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# Clinical evaluation of hydration index using a corneometer in metastatic melanoma patients treated with BRAF/MEK inhibitors: a prospective study

Adverse skin effects of antineoplastic therapies can reduce compliance, lead to skin complications and be associated with major psychological impact [1]. Xerosis cutis has been associated with targeted therapies, such as BRAFMEK inhibitors used in the treatment of metastatic melanoma (MM) [2].

However, data on this topic are scant. In pivotal trials, xerosis cutis was reported as an adverse event in up to 16% of patients on these agents and up to 23% of those on MEK inhibitors only [3-6]. Xerosis cutis is difficult to diagnose given individual variability due to emollient use, occupational exposure and difficulties in assessing severity. No data are reported regarding the time at onset and modality of assessment.

We therefore sought an objective assessment of the variation of xerosis cutis according to the main risk factors within a group of patients on BRAF/MEK inhibitors.

The degree of xerosis cutis was evaluated based on the hydration index (HI) using the Corneometer CM825, which allows an accurate evaluation of the hydration levels of the skin, expressed as arbitrary units (a.u.), even in cases with low hydration levels [7, 8]. HI measurements, performed in triplicate, were compared with the clinical evaluation of xerosis cutis based on overall dry skin score (ODS) (0-4 scale) [9].

Thirty-five patients with MM were included (16 males; median age: 62 years; range: 35-92). The study was divided into two parts, the first included 20 patients already receiving BRAF/MEK inhibitors who served as controls, and the second included 15 MM patients with metastatic melanoma, naïve, but eligible for those agents (five of them had received previous antineoplastic therapy: interferon, $n$=2; radiotherapy, $n$=2; chemotherapy, $n$=1).

In the first part, the median time from the initiation of targeted therapy was 16 months (range: 1.8–29.8). Fifteen patients (75%) showed HI mean values <30, suggesting very dry skin [7]. On clinical evaluation, six patients did not show any abnormality (ODS=0), 11 had mild xerosis cutis (ODS=1), and only three had mild-to-moderate xerosis cutis (ODS=2).

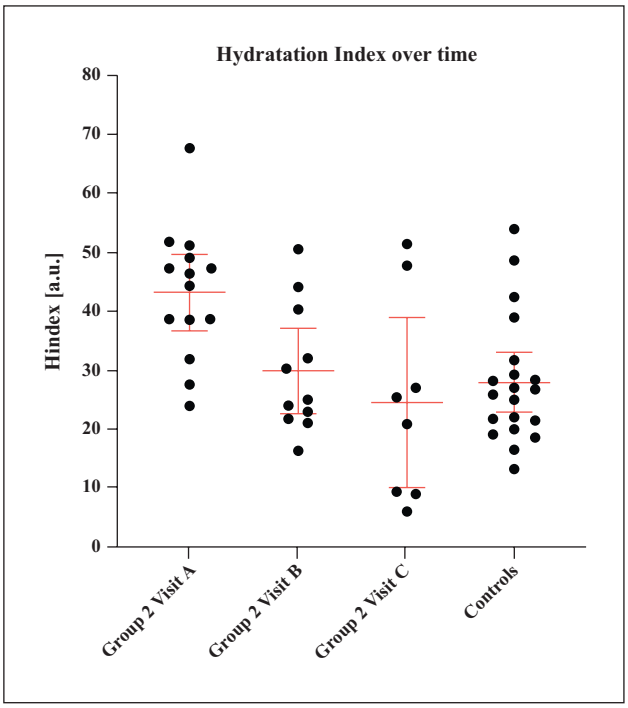


**Figure 1.** HI values measured in the different patient groups. Horizontal red bars represent mean values and 95% CI levels.

In the second part, we investigated HI and ODS on the first day before the initiation of BRAF/MEK inhibitors (Visit A; 15 patients), then at two and four months (Visit B, available for 12 patients; and C, for nine patients, respectively). At Visit A, the proportion of patients showing HI values <30 was 13.33% (2/15), significantly lower than that of controls from the first part ($p$=0.0003). HI at Visits B and C confirmed a significant reduction of this parameter: from 43.36±10.79 a.u. at Visit A (95% CI: 37.15-49.10) to 30.47±10.68 a.u. at Visit B (95% CI: 23.70-37.29; $p$=0.0046) and 25.81±16.68 a.u. at visit C (95% CI: 13.00-38.63; $p$=0.0046) (*figure 1*). Similarly, the percentage of patients with HI <30 a.u. increased from 13.3% at Visit A to 50% at Visit B (6/12) and 66.6% at Visit C (6/9). At Visit C, three patients showed a HI value <10 a.u. No differences in HI associated with gender/age/BMI were disclosed. Similarly, occupational risk factors (reported in five patients) and dermatological conditions (two patients had psoriasis) were not related to any HI difference. According to clinical examination, xerosis cutis was not detected(ODS=0) in 13/15 patients at baseline, 9/12 at Visit B and 5/9 at Visit C.

Although a more detailed statistical analysis was not possible due to the small sample size, these data show, for the first time, HI trends during targeted therapies and suggest that HI reduction may represent a side effect of BRAF/MEK inhibitors from the second month of treatment, reaching clinically relevant values within a short time. Indeed, the presence of HI was associated with mild but noticeable rash and pruritus. The percentage of patients showing severe HI deterioration appears to be higher than that determined at clinical examination and reported in clinical trials, suggesting that HI worsening may anticipate the onset of overt xerosis cutis, which is an additional burden on the QoL

of oncological patients. Therefore, the identification of patients with lower HI and early use of moisturizers and emollient creams could help prevent clinical symptoms. Collaborative studies, with larger sample sizes, on the role of HI in the evaluation of skin tolerability for targeted therapies are ongoing. ■

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## IgA nephropathy preceded by erythroderma with eosinophilia

A 60-year-old male was referred to us with a one-year history of erythroderma on his whole body. His skin lesions had been refractory to topical treatment. His medical history was unremarkable, except for hypertension and hyperlipidaemia. His family had no health problems. Examination revealed flat erythematous lesions scattered on the whole body, often coalesced into plaques (*figure 1A, B*). The eruptions were very itchy. Skin biopsy specimens showed mild spongiosis in the epidermis, with a focal vacuolar change in basal keratinocytes (*figure 1C).* There was no atypical lymphocyte infiltration in the skin specimens. Direct immunofluorescence showed no deposition of immunoglobulins or complements in the skin. Laboratory examination revealed severe eosinophilia: white blood cells at $11.6\times10^9$ cells/L (reference range: 4.0-10 $\times10^9$ cells/L), with 29.0% eosinophils (reference range: 0.4-8%). Hepatic function and renal function were within normal limits. Neither anti-nuclear antibodies nor anti-HTLV1 antibodies were detected.
The cessation of medications, which included antihypertensive drugs, did not improve his symptoms. Whole-body computed tomography revealed multiple lymphadenopathies in the inguinal area. However, lymph node biopsy specimens showed no malignancies. Bone marrow aspiration did not reveal any atypical blood cells. Flow cytometric analyses of the bone marrow revealed $CD3^+$ (75.4%), $CD4^+$ (36.4%), $CD8^+$ (41.2%), and $CD2^+$ cells (82.3%). FIPIL1-PDGFRa fusion, a hallmark of chronic eosinophilic leukaemia, was not detected. During physical and laboratory examinations, his renal function gradually deteriorated, prompting a renal biopsy. The kidney specimens showed sclerotic changes in the glomeruli. Immunofluorescence revealed IgA deposition in the mesangial area (*figure 1D*). The diagnosis of IgA nephropathy was made. The patient underwent pulsed corticosteroid therapy, which resulted in the complete remission of the renal dysfunction, skin symptoms, and eosinophilia. The corticosteroids were gradually reduced to 4 mg prednisolone/day. No obvious recurrence of nephropathy, erythroderma, or eosinophilia was observed at five years.
Erythroderma is a skin condition characterized by diffuse erythema and scaling of the skin all over the body (≥90% based on the most common definition) [1]. Differential diagnoses of erythroderma include psoriasis, lichen planus, eczema, ichthyosis, mycosis fungoides and Sézary syndrome. Underlying diseases, such as graft-versus-host disease, diabetes mellitus and internal malignancy, are also known causes [1]. To the best of our knowledge, IgA nephropathy has not been associated with erythroderma in