SOCIEDADE BRASILEIRA DE DERMATOLOGIA

Anais Brasileiros de Dermatologia

www.anaisdedermatologia.org.br

LETTER - RESEARCH

Scanning electron microscopy of ibrutinib-induced hair shaft changes☆

Dear Editor,

Bruton's tyrosine kinase (BTK) is essential for the development and maturation of B-lymphocytes. These cells do not mature in individuals with mutations in this enzyme, and they have X-linked agammaglobulinemia, the most common type of congenital agammaglobulinemia.[1]

BTK is also expressed in tumor cells, and its inhibition is gaining increasing importance in the treatment of B-lineage neoplasms.[2] BTK participates in the activation of these cells, being important for the survival of malignant B cells and, therefore, its inhibition decreases their proliferation and survival.

Ibrutinib is a potent irreversible BTK inhibitor and was the first inhibitor of this enzyme approved by the FDA for the treatment of the following diseases in adults: 1) Chronic graft-versus-host disease, after the failure of one or more systemic therapy lines; 2) Chronic lymphocytic leukemia/small cell lymphocytic lymphoma (CLL/SCLL); 3) CLL/SCLL in adults with 17p deletion; 4) Mantle-cell lymphoma in adults who have received at least one prior therapy; 5) Relapsed/refractory marginal zone lymphoma, in adults who require systemic therapy and have received at least one prior anti-CD20-based therapy; and 6) In Waldenström's macroglobulinemia.[3]

The described side effects are fatigue, diarrhea, peripheral edema, cardiac arrhythmia (atrial fibrillation), bleeding, and infections (respiratory tract).[4–6]

Ibrutinib can have cutaneous adverse effects, with a peak incidence in the first year of treatment. The most common manifestations are skin rash, petechiae and ecchymosis. Also, urticaria, herpes simplex and herpes zoster reactivation, panniculitis, and Stevens-Johnson syndrome may occur.[6,7]

Despite the specificity for BTK, some skin effects are similar to those produced by EGF (epidermal growth factor) inhibitors,[8] such as the described acneiform rash, changes in hair/eyelashes,[9] and longitudinal grooves on nails.

A 72-year-old patient who had received ibrutinib for six months to treat mantle lymphoma unresponsive to conventional therapy was assessed. The patient reported a slight alteration in his hair, with a change in its curling (Fig. 1). Some hair shafts were cut and examined *in natura* with scanning electron microscopy. At medium magnification, discreet longitudinal channels were observed in the hair shafts (Fig. 2A and B), which are not seen in normal hair (Fig. 2C). At high magnification, these channels were very evident (Figs. 3 and 4).

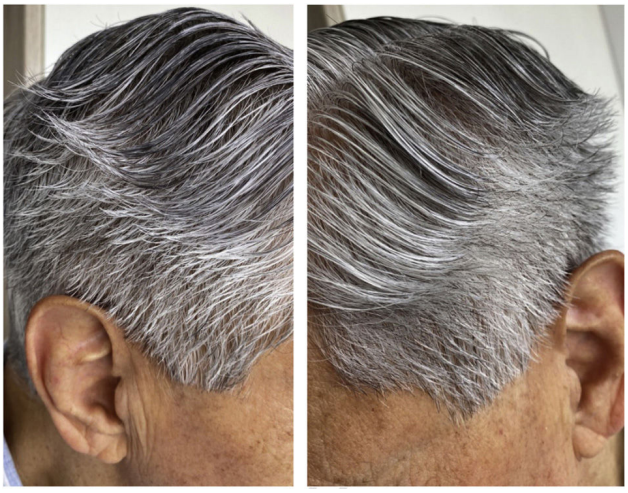

Figure 1 Modification in hair curl pattern.

The authors did not find any reports in the literature of an examination of hairs shafts with scanning electron microscopy showing alterations caused by ibrutinib. There are some reports with EGF inhibitors, in which channels were also described in the hair shafts,[9] in this case with greater clinical consequences, making the hair frizzy and the eyelashes elongated (trichomegaly) and without curvature. The channels seen in these drug-induced cases are similar to those seen in families with uncombable hair,[10] and in a syndromic type of pili canaliculi associated with a central nervous system degeneration called giant axonal neuropathy.[11]

The findings of this patient demonstrate, on ultrastructural examination, a similarity between the alterations of EGF and BTK inhibitors.

BTK inhibition is an expanding concept in the treatment of hematologic malignancies, with 22 drugs under development, and the emergence of drugs with less systemic and cutaneous toxicity is possible in the near future.[10,12]

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

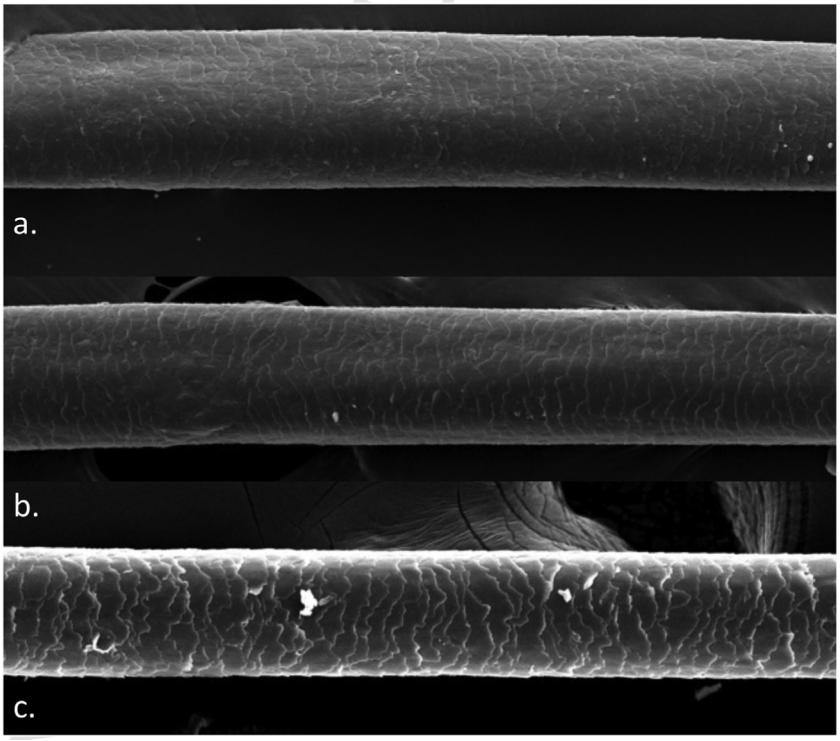

Figure 2 Scanning electron microscopy. (A. and B) Medium magnification showing discreet hair shaft channels (×300 and 270). (C) normal control (×300).

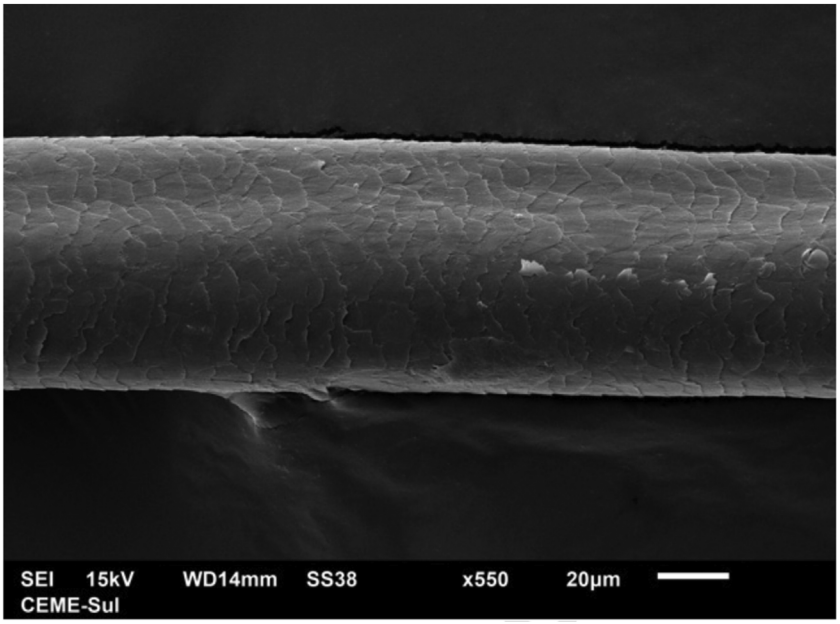

Figure 3 Scanning electron microscopy. High magnification revealing a channel in the hair shaft (×550).

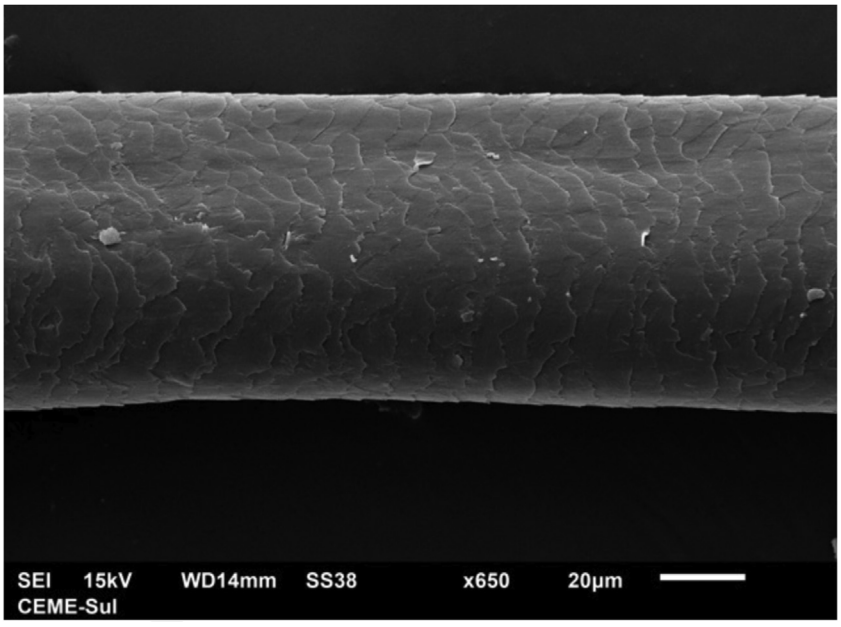

Figure 4 Scanning electron microscopy. High magnification showing a channel in the hair shaft (×650).

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.

Douglas Malkoun: 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.

Carlos Eduardo Pouey Cunha: 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. Cardenas-Morales M, Hernandez-Trujillo VP. Agammaglobulinemia: from X-linked to Autosomal Forms of Disease. Clin Rev Allergy Immunol. 2022;63:22–35.
2. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. Mol Cancer. 2018;17:57.
3. update.com [Internet]. Ibrutinibe: informações sobre medicamentos. UpToDate. [cited 2022 Aug 08]. Available from: https://www.uptodate.com/contents/ibrutinib-drug-information.
4. Paydas S. Management of adverse effects/toxicity of ibrutinib. Crit Rev Oncol Hematol. 2019;136:56–63.
5. Lasica M, Tam CS. Management of Ibrutinib Toxicities: a Practical Guide. Curr Hematol Malig Rep. 2020;15:177–86.
6. Lipsky A, Lamanna N. Managing toxicities of Bruton tyrosine kinase inhibitors. Hematology Am Soc Hematol Educ Program. 2020;2020:336–45.
7. Sibaud V, Beylot-Barry M, Protin C, Vigarios E, Recher C, Ysebaert L. Dermatological Toxicities of Bruton's Tyrosine Kinase Inhibitors. Am J Clin Dermatol. 2020;21:799–812.
8. Singer S, Tan SY, Dewan AK, Davids M, LaCasce AS, Treon SP, et al. Cutaneous Eruptions from Ibrutinib Resembling EGFR Inhibitor-Induced Dermatologic Adverse Events. J Am Acad Dermatol. 2019;20:S0190-962233308-0.
9. Sartori DS, Almeida AL, Oliveira GSP, Almeida Jr HL. Scanning electron microscopy of panitumumab-induced eyelash and hair alterations - Pili canaliculi. An Bras Dermatol. 2022;97:240–2.
10. Cunha Filho RR, Almeida Jr HL, Rocha NM, Castro LAS. Uncombable hair syndrome (pili trianguli et canaliculi): clinical variation in 12 members of one family. An Bras Dermatol. 2008;83:53–5.
11. Almeida HL Jr, Garcias G, Silva RM, Batista SL, Pasetto F. Pili canaliculi as manifestation of giant axonal neuropathy. An Bras Dermatol. 2016;91:125–7.
12. Estupiñán HY, Berglöf A, Zain R, Smith CIE. Comparative Analysis of BTK Inhibitors and Mechanisms Underlying Adverse Effects. Front Cell Dev Biol. 2021;9:630942.

Hiram Larangeira de Almeida Jr. [a,b,*], Debora Sarzi Sartori [b], Douglas Malkoun [a], Carlos Eduardo Pouey Cunha [a]

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

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

Received 4 September 2022; accepted 18 October 2022; Available online 2 March 2023

https://doi.org/10.1016/j.abd.2022.10.005

Thyroid function and thyroid antibodies in patients with alopecia areata: a comparison of clinical patterns☆

Dear Editor,

Alopecia areata (AA) is a disease that affects both men and women, with an overall prevalence of 1.2% to 2.2%.[1,2] A strong connection has been reported between AA and thyroid gland diseases, this is because both diseases share a common autoimmune component with similar genetic variations.[1] Several case-control studies have reported a higher proportion of cases with a diagnosis of thyroid diseases or with altered parameters in thyroid function and autoantibody tests, as compared to the general population.[3,4] However, the studies analyzing this association according to the clinical presentations of AA (e.g., diffuse AA, multilocular AA, and ophiasis AA) are still limited.

The objective of this study was to compare, according to the clinical patterns of AA, the result variations in thyroid function tests (Thyroxine – T4 and thyroid stimulating hormone - TSH) and in thyroid antibody tests (Thyroglobulin Antibody – TGAb and Thyroid Peroxidase Antibody – TPOAb) in a cohort of patients that were screened for thyroid abnormalities during the diagnostic process of AA in a Latin American center.

We performed a retrospective review of cases with AA diagnosed between 2017 and 2020 in Cali, Colombia. Adults identified with a clinical pattern compatible with diffuse AA, multilocular AA, or ophiasis AA, who underwent thyroid function screening during the diagnosis of AA were analyzed. Only patients who had at least one measurement of T4 or TSH and TGAb or TPOAb were included in this report. Ethical approval was obtained from the Institutional review board.

T4 or TSH values outside the normal range were classified as abnormal thyroid function. Similarly, an altered thyroid antibody level was defined by measurements of TPOAb or TGAb. The normal cut-off ranges were 5.0–11.0 ug/dL for T4, 0.4–4.0 IU/mL for TSH, less than 35 IU/mL for TPOAb, and less than 20 IU/mL for TgA. Cases with a previous diagnosis of thyroid disease were considered with abnormal thyroid function and altered antibody levels. All analyses were carried out in Stata version 16.0 (StataCorp, Texas, USA). The Kruskal-Wallis nonparametric test was used for the comparison of quantitative variables. Qualitative variables were tested using the Chi-square or Fisher's exact test. A p-value less than 0.05 was considered statistically significant.

A total of 89 patients with AA were included in this study, 32 (36.0%) of them had a diffuse pattern, 31 (34.8%) had a multilocular pattern, and 26 (29.2%) had an ophiasic pattern. The median age was 40 years (Interquartile Range – IQR 35 to 52 years), and 85.4% (76) were women. Approximately one in four AA patients reported a concomitant diagnosis of thyroid pathology, and all were being treated with levothyroxine. The most frequent concomitant thyroid condition was hypothyroidism (n = 20), followed by thyroid nodules (n = 2) and cancer (n = 1) (Table 1).

The proportion of cases with altered values on T4, TSH, TPOAb, or TGAb according to clinical AA patterns is shown in Table 1. The proportion of AA cases with altered antibody levels (42.7%) was higher than that with abnormal thyroid function (31.5%). In approximately half of AA cases, at least one abnormal thyroid result was reported as ''Thyroid dysfunction'' (Fig. 1). There were no statistically significant differences between cases with diffuse AA, multilocular AA, and ophiasis AA with respect to thyroid function and altered antibody levels ($p > 0.05$). Abnormal T4/TSH values were more common among patients with ophiasis AA (38.5%). Thyroid dysfunction was more common in cases with a multilocular and ophiasis pattern (≈50%).

Thus, the main finding of this study revealed that thyroid dysfunction is present in half of the patients with AA, without differences between the following patterns: diffuse, multilocular, and ophiasis. This estimate is higher than the reported rates for the general population (0.3% to 11.3%),[5] suggesting a possible causal association between AA and thyroid dysfunction. However, the causal relationship remains unclear, with inconclusive results that give cause for further study. For example, in the recent study performed by Dai et al., a high risk of AA in patients with thyroid diseases and an increased risk of thyroid diseases in AA patients were reported, suggesting a bidirectional association between these conditions.[1]

☆ Study conducted at the Clínica Imbanaco Grupo Quirón Salud, Cali, Colombia.