



# Late Diagnosis In Netherton Syndrome in Adult: A Case Report

Oyamada LH, Militão LM, Pozetti M, Adami A, Sá APM, Coimbra RTLA, Lages TSFA, Rodrigues TAOV, Amorim MF<sup>3</sup> and Monson CA\*

Departament Dermatologia, Faculdade de Ciências Médicas IPEDMED and UNIFESP, Brazil

\*Corresponding author: Monson CA, Departament Dermatologia, Faculdade de Ciências Médicas IPEDMED, UNIFESP, São Paulo, Brazil

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## Abstract

This is a case report at the Dermatology Service of the Institute of Research and Medical Education (IPEDMED, São Paulo Campus), a patient with suspected Netherton syndrome (NS), male, aged 40, who did not dermatological disease throughout childhood and even in adult life. Prior use of sporadic topical steroid alone, with temporary improvement of the cutaneous condition. After discussion about the challenges for the diagnosis of this syndrome, the patient underwent appropriate treatment, starting Retinoid orally, which resulted in a satisfactory clinical outcome after one month of starting therapy.

**Keywords:** Netherton; Erythroderma; Ichthyosis; Tricostomy

## Background

The Netherton Syndrome (NS) consists of a rare, autosomal recessive genodermatosis with defective production or retention of the stratum corneum, which belongs to the group of ichthyoses. It is associated with a genetic defect, described in the SPINK 5 gene, located on chromosome 5q31-32, which encodes a serum protease inhibitor, LEKT 1, expressed on skin and lymphoid tissue. This mutation results in alteration of keratinization, increasing the proteolytic activity of the skin, leading to premature peeling and skin barrier impairment. As a result, disorders and alterations of hair and skin, such as circumflex linear ichthyosis, eczematous rash, diffuse erythema, atopic diathesis and specific hair shaft alteration - called invaginated trichorrhexis or bamboo hair - may also occur, with intellectual disability. Its early diagnosis is critical in the neonatal period, since the disease can be even more severe and fatal, since it presents, more frequently, serious complications due to hypernatremic dehydration, important weight loss, hypothermia, respiratory infection and sepsis. Therefore, other diseases, such as primary immunodeficiency syndrome, lamellar ichthyosis, erythrodermic psoriasis, congenital ichthyosiform

erythroderma or seborrheic dermatitis should always be excluded. Its diagnosis can be confirmed through skin biopsy, electron microscopy and immunohistochemical study, however, because it

requires careful evaluation, it tends to be late confirmed. Currently there is no known cure or specific treatment satisfactory for such a syndrome. However, treatment modalities, such as topical calcineurin inhibitors, topical retinoids, narrowband ultraviolet B phototherapy, psoralen and ultraviolet irradiation and oral acitretin have been used with variable success. In people with severe disease, intravenous immunoglobulin and anti-TNF- $\alpha$  are new therapeutic options.

## Case Report

We declare that all the precepts of Bioethics were fulfilled in the present case report, including with the signature by the patient of Term of Free and Informed Consent. Male patient, born in Barreiras - BA, 40 years old, with a history of skin eruption from birth, complained of "fine and brittle hair", scaling in the body, diffuse erythema of the skin, accompanied by pruritus, with temporary improvement when treated with topical corticosteroids and various antimicrobials. Dermatological examination revealed desquamative areas and diffuse erythema on the trunk, with serpiginous squamous plaques, as well as annular lesions and erythematous plaques on hands (Figures 1 & 2). She had thin, opaque, rarefied and thin hair and eyebrows (Figure 3). Examination of the capillary rods under optical microscopy (100x) revealed trichorrhexis invaginata (Figure 4). The histopathological picture was non-specific, with moderate epidermis and regularly thickened by acanthosis and elongation of

the interpapillary ridges, hypergranulosis with stratum corneum replaced by parakeratosis, sometimes continuous. In the papillary dermis, dilation of the blood and lymphatic vessels with mild perivascular lymphocytic infiltrate was observed. Dermis reticular and hypodermic unchanged. It may, however, correspond to the Netherton syndrome (NS). In view of such findings, the diagnosis of (NS) was closed, and Acitretin 25mg daily was instituted in a single dose, and an important improvement was observed in a period of one month, and there was also a report of decreased pruritus and

erythema . It was also reported a subsequent growth of eyebrows and hair. Clinical and laboratory evidence indicates that Acitretin, because it is derived from vitamin A and belongs to the retinoid group, shows a satisfactory action when applied in keratinization disorders. It is therefore frequently used in the ichthyoses in general. Thus, the benefits are evident, with a significant reduction in the indexes of desquamation, in the reduction of the scales, and in a greater skin elasticity [1-5].



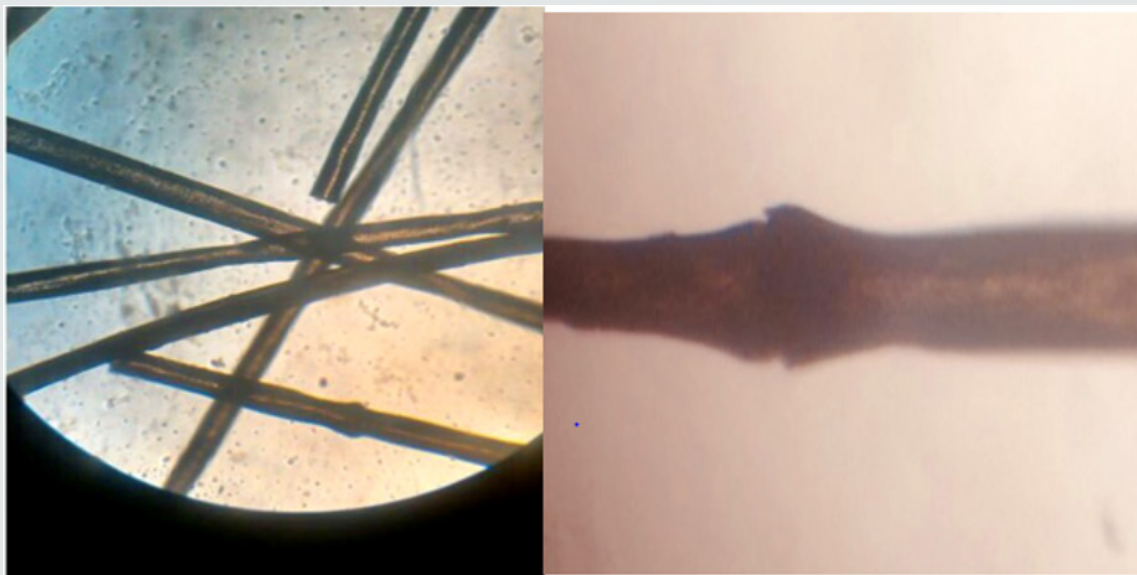
**Figure 1:** Erythema diffuse in the trunk; erythematous-serpiginous and polycyclic lesions, with margins presenting double scaling edge.



**Figure 2:** Annular and serpiginous lesions with eczematous areas; erythematous plaques with circinate scaling on hand fingernails.



**Figure 3:** Madarose; hair opaque, thin, thin and brittle.



**Figure 4:** Microscopic examination of the hair demonstrating a typical bamboo alteration, characterizing the invaginated trichorrexe (in increase of 100x).

## Discussion

(NS) is a dermatological disorder characterized by atopic manifestations, congenital ichthyosiform erythroderma, usually having its first appearance in the neonatal period, with erythroderma and/or hypotrichosis. There are also reports of characteristic capillary abnormalities, which are considered pathognomonic of the Syndrome, and are called "trichorrexe invaginated" (TI). (TI) consists of changes that occur due to a transient defect in hair keratinization due to an incomplete conversion of sulphhydryl to sulphide bridges in the cortical region, so the internal root sheath is keratinized, but the hair shaft does not, resulting in a fragility in the cortical region of the hair with invagination of the distal part on the proximal of the stem (striking zigzag pattern), which is described as

brittle hair and hair (bamboo hair), and can be observed under light microscopy. Atopic signs and areas of peeling, usually polycyclic and migratory are seen, and may still manifest intellectual deficiency in some cases. The transmission of the defect is autosomal recessive due to a genetic defect associated with the mutation of the SPINK 5 gene, located on chromosome 5q31-32, responsible for encoding a serum protease inhibitor, LEKT 1, present in the epidermis and lymphoid tissue, being, its expressiveness, variable. The dysfunction of this inhibitor, or even the absence thereof, alters cell differentiation, thus justifying the association of the atopic condition and the keratinization disorder, since the abnormal expression of the inhibitor influences the differentiation of T cells, leading to the Th2 immune response, thus evidencing high levels of IgE and

immunological fragility, corroborating with atopic manifestations, both cutaneous and alimentary or, still, respiratory. Differential diagnosis is therefore challenging, mainly because there are no typical cutaneous signs of the syndrome, and the same changes can be seen in many other erythrodermae. Concomitant atopy may also lead to misdiagnosis of atopic dermatitis and severe eczema. On the other hand, the pillar alterations, although pathognomonic, are not always visualized in a first sampling, therefore, they may require numerous analyzes, since they are not present in all the filaments, making the diagnosis even more difficult, which with high frequency is confirmed after several months and even years after the start of follow-up. Thus, complementary examinations may help in the establishment of differential and conclusive diagnosis, especially with skin biopsy, as well as electron microscopy, since this examination evidences "invaginated trichorrexe", which elucidates the striking zigzag pattern characteristic. On the other hand, the histopathological examination shows non-specific psoriasiform changes, with parakeratosis and acanthosis, which are of little value in the diagnosis, but can still be collaborative [6-8].

Because it is a complex disease, with keratinization disorder and frequent complications, especially in the neonatal period, the use of systemic retinoids, such as acitretin, is usually recommended as soon as possible, which represents a greater chance of significant improvements in both the lesions as well as changes in capillaries. Concerning eczematous changes, these may be controlled with corticosteroids, when necessary.

One of the objectives of disclosing the present case report is to illustrate, therefore, the difficulty in performing the diagnosis of (NS) in a 40-year-old adult male without a diagnosis of confirmed skin disease since childhood, and was treated occasionally with steroids, but did not present clinically significant improvement responses. In the present case, the diagnosis, although late, was confirmed by electron microscopy and corroborated by histopathology. Of note, improvement in signs and symptoms was observed 1 month after initiation of oral Acitretin treatment [9-11].

## Final Considerations

Clinical findings of (SN) tend to be inconclusive, since not all hair filaments present (TI) and cutaneous presentations are variable, which contributes to the fact that the diagnosis of the disease in

the present case has been challenging and obscure for a long time, which happens, in most cases, late, usually after many tests, and at different times, which causes the patient to have poor quality of life. Thus, it is strongly recommended that health professionals provide the diagnostic hypothesis of (SN) in cases of erythroderma and associated capillary complaints without response to previous treatments and non-conclusive skin diagnoses, and perform thorough trichoscopy in suspected cases, whether in the and the avoidance of indiscriminate and unnecessary use of corticosteroids and steroids in the long term, thus improving quality of life, as well as increasing the expectation of life of these patients.

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