3. Lee JY, Her Y, Kim CW, Kim SS. Topical corticosteroid phobia among parents of children with atopic eczema in Korea. Ann Dermatol. 2015;27:499–506.
4. Moret L, Anthoine E, Aubert-Wastiaux H, le Rhun A, Leux C, Mazereeuw-Hautier J, et al. TOPICOP©: a new scale evaluating topical corticosteroid phobia among atopic dermatitis outpatients and their parents. PLoS One. 2013;8:e76493.
5. Dufresne H, Bataille P, Bellon N, Compain S, Deladrière E, Bekel L, et al. Risk factors for corticophobia in atopic dermatitis. J Eur Acad Dermatol Venereol. 2020;34:e846–9.
6. Saito-Abe M, Futamura M, Yamamoto-Hanada K, Yang L, Suzuki K, Ohya Y. Topical corticosteroid phobia among caretakers of children with atopic dermatitis: a cross-sectional study using TOPICOP in Japan. Pediatr Dermatol. 2019;36:311–6.
7. Gomes TF, Kieselova K, Guiote V, Henrique M, Santiago F. A low level of health literacy is a predictor of corticophobia in atopic dermatitis. An Bras Dermatol. 2022;97:704–9.
8. Hon KL, Tsang YCK, Pong NH, Luk DCK, Lee VW, Woo WM, et al. Correlations among steroid fear, acceptability, usage frequency, quality of life and disease severity in childhood eczema. J Dermatolog Treat. 2015;26:418–25.
9. Mueller SM, Itin P, Vogt DR, Walter M, Lang U, Griffin LL, et al. Assessment of ''corticophobia'' as an indicator of nonadherence to topical corticosteroids: a pilot study. J Dermatolog Treat. 2017;28:104–11.
10. Song SY, Jung SY, Kim EY. Steroid phobia among general users of topical steroids: a cross-sectional nationwide survey. J Dermatolog Treat. 2019;30:245–50.

Bruna Ossanai Schoenardie [a,*], Gabriela Fortes Escobar [a], Jéssica Pauli Damke [a], Gabriel Cardozo Müller [b,c], Renan Rangel Bonamigo [a,d]

[a] *Dermatology Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil*
[b] *Programa de Pós-Graduação em Epidemiologia, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil*
[c] *Programa de Pós-Graduação em Ciências Médicas, Universidade do Vale do Taquari, Lajeado, RS, Brazil*
[d] *Dermatology Service, Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, RS, Brazil*

* Corresponding author.
E-mail: bruna@ossanai.com (B. Ossanai Schoenardie).

Received 23 January 2023; accepted 5 April 2023
Available online 19 February 2024

https://doi.org/10.1016/j.abd.2023.04.008

Pili canaliculi caused by cetuximab – A three-dimensional ultrastructural analysis☆

Dear Editor,

Monoclonal antibodies (mAb) have, since the end of the 1990s, been increasingly used in antitumor therapies, as part of antineoplastic treatments called targeted therapy. Since they have the advantage of being directed directly and mainly to the lesion and its microenvironment, their use reduces damage to healthy cells and most adverse effects of non-specific therapies.[1]

Due to binding to the extracellular portion of epithelial growth factor receptors (EGFR) and interrupting the coupling of their usual ligands, anti-EGFR monoclonal antibodies prevent the cascade reactions triggered by their activation. As a rule, activation of these receptors, which are known to be part of a family comprising four distinct members, but which share common structural elements, culminates in cell proliferation, angiogenesis, inhibition of apoptosis, and metastasis. For this reason, EGFR blockade has been used as a targeted therapy for several neoplasms that produce their overexpression, which is, in itself, considered a criterion for worse prognosis.[2,3]

EGFR inhibition also affects the proliferation of non-neoplastic cells, due to the natural presence of these receptors in keratinocytes, sebaceous glands and hair follicles. Therefore, this therapeutic modality has the potential to trigger adverse cutaneous effects that, although generally well tolerated and self-limited, when severe can restrict the use of these medications.[4]

Among the most common dermatological reactions is the acneiform rash that appears on the trunk and face, without the presence of comedones. Nail and hair involvement and the appearance of telangiectasias can also be part of the condition; paronychia, pyogenic granuloma, alopecia, eyelash trichomegaly, and facial hypertrichosis can also be observed. Studies demonstrate that lengthening and straightening of eyelashes, associated with changes in hair texture, can be present with ultra-structural and subclinical changes. Another less common effect is the appearance of melanocytic nevi and angioedema.[5]

The effects of three drugs that act by inhibiting EGFR – panitumumab, erlotinib and gefitinib – have already been evaluated using scanning electron microscopy, and hair channels and twisted hair shafts have been observed. Through these investigations, changes were evidenced that generated clinical or subclinical variants of the phenotype described as *pili canaliculi*, characterized by curly or wavy hair.[6]

Cetuximab is a monoclonal antibody that inhibits EGFR and, in combination with chemotherapy, is approved as a first-line treatment for metastatic colorectal cancer with expression of the aforementioned receptor, and even as isolated therapy in patients intolerant to chemotherapy.

Even though they have action mechanisms that are similar to those of drugs whose effects on hair have already been observed, it is speculated whether the structural differences between cetuximab and these other drugs may result in

☆ Study conducted at the Postgraduation in Health and Behavior, Universidade Católica de Pelotas, Pelotas, RS, Brazil.

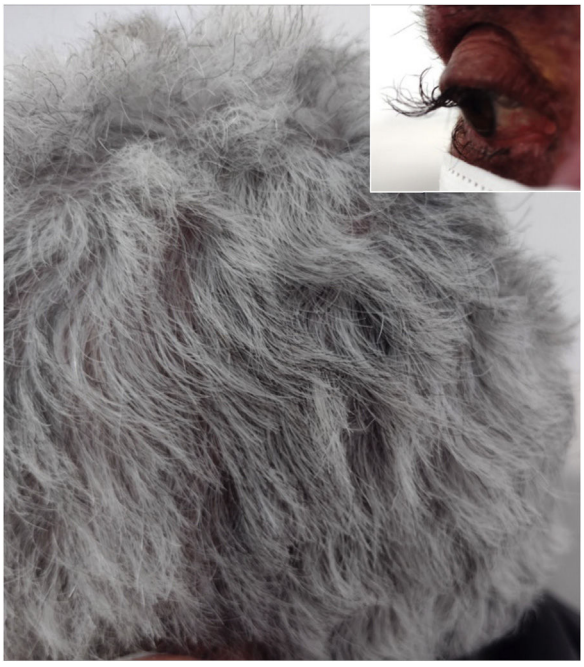

Figure 1 Clinical appearance with curly hair, elongated eyelashes in the insert.

different effects. In this context, the present study aims to observe, using scanning electron microscopy, the three-dimensional ultrastructure of the eyelashes and hair shafts of patients receiving this therapy.

A 64-year-old female patient who presented with colon carcinoma and liver metastases was treated with chemotherapy (FOLFIRI protocol: fluorouracil + leucovorin + irinotecan) and cetuximab for 12 months. She was referred for the treatment of acneiform rash on the trunk and face, which responded to treatment with oral tetracycline (500 mg twice a day for ten days). She reported changes in hair waviness (Fig. 1), which became frizzy after the start of the oncological therapy. The eyelashes changed their curvature and became elongated (Fig. 1).

Hair shafts and eyelash samples were collected and examined *in natura* using scanning electron microscopy.

Hair shafts showed on low power, longitudinal channels and discrete twists (Fig. 2). On higher magnifications, the channels become quite evident (Fig. 3). The examination of the eyelashes showed more pronounced changes, with well-developed, double (Fig. 4a) or single (Fig. 4b) channels.

These findings show that the change caused by cetuximab causes channels in the shafts, they may modify the elasticity of hairs shafts, altering their curvature or making them frizzy. These changes overlap with those caused by panitumumab[6] and oral EGF inhibitors and are similar to the genetic forms of *pili canaliculi*, which are within the spectrum of the uncombable hair syndrome. The twisting was discreet, not characterizing *pili torti*, as they would have to rotate 180 degrees.[7]

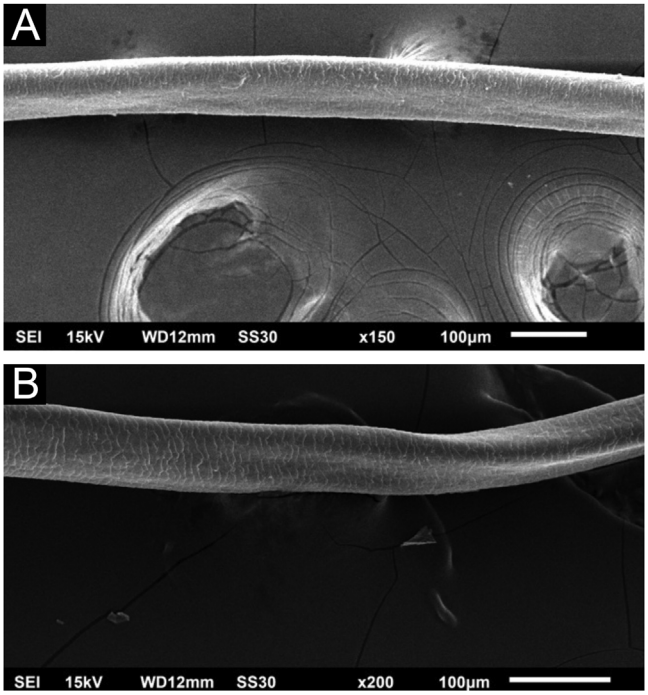

Figure 2 Scanning electron microscopy – (A) Hair shaft with longitudinal channel (×150). (B) Hair shaft with longitudinal channel and discrete twisting (×200).

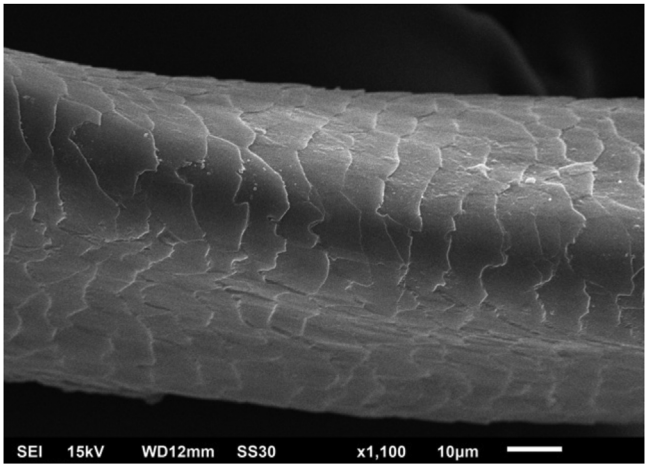

Figure 3 Scanning electron microscopy – high magnification detail of channel and twisting (×1.100).

With both cetuximab and panitumumab,[6] eyelashes show ultra-structurally more prominent channels, and the authors presume that this may be due to their slower or shorter anagen phase.

Other medications used concomitantly, following the protocol for colon cancer metastatic disease, should not be the cause of the hair changes reported herein, as these are characteristic of EGFR inhibitors.

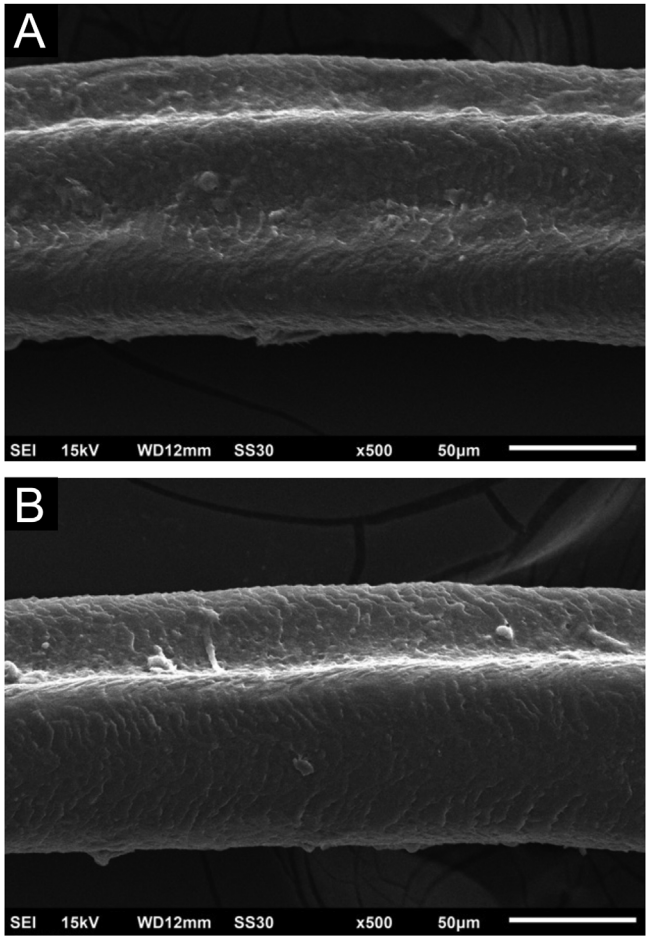

Figure 4 Scanning electron microscopy – (A) Eyelash with two channels (×500); (B) Eyelash with clearly visible single channel (×500).

Financial support

None declared.

Authors' contributions

Hiram Larangeira de Almeida Jr.: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Debora Sarzi Sartori: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript;

Felipe Yusuke Sato Shinzato: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Samuel da Silva Julião: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Sílvia Saueressig: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Conflicts of interest

None declared.

References

1. Chidharla A, Parsi M, Kasi A. Cetuximab. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.
2. Fornasier G, Francescon S, Baldo P. An update of efficacy and safety of cetuximab in metastatic colorectal cancer: a narrative review. Adv Ther. 2018;35:1497–509.
3. Muraro E, Fanetti G, Lupato V, Giacomarra V, Steffan A, Gobitti C, et al. Cetuximab in locally advanced head and neck squamous cell carcinoma: biological mechanisms involved in efficacy, toxicity and resistance. Crit Rev Oncol Hematol. 2021;164:103424.
4. Santiago F, Gonçalo M, Reis JP, Figueiredo A. Adverse cutaneous reactions to epidermal growth factor receptor inhibitors: a study of 14 patients. An Bras Dermatol. 2011;86:483–90.
5. Rodarte CM, Abdallah OA, Barbosa NF, Koch LO, Resende UM. Cutaneous reactions due to the use of epidermal growth factor receptor inhibitors: two case reports. An Bras Dermatol. 2009;84:667–70.
6. Sartori DS, Almeida AL, Oliveira GS, Almeida Jr HL. Scanning electron microscopy of panitumumab-induced eyelash and hair alterations – Pili canaliculi. An Bras Dermatol. 2022;97:240–2.
7. Hoffmann A, Waśkiel-Burnat A, Żółkiewicz J, Blicharz L, Rakowska A, Goldust M, et al. Pili torti: a feature of numerous congenital and acquired conditions. J Clin Med. 2021;10:3901.

Hiram Larangeira de Almeida Jr. [a,b,*],
Debora Sarzi Sartori [a],
Felipe Yusuke Sato Shinzato [c],
Samuel da Silva Julião [c],
Sílvia Saueressig [c]

[a] *Postgraduation in Health and Behavior, Universidade Católica de Pelotas, Pelotas, RS, Brazil*
[b] *Department of Dermatology, Universidade Federal de Pelotas, Pelotas, RS, Brazil*

[c] *Universidade Federal de Pelotas, Pelotas, RS, Brazil*

[*] Corresponding author.
E-mail: hiramalmeidajr@hotmail.com (H.L. Almeida Jr.).

Received 22 March 2023; accepted 20 April 2023
Available online 4 March 2024

https://doi.org/10.1016/j.abd.2023.04.010

Prevalence of the association of vulvar lichen sclerosis with Hashimoto's thyroiditis[☆]

Dear Editor,

Lichen sclerosis (LS) is a chronic inflammatory and cicatricial disease of unknown etiology, which mainly affects the anogenital region of women in the pre-pubertal and post-menopausal period.[1–3] Its actual prevalence remains unknown, mainly due to underdiagnosis.[4] The absence of symptoms is observed in up to 39% of cases and the omission of anogenital complaints by female patients contribute to this scenario.[4]

Clinically, vulvar lichen sclerosis (VLS) manifests as erythematous papules or ivory patches, sometimes hyperkeratotic, which can coalesce to form plaques. Overall, the lesions are symmetrical and affect the labia minora and majora, the perineum and the skin of the perianal region. In more advanced stages, there may be effacement of the labia minora and clitoris. Pruritus, pain and dyspareunia are among the most frequently reported symptoms and tend to worsen at night.[2,4] Dysuria, urinary dysfunction and urinary bleeding due to fissures may also occur.[2,5] Histopathology shows atrophy of the epidermis, hyperkeratosis and basal cell degeneration. Dense fibrosis, edema and chronic perivascular inflammation can be observed in the papillary dermis, with a predominance of eosinophils.[2]

The etiology of VLS is yet to be fully elucidated, but there is growing evidence of a multifactorial origin, including genetic, autoimmune, hormonal aspects and infectious history.[2] The involvement of autoimmunity has been proposed by the frequent association between VLS and a personal or family history of autoimmune diseases.[4] Tissues affected by VLS show dysfunction of T-regulatory cells (Tregs), and low levels of interleukin-10, creating an environment favorable to autoimmunity.[4,6] This hypothesis is strengthened by the detection of autoantibodies in the serum of patients with VLS, such as antibodies against extracellular matrix protein 1, found in nearly 74% of cases.[1,7] Moreover, antibodies against members of the basement membrane zone, especially the transmembrane proteins BP180 and BP230, have been described in 30% of patients with VLS, without correlation to clinical severity and pruritus.[7,8] Up to 40% of patients with VLS have the NC16A domain of BP180 as a target for circulating T cells.[7]

Recently, a case was described of a 77-year-old woman, previously diagnosed with VLS and localized scleroderma (LS), who developed bullous pemphigoid, with lesions manifesting exclusively in areas previously affected by VLE and LS. The authors believe that pre-existing VLS and LS acted as facilitators in the development of bullous pemphigoid, due to the reactivity of T-cells to BP180, often associated with VLS, and the increase in Th2 signaling associated with LS.[7]

Thyroid diseases are the autoimmune disorders most frequently associated with VLS, present in up to 39% of cases.[4,9] Hashimoto's thyroiditis (HT) is characterized by thyroid hyperplasia, infiltration of lymphocytes in the glandular parenchyma and presence of antibodies against thyroid antigens. It is considered the main cause of hypothyroidism in Brazil and affects around 2% of women worldwide.[10] Several authors support the association between VLS and autoimmune thyroid diseases, with autoimmunity being the likely link between these conditions.[1,2,4]

The measurement of thyroid-stimulating hormone (TSH) is considered the reference testing for the detection of hypothyroidism. When elevated, it suggests gland hypofunction, and the measurement of free thyroxine (FT4) is indicated to differentiate overt hypothyroidism (low FT4) from subclinical hypothyroidism (normal FT4). The presence of anti-thyroid peroxidase (anti-TPO) and/or anti-thyroglobulin autoantibodies identifies Hashimoto's thyroiditis.[10] Anti-TPO positivity is the most important characteristic of HT, present in approximately 95% of patients, in addition to having a sensitivity of 90% in the diagnosis of autoimmune thyroid diseases.[10]

VLS attracts the attention of dermatologists and gynecologists, largely due to the enormous damage it inflicts on patients quality of life, in addition to favoring the emergence of squamous cell carcinoma (SCC).[4]

A prospective observational study was conducted at a University Hospital. During two years, 63 women with typical signs and symptoms of VLS were selected at the Vulvar Diseases Clinic and histopathological confirmation was subsequently carried out. For the investigation, TSH, FT4 and anti-TPO were requested, and patients with elevated TSH levels (above the upper limit of the reference value), associated with reduced FT4 (below the lower limit of the reference value), and positive anti-TPO were considered to have HT. All patients with a previous diagnosis of hypothyroidism were excluded from the study.

The project was approved by the Ethics Committee of the University Hospital on 07/31/2018, under CAAE number: 92818418.8.0000.565. For the statistical analysis of data, the chi-square test and confidence interval

[☆] Study conducted at the Hospital Universitário Cassiano Antônio Moraes; Hospital da Santa Casa de Misericórdia de Vitória; Instituto de Assistência Médica ao Servidor Público Estadual de São Paulo.