

# Nail alterations in patients affected by endemic pemphigus foliaceus in el Bagre, Colombia

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## ABSTRACT

**Background:** We have characterized a new variant of endemic pemphigus foliaceus in El Bagre (El Bagre-EPF) (AKA pemphigus Abreu-Manu) and surrounding municipalities. Herein, we describe nail alterations in several patients affected by this disease. In the pre-steroid era, patients with endemic pemphigus foliaceus (EPF), especially in Brazil where the disease is known as fogo selvagem (FS), were described to have some nails changes including the Viera's sign (yellowish of the nail). In this study, we have attempted to describe a range of nail alterations in patients affected by El Bagre-EPF. **Methods:** A case-controlled study was conducted where 40 cases and 40 controls were evaluated for nail changes. A clinical exam was performed in the cases and in a series of control patients from the same geographic region who were matched by age, gender and work activities. Gram stains and cells cultures for fungus and bacteria were done on affected nails. **Results:** In 25 chronic patients (affected for more than two decades) presented with toenail alterations. These changes included change of color nail (yellowish) (Viera sign), atrophy, dystrophy, chronic paronychia, onycholysis, nail bed erosion, subungual hyperkeratosis and trachyonychia. All of these findings were over-represented in patients compared with control population ( $p < 0.05$ ). Cell cultures and gram stains were negative in all study participants. **Discussion:** Chronic patients have nail damage, maybe due to the presence of chronic inflammatory process affecting the nail bed cell, matrix, and/or the nail fold cells junctions.

**Key words:** Nails; Endemic pemphigus foliaceus in El Bagre; Autoimmunity

## INTRODUCTION

Pemphigus foliaceus (PF) is an autoimmune skin disorder characterized by the loss of intercellular adhesion of keratinocytes in the upper parts of the epidermis (acantholysis), resulting in the formation of superficial blisters [1,2]. It has an endemic forms, and previously, we described a new variant of endemic pemphigus foliaceus (EPF) in El Bagre, Colombia (El Bagre-EPF), (AKA pemphigus Abreu-Manu). It is an

autoimmune disease presenting in a circumscribed geographic area with genetic and environmental factors influencing its pathogenesis [1]. This new variant, El Bagre-EPF, occurs in a gold-mining region; it predominantly affects males between 30 and 60 years of age, as well as a few post-menopausal females [1-8]. El Bagre-EPF patients demonstrate complex clinical, epidemiological and immunopathologic features, differing from Fogo selvagem and the Tunisian EPF [1-8]. El Bagre-EPF patients have polyclonal

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autoantibodies directed not only to epidermal cell junctions, but also to the cell junctions in the skin appendices, their neurovascular bundles and to mesenchymal-endothelial cell junctions [1-8]. The main laboratory findings found in El Bagre-EPF patients include autoantibodies to multiple cell junctions in the skin, and in one third of the patients against cells junctions in multiple organs [1-8]. A subclinical oral involvement [9], and in about one third of the patients, we discovered autoantibodies that appeared to be directed against the optic nerve envelope and its cell junctions [10], to cutaneous nerves and receptors [11], to the cell junctions of the cardiovascular system including its conductive system [12-14], and to cell junctions within the kidney [15]. In this study, we investigated nail abnormalities in patients affected by El Bagre-EPF as reported in the old Portuguese literature in patients affected by FS.

## METHODS

The study was approved by a human quality assurance review board at the hospital in El Bagre, and all participants provided signed informed consent. We performed a case–controlled study of 40 patients with El Bagre-EPF and 40 healthy controls from the endemic area, matched by age, gender, race, demographics, comorbidities, and living and work activities. All subjects were evaluated clinically for the presence of nail alterations. The clinical examination was done independently by two board-certified dermatologists. Bacteriological and mycological studies were performed.

The majority of these patients were not included in our initial description of EPF [1-9]. Only four of the patients originally studied were still alive at the time of this study. Each year, there is a prevalence of around 4–6 new patients, but also 3–4 deaths/year, creating a steady prevalence of the disease endemicity [1-9].

We included only patients who fulfilled the complete diagnostic criteria for El Bagre-EPF: including: clinical and epidemiological features as previously described [1-9], residence in the endemic area [1-9], serum displaying intercellular staining between keratinocytes by direct immunofluorescence (DIF) and to the basement membrane zone (BMZ) of the skin by either DIF or by indirect immunofluorescence (IIF), using fluorescein isothiocyanate (FITC) conjugated monoclonal antibodies to IgG and/

or to IgG4, as described previously [1-9]. The patients also must have serum reactivity against desmoglein 1 (Dsg1) and plakin molecules using immunoblotting (IB) [7,8]. The patient's serum should also immunoprecipitated a Concanavalin A affinity-purified 45 kDa fragment of Dsg1 [1-9]. The final diagnostic criteria are that the patients must show positive for autoantibodies to pemphigus foliaceus antigens by ELISA [9]. All the patients and controls from the endemic area were tested by the same techniques.

For ethical reasons, we did not take biopsies because the patients have to walk in the jungles, and work inside dirty rivers and creeks and biopsies with open shoes and a biopsy would increase their risk for overt infection especially, in the toenails of the lower limbs.

## Direct Microscopy, Nail Stain and Mycology as Well Bacterial Studies

Before obtaining a specimen, the nails were clipped and cleansed with an alcohol swab to remove bacteria and debris. We studied for the presence of dermatophytes such as *Trichophyton rubrum* (T. rubrum), *T. interdigitale* (tinea unguium), for yeasts infections such as *Candida albicans* and for molds, especially *Scopulariopsis brevicaulis* and *Fusarium* species. We test for them using the standard 20% potassium hydroxide solution (KOH) technique. We clipped the nails from crumbling tissue at the end of the nail. The discolored surface of the nails was also scraped off. The nail debris was scooped out from under the nails for the culture.

## Statistical Analysis

We used the Fisher exact test to compare two nominal variables (e.g. positive and negative presence of any nail alteration). We also compared the differences between patient cases and controls.  $p < 0.05$  with 95% CI (or better) was considered statistically significant. For all statistical analyses, we used the software GraphPad QuickCalcs (GraphPad Software Inc., La Jolla, CA, USA).

## RESULTS

The toenails were involved in 25/40 El Bagre-EPF and the changes in the nails were seen in patients with the chronic form of the disease ( $p < 0.05$ ). Acute patients suffering El Bagre-EPF for less than six months showed no alterations. No patients hand finger

nails were affected ( $p < 0.05$ ). The more common nail alterations included change of color yellowish (Viera's sign) (25/40) ( $p < 0.05$ ). This yellowish stain resembles the one seen as if dipped in iodine, Vieira's sign). None of the controls presented with the Viera's sign. Subungual hyperkeratosis was also very common 20/40 (Fig. 1), and was often associated with distal onycholysis (18/40) ( $p < 0.05$ ). In 2/40 controls that had psoriasis, distal onycholysis was also observed (Fig. 1). Other toenails alterations included paronychia, onychorrhexis, onychatrophia in some areas of the area near the nail cuticle, and onychomadesis (most were often seen together) (18/40) in El Bagre-EPF patients, and no such changes were seen in controls. Onychogryphosis (nail thickening and scaling under the nail), common in the elderly, was seen equally in cases and controls (10/40) (Fig 1).

### Direct Microscopy, Nail Stain and Mycology as Well Bacterial Studies

Direct microscopy, bacterial and fungal cultures were negative, except in one El Bagre-EPF patient who presented *T rubrum* in his foot toe nail and was treated accordingly.



**Figure 1:** (a-c) Distal onycholysis, in b, onychatrophia in the area near the nail cuticle resembling alterations seen in nail-patella syndrome; c, distal subungual onychomycosis of the great toe nail and dystrophic alterations with ridges, pits, and/or triangular lunulae, subungual hyperkeratosis, with some dystrophy. (In Figure 1a, and 1b the white arrows pointed to a healed blister with some desquamation. The red toe nail arrow in a, shows abnormal growth of the small nail; In figure 1b, pointed in the large toe to a proximal depression of the nail, possibly due to the subcorneal blisters).

## DISCUSSION

Involvement of the nail unit in pemphigus is believed to be uncommon, especially in pemphigus foliaceus (PF) [16-18]. In this study, we found that in patients with a chronic El Bagre-EPF variant, the toenails are altered as described by the old Portuguese literature in patients affected by FS. We speculate that the cell junctions are targets within the nails in El Bagre-EPF patients, and are likely damaged by the autoantibodies; however, this is just speculation because for ethical reasons we did not perform biopsies. We can speculate that the toenails were affected because the continue trauma that these nails embrace due to the outside working activities of these patients often using open shoes. The autoantibodies, the continue inflammation and the trauma can make the toenails more prone for the clinical findings we observed. We were not able to determine the cause of the Viera's sign in this study.

With regards to the putative cause of the chronic paronychia we can speculate it to be a result of acantholysis of the lateral nail fold and the chronic inflammation in the adjacent dermis. With regards to the onychomadesis, we hypothesize that this may be the result of inhibition of normal nail plate growth and development; alternatively, the formation of blisters underneath the nail may result in detachment of the nail plate.

Unknown etiologies, predisposing factors and discrepancies evident in the current literature suggest that further investigation of endemic pemphigus foliaceus of the nail may result in additional clinical findings and may contribute to our understanding of the extent of the disease.

## CONCLUSION

Our findings indicate that patients affected by El Bagre-EPF demonstrate significant toenail findings, especially in chronic cases. We suggest that the nails in the patients affected by other variants of EPF including FS and the Tunisian EPF need to be study.

## Abbreviations

Endemic pemphigus foliaceus (EPF), endemic pemphigus foliaceus in El Bagre (El Bagre-EPF), fogo selvagem (FS), hematoxylin and eosin (H&E), direct and indirect immunofluorescence, (DIF, IIF), base

membrane zone (BMZ), intercellular stain between keratinocytes (ICS), fluorescein isothiocyanate (FITC), 4',6-diamidino-2-phenylindole (DAPI), desmoglein 1 (Dsg1).

### Statement of Human and Animal Rights

None animal studies were perform.

### Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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