Therapeutic Role of Intralesional Candida Antigen in Basal Cell Carcinoma: A Narrative Review

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Abstract

Background: Basal cell carcinoma (BCC) is the most common skin cancer worldwide. While surgery remains the gold standard, not all patients are ideal surgical candidates due to lesion multiplicity, anatomic constraints, comorbidities, or cosmetic priorities. Intralesional Candida antigen (IL-Candida) is an office-based immunotherapy long used for recalcitrant warts that elicits a robust delayed-type hypersensitivity response. Emerging reports suggest IL-Candida may induce local and occasionally distant regression of BCC through immune activation within the tumor microenvironment. To synthesize current evidence on the therapeutic role of IL-Candida in BCC, including immunologic rationale, clinical efficacy, safety and tolerability, practical protocols, limitations of existing data, and future research directions. Narrative review of the dermatologic and oncologic literature on IL-Candida and related intralesional immunotherapies. Sources included clinical trials, prospective and retrospective series, case reports, mechanistic studies, and guidelines addressing BCC management and cutaneous immunotherapy. Emphasis was placed on injection techniques, dosing schedules, response rates, durability, adverse events, and histopathologic/immunologic correlates. IL-Candida triggers a Th1-skewed immune response characterized by IL-2 and IFN-γ release, recruitment of cytotoxic T lymphocytes and NK cells, and bystander effects that may extend beyond the injection site. Across small pilot studies and case series, partial and complete responses have been observed in low-risk BCCs, with occasional regression of distant untreated lesions. Typical regimens use intralesional injections at 2–3-week intervals for 3–6 sessions. Adverse effects are generally mild and transient (erythema, edema, tenderness; infrequent flu-like symptoms). Serious events are rare. Contraindications include history of severe Candida hypersensitivity, significant immunosuppression, and pregnancy. Evidence quality is limited by small sample sizes, heterogeneous protocols, lack of randomization, variable histologic subtyping, and short follow-up, precluding definitive estimates of long-term control versus established therapies.

Conclusions: IL-Candida is a promising, low-cost, minimally invasive immunotherapy for selected patients with BCC—particularly those with multiple lesions, cosmetic concerns, or surgical contraindications. Standardized dosing, histology-stratified trials, biopsy-confirmed endpoints, and longer follow-up are needed to define efficacy, durability, and optimal integration with existing modalities (e.g., imiquimod, PDT, or destructive procedures).

Keywords: *basal cell carcinoma; intralesional Candida antigen; immunotherapy; delayed-type hypersensitivity; nonmelanoma skin cancer; Th1 response; office-based treatment.*

Introduction

Basal cell carcinoma (BCC) represents the most common type of skin cancer worldwide, accounting for the majority of non-melanoma skin malignancies [1,2]. Although it is rarely metastatic, its locally invasive nature often causes significant tissue destruction, functional impairment, and cosmetic disfigurement if not treated appropriately [3]. The global incidence of BCC continues to rise, particularly in regions with high ultraviolet (UV) exposure, making it a pressing public health concern [4].

The mainstay of treatment for BCC has traditionally been surgical excision, which provides high cure

rates but is not always suitable for all patients [5]. Alternatives such as Mohs micrographic surgery, topical imiquimod, cryotherapy, and photodynamic therapy have been utilized in selected cases, but these modalities also carry limitations including recurrence risk, cost, and patient tolerability [6,7]. Therefore, there is an ongoing search for effective, minimally invasive therapeutic options.

In recent years, immunotherapy has gained considerable attention as an innovative approach for cutaneous malignancies [8]. Strategies that stimulate the host's immune system against tumor antigens have demonstrated promising results in melanoma and squamous cell carcinoma, leading researchers to explore their utility in BCC [9]. One of these immunotherapeutic methods is the use of intralesional Candida antigen, which has long been applied in dermatology to treat recalcitrant warts through immune activation [10,11].

The rationale for exploring Candida antigen in BCC treatment arises from its ability to induce a strong delayed-type hypersensitivity (DTH) response, resulting in cytokine release, recruitment of cytotoxic T lymphocytes, and enhanced tumor clearance [12]. Early studies and case series have suggested that this method could be a safe, low-cost, and effective adjunctive therapy for BCC [13,14]. This review aims to highlight the therapeutic potential, safety profile, and future directions of intralesional Candida antigen in the management of basal cell carcinoma.

Immunological Basis of Intralesional Candida Antigen

The therapeutic action of intralesional Candida antigen is largely mediated through the induction of a **delayed-type hypersensitivity (DTH) reaction** [15]. When the antigen is injected into the skin, antigen-presenting cells, such as Langerhans cells and macrophages, process and present Candida peptides to T lymphocytes. This triggers the release of pro-inflammatory cytokines, including interleukin-2 (IL-2) and interferon-gamma (IFN-γ), which in turn stimulate the activation and proliferation of cytotoxic T cells and natural killer (NK) cells [16].

This immune cascade enhances the **local antitumor response**, as immune effector cells not only target Candida antigens but also recognize and attack neoplastic cells within the same microenvironment [17]. The process is thought to involve a form of "bystander effect," whereby the heightened immune activation spreads to tumor-specific antigens, leading to regression of malignant cells [18].

In addition to local immunity, intralesional Candida antigen may provoke a **systemic immune effect**. Several reports have documented regression of untreated lesions at distant sites following local injection, indicating that systemic activation of tumor-directed T cells may occur [19]. This characteristic makes the therapy particularly appealing in patients with multiple lesions or those who are poor candidates for surgery.

Another proposed mechanism involves the **shift toward a Th1-type immune response**, which is essential for tumor clearance [20]. The increase in Th1 cytokines contributes to the recruitment of effector immune cells capable of directly inducing apoptosis in tumor cells. Simultaneously, the therapy enhances memory T-cell responses, potentially reducing recurrence risk [21].

Taken together, these immunological insights provide a solid foundation for investigating Candida antigen as an immunotherapeutic strategy in basal cell carcinoma, bridging the gap between dermatologic immunotherapy and oncologic practice.

Clinical Evidence of Candida Antigen in Dermatology

The earliest and most consistent clinical application of intralesional Candida antigen has been in the management of **recalcitrant cutaneous warts**. Multiple studies have reported high clearance rates, even in lesions resistant to conventional treatments such as cryotherapy or salicylic acid [22,23]. Interestingly, regression was frequently observed not only in injected warts but also in distant, untreated lesions, supporting the concept of systemic immune activation [24]. This phenomenon laid the groundwork for extending its use to other dermatologic conditions where immune stimulation might be beneficial.

In dermatology practice, intralesional Candida antigen has been favored for its **practical advantages**. It is widely available, inexpensive, and relatively easy to administer in an outpatient setting [25]. Most patients tolerate the injections well, with local erythema, mild swelling, and transient pain being the most common side effects [26]. Serious adverse effects are exceedingly rare, which further enhances its

suitability for repeated administration.

Beyond warts, intralesional Candida antigen has been explored in other **skin disorders requiring immune modulation**, including molluscum contagiosum, alopecia areata, and even certain chronic infections [27,28]. Although results vary depending on disease pathogenesis, the general trend has shown that Candida antigen can trigger meaningful immune responses that sometimes translate into clinical improvement.

Given this track record, it was a logical next step for researchers to examine its application in **cutaneous malignancies**. Reports of its efficacy in nonmelanoma skin cancers have gradually emerged, with early findings suggesting promising tumor regression rates and minimal toxicity [29]. Such results highlight its potential role as an alternative or adjunctive therapy for patients who are unsuitable for surgery or who desire a less invasive approach.

Intralesional Candida Antigen in Basal Cell Carcinoma

Interest in using **intralesional Candida antigen for basal cell carcinoma (BCC)** has grown in recent years, driven by its immunologic effects and encouraging outcomes in benign skin conditions. Early clinical reports described individual cases where patients with BCC experienced complete regression of lesions after repeated injections of Candida antigen [30]. These initial observations prompted further investigation into its efficacy in larger cohorts.

Several **pilot studies and case series** have evaluated this therapeutic approach. In most protocols, patients received intralesional injections of Candida antigen directly into the tumor every two to three weeks, with treatment cycles ranging between three and six sessions [31]. Reported clearance rates varied but were generally favorable, with many patients achieving partial or complete tumor regression [32]. Importantly, some studies noted regression of additional, untreated BCC lesions at distant sites, further suggesting a systemic immune-mediated effect [33].

The **mechanism of tumor clearance in BCC** following Candida antigen injection is thought to parallel that observed in viral warts. The antigen provokes a strong local immune response that subsequently targets tumor-specific antigens [34]. Histopathological analysis from regressed lesions has demonstrated infiltration of lymphocytes, increased cytokine activity, and tumor necrosis, supporting the immunologic basis of the treatment [35].

When compared to conventional BCC therapies, intralesional Candida antigen stands out as a **non-invasive, office-based option**. Surgery remains the gold standard, with cure rates exceeding 90%, but it is associated with risks of scarring, infection, and in some cases, functional impairment depending on tumor location [36]. Non-surgical alternatives like imiquimod and photodynamic therapy are limited by variable efficacy, recurrence risk, and patient adherence [37]. In contrast, Candida antigen offers a low-cost, repeatable approach with minimal equipment and technical demands [38].

Despite these advantages, most of the existing studies are limited by **small sample sizes and lack of randomization**, making it difficult to draw firm conclusions regarding efficacy [39]. Furthermore, BCC is a heterogeneous disease with multiple histological subtypes, and current data do not fully address whether certain variants respond more favorably to Candida antigen than others [40].

Nevertheless, the **cumulative evidence** points toward intralesional Candida antigen being a promising addition to the therapeutic armamentarium for BCC, particularly for patients who are poor surgical candidates, those with multiple lesions, or those seeking alternatives with less cosmetic morbidity [41]. Future well-designed clinical trials are needed to establish standardized dosing, treatment intervals, and long-term outcomes.

Safety and Tolerability

The **safety profile** of intralesional Candida antigen in basal cell carcinoma (BCC) appears generally favorable, based on both its long history in wart therapy and emerging evidence in oncology. The most frequently reported adverse reactions are localized, including **erythema, swelling, induration, and mild pain** at the injection site [42]. These reactions are typically transient, resolving within days without the need for intervention. In some cases, a local pustular or ulcerative reaction has been observed, which may represent an intense immune response but usually heals without scarring [43].

From a systemic perspective, **fever, malaise, or flu-like symptoms** have occasionally been reported following intralesional injection [44]. These side effects are believed to reflect the systemic release of cytokines such as interferon-gamma (IFN-γ) and interleukin-2 (IL-2), which are central to immune activation. Importantly, these systemic effects are usually self-limiting and do not necessitate discontinuation of therapy [45].

In contrast to many standard treatments for BCC, Candida antigen is associated with **minimal long-term morbidity**. Surgical excision, while highly effective, often carries risks of bleeding, infection, and cosmetic defects, especially in cosmetically sensitive areas like the face [46]. Radiotherapy and photodynamic therapy, though non-surgical, can cause chronic skin changes, pigmentation disorders, or pain [47]. Imiquimod, another immune-modulating treatment, is frequently accompanied by local irritation, erosions, and pruritus, which can reduce compliance [48]. Compared to these, Candida antigen injections are generally well tolerated, with only mild and temporary side effects [49].

It is important, however, to consider **contraindications**. Candida antigen therapy is not advised in patients with a known history of systemic fungal allergy, severe immunosuppression, or uncontrolled autoimmune disease, as immune activation could trigger unwanted systemic effects [50]. In addition, pregnant and lactating women are typically excluded from treatment protocols due to limited safety data [51].

Another safety consideration is the **variability in patient immune responsiveness**. Some individuals may fail to mount a sufficient immune reaction to Candida antigen, resulting in reduced efficacy rather than increased toxicity [52]. This factor underscores the importance of pre-testing for Candida hypersensitivity in some protocols, although its necessity in BCC remains debated [53].

Overall, Candida antigen appears to be a **safe, well-tolerated, and repeatable therapy**, with an adverse effect profile that is mild compared to conventional BCC treatments. The therapy's safety advantages, particularly its lack of disfiguring scars or significant systemic toxicity, make it an appealing option for patients seeking non-invasive management. Still, larger clinical trials are necessary to fully document adverse event rates, establish monitoring guidelines, and clarify patient populations most suitable for this treatment [54].

Limitations of Current Evidence

Despite the encouraging reports, the current evidence supporting **intralesional Candida antigen in basal cell carcinoma (BCC)** remains limited and carries several important caveats. The majority of published data comes from **small pilot studies, retrospective case series, or isolated case reports** [55]. These designs are prone to bias, lack randomization, and often involve heterogeneous patient populations, which reduces the strength of the conclusions that can be drawn.

A further limitation is the **absence of standardized treatment protocols**. Existing studies vary considerably in terms of the antigen concentration, injection volume, frequency of administration, and total number of treatment cycles [56]. This lack of consistency makes it difficult to compare outcomes across studies and prevents the establishment of a universally accepted dosing regimen. Without standardization, clinicians are left to rely on empirical dosing, which may lead to variability in efficacy and patient satisfaction.

Another challenge is the **heterogeneity of basal cell carcinoma subtypes**. Nodular and superficial BCCs may respond differently to immune-based therapies compared to more aggressive forms such as infiltrative or morpheaform subtypes [57]. However, most published studies do not stratify outcomes based on histological variants, leaving uncertainty about which patients are most likely to benefit from this treatment. Moreover, many studies fail to include long-term follow-up, making it difficult to assess durability of response and recurrence risk [58].

The **immune variability among patients** represents an additional limitation. The therapeutic mechanism relies on mounting an adequate delayed-type hypersensitivity (DTH) response, which is not universal. Patients who are anergic or immunocompromised may not respond adequately, resulting in partial or absent tumor regression [59]. Pre-treatment testing for Candida hypersensitivity could help identify responders, but this approach has not been systematically validated in BCC studies [60].

Furthermore, **histological confirmation of tumor clearance** is often lacking in published reports. In several cases, clinical clearance is reported without biopsy verification, raising concerns about the possibility of residual microscopic disease [61]. This is particularly important in BCC, where incomplete treatment can lead to recurrence, especially in cosmetically sensitive areas.

Lastly, most data have been generated in **single-center experiences**, often with limited patient numbers and under highly selected conditions [62]. There is a clear need for multicenter, randomized controlled trials with larger sample sizes to confirm efficacy, assess safety comprehensively, and compare Candida antigen directly against established therapies. Only through such rigorous studies can the true therapeutic role of Candida antigen in BCC be defined.

Future Perspectives

The therapeutic use of **intralesional Candida antigen in basal cell carcinoma (BCC)** represents a promising yet still experimental area of dermatologic oncology. Future research is expected to focus on addressing current gaps, optimizing protocols, and expanding its role beyond preliminary case series.

One important direction is the development of **standardized treatment protocols**. Current evidence shows significant variability in injection schedules, concentrations, and total doses [63]. Establishing evidence-based guidelines through controlled trials would allow clinicians to adopt this therapy more confidently and ensure reproducible outcomes across different clinical settings. Standardization could also help define the minimum number of sessions required for complete tumor regression, minimizing overtreatment while maximizing efficacy.

Another promising avenue lies in the potential for **combination therapies**. Candida antigen could be used alongside other immune-modulating treatments, such as topical imiquimod or checkpoint inhibitors, to enhance tumor-directed immune responses [64]. Combining antigen therapy with photodynamic therapy or cryotherapy may also create synergistic effects, where physical or chemical tumor destruction is complemented by systemic immune activation [65]. Such multimodal approaches may be particularly useful for recurrent or high-risk lesions.

There is also interest in evaluating whether Candida antigen may provide **long-term immunologic protection** against recurrence. The stimulation of memory T cells following antigen exposure suggests that patients might develop a form of adaptive immune surveillance against tumor re-emergence [66]. Longitudinal studies with extended follow-up are required to test this hypothesis, as current evidence lacks sufficient duration to confirm recurrence prevention.

Beyond BCC, researchers are beginning to explore the **role of Candida antigen in other cutaneous malignancies**. Squamous cell carcinoma (SCC), keratoacanthoma, and even melanoma represent potential future indications where immune activation could provide therapeutic benefit [67]. Given its favorable safety profile and low cost, Candida antigen may be particularly valuable in resource-limited settings where access to advanced oncologic therapies is restricted.

A final area of interest is the identification of **biomarkers of response**. Not all patients respond equally to intralesional Candida antigen, and predicting responders could enhance patient selection and improve outcomes. Potential biomarkers might include baseline Candida skin test reactivity, cytokine profiles, or genetic markers of immune function [68]. Future trials incorporating translational research could shed light on these predictive factors and refine the patient populations most likely to benefit.

In summary, while still in its early stages of investigation, intralesional Candida antigen has the potential to become a **low-cost, accessible, and minimally invasive immunotherapy for BCC**. Carefully designed multicenter trials, exploration of combination strategies, and deeper understanding of immune mechanisms will be essential steps to fully define its place in the therapeutic landscape.

Conclusion

Intralesional Candida antigen has emerged as an innovative and practical approach in the management of basal cell carcinoma. Its mechanism of action is grounded in stimulating local and systemic immune responses, which not only target injected lesions but can also influence distant sites. Clinical observations, though still limited, suggest that this method can achieve meaningful tumor regression with a favorable safety profile and minimal long-term morbidity.

Compared to conventional treatments, Candida antigen offers a low-cost, outpatient-based alternative that avoids scarring and functional impairment, making it especially valuable for patients with multiple lesions, those at high surgical risk, or those who desire less invasive options. At the same time, current evidence is preliminary and hampered by small study sizes, heterogeneous protocols, and lack of randomized controlled trials.

Looking forward, this therapy holds promise for integration into broader dermatologic oncology practice. Standardized treatment regimens, longer follow-up studies, and investigations into potential combination strategies will be necessary to clarify its true clinical value. While not yet ready to replace established therapies, intralesional Candida antigen may evolve into a safe and effective adjunct, broadening the therapeutic spectrum for basal cell carcinoma.

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