

Tropical medicine rounds

Netherton's syndrome and lepromatous leprosy: a mere coincidence?

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Abstract

Objectives Netherton's syndrome (NS) is a rare autosomal recessive condition, first described in 1958, which involves a complex immunological dysfunction, ichthyosiform dermatitis, and erythroderma, characteristic defects of the hair shaft and atopy. Recurrent bacterial infection in the skin of patients with NS is frequent.

Methods This paper represents the first case report of leprosy and concurrent NS.

Discussion This case merits discussion among doctors in endemic and non-endemic areas to evaluate the chronic use of systemic corticosteroids as a risk factor for leprosy. The present patient came from an endemic area of leprosy and was treated chronically with systemic corticosteroids for erythroderma. This treatment, along with the immunodeficiency related to the syndrome and caused by a genetic mutation in *SPINK5*, may be a facilitating factor for the infection.

Introduction

Netherton's syndrome (NS) is a rare autosomal recessive disease. Infants can present erythroderma at 1–6 weeks after birth. The syndrome is characterized by congenital ichthyosiform erythroderma, ichthyosis linearis circumflexa (ILC),¹ “bamboo hair” (trichorrhexis invaginata [TI]), and atopic diathesis with elevated immunoglobulin E (IgE).²

Bamboo hair, or TI, is characterized by the presence of nodules along the follicular hair shaft in a ball and socket pattern caused by the invagination of the distal hair shaft in the cup formed by the proximal hair shaft. This invagination occurs at the site of a defect in the intermittent keratinization of the hair cortex caused by the incomplete conversion of sulfhydryl compounds (SH) in disulfide bridges in the proteins of cortical fibers. This defect leads to cortical softening, bulging, and a deformity that is visually reminiscent of bamboo.¹

Ichthyosis linearis circumflexa is characterized by migratory lesions with a double border caused by an influx of dermal inflammatory cells that are captured and digested by keratinocytes, resulting in the interruption of keratinization.¹

Infants with NS are usually born with a generalized erythroderma covered by fine, translucent scales, which can be difficult to distinguish from other types of infantile erythroderma, particularly other ichthyosiform erythroderma.³

Diagnosis of NS may be delayed because the pathognomonic TI or ILC often does not become evident until after the first year of life.⁴ Patients may be wrongly diagnosed with congenital non-bullous ichthyosiform erythroderma, Leiner's disease, or simply atopic eczema.¹

By contrast, leprosy occurs in response to the interaction between humans and *Mycobacterium leprae*. It manifests in a number of different ways, giving rise to various forms of the disease which can be classified according to either of the two main systems of classification: the Madrid classification, and the Ridley and Jopling classification.⁵ Therefore, leprosy can be described as a mainly cutaneous–neural disease, although damage to internal organs, demonstrating its systemic nature, has been observed. Such manifestations are closely linked to exposure to *M. leprae* and specific immunodeficiency to the agent, which is more pronounced in the multibacillary form (lepromatous leprosy [LL]).⁵

Case report

A 26-year-old man, born and resident in Eunápolis Bahía, Brazil, presented at our department complaining of redness, desquamation, and itching all over the body, which had been present since childhood, especially in the flexures. At the age of four years, the patient had been underweight and had shown stunted growth. This status continued throughout his childhood and teenage years, which were characterized by periods of remission and aggravation, respectively. Since the age of 15 years, the patient had been using oral corticosteroids continuously, in addition to intermittent etretinate and acitretin to control his erythroderma, which had been interpreted as a defect of keratinization. He had been started on etretinate before presenting at our department. Nowadays, he is prescribed acitretin as production of etretinate has ceased.

The patient reported the progressive appearance of disseminated papular and nodular skin lesions over the five years prior to presentation. He reported no family members with a similar clinical picture but described a cousin with atopic dermatitis. It is of note that he lived in an area endemic for leprosy.

Physical examination revealed that the subject was of low weight and short stature for his age and displayed a genu valgum-type bone deformity. Dermatological examination revealed numerous findings, including diffusely affected skin that was erythrodermic and scaly with areas of lichenification. Polycyclic plaques and erythema were observed on the trunk (Fig. 1) and limbs, with peripheral



Figure 1 Polycyclic plaques and erythema on the trunk at presentation

scaling. Double-bordered peeling on the backs of the hands was also observed (Fig. 2); this is a principal feature of ILC. Multiple erythematous papulonodular and brown papulotuberosus lesions were disseminated over the body, mainly on the elbows, knees, buttocks, pubic area, ears (Fig. 3), and face. Cushing's syndrome was also diagnosed, particularly in the increased infiltration of the forehead and ears, as well as the loss of the lateral third of the eyebrows. Scaling on the face and scalp in areas of close-cut hair and occipital thinning was also observed.

Dermatoscopy revealed the widespread presence of nodules along the hair shafts, and TI was diagnosed. Optical microscopic examination identified a pattern representing the invagination of the distal section and the



Figure 2 Double-bordered peeling is seen on the back of the hand



Figure 3 Ear infiltration is characteristic of leprosy



Figure 4 Microscopy shows the presence of nodules along the hair shaft in a ball and socket pattern

cup-shaped dilation of the proximal section of the hair shaft, confirming the diagnosis of TI (Fig. 4).

Laboratory tests were performed to obtain an accurate diagnosis: histopathological findings in a skin biopsy from an area of erythroderma were consistent with a psoriasiform dermatosis.

Histopathological examination of the papulonodular lesions on the face (using Wade's stain) revealed the presence of globi, which is characteristic of LL. This provisional diagnosis was reinforced by findings of a bacilloscopy index (BI) of ≥ 3.83 and globi in a lymph examination. Mycological examination and cultures of the nails and scales from the back of the hand revealed the presence of septate hyphae and positivity for *Trichophyton rubrum*, respectively. Other relevant laboratory findings were: serum basal cortisol (at 8.00 hours), 0.1 $\mu\text{g/dl}$ (normal range: 2–25 $\mu\text{g/dl}$); serum growth hormone after exercise, 5.6 ng/ml (normal range: ≤ 10 ng/ml); IgE total serum, 395.2 U/ml (normal range at >15 years: <160 U/ml); differential percentage of peripheral eosinophils, 25% (normal range: 1–7%); global white blood cell count: 10,600 cells/ mm^3 (normal range: 4800–10,800 cells/ mm^3); total serum protein, 8.8 g/dl (normal range: 6.1–7.9 g/dl); serum albumin, 4.0 g/dl (normal range: 3.5–4.8 g/dl); and serum globulin, 4.8 g/dl (normal range: 2.6–3.1 g/dl). Urine examination revealed proteinuria. The patient was successfully treated with multi-drug therapy according to the World Health Organization protocol for LL. The cutaneous aspects of NS were treated with low-dose acitretin (10 mg/d) and improved greatly, in line with a previous report.⁶

Discussion

The present patient demonstrated typical manifestations of NS, TI (confirmed by dermoscopic optical microscopy),

atopic diathesis accompanied by high levels of IgE, and ILC. There have been reports of treating NS with oral retinoids (etretinate and acitretin). The use of high doses can cause the disease to accelerate, augmenting the fragility of the skin. However, acitretin administered at a low dose of 10 mg/d and etretinate 50 mg administered every other day are helpful for patients with this condition.^{6,7}

The papulonodular lesions in the present patient were consistent with clinical LL, a diagnosis that was corroborated by the presence of numerous globi and a BI of ≥ 3.83 .

In an endemic country such as Brazil, dermatologists should be aware of the possibility of leprosy when faced with cutaneous changes that are not characteristic of the principal diagnosis. In our patient, leprosy was suspected on the basis of nasal obstruction and the development of diffuse infiltration of the skin and ear lobes.

Multibacillary leprosy is treated with multi-drug therapy under a schedule that includes a supervised dose of 600 mg rifampicin, 300 mg clofazimine, and 100 mg dapsone, and self-administered doses of 100 mg dapsone and 50 mg clofazimine per day, to a total of 12 supervised doses in ≤ 18 consecutive months. Subsequently, thalidomide and prednisone may be introduced into the therapeutic regimen in response to the development of a type II reactional leprosy, or erythema nodosum leprosum, an acute manifestation that occurs in leprosy patients more frequently during treatment. The full clinical picture is characterized by the sudden onset of generalized, painful, erythematous subcutaneous nodules or erythematous plaques, accompanied by impairment of the patient's general condition, fever, generalized lymphadenopathy, iritis, iridocyclitis, neuritis, and arthritis, and acute visceral manifestations. Thalidomide is used as it reduces the production of tumor necrosis factor- α (TNF- α) by blocking messenger RNA that controls the production of cytokines, which may explain its effect in erythema nodosum leprosum.

Our patient was underweight and of low height, although tests revealed no alteration in his growth hormones. However, basal cortisol was suppressed, and the chronic use of corticosteroids, both topically and systemically, had contributed to his growth deficit and also to an immunological depression, thereby increasing his vulnerability to leprosy infection. This immunological depression caused by systemic corticotherapy includes the inhibition of macrophage function.⁸ The other mechanism reflects the deviation of the Th2 response induced by corticotherapy, which inhibits the production of interleukin-12 (IL-12) by macrophages and monocytes, thereby influencing the Th1/Th2 balance.⁸

Inhibition of IL-12 secretion and of the expression of its receptors on T lymphocytes and natural killer (NK)

lymphocytes favors IL-4 production. IL-12 is a strong stimulator of interferon- γ (IFN- γ) synthesis and an inhibitor of IL-4 secretion.⁸ In LL, IL-4 is augmented; hence corticotherapy in high doses may play a role in the immunopathological mechanism of LL.⁹

To our knowledge, this is the first report to describe the presence of both LL and NS in one patient.

The infection with *M. leprae* may have been facilitated by the chronic use of corticosteroids. In general, an increased predisposition to bacterial infection is associated with the pathogenesis of NS; a previous study has proposed that a genetic mutation in *SPINK5* may result in insufficient *LEKTI* at the mRNA level, which may, in turn, lead to the premature activation of the stratum corneum tryptic enzyme, causing the premature degradation of corneodesmosomes, flaking, and premature thinning of the stratum corneum.¹⁰ In addition, serine proteases can also convert the stratum corneum IL-1 from an inactive to an active form,¹¹ causing severe inflammation. The role of proteases in NS has been reinforced by the discovery of the aberrant expression of other proteins, especially transglutaminases 1 and 3, which probably contributes to the impaired epidermal barrier in this syndrome.¹²

The role of a *SPINK5* mutation in the pathogenesis of the disease was suggested by the finding of high electrolyte activity in the stratum corneum in patients with NS, as well as a defect in the barrier to the passage of substances and microorganisms, a role also played by the stratum corneum.¹³ It should be remembered that leprosy is most commonly spread through direct inoculation that occurs through the nasal mucosa and, exceptionally, through breaks in the skin surface. The mucosa and epidermis are the two sites affected by the failure of *LEKTI* that occurs in the syndrome under review and may result in a predisposition to eventual infection by *M. leprae*.

From an immunological standpoint, high serum IgE levels in many patients with NS may point to a dysfunction in T cells or suggest a link,⁷ as seen in cases of atopic dermatitis. An atopic condition is common in NS; in a study by Greene and Muller of 43 patients with this syndrome, 28 reported atopic manifestations.¹⁴ Findings in our patient confirm the high incidence of atopy as part of the syndrome as he presented with eczema, itching, and peripheral hypereosinophilia accompanied by increased serum total IgE.

In turn, the T cell dysfunction present in the syndrome is associated with the depression of cellular immunity and therefore the reduced resistance to infection by *M. leprae* (i.e. the ability of macrophages to lyse the bacillus). At the lepromatous pole, the Th2 cell response prevails through the release of IL-4, IL-6, and IL-10, which decrease macrophage activation and stimulate B lymphocytes and mast cells.⁹ The release of IL-4 as part of the

Th2 cell response is closely involved in the production of IgE and the differentiation and activation of eosinophils, which are involved in the mediation of cell damage in cases of atopic eczema. This leads to the maintenance of the immunopathological mechanism that causes the skin damage associated with the syndrome.

Leprosy also has a strong genetic component; recently, a leprosy susceptibility locus to chromosome 6 region q25-q26 was mapped.¹⁵ Another study using different ethnic backgrounds (Vietnamese and Brazilian subjects) identified specific variants of the 5' region of *PACRG* and *PARK2* as worldwide risk factors for leprosy.¹⁶ This research revealed a significant association between leprosy and 17 markers located in a block of 80 kilobases overlapping the 50 regulatory region shared by the Parkinson's disease gene *PARK2* and the co-regulated gene *PACRG*. Possession of as few as two of the 17 risk alleles was highly predictive for leprosy.¹⁶ This was confirmed in a sample of 975 unrelated leprosy cases and controls from Brazil in whom the same alleles were strongly associated with leprosy.¹⁶ Both genes are expressed in varying degrees in different tissues, including Schwann cells and monocyte-derived macrophages. As skin macrophages and Schwann cells are the primary host cells for *M. leprae*, these results suggest that ubiquitin-mediated proteolysis, a biochemical pathway that has so far received little attention in the study of leprosy pathogenesis, plays an important function in the control of *M. leprae* infection.¹⁷ Ubiquitination is a very general regulatory process for proteins, including those involved in the immune system.¹⁷ Although NS and leprosy both present genetic components, it is important to note that NS has a different gene locus localized on chromosome 5q32.¹⁸

Another immunogenetic aspect which involves leprosy is the Mendelian susceptibility to mycobacterial disease (MSMD). Disease-causing mutations have been found in five autosomal (*IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, and *IL12RB1*) and one X-linked (*NEMO*) gene.¹⁹ These genes are physiologically related because their products are involved in IL-12/IL-23-dependent, IFN- γ -mediated immunity. IFN- γ is a cytokine produced by NK and T lymphocytes that binds to a heterodimeric ubiquitous receptor.¹⁹ As noted, NS is not caused by mutations in these genes, but the possibility of a T cell dysfunction in NS¹⁴ may influence IFN- γ production and consequently affect the production of IL-12. As IL-12 deficiency is principally associated with infectious diseases caused by mycobacteria,¹⁹ we suspect that these patients are more susceptible to leprosy, whether the deficiency is genetically determined or induced by the use of systemic corticosteroids.

In conclusion, the concurrent presentation of both diseases (NS and LL) in the same patient warrants

attention. This represents the first case report to describe the development of LL in a patient with NS. This complication should be kept in mind as it may have disastrous effects in the course of the syndrome as a result of possible motor limitations and neural complications in the long term and reactional states of leprosy. Although speculative, this coincidence of NS and LL may justify the continuation of genetic studies with respect to the mutation and the association of *SPINK5* with mycobacterial infectious diseases (such as leprosy).

References

- 1 Netherton EW. A unique case of trichorrhhexis nodosa: "bamboo hairs". *Arch Dermatol* 1958; 78: 483-487.
- 2 Smith DL, Smith JG, Wong SW, et al. Netherton's syndrome: a syndrome of elevated IgE and characteristic skin and hair findings. *J Allergy Clin Immunol* 1995; 95: 116-123.
- 3 Pruszkowski A, Bodermer C, Fraitag S, et al. Neonatal and infantile erythrodermas. A retrospective study of 51 patients. *Arch Dermatol* 2000; 136: 875-880.
- 4 Judge MR, Morgan G, Harper JL. A clinical and immunological study of Netherton's syndrome. *Br J Dermatol* 1994; 131: 615-621.
- 5 Piris A, Lobo AZ, Moschella SL. Global dermatopathology: Hansen's disease – current concepts and challenges. *J Cutan Pathol* 2010; 1: 125-136.
- 6 Hartschuh W, Hausser I, Petzoldt D. Successful retinoid therapy of Netherton syndrome. *Hautarzt* 1989; 40: 430-433.
- 7 Seraly MP, Sheehan M, Collins M, Mostow E. Netherton syndrome revisited. *Pediatr Dermatol* 1994; 11: 61-64.
- 8 Prigent H, Maxime V, Annane D. Clinical review: corticotherapy in sepsis. *Crit Care* 2004; 8: 122-129.
- 9 Goulart IM, Penna GO, Cunha G. Immunopathology of leprosy: the complexity of the mechanisms of host immune response to *Mycobacterium leprae*. *Rev Soc Bras Med Trop* 2002; 35: 365-375.
- 10 Allen A, Siegfried E, Silverman R, et al. Significant absorption of topical tacrolimus in three patients with Netherton syndrome. *Arch Dermatol* 2001; 137: 747-750.
- 11 Nylander-Lundqvist E, Egelrud T. Formation of active IL-1 beta from pro-IL-1 beta catalyzed by stratum corneum chymotryptic enzyme *in vitro*. *Acta Derm Venereol (Stockh)* 1997; 77: 203-206.
- 12 Descargues P, Dearaison C, Prost C, et al. Cornodesmosomal cadherins are preferential targets of stratum corneum trypsin and chymotrypsin-like hyperactivity in Netherton syndrome. *J Invest Dermatol* 2006; 126: 1622-1632.
- 13 Komatsu N, Takata M, Otsuki N, et al. Elevated stratum corneum hydrolytic activity in Netherton syndrome suggests an inhibitory regulation of desquamation by *SPINK5*-derived peptides. *J Invest Dermatol* 2002; 118: 436-443.
- 14 Greene SL, Muller SA. Netherton's syndrome. Report of a case and review of the literature. *J Am Acad Dermatol* 1985; 13: 329-337.
- 15 Mira MT, Alcaïs A, Van Thuc N, et al. Chromosome 6q25 is linked to susceptibility to leprosy in a Vietnamese population. *Nature Genet* 2003; 33: 412-415.
- 16 Mira MT, Alcaïs A, Nguyen VT, et al. Susceptibility to leprosy is associated with *PARK2* and *PACRG*. *Nature* 2004; 12: 636-640.
- 17 Alcaïs A, Mira M, Casanova JL, et al. Genetic dissection of immunity in leprosy. *Curr Opin Immunol* 2005; 17: 44-48.
- 18 Müller FB, Hausser I, Berg D, et al. Genetic analysis of a severe case of Netherton syndrome and application for prenatal testing. *Br J Dermatol* 2002; 146: 495-499.
- 19 Picard C, Fieschi C, Altare F, et al. Inherited interleukin-12 deficiency: IL12B genotype and clinical phenotype of 13 patients from six kindreds. *Am J Hum Genet* 2002; 70: 336-348.