Guide in Global Health*. Springer, Berlin, Germany (2011) (In Press).

23 Walker SL, Lockwood DN. Leprosy type 1 (reversal) reactions and their management. *Lepr. Rev.* 79(4), 372–386 (2008).

24 Van Veen NH, Lockwood DN, Van Brakel WH, Ramirez J Jr, Richardus JH. Interventions for erythema nodosum leprosum. A Cochrane review. *Lepr. Rev.* 80(4), 355–372 (2009).

25 Lockwood DN, Sarno E, Smith WC. Classifying leprosy patients–searching for the perfect solution? *Lepr. Rev.* 78(4), 317–320 (2007).

26 Deps P, Lockwood DN. Leprosy presenting as immune reconstitution inflammatory syndrome: proposed definitions and classification. *Lepr. Rev.* 81(1), 59–68 (2010).

• **Recent review on the literature about leprosy–HIV with detailed data analysis of published papers.**

27 Massone C, Talhari C, Talhari S *et al.* Immunophenotype of skin lymphocytic infiltrate in *M. leprae* and HIV co-infected patients: a scenario dependent of $CD8^+$ and/or $CD20^+$ cells. *Br. J. Dermatol.* (2011) (In Press).

•• **Largest immunohistochemical study on HIV–leprosy patients.**

28 Streeck H, Nixon DF. T cell immunity in acute HIV-1 infection. *J. Infect. Dis.* 202(Suppl. 2), S302–S308 (2010).

29 Massone C, Nunzi E, Ribeiro-Rodrigues R *et al.* T regulatory cells and plasmocytoid dendritic cells in Hansen disease: a new insight into pathogenesis? *Am. J. Dermatopathol.* 32(3), 251–256 (2010).

30 Gulia A, Fried I, Massone C. New insights in the pathogenesis and genetics of leprosy. *F1000 Med. Rep.* 2, 30 (2010).

31 Nery JA, Sampaio EP, Galhardo MC *et al.* *M. leprae*-HIV co-infection: pattern of immune response *in vivo* and *in vitro*. *Indian J. Lepr.* 72(2), 155–167 (2000).

32 Sampaio EP, Caneshi JR, Nery JA *et al.* Cellular immune response to *Mycobacterium leprae* infection in human immunodeficiency virus-infected individuals. *Infect. Immun.* 63(5), 1848–1854 (1995).

33 Naafs B, Chin-A-Lien RA, Tank B, van Joost T. Human immunodeficiency virus and leprosy. *Trop. Geogr. Med.* 46(2), 119–122 (1994).

34 Taflin C, Miyara M, Nochy D *et al.* $FOXP3^+$ regulatory T cells suppress early stages of granuloma formation but have little impact on sarcoidosis lesions. *Am. J. Pathol.* 174(2), 497–508 (2009).

35 Iyer AM, Mohanty KK, van Egmond D *et al.* Leprosy-specific B-cells within cellular infiltrates in active leprosy lesions. *Hum. Pathol.* 38(7), 1065–1073 (2007).

36 Arora DR, Gautam V, Gill PS, Mishra N. Recent advances in antiretroviral therapy in HIV infection. *J. Indian Med. Assoc.* 108(1), 29–34 (2010).

37 Talhari C, Machado PR, Ferreira LC, Talhari S. Shifting of the clinical spectrum of leprosy in an HIV-positive patient: a manifestation of immune reconstitution inflammatory syndrome? *Lepr. Rev.* 78(2), 151–154 (2007).

38 Talhari C, Ferreira LC, Araujo JR, Talhari AC, Talhari S. Immune reconstitution inflammatory syndrome or upgrading type 1 reaction? Report of two AIDS patients presenting a shifting from borderline lepromatous leprosy to borderline tuberculoid leprosy. *Lepr. Rev.* 79(4), 429–435 (2008).

39 Sarno EN, Illarramendi X, Nery JA *et al.* HIV-*M. leprae* interaction: can HAART modify the course of leprosy? *Public Health Rep.* 123(2), 206–212 (2008).

40 Whalen C, Horsburgh CR, Hom D *et al.* Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am. J. Respir. Crit. Care Med.* 151(1), 129–135 (1995).

41 Whalen CC, Nsubuga P, Okwera A *et al.* Impact of pulmonary tuberculosis on survival of HIV-infected adults: a prospective epidemiologic study in Uganda. *AIDS* 14(9), 1219–1228 (2000).

42 Pereira GA, Stefani MM, Araujo Filho JA, Souza LC, Stefani GP, Martelli CM. Human immunodeficiency virus type 1 (HIV-1) and *Mycobacterium leprae* co-infection: HIV-1 subtypes and clinical, immunologic, and histopathologic profiles in a Brazilian cohort. *Am. J. Trop. Med. Hyg.* 71(5), 679–684 (2004).

43 de Almeida AM, Roselino AM, Foss NT. Leprosy and HIV infection. *Int. J. Lepr. Other Mycobact. Dis.* 62(1), 133–135 (1994).

44 Moran CA, Nelson AM, Tuur SM, Luengu M, Fonseca L, Meyers WM. Leprosy in five human immunodeficiency virus-infected patients. *Mod. Pathol.* 8(6), 662–664 (1995).

45 Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M; IeDEA Southern and Central Africa. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect. Dis.* 10(4), 251–261 (2010).

46 Opromolla DVA, Tonello CJS, Fleury RN. Borderline leprosy and HIV infection. *Hansen Int.* 25, 54–59 (2000).

47 Abels S, Helenon R, Ray V, Sobesky G, Cubie A. Tuberculoid leprosy neuritis following initiation of combination antiretroviral therapy. Presented at: *13th International AIDS Conference.* Durban, South Africa, 9–14 July 2000.

48 Pignataro PE, Nery JAC, Miranda A *et al.* Leprosy and AIDS: report of two cases in the beginning of HAART and inflammatory reactions. Presented at: *16th International Congress of Leprosy.* Salvador, Brazil, 4–9 August 2002.

49 Pavie J, De Castro N, Molina JM, Flageul B. Severe peripheral neuropathy following HAART initiation in an HIV-infected patient with leprosy. *J. Int. Assoc. Physicians AIDS Care (Chic. Ill.)* 9(4), 232–235 (2010).

50 Naafs B. Treatment of leprosy: science or politics? *Trop. Med. Int. Health* 11(3), 268–278 (2006).

51 Worobec SM. Treatment of leprosy/ Hansen's disease in the early 21st Century. *Dermatol. Ther.* 22(6), 518–537 (2009).

52 Roy S, Frodsham A, Saha B, Hazra SK, Mascie-Taylor CG, Hill AV. Association of vitamin D receptor genotype with leprosy type. *J. Infect. Dis.* 179(1), 187–191 (1999).

53 Meisner SJ, Mucklow S, Warner G, Sow SO, Lienhardt C, Hill AV. Association of *NRAMP1* polymorphism with leprosy type but not susceptibility to leprosy *per se* in West Africans. *Am. J. Trop. Med. Hyg.* 65(6), 733–735 (2001).

54 Rajalingam R, Singal DP, Mehra NK. Transporter associated with antigen-processing (*TAP*) genes and susceptibility to tuberculoid leprosy and pulmonary tuberculosis. *Tissue Antigens* 49(2), 168–172 (1997).

55 Moraes MO, Pacheco AG, Schonkeren JJ *et al.* Interleukin-10 promoter single-nucleotide polymorphisms as markers for disease susceptibility and disease severity in leprosy. *Genes Immun.* 5(7), 592–595 (2004).

56 Vanderborght PR, Pacheco AG, Moraes ME *et al. HLA-DRB1*04* and *DRB1*10* are associated with resistance and susceptibility, respectively, in Brazilian and Vietnamese leprosy patients. *Genes Immun.* 8(4), 320–324 (2007).

57 Mira MT, Alcaïs A, Nguyen VT *et al.* Susceptibility to leprosy is associated with PARK2 and PACRG. *Nature* 427(6975), 636–640 (2004).

58 Alcais A, Alter A, Antoni G *et al.* Stepwise replication identifies a low-producing lymphotoxin-α allele as a major risk factor for early-onset leprosy. *Nat. Genet.* 39(4), 517–522 (2007).

59 Moraes MO, Duppre NC, Suffys PN *et al.* Tumor necrosis factor-α promoter polymorphism TNF2 is associated with a stronger delayed-type hypersensitivity reaction in the skin of borderline tuberculoid leprosy patients. *Immunogenetics.* 53(1), 45–47 (2001).

60 Alter A, de Léséleuc L, Van Thuc N *et al.* Genetic and functional analysis of common *MRC1* exon 7 polymorphisms in leprosy susceptibility. *Hum. Genet.* 127(3), 337–348 (2010).

61 Alter A, Grant A, Abel L, Alcaïs A, Schurr E. Leprosy as a genetic disease. *Mamm. Genome.* 22(1–2), 19–31 (2010).

•• **Outstanding review on leprosy genetics.**

62 Wong SH, Hill AV, Vannberg FO *et al.* Genomewide association study of leprosy. *N. Engl. J. Med.* 362(15), 1446–1447 (2010).

63 An P, Winkler CA. Host genes associated with HIV/AIDS: advances in gene discovery. *Trends Genet.* 26(3), 119–131 (2010).

64 Malhotra D, Darvishi K, Sood S *et al.* IL-10 promoter single nucleotide polymorphisms are significantly associated with resistance to leprosy. *Hum. Genet.* 118(2), 295–300 (2005).

65 Shin HD, Winkler C, Stephens JC *et al.* Genetic restriction of HIV-1 pathogenesis to AIDS by promoter alleles of IL10. *Proc. Natl Acad. Sci. USA* 97(26), 14467–14472 (2000).

66 Cobat A, Gallant CJ, Simkin L *et al.* Two loci control tuberculin skin test reactivity in an area hyperendemic for tuberculosis. *J. Exp. Med.* 206(12), 2583–2591 (2009).

67 Zhang, FR, Huang W, Chen SM *et al.* Genomewide association study of leprosy. *N. Engl. J. Med.* 361(27), 2609–2618 (2009).

•• **The first leprosy genome-wide association study on leprosy, performed in a Chinese population.**

68 Sopoh GE, Dossou AD, Brun LV *et al.* Severe multifocal form of buruli ulcer after streptomycin and rifampin treatment: comments on possible dissemination mechanisms. *Am. J. Trop. Med. Hyg.* 83(2), 307–313 (2010).

69 Kibadi K, Colebunders R, Muyembe-Tamfum JJ, Meyers WM, Portaels F. Buruli ulcer lesions in HIV-positive patient. *Emerg. Infect. Dis.* 16(4), 738–739 (2010).

70 Johnson RC, Nackers F, Glynn JR *et al.* Association of HIV infection and *Mycobacterium ulcerans* disease in Benin. *AIDS* 22(7), 901–903 (2008).

71 Silva MT, Portaels F, Pedrosa J. Pathogenetic mechanisms of the intracellular parasite *Mycobacterium ulcerans* leading to Buruli ulcer. *Lancet Infect. Dis.* 9(11), 699–710 (2010).

Websites

101 HIV Prevalence Estimates – Updated June 2010 www.measuredhs.com/pubs/pub_details.cfm?ID=1009

102 Hanseníase http://portal.saude.gov.br/portal/saude/profissional/area.cfm?id_area=1466

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