

LITERATURA CORRENTE

CURRENT LITERATURE

BIOLOGIA MOLECULAR/ GENÉTICA

Vanderborght PR, Matos HJ, Salles AM, Vasconcellos SE, Silva-Filho VF, Huizinga TW, Ottenhoff TH, Sampaio EP, Sarno EM, Santos AR, Moraes MO. single nucleotide polymorphisms (SNPs) at -238 and -308 positions in the TNFalpha promoter: clinical and bacteriological evaluation in leprosy. *Int j lepr* 2004; 72(2):143-8.

Tumor necrosis factor alpha (TNFalpha) plays a key role in orchestrating the complex events involved in inflammation and immune response. The presence of single nucleotide polymorphisms (SNPs) within the promo-ter region of the TNFa gene has been associated with a number of diseases. The aim of this study was to investigate the distribution of polymorphisms at positions -238 (G/A) and -308 (G/A) at the TNFalpha promoter, and its association to the outcome of different clinical forms of leprosy. Furthermore, the bacteriological index (BI) was evaluated among genotyped multibacillary (MB) patients in order to investigate the possible influence of each polymorphism on the bacterial load. This study included a total of 631 leprosy patients being 401 MB and 230 paucibacillary (PB), that was further separated according to its ethnicity (Afro- and Euro-Brazilians). The combination of SNPs in haplotypes generated three different arrangements: TNFG-G, TNFG-A and TNFA-G. In spite of the marked differences observed in the frequency of the haplotypes along the ethnic groups, no statistical differences were observed in haplotype frequencies between MB and PB patients. The BI analyses showed a lower bacteriological index among the -308 carriers, while the BI of the -238 carriers was higher. Although no significance has been achieved in this analysis regarding the influence of the polymorphisms to the development of the clinical outcome, it seems that in a different stage (among the MB patients) the polymorphisms could contribute to the degree of severity observed.

CIRURGIA/ ÚLCERA

Jayaseelan E, Aithal VV. Pinch skin grafting in non-healing leprosy ulcers. *Intl Lepr* 2004; 72(2):139-42.

Treatment of leprosy ulcers has remained inadequate, owing to the fact that most of these ulcers are still being managed conservatively especially in developing nations, probably due to financial constraints. Pinch skin grafting, though obsolete now (2), tries to bridge this gap between cost and effectiveness. It is a simple office-based technique, not requiring much expertise or investment, and can be done in a simple set-up such as a side room

(3). Also, pinch skin grafting has an added advantage over single grafts, in that even if one graft is rejected, there are other grafts, which successfully heal, and epidermize to the surrounding. Moreover, if the ulcer is draining, the discharge flows out in between the grafts, thus preventing the whole graft from being rejected. The only disadvantage to pinch skin grafting is the final cosmetic appearance, which might not be most pleasing. We had very good results with all four patients who underwent this procedure in our institution. The procedure and the final result are described in detail in this report.

CLÍNICA

Dawe S, Lockwood DN, Creamer D A case of post-partum borderline tuberculoid leprosy complicated by a median nerve abscess, peptic ulceration and rifampicin-induced haemolytic renal failure. *Lepr rev* 2004; 75(2):181-7.

We report a case of borderline tuberculoid leprosy complicated by a median nerve abscess, acute renal failure secondary to rifampicin-induced haemolysis and duodenal ulceration secondary to steroid use. Rifampicin induced haemolysis is a rare and probably under-reported complication of leprosy multi-drug therapy. It should be considered when patients complain of flu-like symptoms after taking their monthly rifampicin.

Lomonte C, Chiarulli G, Cazzato F, Giammaria B, Marchio G, Losurdo N, Antonelli M, Casucci F, Basile C. End-stage renal disease in leprosy. *I nephrol* 2004; 17(2):302-5.

Background, Leprosy or Hansen's disease (HAD) undoubtedly remains an emergency in certain countries. It is an ancient deforming disease caused by *Mycobacterium leprae*. The countries with the highest endemic leprosy rate in 2000 were Brazil, India and Madagascar. In Italy, the old epidemic has been defeated and there are approximately 400 patients under constant monitoring with three to four new cases per year involving Italian residents. The kidney is one of the target organs during the splanchnic localization of leprosy. The histopathological renal lesion spectrum includes glomerulonephritis (GN), renal amyloidosis (RA) and interstitial nephritis (IN). Both proteinuria and chronic renal failure are the main clinical expressions of renal damage in leprosy. To the best of our knowledge, very little is reported concerning end-stage renal disease (ESRD) in leprosy patients both in the most important national and international renal registries and in the available literature. This study aimed to report the

long-term experience of our department in this field. Methods: To achieve this, we analyzed retrospectively the HAD Center (Gioia del Colle) database at our hospital. Results: Eight leprosy patients were dialyzed from 1980 to June 2003 (six males and two females), with a mean age of 61.0+/-8.9 SD yrs (range: 51-76) and a mean HAD duration of 36.1+/-5.1 yrs. The first clinical nephropathy manifestations were non-nephrotic proteinuria associated with chronic renal failure in four patients, and nephrotic proteinuria in four patients. Kidney biopsies performed in three patients showed two had RA, and one had IN. Two patients were treated initially by peritoneal dialysis; they were then switched to hemodialysis (HD) after 3 and 10 months because of recurrent peritonitis. HD treatment lasted 40.6+/-31.4 months (range: 9-101). Six patients died, one due to hyperkalemia, one because of a technical dialysis accident, and the remainder due to causes unrelated to the dialysis treatment. Two patients are still alive, treated with HD for 17 and 44 months. Conclusions: Uremia represents a late complication of leprosy and has a multifactorial genesis, although RA is among the most frequent causes, conventional bicarbonate HD appears to offer good results in the treatment of uremia in leprosy patients.

Rijal A, Agrawal S, Agarwalla A, Lakhey M.

Bullous erythema nodosum leprosum: a case report from Nepal. *Lepr rev* 2004; 75(2):177-80.

A patient with lepromatous leprosy, while on WHO multidrug therapy (MDT) for multibacillary disease, was diagnosed as having dapsone syndrome with recurrent episodes of bullous lesions on the lower extremities for 4-5 years. The lesions were associated with high-grade fever. Examination revealed multiple hypopigmented macules on the limbs. Multiple atrophic scars were also found on the buttocks and lower limbs. Bilateral ulnar, radial cutaneous and lateral popliteal nerves were thickened. On day 10 of WHO-MB-MDT he developed a flaccid bulla on the lower leg. Skin slit smear showed a bacterial index (BI) of 3+ and the histopathology was consistent with type II reaction. High dose corticosteroid therapy was started but he continued to have new lesions, and was therefore referred to a centre where thalidomide was available. Clinical response was good and he remained symptom-free after gradual reduction in dosage. ENL should be differentiated from bullous drug reactions, pemphigus vulgaris, bullous pemphigoid and other blistering diseases.

EPIDEMIOLOGIA

Brandsma W, Larsen M, Richard C, Ebenezer M. Inter-rater reliability of WHO 'disability' grading. *Lepr rev* 2004; 75(2):131-4.

The World Health Organization 'disability' grading system was introduced in 1960. It is mainly used as an indicator for early diagnosis or reporting. Disability

grades are usually aggregated at national levels. Comparison of data with previous years or comparison of data between programmes may show that patients report earlier for treatment, alternatively, are diagnosed earlier, that is without, or with fewer 'disabilities'. Despite its long and universal use as an epidemiological parameter, the WHO disability grading has not been the subject of reliability studies. In this study, three testers unfamiliar with the grading prior to the study each graded 65 (former) leprosy affected persons. The weighted kappa ranged from 0.87 to 0.89 (95% CI 0.73-1.00) for the highest score and from 0.90 to 0.96 (95% CI 0.90-0.99) for the EHF (Eye, Hand, Foot) score, indicating excellent reliability. The study shows that with limited training and little experience a high degree of reliability in grading 'disabilities' between testers is attainable.

Jianping S, Wenzhong L, Meiwen Y, Jun Y, Longchao Z, Rongmao W, Lufang H, Hongjiang M, Fuchang Y, Xinguo H, Ljangde P. Analysis on the detection of new leprosy cases before, during and after the year of leprosy elimination campaigns. *Lepr rev* 2004; 75(2):157-63.

To analyse the impact on of case finding of leprosy elimination campaigns (LECs), data on newly detected leprosy cases in a leprosy endemic area were collected before, during and after the year of LEC. The number of new leprosy cases detected during the year of LEC was significantly higher than previously. The number of newly detected cases after the year of LEC was similar to that of detected before the year of LEC in counties with persisting case finding activities. However, the number of newly detected cases after the year of LEC significantly decreased in counties without active case finding activities. The average distance from the homes of leprosy cases detected during LEC to the leprosy control unit at the count town was 62.8 km, which is farther than that of other leprosy cases detected before and after the year of LEC. The average time from disease onset to diagnosis of leprosy cases detected after the year of LEC shortened. The results also showed that carrying out LECs is unlikely to have a significant impact on the trend of case finding within a short time in local areas, but it may improve some indicators of leprosy patients and so promote leprosy control in local areas.

EPIDEMIOLOGIA/ CLÍNICA

Kumar B, Dogra S, Kaur I. Epidemiological characteristics of leprosy reactions: 15 years experience from north India. *Int j lepr* 2004; 72(2):125-33.

A retrospective analysis of patient's leprosy clinic records at PGIMER, Chandigarh, India for the period 1983 to 1998 was undertaken to study the frequency, time of onset, and risk factors for leprosy reactions. Of the 2600 cases analyzed, 1494 were multibacillary and 1106 had

paucibacillary disease. Presentation with reaction was common with 30.9% of our patients having reactions at the time of first visit. The incidence of reversal reaction (RR) was highest during 6 to 12 months after starting multi-drug therapy (MDT), thereafter declining gradually. Late RR occurred in 9.5% of all cases and was noted up to 7 years after treatment. Female gender, widespread disease, and multibacillary disease were identified as risk factors for RR. Erythema nodosum leprosum (ENL) reactions were noted to occur mostly during second or third year after starting MDT. Of the total number of patients who experienced ENL, 64.3% had recurrent episodes which continued for up to 8 years after the start of treatment. Lepromatous leprosy, female gender, and high Bacterial Index ($>1=3$) were recognized as risk factors for developing ENL. Occurrence of recurrent and late reactions, even though of mild severity, highlights the importance of recognizing and treating them promptly to prevent or reduce morbidity, complications, and further deterioration in the disability status. Although it is hoped that leprosy will have been eliminated at all levels by 2005, the recognition and management of these reactions will continue to be the most essential/significant task in the post elimination era.

EPIDEMIOLOGIA/CONTROLE

Al Samie AR, Al Qubati Y. Leprosy control in the Republic of Yemen: co-operation between government and non-government organizations, 1989-2003. *Lepr rev* 2004; 75(2):164-70.

Although the prevalence rate of leprosy in the Republic of Yemen has dropped below the WHO elimination level of less than one case per 10,000 of the population, it is still regarded as a serious public health problem calling for continued vigilance, notably in the detection and treatment of hidden and undiagnosed cases. In the past, religious misinterpretation has generated adverse patterns towards people affected by leprosy, characterized by aggression, negligence and isolation. Until about 1982, following a visit of a leprologist (Dr S. K. Noordeen) from the World Health Organization, there was no leprosy control programme and attempts to establish one remained ineffective until in 1989, when an agreement was signed between the Ministry of Public Health and Population and the German Leprosy Relief Association. This led to the development of a leprosy control programme in four governorates, later extended to the rest of the country. This paper describes the progress made in the control of leprosy in the Yemen, 1989-2003, by the Ministry of Health and Population and the GLRA, in association with two local societies.

EPIDEMIOLOGIA/INCAPACIDADE

Nienhuis WA, van Brake! WH, Butlin CR, van der Werf TS. Measuring impairment caused by

leprosy: inter-tester reliability of the WHO disability grading system. *Lepr rev* 2004; 75(3):221-32.

This paper reports the results of a study on the inter-tester reliability of the WHO disability grading system. The WHO disability grading system is the most frequently used method of grading impairment in leprosy patients. With this method, a grade of 0-2 is assigned to each of six individual body sites (both eyes, hands and feet). The maximum grade of any of these sites is used as an overall indicator of the person's impairment status. To date, the WHO disability grading scale has not been subjected to reliability testing. The reliability of the grading system depends on the operational definitions of the grades, the way the tester interprets these definitions and the skill of the tester. It is therefore important that the definitions are unambiguous and leave as little room as possible for multiple interpretations. Three testers with varying degrees of experience did paired assessments on a total of 150 leprosy patients in the Leprosy Mission Hospital Purulia, India, using recently published operational definitions of the WHO disability grades. For every patient, they determined the maximum grade (minimum 0, maximum 2), and calculated the impairment sum-score (EHF score), adding up the six grades for eyes, hands and feet (minimum 0, maximum 12). The weighted Kappa statistic (Kw) was used as the coefficient of inter-tester reliability. A kappa of 0 represents agreement no better than chance, and 1.0 complete (chance-corrected) agreement. Kw values of $>$ or $=$ 0.80 are considered very good and adequate for monitoring and research. Weighted Kappa analysis yielded a reliability coefficient of 0.89 (95%CI 0.84-0.94) for the maximum grade and a Kw of 0.97 (95%CI 0.96-0.98) for the EHF score. We concluded that, when using standard operational definitions, the WHO disability grading system can be used reliably in the hands of both experienced and inexperienced testers, provided adequate training has been given. Reliability should be evaluated further in a field setting, when used by primary health care workers. It is recommended that the 'WHO disability grading' be renamed 'WHO impairment grading', using the terminology as defined by the International Classification of Functioning, Disability and Health (ICF).

GENÉTICA

Buschman E, Skamene E. Linkage of leprosy

susceptibility to Parkinson's disease genes. *Int j lepr* 2004; 72(2):169-70.

In early 2003, an international team of scientists conducted a genome scan in Vietnamese multiplex leprosy families and found that susceptibility to leprosy was significantly linked to region q25 on the long arm of chromosome 6. Further confirmation of the chromosome 6 locus was provided by high-resolution linkage mapping in simplex leprosy families. Now, in a continuation of these findings, the team has pinpointed

the chromosome 6 susceptibility locus to the 5' regulatory promoter region shared by both the Parkinson's disease gene PARK2 and its co-regulated gene PACRG. The surprising discovery has important implications for the understanding of leprosy pathogenesis and for the strategy of genetic analysis of infectious diseases.

Fitness J, Floyd S, Warndorff DK, Sichali L, Mwaungulu L, Crampin AC, Fine PE, Hill

AV. Large-scale candidate gene study of leprosy susceptibility in the Karonga district of northern Malawi. *Am J trop med hyg* 2004; 71(3):330-40.

We present a large case-control candidate gene study of leprosy susceptibility. Thirty-eight polymorphic sites from 13 genes were investigated for their role in susceptibility to leprosy by comparing 270 cases with 452 controls in Karonga district, northern Malawi. Homozygotes for a silent T→C change in codon 352 of the vitamin D receptor gene appeared to be at high risk (odds ratio [OR] = 4.3, 95% confidence interval [CO] = L6-11.4, P = 0.004), while homozygotes for the McCoy b blood group defining variant K1590E in exon 29 of the complement receptor 1 (formerly CD35) gene appeared to be protected (OR = 0.3, 95% CI = 0.1-0.8, P = 0.02). Borderline evidence for association with leprosy susceptibility was found for seven polymorphic sites in an additional six genes. Some of these apparent associations may be false-positive results from multiple comparisons, and several associations suggested by studies in other populations were not replicated here. These data provide evidence of inter-population heterogeneity in leprosy susceptibility.

Jamieson SE, Miller EM, Black CF Peacock CS, Cordell HJ, Howson JM, Shaw MA, Burgner D, Xu W, Lins-Lainson Z, Shaw JJ, Ramos F, Silveira F, Blackwell JM. Evidence for a cluster of genes on chromosome 17q11-q21 controlling susceptibility to tuberculosis and leprosy in Brazilians. *Genes Immun* 2004; 5(1):46-57.

The region of conserved synteny on mouse chromosome 11/human 17q11-q21 is known to carry a susceptibility gene(s) for intramacrophage pathogens. The region is rich in candidates including NOS2A, CCL2/MCP-1, CCL3/MIP-1 alpha, CCL4/MIP-1 beta, CCL5/RANTES, CCR7, STAT3 and STAT5A/5B. To examine the region in man, we studied 92 multicasle tuberculosis (627 individuals) and 72 multicasle leprosy (372 individuals) families from Brazil. Multipoint nonparametric analysis (ALLEGRO) using 16 microsatellites shows two peaks of linkage for leprosy at D17S250 (Z(Ir) score 2.34; P=0.01) and D17S1795 (Z(Ir) 2.67; P=0.004) and a single peak for tuberculosis at D17S250 (Z(Ir) 2.04; P=0.02). Combined analysis shows significant linkage (peak Z(Ir) 3.38) at D17S250, equivalent to an allele sharing LOD score 2.48

(P=0.0004). To determine whether one or multiple genes contribute, 49 informative single nucleotide polymorphisms were typed in candidate genes. Family-based allelic association testing that was robust to family clustering demonstrated significant associations with tuberculosis susceptibility at four loci separated by intervals (NOS2A-8.4 Mb-CCL18-32.3 kb-CCL4-6.04 Mb-STAT5B) up to several Mb. Stepwise conditional logistic regression analysis using a case/pseudo-control data set showed that the four genes contributed separate main effects, consistent with a cluster of susceptibility genes across 17811.2.

Miller EM, Jamieson SE, Joberty C, Fakiola M, Hudson D, Peacock CS, Cordell HJ, Shaw MA, Lins-Lainson Z, Shaw JJ, Ramos F, Silveira F, Blackwell JM. Genome-wide scans for leprosy and tuberculosis susceptibility genes in Brazilians. *Genes immun* 2004; 5(1):63-7.

Genome-wide scans were conducted for tuberculosis and leprosy per se in Brazil. At stage 1, 405 markers (10 cM map) were typed in 16 (178 individuals) tuberculosis and 21 (173 individuals) leprosy families. Nonparametric multipoint analysis detected 8 and 9 chromosomal regions respectively with provisional evidence (P<0.05) for linkage. At stage 2, 58 markers from positive regions were typed in a second set of 22 (176 individuals) tuberculosis families, with 22 additional markers typed in all families; 42 positive markers in 50 (192 individuals) new leprosy families, and 30 additional markers in all families. Three regions (10g26.13, 11q12.3, 20p12.1) retained suggestive evidence (peak LOD scores 1.31, 1.85, 1.78; P=0.007, 0.0018, 0.0021) for linkage to tuberculosis, 3 regions (6p21.32, 17q22, 20p13) to leprosy (HLA-DQA, 3.23, P=5.8 x 10⁻⁵); D17S1868, 2.38, P=0.0005; D20S889, 1.51, P=0.004). The peak at D20S889 for leprosy is 3.5 Mb distal to that reported at D20S115 for leprosy in India.

Wallace C, Fitness J, Hennig B, Sichali L, Mwaungulu L, Pönnighaus TM, Warndorff DK, Clayton D, Fine PE, Hill AV. Linkage analysis of susceptibility to leprosy type using an IBD regression method. *Genes Immun* 2004; 5(3):221-5.

Leprosy is a chronic disease caused by infection with *Mycobacterium leprae*, which is manifested across a wide clinical spectrum. There is evidence that susceptibility both to leprosy per se and to the clinical type of leprosy is influenced by host genetic factors. This paper describes the application of an identity by descent regression search for genetic determinants of leprosy type among families from Karonga District, Northern Malawi. Suggestive evidence was found for linkage to leprosy type on chr 21q22 (P<0.001). The methodological implications of the approach and the findings are discussed.

IMUNOLOGIA

Faber WR, Iyer AM Fajardo TT, Dekker T, Villahermosa LG, Abalos RM, Das PK. Serial measurement of serum cytokines, cytokine receptors and neopterin in leprosy patients with reversal reactions. *Lepr rev* 2004; 75(3):274-81, 2004.

Serum levels of cytokines (IL-4, IL-5, IFN-gamma, TNF-alpha), cytokine receptors (TNFR I and II) and one monokine (neopterin) were estimated in seven leprosy patients to establish disease associated markers for reversal reactions (RR). Sera were collected at diagnosis of leprosy, at the onset of reversal reaction and at different time points during and at the end of prednisone treatment of reactions. It was expected that the serum cytokine and monokine profile before and at different time points during reactions would provide guidelines for the diagnosis and monitoring of reversal reactions in leprosy. The cytokines and cytokine receptors were measured by ELISA, whereas a radioimmunoassay was used for neopterin measurement. Six of the seven patients showed increased levels of neopterin either at the onset of RR or 1 month thereafter, and levels declined on prednisone treatment to that seen at the time of diagnosis without reactions. No consistent disease associated cytokine profile was observed in these patients. Interestingly, serum TNF-alpha levels were increased in the same patients even after completion of prednisone treatment, indicating ongoing immune activity. In conclusion, this study demonstrates that despite cytokines levels in leprosy serum being inconsistent in relation to reversal reactions, serum neopterin measurement appears to be a useful biomarker in monitoring RR patients during corticosteroid therapy.

Kimura H, Maeda Y, Takeshita F, Takaoka LE, Matsuoka M, Makino M. upregulation of T-cell-stimulating activity of mycobacteria-infected macrophages. *Scand j immunol* 2004; 60(3):278-86.

Macrophages are one of the most abundant host cells to come in contact with mycobacteria. However, the infected macrophages less efficiently stimulate autologous T cells in vitro. We investigated the effect of the induction of phenotypic change of macrophages on the host cell activities by using *Mycobacterium leprae* as a pathogen. The treatment of macrophages with interferon-gamma (IFN-gamma), GM-CSF and interleukin-4 deprived macrophages of CD14 antigen expression but instead provided them with CD1a, CD83 and enhanced CD86 antigen expression. These phenotypic features resembled those of monocyte-derived dendritic cells (DC). These macrophage-derived DC-like cells (MACDC) stimulated autologous CD4+ and CD8+ T cells when infected with *M. leprae*. Further enhancement of the antigen-presenting function and CD1a expression of

macrophages was observed when treated with IFN-gamma. The *M. leprae*-infected and treated macrophages expressed bacterial cell membrane-derived antigens on the surface and were efficiently cytolysed by the cell membrane antigen-specific CD8+ cytotoxic T lymphocytes (CTL). These results suggest that the induction of phenotypic changes in macrophages can lead to the upregulation of host defence activity against *M. leprae*.

Mohanty KK, Joshi B, Katoch K, Sengupta U. Leprosy reactions: humoral and cellular immune responses to *M. leprae*, 65kDa, 28kDa, and 18 kDa antigens. *Int j lepr* 2004; 72(2):149-58.

This study examines the immune responses against some stress proteins of *Mycobacterium leprae* in leprosy patients with and without leprosy reactions. Leprosy patients showed a higher level of antibodies to all antigens compared to healthy controls. The antibody response to 18kDa antigen was significantly higher in patients with Type 1 reaction compared to those of TT or borderline patients without Type 1 reaction, or those with Type 2 reaction. Borderline (BT/BL), lepromatous (LL) and patients with reactions (Type 1 and Type 2) had higher levels of antibodies to *M. leprae* soluble extract (MLSE) and 65kDa than those of the tuberculoid (TT) group. LL, borderline patients, and patients with Type 1 reaction had a higher level of antibody to 28kDa than those of healthy controls. However, no significant differences could be observed in antibody response to these antigens (MLSE, 65kDa, and 28kDa) between patients with reaction and without reaction. A significant proportion of TT/BT patients showed positive lymphoproliferative response to MLSE compared to BULL patients. In addition, the lymphoproliferative response to MLSE was significantly greater in patients with Type 1 reaction compared to patients without reaction. No difference in proliferative response to 65kDa could be observed in any of these groups. The finding of high levels of antibodies against stress proteins in patients with Type 1 reactions, especially to 18 kDa antigen, along with a heightened lymphoproliferative response to MLSE is suggestive of a coexistence of cell mediated and humoral immunity in leprosy patients during Type 1 reactions. On the other hand, in Type 2 reactions no significant role of stress proteins could be demonstrated except a heightened lymphoproliferative response to the 28 kDa antigen.

Quiroga MF, Martinez GJ, Pasquinelli V, Costas MA, Bracco MM, Malbrán A, Olivares LM, Sieling PA, Garcia VE. Activation of signaling lymphocytic activation molecule triggers a signaling cascade that enhances Th1 responses in human intracellular infection. *J immunol* 2004; 173 (6):4120-9.

T cell production of IFN-gamma contributes to host defense against infection by intracellular pathogens,

including mycobacteria. Lepromatous leprosy, the disseminated form of infection caused by *Mycobacterium leprae*, is characterized by loss of cellular response against the pathogen and diminished Th1 cytokine production. Relieving bacterial burden in Ag-unresponsive patients might be achieved through alternative receptors that stimulate IFN-gamma production. We have previously shown that ligation of signaling lymphocytic activation molecule (SLAM) enhances IFN-gamma in mycobacterial infection; therefore, we investigated molecular pathways leading from SLAM activation to IFN-gamma production in human leprosy. The expression of the SLAM-associated protein (an inhibitory factor for IFN-gamma induction) on *M. leprae*-stimulated cells from leprosy patients was inversely correlated to IFN-gamma production. However, SLAM ligation or exposure of cells from lepromatous patients to a proinflammatory microenvironment down-regulated SLAM-associated protein expression. Moreover, SLAM activation induced a sequence of signaling proteins, including activation of the NF-kappaB complex, phosphorylation of Stat1, and induction of T-bet expression, resulting in the promotion of IFN-gamma production, a pathway that remains quiescent in response to Ag in lepromatous patients. Therefore, our findings reveal a cascade of molecular events during signaling through SLAM in leprosy that cooperate to induce IFN-gamma production and strongly suggest that SLAM might be a focal point for therapeutic modulation of T cell cytokine responses in diseases characterized by dysfunctional Th2 responses.

Youn JH, Myung HJ, Liav A, Chatterjee D, Brennan PJ, Choi IH, Cho SN, Shin JS. Production and characterization of peptide mimotopes of phenolic glycolipid-I of *Mycobacterium leprae*. *FEMS Immunol med microbial* 2004; 41(1):51-7.

Phenolic glycolipid-I (PGL-I), a *Mycobacterium leprae* specific antigen, has been widely used for the serodiagnosis of leprosy and has been implicated in the pathogenesis of leprosy. In an effort to produce an alternate antigen of PGL-I, the mimotope peptides of PGL-I, W(T/R)LGPY(V/M), were obtained using a monoclonal antibody, 111603.8, specific to PGL-I by a phage library. The biotin-labeled predominant mimotope peptide of PGL1, WTLGPYV, bound to 111603.8 in a dose-dependent manner in an immunoassay. However, PGLP1 did not bind to anti-PGL-I antibodies in the serum samples from leprosy patients that were reactive to PGL-I. Although the mimotope peptide of WTLGPYV was not effective as an alternate antigen of PGL-I for the serodiagnosis of leprosy, but it would be of interest to know how the mimotope peptides mimic the role of PGL-I antigen in the pathogenesis of *M. leprae* infection.

IMUNOLOGIA EPIDEMIOLOGIA

Sinha S, Kannan S, Nagaraju B, Sengupta U, Gupte MD. utility of serodiagnostic tests for leprosy: a study in an endemic population in South India. *Lepr rev* 2004; 75(3):266-73. In order to evaluate the usefulness of natural disaccharide (PGL1) and 35 kDa antigens based serology in diagnosis of leprosy and in detecting high risk groups for leprosy, this study was conducted in an endemic population in South India. Out of 3346 cases and their households and neighbouring household contacts, serum samples from 2994 and 2875 individuals were screened for antibodies against PGL1 and 35kDa antigens respectively. While the overall positivity for contacts and leprosy cases was 3.3% for PGL1 antibody, the positivity for 35 kDa antibody was 6.3%. The positivity for contact population was 2.7% and 5.4% for PGL1 and 35 kDa antibodies, respectively. Lepromatous and borderline lepromatous patients showed positivity of 35.1% for PGL1 antibody and 45.7% for 35 kDa antibody. Follow-up of contacts showed that the majority (>90%) remained seronegative for both the antibodies and most of the new cases emerged from the seronegative group. The study clearly indicates that specific serological assays are not sensitive enough for application, both for diagnosis and for identifying any individual at risk for leprosy in the south Indian endemic population.

LABORATÓRIO CLÍNICO

Muruganand D, Daniel E, Ebenezer GJ, Rabboni SE, Segar P, Job CK. *Mycobacterium leprae* infection and serum lactoferrin levels. *Lepr rev* 2004; 75(3):282-8.

Serum lactoferrin level, using competitive enzyme linked immunosorbent assay (ELISA) method, was estimated in 298 leprosy patients admitted into the hospital and attending the out-patient department of the Schieffelin Leprosy Research and Training Center. Serum from an equal number of non-leprosy individuals served as control. Mean (SD) of serum lactoferrin in non-leprosy individuals was 0.277 (0-092) microg/ml while in leprosy patients it was 0.494 (0.394) microg/ml, the difference being significant ($P=0.0001$). Serum lactoferrin levels were not significantly associated with type 2 reactions ($P=0.613$). Serum lactoferrin was significantly associated with age ($P=0.006$), duration of the disease ($P=0.0001$), DDS monotherapy ($P=0.007$), deformity ($P=0.005$), average bacterial index (BI) ($P=1.01$) and smear positivity ($P=0.0001$), orbicularis oculi weakness ($P=0.001$), lagophthalmos ($P=0.002$), corneal opacity ($P=0.001$) and cataract ($P=0.004$) in simple regression analysis. All these variables, with the exception of smear positivity ($P=0.019$), lost their significance ($P>0.05$) when analysed

using multiple regression. Serum lactoferrin showed poor association with type 1 ($P = 0.286$) and type II reactions ($P = 0.613$) and iridocyclitis ($P = 0.207$). We conclude that serum lactoferrin is strongly and inversely associated with increasing BI but does not show significant association with type 2 reactions.

NEUROLOGIA

Golan JD, Jacques L. Nonneoplastic peripheral nerve tumors. *Neurosurg clin N Am* 2004;15(2):223-30.

Most of the nonneoplastic tumor-like lesions affecting the peripheral nervous system are rarely encountered. In many situations, a good history of the presenting symptoms can suggest a reactive or infectious neuroma. The physical examination can also suggest an inflammatory or hyperplastic lesion. In some cases, however, the correct diagnosis can only be made at surgery. Nonetheless, awareness of these lesions is important in limiting unnecessarily aggressive surgical procedures. Patients suspected of having nonneoplastic lesions are followed and treated surgically for symptomatic relief or when the diagnosis is unclear. In some situations, the surgical treatment of choice may be debated. Nevertheless, we adopt a conservative approach to these lesions and reserve more aggressive techniques for cases that do not respond to more conservative means.

Jardim MR, Chimelli L, Faria SC, Fernandes PV, Da Costa Néri JÁ, Sales AM, Sarno EM, Gomes Antunes SL. Clinical, electroneuromyographic and morphological studies of pure neural leprosy in a Brazilian referral centre. *Lepr rev* 2004; 75(3):242-53.

Nineteen patients with pure neural leprosy were analysed with clinical examination, electroneuromyography and histopathology of nerve biopsies. Clinical examination showed sensory loss (78.9%), paresis (78.9%), nerve enlargement (68.4%) and nerve pain (42.1%). Electroneuromyographic study revealed an axonal pattern in 18 patients (94.7%) and a demyelinating pattern in one (0.5%). Mononeuropathy multiplex was the most frequent presentation (78.9%), followed by mononeuropathy simplex (10.5%) and polyneuropathy (10.5%). The histopathological study showed the presence of inflammatory infiltrate composed of epithelioid granuloma (42.1%), mononuclear infiltrate (36.8%) or macrophages positive for bacilli (21%). Fibrosis was present in 78.9% of the biopsies. Examination of semithin sections revealed, besides inflammatory infiltrate, myelinated fibre loss (94.7%), remyelination (42%), axonal degeneration (10%) as well as regeneration (31.5%). Based on these results, the pathogenesis of leprosy neuropathy in this group of patients is briefly discussed.

Kumar A, Girdhar A, Girdhar BK. Nerve thickening in leprosy patients and risk of paralytic deformities: a field based study in Agra, India. *Lepr rev* 2004; 75(2):135-42.

This paper examines the extent of nerve thickening among leprosy patients detected in the field in Agra district. All the clinically diagnosed leprosy patients were examined in detailed for thickening of local cutaneous nerves and peripheral nerve trunks. In each case all the major nerve trunks in both upper and lower extremities, forehead and neck were examined for thickening. Nerve thickening was found in 94% of multibacillary (MB) patients and among 52% paucibacillary (PB) patients. Nerve thickening was found to be more in males, in prevalent cases than in new (untreated) cases and increased significantly with age and delay in diagnosis ($P < 0.001$). Visible deformities of grade $>$ or $=2$ were found in 10% (58/573) of the leprosy patients; paralytic deformity accounted for 78% (45/58). Claw hand alone or in combination was seen in 82% (37/45) of patients with paralytic deformities. Risk (odd ratio) for deformities was observed to be high (15-18 times) with increasing number of nerves among patients with neuritic leprosy but correlated with delay in diagnosis of over 5 years. Likewise, deformities were more often seen in those with skin lesions, provided they had $>$ or $=3$ thickened nerves. Findings suggest that early detection and treatment is useful in preventing deformities.

Ooi WW, Srinivasan J. Leprosy and the peripheral nervous system: basic and clinical aspects. *Muscle nerve* 2004; 30(4):393-409.

Leprosy is one of the most common causes of nontraumatic peripheral neuropathy in the developing world. The causative agent, *Mycobacterium leprae*, has a predilection for Schwann cells, where the organism multiplies unimpeded by organism-specific host immunity, resulting in destruction of myelin, secondary inflammatory changes, and destruction of the nerve architecture. The cardinal diagnostic features of leprosy are anesthetic skin lesions, neuropathy, and positive skin smears for the bacilli. However, patients may rarely present without skin lesions in pure neuritic leprosy. Electrodiagnostic findings early in the disease reveal demyelinating features, such as slowing of conduction velocity and prolongation of latencies, but as the disease progresses secondary axonal damage commonly ensues. Electrodiagnostic studies are also useful to monitor for toxicity secondary to therapy, particularly thalidomide-associated neuropathy. Nerve biopsy of a sensory cutaneous nerve is sometimes essential to confirm a diagnosis of leprosy. Significant advances in understanding of the pathogenesis, mapping of the genome, and other advances in molecular biology may result in better preventive and therapeutic modalities, and the goal of eradicating leprosy as a global problem may yet be realized.

Pimentel MI, Nery JA, Borges E, Gonçalves RR, Sarno EM. Impairments in multibacillary leprosy; a study from Brazil. *Lepr rev* 2004; 75(2):143-52.

This is a retrospective cohort study of 103 multibacillary leprosy patients (18% BB, 48% BL and 34% LL) followed during and after treatment, in a tertiary referral centre with an outpatient clinic in an endemic area in Brazil, for an average period of 65 months since the start of multidrug therapy (24-dose MDT). The objective of the study was to identify the role of overt neuritis (presence of pain in a peripheral nerve trunk, with or without enlargement or neural function damage), in the development of impairments. They were evaluated using the World Health Organization disability grade before treatment, at the end of the treatment, and at the end of the follow-up period. Thirty-four percent of patients presented overt neuritis during MDT, and 45% had overt neuritis episodes during the follow-up period; the most commonly affected nerves were ulnar, fibular and posterior tibial nerves, and the neuritic episodes were carefully treated with steroid therapy and physiotherapy. Impairments were associated with: affected (painful and/or thick) nerves at diagnosis ($P < 0.005$); delay in diagnosis ($P = 0.010$); impairments already present at the start of treatment ($P = 0.00041$ at the end of MDT, and $P = 0.000013$ at the end of follow-up); occurrence of overt neuritis episodes during MDT ($P = 0.0016$) or the whole follow-up ($P = 0.015$). These data draw attention to the importance of early diagnosis and of good neurological examination throughout the follow-up, as well as suggest the importance of neuritis in the induction of impairments in multibacillary leprosy.

NEUROLOGIA/ DOR

Croft R. Neuropathic pain in leprosy. *Int j lepr* 2004; 72(2):171-20.

Neuropathic pain appears to be much more common in leprosy than has been generally appreciated. Emphasis in leprosy control programs has been on the distribution of multidrug therapy, on early and better detection, and on the prevention of disability related to anesthetic limbs. Most have thus been inattentive to the problem of neuropathic pain in leprosy patients. Neuropathic pain does not respond to the usual analgesics employed for reactions, for example, and so it is important that those treating leprosy patients give this problem the special attention it requires, both in diagnosis and in treatment.

Stump PR, Baccarelli R, Marciano LH, Lauris JR, Teixeira MJ, Ura S, Virmond MC. Neuropathic pain in leprosy patients. *Int j lepr* 2004; 72(2):134-8.

The introduction of multidrug therapy by the World Health Organization has dramatically reduced the world

prevalence of leprosy but the disease is still a public health problem in many countries, with a world prevalence of almost 600,000 cases in 2001. Damage to peripheral nerves is a key component of leprosy and the sensory and motor loss that follows is the basis for many of the classical features of this disease, such as skin wounds, cracks, plantar ulcers, clawed hands, drop foot, and incomplete closure of the eyelids. One of the most remarkable aspects of leprosy to lay persons and health care workers alike is that patients are reputed to feel no pain. However, neuropathic pain is arising as a major problem among leprosy patients. It can be nociceptive due to tissue inflammation, which mostly occurs during episodes of immune activation or neuropathic due to damage or dysfunction of the nervous system. This study, conducted among 358 leprosy patients, reveals a considerable prevalence of neuropathic pain and presents evidence that this common problem should be a high priority of those in charge of leprosy control programs.

NEUROFISIOLOGIA

Soysal A, Atay T, Ozu T, Arpacı B. Electrophysiological evaluation of peripheral and autonomic involvement in leprosy. *Can j neurol sci* 2004; 31(3):357-62.

Motor and sensory nerve conductions, F responses, sympathetic skin responses and R-R interval variations (RRIV) were studied to determine the type of peripheral neuropathy among patients with leprosy. **Methods:** Twenty-nine consecutive patients with leprosy (25 male, 4 female) hospitalized in the "Istanbul Leprosy Hospital" between January - December, 1999 were included in this study. Ten patients had borderline lepromatous leprosy, and 19 had lepromatous leprosy. None of the patients studied had the tuberculoid form. The mean age was 55 +/- 12 years. The control group consisted of 30 (26 male, 4 female) healthy volunteers (mean age: 58.1 +/- 7.8 years). All subjects included in the study underwent neurological examination and electrophysiological evaluation. Standard procedures were performed for evaluating sensory and motor conduction studies. Motor studies were carried out on both left and right median, ulnar, tibial and common peroneal nerves while median, ulnar, sural and superficial peroneal nerves were examined for sensory studies. Sympathetic skin response recordings on both hands and RRIV recordings on precordial region were done in order to evaluate the autonomic involvement. **Results:** The lower extremity was found to be more severely affected than the upper, and sensory impairment predominated over motor. Of 58 upper limbs examined, no sympathetic skin responses was recorded in 46 (79.3%). Compared with the controls, the RRIVs of the leprosy patients were found to be reduced during both resting and deep forced hyperventilation. **Conclusion:** Our results indicate that leprosy causes a predominantly axonal polyneuropathy that is more severe in the lower extremities. Sensory nerve damage is accompanied by autonomic involvement.

NEUROATOLOGIA

Furuta M, Hatano K, Okano Y, Matsuki T, Ikeda T, Nakatani K, Sato A, Mizushima M. Axonal spherical bodies in the peripheral nerves of leprosy patients. *Int j lepr* 2004; 72(2):159-65.

Spherical bodies, roughly 10 micro m in diameter, which have not been reported before, were found in the peripheral nerve axons of specimens collected during post-mortem examination of leprosy patients. These bodies were found in the fascicles of all peripheral nerves of the extremities examined (median, radial, ulnar, peroneal and sciatic nerves). Their incidence was not related to the type of leprosy. The area immediately below the thickened perineurium, a feature associated with leprosy, often showed a large number of spherical bodies. When observed under a transmission electron microscope, the spherical lesions often showed a lamellar structure, although some of them were amorphous. No structure resembling organelles was seen within the bodies. Observation with the merge technique showed a clearly lamellar structure in most of the spherical bodies. These bodies and the surrounding myelin sheaths were partially polarized. The axonal spherical bodies observed in our study seem to represent lesions gradually formed due to glycoprotein denaturation over long periods of time and to be associated with leprosy-caused thickening of the perineurium of peripheral nerves.

Porichha D, Mukherjee A, Ramu G. Neural pathology in leprosy during treatment and surveillance. *Lepr rev* 2004; 75(3):233-41.

The histological findings of 22 patients with neuritis, 14 developing pain, tenderness and swelling during treatment and 8 during surveillance are presented in this study. Seven patients' biopsies showed macrophage type and 14 had epithelioid cell type of granulomas. All biopsies showed evidence of active disease, except for two patients with macrophage granulomas where some regressive changes were evident. One biopsy showed fibrosis with lymphocytic infiltration. The histology of epithelioid cell granulomas had varied histopathological presentations ranging from non-reacting BT to those with severe type I reaction with caseation necrosis, liquefaction and calcification. Two macrophage granulomas showed partial regression though there was neuritis clinically and features of ENL in the biopsy sections. One biopsy showed histoid changes. All the biopsies showed similar histopathological features irrespective of whether neuritis appeared during treatment or surveillance. The features of reaction were severe in nerves, probably due to the adjuvant nature of lipid and myelin in the nerve tissue. The histopathological features of nerve biopsies from patients under surveillance appeared to be ongoing active disease rather than relapse.

REABILITAÇÃO

Knuuttila JP. The fulfilment of health care needs of leprosy patients from Kaski District, Nepal. *Lepr rev* 2004; 75(2):153-6.

Hospital records of 142 leprosy patients from Kaski district in Western Nepal were reviewed to assess their use of leprosy related health services and the fulfilment of these needs. Use of services was reviewed from diagnosis until release from treatment. Voluntary muscle and sensory testing were on average done 15.2 times per patient. Of MB patients, 65.5% had longer intervals between testing than recommended. A course of prednisolone was indicated in 40% of cases, but 10% of needed courses were not given. Twenty-eight percent needed protective footwear. Of the cohort, 10% had complicated ulcers and 28% had at least one admission. Paralytic impairments that could be corrected were present in 10% of the cohort.

REABILITAÇÃO/ CIRURGIA

Chaise F. Current management of hand leprosy. *La prise en charge actuelle des mains lépreuses*. *Chir main* 2004; 23(1):1-16.

Leprosy, a chronic infectious disease caused by *Mycobacterium leprae* affects an estimated 700,000 persons each year. Clinically, leprosy can be categorized as paucibacillary or multibacillary disease. Leprosy is important largely because of the deformities, disabilities and handicap it causes in a proportion of those affected by the disease. There are surgical procedures and techniques to correct or limit the deterioration of these conditions. In the past these surgical procedures were only performed in special institutions for treating leprosy and their complications. However, with the widespread use of multidrug therapy (PCT) and the consequent reduction in the prevalence of leprosy, there is progressive integration of the care of people affected by leprosy into the general health services. Surgery, as in intervention in the management of leprosy and its complications is used in patients who are already under anti-leprosy treatment, or after they have completed it satisfactorily. Therefore, preventive surgery like nerve decompression and corrective surgery should not be practiced in places where there is no leprosy program. This paper describes the nerve decompression for preventing paralytic deformities. Procedures for correction of claw deformity of finger and thumb resulting from ulnar or combined ulnar and median nerve paralysis, so commonly seen in leprosy-affected persons are given separately. In order to carry out these procedures, many involving tendon transfers with or without tendon grafting, the surgeon has to be well versed in the structural and functional anatomy of the

hand and should training in hand surgery. Furthermore, supportive physiotherapy and if possible, occupational therapy services for pre and post-operative management of the hand should be available. If the corrective procedures are carried out in the absence of any of these requirements, the venture is bound to result in failure, worsen the hand disability as well as make any subsequent correction very much more difficult.

Joshua J, Sarkar S. Management of 34 chronic heel sinuses in leprosy, using a modification of a local rotation flap in Kolkata, India. *Lepr rev* 2004; 75(3):254-65.

We have seen 55 trophic ulcers of the heel in 2 years in our hospital, between March 2000 and February 2002. Thirty-four were chronic heel sinuses, six cases of multiple sinuses and 28 cases of single sinus of the plantar aspect of the heel. All these cases were treated by excision of the sinus, paring the prominence of the calcaneum, or excision of the cavity within the calcaneum and coverage by a rotation flap or a modification of this flap. Over the past 6 years, we have evolved a modification of a rotation flap that requires a fusiform incision to excise the sinus, and a curved incision for the flap extending through the instep and the non-weight bearing heel. The fusiform excision, rather than the traditional triangulation, causes the flap to partly transpose rather than rotate completely. The flap is raised superficial to the plantar aponeurosis, exposing the aponeurosis from mid-sole to the heel. It is a modification of a rotation flap. The scarring over the weight-bearing sole is minimal, restricted only to the incision necessary for the excision of the heel sinus and this is its main advantage. Twenty-one of the 34 cases healed without complications. Thirteen cases had complications, of which six were treated non-operatively and seven required either a redo of the flap or another flap cover.

Schwarz RJ, Macdonald M. A rational approach to nasal reconstruction in leprosy. *Plast reconstr surg* 2004; 114(4):876-82.

Destruction of the nasal septum and nasal bones by *Mycobacterium leprae* and subsequent infection is still seen regularly in leprosy endemic areas. The social stigma associated with this deformity is significant. Many different procedures have been developed to reconstruct the nose. Patients operated on at Anandaban Hospital and the Green Pastures Hospital and Rehabilitation Center between 1986 and 2001 were reviewed. There were 48 patients with an average age of 47 years. Five deformities were mild, 22 were moderate, 13 were severe, and eight were not graded. Bone grafting with nasolabial skin flaps was performed in 14 cases, bone grafting alone was performed in 10 cases, flaps alone were performed in seven cases, and cartilage grafting was

performed in 10 cases. In three patients, a prosthesis was inserted, and in three patients a gull wing forehead flap was performed. Overall, excellent or good cosmetic results were obtained in 83 percent of cases. Grafting with conchal cartilage was associated with the best cosmetic results and had minimal complications. Bone grafting with or without nasolabial flaps was associated with a 50 percent complication rate of infection or graft resorption. In mild to moderate deformities, cartilage grafting is recommended; for more severe deformities, bone grafting with bony fixation and skin flaps is recommended. Perioperative antibiotics must be used, and these procedures should be performed by an experienced surgeon. In very severe cases with skin deficiency, reconstruction with a forehead flap gives good results.

Taylor NL, Raj AD, Dick HM, Solomon S. The correction of ulnar claw fingers: a follow-up study comparing the extensor-to-flexor with the palmaris longus 4-tailed tendon transfer in patients with leprosy. *hand sur [Am]* 2004; 29(4):595-604.

Purpose: The extensor to flexor 4-tailed tendon transfer (EF4T) and the palmaris longus 4-tailed tendon transfer (PL4T) are 2 surgical procedures used to correct intrinsic paralysis of the hand in leprosy. The EF4T traditionally is the more common procedure and requires the transfer of a wrist extensor muscle. The PL4T requires the transfer of the palmaris longus and morbidity is expected to be lower. A follow-up study was performed to determine whether the clinical outcome of the PL4T is superior to the EF4T procedure in leprosy patients with ulnar claw fingers that are considered mobile before surgery. **Methods:** Fifty-five patients presented 65 affected hands, of which 40 hands had the PL4T and 25 had the EF4T procedure. Each hand was assessed before surgery and at follow-up evaluation by predetermined angle measurements, standardized photographs, mechanical function, and patient satisfaction. Each hand was given an overall technical grade according to previously published standards. **Results:** After an average follow-up period of 33 months there was no statistically significant difference in the technical outcome or patient satisfaction between the 2 tendon transfer procedures. **Conclusions:** Whenever the palmaris longus is available it may be considered to be the motor tendon of choice to undertake a many-tailed procedure for claw finger reconstruction in mobile hands paralyzed by leprosy. The palmaris longus should be considered as a possible motor tendon when correcting intrinsic muscle paralysis of the hand.

TERAPÉUTICA

Joglekar S, Levin M. The promise of thalidomide: evolving indications. *Drugs today (Bare)* 2004; 40(3):197-204.

Thalidomide was first used in the late 1950s but it was withdrawn from the market in the 1960s for its notorious teratogenic effects. This drug was more recently rediscovered as a powerful immunomodulatory and anti-inflammatory agent and was approved by the FDA in 1998 for treatment of erythema nodosum leprosum. Thalidomide has shown great promise in advanced or refractory multiple myeloma either alone or in combination with other agents. It has also demonstrated benefits in a wide variety of disparate conditions such as aphthous and genital ulcers, cancer cachexia, HIV, tuberculosis and chronic graft versus host disease. Thalidomide is being investigated for treatment of renal cell carcinoma, and liver and thyroid cancers. Better understanding of its many mechanisms of action has provoked great interest in its potential use for treatment of various disorders. This review focuses on thalidomide's mechanisms of action, biochemistry, pharmacokinetics and its use in erythema nodosum leprosum as well as multiple myeloma, graft versus host disease, and renal cell carcinoma.

TERAPÊUTICA/ REAÇÕES ADVERSAS

Pais AV, Pereira S, Garg I, Stephen J, Antony M, Inchara YK. Intra-abdominal, crystal-storing histiocytosis due to clofazimine in a patient with

lepromatous leprosy and concurrent carcinoma of the colon
Lepr rev 2004; 75(2):171-6.

We report a case with abdominal complications of clofazimine treatment which included blackish discolouration of the lymph nodes, omentum and peritoneum. A 44-year-old female with lepromatous leprosy and a history of adverse reaction to clofazimine 2 years previously, presented with rectosigmoid junction adenocarcinoma. Laparotomy revealed an inoperable tumour with pigmentation of the bowel, serosa and peritoneum. A second operation had to be performed for transverse loop colostomy and a mesenteric lymph node biopsy sent for frozen section showed typical clofazimine crystals. Despite widespread use for many years in the treatment of leprosy, this drug is not known to be carcinogenic and this case provides no evidence for an association or link between its use and the patient's cancer. Apart from its use in leprosy, clofazimine may be used in the treatment of disseminated *Mycobacterium avium-intracellulare* infection, Buruli ulcer due to *M. ulcerans* and occasionally in other mycobacterial infections. An awareness of the rare side-effect described above may help in the clinical assessment and management of such cases, including the avoidance of unnecessary laparotomy.