

# LEPROSY AND MULTIPLE ENDOCRINE NEOPLASIA TYPE I: A CASE REPORT AND REVIEW OF LITERATURE

## *Hanseníase e neoplasia endócrina múltipla tipo 1: relato de caso e revisão de literatura*

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### ABSTRACT

**Context:** Leprosy is an infectious disease in which progress to disease and clinical expressions are influenced by environmental factors and by the genetics of the host. The multiple endocrine neoplasia type 1 syndrome (MEN-1) is an inherited disorder that predisposes to endocrine and non-endocrine tumors. **Case report:** A case of multi-bacillary leprosy in the 18-year-old female patient with MEN-1, this association was probably an incidental case of an endemic disease in a susceptible individual with a rare syndrome. The investigation of comorbidities, especially neglected or emergency disease, is very importance, because the lack of early diagnosis may result in serious complications as development of disabilities especially when there is a leprosy late diagnosis.

**Key-words:** Leprosy. Leprosy Borderline. Multiple endocrine neoplasia type 1.

## RESUMO

**Contexto:** A hanseníase é uma doença infecciosa cuja evolução e expressões clínicas são influenciadas por fatores ambientais e pela genética do hospedeiro. A síndrome neoplasia endócrina múltipla tipo 1 (NEM-1) é uma desordem hereditária que predispõe a tumores endócrinos e não-endócrinos. **Relato de caso:** Relata-se um caso de hanseníase multibacilar em paciente de 18 anos de idade com NEM-1. Esta associação foi, provavelmente, um caso incidental de uma doença endêmica em um indivíduo suscetível com uma síndrome rara. A pesquisa de comorbidades, especialmente entre as doenças negligenciadas ou emergentes é muito importante, porque a falta de diagnóstico precoce pode resultar em complicações graves como o desenvolvimento de deficiências especialmente quando há um diagnóstico de hanseníase tardio.

**Palavras - chave:** Hanseníase. Hanseníase Dimorfa. Neoplasia endócrina múltipla tipo 1.

## INTRODUCTION

Leprosy is a chronic granulomatous infection, caused by *Mycobacterium leprae* (*M. leprae*), primarily involving peripheral nerves and skin considered a neglected/emergency disease. At the beginning of 2010, the registered global prevalence of leprosy was 211 903 cases, in Brazil 37 610 (a prevalence of less than 1: 10,000) and 14 320 of new cases were diagnosis with deformities (WHO, 2010). Development to disease and its clinical manifestations are determined by *M. leprae* and the host response to the organism (NAAFS et al., 2001). Studies demonstrate higher concordance rates for leprosy among monozygotic compared to dizygotic twins. Various genes and loci have been associated with susceptibility to leprosy or with the pattern of disease – loci on chromosome 10p13, PARK2 and PACRG genes, and genes associated with human leukocyte antigen (HLA), tumor necrosis factor alpha, interleukin 10, vitamin D receptor, toll-like receptor 2, natural resistance-associated macrophage protein one (NRAPI), among others (BRITTON and LOCKWOOD, 2006; MORAES et al., 2006; WALKER and LOCKWOOD, 2006; SOUZA et al., 2007). It is believed that leprous leprosy is associated to a shift from Th1 to Th2 type immune response, to deletion of *M. leprae*-specific T cells, or to the presence of regulatory/suppressor T cells (BRITTON and LOCKWOOD,

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2006). Reports suggest that, in contrast to tuberculosis, human immunodeficiency virus (HIV) does not significantly modify the natural history of leprosy, except for a higher incidence of reactional states and a longer incubation period (NAAFS, 2000; TRINDADE *et al.*, 2005; USTIANOWSKI, LAWN, LOCKWOOD, 2006). Environmental features like nutrition, BCG (*Bacillus Calmette-Guérin*) vaccination and exposition rates to *M. leprae* and environmental mycobacteria also contribute to the disease (NAAFS *et al.*, 2001; BRITTON and LOCKWOOD, 2006).

Multiple endocrine neoplasia type 1, is an autosomal dominant disease, caused by mutation in MEN 1 gene, localized at chromosome 11q13, that codes for a tumor suppressor protein, menin. Main clinical features include parathyroid hyperplasia, pituitary adenoma and/or entero-pancreatic endocrine tumor (mostly gastrinoma and insulinoma). Prevalence is estimated at 0.1-1.75 per 10,000 (PIECHA, CHUDEK, WIECEK, 2008). It is recommended that carriers of multiple endocrine neoplasia type 1 syndrome (MEN-1) mutation be periodically screened for endocrine tumors that account for most of the disease-related morbidity and mortality (CARLING *et al.*, 1997; BRANDI *et al.*, 2001; LAIRMORE *et al.*, 2004). MEN 1 predispose to endocrine and nonendocrine tumors as well cutaneous diseases, like angiofibromas, lipomas and collagenomas (DARLING *et al.*, 1997) however, it is unknown whether the development of leprosy can be influenced by the syndrome. In literature we only found three reports about MEN-1 and infection disease, but they weren't with *Mycobacterium*, this can suggest that the immune response in MEN-1 is maintained in infections disease.

We report a case of leprosy in a young female carrier of MEN-1 syndrome, an association never described in literature.

## CASE REPORT

A 18-year old White female reported a 5-month history of multiple asymptomatic cutaneous lesions on her trunk and limbs. She had a medical history of asymptomatic multiple endocrine neoplasia type 1. As the patient had a family history of MEN-1, she underwent genetic testing and screening for endocrine tumors: genetic analysis resulted positive for MEN-1 mutation, laboratory tests revealed a hyperparathyroidism and magnetic resonance imaging found a pituitary micro-adenoma. She was on therapy with calcium and vitamin D. Physical examination revealed erythematous and infiltrated papules and plaques on her trunk (**Figure 1**) and extremities, foveolar

lesions on elbows, as well as facial erythema. She presented neither nerve enlargement, nor sensory or motor loss.



Figure 1 - Erythematous and infiltrated papules and plaques on the trunk.

Histopathological examination of an abdominal skin lesion showed a lymphohistiocytic inflammatory infiltrate along with poorly formed granulomas containing vacuolated macrophages, with a perivascular, periadnexal and perineural distribution. Staining for acid-fast bacilli (Fite-Faraco) was positive (+++/6+), showing solid bacilli isolated and in globi (**Figure 2**).

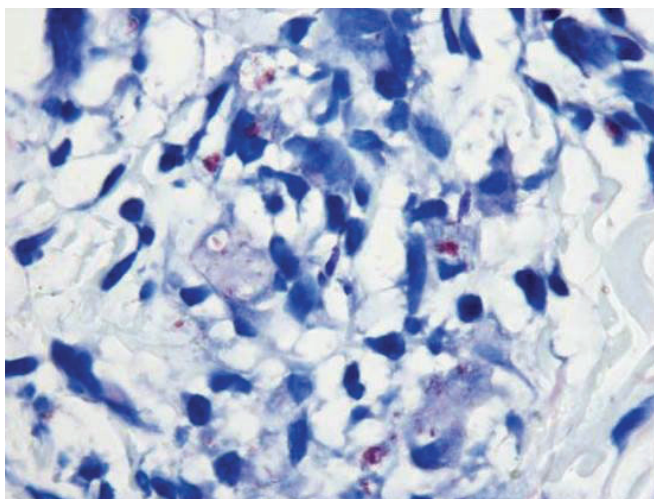


Figure 2 – Positive result for acid-fast bacilli (Fite-Faraco) with solid bacilli isolated and in globi.

Laboratory examination showed normal blood count, liver and renal function tests, as well as glucose-6-phosphate dehydrogenase.

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Abnormal laboratory tests included: parathormone 131 pg/mL (normal range 16-87 pg/mL), total serum calcium 11,5 mg/mL (8,6-10,2 mg/dL) and ionized calcium 6,2 mg/dL (4,6-5,3 mg/mL), serum phosphorus 2,7 mg/dL (2,7-4,5 mg/dL), osteocalcin 124,1 ng/mL (11-43 ng/mL), PINP (N-terminal propeptide of type 1 procollagen) 222 ng/mL (15,1-58,6 ng/mL), CTX (serum carboxy-terminal collagen crosslinks) 1,77 ng/mL (< 0,57 ng/mL).

25-hydroxyvitamin-D, thyroid function, prolactin, ACTH, cortisol, GH, insulin, gastrin and sex hormones were within normal range. The immune-phenotyping showed moderate lymphopenia to the B cell and slow to the T and NK cells. Lymphocyte cultures stimulated with mitogens of lymphocytes T showed negativity only for antigens: CMA (Candida Albicans), PPD (Purified Protein Derivative), varicella and TT (tetanus-toxoid).

Based on clinical and histological findings borderline lepromatous leprosy was diagnosed. Multiple-drug therapy (MDT) was introduced according to World Health Organization (WHO) recommendation for multibacillary leprosy: 600 mg rifampin and 300 mg clofazimine once monthly, in addition to 50 mg clofazimine and 100 mg dapsone daily for 12 months. After about three years the patient was showing without skin lesions and without intact, solid staining, bacilli in the histopathology and she haven't leprosy reaction or disabilities. Only, then, she referred to a cousin who has had the diagnosis of leprosy.

## DISCUSSION

MEN-1 is a hereditary syndrome, rare, also name Wermer syndrome, expressed by a combination of endocrine and nonendocrine tumors. Diagnosis is based on the occurrence of at least two of the three main MEN-1-associated endocrine tumors: parathyroid adenoma, entero-pancreatic endocrine tumor and pituitary tumor (BRANDI *et al.*, 2001). Leprosy is a chronic infectious disease, endemic in developing countries like India and Brazil, caused by *Mycobacterium leprae*. The disease affects peripheral nerves and skin, may lead to physical disabilities, and its clinical features are influenced by host genetics and environmental factors (NAAFS *et al.*, 2001; MORAES *et al.*, 2006).

The case report showed borderline leprosy and MEN with good response to the MDT but without leprosy immune reaction. Although, many leprosy susceptibility genes have been described, none of these is associated with MEN 1 gene. There is evidence of the vita-



min D receptor polymorphisms, one of possible mechanisms of susceptibility to leprosy, is associated with sporadic hyperparathyroidism, but not with MEN-1-related hyperparathyroidism (CARLING *et al.*,1997). In the patient described, the disease manifested as pituitary microadenoma and hyperparathyroidism.

## CONCLUSIONS

In conclusion, the association of leprosy with MEN-1 described in this report was probably an incidental case of an endemic disease in a susceptible individual with a rare syndrome, but emphasizes the importance of searching comorbidities especially neglected or emergency infections disease, like tuberculosis, leishmaniosis, Chagas' disease. The lack of early diagnosis leprosy may result in serious clinical complications as development of reactions requiring prolonged therapy with immunosuppressive drugs which can improve disabilities of late diagnosis the leprosy. This patient probably hadn't reactions and disabilities by slow immunity response showed by lymphopenia. This is an issue not only for areas where leprosy is endemic, but also for developed countries, which are increasingly involved in the treatment of patients with leprosy diagnoses due to the increased migratory movements (TRINDADE *et al.*,2011) and showed the importance of epidemiological surveillance of contacts when years after years a cousin was diagnosed (TRINDADE *et al.*, 2005).

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