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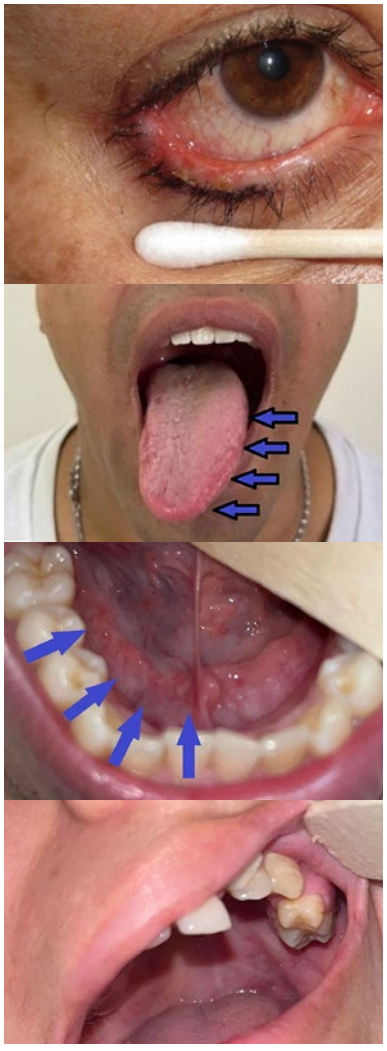

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EDITORIAL

Artificial intelligence in dermatology journals

La inteligencia artificial en las revistas de dermatología

Carlos García-Rementería

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Artificial intelligence (AI) has ceased to be a fantasy. It is now a widely accessible technology that is revolutionizing all aspects of medicine[1]. The question is no longer whether we are going to use it, but how we can use it effectively, responsibly, and ethically for the benefit of our specialty. The most realistic future is not one in which AI replaces the specialist, but one in which both work together to advance, innovate, and help patients. Dermatology, unlike most specialties, relies heavily on visual recognition and pattern analysis, which places it among the fields most impacted by AI.

In this editorial, I will focus specifically on issues related to the use of AI in the publication of articles in dermatology journals. Naturally, technology affects the editorial process as much as it affects clinical practice; therefore, this is the time to plan and decide how to govern its integration and define the appropriate role of AI in our scientific literature[2,3]. Here, I will limit myself to briefly analyzing the pros and cons of this remarkable technology to avoid fostering either excessive enthusiasm or harmful skepticism. My aim is simply to offer an honest and balanced analysis of how AI can strengthen our dermatology journals, while highlighting the editorial aspects that require caution and care to preserve our professional and scientific integrity.

Advantages

One of the greatest advantages of AI is its incredible speed in acquiring and processing new information in a field where new articles emerge almost daily. Language models can draft introductions, improve the flow of arguments, refine academic tone, and identify inconsistencies. AI provides a structure or skeleton from which to communicate ideas and results, minimizing the time invested in formatting and language polishing. Rather than replacing the authors' scientific creativity, AI can support them so they can focus more on hypothesis generation, data interpretation, and clinical judgment.

Another huge benefit is global accessibility. The traditional culture of scientific publishing has tended to favor authors who master the English language, inadvertently marginalizing authors from regions with great dermatologic diversity. With AI assistance, these authors can now publish more easily and enrich our literature with studies on different diseases and skin types, and from diverse clinical contexts.

In research, AI-based image recognition has demonstrated effectiveness in differentiating pigmented lesions, quantifying degrees of inflammation, and analyzing histological slides. In fact, when articles incorporate solid information generated by algorithms, journals can disseminate more objective, reproducible, and quantitative evidence[4]. Additionally, if peer review is conducted seriously and responsibly, AI may raise scientific standards and offer improved resolution or precision in image analysis.

Limitations

The risks of AI are real and should not be minimized. The most widely discussed to date is data bias. For example, a model trained on lighter skin types may

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underperform on darker skin, perpetuating underdiagnosis and classification errors. If such a study is published without due care, the literature may amplify errors and inequalities rather than clarify them. In dermatology, this has very serious implications regarding responsibility for inclusive data representation.

Another challenge is reliability. Although AI-generated text may be elegant and polished, it may not be accurate or precise. It can generate nonexistent or false "references" that appear legitimate, misrepresent studies, and produce conclusions not supported by evidence. The peer-review process may fail to detect one or more of these problems unless an extensive, slow, and laborious examination is undertaken. Here lies one of the great paradoxes of AI: while it can greatly accelerate manuscript drafting, it can also substantially increase the workload of reviewers who must verify its authenticity.

Another major concern relates to authorship and author responsibility[5]. If part of the text is generated by AI, who owns the intellectual product? And how should AI assistance be cited? As a "non-human coauthor"? A "support tool"? An "assistant"? Journals and editors will need to define these concepts rigorously, because without clear authorship declarations, academic transparency, originality, and scientific credibility may be weakened.

Finally, there are also issues related to the opacity of deep learning models, often referred to as "black box algorithms," that is, those that generate results with a high degree of confidence without revealing how decisions were made. This can affect methodology, reproducibility, and interpretability of data and studies. Currently, most reviewers cannot evaluate the internal logic of these models, and there is a risk of approving false conclusions or results that cannot be questioned or reproduced.

Conclusions

AI is already part of our daily practice in dermatology and, of course, in the world of scientific publishing. Its advantages are clear: it helps revise texts more quickly, improves the way we communicate ideas, and opens the door for more authors from different regions to share their experience and enrich the literature. However, along with these opportunities come important challenges. Data bias, potential errors, uncertainty about true authorship, and the lack of transparency of some algorithms are issues that must be handled with great care. Editors and reviewers will play a key role in ensuring that the quality and reliability of articles are not compromised.

Ultimately, the goal is not for AI to replace the specialist, but for us to work with it responsibly. If we achieve that balance, we can harness its potential without losing the rigor and integrity that characterize scientific dermatology. In this regard, education on AI for dermatologists, editors, and reviewers will be essential.

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ORIGINAL ARTICLE

Treatment of chronic pruritus on atopic dermatitis patients with non-invasive brain stimulation

Tratamiento del prurito crónico atópico mediante estimulación cerebral no invasiva

Helena R. Camasmie[1], Adriane S. Manhães[2], Alessandra Sayao[2], Omar Lupi[1], and Egas Caparelli-Dáquer[2]*

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Abstract

Background/Objective: *Chronic itch is a multidimensional phenomenon, which contains similar cognitive and emotional aspects to chronic pain. Our objective was to explore the effect of a 6-day treatment with anodal transcranial direct current stimulation (tDCS) of the motor cortex on chronic pruritus in patients with atopic dermatitis (AD).* **Materials and methods:** *Fourteen patients with moderate/severe AD and chronic pruritus were recruited. All patients underwent 2 consecutive weeks of treatment with tDCS 3 times a week, blindly divided into 2 groups. Group A was treated with a constant current of 1.0 mA, while Group B was treated with a 2.0 mA current, both for 20 min. After an 8-week wash-out period, patients were asked to return to a second treatment cycle where the current intensity was switched between the groups.* **Results:** *Our study demonstrated a tendency of improvement in Scoring AD levels after each treatment cycle, sustained for 30 days, regardless of the current intensity applied. Both treatments demonstrated a tendency of reduction on itch severity with significant improvement in the patient's quality of life after 1 mA tDCS.* **Conclusions:** *We were able to achieve significant improvement in patient's quality of life, indicating that tDCS may be a promising therapeutic tool in chronic itch.*

Keywords: *Pruritus. Atopic dermatitis. Electric stimulation.*

Resumen

Antecedentes/Objetivo: *El prurito crónico es un fenómeno multidimensional con aspectos similares al dolor crónico. Exploramos el efecto de 6 días de estimulación transcraneal de corriente continua (tDCS) de la corteza motora en pacientes con dermatitis atópica (DA) y prurito crónico.* **Materiales y métodos:** *Catorce pacientes con DA moderada/grave y prurito crónico se sometieron a 2 semanas de tratamiento con tDCS 3x por semana, divididos a ciegas en 2 grupos. El grupo A recibió una corriente de 1,0 mA; el grupo B recibió una corriente de 2,0 mA, durante 20 minutos. Después de 8 semanas, se solicitó a los pacientes a regresar a un segundo ciclo, en el que se alternó la intensidad de la corriente entre los grupos.* **Resultados:** *Demostramos una tendencia a la mejora en los niveles de SCORAD, mantenida durante 30 días, independientemente de la intensidad de la corriente, y una tendencia a la reducción de la intensidad del prurito, con una mejora significativa del DLQI con tDCS de 1 mA.* **Conclusiones:** *Se logró una mejora significativa de la calidad de vida, lo que indica que la tDCS puede ser una herramienta terapéutica prometedora para el prurito atópico.*

Palabras clave: *Prurito. Dermatitis atópica. Estimulación eléctrica.*

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Introduction

Pruritus or itch is a sensorial experience characterized by an urge to scratch[1]. It is strongly associated with emotional and cognitive suffering, with severe compromise of the quality of life of those affected. There are many causes of chronic pruritus, defined as itch lasting more than 6 weeks[2,3].

Atopic dermatitis (AD) is the most common skin disease, causing chronic itch, frequently characterized as "the itch that rashes," and chronic pruritus is the principal symptom of AD. Diverse pruritogens activate peripheral receptors to drive atopic itch, and histamine -evoked itch plays a minor role[4]. The mechanism of acute histaminergic itch is partially understood, but there are major inconsistencies regarding the pathophysiology of chronic pruritus[5].

Chronic itch is a multidimensional phenomenon, which contains very similar affective, cognitive, and emotional aspects to chronic pain[6]. Patients with chronic itch usually present increased innervation density and higher expression of inflammatory neuropeptides[4]. Itch sensations are transmitted to the brain through C-fibers and the spinothalamic tract[7].

On the central level, brain imaging of chronic itch patients with AD demonstrated activation of the anterior cingular cortex (ACC), posterior cingular cortex, insula and dorsolateral prefrontal cortex (DLPFC), cortical areas typically involved in emotional processing, memory, and reward behavior[6].

The ACC and DLPFC are known to be involved in hypersensitization phenomena of chronic pain. Similarly, patients with chronic pruritus exhibit reduced thresholds for itch, as well as the perception of itch in response to previously non-itchy stimuli (alloknesis)[8]. This is analogous to the more familiar phenomenon of allodynia in chronic pain[2].

Treatment of chronic pruritus is challenging for both dermatologists and neurologists. Adding to the complex pathophysiology of chronic pruritus, the scarcity of approved therapies also contributes to the high refractory rates[3]. Topical treatments, such as glucocorticosteroids, tacrolimus, capsaicin, local anesthetics, and others, may be viable options for small skin areas. Antihistamines are not usually the choice for chronic pruritus and may only play a role because of its sedating effects, but increased drowsiness may be a problem, especially in the elderly[9].

Treating the underlying disease with etiology-specific treatment for underlying dermatoses is important but not always sufficient. Opioids, tricyclic antidepressants, GABA-inhibitors, and serotonin receptor antagonists are frequently prescribed[9]. Psychological interventions have positive effects on itch and scratching, such as cognitive behavioral therapy, meditation, and mindfulness[10].

Considering the similar mechanisms between chronic pain and itch, non-invasive brain stimulation should be considered as an alternative option in the treatment of chronic itch. These techniques have been increasingly used in the setting of different clinical conditions. Several studies demonstrated the positive effects of transcranial direct current stimulation (tDCS) in the treatment of neuropathic pain, phantom limb pain, as well as other neurologic and psychiatric disorders[11].

These techniques are considered safe, with minimal side effects, and can manipulate neural activity by applying weak magnetic or electrical stimuli through the scalp[10]. Repetitive sessions were able to alleviate chronic pain, with clinical effects that outlast the periods of stimulation[12].

Here we explored the effect of a 6-day treatment with anodal tDCS of the motor cortex on chronic pruritus, with the primary goal of establishing enduring antipruritic effects in patients with chronic pruritus caused by AD.

Materials and methods

Fourteen patients with moderate to severe AD and chronic pruritus were recruited from the outpatient population of the Immunology Department of the "Clementino Fraga Filho" University Hospital in Rio de Janeiro (Brazil). Demographic and clinical data of the patients are reported in table 1.

We recruited patients with age > 18 with a clinical diagnosis of AD with chronic pruritus according to Scoring AD (SCORAD) levels. SCORAD assesses active acute or chronic AD lesions, xerosis, pruritus, and sleeplessness, ranging from mild (0-25 points), moderate (26-50 points) to severe (51-103 points). The patients who were invited to participate had moderate to severe SCORAD levels, despite optimal topical and systemic DA treatment at the moment.

Exclusion criteria were as follows: (1) coexistence of major neurologic, neuropsychological, or psychiatric diseases; (2) contraindication to non-invasive brain stimulations, such as open scalp wounds, presence of metal in the skull, and others; (3) severe or uncontrolled clinical respiratory or cardiac conditions.

The study was conducted at the Laboratory of Electric Stimulation of the Nervous System (LabEEL) of the "Pedro Ernesto" teaching Hospital of Rio de Janeiro State University. The protocol followed the guidelines

Table 1. Patient's demographic and clinical data

Patient	Gender	Age	SCORAD: baseline	Immunosuppressive therapy	Protocol group
1	F	20	Severe	No	A; no return for B
2	M	27	Moderate	No	A → B
3	F	22	Moderate	Yes (cyclosporine)	B (drop-out)
4	M	31	Moderate	Yes (cyclosporine)	A; no return for B
5	F	22	Moderate	Yes (cyclosporine)	A; no return for B
6	F	58	Severe	Yes (cyclosporine)	B; no return for A
7	M	20	Moderate	Yes (metothrexate)	A; no return for B
8	F	54	Moderate	No	B (drop-out)
9	M	50	Moderate	Yes (prednisone)	A (drop-out)
10	M	21	Moderate	No	B; no return for A
11	M	32	Severe	Yes (cyclosporine)	B → A
12	M	64	Severe	Yes (prednisone)	B → A
13	F	29	Moderate	No	B → A
14	F	20	Moderate	Yes (cyclosporine)	B → A

SCORAD: Scoring Atopic Dermatitis.

of the Declaration of Helsinki and was approved by the local ethics committee (CAAE 04208818.9.0000.5259). Each patient gave informed consent before participating in the study.

All patients underwent 2 consecutive weeks of treatment with tDCS 3 times a week (Monday, Wednesday, and Friday). Patients continued their usual drug intake during treatments. tDCS was delivered with a battery-driven constant current stimulator (Soterix Medical Inc., New York, NY, USA 1300A) using a pair of surface saline-soaked sponge electrodes placed on the scalp. The anodal electrode was placed over C3 (according to the 10-20 electroencephalograph system for electrode placement) and the cathode electrode over the contralateral supraorbital area. This choice was guided by the majority of the studies involving tDCS and chronic pain to stimulate the motor cortex M1[13,14].

The patients were blindly divided into 2 groups. Group A was treated with a constant current of 1.0 mA for 20 min, while group B was treated with a 2.0 mA current intensity also for 20 min. Both groups were required to return after an 8-week washout period to repeat the treatment. On the second treatment cycle, the current intensity was switched between the groups, so that group A was treated with a 2.0 mA current intensity, while group B, with a 1.0 mA current intensity.

On the 1st day of each cycle (baseline), each patient was required to fill the dermatology life quality index (DLQI) questionnaire. The DLQI comprises ten questions that evaluate how the clinical dermatologic condition impacts patient's quality of life. Also, the clinical severity outcome measure SCORAD was performed by a dermatologist.

During the 2 weeks of tDCS treatment, in both treatment cycles, patients were asked to rate their current pruritus state on a 10-cm Visual Analog Scale (VAS) immediately before each tDCS application (0 = absent, 10 = the worst possible). On the last day of each cycle, DLQI and SCORAD were performed once again. Participants were required to return 30 days after the ending of each cycle to reassess DLQI, SCORAD, and pruritus-VAS.

The changes induced in SCORAD, VAS and DLQI by active 1 mA or 2 mA tDCS were transformed according to the general formula X/Bl+X, in which "Bl" represents baseline values, and "X" the subsequent measures. Values = 0.5 indicate no change, while > 0.5 indicates an increase in SCORAD, VAS or DLQI scores. According to our treatment protocol, we obtained six different indexes for VAS: iV1-iV4, iVf (final), iVt (late); 2 for SCORAD: iSCDf (final), iSCDt (late); 2 for DLQI: iDLf (final), iDLt (late).

To examine the change of VAS in each phase we used repeated measures analysis of variance (ANOVA) with 2 within-subject factors: treatment current intensity (2 levels) and VAS scores (6 levels). The same approach was employed to examine DLQI (2 levels) and SCORAD (2 levels). Level of significance was set at a = 0.05.

To examine changes in VAS, DLQI and SCORAD before and after the end of the treatment, as well as before and 1 month after the treatment were assessed with paired t-tests.

Results

Out of fourteen patients, 3 dropped out. Eleven patients completed the first treatment cycle, but only 5 patients returned after the 8-week wash-out period to initiate the second treatment cycle. After contacting the 6 missing patients, 2 did not answer our messages, 3 declared logistical difficulties and 1 did not want to return, because she did not see any improvement after the first cycle. More details in figure 1. The treatment was well tolerated by all patients, without any side effects. Absolute measurement values at baseline, final and late (after 30 days) are described in table 2.

With respect to itch intensity, the repeated measures ANOVA did not show a significant effect of the tDCS treatment, assessed through result index (IR) VAS (tDCS 1 mA × tDCS 2 mA) ($F(1,4) = 0.19$; $p = 0.69$). Also, no significant changes between treatments ($F(5,20) = 1.59$; $p = 0.21$) and no interaction effect between itch severity and current intensity were demonstrated ($F(5,20) = 0.50$; $p = 0.78$) (Fig. 2).

As for the clinical severity scale SCORAD, regardless of the current intensity, repeated measures ANOVA demonstrated a changing tendency between the end of the treatment and 1 moth past, in both treatment groups ($F(1,4) = 5,35$; $p = 0.08$). However, without significancy ($F(1,4) = 0,32$; $p = 0.87$) or interaction effect ($F(1,4) = 1,95$; $p = 0.23$) (Fig. 3).

Also, no significant results were found regarding changes in quality of life (DLQI) (Treatment: $F(1,4) = 0.18$; $p = 0.69$; DLQ: $F(1,4) = 1.61$; $p = 0.27$; Treatment X DLQI: $F(1,4) = 1.95$; $p = 0.23$) (Fig. 4).

Clinical response analysis through one sample t-tests indicated a tendency of improvement in itch intensity after 1mA tDCS ($t(8) = -1.93$; $p = 0.09$) and 2mA tDCS ($t(6) = -2.41$, $p = 0.05$). Significant changes in DLQI at the end of 1mA tDCS treatment (($t8) = -2.36$, $p < 0.05$) as well as a tendency of improvement after 2mA tDCS ($t(6) = -2.14$, $p = 0.76$) were demonstrated (Figs. 5 and 6).

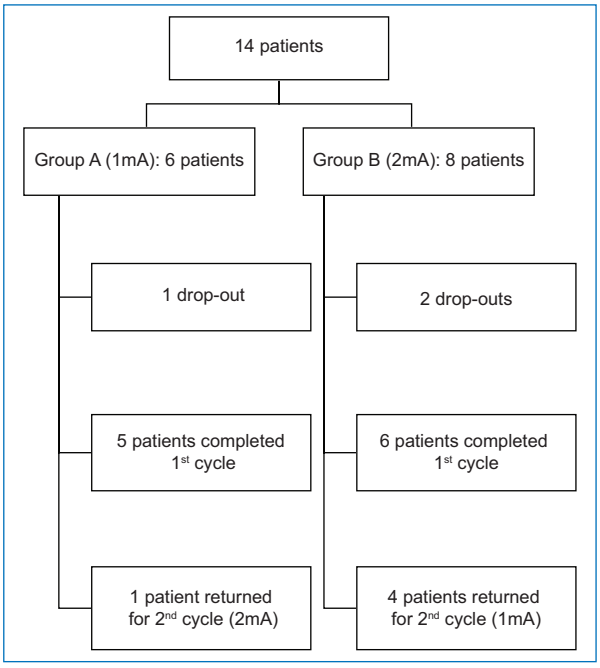

Figure 1. Patient's course throughout the study.

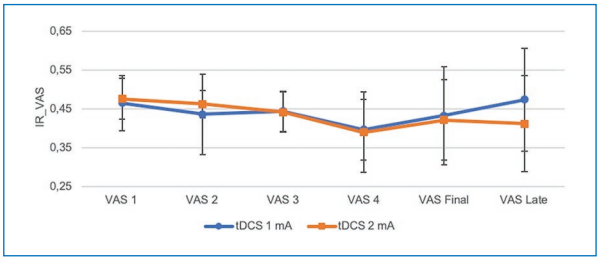

Figure 2. Visual Analog Scale (VAS) – Results after each 1 mA and 2 mA treatment session (VAS 1-4), final session (VAS Final) and 30 days after (VAS Late).

Discussion

Analyzing the patients that completed both treatment cycles (1 mA and 2 mA), our study demonstrated a tendency of improvement in SCORAD levels after each treatment cycle, sustained for 30 days, regardless of the current intensity applied.

Separately, both treatments (1 mA and 2 mA) demonstrated a tendency of reduction on itch severity (lower VAS scores), with significant improvement in patient's quality of life after 1 mA tDCS.

Noticeable is the perception that group B had a higher return rate than group A, and that leads up to the question whether higher current intensities lead to greater reduction of pruritus.

Table 2. Absolute measurement values at baseline, final, and late (after 30 days)

Patient - Protocol	SCORAD/VAS/DLQI at day 0 (baseline)	SCORAD/VAS/DLQI at the end of the protocol (final)	SCORAD/VAS/DLQI after 30 days (late)
1 - A	55.5/6.2/13	42.6/7/11	51/8.1/7
2 - A	35/3.8/1	29.7/6,4/2	48.7/6.4/13
2 - B	35.9/4,9/3	40.2/6.55/4	40,9/4.8/7
4 - A	46.8/8.6/15	34.3/2.2/4	Did not return
5 - A	44.8/7.4/20	35.4/5.8/2	50.2/7.1/14
6 - B	50.3/10/21	53.3/5/15	34.9/8/22
7 - A	30.5/6/7	41.3/4.7/4	37.9/4.9/10
10 - B	42.1/7.2/10	34.5/6.2/4	41.3/7.3/4
11 - B	54.9/8/16	30.9/4/9	46.3/3.3/8
11 - A	33.4/5.6/12	35.7/2.4/7	30.9/6.9/15
12 - B	66.7/7/13	56.9/6.6/9	70.7/6.2/10
12 - A	61.7/7.9/11	56.9/7.2/12	42.1/3/8
13 - B	46.2/5.2/11	54.5/2.9/11	60.9/6/16
13 - A	53.8/4.3/11	42.5/2.8/3	46.2/3.5/5
14 - B	46.2/6.6/13	36.3/3.7/10	28.7/2.4/3
14 - A	53.1/5.7/14	45.5/3.3/8	70.9/5/15

SCORAD: Scoring Atopic Dermatitis; VAS: Visual Analog Scale; DLQI: Dermatology Life Quality Index.

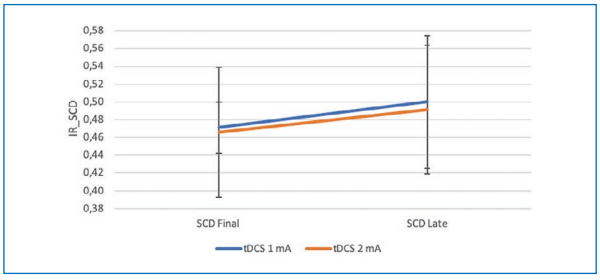

Figure 3. Scoring atopic dermatitis: results after 1 mA and 2 mA final session (SCD Final) and 30 days after (SCD Late).

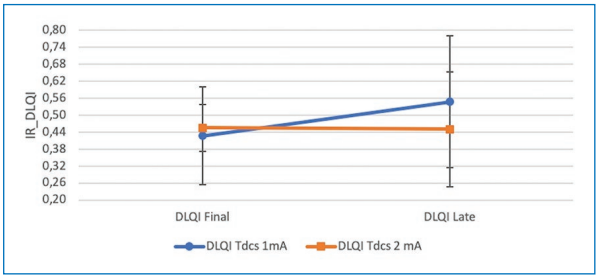

Figure 4. Dermatology life quality index: results after 1 mA and 2 mA final session (SCD Final) and 30 days after (SCD Late).

While VAS is a direct pruritus measure, performed by the patient, SCORAD and DLQI are indirect pruritus measures.

SCORAD is divided in three steps: evaluation of the extension of the skin lesions according to the body surface area (responsible for 20% of the total score); severity of these lesions (60% of the total score); and subjective symptoms (pruritus and sleeplessness, 20% of the total score). The first two steps are assessed by a dermatologist, and the last step by the patient itself.

DLQI is not a specific questionnaire for AD and it can be applied to any skin disease. It comprises ten questions that evaluate how much the skin disease is affecting the patient's daily activities and social relations.

It is understandable that, when achieving a reduction in chronic pruritus and, therefore, skin scratching, the patient's skin lesions and quality of life both improve.

There is a growing body of evidence showing the efficacy of anodal tDCS of the motor cortex in chronic pain syndromes, such as neuropathic pain, phantom

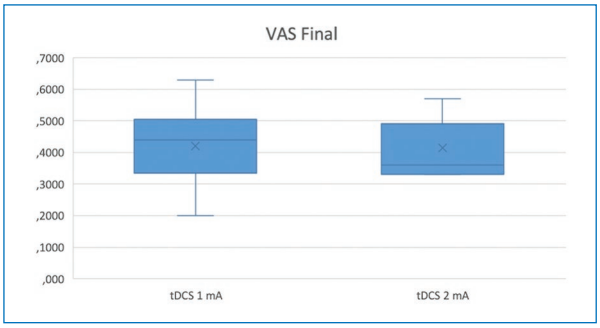

Figure 5. Visual analog scale: one sample t-tests for 1 mA and 2 mA.

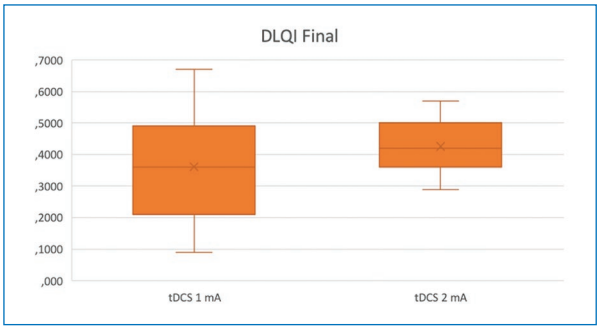

Figure 6. Dermatology life quality index: one sample t-tests for 1 mA and 2 mA.

limb pain, fibromyalgia, and others that are usually associated to maladaptive plastic changes in the central and peripheral nervous systems[15-17].

Similarly to chronic pain, chronic pruritus can also induce central sensitization, but it is not yet clear into what extent it can cause neurophysiological alterations[18].

In patients with AD, several studies demonstrated increased innervation density and expression of inflammatory neuropeptides[4]. Endogenous inhibitory mechanisms have also been detected in both pain and itch processes, explaining why painful stimuli, including acetylcholine and bradykinin evoke itch rather than pain in patients with chronic pruritus[7].

In AD, activation of the ACC and DLPFC, brain areas commonly involved in central hypersensitization, is directly correlated with disease severity[2]. Also, selective serotonine reuptake inhibitors, antidepressants and opioids are commonly prescribed as therapeutic options in these patients[4].

This growing evidence that supraspinal processing of itch is altered in AD patients suggests that effectively targeting the neural circuits involved in itch transmission may improve chronic pruritus[4].

Unlike the significant amount of literature demonstrating the possible benefits of tDCS for chronic pain, there are few studies evaluating tDCS and chronic itch. During our search, only 3 publications were found.

One of the publications reports a single patient treated with 20 min sessions of tDCS on 5 consecutive days for chronic neuropathic pain associated with syringomyelia. His dysesthesias also included a fluctuated itch sensation. There was no change in pain after the tDCS sessions, but the itch dramatically improved[19].

Nakagawa et al. performed a double-blind, sham-controlled and cross-over experimental design inducing histaminergic itch on the forearm of healthy patients, followed by a single tDCS session. The intervention suppressed the peak and lasting itch sensation, but the effects lasted only for a few minutes[7].

In another study, the effects of tDCS on post-burn neuropathic pain and itch were evaluated through a controlled clinical trial comprised of two phases of active or sham M1 tDCS. Ten sessions of active tDCS did not reduce the level of pain or itch[20].

Our study differs from the previous publications, because chronic itch cannot be compared to post-burn or induced itch. The fact that AD patients experience this symptom for years, many since their childhood, elevates the chances of central sensitization. Our findings provide a new step toward the investigation of non-invasive brain stimulation as a treatment option for chronic pruritus.

The limitations of the present study include the small sample size, the short follow-up period, and the lack of a placebo control group (sham tDCS).

The small sample size may be responsible for the fact that some of our results demonstrated only a tendency of improvement instead of statistical significance. Recruiting patients was challenging, probably justified by commute difficulties in a big city, such as Rio de Janeiro, so that many patients did not have the availability to show up for our study 3-times per week due to work or other engagements.

The choice not to include a placebo group is explained by our desire to offer treatment to every single patient, since chronic pruritus is a very distressing condition. The patients had high expectations and were all investing their time and efforts to show up to their sessions.

Conclusions

Despite these limitations, we were able to achieve significant improvement in patient's quality of life, indicating that tDCS may be a promising therapeutic tool. Further clinical trials on the antipruritic potential of non-invasive brain stimulation, with greater sample size, should be encouraged.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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REVIEW ARTICLE

Optimization of immunotherapy through therapeutic vaccines in cutaneous melanoma: a review of clinical trials

Optimización de la inmunoterapia mediante vacunas terapéuticas en el melanoma cutáneo: una revisión de ensayos clínicos

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Abstract

Cutaneous melanoma is responsible for approximately 80% of skin cancer–related mortality. While immunotherapy has significantly improved disease management, recurrence remains frequent due to the progressive loss of immune responsiveness. Immunomodulatory vaccines offer a potential strategy to restore antitumor immunity; however, their diverse formulations and mechanisms of action pose challenges in identifying the most effective approach. This review included clinical trials of immunomodulatory vaccines in patients with cutaneous melanoma available in PubMed, conducted between January 2015 and March 2024. A total of 34 clinical trials were analyzed: 64.7% were phase II, 29.4% were phase I, and 5.9% were phase III. The mean follow-up duration was 47 ± 41.2 months. Phase I studies demonstrated the potential of vaccines such as UV1 and GEN0101 to induce tumor regression and antigen-specific immune responses. Phase II trials of peptide- and dendritic cell-based vaccines showed improvements in both overall and disease-free survival. Phase III results, however, were inconclusive. No severe adverse events attributable to vaccination were reported. Immunomodulatory vaccines, particularly when integrated with genotypic and phenotypic profiling, represent a promising therapeutic option for cutaneous melanoma. Nevertheless, confirmation of their efficacy requires further evaluation in adequately powered phase III trials.

Keywords: *Clinical trials. Immunotherapy. Cutaneous melanoma. Antitumor immune response. Therapeutic vaccines.*

Resumen

El melanoma cutáneo ocasiona el 80% de las muertes por cáncer de piel. Aunque es tratable mediante inmunoterapia, esta neoplasia tiende a recurrir por la pérdida de la reactividad inmunitaria. Las vacunas inmunomoduladoras pueden recuperar la reactividad inmunitaria, pero sus diferentes composiciones y mecanismos dificultan la selección de la más eficaz. Se realizó una revisión de los ensayos clínicos con vacunas inmunomoduladoras en pacientes con melanoma cutáneo disponibles en PubMed realizados desde enero de 2015 hasta marzo de 2024. Se incluyeron 34 ensayos clínicos,

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de los cuales el 64.7% fueron de fase II, el 29.4% de fase I y el 5.9% de fase III. La duración media del seguimiento fue de 47 ± 41.2 meses. En los ensayos de fase I destacó el potencial de vacunas como UV1 y GEN0101 para inducir la regresión tumoral y la respuesta inmunitaria específica de antígeno. En los ensayos de fase II, las vacunas basadas en péptidos y células den-dríticas incrementaron la supervivencia tanto global como libre de enfermedad. Los ensayos de fase III mostraron resultados inconcluyentes. No se presentaron efectos adversos importantes debidos a la vacunación contra el melanoma. Las vacunas inmunomoduladoras en combinación con el cribado genotípico y fenotípico de los pacientes ofrecen una alternativa terapéutica prometedora para el melanoma cutáneo que requiere ser explorada en estudios de fase III.

Palabras clave: *Ensayos clínicos. Inmunoterapia. Melanoma cutáneo. Respuesta inmunitaria antitumoral. Vacunas terapéuticas.*

Introduction

Cutaneous melanoma is the most common subtype of melanoma and accounts for approximately 80% of skin cancer–related deaths[1]. Its incidence rate ranges between 17 and 42 cases per 100,000 inhabitants per year, and a significant increase in cases is projected by the year 2040, mainly among young individuals[2]. Due to the immunogenicity of this neoplasm and its resistance to conventional chemotherapy, its treatment is based on immunotherapy[3]. However, most patients experience a progressive decline in immune reactivity and therapeutic efficacy. The administration of immunomodulatory vaccines in melanoma promotes the generation of more immunogenic and tumor-specific neoantigens[4]. Nevertheless, there remains a need to evaluate vaccine formulations that offer greater stability and immunogenicity, as well as the ability to resist degradation within the human body[5]. In this context, we conducted a systematic review was conducted to analyze the antitumor efficacy and tolerability of these vaccines in randomized clinical trials on cutaneous melanoma to assess their therapeutic potential.

Method

We conducted a systematic search across the digital repositories PubMed, Embase, and Scopus using the following keywords: “Melanoma and dendritic cell vaccines,” “Melanoma and vaccine inhibitors,” “Melanoma and immunogenicity vaccines,” “Melanoma and mRNA vaccines,” and “Melanoma and vaccines.” The review included only randomized clinical trials published from January 2015 through March 2024. Eligible studies were those published in English or Spanish that included patients with cutaneous melanoma who had received any therapeutic modality in combination with vaccines designed to enhance the immune response. Systematic reviews, meta-analyses, expert consensus documents, and pre-experimental studies were excluded. Similarly, studies with incomplete clinical information were discarded.

Due to the large number of duplicates obtained in the initial screening, we decided to consider only the records identified in PubMed, given its broad coverage of peer-reviewed biomedical literature and clinical studies. Initially, a total of 226 articles were identified and evaluated based on titles and abstracts. Of these, 168 studies were excluded for the following reasons: 60 for incomplete information, 48 for not meeting the required methodological design, and 63 for addressing topics beyond the scope of this review. Additionally, 18 duplicate records and 6 studies published in languages other than English or Spanish were removed. Finally, 34 studies were included in the final analysis (Fig. 1).

Results

Of the 34 studies selected for this review, 22 (64.7%) were phase II clinical trials, 10 (29.4%) were phase I, and 2 (5.9%) were phase III. Follow-up duration showed wide variability, with a mean of 47 ± 41.2 months. In total, the trials analyzed data from 3,408 patients with a mean age of 55.9 ± 10.6 years; of these, 1,480 (43.4%) were women and 1,928 (56.6%) were men (Table 1). Regarding clinical characteristics, 94.1% of patients had stage III or IV tumors, while 5.9% were classified as stage II according to the TNM classification.

The included studies employed immunotherapy regimens and adjuvant treatments, mainly radiotherapy, in combination with various vaccines developed through heterogeneous biotechnological approaches. These included modified oncolytic viruses, genetically modified vectors, purified peptides, modified interleukins, dendritic cell concentrates, activated lymphocytes, messenger RNA–based platforms, tumor lysates, and other compounds.

Table 1. Comparison of baseline characteristics of the analyzed population according to clinical trial phase

Parameter	Phase I studies	Phase II studies	p
Sex	Female: 48.5% Male: 51.5%	Female: 40.8% Male: 59.2%	0.321
Age	54.7 ± 17.3 years	56.7 ± 7.2 years	0.698
1-year survival	91.3% ± 6.6%	70.8% ± 17.7%	0.153
2-year survival	56.7% ± 23.5%	62.8% ± 22.8%	0.740
Complete response	23.8% ± 9.2%	9.1% ± 7.0%	0.060
Partial response	26.3% ± 13.2%	28.4% ± 14.5%	0.806
Stable disease	25.5% ± 16.8%	34.8% ± 14.3%	0.394
Disease progression	39.7% ± 6.3%	42.2% ± 19.1%	0.789
Adverse effects	83.0% ± 10.6%	68.5% ± 27.8%	0.132

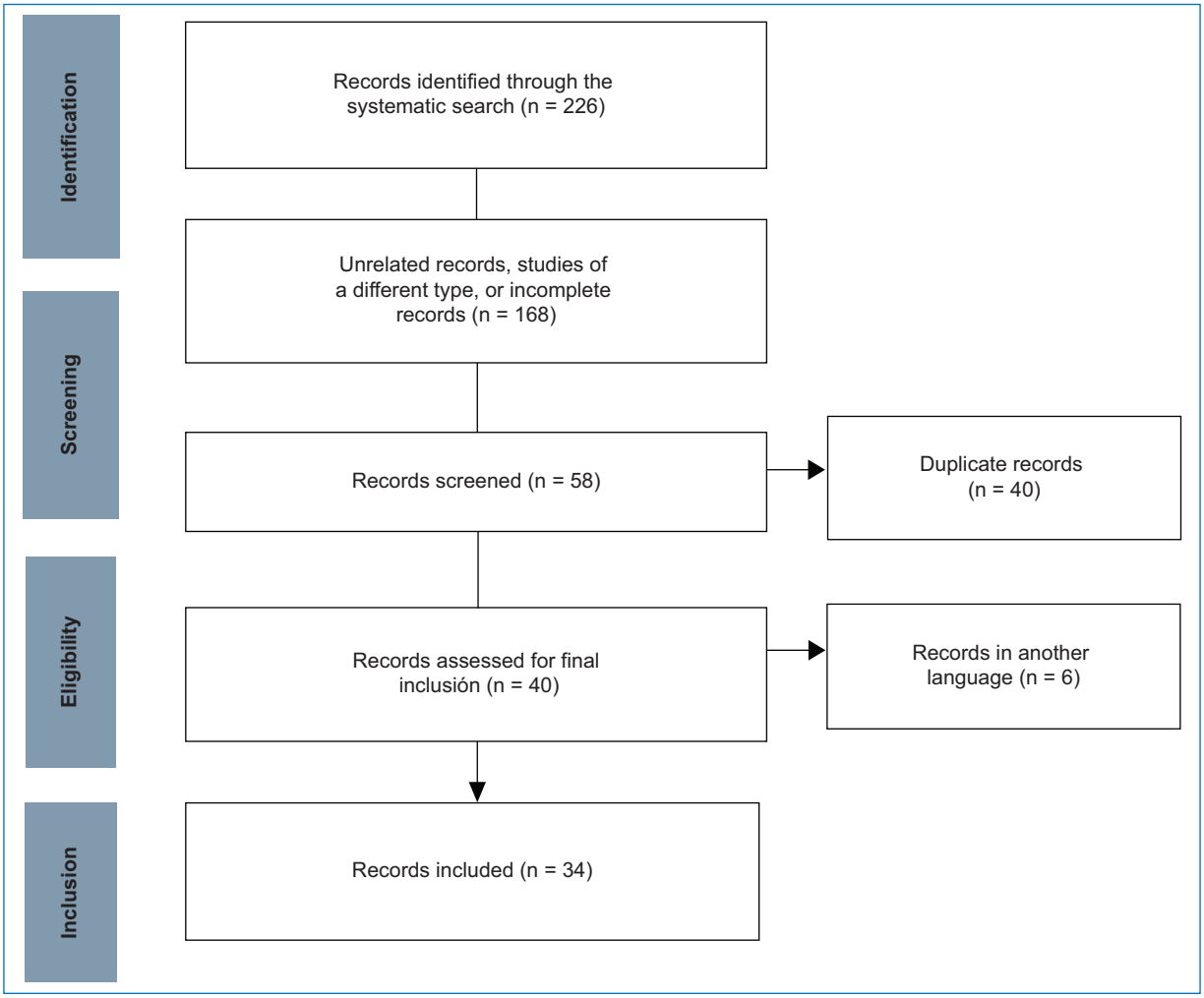

Figure 1. General article search strategy.

Table 2. Comparison of the main clinical outcomes according to the dose used in phase II clinical trials

Variable	Dose < 100 µg	Dose 100-200 µg	Dose 300 µg	p
1-year survival	77.5 ± 1.42%	92.0 ± 1.39%	75.0 ± 1.43%	0.001
Partial response to treatment	33.0 ± 3.5%	25.50 ± 2.50%	25.9 ± 1.9%	0.513
Adverse effects	92.0 ± 2.0%	100.0%	71.1 ± 28.75%	0.513

Results of phase I clinical trials

Tolerability and adverse effects

Overall, all compounds used demonstrated acceptable tolerability, with a mean adverse event incidence rate of 82.1%. The most frequently reported effects were local erythema (90%), local pain (80%), fever and dryness (70%), pyrexia, nausea, fatigue, and general malaise (60%), vomiting, diarrhea, pruritus, and electrolyte imbalance (50%), chills and ulceration (40%), lower back pain, dermatitis, cytopenias, neutropenia, and thrombocytopenia (30%), and colitis, headache, anemia, hepatic dysfunction, and vitiligo (20%). Rare adverse events, reported in at least one study (10%), included rectal bleeding, hypothyroidism, arthralgia, anorexia, edema, stomatitis, pulmonary embolism, ocular hemorrhage, pulmonary edema, blurred vision, constipation, hypophysitis, and diaphoresis.

Pharmacokinetic and pharmacodynamic response

All patients analyzed in the studies exhibited pharmacokinetic parameters consistent with the expected profiles for therapeutic vaccines, without significant alterations in bioavailability, tissue distribution, or elimination of the evaluated compounds. No systemic accumulation or relevant variations between administration regimens were observed, suggesting good stability and appropriate metabolism of the biological product.

From a pharmacodynamic perspective, oncologic vaccines induced measurable immune responses, evidenced by increased natural killer cell activity, proliferation of $CD4^+$ and $CD8^+$ T lymphocytes, and greater intratumoral lymphocytic infiltration. Additionally, increases in serum levels of proinflammatory cytokines, such as interferon gamma, and clonal expansion of tumor antigen-specific T cells were recorded. These immune responses were consistent with the proposed mechanisms of action and correlated with the administered dose, without observing significant immunological toxicity[6-15].

Results of phase II clinical trials

Overall survival

In these studies, the mean 1-year survival rate was 70.8% ± 17.7%; at 2 years it moderately dropped (62.8% ± 22.8%), and at 5 years it was 51.2% ± 23.6%. None of the reviewed studies included longer-term survival analyses. Regarding comparison according to the administered vaccine dose, doses between 100 and 200 µg of active component showed the greatest clinical benefit in terms of one-year survival percentage; the remaining analyzed parameters showed no differences according to administered dose (Table 2).

Therapeutic respons

On average, complete clinical response was achieved in 9.1% of participants, while 28.4% showed partial responses, mainly reflected in tumor size reduction. Stable disease was observed in 34.4% of cases, whereas 42.2% experienced neoplastic progression despite treatment. Additionally, a mean regression of 4.3% of preexisting lesions was documented. On the other hand, recurrence rates could not be analyzed across studies due to inconsistent reporting.

Tolerability and adverse events

In these trials, the mean incidence rate of adverse events was 68.5%, with the most common being local erythema and pain at the injection site (68.2%, 15 cases), followed by fatigue and fever (59.1%, 13 cases), general malaise (54.5%, 12 cases), dry skin (50.0%, 11 cases), pruritus (41.0%), dermatitis (36.4%), and lower back pain (31.8%). Other moderate adverse effects, such as headache and ulceration, were reported in 27.3% of cases. Symptoms such as chills, nausea, arthralgia, and edema were documented at frequencies between 18.2% and 22.7%. Rare events (4.5%) included rectal bleeding, hypothyroidism, hepatic dysfunction, dysarthria, dyspnea, blurred vision, and sepsis.

Dendritic cell–based vaccines: survival and tumor recurrence

The studies reported favorable outcomes in terms of survival and tumor recurrence. In one study, vaccination significantly increased disease-free survival vs the untreated group (62.9% vs 34.8%; p = 0.041), with a similar rate of adverse events in both cohorts[16]. Consistently, in a population previously undergoing surgical resection, vaccinated patients achieved a 2-year overall survival rate of 43%, vs 0% in the placebo group. Among those with recurrent disease, 2-year disease-free survival was 88.9% in the vaccinated group and 33.3% in the placebo group (p = 0.001)[17].

Regarding recurrence prevention, a study including 144 vaccinated patients reported a 36-month disease-free survival of 55.8%, vs 30.0% in the placebo group (p = 0.010)[18]. Overall survival rate at 36 months was also significantly higher in the vaccinated group (94.2% vs 70.9%; p = 0.024). Interestingly, the addition of adjuvant factors, such as granulocyte colony-stimulating factor (G-CSF), appeared to reduce the therapeutic efficacy of the vaccine[18].

Comparative studies of vaccine platforms with and without dendritic cells

The use of tumor lysate combined with dendritic cells (TLPLDC) vs tumor lysate alone (TL) did not show statistically significant differences in terms of therapeutic efficacy[19]. However, in a study analyzing outcomes in 187 patients assigned to receive TL or TLPLDC, disease-free survival rate was significantly higher in patients treated with TLPLDC without G-CSF (55.4%) and in the group treated with TL (60.9%) vs the other groups (p = 0.001). Similarly, overall survival was higher in these two groups: 93.6% with TLPLDC without adjuvant and 94.6% with TL (p = 0.002)[20].

An additional study found that dendritic cell vaccines + tumor cells significantly increased 5-year survival rate vs vaccines using irradiated tumor cells (51% vs 32%; p = 0.004)[21]. Consistently, another study involving 42 vaccinated patients reported a median overall survival of 43.4 months and a 70% reduction in mortality risk[22].

Dendritic cell vaccines and immune activation

A cohort of 16 patients with advanced melanoma was treated with dendritic cell vaccines loaded with HLA-A2–restricted peptides. Following vaccination, six patients developed robust $CD8^+$ T-cell responses, including 4 partial responses and 2 cases of stable disease. Notably, immune responses were more persistent in those who concomitantly received conventional immunotherapy[23].

In another trial involving patients with resected melanoma, adjuvant vaccination with naturally derived dendritic cells was administered. Subsequent evaluations demonstrated antigen-specific $CD8^+$ T cells in 80% of patients, according to intradermal reactivity assays, and circulating antigen-specific antibodies in 55% of cases[24].

Peptide vaccines in melanoma

Four studies evaluated the efficacy profile of melanoma vaccines composed of immunogenic peptides. Two focused on survival outcomes after vaccination, while the remaining studies examined immune responses induced by the administered peptides. These studies reported increases in disease-free survival and overall survival among patients receiving formulations containing 12 peptides vs formulations containing 6 peptides (15-year overall survival: 61% vs 45%; p = 0.008)[25]. Similar results were reported in another long-term survival study in patients with metastatic melanoma. Those vaccinated with the 12-peptide formulation demonstrated significantly higher survival vs non-vaccinated controls (p = 0.001). Moreover, in matched analysis adjusted for metastatic site, surgical status, and age, median survival was markedly higher in the vaccinated group (5.4 vs 1.3 years; p < 0.001)[26].

Induction of immune response by peptide vaccines

A study demonstrated that more durable immune responses were achieved with peptide vaccine formulations combined with incomplete Freund's adjuvant (IFA) and Toll-like receptor 3 (TLR3) agonists, reaching IgG humoral response rates of up to 67%[27]. In another trial involving long-peptide vaccines administered to patients with resected melanoma, the addition of adjuvants significantly improved immunogenicity vs formulations containing only TLR agonists (24% vs 6%). Overall immune response rates were 30% for total T cells directed vs LPV7, 40% for $CD4^+$ T cells specific to tetanus toxoid, and 84% for IgG antibodies against LPV7. These values were considerably higher in regimens including IFA (36%, 48%, and 97%, respectively) vs regimens without IFA (18%, 24%, and 60%, respectively)[28].

UV1-based vaccines

Studies detected specific immune responses in 91% of treated patients, and 30% exhibited a clinical antitumor response. Median progression-free survival was 6.7 months, while median overall survival reached 66.3 months. Importantly, both immune reactivity and clinical response were observed independently of predictive efficacy biomarkers[29]. In another study, UV1 was administered along with granulocyte-macrophage colony-stimulating factor (GM-CSF) as an adjuvant and ipilimumab[30]. A Th1-type immune response against UV1 peptides was observed in 50% of participants, with 15% achieving complete response and an additional 5% achieving partial response. The median 5-year overall survival was 50%, and only mild adverse events were reported. Rapid expansion of UV1-specific Th1 cells in most patients suggests robust and sustained immune activation.

Studies based on other vaccines

In a cohort of 153 patients treated with autologous tumor-infiltrating lymphocytes, the objective response rate reached 31.4%, complete therapeutic response occurred in 8 patients (31.4% of cases), and nearly 40% partial responses; median response duration was 27.6 months, and in 41.7% of cases it was maintained for > 18 months, with mild hematopoietic adverse effects[31]. In another trial including 126 patients, administration of irradiated autologous melanoma cells conjugated with dinitrophenyl and BCG achieved a median overall survival of 88 months and a 5-year survival rate of 54%. Additionally, those who received ipilimumab after post-vaccination progression had a 3-year survival rate of 46%, significantly higher than the 19% observed in the non-vaccinated group ($p = 0.007$)[32].

Similarly, the AGI-101H vaccine demonstrated a median overall survival of 17.3 months, with complete responses in 19.4% and partial responses in 9%, achieving a disease control rate of 54.5% and a mean response duration of 32 months, without relevant adverse events[33]. In contrast, the combination of interleukin-2 with an allogeneic vaccine showed no significant differences in outcomes[34], whereas the formulation based on poly-ICLC and the NY-ESO-1 protein induced a measurable immune response[35]. Finally, in the TriMixDC-MEL vaccine study, 71% of patients remained disease-free at 1 year, vs 35% in the control group. Moreover, with a median follow-up of 53 months, the treated group showed fewer unresectable recurrences (9 vs 14 cases) and a significantly prolonged time to relapse (median not reached vs 8 months; $p = 0.044$)[36].

Results of phase III clinical trials

Overall survival

In one of these studies, the 10-year overall survival rate was 72.5%, while disease-free survival rate during the same period was 62%. In contrast, the other study reported a 5-year overall survival rate of 52.3%, with a disease-free survival rate of 31.2%. Since both trials focused on patients who were clinically disease-free at enrollment, no data were reported regarding complete or partial clinical responses, disease stability, or tumor progression. However, one study reported that median overall survival in the vaccinated group was 69.1 months.

Tolerability and adverse effects

In one study, 9 patients (1.1%) discontinued vaccination due to intolerance or adverse events. The most frequently reported side effects were edema, erythema, local pain, and fever. Other less common reactions included chills, fatigue, headache, localized pruritus, general malaise, and localized dry skin.

Key findings of phase III clinical trials

One of the phase III trials (S9035) evaluated the Melacine vaccine as adjuvant therapy in patients with stage II melanoma, without observing significant differences in overall survival or disease-free survival in the general population. However, in the subgroup with HLA-A2 or HLA-Cw3 serotypes, vaccination was associated with a marginal improvement in disease-free survival (adjusted $p = 0.02$) and significantly higher 10-year overall survival rate (75% vs 63%; hazard ratio [HR], 0.62; 99% confidence interval: 0.37–1.02; $p = 0.01$). These findings suggest that certain HLA haplotypes may influence vaccine efficacy and support the importance of considering HLA-immunotherapy interactions in future studies[37]. In another trial involving 815 patients with completely resected high-risk melanoma, a peptide vaccine plus GM-CSF was evaluated, stratifying participants according to HLA-A2 status. No significant improvements were observed in overall survival (HR, 0.94; $p = 0.528$) or disease-free survival (HR, 0.88; $p = 0.131$) vs placebo. None of the interventions showed clinically relevant benefit; however, the study

suggested that GM-CSF could be potentially useful in patients with resected visceral metastases[38].

Both clinical trials provide valuable information to support evidence-gathering processes for regulatory purposes. Taken together, the studies by Carson et al.[37] and Lawson et al.[38] demonstrate the feasibility, safety, and long-term clinical outcomes of adjuvant vaccines based on tumor antigens and immunomodulatory factors. Despite their heterogeneity, these results constitute a solid body of clinical, immunological, and safety data that supports the systematic compilation of preclinical and clinical evidence necessary for future regulatory approval of this type of vaccine, emphasizing the importance of including genetic markers (such as HLA) in study design and patient stratification for approval and clinical use[39].

The next step toward regulatory approval of these vaccines involves consolidating clinical and immunological evidence through integration into a comprehensive technical dossier including efficacy, safety, and product characterization results under good manufacturing practice standards. Subsequently, a multicenter confirmatory clinical trial in a population stratified by HLA haplotype (particularly HLA-A2, HLA-Cw3, or both) should be conducted to validate the observed benefits and meet the efficacy criteria required by regulatory agencies. In parallel, standardization of the production process, quality controls, and biological product stability studies will be required to implement pharmacovigilance and post-authorization monitoring programs ensuring safety and effectiveness in clinical use[40].

Discussion

This review supports the use of therapeutic vaccines as an adjuvant or palliative option in cutaneous melanoma. Phase I and II trials demonstrated good tolerability and induction of relevant immune responses. In particular, phase II studies using dendritic cell vaccines pulsed with tumor lysate achieved improved disease-free survival. Additionally, dose comparison indicates that the best clinical effects in terms of partial response, and therefore survival, were obtained with doses of approximately 200 μg (weekly regimens). On the other hand, phase III trials yielded mixed results, underscoring the need for future studies incorporating biomarker stratification and therapeutic combinations, which are required for regulatory approval and implementation in routine clinical practice.

A key finding of this review is the limited clinical benefit observed in phase III studies. While in phase II, vaccines based on dendritic cells transfected with mRNA, tumor lysates, or neoantigens achieved clinical efficacy rates exceeding 50%, no phase III vaccine achieved comparable results[39]. This discrepancy may be explained by the predominance of more established therapies in clinical practice, such as checkpoint inhibitors or tyrosine kinase inhibitors, as well as by the fact that many phase III trials involving promising vaccines are still ongoing, given the technical complexity of their development[41].

These findings have important methodological implications. Studies reporting clinical efficacy highlight the need to stimulate $CD4^+$ and $CD8^+$ T lymphocytes through epitopes recognized by MHC class I and II to generate sustained antitumor immunity[42]. Similarly, phase III trials suggest that specific serotypes, such as HLA-A2 and HLA-Cw3, influence vaccine response, making it evident that future trials must incorporate more advanced HLA typing, with the consequent increase in development timelines[43].

Another relevant aspect is the safety profile of the analyzed vaccines, characterized predominantly by mild or moderate adverse effects. This is consistent with their immunomodulatory nature and with a lower risk of systemic autoimmune events vs checkpoint inhibitors. Such tolerability facilitates their integration with other therapeutic modalities, such as radiotherapy or targeted immunotherapy, potentially allowing dose reduction without loss of efficacy, thereby justifying their clinical application in controlled settings[44].

Of note, this review presents an important limitation due to study heterogeneity, which complicates direct comparison of results and limits the possibility of conducting robust meta-analyses. Additionally, the relatively small number of available articles restricts the strength of the conclusions, highlighting the need to continue generating high-quality evidence through multicenter trials with larger populations. Nevertheless, despite these limitations, the synthesis presented here demonstrates the rapid progress of immunotherapy research and its applicability as an essential component of combined treatment strategies for cutaneous melanoma. To achieve this, it will be indispensable to integrate precision medicine tools to guide the design of phase III clinical trials and confirm the true therapeutic potential of these strategies[45,46].

Future directions in melanoma immunotherapy vaccines will likely focus on the design of personalized vaccines based on neoantigen profiles and individual HLA typing, combined with checkpoint inhibitors to enhance clinical efficacy.[47] Similarly, priority is expected to be

given to the development of RNA-based platforms and genetically modified dendritic cells, with standardized manufacturing protocols that facilitate scalability and clinical availability. The incorporation of predictive biomarkers, such as tumor mutational burden and tumor-infiltrating lymphocyte density, will enable optimization of patient selection and maximization of therapeutic benefit.

Conclusions

Therapeutic vaccines for cutaneous melanoma demonstrate a favorable safety profile and promising efficacy in early phases, with greater clinical benefits observed when moderate doses are administered consistently. Despite this, the mixed results in phase III studies underscore the need for biomarker-stratified trials to validate their true clinical potential.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. Not applicable (research without experimentation).

Confidentiality, informed consent, and ethical approval. The study does not involve personal data, medical records, or human biological samples; therefore, ethical approval was not required. SAGER guidelines were not applicable.

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CLINICAL CASE

Oral manifestations in Parry-Romberg syndrome

Manifestaciones orales en el síndrome de Parry-Romberg

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Abstract

The Parry-Romberg syndrome is a rare subtype of linear cephalic morphea that poses a challenge for the medical team. It primarily affects the area innervated by the trigeminal nerve, resulting in unilateral facial atrophy. Cutaneous manifestations and oral involvement can coexist in approximately 26-47% of cases. Early treatment during the inflammatory stage prevents progression to fibrotic stages. Here, we present a series of three clinical cases with diverse oral manifestations, their treatment response, and their longitudinal management.

Keywords: *Morphea. Progressive hemifacial atrophy. Progressive facial hemiatrophy. Parry-Romberg Syndrome. Oral manifestations.*

Resumen

El síndrome de Parry-Romberg es un subtipo de morfea lineal cefálica poco frecuente y que representa un desafío para el equipo médico, tanto en el manejo terapéutico como en una evaluación pronóstica fidedigna. Afecta principalmente el territorio inervado por el nervio trigémino y tiene como resultado una atrofia facial unilateral. Las manifestaciones cutáneas y el compromiso bucal pueden coexistir en aproximadamente el 26-47% de los casos. El tratamiento en su etapa inflamatoria temprana evita llegar al estadio de fibrosis. Se presenta una serie de tres casos clínicos con diversas manifestaciones orales, su respuesta al tratamiento y su control evolutivo.

Palabras clave: *Morfea. Atrofia hemifacial progresiva. Hemiatrofia facial progresiva. Síndrome de Parry-Romberg. Manifestaciones orales.*

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Introduction

Parry-Romberg syndrome (PRS), also known as progressive hemifacial atrophy, is a rare subtype of cephalic linear morphea. PRS is characterized by affecting the territory innervated by the trigeminal nerve[1] and is usually unilateral, although it can occasionally affect both sides of the face[2].

The activity of PRS is assessed through clinical and laboratory parameters. Clinically, the following parameters are considered to evaluate disease activity: appearance of new characteristic cutaneous lesions such as sclerotic-atrophic plaques that may be either hypo- or hyperpigmented, increase in size of existing lesions, erythema, induration, and presence of a peripheral violaceous halo. Regarding laboratory findings, activity is evaluated by the presence of peripheral blood eosinophilia and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)[1].

Below, we present a 3-case series of PRS to highlight the multiple oral cavity manifestations caused by this disease, including mucosal, adipose tissue, muscle, dental, or bone structure involvement, as well as their treatment and clinical course[2].

Case report 1

A 22-year-old male with no relevant past medical history presented with a 5-year history of an asymptomatic dermatosis that began as hyperpigmentation in the right zygomatic region and progressively enlarged, associated with facial anatomical changes, evidenced through prior photographs provided by the patient. Additionally, he reported severe xerostomia as a relevant symptom.

Physical examination showed facial asymmetry predominating on the right side, with atrophy of the right lower hemilabium and deviation of the ipsilateral labial commissure. On the right hemiface, asymmetrical hyperpigmented sclerotic-atrophic plaques with ill-defined borders were observed over the frontal, malar, and mental regions, involving territories innervated by the trigeminal nerve. The malar plaque, in the maxillary V2 trigeminal area, extended to the ipsilateral lower eyelid. The eye showed atrichia of the outer two-thirds of the right lower eyelid, sparing the last segment, and mild conjunctival injection (Fig. 1A).

Intraorally, clinical examination revealed absence of salivary lakes, atrophy and deviation of the right hemilingual side, lingual coating and plaques, along with multiple grade I caries (Figs. 1 B and C), atrophy of the lower frenulum, and gum recession in the lower right incisors. Additionally, atrophy of the muscles of the ipsilateral floor of the mouth was observed, and palpation revealed atrophy of the right submandibular salivary gland and hypoplasia of its duct (Fig. 1D) vs the contralateral side.

A presumptive diagnosis of PRS was made, and the patient was managed through a multidisciplinary approach with neurology and dentistry services.

Laboratory tests including ESR, CRP, and complete blood count were ordered, along with a head CT scan, which revealed no pathological findings.

A dental evaluation with panoramic X-ray revealed dental abnormalities, with vertical bony retention of the upper third molars and the lower left third molar, and mesioangular retention of the right lower third molar, for which extraction was indicated. Multiple superficial caries were also noted.

Ophthalmologic evaluation, including visual acuity testing, fundoscopy, retinography, and optical coherence tomography, showed no significant findings.

Treatment was initiated with a 6-month regimen of monthly pulses of 500 mg/day of methylprednisolone for 3 consecutive days, in combination with subcutaneous methotrexate at escalating doses up to 20 mg weekly, folic acid 5 mg weekly, and 0.1% tacrolimus ointment applied to the sclerotic plaque in the right zygomatic region. After the third corticosteroid pulse, a marked clinical improvement was observed, with a reduction in the size and pigmentation of the sclerotic plaques and less sclerosis and atrophy. In the oral cavity, there was decreased tongue muscle atrophy and reduced deviation (Fig. 1B), with moist mucosa. The eye showed partial regrowth of eyelashes on the right lower eyelid.

Superficial caries were restored, and the patient is currently undergoing periodontal therapy with planned extraction of all third molars.

Case report 2

An 18-year-old female with PRS diagnosed at age 6, with poor adherence to medical follow-up and treatment limited to topical agents without improvement, presented to the clinic after noticing clinical worsening and the appearance of a new lesion in the left nasogenian region.

She reported that the condition began with a hyperpigmented frontotemporal macule on the left side, later extending posteriorly to the left malar region, which progressed into left hemifacial atrophy involving the

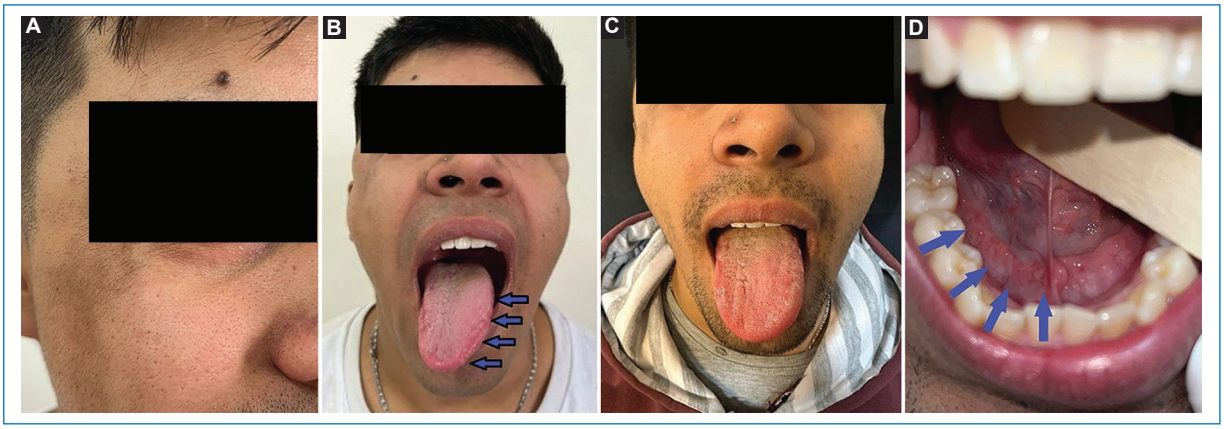

Figure 1. Case report 1. **A:** atrichia of the outer two-thirds of the right lower eyelid, sparing the final segment, and mild conjunctival injection. **B:** atrophy of the right half of the tongue with deviation. **C:** improvement after treatment, with reduced degree of tongue deviation. Fissures and coated plaques on the tongue are seen in **B** and **C**. **D:** hypoplasia of the ductal opening of the right lower maxillary salivary gland and atrophy of the muscles on the right side of the mouth floor.

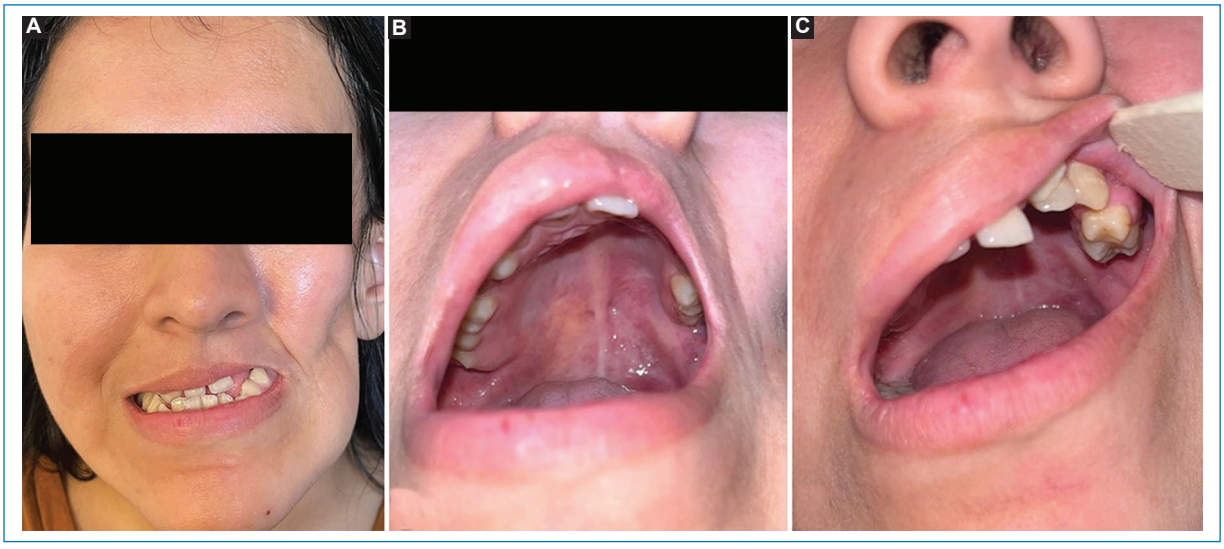

Figure 2. Case report 2. **A:** facial asymmetry predominantly on the left side. Atrophy of the left upper hemilip and deviation of the labial commissure. Dental crowding of the central and lateral incisors and canines in the lower arch. **B:** decreased oral opening and asymmetry of the hard and soft palate. **B** and **C:** dental crowding and absence of the first and second premolars in the left upper maxillary arch, along with dental surface demineralization.

territories innervated by the left maxillary (V2) and mandibular (V3) branches of the trigeminal nerve.

On physical examination, facial asymmetry predominated on the left, with lipoatrophy of the ipsilateral temporal, zygomatic, and malar fossae, deviation of the labial commissure, and atrophy of the left upper hemilabium (Fig. 2A). A shiny, hyperpigmented, diffusely bordered, slightly indurated sclerotic plaque was observed in the left hemifrontal region. A violaceous halo was seen surrounding the nasogenian plaque. There was reduced mouth opening, asymmetry of the hard and soft palate (Fig. 2B), crowding and absence of the first and second premolars in the upper left maxillary arch, and dental surface demineralization (Figs. 2 B and C). The ipsilateral Stensen's duct was absent.

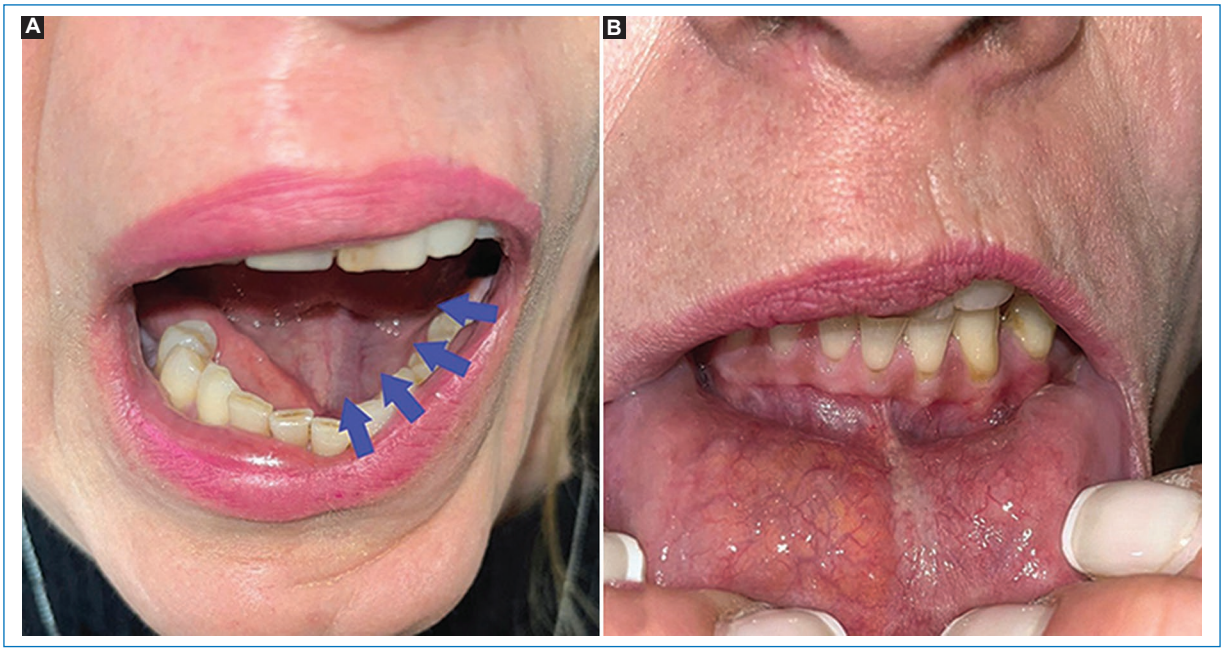

Figure 3. Case report 3. **A:** hypoplasia of the ductal opening of the left lower maxillary salivary gland. **B:** atrophy of the retrolabial mucosa and gingival retraction at the level of the left lower incisors.

The case was interpreted as a reactivation of the underlying disease, so a multidisciplinary approach was initiated, and additional studies were requested. ESR, CRP, complete blood count, visual acuity testing, fundoscopy, retinography, and OCT showed no pathological changes.

Craniofacial CT revealed reduced orbital volume on the left, with decreased intra- and extraconal fat tissue and enophthalmos, without cortical abnormalities. Panoramic dental X-ray showed retention of the third molar, tooth crowding, and missing teeth.

Treatment was started with monthly pulses of 500 mg/day of methylprednisolone for 3 consecutive days over 6 months, combined with subcutaneous methotrexate up to 20 mg weekly and folic acid 5 mg weekly. During the fourth corticosteroid pulse, an alopecic plaque appeared in the left frontal region, leading to a clinical diagnosis of coexisting linear morphea ("en coup de sabre"). Six months after completing treatment, partial capillary regrowth was noted, along with slight improvement in the cutaneous plaques' size and hyperpigmentation. However, no changes were observed in the oral signs.

Case report 3

A 46-year-old woman with PRS diagnosed at age 16, who had only undergone aesthetic treatments without clinical improvement, reported that symptoms began at age 13 with adipose tissue resorption in the left hemiface, accompanied by ipsilateral paresthesias that worsened at age 16 after pregnancy. She was evaluated by the plastic surgery department and underwent injections of methacrylate and autologous fat in the affected facial region. After no improvement, she was referred to dermatology.

Physical examination revealed left-predominant facial asymmetry with lipoatrophy of the temporal, zygomatic, and malar fossae, deviation of the labial commissure, and atrophy of the ipsilateral upper and lower hemilabium. Intraorally, there was asymmetry of the hard and soft palate, atrophy and deviation of the left hemilingual side, hypoplasia of the submandibular duct (Fig. 3A), atrophy of the retrolabial mucosa, and atrophy and recession of the gums around the left incisors (Fig. 3B).

With a diagnosis of PRS, further tests were conducted to assess disease activity and treatment options. Soft tissue ultrasound showed an echogenic area overlying the bone plane between the mandibular angle and anterior lip in the left cheek, an anechoic area near the left nasal ala, and two hypoechoic formations, possibly residual injected material.

It was concluded that the disease was inactive, so a watchful waiting approach was taken, with plans for facial lipoinjection surgery.

Table 1. Comparison of the different oral conditions in the clinical cases

Clinical signs	Case 1	Case 2	Case 3
Unilateral tongue atrophy and deviation	✓		✓
Hard and soft palate abnormalities		✓	✓
Atrophy and weakness of masticatory muscles		✓	✓
Absence of lower maxillary salivary gland	✓		
Hypoplasia of salivary gland duct outlets	✓	✓	✓
Facial asymmetry	✓	✓	✓
Lip atrophy with deviation of labial commissure	✓	✓	✓
Short dental roots and gingival recession	✓	✓	✓
Missing teeth		✓	✓
Malocclusion and crossbite due to dental problems	✓	✓	✓
Dental crowding		✓	✓

Table 1 illustrates additional findings and a comparison of the various oral signs among the patients.

Discussion

PRS is a rare condition with an incidence rate of 0.3 to 3 cases per 100,000 people per year. It more frequently affects women, with a ratio of 4.6:1. In children, 90% of cases are diagnosed between the ages of 2 and 14, while in adults the peak incidence occurs in the fifth decade of life[3]. According to a recent article, the predominant type of morphea is linear, followed by pansclerotic and circumscribed forms. The linear subtype most commonly affects the limbs, followed by PRS and the "en coup de sabre" variant[4]. Cutaneous and oral involvement may coexist in approximately 26%-46% of cases[5].

The pathogenesis of morphea is still not fully understood. It involves several factors, including genetic (HLA class I and II genes), environmental (such as Epstein-Barr virus, varicella-zoster virus, and *Borrelia burgdorferi*), local trauma, surgical procedures, radiation, vaccines, autoimmune dysfunction with abnormal cytokine production or vascular dysfunction which can play a role in the development of morphea. In general, 3 stages can be distinguished here: an early inflammatory stage, a fibrous/sclerotic phase, and an atrophic phase[6].

PRS has a slow and progressive course, from 2 to 20 years, and then reaches the stabilization stage[6]. It is characterized by hemifacial atrophy of the skin, skin adnexa, mucous membranes, subcutaneous tissue, muscles, and cartilage, and it affects bone structures of the face and skull[7,8].

Regarding its severity, PRS is classified as mild, characterized by atrophy of the skin and subcutaneous tissue, affecting only the territory of one of the trigeminal nerve's sensory branches, without bone involvement; moderate, with skin and subcutaneous tissue atrophy, affecting two trigeminal nerve territories, without bone involvement; and severe, with extended atrophy affecting all 3 trigeminal nerve territories, or with any bone involvement[9].

In the oral cavity, involvement of soft tissues, mucous membranes, tongue and masticatory muscles, mandible, salivary glands, and ducts is described. Additionally, dental involvement occurs, with enamel deterioration and tooth loss due to a lack of saliva, causing difficulty with certain oral functions such as eating, gesturing, and smiling. Affectation of the masticatory muscles can cause speech problems, painful chewing, spasms, jaw locking, and temporomandibular joint pain. These alterations are described in greater depth in table 2.

The diagnosis of PRS is clinical[10]. If there's diagnostic uncertainty, a deep biopsy can be obtained from the inflammatory border or the central sclerotic area[1]. It doesn't present pathognomonic elements, but rather suggestive ones. Histologically, in early stages, it's characterized by a perivascular lymphocytic infiltrate with plasma cells in the reticular dermis, endothelial

Table 2. Description of oral involvement in the Parry-Romberg syndrome

Soft tissues	Bone and dental structures
Unilateral atrophy of the tongue and deviation[2,4,8]	Hypoplasia of the mandible and maxilla[3,4,7]
Deficiencies in the hard and soft palate, with asymmetry[2,8]	Malocclusion and crossbite due to dental problems[4,7]
Atrophy and weakness of the muscles of mastication and the floor of the mouth[2-4,8]	Missing teeth[3,4,7,8]
Atrophy or absence of upper or lower salivary glands[2,4]	Delayed tooth eruption[3,4,7,8]
Hypoplasia of salivary gland duct openings	Dental crowding[3,4,7]
Facial asymmetry[2,4]	Short roots and gum recession[3,4,7]
Atrophy of the upper or lower lip with tooth exposure[2,4]	Root atrophy[3,4,7,8]
Deviation of the labial commissure[2,7,8]	Loss of tooth enamel with increased early caries[4,8]

cells, and thickened collagen bundles; in late stages, the inflammatory infiltrate disappears, and the collagen bundles from the dermis infiltrate and extend into the subcutaneous fat[11].

Evaluating disease activity is of utmost importance for making therapeutic decisions. For this purpose, the LoSCAT scalecan be used, which comprises an activity index (LoSAI) and a damage index (LoSDI), along with the physician's global assessment of both disease activity (PGA-A) and damage (PGA-D). LoSAI scores from 0 to 4 indicate mild activity, 5 to 12 indicate moderate activity, and 13 or more indicate severe activity[12].

Regarding the classification of the scales into mild, moderate, and severe activity, these correspond to the scores of the LoSCAT activity index (LoSAI) of 0-4, 5-12, and ≥ 13, and to the physician's global assessment of activity (PGA-A) scores of 0-10, 11-30, and ≥ 31, respectively. For the damage scales, mild, moderate, and severe damage correspond to LoSCAT (LoSDI) scores of 0-10, 11-15, and ≥ 16, and to physician global assessment of damage (PGA-D) scores of 0-18, 19-30, and ≥ 31[12]. Doppler ultrasound is also used; the most sensitive signs for detecting disease activity are dermal or hypodermal hypervascularization and increased echogenicity in the hypodermis[13]. Compared to inactive lesions, thermographyhas revealed an increase in surface temperature and blood flow in active lesions[14]. Laboratory parameters such as ESR, CRP, and eosinophilia are also considered; elevated values may indicate disease activity[15].

The primary goal of treatment is to halt disease activity and, secondarily, to achieve clinical and aesthetic improvement. In clinical cases 1 and 2, methotrexate was used, which is the standard therapy in the early stages of PRS[2]. Due to its delayed onset of action (2–3 months), treatment was initiated simultaneously with monthly corticosteroid pulses[7]. Other immunosuppressive agents that have been tested with variable success include cyclosporine, mycophenolate mofetil, cyclophosphamide, antimalarials, and phototherapy (PUVA, UVA1, broadband UVA, and narrowband UVB)[11]. Although oral corticosteroids may be used, in these cases IV pulses were preferred due to fewer adverse effects.

In advanced stages of the disease, where irreversible lesions are evident, rehabilitation treatment with physical therapy should be considered. Surgical options include fat grafting, lipoinjection, soft tissue fillers, autologous fat injections, dermal fat grafts, and adipofascial flaps[16].

Despite the wide range of therapies available, treating morphea remains a challenge due to the high morbidity associated with long-term treatments. Additionally, many patients relapse after discontinuing therapy, and others do not respond to standard treatment options. This has led to the exploration of new therapeutic targets currently under investigation, such as the use of abatacept and JAK inhibitors, including tofacitinib and baricitinib, as well as monoclonal antibodies such as tocilizumab and autologous stem cell transplantation[6,11]. Another emerging alternative under investigation is the use of secukinumab[17].

Conclusions

This case series highlights the severe anatomical, functional, and aesthetic compromise caused by PRS,

which leads to a significant deterioration in the patients' quality of life.

It should be managed from the onset in an interdisciplinary manner, involving ophthalmology, neurology, and dentistry services, as well as specialists in oral medicine and pathology, plastic and maxillofacial surgery, and physical therapy.

Based on our own experience, we did not find a correlation between the degree of involvement and the severity of cutaneous or oral mucosal compromise.

A proper oral physical examination with photographic documentation at each visit, along with additional studies, will facilitate early diagnosis and aggressive treatment. The dermatologist's role is to timely halt the inflammatory stage to prevent progression to irreversible fibrosis and atrophy.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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CLINICAL CASE

Case series and considerations in the approach of sebaceous carcinoma: clinical and histopathological high-risk factors and proposal of a histopathologic report guideline

Serie de casos y consideraciones en el abordaje del carcinoma sebáceo: factores de alto riesgo clínicos e histopatologicos y propuesta de una guía para el reporte histopatológico

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Abstract

Background: *Sebaceous carcinoma (SC) is a rare, aggressive tumor often misdiagnosed due to variable presentation.* **Objective:** *The aim of this study was to describe clinical and histopathological features of SC, identify high-risk factors for adverse outcomes, and propose a standardized pathology report.* **Methods:** *This was a case series of 15 patients in Bogotá, Colombia.* **Results:** *Histological evaluation revealed diverse differentiation patterns, with key prognostic features including perineural invasion, pagetoid spread, and high Ki67 proliferation index. Mohs micrographic surgery was the most frequently used treatment. Only one recurrence was observed.* **Conclusions:** *Functional and histological heterogeneity in SC highlights the need for standardized reports to guide treatment and improve outcomes.*

Keywords: *Sebaceous gland neoplasms. Eyelid neoplasms. Muir-Torre syndrome. Mohs surgery. Skin neoplasms.*

Resumen

Introducción: *El carcinoma sebáceo (CS) es un tumor raro y agresivo, frecuentemente mal diagnosticado debido a su presentación variable.* **Objetivo:** *Describir las características clínicas e histopatológicas del CS, identificar factores de alto riesgo para desenlaces adversos y proponer un informe patológico estandarizado.* **Métodos:** *Serie de casos de 15 pacientes en Bogotá, Colombia.* **Resultados:** *La evaluación histológica mostró patrones de diferenciación diversos, con características pronósticas clave como invasión perineural, patrón pagetoide e índice de proliferación Ki67 elevado. La cirugía micrográfica de Mohs fue el tratamiento más utilizado. Solo se observó una recurrencia.* **Conclusiones:** *La heterogeneidad funcional e histológica del CS resalta la necesidad de informes estandarizados que orienten el tratamiento y mejoren los resultados.*

Palabras clave: *Neoplasias de las glándulas sebáceas. Neoplasias del párpado. Síndrome de Muir-Torre. Cirugía de Mohs. Neoplasias cutáneas.*

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Introduction

Sebaceous carcinoma (SC) is a rare malignant tumor originating from the sebaceous glands and is the third most common malignancy of the eyelid. SC has high rates of recurrence, the potential to metastasize, and can be fatal in some cases[1]. Therefore, performing a timely diagnosis and considering the available therapeutic options is important to improve the patient's prognosis. SC has an estimated incidence of 1-2 cases/1,000,000 people[2]. Up to 60% of all reported SCs are periocular, located in the superior eyelid, originating from hair follicle-associated sebaceous glands or Meibomian and Zeis glands of eyelids and caruncles[3]. On the other hand, extraocular SC often appears on the head and neck[4]. Depending on the anatomic classification, the tumor has different behaviors, origins, genetic backgrounds, and associations with other neoplasms such as Muir-Torre Syndrome (MTS)[3,5-7]. SC has a clinical presentation similar to other benign or malignant tumors and inflammatory diseases, often delaying diagnosis and worsening prognosis.

We aim to present a clinical characterization of patients diagnosed with periocular and extraocular SC in our population and to evaluate the risk factors associated with an increased likelihood of locoregional or distant spread, recurrence, and mortality. This will help identify patients who may benefit from more extensive staging studies. We also seek to, based on our experience, the case series and the literature review, to standardize the features of its clinical presentation and histopathological findings, and propose a histopathological report guideline. Our goal is to contribute to a better understanding of SC, ultimately influencing future management strategies for these patients.

Materials and methods

We report a case series of fifteen patients diagnosed with periocular and extraocular SC from 2015 to 2023 in two dermatological centers in Bogotá, Colombia. Medical records of patients were reviewed. Sociodemographic and clinical variables, including sex, phototype, comorbidities, anatomical classification of SC, histopathological findings, and presence of risk factors (upper eyelid, orbital extension, differentiation grade, immunohistochemistry markers, pagetoid spread, perineural invasion, history of immunosuppression, or radiotherapy), were analyzed. Care of the majority of the patients was coordinated with Mohs and oculoplastic surgeons. Missing information was labeled as not reported.

Results

In our series of 15 patients with SC, six had periocular SC, and nine had extraocular SC. The female-to-male ratio was 1: 2, with a mean age of 71.8 years. Almost all patients had Fitzpatrick skin phototype III or IV. Notably, nearly all male patients had extraocular tumors, while all periocular tumors were located on the lower eyelid, and extraocular SC was more frequently found on the scalp. Eight cases exhibited a diffuse clinical presentation. The mean duration of the tumor before diagnosis was 24 months, with a median duration of 13.1 months. Only one patient had a history of immunosuppression, and one had a prior diagnosis of MTS (Table 1).

Histopathological analysis revealed five cases with basaloid differentiation, four with squamous differentiation, and two with perineural invasion. Immunohistochemical staining showed positivity for epithelial membrane antigen (EMA) in nine cases and androgen receptors in seven cases. None of the patients with periocular SC had orbital or canthal extension or metastatic disease at the time of diagnosis (Table 2). Mohs micrographic surgery (MMS) was performed in 80% of the patients. There was one local recurrence in the youngest patient of the series, occurring 7 months post-MMS, who is currently undergoing exenteration. There have been no other recurrences, with follow-up periods ranging from 1 to 8 years.

In figure 1, we show the clinical image of a 48-year-old female patient with a history of 18 months of a rapidly growing tumor in her inferior eyelid (Case No. 5). In figure 1, we show the clinical image of a 48-year-old female patient with an 18-month history of a rapidly growing tumor in her inferior eyelid (Case No. 5), and in figure 2, the clinical image of a 72-year-old male with a 3-year history of a slowly growing, asymptomatic subcutaneous nodule on his right cheek (Case No. 15).

Discussion

SC generalities

SC represents 0.2-4.6% of all malignant skin neoplasms[5] 0.6-10.2% of eyelid tumors[8]. It is considered rare but potentially aggressive and lethal due to its behavior, ranging from local invasion and recurrence to the development of metastases in regional lymph nodes and distant organs[4] with a reported overall

Table 1. Sociodemographic characteristics

No.	Age	Gender	Skin phototype	SC subtype	Localization	Tumor Size (mm)	Evolution time (months)	History of skin cancer	Associated conditions
1	62	Male	III	Ocular	Lower lid	4	1	No	No
2	68	Female	IV	Ocular	Lower lid	144	1.4	No	No
3	74	Female	III	Ocular	Lower lid	24	Unknown	BCC	No
4	75	Male	III	Ocular	Lower lid	36	1.5	SCC	No
5	48	Female	IV	Ocular	Lower lid	18	2.5	No	No
6	84	Female	II	Ocular	Lower lid	22	1	No	No
7	75	Male	III	Extraocular	Cheek	6	3.5	SC	MTS
8	58	Male	III	Extraocular	Nose	12	0.8	No	No
9	78	Male	III	Extraocular	Extremity	12	2.5	BCC	No
10	89	Male	IV	Extraocular	Scalp	2	5	No	No
11	83	Male	III	Extraocular	Scalp	11	1.5	No	No
12	68	Male	III	Extraocular	Scalp	2	2.5	No	Immunosuppression
13	75	Female	II	Extraocular	Scalp	25	6	No	No
14	68	Male	IV	Extraocular	Nose	12	1	No	No
15	72	Male	III	Extraocular	Cheek	36	3	No	No

BCC: basal cell carcinoma; SCC: squamous cell carcinoma; MTS: Muir-Torre syndrome; SC: Sebaceous carcinoma; Ca: cancer.

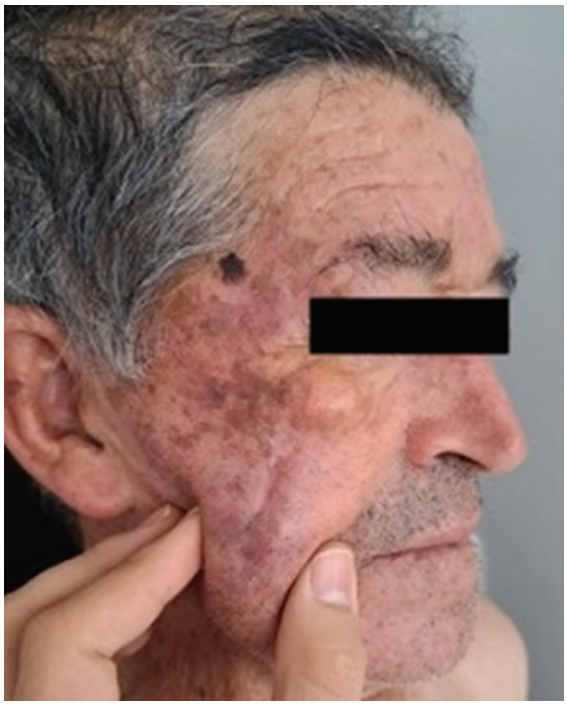

Figure 1. Subcutaneous nodule on the right cheek.

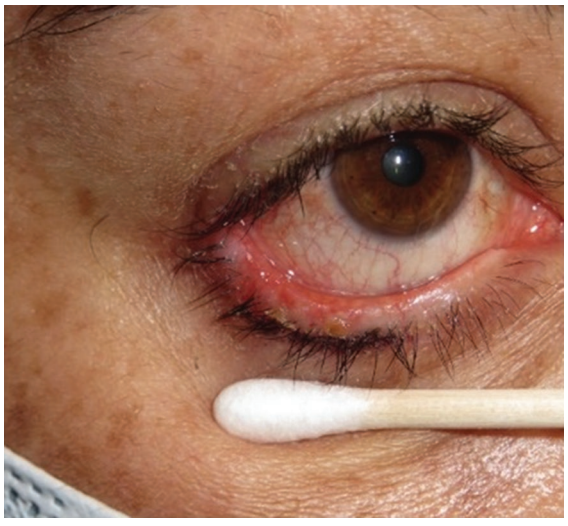

Figure 2. In the right lower eyelid margin of a female patient, we can observe a diffuse erythematous plaque, with ill-defined borders and yellowish scales in the lateral canthus, with mild erythema of the conjunctiva.

5-year survival rate of 78% for localized or regional disease and 50% for metastatic disease[9].

Table 2. Clinical and histopathological characteristics

Patient No.	Clinical pattern	Growth pattern	Predominant infiltrative cell type	Grade of differentiation	Other histologic features			IHQ					
					Perineural invasion	Lymphovascular invasion	Pagetoid spread	AR	Adipohilin	Factor XIIIa	Ki 67	EMA	Ber EP4
1	Nodular	Lobular	Not reported	Not reported	–	–	+	N/A	N/A	N/A	N/A	N/A	N/A
2	Nodular	Lobular	Basaloid	Not reported	–	–	–	N/A	+	–	N/A	+	N/A
3	Diffuse	Comedoacinar	Basaloid	Well	+	–	–	N/A	N/A	N/A	N/A	N/A	N/A
4	Nodular	Not reported	Squamoid	Well	–	–	–	N/A	N/A	N/A	N/A	N/A	N/A
5	Diffuse	Comedoacinar	Basaloid	Moderately	–	–	–	N/A	N/A	N/A	+	+	N/A
6	Diffuse	Not reported	Not reported	Not reported	–	–	–	+	N/A	N/A	N/A	+	–
7	Diffuse	Lobular	Basaloid	Well	–	–	–	N/A	N/A	N/A	N/A	N/A	N/A
8	Diffuse	Not reported	Not reported	Moderately	–	–	–	N/A	N/A	N/A	N/A	N/A	N/A
9	Diffuse	Not reported	Squamoid	Moderately	–	–	–	+	N/A	N/A	N/A	+	–
10	Nodular	Not reported	Squamoid	Moderately	–	–	–	N/A	N/A	N/A	N/A	+	N/A
11	Diffuse	Lobular	Squamoid	Poorly	–	–	–	+	N/A	N/A	N/A	+	–
12	Diffuse	Lobular	Squamoid	Moderately	–	–	–	+	N/A	N/A	N/A	+	+
13	Nodular	Lobular	Not reported	Not reported	–	–	–	+	N/A	N/A	N/A	+	+
14	Nodular	Lobular	Basaloid	Not reported	–	–	–	+	+	N/A	N/A	+	–
15	Nodular	Not reported	Not reported	Moderately	+	–	–	+	N/A	N/A	+	+	+

AR: androgen receptors; N/A: not available information; IHQ: immunohistochemistry.

It is the third most common eyelid malignancy worldwide after basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)[5]. SC occurs more frequently in older adults, with an age range of 60-79 years, as in our series. It affects both men and women equally (58% vs. 60%), with a higher proportion of ocular SC in women (70% vs. 51%)[10].

Ocular SC has a diverse clinical presentation and usually affects the upper lid, given the richness of Meibomian glands[11]. It commonly presents as a solitary, painless, solid, firm, and yellowish or pinkish nodule, with a rapid growth rate[5]. However, it can also manifest as diffuse, unilateral, thickening of the eyelid, usually lacking a well-defined margin and exhibiting an inflammatory appearance[12]. Due to its nonspecific presentation, ocular SC is frequently mistaken in its early stages for benign inflammatory conditions such as chalazion, blepharitis, and/or keratoconjunctivitis. Other differential diagnoses include pyogenic granuloma, BCC, SCC, and Merkel cell tumor[5,8]. This often leads to a significant delay in diagnosis and a potential worsening of prognosis, with a diagnostic delay reported to be up to 3 years[10].

Extraocular SC accounts to be 25-30% of all SC, it often presents in the head and neck, which are areas rich in sebaceous glands; however, it could appear in the genital area, parotid and submandibular glands, the external auditory canal, and the trunk or upper extremities. It often presents as pink, red, or yellow slowly enlarging firm and painless dermal or subcutaneous nodules ranging from 6 mm to 20 cm in size[13].

Pathogenesis and risk factors

Most SCs occur de novo, SC originates from cells within the sebaceous glands, which is why most of these tumors occur in the periocular region, commonly in the upper eyelid. Recent studies in animals and humans suggest that they can also originate from other populations of more primitive multipotent stem cells with the ability to differentiate in multiple directions, including the sebaceous lineage, emerging in approximately 25% of cases extraocularly, such as in the head and neck (20%), trunk areas with hair, and genital area (5%)[4]. Its pathogenesis is not fully understood yet, however, there are certain risk factors associated with the development of SC including ultraviolet radiation, advanced age, genetic predisposition, immunosuppression, previous radiotherapy, and in some reports exposure to human papillomavirus which have been described[14].

Dermoscopy

Dermoscopy findings in SC are non-specific but could be a valuable tool that aids in the differentiation of benign and malignant sebaceous neoplasms and other skin tumors. Usually, SC has and heterogeneous yellowish background[13], whitish-pink areas, blue ovoid nests, bluish structureless areas[15], polymorphic vessel pattern with linear irregular and arborizing vessels, and ulceration[5]. Cheng et al. reported that yellowish structures in SCs are the main dermoscopic finding to differentiate from SCC and BCC, whereas purplish globules, shiny white blotches, and strands and whitish-pink area distinguish SCs from other sebaceous tumors[5]. However, relying solely on dermoscopy is not feasible; history and pathology are crucial for diagnosis.

Histopathologic features

Biopsy is remarkable for making the diagnosis of SC, the sample should be representative of the lesion. Histopathological findings are variable; in general, a SC is a non-encapsulated dermal tumor composed of basophilic sebaceous cells with cytoplasmic vacuolation positioned in lobules or sheets separated by a fibrovascular stroma[16]. There could be variable degrees of sebaceous gland differentiation and atypia, with hyperchromatic nuclei, prominent nucleoli, and scant cytoplasm. Given its histological resemblance to other neoplasms, special stains and clinicopathologic correlation are mandatory to make the correct diagnosis.

Growth patterns could be lobular, comedo-acinar, papillary, and mixed. There could also be pagetoid spread, commonly in ocular SC, posing a worse prognosis[16]. SC can also express histopathological differentiation and different infiltrative cell types: squamoid, basaloid, adenoid, spindle cell, and differentiated SCs[17].

Immunohistochemistry is important in differentiating from other epithelial and adnexal tumors (Table 3). Despite SC is not a prevalent tumor, clinicians and pathologists should be aware of this possible diagnosis. In the right clinical context, with a high suspicion of the hematoxylin-eosin stain, proper immunohistochemistry will drive a correct and early diagnosis.

Nuclear factor XIIIa is a superior marker in discriminating between sebaceous and non-sebaceous neoplasms, with higher sensitivity and specificity in the diagnosis of sebaceous neoplasms compared to other markers[18]. Adipophilin and androgen receptors are sensitive markers with good sensitivity for SC, especially in poorly differentiated tumors[19,20]. Perilipin is another

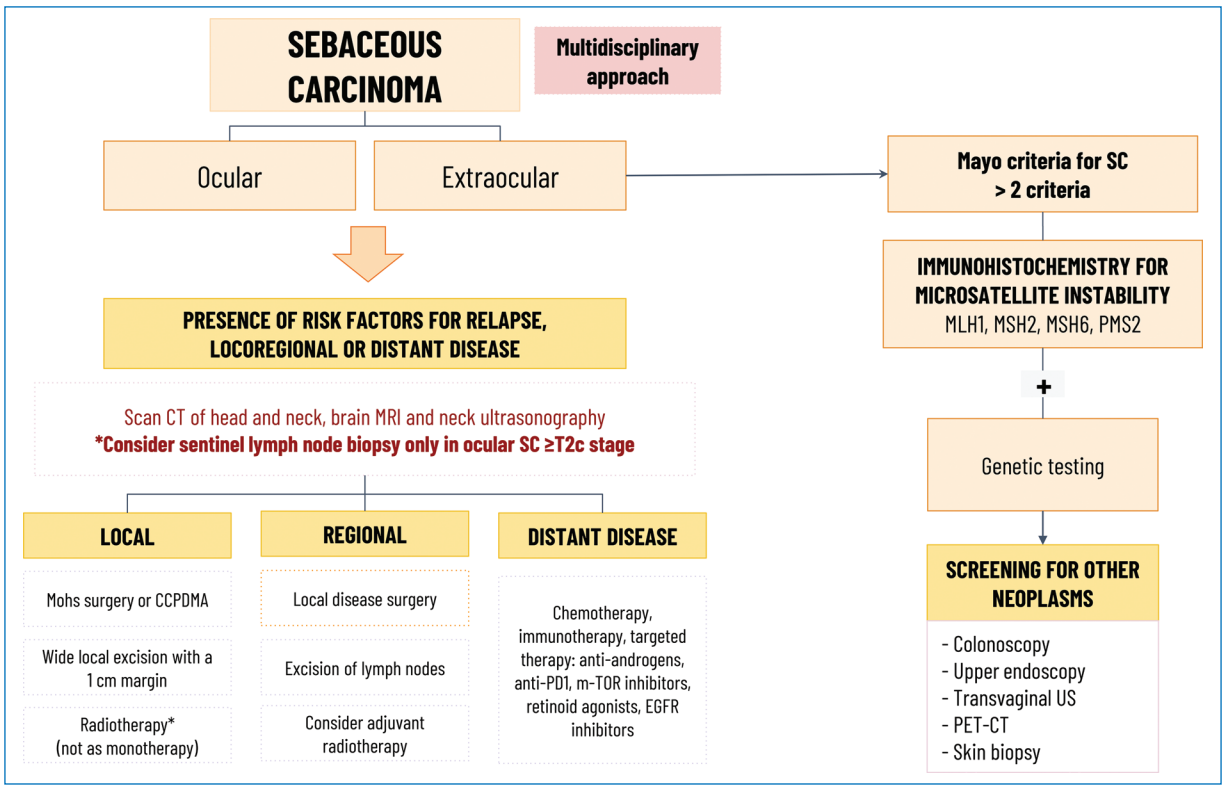

Figure 3. Algorithm for the approach of sebaceous carcinoma.

lipid droplet-associated protein with a high specificity close to 98% but a low sensitivity[21].

Other stains used to differentiate SC with other neoplasms such as BCC or SCC include EMA and epithelial cell adhesion molecule (BerEP4)[19]. Furthermore, the Ki-67 proliferation index and the percentage of p53-positive tumor nuclei appear to have diagnostic and prognostic value in SC[17].

There is currently no consensus on which histologic variables should be included in SC pathology reports. As seen in our cases and many others reported in the literature, histopathology reports and immunohistochemical stains vary widely. Similar to the approach taken with melanoma, it is crucial to propose a synoptic pathology report for SC, and standardize the stains needed to make a right diagnosis when there is a high suspicion of a SC.

In table 4, we propose a report model grounded in our experience at two centers in Bogotá and supported by the reviewed literature; its definitive adoption will require multicenter studies and expert consensus. This would not only enhance patient management by ensuring consistency in reporting but also facilitate easier data access, thereby supporting further research advancements in this area.

Table 3. Immunohistochemistry in the differential diagnosis of sebaceous carcinoma

Immunohistochemistry marker	SC	BCC	SCC
Nuclear factor XIIIa	+	–	–
Androgen receptor	+	+/– (focal)	–
Adipophilin	+	–	–
Peripilin	+	–	–
BerEP4	+/–	+	–
EMA	+	–	+

BCC: basal cell carcinoma; SCC: squamous cell carcinoma; SC: sebaceous carcinoma; EMA: epithelial membrane antigen; BerEP4: epithelial cell adhesion molecule.

Approach to a patient with suspicion of SC (Fig. 3)

When clinical suspicion of SC arises, a systematic and well-structured approach is essential to ensure optimal patient care. The first step is to obtain histopathological

Table 4. Proposed pathology report for sebaceous carcinoma

Location	Eyelid (upper, lower) extraocular
Histologic growth pattern	Lobular, comedo-acinar, papillary, mixed
Predominant infiltrative cell type	Squamoid, basaloid, adenoid, spindle cell, and differentiated SC
Histologic differentiation	Well, moderately or poorly differentiated
Other histologic features	Perineural invasion → positive (< 100 m, > 100 m) or negative Lymphovascular invasion → positive or negative Pagetoid spread → positive or negative
IHQ	Androgen receptor Nuclear factor XIIIa Adipophilin Peripilin Ki67 (proliferation index) Additional markers to differentiate from other epidermal neoplasms: EMA, BerEP4, CK-19

SC: sebaceous carcinoma; IHQ: immunohistochemistry; EMA: epithelial membrane antigen; BerEP4: epithelial cell adhesion molecule; CK-19: cytokeratin 19.

Table 5. Risk factors for relapse, locoregional or distant disease

AJCC 8th edition staging	Greater than T2c
Location	Ocular (x5 risk of metastasis) Lower eyelid Orbital involvement at diagnosis
Histopathological characteristics	Poor differentiation Perineural involvement Androgen receptor positivity > 50% (recurrence and metastasis) Pagetoid spread High Ki67
History of immunosuppression	Solid organ transplant Lymphomas
History of radiotherapy	For previous neoplasms (retinoblastoma)

In eyelid SC, restricted ocular mobility, proptosis, globe displacement, and pupillary abnormalities can be observed.
AJCC: American Joint Committee on Cancer.

confirmation, as this remains the gold standard for diagnosis. It is critical to consider the specific histological features that differentiate SC from other cutaneous malignancies, it is important to distinguish all the items mentioned in our proposed histopathological report, given that each item could confer a different prognosis and could aid in a better diagnosis.

Once a definitive diagnosis is established, the next step is to stage the patient based on the tumor's anatomical location, size, and extent of local invasion. Eyelid SCs should be classified according to the Eighth Edition of the American Joint Committee on Cancer (AJCC) staging system for eyelid carcinoma; however, extraocular SC do not have an specific staging system; recently, it has been suggested to use the Eighth Edition of the Union for International Cancer Control TNM staging system for skin carcinomas to guide treatment[22]. A higher stage of AJCC eyelid staging has been associated with local recurrence, nodal metastasis, distant metastasis, and death from disease[10].

There are some risk factors (Table 5) that should heighten vigilance for potential relapse or the development of locoregional or distant disease. In cases where clinical presentation and symptoms suggests a more advanced or aggressive form of SC, imaging studies such as magnetic resonance imaging (MRI), computed tomography (CT), or ultrasonography should be considered to evaluate the extent of the disease. In locally advanced tumors, MRI may aid in delineating soft tissue involvement, specially in ocular SC in which extension to orbit, orbital nerves, temporal fossa, parotid gland, and skull base must be ruled out[23]. If nodal involvement is identified through physical examination, a lymph node biopsy is recommended, and CT or CT-positron emission tomography (PET) may be helpful in correct characterization of the mass. If nodal involvement is confirmed or when suspecting a MTS, CT-PET is the most reliable imaging study[3,23]. Recent expert guidelines recommend sentinel lymph node biopsy in ocular SC with a staging > T2c[22].

Moreover, in the context of SC, especially when multiple sebaceous tumors are present or there is a family history of similar tumors, the possibility of MTS should be carefully considered. MTS is a hereditary condition associated with sebaceous neoplasms and visceral malignancies. To assess the likelihood of MTS, the Mayo criteria can be employed. If MTS is suspected, performing immunohistochemistry to evaluate for microsatellite instability is recommended, as MSI is a hallmark of this syndrome and can aid in the diagnosis and management.

Conclusion

SC, while rare, presents significant diagnostic and therapeutic challenges due to its clinical mimicry, histopathological variability, and potential for aggressive behavior. Our case series illustrates the heterogeneity in presentation, emphasizing the need for early clinical

suspicion, particularly in persistent or atypical periocular and extraocular lesions in older patients. Despite the known risk factors, the extended diagnostic delay seen in several patients in our cohort points to a critical gap in recognition and reinforces the value of timely biopsy and histopathologic evaluation. In addition, our findings highlight the prognostic relevance of specific histological features such as tumor differentiation, perineural invasion, pagetoid spread, and immunohistochemical markers such as androgen receptor expression and Ki67 index, which can inform both diagnostic certainty and risk stratification.

Given the absence of standardized histopathological reporting protocols for SC, the creation and implementation of a synoptic report model, as proposed here, may represent a pivotal step toward improving consistency and clinical decision-making. This approach would not only foster better communication between dermatopathologists and treating clinicians but also enable more precise, evidence-based management tailored to individual risk profiles. A multidisciplinary strategy, incorporating dermatology, surgery, pathology, radiology, oncology, and genetics, is essential, especially in patients with features suggestive of syndromic associations such as MTS. Continued documentation of cases and collaborative research efforts are vital to strengthen the evidence base and support the development of comprehensive guidelines for this complex neoplasm. The criteria presented here constitute a preliminary framework and is meant to serve as a starting point for validation and future consolidation.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

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